ASRM 2018

Scientific Abstracts to be presented at the 74th Scientific Congress of the American Society for Reproductive Medicine, October 6-10, 2018, Denver, Colorado.

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October 6-10, 2018
Denver, Colorado

These abstracts of research studies, published as submitted by the authors, are presented in the ASRM 2018 Congress sessions and are published in the order of their presentation. Abstracts of plenary lectures, symposia and interactive sessions are not included.
The first six papers are candidates for the ASRM Scientific Congress Prize Paper Awards. Six additional candidates will be presented during the Prize Paper Candidates’ session on Tuesday.

SCIENTIFIC CONGRESS PRIZE PAPER SESSION 1

O-1 Monday, October 8, 2018 10:45 AM

THREE-ARM RCT: VAGINAL ONLY PROGESTERONE IS INFERIOR, BUT VAGINAL PLUS INTRAMUSCULAR (IM) PROGESTERONE EVERY THIRD DAY IS EQUIVALENT, TO DAILY IM PROGESTERONE FOR VITRI-FIED-WARMED BLASTOCYST TRANSFER IN TERMS OF LIVE BIRTH. K. Devine,1 K. S. Richter,1 E. A. Widra,1 J. McKeely,1 Reproductive Endocrinology and Infertility, Shady Grove Fertility, Washington, DC; 2Research, Shady Grove Fertility, Rockville, MD; 3SG Fertility, Washington, DC; 4Reproductive Endocrinology and Infertility, Shady Grove Fertility, Annapolis, MD.

OBJECTIVE: To compare three different progesterone (P) replacement protocols for vitrified-warmed blastocyst transfer (VBT).

DESIGN: Three-arm non-inferiority randomized controlled trial (RCT).

MATERIALS AND METHODS: Planned transfers of vitrified-warmed high quality (Grade BB or better at time of vitrification) un-biopsied blastocyst(s) were randomized to receive: (1) 50 mg/d IM P only; (2) 200 mg twice daily vaginal Endometrin; or (3) 200 mg twice daily Endometrin plus 50 mg IM P every third day. The primary outcome was live birth per transfer. Secondary outcomes included pregnancy (positive hCG 2 weeks after transfer), clinical pregnancy (ultrasound confirmation of intrauterine gestational sac 4-5 weeks after transfer), biochemical pregnancy losses, and clinical pregnancy losses. Outcomes were compared among treatment arms by three-group X², followed by pairwise X² comparisons as appropriate.

RESULTS: 997 cycles were randomized, underwent VBT, and administered the study medications per assigned protocol. A planned interim analysis, performed once 50% of subjects had completed the final study visit, revealed significantly lower ongoing pregnancy in the Endometrin only arm. This arm only was unblinded and enrollment terminated. The study was completed according to our predetermined enrollment goals in the two remaining arms, which remained blinded to clinicians and the statistician until after analysis was complete. There were no differences in any treatment outcomes between the daily IM P only arm and the daily Endometrin plus IM P every third day arm.

There was a 40% reduction in live birth in the Endometrin only arm relative to cycles that included IM administration of P (28.6% vs 47.3%). This difference in live birth was primarily due to a biochemical loss rate that was more than twice as high for Endometrin only compared to the groups administering IM P (33% vs 15%). Increased clinical pregnancy loss and, to a lesser extent, decreased implantation (positive hCG) likely also contributed to the poorer birth outcomes with Endometrin only.

CONCLUSIONS: Live birth following VBT with vaginal-only P replacement was reduced by 40% relative to VBT where IM P was used. This difference was attributable to an increased rate of pregnancy loss. These RCT data indicate that vaginal-only P replacement for VBT should be avoided. In contrast, pregnancy and birth outcomes are equivalent between daily IM P or daily vaginal P supplemented with IM P every third day.

Supported by: Endometrin and limited study funding were provided by Ferring Pharmaceuticals Inc. Specifically, funding from Ferring covered study drug, IRB fees, external data monitoring committee fees, and subject compensation, in part. This is an investigator-initiated trial, and Shady Grove Fertility is the sponsor-investigator. The investigators were not compensated by Ferring for conduct of the trial, and Ferring did not influence study design, analysis, or interpretation of results.

O-2 Monday, October 8, 2018 11:00 AM

SINGLE CELL RNASEQ PROVIDES A MOLECULAR AND CELLULAR CARTOGRAPHY OF CHANGES TO THE HUMAN ENDOMETRIUM THROUGH THE MENSTRUAL CYCLE. W. Wang,1 F. Vilella,1 I. Moreno,1 W. Pan,1 S. Quake,2 C. Simon,2,3,4 Bioengineering, Stanford University, Stanford, CA; 3Igenomix Foundation, INCLIVA Health Research Institute, Valencia, Spain; 4Obstetrics & Gynecology, Stanford University, Stanford, CA; 5Chan Zuckerberg Biohub, San Francisco, CA; 6Obstetrics & Gynecology, University of Valencia, Valencia, Spain.

OBJECTIVE: Despite its relevance, mechanistic understanding of the human endometrium remains rudimentary. Here, we characterized the transcriptomic transformation of human endometrium at single cell resolution, dissecting multidimensional cellular heterogeneity across the entire natural menstrual cycle.

DESIGN: Single cell RNAseq analysis was performed on 2,149 single cells obtained from 19 endometrial biopsies across the menstrual cycle, presenting a high resolution transcriptomic map decoupled in cell type and state.

MATERIALS AND METHODS: After tissue dissociation, single cell capture, mRNA reverse-transcription and cDNA amplification were performed on the Fluidigm C1 system using default mRNASeq script. Capture site images were recorded using an in-house built microscopy system. Fusion of reads mapped to ERCC was used as the quality filtering metric and empty capture sites as the null model. 2,149 single cells were retained for downstream analysis.

RESULTS: Dimensional reduction via t-distributed stochastic neighbor embedding revealed that human endometrium consists of six cell types that are not time-associated across the menstrual cycle. Canonical markers and highly differentially expressed genes enabled identification of endocellular, macrophage, lymphocyte, struma, unciliated epithelium, and pre-implantation ciliated epithelium. Unbiased analysis identified four major phases of endometrial transformation across a menstrual cycle. Single cell temporal analysis revealed the global transcriptomic dynamics for epithelial and stromal cells across the entire cycle, where we discovered that the window of implantation (WOI) opens with an abrupt and discontinuous transcriptomic activation in unciliated epithelium, accompanied with widespread decidualized feature in the stromal counterparts with a less abrupt transition. Also, transcriptome signatures in deviating glandular and luminal epithelium supports a mechanism for adult epithelial gland formation. Lastly, we provided evidence for the direct interplay between struma and lymphocytes during decidualization, where stromal cells are responsible for the activation of lymphocytes through IL2-elicited pathways.

CONCLUSIONS: Our unbiased single cell analysis framework allows for the definition of global feature of endometrial transcriptomic dynamics as a step forward to the classical histological definition of the human menstrual cycle. Our results reveal unique molecular characteristics of transitions between non-receptive and receptive endometrial state, as well as insights in mechanistic understanding in the relationship between cell remodeling, proliferation and differentiation during endometrial homeostasis.

Supported by: Howard Hughes Medical Institute, March of Dimes, Chan Zuckerberg BiohubMINECO/FEDER SAF-2015-67164-R(CS).

Outcomes by Treatment Arm among Cycles Completed Per Protocol

<table>
<thead>
<tr>
<th></th>
<th>IM P only</th>
<th>Endometrin + IMP</th>
<th>Overall Chi-square (p val)</th>
<th>IMP only vs. Endometrin only (p val)</th>
<th>IMP only vs. Endometrin + IMP (p val)</th>
<th>IM + Endometrin vs. Endometrin only (p val)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitrified Blastocyst Transfers (N)</td>
<td>399</td>
<td>388</td>
<td>210</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Positive hCG per transfer (%)</td>
<td>68.9</td>
<td>64.9</td>
<td>59.0 (0.05)</td>
<td>0.015</td>
<td>0.24</td>
<td>0.15</td>
</tr>
<tr>
<td>Biochemical loss per positive hCG (%)</td>
<td>17.1</td>
<td>13.1</td>
<td>33.1 (&lt;0.0001)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clinical pregnancy per transfer (%)</td>
<td>57.1</td>
<td>56.4</td>
<td>39.5 (&lt;0.0001)</td>
<td>&lt;0.0001</td>
<td>0.84</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pregnancy loss per clinical pregnancy (%)</td>
<td>14.9</td>
<td>18.7</td>
<td>27.7 (0.036)</td>
<td>0.01</td>
<td>0.28</td>
<td>0.09</td>
</tr>
<tr>
<td>Total pregnancy loss (biochemical plus clinical) per positive hCG (%)</td>
<td>29.5</td>
<td>29.4</td>
<td>51.6 (&lt;0.0001)</td>
<td>&lt;0.0001</td>
<td>0.98</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Live birth per transfer (%)</td>
<td>48.6</td>
<td>45.9</td>
<td>28.6 (&lt;0.0001)</td>
<td>&lt;0.0001</td>
<td>0.44</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
OBJECTIVE: To evaluate the joint influence of age and BMI on cumulative live birth, in order to determine when taking time off from attempting conception to achieve a lower BMI may be detrimental to the cumulative live birth rate (CLBR) following IVF, and to develop a personalized counseling tool.

DESIGN: Retrospective study using linked fresh and frozen cycles from 1/2014-12/2015 from the Society for Reproductive Technology Clinic Outcome Reporting System (SART CORS).

MATERIALS AND METHODS: Demographic and outcome data from 51,959 fresh and 16,067 linked frozen embryo transfer (FET) IVF cycles performed between 1/2014-12/2015 were obtained from SART CORS. Poisson and logistic regression were used to calculate risk and odds ratios with 95% confidence intervals (CI) to determine differences in implantation and clinical pregnancy, respectively, among first fresh IVF cycles compared across age (y) and BMI (kg/m2) categories. Cox regression was used to calculate hazard ratios with 95% CI to determine differences in CLBR using fresh plus linked FET cycles. Models were adjusted for age, BMI, AMH, smoking, and age (linear trend p<0.001 for all). For some age and BMI combinations, models revealed that not all animals develop bilateral occlusion after this treatment. We hypothesized that administration of a co-sclerosant with PF might improve the rate of occlusion. To test this hypothesis, we assessed the effect of a combination polidocanol-doxycline foam (PDF) plus DMPA in baboons.

RESULTS: Treatment with PDF plus DMPA resulted in functional failure to recover sperm following tubal lavage and histologic (loss of tubal epithelium, destruction, and reorganization of the underlying lamina propria and accumulation of collagen-dense extracellular matrix) evidence of bilateral occlusion of the intramural tube in all 6 animals (100%). In comparison, a recent experiment with PF + DMPA resulted in only a 63% rate of tubal occlusion (1 bilateral; 3 unilateral out of 4 Hamadryas baboons). Moreover, compared to animals treated with 5% PF in prior protocols, treatment with PDF resulted in the histologic evidence of bilateral occlusion in all 6 animals.

CONCLUSIONS: Counseling women about weight loss prior to IVF should consider the combination of age and BMI.

References:
OBJECTIVE: Exposure to excess prenatal testosterone (T) has been shown to culminate in a polycystic ovary syndrome (PCOS)-like phenotype in female offspring of many species. In the sheep model, prenatal T excess also leads to fetal growth restriction and low birth weight (LBW) offspring, raising the possibility of placental compromise. Prior work found that prenatal T treatment improved placental function at gestational day (GD) 65, but ultimately reduced placental function at GD 140 (term) (Beckett et al. 2014). In this study, we tested the hypothesis that alterations in placental angiogenesis, oxidative stress, and inflammation contribute to the distinct placental phenotypes observed in T-treated sheep at GD 65 and 140.

RESULTS: At GD 65, T-treated sheep demonstrated large magnitude increases (Cohen’s d>0.8) in placental expression of VEGF, with medium magnitude decreases (Cohen’s d<0.5) in IL-1α and IL-6, and a trend towards decreased mRNA expression of all pro-inflammatory genes. On the contrary, by GD 140, T treatment was associated with increased placental mRNA expression of pro-inflammatory, angiogenic, and antioxidant genes, with large magnitude increases in IL-1α, IL-8, TNF-α, CCL2, GSR, VEGF, and HIF-1α.

CONCLUSIONS: Increased placental angiogenesis and decreased inflammation at GD 65 in T-treated sheep is consistent with improved placental function at mid-gestation. In contrast, the increase in pro-inflammatory markers in late gestation of T-treated sheep may contribute to placental dysfunction observed at GD 140. The accompanying increase in angiogenic and antioxidant gene expression at this time point may reflect compensatory mechanisms to overcome inflammatory insults. These findings provide important translational insights into optimizing placental function and pregnancy outcomes in PCOS women.


ACCESS TO CARE AND HEALTH DISPARITIES

O-7 Monday, October 8, 2018 10:45 AM

DISPARITIES IN ACCESS TO INFERTILITY CARE IN THE UNITED STATES: RESULTS FROM THE NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY, 2013-2016.

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OBJECTIVE: Despite improved awareness of infertility as a disease, access to infertility care remains challenging. To guide policy interventions, more knowledge is needed regarding factors associated with limited access to infertility services. Using the National Health and Nutrition Examination Survey (NHANES), we investigated the prevalence of infertility among a representative sample of women in the United States (US) and identified factors associated with lower access to care.

DESIGN: Retrospective, cross-sectional.

MATERIALS AND METHODS: NHANES is a population-based program maintained by the Centers for Disease Control, involving interviews and examinations of US residents, weighted to represent the US population. We included females 20-44 years old from the 2013-2016 NHANES database (n=2160). Women with infertility were identified as those who answered “yes” to the question, “Have you ever attempted to become pregnant over a period of at least a year without becoming pregnant?” Access to infertility care was evaluated with the question, “Have you ever been to a doctor or other medical provider because you have been unable to become pregnant?” We evaluated the relationship between infertility and access to care by age, body mass index (BMI), race/ethnicity, income, education, insurance status, and primary location of healthcare using Rao-Scott adjusted chi-square tests.
RESULTS: 12.5% of women reported infertility, and higher rates of infertility were noted with increasing age and BMI (p<0.01). There were no differences in rates of infertility by race/ethnicity, income, education, insurance, or primary location of healthcare. However, women with incomes <$24,999 received infertility care less frequently than women with incomes $100,000 (5.4% vs. 11.6%, p<0.01). Women with a high school diploma or less reported decreased access to infertility care compared to those with at least a college degree (5.0% vs. 11.6%, p<0.01), and uninsured women pursued infertility care less often than insured women (5.9% vs. 9.9%, p<0.01). Non-Hispanic blacks and Mexicans reported reduced access to care than Non-Hispanic whites and Asians (6.8% and 6.3% vs. 10.6% and 10.3%, respectively), although these differences did not reach statistical significance (p=0.06). Finally, women whose primary healthcare location was the emergency department reported lower access to infertility care compared to those whose primary healthcare location was a doctor’s office (1.4% vs. 11.8%, p<0.01).

CONCLUSIONS: Despite equivalent infertility rates among socioeconomic groups, decreased access to infertility care is reported by women with lower incomes, less education, without health insurance, and with an unstable primary healthcare location. These nationally-representative findings highlight the need for policy makers to address disparities in access to infertility care by targeting these particular populations of underserved women.

O-8 Monday, October 8, 2018 11:00 AM

NATIONAL SURVEY OF SART MEMBERS REGARDING INSURANCE COVERAGE FOR ART. D. B. Seifer,1 E. Wantman,1 A. E. Sparks,1 B. Luke,1 K. J. Doody,1 J. P. Toner,1 B. J. Van Voorhis,1 P. C. Lin,1 2 REI, Yale Fertility Center, New Haven, CT; 3Redshift Technologies, Inc., New York, NY; 4Obstetrics and Gynecology, University of Iowa, Iowa City, IA; 5Obstetrics, Gynecology, and Reproductive Biology, Epidemiology, East Lansing, MI; 6Ob-Gyn, Center for Assisted Reproduction, Bedford, TX; 7Atlanta Center for Reproductive Medicine, Atlanta, GA; 8Ob-Gyn, University of Iowa, Iowa City, IA; 9Seattle Reproductive Medicine, Seattle, WA.

OBJECTIVE: Assess the attitudes of SART members regarding insurance coverage and identify factors which may influence such attitudes.

DESIGN: Anonymous self-administered 14 question online survey of SART membership.

MATERIALS AND METHODS: 1556 surveys were sent through the SART Research Portal between June and December, 2017. Questions were incremental in scope beginning with insurance coverage for ART for vulnerable populations (ie. fertility preservation for cancer, couples with same recessive gene, fertility preservation for transgender individuals) and expanding to include patients who were uninsured for ART. Additional questions assessed attitudes about assuming some responsibility if mandated insurance were contingent upon eSET and lower charges in anticipation of increased number of cases.

RESULTS: Overall response rate was 43.4% (675/1556). 95+% were supportive of insurance coverage for another vulnerable population (transgender). 78% supported mandated insurance for the broadest segment of the general uninsured population. 76.7% supported mandated insurance contingent upon eSET. 51% would consider mandated insurance contingent on lowering charge per cycle in general but only 23% responded as to what lower charge would be acceptable. Three of 4 factors were shown by multivariable logistic regression to be predictive of attitudes willing to expand insurance: practice setting (academic / hybrid / private), practicing in a mandated state, and higher annual volume of cases (>500 cycles); these had significant increased Adjusted Odds Ratios (AOR) ranging from 1.7-2.9. A fourth factor, the role in practice was not found to be of significant predictive value.

CONCLUSIONS: The majority of respondents are supportive of mandatory insurance for specific segments of vulnerable populations and for the uninsured. SART members are open to expanded insurance coverage contingent upon age appropriate eSET, but have concern about reduced reimbursements.
cancer, among infertile participants, although overall cancer rates were low given the relatively young mean age of participants. There were no differences in cardiovascular risk factors (hypertension, hyperlipidemia) between groups (Table 1).

CONCLUSIONS: This is a novel investigation of reproductive health and chronic disease in US women Veterans, and the data add to the growing literature on infertility as a marker for overall poorer health. Patients who present with infertility may warrant additional counseling and screening regarding chronic health issues, and future research is needed to better explore these concerning associations.

Supported by: Source of Funding: Department of Veterans Affairs, Health Services Research and Development: NRI 04-194-1

O-10 Monday, October 8, 2018 11:30 AM

AFRICAN AMERICAN PATIENTS EXPERIENCE REDUCED PREGNANCY, HIGHER PREGNANCY LOSS, AND LOWER LIVE BIRTH FROM IVF EMBRYO TRANSFERS DESPITE PRODUCING MORE OOCYTES AND MORE TRANSFER QUALITY EMBRYOS THAN CAUCASIAN PATIENTS. L. A. Bishop, K. Devine, I. Sasson, T. C. Flowden, M. J. Hill, A. H. DeCherney, K. S. Richter, NIH, Arlington, VA; 4Reproductive Endocrinology and Infertility, Shady Grove Fertility, Washington DC, MD; 5Shady Grove Fertility, Wayne, PA; 6Program in Reproductive and Adult Endocrinology, National Institutes of Health, Bethesda, MD; 7NIH, Germantown, MD; 8NICHD, Bethesda, MD; 9Research, Shady Grove Fertility, Rockville, MD.

OBJECTIVE: To compare IVF outcomes among African American versus Caucasian women.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: All retrievals for fresh autologous IVF from 2004-2016 at a private IVF center among women self-identifying as Caucasian or African American were reviewed. Unadjusted comparisons were evaluated by t-test or chi-square. Adjusted comparisons were performed with multivariate generalized estimating equations (GEE) analyses accounting for multiple retrievals per patient and adjusted for differences in age, body mass index (BMI), diagnoses, and treatment year.

RESULTS: 36,217 retrievals for fresh autologous IVF were performed among Caucasian (29,547) and African American (6,670) women. African Americans were one year older, nearly 3kg/m2 higher BMI, diagnoses, and treatment year. ing for multiple retrievals per patient and adjusted for differences in age, with multivariate generalized estimating equations (GEE) analyses account-

were evaluated by t-test or chi-square. Adjusted comparisons were performed for Caucasian or African American were reviewed. Unadjusted comparisons

CONCLUSIONS: By current standard clinical measures, African Americans respond better to IVF stimulation than comparable Caucasian women, with higher serum estradiol, thicker endometrium, more oocytes, and more surplus high-quality blastocysts available after fresh embryo transfer. Despite these advantages, clinical pregnancy was 9% lower, clinical pregnancy loss was 24% higher, and live birth was 14% lower for African Americans relative to comparable Caucasians. Poorer IVF outcomes among African Americans may result either from aspects of embryo quality not captured by current grading systems or as yet unidentified uterine factors, suggesting these as potentially fruitful areas of future research.

O-11 Monday, October 8, 2018 11:45 AM

KNOWLEDGE, ATTITUDES, AND PERCEPTIONS OF INFERTILITY: A NATIONAL SURVEY. L. Farrell, L. Brennan, M. Lanham, Michigan Medicine, Ann Arbor, MI.

OBJECTIVE: The negative psychosocial impact from infertility on patients and couples is well-established; however, little is known about the general public’s knowledge and perception of infertility. The purpose of this study was to assess the knowledge and attitudes of the general U.S. population regarding the causes, prevalence, and emotional effect of infertility, and to investigate the relationships between prior infertility history, obstetric history, birth control use, and race on these beliefs.

DESIGN: Internet survey.

MATERIALS AND METHODS: A 46-question survey was developed by the authors in Qualtrics. One-thousand respondents were recruited for a small monetary incentive to complete the survey via Amazon’s Mechanical Turk (MTurk) in February 2018. Individuals were eligible if they were American residents and aged 18 to 69 years at the time of the survey. Responses were analyzed with Chi-squared test, Fisher exact test, and logistic regression where appropriate, using SAS software, Version 9.4.

RESULTS: Nine-hundred ninety-three (99.3%) respondents completed the survey. Respondents predominantly identified as non-Hispanic White (79%), followed by Black or African American (7.8%), Hispanic White (6.8%), and Asian (6.6%). 73% of respondents were between age 21 and 40 years, 68% of the respondents were female, and of those, 67% had previously been pregnant, 44% had experienced a miscarriage, and 19% had a history of pregnancy termination. 24% of respondents reported that they and/or their partner had a history of infertility. 53% of respondents believed more than 20% of individuals will experience infertility in their lifetime, with individuals with a history infertility estimating a higher incidence of infertility in the population than those without that history (OR 2.0, 95% CI 1.5-2.7). The majority of respondents feel that infertility treatment should be covered by insurance (70%) and that women undergoing fertility treatment should have paid time off to for those appointments (54%).

CONCLUSIONS: Among a national sample of adults in the United States, knowledge and perceptions about the causes and incidence of infertility vary. Misperceptions about the causes of infertility are common, and this diminished health literacy may predispose individuals to inequity in access to fertility care. Providers may benefit from learning of these common misperceptions and the associated risk factors in order to tailor patient education and community outreach programs to improve health literacy, eliminate misperceptions around the diagnosis of infertility, and improve access to care.

Supported by: University of Michigan Department of Obstetrics and Gynecology.

<table>
<thead>
<tr>
<th></th>
<th>Caucasian</th>
<th>African American</th>
<th>P-value</th>
<th>Caucasian (adj)</th>
<th>African American (adj)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum estradiol at trigger (pg/mL)</td>
<td>222.1 1110</td>
<td>246.5 1275</td>
<td>&lt;0.0001</td>
<td>220.9 1131</td>
<td>257.4 1168</td>
<td>&lt;0.0001</td>
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<tr>
<td>Endometrial thickness at trigger (mm)</td>
<td>11.6 2.5</td>
<td>11.9 2.9</td>
<td>&lt;0.0001</td>
<td>11.6 2.6</td>
<td>11.9 2.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Oocytes retrieved</td>
<td>13.7 8.0</td>
<td>13.7 9.0</td>
<td>NS</td>
<td>13.5 8.0</td>
<td>14.5 8.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mature (MII) oocytes</td>
<td>10.3 6.5</td>
<td>9.4 6.8</td>
<td>&lt;0.0001</td>
<td>10.7 6.7</td>
<td>10.7 6.8</td>
<td>NS</td>
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<tr>
<td>Fertilized (2pn)</td>
<td>7.9 5.4</td>
<td>7.2 5.5</td>
<td>&lt;0.0001</td>
<td>7.7 5.4</td>
<td>7.6 5.4</td>
<td>NS</td>
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<tr>
<td>Embryos per transfer</td>
<td>2.0 0.8</td>
<td>2.0 0.8</td>
<td>NS</td>
<td>2.0 0.7</td>
<td>2.0 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Cryopreserved blastocysts</td>
<td>1.2 2.3</td>
<td>1.4 2.6</td>
<td>&lt;0.0001</td>
<td>1.2 2.3</td>
<td>1.6 2.3</td>
<td>&lt;0.0001</td>
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<tr>
<td>Positive ICG per transfer</td>
<td>57.8%</td>
<td>49.7%</td>
<td>&lt;0.0001</td>
<td>57.5%</td>
<td>52.4%</td>
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<tr>
<td>Clinical pregnancy per transfer</td>
<td>49.0%</td>
<td>42.0%</td>
<td>&lt;0.0001</td>
<td>48.6%</td>
<td>44.5%</td>
<td>&lt;0.0001</td>
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<td>Clinical pregnancy loss</td>
<td>18.2%</td>
<td>26.1%</td>
<td>&lt;0.0001</td>
<td>17.7%</td>
<td>21.9%</td>
<td>&lt;0.0001</td>
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<tr>
<td>Live birth per transfer</td>
<td>40.0%</td>
<td>31.0%</td>
<td>&lt;0.0001</td>
<td>38.8%</td>
<td>33.3%</td>
<td>&lt;0.0001</td>
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LOWER GESTATIONAL AGE AND INCREASED RISK OF PRETERM BIRTH ASSOCIATED WITH SINGLETON LIVE BIRTH RESULTING FROM IN VITRO FERTILIZATION (IVF) AMONG AFRICAN AMERICAN VERSUS COMPARABLE CAUCASIAN WOMEN. L. A. Bishop, K. Devine, I. Sasson, T. C. Plowden, M. J. Hill, A. H. DeCherney, K. S. Richter. *NIH, Arlington, VA; Reproductive Endocrinology and Infertility, Shady Grove Fertility, Washington DC, MD; Shady Grove Fertility, Wayne, PA; Program in Reproductive and Adult Endocrinology, National Institutes of Health, Bethesda, MD; *NIH, Germantown, MD; NICHD, Bethesda, MD; *Research, Shady Grove Fertility, Rockville, MD.

OBJECTIVE: To compare singleton gestational age at birth between minority racial/ethnic groups (African American, Asian, and Hispanic) and Caucasian IVF patients.

DESIGN: Retrospective cohort study

MATERIALS AND METHODS: All singleton IVF pregnancies ending in live birth among women self-identifying as Caucasian, African American, Asian, or Hispanic from 2004-2016 at a private IVF practice were reviewed. Gestational age at birth was calculated as the number of days from oocyte retrieval to birth, plus fourteen. Unadjusted comparisons between racial/ethnic groups were evaluated by t-test or chi-square. Generalized estimating equations (GEE) analyses accounted for parity and adjusted for differences in age, body mass index (BMI), infertility diagnoses, and treatment year.

RESULTS: 10,371 singleton births were available for analysis. In unadjusted comparisons, African American births occurred over 6 days earlier than Caucasian births. Some of the shorter gestation among African Americans was explained by their higher BMI (p < 0.0001) and higher incidence of uterine factor (p < 0.0001), both of which are risk factors for earlier delivery. After adjusting for these and other demographic variables, African Americans still delivered 5.5 days earlier than Caucasians (p < 0.0001). In adjusted GEE analyses, African American births were more than three times as likely to be either very preterm (2.9% vs 0.9%, p < 0.0001) or extremely preterm (1.4% vs 0.4%, p < 0.0001). Gestational ages of Asian and Hispanic births were both comparable to Caucasian births.

CONCLUSIONS: Unlike other minority groups (Asians and Hispanics), ART singleton live births occurred at a significantly earlier gestational age in both unadjusted and adjusted comparisons of African American versus Caucasian births. The higher risk of preterm delivery in African Americans seen in unassisted conceptions also exists in ART conceptions and persists despite adjustment for known confounders.

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<tr>
<th></th>
<th>Caucasian</th>
<th>African American</th>
<th>Asian</th>
<th>Hispanic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Births</td>
<td>7105</td>
<td>1204</td>
<td>1601</td>
<td>461</td>
</tr>
<tr>
<td>Age at Birth, mean SD</td>
<td>272.7 13.7</td>
<td>266.4 19.7*</td>
<td>271.9 13.0</td>
<td>271.2 14.7</td>
</tr>
<tr>
<td>Term (37 weeks)</td>
<td>90.4%</td>
<td>80.9%*</td>
<td>90.0%</td>
<td>86.1%</td>
</tr>
<tr>
<td>Moderately Preterm (32-37 weeks)</td>
<td>8.4%</td>
<td>14.2%*</td>
<td>9.1%</td>
<td>12.2%</td>
</tr>
<tr>
<td>Very Preterm (&lt;28 weeks)</td>
<td>0.9%</td>
<td>3.2%*</td>
<td>0.6%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Extremely Preterm (&lt;28 weeks)</td>
<td>0.4%</td>
<td>1.8%*</td>
<td>0.4%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

* p < 0.0001 versus Caucasian

ANDROGEN EXCESS AND POLCYSTIC OVARY SYNDROME

O-12 Monday, October 8, 2018 12:00 PM


OBJECTIVE: Diet and exercise are the cornerstone of counseling for women with PCOS. Yet, efforts to accomplish meaningful change in this arena may be hampered by disordered eating attitudes. We sought to characterize the prevalence of eating disorder psychopathology in women with PCOS compared to a normative population and to identify clinical predictors indicative of risk.

DESIGN: Cohort study; comparison to a normative population

MATERIALS AND METHODS: Women with PCOS-Rotterdam ages 16-44 were enrolled in a cohort study after a clinic visit between 2006-2017. A follow-up survey was distributed via email in 2017 which included validated instruments. Eating Disorder Examination-Questionnaire (EDE-Q) algorithm yields four subscale scores (0-6, with 6 most severe): eating concern, shape concern, weight concern and restraint. The global score is the mean of the subscales. Depression risk was established using a cut-off score of >4 on the Beck Depression Index Fast Screen (BDI-FS). EDE-Q scores were compared between PCOS women and a normative population control cohort (1). PCOS women were divided into tertiles based on global EDE-Q scores; logistic regression models identified factors associated with scoring in the highest symptom tertile.

RESULTS: 164 women with complete EDE-Q data at follow-up were included in the study cohort. Average follow-up interval was 5.3 yrs; at follow-up, average age was 34.5; average BMI 29.8 kg/m2. Compared to controls, women with PCOS had higher EDE-Q global scores (2.3 vs. 1.5; p < .001) and scored higher on all subscales. Prevalence of regular binge eating was 20% in PCOS vs 11% in controls (p<0.001). Within the PCOS cohort, regression models controlling for age and follow-up interval identified parameters associated with scoring in the most severe EDE-Q global tertile: increasing BMI, waist circumference, hyperandrogenemia, high sensitivity C-reactive Protein (hsCRP) and depression risk (Table). When BMI was added to the model, depression, biochemical hyperandrogenism, and CRP remained associated at the p < .10 level. Women at risk for depression were four times more likely to score in the highest tertile on the EDE-Q (aOR 4.3, 95% CI 2.0, 9.2; p < .01).

CONCLUSIONS: Women with PCOS are at elevated risk of disordered eating attitudes and behaviors, which may hamper attempts at lifestyle change. Clinicians should screen women with PCOS for eating disorder pathology, especially those with depression, obesity and hyperandrogenemia, independent predictors of severe EDE-Q score risk. Future research should address interventions for PCOS women with altered eating attitudes and behaviors.

References:

Model 1 Adjusted for age and follow-up interval; Model 2 Further adjusted for BMI; NS: p > .10

<table>
<thead>
<tr>
<th>Clinical Correlate</th>
<th>Model 1 aOR (95% CI); p</th>
<th>Model 2 aOR (95% CI); p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>1.07 (1.03, 1.12); &lt;0.01</td>
<td>-</td>
</tr>
<tr>
<td>Waist (in)</td>
<td>1.07 (1.02, 1.12); NS</td>
<td>0.01</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>1.01 (1.00, 1.01); 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>2h glucose (mg/dL)</td>
<td>1.02 (1.00, 1.03); &lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>1.16 (1.01, 1.34); 0.03</td>
<td>1.13 (0.98, 1.31); 0.09</td>
</tr>
<tr>
<td>Hyperandrogenemia (y/n)</td>
<td>2.09 (0.98, 4.46); 0.06</td>
<td>2.24 (1.00, 5.03); 0.05</td>
</tr>
<tr>
<td>Depression Risk (y/n)</td>
<td>5.14 (2.47, 10.7); &lt;0.01</td>
<td>4.29 (2.00, 9.20); &lt;0.01</td>
</tr>
</tbody>
</table>

O-14 Monday, October 8, 2018 11:00 AM


OBJECTIVE: Excessive androgen production and hyperplasia of theca cells are central features of polycystic ovary syndrome (PCOS). Since...
PCOS is associated with systemic inflammation, this study evaluated the effects of inflammatory stimuli on gene expression in theca-interstitial cells (TICs).

**DESIGN:** In vitro study evaluating effects of lipopolysaccharide (LPS) and interleukin 18 (IL18) on gene expression in TICs.

**MATERIALS AND METHODS:** Isolated rat TICs were cultured without or with LPS (1 μg/ml) or IL18 (1 ng/ml). RNAseq analysis was conducted by standard methods using Illumina HiSeq. Reads were mapped to Rat genome and differential expression was analyzed using DESeq2 package in R. We report on differentially expressed genes shifted in expression by at least 1.5-fold (log2) with an adjusted p-value (q-value) of ≤0.05. Enriched functional categories were identified using gene ontology (GO) analysis and Ingenuity® Pathway Analysis (IPA®).

**RESULTS:** Using the stringent criterion described above, we identified 104 (Log2 fold change > 2.5) differentially expressed genes (DEGs) between the LPS-treated and control cells, 125 DEGs (Log2 fold change > 2.5) between the IL18-treated and control cells, and 48 DEGs (Log2 fold change > 1.5) between the LPS-treated and IL18-treated cells. Enriched functional categories of genes shifted in expression by LPS and by IL18 treatment include those involved in the inflammatory response, the IL-17 signaling pathway, the humoral immune response, cell proliferation, cell cycle progression, inhibition of apoptosis, and hormone biosynthesis. LPS treatment as well as IL18 treatment upregulated the inflammusome pathway (including Tlr4, NF-kB, Nlrp1, Nlrp3 and Caspase 1), key pathways associated with proliferation (including PI3K/Akt and Erk1/2), as well genes relevant to inhibition of apoptosis (Bcl-2 and Bcl-x). LPS and IL18, each, also showed expression of key genes involved in androgen biosynthesis (Cyp11a, Hsd3b1, and Cyp17a1). Also upregulated by LPS and by IL18 were several genes in the mevalonate pathway, including those encoding enzymes involved in synthesis of isoprenylation substrates, which would be predicted to activate small GTPases such as RAS and RHO.

**CONCLUSIONS:** RNAseq analysis revealed that inflammatory stimuli promote inflammatory effects in a subset of gene expression in TICs. Among the categories of genes significantly affected were those involved in the regulation of growth and androgen production. Given that excessive growth and androgen production by theca cells is a hallmark of PCOS, our results support the hypothesis that chronic inflammation in PCOS contributes to the altered function of theca cells and may play a role in the pathophysiology of PCOS.

References: 1. Supported by: NICHD P50 HD012303

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**O-15 Monday, October 8, 2018 11:15 AM**

**ANDROGENIC ALOPECIA ASSOCIATED WITH THE HSD3B1 (1245A>C) IN OVERWEIGHT WOMEN WITH POLYCYSTIC OVARY SYNDROME.**

**Y. Tu, S. Chen, J. Yang, H. Ho, M. Chen. National Taiwan University Hospital, Taipei, Taiwan.**

**OBJECTIVE:** HSD3B1 (1245A>C) has been mechanistically linked to polycystic ovarian syndrome (PCOS) because it encodes an altered enzyme that augments dihydrotestosterone synthesis from non-gonadal precursors. We postulated that women inheriting the HSD3B1 1245C allele would exhibit specific phenotypic variances in women with PCOS.

**DESIGN:** A cross-sectional study conducted in a university-associated tertiary care medical center.

**MATERIALS AND METHODS:** A total of 472 Taiwanese women with PCOS were enrolled according to the Rotterdam criteria. HSD3B1 genotype was determined in all patients to correlate with various phenotypic outcomes, including androgenic alopecia (AGA), acne, hirsutism, obesity, hypertension, and laboratory evidences of androgen excess and dyslipidemia. Databases of 1000 Genomes Project and Taiwan BioBank were applied to compare the frequency of the C allele of HSD3B1 among different populations.

**RESULTS:** The presence of AGA was higher in women with HSD3B1 variant AC or CC genotype (23.2%), compared to that with wild-type AA genotype (13.5%, p = 0.068). The association between HSD3B1 genotype and the presence of AGA is especially stronger in overweight women with PCOS (OR: 3.53, P = 0.009) but not in those normal-weight women with PCOS (OR: 1.087, P = 0.883). In PCOS women with AGA, compared to those without AGA, we found a significantly higher BMI (26.9 vs. 23.0 kg/m², P = 0.0004), lower HDL-C levels (47.5 vs. 50.5 mg/dL, P = 0.008), higher tri-glyceride (TG) levels (119.9 vs. 88.4 mg/dL, P < 0.0001), lower sex hormone binding globulin (SHBG) levels (30.6 vs. 37.3 nmol/L, P = 0.002), and higher proportion of hypertension (17.6 vs. 9.0%, P = 0.049). The strong association between the presence of AGA and the HSD3B1 AC/CC genotypes still existed (OR: 2.312, P = 0.021) by using stepwise logistic regression analysis after considering confounders as age, BMI, levels of fasting sugar, HDL-C, TG, free androgen index and SHBG, and the presence of hypertension. The frequency of the C allele among Taiwanese women with PCOS was 6.4%, which was significantly lower than that observed in the individuals of European ancestry (34%), but similar to the prevalence of that observed in the general Taiwanese population (6.6%).

**CONCLUSIONS:** The presence of AGA in women with PCOS associates with the higher risk of metabolic disturbances as higher BMI and TG levels, higher risk of hypertension, but lower HDL and SHBG levels. Although the frequency of HSD3B1 1245C allele are not significant different between women with PCOS and non-population, the inheritance of such variant type in overweight women with PCOS comprise significantly higher risk of AGA phenotype than those women with wild type of HSD3B1.

Supported by: The study was supported by grants from the Ministry of Science and Technology of Taiwan (MOST 105-2628-B002-043-MY4).

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**O-16 Monday, October 8, 2018 11:30 AM**

**HALLMARK EVIDENCE OF LIPOPOLYSACCHARIDE (LPS) TOLERANCE IN OBESE WOMEN WITH POLYCYSTIC OVARY SYNDROME (PCOS) - LPS-INDUCED NFKB SUPPRESSION IN MONONUCLEAR CELLS (MNC) IS LINKED TO HYPERANDROGENISM IN PCOS.**

**F. Gonzalez, R. V. Considine, O. A. Abdelhadi, A. J. Acton. University of Illinois at Chicago College of Medicine, Chicago, IL; Indiana University School of Medicine, Indianapolis, IN.**

**OBJECTIVE:** LPS from gut-related bacteria promotes obesity-related metabolic inflammation. Circulating LPS after lipid ingestion is higher in obese women with PCOS compared with obese ovulatory women. In preclinical studies, LPS tolerance suppresses inflammation after repetitive exposure to proinflammatory stimuli involving LPS. In vivo LPS exposure after lipid ingestion suppresses cytokine secretion from MNC of obese women with PCOS. Androgens also suppress LPS action. We examined the in vitro effect of exposing MNC to lipid alone versus lipid+LPS on NFκB activation in women with PCOS compared with ovulatory controls, and their relationship to androgen secretion.

**DESIGN:** Cross-sectional study.

**MATERIALS AND METHODS:** We studied 19 women with PCOS (10 lean; 9 obese) diagnosed on the basis of oligo- or amenorrhea and hyperandrogenemia, and 18 ovulatory controls (9 lean; 9 obese) all between ages 18-40. MNC isolated from fasting blood samples were exposed to palmitate in culture under pre- (0.4 mM) and post-prandial (0.2 mM) conditions with or without LPS. Intracellular NFκB was quantified by electrophoretic mobility shift assay. Androgens measured by RIA from blood samples drawn while fasting and 24, 48 and 96 hours after HCG administration. Insulin sensitivity was derived by ISOGTT.

**RESULTS:** In response to lipid alone, the change from baseline (%, Δ) in NFκB between the pre- and post-prandial culture conditions increased (p < 0.007) in lean and obese women with PCOS and obese controls, and was significantly different (p < 0.0001) compared with lean controls which decreased (19±3, 25±6, 14±3 vs. -12±1). In response to lipid+LPS, ΔNFκB increased (p < 0.01) in lean women with PCOS and obese controls, and was significantly different (p < 0.0001) compared with lean controls and obese women with PCOS which decreased (30±4, 25±6 vs. -19±7, -26±4). Compared with lipid alone, supershift experiments revealed the disappearance of NFκB p65 and a 75% increase in NFκB p50 in obese women with PCOS after lipid+LPS. Compared with weight-matched controls, women with PCOS exhibited a greater HCG-stimulated area under the curve (AUC) for testosterone (T) (lean: 6371±717 vs. 3463±461, p < 0.01; obese: 7891±1220 vs. 3621±190, p < 0.004) and androstenedione (Δ) (lean: 123±30 vs. 307±27, p < 0.0003; obese: 576±51 vs. 327±37, p < 0.0001). For the combined groups, ΔNFκB after lipid alone was directly correlated with AUC for T (r = 0.42, p < 0.02) and A (r = 0.51, p < 0.002) and inversely correlated with ISOGTT (r = 0.58, p < 0.0003). In women with PCOS, ΔNFκB after lipid+LPS was inversely correlated with basal T (r = -0.51, p < 0.04) and directly correlated with ISOGTT (r = -0.66, p < 0.004).

**CONCLUSIONS:** In PCOS, lipid-induced NFκB suppression is independent of obesity. We also offer hallmark evidence of LPS tolerance when obesity accompanies PCOS indicative of a more profound inflammatory state that may be potentiated by hyperandrogenism to limit insulin resistance.

**References:**
1. Abdelhadi OA, Considine RV, Acton AJ, Gonzalez F. Saturated fat ingestion stimulates suppressor of cytokine signaling-3 and toll-like
OBJECTIVE: Physical activity has been considered to be effective in the treatment of metabolic alterations and infertility of Polycystic Ovarian Syndrome (PCOS). Thus, we evaluate the effects of two aerobic physical training protocols in women with PCOS.

DESIGN: Randomized controlled clinical trial study.

MATERIALS AND METHODS: PCOS women were stratified by body mass index (BMI) in continuous aerobic training (n=28), intermittent aerobic training (n=29) and control group without training (n=30). Testosterone, androstenedione, follicle stimulating hormone, luteinizing hormone, sex hormone binding globulin, estradiol, cholesterol, triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL), glycemia, fasting insulin, homocysteine and C-reactive protein were measured. Body composition was determined by anthropometric assessment and dual-energy x-ray absorptiometry (DXA). All characteristics were evaluated before and after 16-week of aerobic training or observation. Statistical analyses were carried out using SAS 9.0 software.

RESULTS: Waist (WC, p=0.045) and hip circumference (p=0.032), as cholesterol (p=0.01), LDL (p=0.03) and testosterone (p<0.01) reduced after continuous training. The intermittent training decreased WC (p=0.014), waist-hip ratio (p=0.012), testosterone (p=0.019) and free androgen index (p=0.037). In the PCOS women without training (observation) there was an increase in WC (p=0.049), total body fat (p=0.015) and body fat percentage (p=0.034), total arms mass (p=0.01), trunk fat percentage (p=0.033), leg fat percentage (p=0.021) and total gynoid mass (p=0.011). We did not observe differences in others features measured.

CONCLUSIONS: The intermittent training seems to be more efficient in the control of hyperandrogenism and the continuous training in the control of lipid parameters. However, both training protocols reduced anthropometric indexes and hyperandrogenism, relevant features of PCOS, and may represent an important treatment strategy for this women.

References:

Supported by: Fundação de Amparo a Pesquisa do Estado de São Paulo; FAPESP; Process: 2015/14031-0.

O-18 Monday, October 8, 2018 12:00 PM

INCREASED ANDROGEN, ANTI-MULLERIAN HORMONE AND NEONATAL OUTCOMES IN FERTILE WOMEN WITHOUT PCOS. L. Sjarda,4 S. Mumford,4 M. T. Connell,1 K. Kim,5 M. J. Hill,2 N. Perkins,4 R. Silver,1 E. Schisterman; "NICHD, Bethesda, MD; 2NIH, Germantown, MD; 4University of Utah, Salt Lake City, UT.

OBJECTIVE: Polycystic ovary syndrome (PCOS) in pregnancy is frequently linked to poor neonatal health, but underlying pathways are unclear. Further, it is unknown whether markers of PCOS (i.e., higher androgens and/or anti-Müllerian hormone [AMH]) in fertile populations without clinical PCOS are associated with greater risk to neonates. Therefore, our objective was to examine whether higher testosterone and/or AMH were linked to neonatal health in live births of women without diagnosed PCOS.

DESIGN: Prospective cohort study of 583 women with live birth following unassisted conception, participating in a randomized controlled trial of pre-conception-initiated low-dose aspirin, with preconception measures of total testosterone (T) and AMH.

MATERIALS AND METHODS: Women were categorized by preconception serum T and AMH concentrations; the top quartile (i.e., highest 25%) for each was “high” and lower three quartiles were assigned “low,” forming four groups: low T/low AMH (n=359), low T/high AMH (n=89), high T/low AMH (n=75), and high T/high AMH (n=61). Cut-points defining the top quartiles were >26.8 ng/dL for T and >4.75 ng/mL for AMH. Log-binomial regression models estimated risk ratios (RR) and 95% confidence intervals (CI) for associations between T/AMH groups and preterm (<37 weeks’ gestation) and early term (37 to <39 weeks’ gestation) birth, NICU admission, and 5-minute Apgar score <7, relative to low T/low AMH. All models adjusted for age, BMI, and current smoking.

RESULTS: Across the four groups, birthweight (p=0.60), rate of multiple birth (p=0.67), and incidence of gestational diabetes (p=0.51) was similar. Risk of NICU admission was nearly double for babies born to women in the high T/high AMH group relative to low T/low AMH (20.3% vs 9.4%; RR: 1.85, 95%CI: 0.97, 3.53), but without differences in preterm (8.2 vs. 9.8%; RR: 0.69, 95%CI: 0.25, 1.88) or early term birth (44 vs. 39%; RR: 1.01, 95%CI: 0.71, 1.44). Apgar score at 5-minutes varied across the four groups (p=0.02) with the numerically lowest mean Apgar score in the high T/ high AMH group (8.65, 95%CI: 8.34, 8.96; low T/low AMH: 8.9, 95%CI: 8.85, 8.95), although Apgar score <7 occurred in only four babies overall. No differences in preterm or early term birth, NICU admission, or low Apgar score were evident in the low T/low AMH or high T/low AMH groups, compared to low T/low AMH group.

CONCLUSIONS: The combination of relatively higher preconception T and AMH is a marker of adverse neonatal health risk, as indicated by greater NICU admission, even without overt PCOS and its associated comorbidities. Relationships between a PCOS-related hormonal milieu and specific indications for NICU admission warrant further investigation.

Supported by: Intramural Research Program, DIPHR, NICHD, NIH.

O-19 Monday, October 8, 2018 10:45 AM

INCREASED RISK OF MATERNAL MORTALITY IN INFERTILE WOMEN: ANALYSIS OF US CLAIMS DATA. G. Murugappan, S. Li, R. B. Lathi, M. L. Baker, M. L. Eisenberg; 1Department of Reproductive Endocrinology & Infertility, Stanford Hospital and Clinics, Sunnyvale, CA; 2Department of Urology, Stanford Hospital and Clinics, Stanford, CA.

OBJECTIVE: To assess whether risk of severe maternal morbidity is increased in women with a diagnosis of infertility or women who undergo fertility treatment compared to women without an infertility diagnosis who conceived without fertility treatment.

DESIGN: Retrospective analysis.

MATERIALS AND METHODS: We analyzed the Optum® insurance claims database covering data from 2003-2016. Infertile women who conceived without fertility treatment were identified by diagnosis and
testing codes, and those that went on to have fertility treatment were identified by treatment codes. Delivery outcomes from both groups were then compared to a control group of women without an infertility diagnosis who conceived without fertility treatment. Women with a prior cancer diagnosis or with a cancer diagnosis within 6 months of data collection were excluded. Indicators of severe maternal morbidity as established by the Centers for Disease Control and Prevention were identified by ICD-9/ICD-10 diagnosis and procedure codes occurring within 6 months prior to or following delivery. The risk of maternal morbidity was assessed using a GEE model with repeated measures, adjusting for maternal age, smoking, obesity, gestational age at delivery, plurality, and mode of delivery. Analyses were performed using SAS (version 9.4, SAS Institute, Inc., Cary, NC, USA).

RESULTS: Outcomes from 1,822 deliveries from women who had a diagnosis of infertility and 782 deliveries from women who received fertility treatment were compared to 37,944 deliveries from women in the control group. In women diagnosed with infertility compared to controls, the risk of severe anesthesia complications (0.38% v 0.11%, OR 3.83, CI 1.69-8.70), intra-operative heart failure (0.71% v 0.31%, OR 1.88, CI 1.05-3.34), and hysterecomy (1.04% v 0.28%, OR 3.30, CI 2.02-5.40) were significantly increased. In women undergoing fertility treatment compared to controls, the risk of disseminated intravascular coagulation (2.81% v 0.91%, OR 2.66, CI 1.66-4.24), shock (0.90% v 0.15%, OR 5.17, CI 2.21-12.06), blood transfusion (3.71% v 1.64%, OR 1.61, CI 1.07-2.42), and need for cardiology monitoring (13.17% v 8.14%, OR 1.43, CI 1.14-1.79) were significantly increased.

CONCLUSIONS: While the absolute risks are low, an infertility diagnosis or undergoing fertility treatment prior to delivery are associated with increased risk of severe maternal morbidity compared to a group of women without an infertility diagnosis who conceived without fertility treatment. Further investigation is warranted to identify underlying etiologies and co-existing health conditions that may disproportionately affect women with infertility and those undergoing fertility treatment.

O-20 Monday, October 8, 2018 11:00 AM


OBJECTIVE: To investigate the numbers and etiology of women’s deaths in fertile, subfertile and ART-treated women.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: We used the Massachusetts Outcome Study for Assisted Reproductive Technology (MOSART) database that links the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) with vital records and hospital discharges in the Pregnancy to Early Life Longitudinal (PELL) system. MOSART was selected for comparison; those with an indication of infertility treatment or following delivery. The risk of maternal morbidity was assessed using a GEE model with repeated measures, adjusting for maternal age, smoking, obesity, gestational age at delivery, plurality, and mode of delivery. Analyses were performed using SAS (version 9.4, SAS Institute, Inc., Cary, NC, USA).

RESULTS: The study population included 483,556 women: 16,429 ART, 11,696 subfertile, and 455,431 fertile among whom there were 1,072 deaths (average follow up time 64 months), with 116, 128, and 223 deaths per 100,000 women respectively in these groups. Deaths occurred on average 46 months after delivery and means for this timeframe were 34, 41, and 47 months for ART-treated, subfertile and fertile groups. The mean [mean ±SD] ages of women at time of death were 42.6 ±3.9 for ART-treated, 38.1 ±7.0 for subfertile, and 34.2 ±7.1 for fertile women. Violence, accident and poisonings were the most common causes of death in the fertile group. Eliminating deaths from these causes from the study sample resulted in there being 103, 94, and 133 per 100,000 women in ART-treated, subfertile and fertile groups. When violence and accident were excluded, major causes of death in all groups were cancer, circulatory problems, infectious disease, and complications from pregnancy, however, the fertile group also had a notable percentage of deaths from mental health and behavioral disorders while the ART-treated and subfertile groups had none.

CONCLUSIONS: While higher rates of all-cause mortality were observed in the fertile group, death from medical causes does not appear to be more common in ART-treated and subfertile women after delivery than in fertile women. Etiologies of women’s mortality after delivery also appear similar in the three groups.

Supported by: NIH Grant

O-21 Monday, October 8, 2018 11:15 AM


OBJECTIVE: To evaluate the risks of prematurity and neonatal and infant mortality by maternal fertility status and the presence of pre-gestational or gestational hypertension and diabetes.

DESIGN: Longitudinal cohort study.

MATERIALS AND METHODS: Women in 14 States who had in vitro fertilization (IVF)-conceived live births using autologous oocytes and fresh embryos during 2004-13 were linked to their infant’s birth and death certificates; a 10:1 sample of births from non-IVF deliveries were selected for comparison; those with an indication of infertility treatment on the birth certificate were categorized as subfertile, all others were categorized as fertile. Risks were modeled separately by plurality at birth using logistic regression, adjusted for maternal age, parity, mode of delivery, fertility status, hypertension, diabetes, small-for-gestation (SGA) birthweight, infant sex, State and year of birth, and length of gestation, and reported as adjusted odds ratios and 95% confidence intervals.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Factors</th>
<th>&lt;28 Weeks</th>
<th>28-32 Weeks</th>
<th>33-36 Weeks</th>
<th>SGABirthweight</th>
<th>NeonatalDeath</th>
<th>InfantDeath</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertile</td>
<td>Subfertile</td>
<td>2.1(1.8-2.6)</td>
<td>1.5 (1.4-1.7)</td>
<td>1.4 (1.3-1.5)</td>
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<td>IVF</td>
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<td>Gestational</td>
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<tr>
<td>No Diabetes</td>
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<td>2.3 (2.2-2.4)</td>
<td>0.7 (0.6-0.8)</td>
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<td>1.3 (1.1-1.6)</td>
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<td>Gestational</td>
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<td>Non-SGA</td>
<td>SGA</td>
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<td>1.3 (1.2-1.3)</td>
<td>1.0 (0.9-1.0)</td>
<td>3.5 (3.3-3.8)</td>
<td>3.3 (3.1-3.5)</td>
<td></td>
</tr>
</tbody>
</table>
RESULTS: The study population included 2,411,626 births and 12,269 deaths (fertile: 2,258,742 births, 10,384 deaths; subfertile: 12,192 births, 210 deaths; IVF: 140,692 births, 1,675 deaths). Results for singletontons are shown below. Risks of prematurity were increased for subfertile and IVF women, and with hypertension, diabetes, and small-for-gestation birthweight (SGA). Neonatal and infant mortality were most strongly associated with prematurity, as well as SGA and subfertility; IVF was associated with a decreased risk.

CONCLUSIONS: Pre-existing chronic disease was associated with an increased risk of prematurity, particularly hypertension. While prematurity was the single greatest factor associated with mortality, diabetes, SGA, and subfertility were also significant. Women with subfertility had greater risks of very early preterm birth with higher neonatal and infant mortality than women treated with IVF. Compared to fertile women, IVF was associated with a decreased risk of neonatal and infant death.

Supported by: NIH grant R01CA151973 and SART

O-22 Monday, October 8, 2018 11:30 AM

PERINATAL MORTALITY AMONG TWINS STRATIFIED BY MODE OF CONCEPTION IN THE UNITED STATES (2014-2015). S. Arian,a H. Erfani,b C. Valdes,a A. A. Shamshirsaz,a W. Gibbons,a *Reproductive Endocrinology and Infertility, Baylor College of Medicine, Houston, TX; Mater- nal-Fetal Medicine, Baylor College of Medicine, Houston, TX; Maternal-Fetal Medicine, Baylor College of Medicine, Houston, TX.

OBJECTIVE: To perform an epidemiological study of perinatal mortality rate among twins based on their mode of conception: Assisted Reproductive Technology (ART), less invasive fertility treatments including ovulation induction (OI) and intrauterine insemination (IUI), and spontaneous conception (SC).

DESIGN: A retrospective population-based study.

MATERIALS AND METHODS: We performed a population-based retrospective analysis of twin perinatal mortality in the United States among newborn twins without congenital malformations and/or chromosomal abnormalities from 2014-2015. We utilized ‘Period Linked Birth - Infant death’ and ‘Fetal Death’ data files from the National Center for Health Statistics for years 2014 - 2015. Perinatal mortality was defined as stillbirth at ≥22 weeks gestation or neonatal death up to 28 days after birth. Perinatal mortality was calculated for different categories of mode of conception: 1) ART (including in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), 2) fertility enhancing drugs for OI/IUI, and 3) SC. Statistical analysis was performed using R-3.4.1.

RESULTS: Included in this study were 388,045 twin deliveries of which 334,677 (86.2%) were from conceived spontaneously, and 36,883 (9.5%) and 16,485 (4.2%) were results of ART and OI/IUI treatments, respectively. Rate for perinatal mortality was 379/23,34677 (11 per 1000; 95% CI 10-12) in SCs, 464/36883 (13 per 1000; 95% CI 12-14) in ART fertility treatments and 215/16485 (13 per 1000; 95% CI 11-15) in twin deliveries conceived from OI/IUI. (Chi² = 8.05, P=0.01).

CONCLUSIONS: We observed that perinatal mortality rate is higher among twins conceived following fertility treatments, including ART and OI/IUI, compared to twins conceived without these treatments. Although this slightly increased risk is clinically insignificant, counselling patients before undergoing any form of fertility treatment should include discussion of the risks of perinatal death.

### Fertility vs. IVF, IVF Siblings, and Subfertile

<table>
<thead>
<tr>
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<th>Fertility</th>
<th>IVF</th>
<th>IVF Siblings</th>
<th>Subfertile</th>
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<tr>
<td>N, children</td>
<td>811,989</td>
<td>106,721</td>
<td>18,651</td>
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<td>Singletons</td>
<td>789,306</td>
<td>57,571</td>
<td>17,443</td>
<td>3,815</td>
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<td>% with birth defects</td>
<td>3.8%</td>
<td>4.9%</td>
<td>4.3%</td>
<td>4.7%</td>
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<tr>
<td>All defects, AOR, 95% CI</td>
<td>1.00 (Reference)</td>
<td>1.29 (1.23, 1.35)</td>
<td>1.23 (1.13, 1.33)</td>
<td>1.17 (1.00, 1.36)</td>
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<tr>
<td>All defects*, AOR, 95% CI</td>
<td>1.32 (1.24, 1.39)</td>
<td>1.22 (1.13, 1.32)</td>
<td>1.16 (1.00, 1.35)</td>
<td>1.744</td>
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<td>Multiples</td>
<td>22,683</td>
<td>49,156</td>
<td>1,208</td>
<td>1,744</td>
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<td>% with birth defects</td>
<td>6.2%</td>
<td>7.1%</td>
<td>8.6%</td>
<td>7.6%</td>
</tr>
<tr>
<td>All defects, AOR, 95% CI</td>
<td>1.00 (Reference)</td>
<td>1.11 (1.02, 1.21)</td>
<td>1.38 (1.11, 1.72)</td>
<td>1.14 (0.94, 1.37)</td>
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<tr>
<td>All defects*, AOR, 95% CI</td>
<td>1.11 (1.01, 1.21)</td>
<td>1.37 (1.10, 1.71)</td>
<td>1.14 (0.94, 1.38)</td>
<td>1.14 (0.94, 1.38)</td>
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</tbody>
</table>

References:

O-23 Monday, October 8, 2018 11:45 AM

RISK OF BIRTH DEFECTS IN IVF, NON-IVF ART, AND SPONTANEOUS CONCEPTIONS: A US STUDY IN FOUR STATES. B. Luke,a M. B. Brown,b E. Wantman,b R. E. Meyer,c N. E. Forester,c S. Watkins,a M. Yazdib, M. Browne,a S. Fisher,a M. A. Canfield,b M. Ethen,c H. B. Nichols,a S. Ohnninger,b K. Doody,b *Obstetrics, Gynecology, and Reproductive Biology, Michigan State University, East Lansing, MI; †Biostatistics, University of Michigan, Ann Arbor, MI; ‡Redshift Technologies, Inc., NY, NY; †Birth Defects Monitoring Branch, North Carolina Department of Health and Human Services, Raleigh, NC; †Women’s and Children’s Health Section, North Carolina Department of Health and Human Services, Raleigh, NC; ‡Massachusetts Center for Birth Defects Research and Prevention, Massachusetts Department of Public Health, Boston, MA; †Congenital Malformations Registry, New York State Department of Health, Albany, NY; †Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, TX; ‡Epidemiology, University of North Carolina, Chapel Hill, NC; †Jones Institute for Reproductive Medicine, Norfolk, VA; †Center for Assisted Reproduction, Bedford, TX.

OBJECTIVE: To evaluate birth defect risk in children conceived with IVF and non-IVF ART (subfertile), IVF siblings, and fertile controls.

DESIGN: Cohort study, with exposure groups defined as IVF-exposed, siblings of IVF-exposed, subfertile, and fertile.

MATERIALS AND METHODS: IVF cycles in SART CORS resulting in live births in 2004-13 were linked to birth certificates and birth defects registries in four states (NY, TX, MA, and NC). Other births to each IVF-treated woman were also identified (IVF siblings). A 10:1 sample of non-IVF births in the same month as the IVF births were selected as controls; those with infertility treatment indicated on the birth certificate (but not in SART CORS) were categorized as subfertile, all others were categorized as fertile. Risks were modeled separately by plurality using logistic regression (AOR, 95% CI), adjusted for maternal age, race, ethnicity, education, parity, pre-gestational and gestational diabetes and hypertension, State and year of birth; children of fertile women were the reference group.

RESULTS: The study population included 942,920 children (see table). Analyses limiting the IVF group to cycles with autologous oocytes and sperm, and fresh embryos are shown by (*). Birth defect risk was increased for IVF, siblings and subfertile children by 32%, 22%, and 16%, respectively, for singletons, and 11%, 37%, and 14% for multiples (see table). The estimated risks for these 3 groups did not differ significantly (their 95% CIs overlap).

CONCLUSIONS: The risk of birth defects was increased for IVF children and IVF siblings, and non-significantly increased for children of subfertile women; some estimates were limited by small sample size.

Supported by: NIH Grant R01HD843777.
A POPULATION-BASED REGISTER STUDY OF INFANT AND LATE CHILD MORTALITY IN SINGLETONS BORN AFTER ASSISTED REPRODUCTIVE TECHNIQUES (ART) VS NATURAL CONCEPTIONS. K. A. Rodriguez-Wallberg, S. Ekberg, A. L. Johansson, A. N. Iliadou. Department of Reproductive Medicine, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden; Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.

OBJECTIVE: A few studies have previously addressed the risk of infant mortality in children born after treatments using Assisted Reproductive Technologies (ART). Much of the risks identified in ART pregnancies had been attributed to multiple births, which are per se explanatory of adverse obstetric outcomes leading to perinatal mortality. As regards to singleton born after ART the data have been rather inconsistent. The aim of this study was to investigate infant (early neonatal and post-neonatal up to one year of age) and late child mortality in a population based cohort of singleton born after ART compared to naturally conceived singletons born after the same study period.


MATERIALS AND METHODS: The children were identified using the Swedish Medical Birth Register and information about the mothers, pregnancy, and delivery were obtained from the register. Of those, 43 520 children were conceived after ART. Utilizing the unique national Personal Identification Number (PIN), that is used in all official and healthcare registers, linkage of individuals was feasible to additional prospectively collected healthcare register data including the Cause of Death register and information about the type of ART (IVF/ICSI). Cox proportional Hazards model was used which yielded Hazard Ratios (HR) with 95 % confidence intervals (CI) as a measure of association between ART treatment and death.

RESULTS: A significant higher infant mortality risk was found in children conceived by ART compared to naturally conceived singletons (adjusted HR 1.51, 95% CI 1.01-2.25). Also a significantly higher mortality risk was observed in children born after transfer of cryopreserved embryos (adjusted HR 1.86, 95% CI 1.09-3.16). Nevertheless, the number of deaths in infants was overall low. There was no increase in late mortality risk after 1 year of age in children conceived through ART.

CONCLUSIONS: Children conceived through ART presented with an increased risk of infant mortality and a specifically elevated risk was seen in children born after the transfer of cryopreserved embryos. There seems to be no increased late child mortality risk after the infant period. The results are quite reassuring with regards to the long term mortality risk in ART children. Inconsistencies in the literature may be due to definitions of the mortality period. The infant period, up to one year of age, seems to be the most crucial time and risks could be associated to adverse perinatal outcomes.

References:

ENDOMETRIOSIS

O-25 Monday, October 8, 2018 10:45 AM

BONE TURNOVER CHANGES IN WOMEN TREATED WITH ELAGOLIX OR PLACEBO DURING THE ELARIS EM-I AND EM-II TRIALS WHO DID NOT CONTINUE IN THE EXTENSION STUDIES. D. Archer, O. Antunez Flores, N. Leyland, H. Palac, P. Peloso, N. Watts. Eastern Virginia Medical School, Norfolk, VA; AbbVie Inc., North Chicago, IL; McMaster University, Hamilton, ON, Canada; Mercy Health Osteoporosis & Bone Health Services, Cincinnati, OH.

OBJECTIVE: To evaluate the effect of elagolix, an oral, non-peptide gonadotropin-releasing hormone antagonist, on bone turnover markers in women with endometriosis-associated pain who were treated for up to 6 months (M) during two, phase 3 studies and did not enroll in the extension studies.

DESIGN: Data were pooled from two 6M, randomized, placebo-controlled phase 3 trials (Elaris EM-I and II) evaluating two doses of elagolix (150mg once daily [QD] and 200mg twice daily [BID]). Women who prematurely discontinued treatment, declined to participate in, or did not qualify for the continuous use extension studies entered a Post-treatment Follow-up Period (PTFU) for up to 12M.

MATERIALS AND METHODS: Participants were 18-49 year old premenopausal women with surgically diagnosed endometriosis and moderate/severe endometriosis-associated pain. The bone turnover marker serum collagen type 1 cross-linked C-telopeptide (CTX) was collected at baseline, treatment M3 and M6, and off therapy in the PTFU M3 and M6. Bone turnover collection at PTFU M12 was only required for women with the greatest bone loss. This analysis included women that had ≥ one on-treatment and one PTFU value and did not enroll in the extension studies (N=296). Differences between treatment groups in mean change from baseline to each time point was analyzed using one-way ANOVA tests.

RESULTS: Baseline CTx serum levels were similar across treatment groups. Women who received elagolix 200mg QD had increased mean CTx serum levels at treatment M6 compared to baseline that were significantly greater than placebo (mean change from baseline[SD] pg/ml: placebo=-34.04[115.62]; 150mg QD=+5.44[148.41], p=0.177; 200mg BID=+179.16[217.79], p<0.001). Mean changes from baseline in CTx serum levels remained elevated and significantly greater than placebo off treatment through PTFU M3 in elagolix 200mg BID (placebo=-37.29[103.98]; 150mg QD=+9.15[156.72], p=0.180; 200mg BID=+42.64[153.37], p<0.001). Mean CTx serum levels were decreased compared to baseline at PTFU M6 across all treatment groups (placebo=-43.45[106.67]; 150mg QD=+29.60[171.08], p=0.565; 200mg BID=-33.33[145.60], p=0.652). Additional bone turnover markers were assessed (i.e. osteocalcin, procollagen type 1 N-terminal propeptide) and exhibited similar patterns of change as CTx; these data will be provided with the presentation.

CONCLUSIONS: In women with endometriosis-associated pain enrolled in the Elaris EM-I and II studies, treatment with elagolix 150mg QD and 200mg BID resulted in dose-dependent increases in mean CTx serum levels during the 6-month treatment period. CTx levels decreased after elagolix discontinuation.

Supported by: AbbVie
however, the degree of E2 suppression produced by elagolix, especially at
N
a. Some women's values in the Placebo and LA groups were excluded because their blood samples were drawn after re-randomization and dosing at week 12:

CO-OCCURRENCE OF DISEASES OF IMMUNE DYSFUNCTION AND ENDOMETRIOSIS.

OBJECTIVE: Previous studies, largely of adult women, have observed an
association between diseases of immune dysfunction and endometriosis. The
objective of this study was to investigate patterns of immune diseases co-
occuring with endometriosis among a younger population.

RESULTS: Participants with endometriosis had a significantly higher odds
of reporting co-morbid allergies (OR: 1.70; 95%CI: 1.21-2.41) and asthma
(OR: 1.66; 95%CI: 1.12-2.45) compared to participants without endometriosis.
Participants with endometriosis were also more likely to report a past
mononucleosis infection (OR: 1.84; 95%CI: 1.11-3.04) and a diagnosis of fi-
bromyalgia (OR: 5.48; 95%CI: 1.13-26.59). There was a positive trend be-
tween number of co-morbid diseases (range 0-4) and endometriosis (p-
trend=.002). No association was observed between endometriosis and sys-
temic lupus erythematosus, rheumatoid arthritis, inflammatory bowel dis-
ease, psoriasis, or eczema among this young cohort.

CONCLUSIONS: In this cohort of primarily adolescents and young
adults, there was a significant association between the co-occurrence of endo-
metriosis with asthma, allergy, and mononucleosis. Clinicians should
consider these co-morbidities in their screening and management of endome-
triosis in adolescent and young adult populations.

References:

1. Vitonis AF, Vincent K, Rahmioglu N, et al. World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project: II. Clinical and covariate phenotype data collection in endome-

Supported by: Supported by the J. Willard and Alice S. Marriott Founda-
tion and the Harvard Medical School Scholars in Medicine Office.

O-28 Monday, October 8, 2018 11:30 AM

USING OF ANTI-IL-6 RECEPTOR MONOCLONAL AN-
TIMBODIES IN TREATMENT OF ENDOMETRIOSIS: PROOF
OF CONCEPT. A. A. El-Zayadi, a S. A. Mohamed,a M. Araf,a A. M. Badawy,a Obstetrics and Gynecology, Mansoura University, Mansoura, Egypt; aPathology, Man-
soura University, Mansoura, Egypt.

OBJECTIVE: In the light of the fact that many pro-inflammatory cyto-
kines are elevated in the peritoneal fluid and serum of patients of

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e13
endometriosis, the one of our interest is interleukin-6 (IL-6) (1,2). Our hypothesis is aiming to assess the role of usage of anti-IL-6 as alternative line of therapy in the pathogenesis of endometriosis. Fertility and Sterility. 2004;82 Suppl 3:1008-13.


The second group (n=5) was given saline solution at a similar volume and frequency. After four weeks, the animals were euthanized, opened and the lesions photographed. Endometriosis was taken from the eutopic lesions and the eutopic endometrium was taken from the intact left uterine horns. All tissue specimens were processed as paraffin embedded tissues. Histopathological examination was performed using H&E stained tissue sections. The presence of endometriotic vesicles was confirmed by the presence of epithelial lining. This epithelium was evaluated as being intact or attenuated. Immunohistochemical staining was performed using antibodies against IL-6. The immunoreactivity was indicated by the presence of cytoplasmic staining in the epithelium of the endometriotic vesicles. The intensity of the stain was scored from none to +++. Capillary electrophoresis was performed from blood samples taken from the rats before and after treatment and from the liver and kidneys of the animals after sacrifice.

RESULTS: The epithelial linings of ectopic endometrium in the test group were attenuated in 6 out of 14 rats (42.8%) with variability in immunohistochemical staining intensity from + to +++. In comparison with the control group, none of the epithelial linings of ectopic endometrium were attenuated with immunohistochemical staining intensity not exceeding +. Regarding the eutopic endometrium epithelial linings in both the test and the control group, they were intact with immunohistochemical staining intensity +. The drug could not be identified in the liver and kidney samples of the animals using capillary electrophoresis, reflecting its safety.

CONCLUSIONS: We explored a proof of concept for the usage of anti-IL-6 receptor monoclonal antibody as a promising biologic drug could be used safely in treatment of endometriosis, planning a step up in its investigation to be tested in a human phase of experiments.

References:

O-29 Monday, October 8, 2018 11:45 AM

CAN GENETIC MARKERS OF ENDOMETRIOSIS PRE-DICT A PATIENT’S RESPONSIVENESS TO LEUROPOLIDE ACETATE?. K. Ward, V. Argyle, P. Cederholm, R. N. Chetter, Juneau Biosciences, LLC

OBJECTIVE: Inherited genetic differences in drug metabolic pathways can affect an individual patient’s response to drugs (both therapeutic effects and adverse effects). A “score” correlates leuprolide acetate (LA) is used to treat endometriosis symptoms. A significant number of patients have little or no improvement with LA therapy, and metabolism of the drug is likely to be affected by several polymorphisms in cytochrome P450 genes, but to date there are no published pharmacogenetic studies regarding LA in the literature. We have discovered endometriosis associated genetic markers as described in another abstract submitted to this meeting. For this study, we tested whether a patient’s genetic profile correlates with response to LA therapy.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: Caucasian women presenting with pelvic pain who were surgically diagnosed with endometriosis and treated with LA were included in this study. Subjects were divided into two groups based on self-report of therapeutic effectiveness: 158 reported significant symptomatic relief with LA therapy and 177 reported no benefit. Patients with minimal or uncertain benefit were excluded. DNA samples were tested for low-frequency variants associated with endometriosis and a genetic risk variant was evaluated. Genotype results for each marker were weighed using the log of the lower bound of 95% confidence interval of the observed odds ratio for endometriosis (as calculated by a discovery set of 2,360 endometriosis patients compared with 55,860 published gnomAD Non-Finnish European population controls). The comparison of the genetic score for the two study groups was performed using one-sided T test.

RESULTS: Patients who reported significant symptomatic relief with LA therapy had a mean genetic score (8.4) that was higher than those who reported no benefit (6.8) (p=0.05). Both responders and non-responders have higher genetic scores than population controls (0.8).

CONCLUSIONS: Disease associated DNA variants are present in almost every endometriosis patient studied, and these variants are likely to contribute to the clinical heterogeneity of endometriosis. Women who responded to LA therapy were likely to carry a higher burden of gene variants than non-responders. Work is underway to pinpoint the subset of DNA markers with greatest effect and to understand the biology of their association with LA responses.

Supported by: Juneau Biosciences, LLC

THE ASSOCIATION BETWEEN ENDOMETRIOSIS AND PREGNANCY COMPLICATIONS. K. Peterson, D. Yeum, C. Peterson, K. Schliep. OhioHealth, Mason, OH, University of Utah, Salt Lake City, UT; Family and Preventive Medicine, University of Utah, Salt Lake City, UT.

OBJECTIVE: To determine association between endometriosis, live births, and pregnancy complications among women in both an operative and population-based cohort.


MATERIALS AND METHODS: The operative cohort (n=473) included menstruating women ages 18-44 years who were scheduled to undergo a diagnostic and/or therapeutic laparoscopy or laparotomy regardless of clinical indication at one of five participating hospital surgical centers located in Salt Lake City, Utah and San Francisco, California. The population cohort (n=127) was matched to the operative cohort by age and residence within the geographic catchment areas for the participating surgical centers. Women with prior surgically confirmed endometriosis were excluded. Women in the operative cohort were diagnosed by surgical laparoscopy or laparotomy; women in the population cohort were diagnosed by magnetic resonance imaging. Associations between incident endometriosis diagnosis and live births and pregnancy complications were analyzed by adjusted prevalence ratios (aPR) taking into account women’s age, study site, BMI, and gravidity.

RESULTS: Among the 600 enrolled women, 40.1% and 11.0% of women in the operative and population cohort were diagnosed with endometriosis, respectively. Mean number of pregnancies among women with versus without endometriosis did not differ in the operative cohort (2.5 ± 2.0 versus 2.6 ± 1.3; p=0.37) or the population cohort (2.5 ± 1.3 versus 2.3 ± 1.3; p=0.40). In contrast, operative cohort women with versus without endometriosis had a lower prevalence of live births (aPR: 0.88; 95% CI: 0.78, 0.99) and a higher prevalence of spontaneous abortion (aPR: 1.43; 95% CI: 1.03, 1.99) and ectopic pregnancies (aPR: 6.24; 95% CI: 1.75, 22.3). Direction and magnitude of estimates were similar in the population cohort (aPR: 0.88; 95% CI: 0.74, 1.04 for live births and aPR: 1.23; 95% CI: 0.56, 1.69 for spontaneous abortion, [no ectopic pregnancies] albeit with wider confidence intervals due to smaller sample size.

CONCLUSIONS: Among women who were asked about pregnancy history prior to gynecologic surgery, we found a near 1.5-fold increased prevalence of spontaneous abortion and over six-fold increased prevalence of ectopic/tubal pregnancies among women with versus without incident endometriosis diagnosis. Future population-based prospective studies among larger samples that capture endometriosis pathology prior to pregnancy outcomes are warranted.

References:

O-30 Monday, October 8, 2018 12:00 PM

ASRM Abstracts Vol. 110, No. 4, Supplement, September 2018
INFERTILITY AND CANCER

O-31 Monday, October 8, 2018 10:45 AM

NO MAGIC FORMULA: AGE IS THE MOST IMPORTANT FACTOR IN PREDICTING RETURN TO BASELINE LEVELS OF OVARIAN RESERVE AFTER CANCER THERAPY. K. E. Cameron,4 M. D. Sammel,9 J. Ginsberg,2 J. Mersemeur,3 H. Su,2 C. R. Gracia.2 1Reproductive Endocrinology and Infertility, Hospital of the University of Pennsylvania, Philadelphia, PA; 2Biostatistics and Epidemiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 3Division of Oncology, Children’s Hospital of Philadelphia, Philadelphia, PA; 4UNC, Chapel Hill, NC; 5Dr. La Jolla, CA; 6University of Pennsylvania, Philadelphia, PA.

OBJECTIVE: Future fertility is an important concern to many cancer survivors. This study sought to model factors associated with the rate of recovery of measures of ovarian reserve (OR) after cancer therapy.

DESIGN: Prospective cohort study.

MATERIALS AND METHODS: Adolescent and young adult females with a new diagnosis of cancer requiring chemotherapy were followed to assess measures of OR (serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, inhibin B, anti-mullerian hormone (AMH), and ultrasound antral follicle count (AFC)) and mean ovarian volume (MOV) at 3-month intervals. Changes in OR from pre-to post-treatment were quantified using linear regression models; for the longitudinal recovery after therapy using mixed effects models adjusted for baseline OR, use of alkylating agent, and exogenous hormone use; and for the probability of return to baseline using multivariable logistic regression models.

RESULTS: 157 women (mean age 27, range 13-41) with at least 1 pretreatment and 2 post-treatment study visits were included (mean follow-up 18 months). Measures of OR demonstrated statistically significant changes during cancer therapy. Alkylating exposure and baseline OR were associated with both the magnitude of OR impairment acutely and the rate of recovery (Table 1). 20% of the women returned to within 75-100% of their baseline AMH level during the 18-month recovery period. In analyses adjusted for baseline OR, receipt of cancer therapy with alkylating agents, treatment length, exogenous hormone use, and receipt of pelvic radiation, only age was associated with the likelihood of recovery, such that each additional year older at the time of cancer therapy decreased the chance of AMH level recovery by 7%.

CONCLUSIONS: Young women undergoing cancer therapy experience acute changes in measures of OR, the magnitude of which are affected by baseline OR and alkylating agent exposure. These measures recover slowly in the months after treatment is complete, and the likelihood of returning to near baseline levels is dependent on age. When counseling women regarding the impact of cancer therapy on their OR, it is important to emphasize the main effect of their age at the time of treatment.

Supported by: K01 L:1-CA-13839-03; R01HD062797

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O-32 Monday, October 8, 2018 11:00 AM

CANCER, SUBSEQUENT SUBFERTILITY, AND FERTILITY TREATMENT: MASSACHUSETTS DELIVERIES LINKED TO SART CORS, HOSPITAL STAYS, AND THE STATE CANCER REGISTRY. L. V. Farland,4 J. E. Stern,2 C. L. Liu,2 H. Cabral,4 R. Knowlton,6 S. T. Gershman,2 H. Diop,4 S. A. Missmer.2 1Obstetrics & Gynecology, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA; 2Ob/Gyn, Dartmouth-Hitchcock, Lebanon, NH; 3MA Department of Public Health, Boston, MA; 4Biostatistics, Boston University SPH, Boston, MA; 5Massachusetts Cancer Registry, Massachusetts Dept of Public Health, Boston, MA; 6Obstetrics, Gynecology, and Reproductive Biology, Michigan State University, Grand Rapids, MI.

OBJECTIVE: To evaluate the association between history of cancer and subsequent subfertility diagnosis and treatment.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: Massachusetts deliveries among women ≥18 years old between 2004-2013 from state vital records were linked to the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS), hospital stays, and the Massachusetts Cancer Registry (n=670,601). Delivery and medically assisted reproduction (MAR) details were obtained from the birth/fetal death certificates and ART details from SART CORS. Subfertility was derived from a combination of birth certificate and hospital stay data. The relative risks (RR) and 95% confidence intervals (CI) of experiencing subfertility, utilizing ART, and number of oocytes retrieved (ART deliveries only) were modeled using generalized estimating equations with a log link and a Poisson distribution. Models were adjusted a priori for maternal age, race/ethnicity, education, insurance status, and delivery year.

RESULTS: Among deliveries in Massachusetts, 1,978 women experienced cancer prior to delivery, with 12.9% of cancers diagnosed before age 20. The most common cancers were thyroid (21.2%), melanoma (17.8%), breast (10.7%), and cancers of the reproductive organs including cervical, endometrial, ovarian, or vaginal (23.1%). The cancer was treated with surgery (83.6%), radiation (20.9%), and/or chemotherapy (18.6%). Compared to women with deliveries and no history of cancer, women with deliveries and a history of cancer had a 38% higher risk of experiencing any subfertility (RR:1.38 (CI:1.25-1.53)), a 50% higher risk of experiencing subfertility without using ART or MAR (RR:1.50 (CI:1.28-1.76)), and a 36% higher risk of using ART (RR:1.50 (CI:1.28-1.76)). Among ART deliveries, those with a history of cancer had lower (Mean[SD]) oocyte yield (9.4[7.5]) compared to women with no history of cancer (11.1[7.9]) (RR:0.83 (CI:0.73-0.95)).

CONCLUSIONS: Among women who delivered pregnancies, those with a history of cancer were more likely to experience subfertility and use ART, and when using ART to have lower oocyte yield, than women with no history of cancer. These data should be useful in counseling newly diagnosed cancer patients intending future pregnancy.

Supported by: NIH R01HD067270

| TABLE 1. Summary of Changes of Ovarian Reserve During and After Cancer Therapy |
|---|---|---|---|
| Baseline Pre-Treatment Level Median (IQR) | Adjusted percent change from baseline to 1st post-treatment visit (95% CI)* | P value | Adjusted percent change per month over 18 month post-treatment period (95% CI)* | P value |
| AMH (pg/mL) | 2750 (1491-4590) | -57 (-40 to -75) | <0.01 | 8.7 (6.0 to 11) | <0.01 |
| FSH (mIU/mL) | 5.6 (3.4-7.6) | 1265 (397 to 2133) | <0.01 | -6.3 (-3.7 to -8.9) | <0.01 |
| Estradiol (pg/mL) | 65.4 (46.7-108.1) | -34 (-23 to -44) | 0.02 | 1.7 (0 to 3.5) | 0.054 |
| LH (mIU/mL) | 3.9 (2.0-7.3) | 370 (-119 to 959) | 0.12 | 0.6 (-1.5 to 2.9) | 0.56 |
| Inhibin B (pg/mL) | 42.9 (12.9-73.2) | -28 (-58 to -45) | 0.16 | -2.9 (-1.2 to -4.7) | <0.01 |
| MOV (cm²) | 7.9 (4.8-11.2) | -3.5 (-1.1 to -6.0) | <0.01 | 0.2 (-0.9 to 1.3) | 0.74 |
| AFC (count) | 20 (11-30) | -42 (-31 to -53) | <0.01 | 4.5 (3.1 to 5.6) | <0.01 |

*models adjusted for hormone levels at baseline and alkylator score. FSH and E2 also adjusted for reported exogenous hormone use in the past month.
REPRODUCTIVE INTENTIONS IN CHILDLESS ADOLESCENT AND YOUNG ADULT FEMALE CANCER SURVIVORS.
C. Lam, a K. Shliakhtitsava, a S. S. Stark, a B. W. Whitcomb, b H. Su, a UCSD, La Jolla, CA; aBiostatistics and Epidemiology, University of Massachusetts, Amherst, Amherst, MA.

OBJECTIVE: Reproductive decisions are complex for cancer survivors, yet little is known about factors related to survivors' reproductive intentions. As chronic disease and disease burden are related to voluntary childlessness in other populations, we tested the hypothesis that cancer treatments and comorbidities are associated with lower desire to have children in female adolescent and young adult (AYA) cancer survivors who are childless.

DESIGN: Cross-sectional.

MATERIALS AND METHODS: Female AYA survivors recruited to the Reproductive Window study on ovarian function completed a web-based questionnaire on desire for future children and demographic, cancer, and reproductive characteristics. Participants were ages 18–40, diagnosed with cancer as AYA (aged 15–35), completed primary cancer treatments, and had at least one ovary. The cohort was restricted to nulliparous participants (n=537). The primary exposures were cancer treatments and comorbidities. The primary outcome was no desire for future children, assessed by questions from the National Survey for Family Growth. Logistic regression models were used to test associations between participant characteristics and voluntary childlessness, adjusting for confounding.

RESULTS: Mean participant age was 31.5±5.2 years, 72% identified as Caucasian, 23% as Hispanic, and the most common cancers were breast (22%), thyroid (20%), and Hodgkin lymphoma (19%). 9.1% of participants self-identified as a gender and sexual minority (GSM). Overall, 22% did not desire future children. In multivariable analysis, prior chemotherapy, radiation, surgery, comorbidities and cancer type were not significantly associated with reproductive intention. Survivors of older reproductive age and GSM identification were more likely to report not desiring future children. Survivors with a history of infertility were more likely to desire children in the future (Table).

CONCLUSIONS: Nearly one-quarter of childless female AYA cancer survivors do not desire to have children in the future. Similar to the general population, survivors of older age and GSM identity were more likely to report the intention not to have children in the future. Contrary to our hypothesis, cancer treatment exposures and increasing number of co-morbidities were not associated with voluntary childlessness, demonstrating the need for fertility and pregnancy care across this population, regardless of prior treatment.

Supported by: HD 080952-04

TABLE. Logistic regression model of characteristics associated with voluntary childlessness (n=537)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adjusted OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-24</td>
<td>0.16 (0.05-0.50)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>25-35</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>36-40</td>
<td>3.33 (1.98-5.59)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GSM (vs. Heterosexual)</td>
<td>5.70 (2.87-11.33)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Partnered (vs. Not Partnered)</td>
<td>0.63 (0.40-1.03)</td>
<td>0.07</td>
</tr>
<tr>
<td>&gt;1 Medical Comorbidities (vs. None)</td>
<td>1.09 (0.63-1.91)</td>
<td>0.75</td>
</tr>
<tr>
<td>History of Infertility (vs. None)</td>
<td>0.20 (0.06-0.63)</td>
<td>0.01</td>
</tr>
<tr>
<td>Chemotherapy (vs. None)</td>
<td>0.55 (0.24-1.25)</td>
<td>0.15</td>
</tr>
<tr>
<td>Radiation (vs. None)</td>
<td>0.88 (0.49-1.58)</td>
<td>0.67</td>
</tr>
<tr>
<td>Surgery (vs. None)</td>
<td>1.62 (0.74-3.54)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

O-33 Monday, October 8, 2018 11:15 AM

OBJECTIVE: The purpose of this study was to evaluate the effectiveness of a personalized educational intervention to increase adolescent and young adult (AYA) cancer survivors' knowledge of their risk for infertility and to determine their preferences for further education.

DESIGN: Prospective study using baseline and follow-up surveys to compare two educational interventions in AYA survivors being seen in survivor clinic.

MATERIALS AND METHODS: Patients aged 18-21 were recruited during an annual survivor clinic visit. Surveys were administered at baseline and at 6 months after the educational intervention. Surveys assessed knowledge of overall risk (at risk/not at risk), level of risk (none, low, moderate, or high), and preferences for additional education on reproductive health. Using components from the PLISSIT model and teach back methods, patients were educated during a private session about their personal risk for infertility, including interpretation of prior reproductive lab results (Phase 1). The impact of the educational intervention on survivor knowledge was evaluated at the midpoint and the educational intervention was modified to include a personalized handout (Phase 2). Descriptive statistics were performed and comparisons of changes in risk knowledge by phase of educational intervention were made using McNemar's test.

RESULTS: Of the 102 survivors approached, 98 (96%) consented to participate (45 M/53 F). Overall, most survivors wanted to have children one day (78%/M/76%/F) and reported importance to have children from their own sperm/egg (86%/M/70%/F). Among those with follow-up surveys (n=72), there was no significant difference in baseline knowledge of overall risk or level of risk between the 2 phases of the study. Significant improvements in knowledge were only seen in Phase 2. The percentage of survivors correctly reporting their overall risk increased from 65% to 77% in Phase 1 (p=0.29) and from 68% to 92% in Phase 2 (p<0.01). Similarly, those correctly reporting their level of risk increased from 55% to 55% in Phase 1 (p=0.06) and from 39% to 87% in Phase 2 (p<0.01). Regardless of phase, nearly all survivors (94%) found the educational session helpful and 78% (97%M/66%F) preferred their parents not be included in discussions (97%M/66%/F). In regard to additional resources, 53% would like a website and 54% would like additional discussions with a provider.

CONCLUSIONS: AYA survivors of childhood cancer want private opportunities to discuss their risk for future infertility and need written information summarizing their personal risk.

References:

Supported by: CURE Childhood Cancer, Inc.

O-34 Monday, October 8, 2018 11:45 AM

ADDRESSING INFERTILITY RELATED KNOWLEDGE GAPS AND NEEDS OF ADOLESCENT AND YOUNG ADULT (AYA) SURVIVORS OF CHILDHOOD CANCER. L. R. Meacham, a,b,c R. Williamson Lewis, a B. Cherven, a J. Gilliland Marchak, a,b "Afflil Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Atlanta, GA; aPediatric Endocrinology, Emory University, Atlanta, GA; aPediatric Hematology/Oncology/BMT, Emory University, Atlanta, GA.

OBJECTIVE: Over the last four decades more than 6 million children were conceived worldwide by assisted reproductive technology (ART). Moreover, pediatric cancer rates have been rising for the past few decades with an established cause. Several studies have raised concerns about children conceived by ART, and especially IVF, may be at an increased risk for pediatric cancers. The results however have been so far inconclusive, mainly due small sample size and the rarity of pediatric cancers. The objective of the present study was to compare the cancer risk among children conceived with or without ART.

DESIGN: Case-control study.

MATERIALS AND METHODS: We obtained data from a cohort comprising all children born in Israel between 1999 and 2016 and medically insured by Maccabi Health Services (MHS), the second largest HMO in Israel, insuring 25.7 % of the total fertility age population. We linked data on all children born in Israel between 1999 and 2016 after ART, with data from the Israeli Registry of Childhood Cancer to identify all children in whom cancer developed before 16 years of age. The overall risk of pediatric cancer was compared to the risk among children conceived by ART. At the
time of data linkage, the latest complete update of the cancer data was April 23, 2018. RESULTS: The cohort consisted of 64,317 MHS insured children born after ART. Overall, 85 cancers were identified in this cohort, as compared with 988 cancers out of 713,165 MHS insured children born during the same time period who were not conceived by ART (Odds Ratio 0.95; 95% CI, 0.76 to 1.19). For the cohort consisting of IVF treatments only, these treatments were also not associated with an increased risk of any form of cancer (Odds Ratio 0.88; 95% CI, 0.64 to 1.20). The median duration of follow-up was 14 years in the general population and 13.5 years in ART group.

CONCLUSIONS: There was no increase in the overall risk of cancer among Israeli children born after ART during period. These encouraging results are based, to the best of our knowledge, on the largest cohort of children born after ART published so far.

References:
2. Bengt Källén, Cancer Risk in Children and Young Adults Conceived by In Vitro Fertilization, Pediatrics, August 2010, VOLUME 126 / ISSUE 2

O-37 Monday, October 8, 2018 10:45 AM

NEAR FUTILITY OF RESCUE INTRACYTOPLASMIC SPERM INJECTION (ICSI) AND THE ADVANTAGE OF VITRIFICATION OVER FRESH TRANSFER.

OBJECTIVE: To evaluate outcomes of rescue ICSI.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: All autologous in vitro fertilization (IVF) rescue ICSI from 2015-2016 at a large assisted reproduction center was reviewed. Rescue ICSI was performed the day after retrieval on oocytes maturing in vitro to MII overnight, or MII oocytes unfertilized by conventional insemination (CI) on the day of retrieval. Outcomes between IVM oocytes and MII oocytes following failed CI were evaluated by chi-square or Fisher’s exact test.

RESULTS: 1,463 oocytes from 436 autologous IVF cycles underwent rescue ICSI the day after oocyte retrieval. Fresh transfer outcomes from IVM oocytes were very poor (1.2% live births per fresh transfer, 1% live born infants per embryo). Outcomes were more than 10 times better, although still not good, for fresh transfers of embryos derived from rescue ICSI of MII oocytes the day after unsuccessful CI (14% live births per fresh transfer and 11% live born infants per embryo). The blastocyst formation rate of rescue ICSI’d oocytes not used for fresh transfer, and therefore allowed to develop in vitro through day 7 after retrieval, was comparable and poor in both groups, with only 5.2% becoming good quality blastocysts for vitrification. Only 11 patients (29% of those with vitrified blastocysts) returned to use them. The outcomes among this small sample of vitrified embryo transfers were much better than those of fresh transfers (45% live birth per transfer and 38% live born infant per transferred embryo), and comparable between the two groups. The 40 times higher success rates for cryopreserved versus fresh embryo transfers were clearly significant within the IVM group (p<0.0001 for both per transfer and per embryo transferred), while the greater than three-fold differences in birth, while suggestive, did not reach statistical significance among the failed CI group (p=0.09 for live birth per transfer and p=0.07 for live born infants per transferred embryo). The end result was 0.4% and 1.5% live infants per rescue-ICSI’d IVM or failed CI MII oocyte, corresponding to 239 or 68 oocytes needed for one additional birth.

CONCLUSIONS: Rescue ICSI is nearly futile with IVM oocytes but has some value after failed CI, although blastocyst conversion rates are low at 5% and live birth per freshly transferred embryo is only 11%. Good birth rates can be achieved by vitrification of the select few developing in vitro to high quality blastocysts.

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O-36 Monday, October 8, 2018 12:00 PM

INCREASED RISK OF CANCER IN INFERTILE WOMEN: ANALYSIS OF US CLAIMS DATA.

OBJECTIVE: To investigate if the diagnosis of infertility is associated with increased risk of cancer.

DESIGN: Retrospective analysis.

MATERIALS AND METHODS: We analyzed the Optum® insurance claims database covering data from 2003-2016. Infertile women were identified through diagnosis and testing codes and compared to a control group of women seeking routine gynecologic care including contraceptive management. Outcomes studied include development of any malignancy as well as individual cancers as identified by ICD-9/ICD-10 codes. Women with a prior cancer diagnosis or with a cancer diagnosis within one year of data collection were excluded. The risk of cancer was assessed using a Cox proportional hazards model while adjusting for age, index year, nulliparity, race, smoking, obesity, number of visits per year and education. Analyses were performed using SAS (version 9.4, SAS Institute, Inc., Cary, NC, USA).

RESULTS: A total of 59,513 women with a diagnosis of infertility or who underwent infertility testing were identified with an average age of 34.9. 2,424,374 women comprised the control group with an average age of 33.4. The majority of patients were followed for at least 4 years from diagnosis. The overall risk of malignancy was increased in women with an infertility diagnosis (2.3%) compared to controls (1.7%; HR 1.09, CI 1.03-1.15) (Table). In the infertile group, the risks of uterine, ovarian and lung cancer and leukemia were increased compared to controls (0.13% vs 0.06%, HR 1.65, CI 1.31-2.09; 0.2% vs 0.08%, HR 1.83, CI 1.52-2.21; 0.09% vs 0.05%, HR 1.39, CI 1.05-1.83; 0.11% vs 0.06%, HR 1.32, CI 1.03-1.70, respectively).

CONCLUSIONS: While the absolute risk of cancer in reproductive age women is low, an infertility diagnosis is associated with increased overall risk of malignancy compared to a group of non-infertile, healthy women. Further investigation is warranted, including controlling for potential confounders including oral contraceptive use, BRCA diagnosis, age at first birth, and oligomenorrhea, all of which may affect both fertility and cancer risk.

---

<table>
<thead>
<tr>
<th>Infertility Diagnosis</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>n (%)</td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>All malignant</td>
<td>1354 (2.28)</td>
</tr>
<tr>
<td>Breast</td>
<td>350 (0.59)</td>
</tr>
<tr>
<td>Uterine</td>
<td>75 (0.13)</td>
</tr>
<tr>
<td>Cervix</td>
<td>66 (0.11)</td>
</tr>
<tr>
<td>Ovary</td>
<td>117 (0.2)</td>
</tr>
<tr>
<td>Lung</td>
<td>54 (0.09)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>115 (0.19)</td>
</tr>
<tr>
<td>Non-Hodgkins Lymphoma</td>
<td>78 (0.13)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>65 (0.11)</td>
</tr>
</tbody>
</table>
RESULTS: Sperm suspensions cryopreserved in solid columns within a 5ml syringe had increased (p<0.05) post-thaw motility loss (>95%) compared to halved columns (44-47%), which were not different than control vials. The poor survival of solid columns did not correlate to their final fluid volumes (x=5.3% motile), although the 1 ml group did tend to show sub-optimal improvement (19.3%). Whereas, solid columns in 1 ml syringes exhibited normal post-thaw motility.

CONCLUSIONS: Syringe containers can be used to effectively store frozen sperm. From a clinical perspective, 1 ml syringe freezing could have practical value for post-thaw direct IUI use. In retrospect, considering the adverse effect of air expansion under zero gravity conditions 5ml syringes would be a poor choice for large volume storage. Conversely, 3 ml syringes are the logical best option for >1ml volumes, since their diameter (i.e., surface area) is similar to cryovials.

REFERENCES:

O-39 Monday, October 8, 2018 11:15 AM

ANALYSIS OF A SIMULATED LIQUID NITROGEN STORAGE TANK FAILURE. D. A. Kelk, a Y. Liu, a S. Nichols-Burns, a J. Lo, a M. Reed, a K. O. Pomeroy, a Yale Fertility Center, Yale University, New Haven, CT; bFertility Center of New Mexico, Albuquerque, NM; cThe World Egg Bank, Phoenix, AZ.

OBJECTIVE: Technology to cryopreserve and store human gametes and embryos has been in use for over 40 years. Monitoring systems for liquid nitrogen (LN2) storage tanks are essential and widely used, but there is little knowledge of the time-frame involved when a tank fails. This study evaluates the time it takes for a standard 47L LN2 storage tank to warm following vacuum jacket failure.

DESIGN: Prospective experimental trial.

MATERIALS AND METHODS: A fully functional MVE XC 47/11 LN2 storage tank (mfg: Jan/1990) was weighed empty (33.6lbs). To simulate normal storage conditions, the six 4" storage canisters were filled with canes of crop. The final suspension was directly loaded into each syringe to a predetermined volume in duplicate (5 replicates/expt.), half of the syringes then had their plungers extended to twice their volume. From a clinical perspective, 1 ml syringe freezing could have practical value for post-thaw direct IUI use. In retrospect, considering the adverse effect of air expansion under zero gravity conditions 5ml syringes would be a poor choice for large volume storage. Conversely, 3 ml syringes are the logical best option for >1ml volumes, since their diameter (i.e., surface area) is similar to cryovials.

REFERENCES:

TABLE 1. Tank Observation Data

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Upper Temp (°C)</th>
<th>Lower Temp (°C)</th>
<th>Tank Weight (lbs)</th>
<th>LN2 Volume (L)</th>
<th>Event / Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-196.8</td>
<td>-197.2</td>
<td>122.8</td>
<td>43.8</td>
<td>Full intact tank prior to breach</td>
</tr>
<tr>
<td>3</td>
<td>-197.7 to -191.7</td>
<td>-197.0</td>
<td>107.6</td>
<td>35.2</td>
<td>Upper probe at LN2 level; Frost on tank lid</td>
</tr>
<tr>
<td>6</td>
<td>-191.9</td>
<td>-197.0</td>
<td>87.2</td>
<td>23.9</td>
<td>Upper probe above LN2</td>
</tr>
<tr>
<td>9</td>
<td>-184.7</td>
<td>-197.0</td>
<td>75.2</td>
<td>17.1</td>
<td>Lower probe submerged in LN2</td>
</tr>
<tr>
<td>12</td>
<td>-182.1</td>
<td>-196.9</td>
<td>64.4</td>
<td>11.0</td>
<td>Lower probe submerged in LN2</td>
</tr>
<tr>
<td>15</td>
<td>-178.6</td>
<td>-194.6</td>
<td>54.2</td>
<td>5.3</td>
<td>Lower probe at LN2 level</td>
</tr>
<tr>
<td>18</td>
<td>-167.3</td>
<td>-182.0</td>
<td>45.6</td>
<td>0.5</td>
<td>Last of LN2 evaporating</td>
</tr>
<tr>
<td>21</td>
<td>-72.5</td>
<td>-79.8</td>
<td>44.8</td>
<td>0.0</td>
<td>Tank above critical temperature</td>
</tr>
<tr>
<td>24</td>
<td>-26.5</td>
<td>-30.1</td>
<td>44.8</td>
<td>0.0</td>
<td>Tank continues to warm</td>
</tr>
<tr>
<td>27</td>
<td>-4.8</td>
<td>-5.8</td>
<td>44.8</td>
<td>0.0</td>
<td>Tank just below 0°C</td>
</tr>
<tr>
<td>30</td>
<td>4.9</td>
<td>4.0</td>
<td>44.8</td>
<td>0.0</td>
<td>Tank above 0°C</td>
</tr>
</tbody>
</table>


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& plastic cryo sleeves (11.2lbs) for total tank weight of 44.8lbs. A temperature probe was set low (8cm from the bottom) where vitrified embryos would be located. A second temperature probe was set high (33cm from the bottom) where a level sensor would typically be located. The tank was filled with LN$_2$ to the neck and reweighed at 122.8lbs. To simulate tank failure, a 1/16" hole was drilled through the vacuum port to breach the tank’s insulating vacuum jacket. The temperature of both probes was continuously monitored and tank weight measured every 30 minutes until the temperature reached 0°C. The tank was then refilled with LN$_2$ and monitored for a second replicate trial.

RESULTS: Upon vacuum jacket breach, hissing was immediately heard as the pressure inside the vacuum equilibrated. Within 5min, LN$_2$ vapor bellowed from the tank lid and by 30 minutes, frost was apparent. Full pressure equilibration of the vacuum took longer than expected (~5h). By 6h, pressure inside the jacket reversed as evidenced by air blowing from the hole as the tank continued to warm. It took 18h for 43.8L of LN$_2$ to evaporate, with threshold of -185°C, notification would have activated 9h post-breach when the tank was completely frosted over, leaving 10h remaining before sample exposure. Temperature monitoring requires precise threshold limits. Storage tank failure is rare, but consequences are devastating. Probe placement must be optimized for each tank and visual observation is useful for early detection. Study of additional tank failures would provide further valuable data.

O-40 Monday, October 8, 2018 11:30 AM

A NEW OPTICAL SYSTEM ALLOWS GAUGING OF HUMAN OOCYTE MATURATION STATUS WITHOUT CUMULUS CELL REMOVAL. D. F. Albertini,123 Y. Ohara,7 A. De Grand,1 V. A. Kushnir,a, D. H. Barad,1 N. Gleicher,123,6,10 Center for Human Reproduction, New York, NY; 2Stem Cell Biology and Molecular Embryology Laboratory, Rockefeller University, New York, NY; 3Olympus America Inc., Waltham, MA; 4Obstetrics & Gynecology, Wake Forest University, Winston-Salem, NC; 5Foundation for Reproductive Medicine, New York, NY; 6Medical University Vienna, Vienna, Austria.

OBJECTIVE: To apply a non-invasive optical approach for the determination of human oocyte maturation status in freshly retrieved intact cumulus-oocyte-complexes (COCs).

DESIGN: Prospective observational study at an academically affiliated private fertility center.

MATERIALS AND METHODS: Freshly isolated COCs (n=12) from 24-28 year old oocyte donors were placed in 35 mm culture dishes containing a glass bottom (MatTek Corp., No.1.5) in Hepes buffered HTF (pH 7.3) for 2-4 min at room temperature. Using Olympus IX73 semi-motorized inverted microscope and a DP74 detector (Waltham, MA), images were taken at 3 focal planes using a combination of relief contrast (Hoffman) and polarization optics for single oocytes prior to and following hyaluronidase-induced removal of cumulus cells. Using a juxtaposition algorithm, CellSens software was used to combine multimodal images for the evaluation of nuclear and cytoplasmic properties of oocytes in addition to oriented structures within the zona pellucida (ZP).

RESULTS: We detected 3 novel parameters that distinguished mature M2 oocytes from either GV or M1 stages. Birifringent granules were dispersed through the ooplasm in M2 oocytes but were centrally aggregated in immature oocytes (8/9 in M2s, 5/3 in M1s). In all M2s there was a pronounced contraction opposite the first polar body where a highly birefringent cortex was observed that was absent in immature oocytes. Finally, filopodia were detected in the perivitelline space and ZP at 180 degrees opposite the site of first polar body extrusion.

CONCLUSIONS: While conventional brightfield optics used in the ART laboratory permit accurate meiotic status assessment in human oocytes, to date, achieving this goal without disturbing the intact COC has been unattainable. Here we show that distinct COC features extracted with a combination of optical modalities may provide reliable indicators of meiotic status and oocyte quality, thereby enabling clinical decision making without the need of removing somatic cell support.

Supported by: The Center for Human Reproduction and The Foundation for Reproductive Medicine; Olympus America, Inc., Waltham, MA.

O-41 Monday, October 8, 2018 11:45 AM

A COMPARISON OF REPRODUCTIVE OUTCOME USING DIFFERENT SPERM SELECTION TECHNIQUES: DENSITY GRADIENT, TESTICULAR SPERM, PICSI, AND MACS FOR ICSI PATIENTS WITH ABNORMAL DNA FragmentATION INDEX. M. M. Hozaien,a K. M. Elqusi,b E. M. Hassanen,c A. A. Hussin,d H. A. Alkhader,b S. M. El Tanbouly,c S. G. El-qassaby,a H. Zaki,a TVF Laboratory, Ganin Fertility Center, Cairo, Egypt; 2Ganin Fertility Center, Cairo, Egypt.

OBJECTIVE: To compare the reproductive outcome of different sperm selection techniques; Density gradient, Testicular sperm, PICSI and MACS for patients with abnormal DNA fragmentation who are undergoing ICSI.

DESIGN: Prospective randomized cohort study included 221 couples having abnormal DNA fragmentation levels who underwent ICSI in Ganin Fertility Center from June 2016 to July 2017. Patients were categorized into four groups; ICSI using ejaculated sperm processed by density gradient (DG), physiological PICSI using ejaculated sperm selected by (PICSI) dishes, ICSI using ejaculated sperm selected by magnetic activated cell sorting columns (MACS), and ICSI using testicular sperm. Women were eligible to participate in the study if they were ≤57 years old and had ≥5 (MII) oocytes.

MATERIALS AND METHODS: This study included 221 couples with abnormal DNA fragmentation Randomized into four groups. Randomization done with Microsoft excel. Sperm DNA fragmentation index (DFI) was done by TUNEL assay using Apodirect kit (BD Pharmigen, San Diego, CA) on BD accuri C6 flow cytometer. DFI cutoff value was 20%. Density gradient was done using Isolate 90% (Irvine, USA), PICSI was done using PICSI dishes (Origio,USA) after DG, MACS was done by Annexin V microbead labeling followed by column separation (Miltenyi Biotech, Germany) after DG. Embryological data (Cleavage, Blastulation, and high-quality blastocyst rates), and clinical data (Pregnancy, Miscarriage, Implantation, and ongoing pregnancy rates) were recorded and results were compared using IMB SPSS Software Version 22 for Microsoft windows. A high quality blastocyst is defined as 3BB Grade or higher according to David Gardner’s assessment criteria. Pregnancy is considered ongoing when exceeding 20 weeks of gestation.

Main results and significance values

<table>
<thead>
<tr>
<th></th>
<th>DG Vs. Testicular sperm</th>
<th>DG Vs. MACS</th>
<th>DG Vs. PICSI</th>
<th>Testicular sperm Vs. MACS</th>
<th>Testicular sperm Vs. PICSI</th>
<th>PISCI Vs. MACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sperm DFI</td>
<td>23.8%</td>
<td>26.7%</td>
<td>27.89%</td>
<td>23.76%</td>
<td>P = 0.7</td>
<td>P = 0.62</td>
</tr>
<tr>
<td>Cleavage rate</td>
<td>77.16%</td>
<td>62.98%</td>
<td>77.15%</td>
<td>72.97%</td>
<td>P = 0.1</td>
<td>P = 0.99</td>
</tr>
<tr>
<td>Blastulation rate</td>
<td>65.17%</td>
<td>38.02%</td>
<td>63.98%</td>
<td>62.82%</td>
<td>P = 0.004</td>
<td>P = 0.89</td>
</tr>
<tr>
<td>High quality Blastocyst rate</td>
<td>58.86%</td>
<td>44.05%</td>
<td>65.42%</td>
<td>57.79%</td>
<td>P = 0.12</td>
<td>P = 0.47</td>
</tr>
<tr>
<td>Pregnancy rate</td>
<td>51.02%</td>
<td>50%</td>
<td>70.9%</td>
<td>70.9%</td>
<td>P = 0.9</td>
<td>P = 0.03</td>
</tr>
<tr>
<td>Miscarriage rate</td>
<td>16%</td>
<td>7.4%</td>
<td>7.69%</td>
<td>10.2%</td>
<td>P = 0.16</td>
<td>P = 0.1</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>26.7%</td>
<td>41.4%</td>
<td>45.09%</td>
<td>66.9%</td>
<td>P = 0.1</td>
<td>P = 0.05</td>
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<tr>
<td>Ongoing pregnancy rate</td>
<td>42.8%</td>
<td>48%</td>
<td>65.4%</td>
<td>63.6%</td>
<td>P = 0.5</td>
<td>P = 0.01</td>
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</table>

FERTILITY & STERILITY® e19
RESULTS: A total 221 cases with abnormal DFI underwent ICSI Randomized into 58 cases injected by ejaculated sperm (D.G), 53 cases injected by testicular sperm, 55 cases injected by ejaculated PICSI and 55 cases injected by ejaculated MACS. There were no significant differences in male age, female age or sperm DFI between the four groups. The difference is considered significant if P value is ≤ 0.05. The data collected and the P values calculated were as in the following table.

CONCLUSIONS: The significant differences in embryological and clinical parameters are favoring the usage of PICSI or MACS along with DG over the usage of testicular sperm or sperm processed by DG alone. These findings should be backed with larger sample size to achieve statistically powered results.

References:

O-42 Monday, October 8, 2018 12:00 PM
THE EFFECT OF ANTI-OXIDANT SUPPLEMENTATION ON SPERM MOTILITY AND SURVIVAL. M. Meintjes, S. Li, M. Dunning, T. Ferguson. Frisco Institute for Reproductive Medicine, Frisco, TX.

OBJECTIVE: Sperm membranes subjected to stress, such as gradient processing or a suboptimum environment, are prone to peroxidation. Lipids in these membranes are the main substrates for peroxidation, producing reactive oxygen species (ROS). ROS induce sperm oxidative stress, leading to sperm dysfunction and reduced motility. Therefore, the objective of this study was to test the protective effect of antioxidants on sperm after gradient separation and also under stressed and non-stressed in vitro culture conditions.

DESIGN: Sperm samples were split and processed with or without antioxidants. In Experiment 1, each sample was split into 4 treatment groups, using a 2x2 factorial design - with or without an oil overlay and with or without antioxidants. In Experiment 2, each sample was similarly tested with good- or poor-quality oil and with or without antioxidants. Results were analyzed with a t-test or an ANOVA as applicable.

MATERIALS AND METHODS: Split sperm samples were processed using a 45:90 Isolate gradient diluted with G-IVF media with or without antioxidants. The sperm pellet was then washed with G-IVF media with or without antioxidants. Following, a 5-day sperm survival assay was initiated with all oil-overlay and anti-oxidant treatments conducted in duplicate, capped, 5-ml tubes at room temperature and ∼0.5x10^6 motile sperm per tube.

Motility evaluations were conducted on days 1, 2, 4 and 5.

RESULTS: In Experiment 1, sperm cultured under an oil overlay had a higher motility after 5 days than sperm cultured without the overlay (66.3% vs. 39.2%; P < 0.001). Similarly, sperm processed and cultured with antioxidants had a higher motility than sperm cultured without antioxidants (55.7% vs. 49.8%; P < 0.005). In Experiment 2, sperm cultured under good quality oil had a higher motility than sperm cultured under poor quality oil (68.5% vs. 50.4%; P < 0.01). Again, sperm processed and cultured with antioxidants had a higher motility than sperm without antioxidants (64.5% vs. 54.4%; P < 0.05).

CONCLUSIONS: Surprisingly, even just the processing of sperm with anti-oxidant-supplemented media, improved post-processing motility. As expected, the protective effect on sperm motility by anti-oxidants in the sperm-handling medium was most effective when the sperm were cultured under stressed conditions (no oil, poor quality oil) and had no effect when sperm were cultured under non-stressed conditions (oil overlay, good quality oil). The results from this study suggest that one should consider anti-oxidant supplementation of sperm-handling media for all assisted reproductive procedures to include sperm preparation for IVF or intra-uterine insemination.

Supported by: Anti-oxidant media provided by Vitrolife AB

Effect of anti-oxidant-supplemented sperm handling media on sperm motility and survival after 5 days

<table>
<thead>
<tr>
<th>Experiment 1 (N=22)</th>
<th>Experiment 2 (n=12)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Good Quality Oil (Ovoil)</td>
</tr>
<tr>
<td></td>
<td>Motility (%)</td>
</tr>
<tr>
<td>Anti-Oxidants</td>
<td>67.9</td>
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<td>No Anti-Oxidants</td>
<td>64.7</td>
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O-43 Monday, October 8, 2018 10:45 AM
NATURAL CYCLE INTRACERVICAL INSEMINATION (IUI) VERSUS OVULATION INDUCTION (OI) IUI FOR NON-INFERTILE WOMEN. O. J. Carpinella, a, b, c, K. S. Richter, a, b, M. Yamasaki, c, M. J. Hill, d, e, A. H. DeCherney, f, K. S. Moon, f, K. Devine, f, A. Lejeune and Jean Franc GueÀrin. Sperm DNA fragmentation decreases the pregnancy rate in an assisted reproductive technique. Human Reproduction Vol. 18, No. 5, pp. 1023±1028, 2003.

OBJECTIVE: To compare outcomes of natural cycle (NC) IUI versus OI/ IUI among non-infertile women.

DESIGN: Retrospective chart review.

MATERIALS AND METHODS: More than 77,000 IUI cycles performed at a single infertility center from 2004-2017 were reviewed. Single women and lesbian couples were included, as well as couples with male factor and no female factors if they used donor sperm or if the male partner produced a good sample for insemination. Women over 42 years or with subfertility diagnoses (including but not limited to endometriosis, PCOS, ovulatory dysfunction, tubal factor, uterine factor, and unexplained infertility) were excluded, as were inseminations with fewer than 8 million total motile sperm. Ovulation induction was by oral administration of clomiphene citrate or letrozole (no gonadotropins). Clinical pregnancy was defined by ultrasound confirmation of an intrauterine gestational sac, with multiple pregnancies having multiple gestational sacs.

RESULTS: 8,315 IUI cycles were available for analysis (4,358 natural cycle and 3,957 OI). There were 1,312 clinical pregnancies (16%), including 80 twins and 5 triplets. While the pregnancy rate was significantly higher for OI versus natural cycle IUI in the 38-40 age group (14% vs 10%), pregnancy did not differ between OI and natural cycle IUI in the three other age groups, suggesting that the significance in the 38-40 year group may have occurred by chance. There were 13 twin pregnancies within the natural cycle IUI group (2% of all pregnancies) and 72 multiple pregnancies (11%), 67 of which were twins (10.1% of pregnancies) and 5 of which were triplets (0.8% of all pregnancies), in the OI/IUI group (p < 0.0001, Fisher’s exact).

CONCLUSIONS: There is no improvement in clinical pregnancy rates with OI versus natural cycle IUI among young, non-infertile women. However, clinical pregnancy rates were higher for older women (age 38-40) with OI/IUI versus natural cycle IUI. Multiple pregnancy rates are much higher with OI compared to natural cycle IUI. Our results indicate that natural cycle IUI may be just as efficacious as OI/IUI in the younger, non-infertile patient but with a reduced risk of multiples.

Supported by: Supported in part by the Intramanal Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health.
**O-44** Monday, October 8, 2018 11:00 AM

**THE EFFICACY OF TESTOSTERONE OR ESTRADIOL THERAPY WITHOUT A GNRH AGONIST OR PROGESTIN TO SUPPRESS ENDOGENOUS GONADAL ACTIVITY IN TRANSGENDER PATIENTS.** I. I. Stewart, L. V. Spratt, W. Craig, J. S. Olshan, D. I. Spratt. The Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Maine Medical Center, Portland, ME; Maine Medical Center Research Institute, Scarborough, ME; The Department of Pediatrics, Division of Pediatric Endocrinology, Maine Medical Center, Portland, ME.

**OBJECTIVE:** To determine the efficacy of testosterone (T) or estradiol (E2) therapy alone, without a GnRH agonist or progestin, to suppress endogenous gonadal activity in female-to-male (FTM) or male-to-female (MTF) transgender patients.

**DESIGN:** A retrospective cohort study of transgender patients undergoing routine therapy in the Reproductive Endocrinology Clinic at Maine Medical Center.

**MATERIALS AND METHODS:** Data were collected from all transgender patients seen in the outpatient clinic between 03/2013 and 01/2018 who met inclusion criteria: 1) age 18-40 years for FTM and 18-50 years for MTF; 2) normal reproductive function prior to therapy; 3) total T within the normal adult male range (348-1197 ng/dL) in FTM patients while on T therapy; 4) serum E2 greater than 100 pg/mL in MTF patients while on E2 therapy unless T was adequately suppressed at lower serum E2 concentrations; 5) no concurrent therapy with a progestin or GnRH agonist; and 6) no history of oophorectomy or orchidectomy. Consistent with Endocrine Society guidelines, effective suppression of ovarian function in FTM patients was assessed by cessation of menses and a serum E2 of (<50 pg/mL). In MTF patients, testicular suppression was assessed by total serum T concentrations below the upper limit of the premenopausal adult female normal range (<35 pg/mL).1

**RESULTS:** FTM patients (n=50) were aged 26.2±5.9 years and received T through subcutaneous (SC, n=58) or intramuscular (IM, n=2) injections. T doses ranged from 40-100 mg per week. All FTM patients were amenorrheic on T therapy alone. The mean serum E2 concentration was 39.8±21.4 pg/mL. Among these 50 patients, 36 (72%) had serum E2 >50 pg/mL. The median serum E2 value for the 14 patients with E2 >50 pg/mL was 55 pg/mL (range, 55-130). Thus, 36 out of 50 (72%) FTM patients had effective biochemical suppression of ovarian function without a GnRH agonist or progestin therapy and all FTM patients had clinical suppression of ovarian function (amenorrhea). MTF patients (n=24) were aged 29.7±9.0 years and received oral (n=25), SC (n=1), or IM (n=1) E2 as well as spironolactone. Oral E2 doses ranged from 3-12 mg per day. Serum total T values for the 24 MTF patients were all within the target range (median 8.2, range 2.7-36 ng/dL). Thus, all MTF patients had effective biochemical suppression of testicular function without GnRH agonist or progestin therapy.

**CONCLUSIONS:** Our results indicate that most transgender patients do not need GnRH agonist or progestin treatment in addition to T or E2 therapy to suppress endogenous gonadal activity. Additional unnecessary endocrine therapies to suppress ovarian or testicular function incur a significant expense and potential adverse effects without providing a clear change in clinical outcome.

**References:**

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**O-46** Monday, October 8, 2018 11:30 AM

**FEMALE TO MALE TRANSGENDER PATIENTS HAVE GOOD EGG YIELDS WITH CONTROLLED OVARIAN HYPERSTIMULATION.** A. Leung, D. Sakak, S. Pang, K. Thornton, N. Resetkova, Boston IVF, Waltham, MA; Ob/Gyn, Beth Israel Deaconess Medical Center, Boston, MA; Ob/Gyn, Beth Israel Deaconess Medical Center, Boston, MA.

**OBJECTIVE:** The transgender population is increasingly seeking access to assisted reproductive technologies (ART). However, there are no studies of substantial sample size that examines ovarian hyperstimulation outcomes in this underserved patient population. Given the increasing demand for ART services by transgender patients and lack of information for providers treating these patients, we seek to inform this area of medicine. This information will serve to counsel transgender patients and their providers on ART outcomes in this population.

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DESIGN: This study is a retrospective analysis that investigated a female to male transgender cohort who underwent ART services and compared their outcomes with matched controls.

MATERIALS AND METHODS: We identified 25 controlled ovarian hyperstimulation cycles performed by female-to-male (FTM) transgender patients who sought care at a large academic-affiliated IVF (in vitro fertilization) clinic from 2013-2017. Each transgender patient was matched with three control patients with tubal factor infertility, using the following factors: age, body mass index (BMI), and anti-mullerian hormone (AMH) levels. Patients with polycystic ovary syndrome (PCOS) were excluded. Oocyte retrieval outcomes were compared, and statistical analysis was performed using Student’s t-test.

RESULTS: 25 cycles completed by 22 FTM transgender patients were matched with 75 cycles completed by controls. Only ovarian stimulation outcomes were examined, as the majority of the transgender group underwent ART for the purpose of oocyte cryopreservation. Therefore, no embryo data or pregnancy outcomes were analyzed. Mean total gonadotropin dose used for stimulation and peak estradiol levels were the same between the two groups (p = 0.11; p = 0.098). The mean number of oocytes retrieved in the transgender group was 19.7 (SD = 8.7) compared to 13.2 (SD = 7.7) in the control group (p = 0.002). Similarly, the transgender group had higher numbers of mean mature oocytes (14.6, SD = 7.9) compared to the control group (10.6, SD = 5.4; p = 0.026). Among the minority of transgender patients who proceeded to oocyte fertilization (n = 11), the mean number of fertilized oocytes was not significantly different from those in the control group (p = 0.297).

CONCLUSIONS: This is the first study of this size investigating ART outcomes in transgender patients. Our results show that transgender men have excellent controlled ovarian hyperstimulation outcomes, in many cases exceeding those of patients with tubal factor infertility.

References:

O-47 Monday, October 8, 2018 11:45 AM

TOTAL MOTILE SPERM IN TRANSGENDER WOMEN SEEKING HORMONE THERAPY: A CASE-CONTROL STUDY. M. McCracken,1 A. K. Nangia, K. Roby, H. McLaren,1 M. Gray,1 C. A. Marsh,1 University of Kansas, Overland Park, KS,1 University of Kansas Health System, Saint Barthélemy,1 OB&GYN, University of Kansas, Overland Park, KS.

OBJECTIVE: This pilot study was undertaken to compare semen quality, hormonal status, and social factors in transgender women seeking fertility preservation with those of cis-men. Long range goals are to establish standard practice measures to ensure optimum semen quality for cryopreservation and fertility preservation in transgender women.

DESIGN: This is an IRB-approved fully consented case-control study carried out at an academic medical center. Sperm parameters in transgender women (cases; n = 11) at the time of fertility preservation were measured and compared to those of cis-men recently fathering a child (controls; n = 16). Exclusion criteria included use of hormones in the prior three months.

All participants completed a questionnaire which included the Depression Anxiety Stress Scales 21 Survey (DASS-21). Follicle stimulating hormone, estradiol and testosterone and risk factors that may alter semen parameters is not known, but use of tight undergarments may play a role in reducing sperm production and enhanced education related to behaviors prior to cryopreservation may improve future fertility potential. On going studies seek to further substantiate the present pilot findings and to investigate the underlying mechanisms leading to oligospermia in order to design low, cryopreservation of sperm prior to the initiation of hormone therapy is a viable option for fertility preservation. The etiology of the differences in semen parameters is not known, but use of tight undergarments may play a role in reducing sperm production and enhanced education related to behaviors prior to cryopreservation may improve future fertility potential. On going studies seek to further substantiate the present pilot findings and to investigate the underlying mechanisms leading to oligospermia in order to design low, cryopreservation of sperm prior to the initiation of hormone therapy is a viable option for fertility preservation.

References:

Supported by: University of Kansas Frontiers Pilot Grant

O-48 Monday, October 8, 2018 12:00 PM

MORE TO THE STORY THAN SPERM: PREGNANCY RATES WITH IN VITRO FERTILIZATION IN SAME-SEX FEMALE COUPLES. A. Napleton, B. M. Steinberg, L. Grimm, R. Jeelani, A. Beltso. Vios Fertility Institute, Chicago, IL.

OBJECTIVE: For same-sex female (SSF) couples, assisted reproductive technology (ART) is prevalent as a means to family building. These couples may face significant burdens in finding insurance coverage for ART, choosing a sperm donor, and taking on the second parent adoption process in many states. Previous reports have compared pregnancy success rates using intratubal insemination (IUI) between the general infertility population and members of same-sex female couples and have shown up to 67% cumulative pregnancy rates over 12 cycles.1 All evolving assisted reproductive technology, in vitro fertilization (IVF) provides the best overall chance of pregnancy. Additionally, IVF lends the unique opportunity for both members of a SSF couple to have involvement in treatment as either oocyte source or recipient. In order to best treat same-sex female couples, a population-specific criteria for prognosis should be established for IVF. The success of SSF in IVF treatment compared to the general infertility population is not yet established. We sought to determine if there exists a difference in IVF pregnancy rates between members of SSF couples and the general heterosexual infertility population.

DESIGN: Retrospective chart review at a private infertility center.

MATERIALS AND METHODS: All IVF treatment cycles performed on patients in SSF relationships from 2016 to 2018 were analyzed. Both fresh and frozen transfers were identified, and we divided the data set into 2 groups, for female patients in same-sex and heterosexual couples. A binomial test was used to analyze the data using SPSS 21.0 (SPSS Inc., Chicago, IL, USA).

RESULTS: A total of 205 treatment cycles were identified: 51 transfer cycles (42 frozen and 9 fresh) for SSF and 154 treatment cycles for heterosexual population (115 frozen and 39 fresh). Baseline characteristics between the SSF group and control group were the same, with a mean age in the SSF couples of 35.9 years old compared to 37.5 in the heterosexual group (p > 0.05). We found that the clinical pregnancy rate in the SSF population was significantly lower than the heterosexual patient population (39.2% vs. 55.8%, p = .025).

CONCLUSIONS: Our analysis shows that patients in same-sex female relationships do not show a higher pregnancy rate with ART than the general infertility population. Given that this population showed a higher pregnancy rate with IUI than the general infertility population, we had expected a higher pregnancy rate with IVF as well. This data can be utilized to establish clinical guidelines in managing patient expectations about the outcomes of their treatment. Treating physicians need to look at SSF couples trying for pregnancy with ART with a very open mind when it comes to exploring all possibilities for care and exercise caution to not assume better pregnancy outcomes with IVF among this population. ART has the power to redefine modern family-building; a realistic view of all reproductive options can empower same-sex female couples to make the best treatment choices possible.
REFERENCES


Supported by: None.

MENOPAUSE

O-49 Monday, October 8, 2018 10:45 AM

EFFECTS OF DEHYDROEPIANDROSTERONE (DHEA) SUPPLEMENTATION ON SEXUAL FUNCTION IN OLDER PRE-MENOPAUSAL INFERTILE WOMEN. V. A. Kushnir,1,2,* S. K. Darmon,1 D. H. Barad,1,2 A. Weghofer,3 N. Gleicher,1,2,3,4,5 Center for Human Reproduction, New York, NY; 1Obstetrics & Gynecology, Wake Forest University, Winston-Salem, NC; 2Foundation for Reproductive Medicine, New York, NY; 3Department of Obstetrics and Gynecology, Medical University Vienna, Vienna, Austria; 4Medical University Vienna, Vienna, Austria; 5Stem Cell Biology and Molecular Embryology Laboratory, Rockefeller University, New York, NY.

OBJECTIVE: In post-menopausal women, sexual dysfunction has been associated with low androgen levels, and has been reported to improve following dehydroepiandrosterone (DHEA) supplementation. Sexual dysfunction and low androgen levels are, however, also common among older pre-menopausal infertile women. The objective of this study was, therefore, to investigate the effects of DHEA supplementation on female sexual function in premenopausal infertile women of advanced ages.

DESIGN: Prospective cohort study in an academically affiliated private fertility center.

MATERIALS AND METHODS: Fifty consecutive infertile women who consented to participate in this study completed Female Sexual Function Index (FSFI) questionnaires and comprehensive endocrine evaluations, including the androgens DHEA, DHEAS, total (TT) and free testosterone (FT) before and 4-8 weeks after initiating 75 mg daily oral DHEA supplementation. A comparison of before - and after - DHEA supplementation was made using paired T-test and Pearson correlation.

RESULTS: The group of infertile women had a mean age of 41.1 ± 24.4 years, BMI 24.4 ± 6.2 kg/m², 89.6% were married, and 44.7% were parous. Caucasian women represented 53.2% of the study population, while African American women 17.0%, Hispanic women 14.9% and Asian women 14.9%.

All serum androgen levels increased following supplementation with DHEA (P<0.001 for all), while FSH levels decreased by 2.6 mIU/mL from a baseline of 10.3 ± 5.5 mIU/mL (95% CI 0.7-4.6, P=0.009). The FSFI score for the whole study group increased by 7% from 27.2 ± 7.0 to 29.1 ± 5.6, P=0.03), while domain scores for desire increased by 17% (from 3.5 ± 1.2 to 4.1 ± 1.0, P=0.006) and by 12% for arousal (from 4.3 ± 1.4 to 4.8 ± 1.0, P=0.01). Domain score for lubrication only demonstrated an 8% trend (8.0 (34%) increase in the mean (SD) 50.7 (3.7) vs. 50.1 (3.5) years, P=0.08), whereas in Cohort 2 the women with prior TL reached menopause an average of 0.3 years earlier (49.6 (4.7) vs. 49.9 (4.5) years, P=0.20). The average age of menopause was the same in Cohort 3 (50.0 (4.4) vs. 50.0 (4.2) years, P=0.80). The type of TL (Cohort 1 only) had no effect on the age of menopause.

CONCLUSIONS: TL did not impact the age at which women underwent natural menopause in any of the 3 large cohorts included in this study, which suggests that TL does not impart negative long-term effects on ovarian function. Salpingectomy for permanent contraception and opportunistic salpingectomy at the time of benign hysterectomy have emerged as potential cancer risk reduction strategies in women at average risk for ovarian cancer. The impact of these procedures on ovarian function requires further study.

O-50 Monday, October 8, 2018 11:00 AM

TUBAL LIGATION DOES NOT IMPACT AGE OF NATURAL MENOPAUSE. A. J. Ainsworth,6 S. Baumgarten,7 J. N. Bakkum-Ganz6, A. Weaver; S. K. Laughlin-Tommaso,8 OB/GYN, Mayo Clinic, Rochester, MN; 6Mayo Clinic, Rochester, MN; 7Clinical Statistics, Mayo Clinic, Rochester, MN.

OBJECTIVE: This study aimed to determine the effect of tubal ligation (TL) on age at natural menopause, as a marker of long-term ovarian function.

DESIGN: We utilized three pre-existing population-based cohorts for this cross-sectional study.

MATERIALS AND METHODS: Data from each cohort was analyzed separately. The cohorts included a referent cohort of women from the Rochester Epidemiology Project (REP, Cohort 1), and participants in the Mayo Clinic Biobank (Cohort 2) or the Mayo Mammography Health Study (Cohort 3). The cohorts for this project were restricted to women who never smoked and had reached natural menopause, without prior hysterectomy or oophorectomy. All cohorts included women from Olmsted County, MN and Cohorts 2 and 3 also included women from six surrounding counties. The following variables were self-reported on a questionnaire by participants in Cohorts 2 and 3: race, age of menarche, age of menopause, history of hysterectomy or oophorectomy, number of pregnancies and live births, tobacco use, and ever use of hormonal contraception. These variables were manually abstracted in Cohort 1, along with the type of TL and age at TL. For Cohorts 2 and 3, history of TL was obtained from a separate institutional form administered to all patients prior to an outpatient clinic visit at the Mayo Clinic and supplemented with procedure information from the resources of the REP. The primary outcome, age at natural menopause, was compared between the two groups (those with and those without a history of TL before natural menopause) using a two-sample t-test.

RESULTS: 555 women from Cohort 1, 1,816 women from Cohort 2, and 1,540 women from Cohort 3 met inclusion criteria. Baseline characteristics did not differ between cohorts. The rate of TL was the same in all cohorts: 26.0%, 25.5%, and 25.0%, respectively. Women who underwent TL were more likely to have had at least one pregnancy and to have used hormonal contraception compared to women who did not have a TL. In Cohort 1, the women with prior TL reached menopause an average of 0.6 years later (mean (SD) 50.7 (3.7) vs. 50.1 (3.5) years, P=0.08), whereas in Cohort 2 the women with prior TL reached menopause an average of 0.3 years earlier (49.6 (4.7) vs. 49.9 (4.5) years, P=0.20). The average age of menopause was the same in Cohort 3 (50.0 (4.4) vs. 50.0 (4.2) years, P=0.80). The type of TL (Cohort 1 only) had no effect on the age of menopause.

CONCLUSIONS: TL did not impact the age at which women underwent natural menopause in any of the 3 large cohorts included in this study, which suggests that TL does not impart negative long-term effects on ovarian function. Salpingectomy for permanent contraception and opportunistic salpingectomy at the time of benign hysterectomy have emerged as potential cancer risk reduction strategies in women at average risk for ovarian cancer. The impact of these procedures on ovarian function requires further study.

P-40 Monday, October 8, 2018 10:45 AM

PREMATURE MENOPAUSE GENOME-WIDE ASSOCIATION STUDY IN 75,000 WOMEN OF EUROPEAN ANCESTRY. G. Galanneau,1 P. Fontanillas,2 T. Hu-Seliger,3 C. Clementi,1 U. Schick,4 D. S. Colaci,5 D. E. Parfitt,6 D. Hinds,7 P. Yurttas Beim,8 Celmatrix Inc., New York, NY; 23andMe, Inc., Mountain View, CA.

OBJECTIVE: To identify genetic variants associated with premature menopause.

DESIGN: Retrospective case-control genome-wide association study (GWAS).

MATERIALS AND METHODS: In collaboration with the personal genetics company 23andMe, Inc., we conducted a GWAS in women of European ancestry who had consented to participate in research. Cases for the study were women who reported experiencing menopause at <40 years old or having been diagnosed with and/or treated for primary ovarian insufficiency (POI). Controls (n=70,156) were women who reported no history of POI treatment or diagnosis and who reported an age of menopause of ≥40 years old. Samples were genotyped on 1 of 4 versions of a custom genome-wide genotyping array targeting 556,955 single nucleotide polymorphisms (SNPs). Up to 15M additional SNPs were imputed using phase-i of the 1000 Genomes Project as a reference data set. On each SNP, we tested each variant for association, using logistic regression on the early menopause phenotype, with age, first 5 principal components, and genotyping array version as covariates.

RESULTS: One locus, overlapping with BRSK1 and TMEM150B, reached genome-wide significance (p<5 × 10⁻⁸) in our GWAS (p=1.7 × 10⁻¹⁰, OR=1.19 [1.13-1.26]). Previous GWASs in European populations have associated the TMEM150B locus with age of menopause, early menopause, and...
The association between the TMEM150B locus and age of menopause has also been observed at a nominal level (p<0.05) in African-American, Han Chinese, and Hispanic populations. In vitro experiments suggest that TMEM150B is involved in cellular quality control via mechanisms of autophagy. BRSK1 is a DNA damage checkpoint gene, which accords with previous findings that variants in DNA repair genes are associated with age of menopause. Of the 16 other loci previously associated with age of menopause in Europeans, 6 were nominally associated (p<0.05) with a consistent direction of effect in our study on premature menopause: ASHL2, FSHB, NLPR11, RHBDL2, TDRD3, and HELQ.

CONCLUSIONS: Our results confirm the association between the BRSK1-TMEM150B locus and early menopause in women of European ancestry and suggest that many loci associated with age of menopause are also associated with premature menopause.

References: NA
Supported by: Celmatix Inc.

**O-52 Monday, October 8, 2018 11:30 AM**

**RELATIONSHIP BETWEEN MENOPAUSAL SYMPTOMS AND OVARIAN RESERVE IN REPRODUCTIVE-AGED CANCER SURVIVORS.** K. E. Cameron, M. D. Sammel, J. Ginsberg, C. A. Carlson, C. R. Gracia. Reproductive Endocrinology and Infertility, Hospital of the University of Pennsylvania, Philadelphia, PA; ‡Biostatistics and Epidemiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; ‡Oncology, The Children’s Hospital of Philadelphia, Philadelphia, PA; ‡University of Pennsylvania, Philadelphia, PA.

OBJECTIVE: Cancer therapies impair reproductive function in survivors, but the relationship of physical symptoms to measures of ovarian reserve in a population of post-pubarchal pre-menopausal survivors is not well documented. This study sought to evaluate the prevalence of menopausal symptoms in a population of reproductive-aged women remote from cancer therapy compared to a group of healthy similar-aged controls, and to a cohort of late reproductive-aged (LR) controls.

DESIGN: Prospective cohort study.

MATERIALS AND METHODS: Participants were seen for annual visits that assessed symptoms of menopause and included early follicular phase hormone analyses and ultrasound examinations. Menopausal symptoms were analyzed in exposed participants and similarly aged (15-39yrs) and LR (40-50yrs) healthy, regularly-menstruating female controls using ANOVA corrected for multiple comparisons (Bonferroni). Pairwise comparisons were performed using ANOVA corrected for multiple comparisons (Bonferroni). Pairwise testing determined the source of statistical differences. A multivariate linear regression model was performed using multiple reactions monitoring, and the results expressed as pmoles/mg protein.

RESULTS: E2 increased GABA production in a concentration-dependent manner in HUVEC. There was a very slight increase in GABA in response to 10 nM of E2 (by 500 pmol/mg protein), followed by a significant increase in GABA in response to 100 nM E2 (by 6000 pmol/mg protein), followed by a slight drop in GABA in response to 300 nM E2 (by 2000pmol/mg protein).

CONCLUSIONS: E2 increases GABA production by endothelial cells, and this may partially explain the beneficial effects of E2 in attenuating atherosclerosis, and other vascular changes in menopause.

References: NA
Supported by: NIH Grant # 1R01HL135606

**O-53 Monday, October 8, 2018 11:45 AM**

**ESTRADIOL INCREASES GAMMA-AMINOBUTYRIC ACID (GABA) LEVELS IN HUMAN UMBILICAL VASCULAR ENDOTHELIAL CELLS.** A. Armstrong, D. Shan, A. Yoon, K. F. Fautl, S. Ramadoss, G. Chaudhuri, L. Nathan. OB/GYN, University of California, Los Angeles, Los Angeles, CA; ‡University of California, Los Angeles, Los Angeles, CA; ‡Department of Psychiatry & Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, CA; ‡OB/GYN Reproductive Endocrinology and Infertility, University of California Los Angeles, Los Angeles, CA; ‡OB/GYN, University of California Los Angeles, Los Angeles, CA.

OBJECTIVE: We have previously demonstrated that vascular endothelial cells release GABA, and that GABA inhibits adhesion of monocytes to endothelial cells. On the basis of these results we hypothesize that estradiol increases vascular endothelial cell GABA production, and this may be partial explanation for the inhibitory effect of estrogens on atherosclerosis.

DESIGN: In-vitro concentration related response in cell culture.

MATERIALS AND METHODS: Human umbilical vein endothelial cells (HUVEC) were seeded in 12-well plates (approximately 100,000 cells/well) and incubated for 24 hrs. The media was replaced with phenol red-free medium containing charcoal stripped serum, and incubated for another 12 hrs. Following this, the cells were treated with or without different concentrations of estradiol [E2] (0, 10, 100 and 300 nM) for 48 hours. Cell pellets were collected and used for the estimation of GABA by combined liquid chromatography/tandem mass spectrometry using multiple reaction monitoring, and total protein was measured by the method of Lowry. The amount of GABA in each sample was normalized for protein, and the results expressed as pmoles/mg protein.

RESULTS: E2 increased GABA production in a concentration-dependent manner in HUVEC. There was a very slight increase in GABA in response to 10 nM of E2 (by 500 pmol/mg protein), followed by a significant increase in GABA in response to 100 nM E2 (by 6000 pmol/mg protein), followed by a slight drop in GABA in response to 300 nM E2 (by 2000pmol/mg protein).

CONCLUSIONS: E2 increases GABA production by endothelial cells, and this may partially explain the beneficial effects of E2 in attenuating atherosclerosis, and other vascular changes in menopause.

References: NA
Supported by: Celmatix Inc.
Per follicle AMH production. Mean (SD)

<table>
<thead>
<tr>
<th>Age</th>
<th>AMH:AFC</th>
<th>p</th>
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<tbody>
<tr>
<td>25-30yo (n=255)</td>
<td>0.23 (0.11)</td>
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<td>31-35yo (n=235)</td>
<td>0.23 (0.12)</td>
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<tr>
<td>36-40yo (n=260)</td>
<td>0.24 (0.16)</td>
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</tr>
<tr>
<td>41-45yo (n=174)</td>
<td>0.19 (0.13)</td>
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<tr>
<td>Overall (n=924)</td>
<td>0.23 (0.13)</td>
<td>&lt;0.001</td>
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p<0.001). In this model, racial differences were apparent in the cohort at large, independent of age, smoking and BMI; Chinese, Mexican and Latin American women had lower AMH:AFC vs White women (coefficient -0.03, p=0.02; coefficient -0.05, p<0.01; and coefficient -0.07, p<0.01, respectively). Among all women, each 1 kg/m² unit increase in BMI was associated with a -0.003 unit reduction in AMH:AFC, independent of age, race and smoking.

CONCLUSIONS: After 40 years of age, there is a decline in per follicle level of AMH, independent of potential confounders. These findings raise the possibility of either a) declining granulosa cell function, or b) higher follicular recruitment with declining total number of oocytes, such that there are proportionally more antral follicles per preantral follicle with aging. Whether the observed decline in AMH:AFC with aging reflects senescence of quality vs quantity (or both) warrants additional investigation.

Supported by: OVA was supported by R01HD044876 (NICHD)

MALE REPRODUCTION AND UROLOGY: TRAVELING SCHOLARS

O-55 Monday, October 8, 2018 10:45 AM

KANK1 PLAYS A KEY ROLE IN GENITOURINARY DEVELOPMENT IN MALE MICE. N. Thirumavallavan, M. O’Neill, M. Haller, C. Cenzig, J. Scovell, J. A. Moore, K. R. Sheth, J. T. White, D. J. Lamb. uROlogy, Center for Reproductive Medicine, Baylor College of Medicine, Houston, TX; uDepartment of Molecular Cellular Biology, Baylor College of Medicine, Houston, TX; uDepartment of Pediatric Urology, Texas Children’s Hospital, Houston, TX; uDepartments of Urology and Genomic Medicine, Weill Cornell Medical College, New York, NY.

OBJECTIVE: Array Comparative Genomic Hybridization analysis (aCGH) of patients with genitourinary(GU) birth defects revealed copy number variants encompassing a candidate gene encoding kidney ankyrin repeat-containing protein 1 (KANK1) for GU birth defects including ambiguous genitalia, micro-penis, cryptorchidism, and small testes1. This study defined the male GU phenotype resulting from loss of function of Kank1 in mice.

DESIGN: Effects of Kank1 copy number loss on the GU system was tested using a de novo murine model of Kank1-haplinsufficiency and null deletion.

MATERIALS AND METHODS: In situ hybridization of murine embryos was done to confirm Kank1 expression in the GU tract. Kank1 homozygous null mice were created using a CRISPR/Cas9 system. Phenotyping was done at 10 weeks of age, and micro-CT allowed standardized measurement of penile structures. 1-year old mouse testes were weighed and histology was assessed using hematoxylin and eosin (H&E) staining. Periodic acid-Schiff (PAS), and trichrome staining. Epidydymides were removed and semen was analyzed. Breeding studies were performed. To assess the kidneys, micro-CT was performed. Histology, immunohistochemistry, and electron microscopy (EM) were performed. All studies were IRB and IACUC approved.

RESULTS: Ten week old Kank1 null- and -haplo-insufficient mice exhibited micro-penis and an abnormally shaped mump in 1 null mouse, but no other abnormalities in 9 haplo-insufficient and 14 null mice. Micro-CT showed that null mice had significantly shorter penis lengths (5.90 +/- 0.15 mm versus 5.62 mm +/- 3.1 mm, p = 0.005). Two of 5 E18.5 mice had inhibited micro-penis and an abnormally shaped mump in 1 null mouse, but no other abnormalities in 9 haplo-insufficient and 14 null mice. Micro-CT showed that null mice had significantly shorter penis lengths (5.90 +/- 0.15 mm versus 5.62 mm +/- 3.1 mm, p = 0.005). Two of 5 E18.5 mice had abnormal uterine ventral clefts. Average normalized testis mass was significantly lower (15 % vs. 25% of body weight) for null mice (p=0.029, 8 null mice vs 6 wild type mice). Total motile sperm counts were significantly lower (5.18 vs 12.36 million/cc) in Kank1 null compared to wild-type mice (p=0.039). Testes showed gross histopathological differences, including the presence of vacuoles in the seminiferous epithelium. Hydrophoresis without vescicoureteral reflux was present in multiple Kank1 null mice. Immunofluorescent microscopy revealed altered glomerular architecture. Collagen replacement and fibrosis was present in the kidney. EM of kank1 haplo-insufficient mice demonstrated altered podocyte structure.

CONCLUSIONS: Gene dosage changes of Kank1 in a mouse model partially mimic the human phenotype showing smaller testis and penile size, histologic anomalies of the seminiferous epithelium, decreased spermatogenic function, decreased fertility, and kidney abnormalities including hydrophoresis and altered podocyte structure.

Supported by: This work is supported in part by Urology Care Foundation Research Scholar Award to JW funded by Society of Pediatric Urology and the Sushil Lacy, MD Foundation, NIH grants K12 DK0083014, the Multidisciplinary K12 Urologic Research (KURE) Career Development Program awarded to DJL (NT is a K12 Scholar) and R01DK078121 from the National Institute of Kidney and Digestive Diseases to DJL.

O-56 Monday, October 8, 2018 11:00 AM


OBJECTIVE: Testicular germ cell tumors (TGCT), although rare, are the most frequent tumors in young men of reproductive age. It may affect spermatogenesis and lead to alterations in sperm parameters such as oligo or azoospermia. Orchiectomy is the standard initial treatment for all patients. However, studies have demonstrated that this procedure can lead to a decrease in sperm production capacity. Nevertheless, we have recently demonstrated that patients orchietomized for TGCT show improved sperm mitochondrial activity and DNA integrity, and decreased seminal plasma lipid peroxidation - even at an average 34 days post-surgery. We do not know yet, however, what underlying molecular mechanisms are in place in these cases. Thus, this study aimed to evaluate the effect of orchiectomy on the seminal plasma proteomic profile of men with testicular germ cell tumors.

DESIGN: Prospective Study.

MATERIALS AND METHODS: Seventeen men with testicular germ cell tumors provided one semen sample before (Pre-orchiectomy) and another 30 days after orchiectomy (Post-orchiectomy). Following liquefaction, an aliquot was used for semen analysis, and the remaining volume was centrifuged for collection of the seminal plasma. Pre-samples were labeled with a light isotope and Post-samples were labeled with a heavy isotope. These were then mixed, to a total of one pooled Pre and Post-orchiectomy sample from each patient (17 total). Pooled samples were submitted to a shotgun proteomics approach using a Thermo Q-Exactive mass spectrometer, and files processed using MaxQuant. Protein quantities were normalized to their ejaculate volume, to account for varying contributions in the ejaculate from each testis (postis/epididymoses/vasa deferentiae, seminal vesicles, and prostate, basically). Post/Pre ratios were presented, and samples were submitted to a one sample Student’s t-test, against a value of 1.0 (±5%).

RESULTS: 207 proteins were identified and quantified with high fidelity, of which 5 (GSHB, APOA1, GP2, B4GALT1, CD14) were increased in the Pre-orchiectomy period. These proteins participate in acute inflammatory response, leukocyte migration and response to oxidative stress. Eight proteins were increased in the Post-orchiectomy period (CATD, GSTP1, USP9Y, ZA2G, DHO5, PFIB, PARK7, TGM4) with reported functions in cellular response to oxidative stress, spermatogenesis process, protein folding and DNA repair.

CONCLUSIONS: Removal of the affected testis alters the seminal plasma molecular environment. The main effects brought upon by orchietomy are a decrease in the inflammatory process caused by the tumor. This can be demonstrated by the presence of proteins in the Post-orchiectomy period (PARK7 and GSTP1), that are related to cellular response to oxidative stress and inflammatory response.

Supported by: Ms. Andrade received a scholarship from CAPES.
**O-57 Monday, October 8, 2018 11:15 AM**

**NITROSO-REDOX IMBALANCE AFFECTS AGE-RELATED DECLINE IN MALE REPRODUCTIVE FUNCTION AND CAN BE REVERSED WITH ASCORBATE.**  J. A. Lee, a H. Arora, b T. Masterson, c E. Ibrahim, d R. Ramasamy. e aDepartment of Urology, University of Miami, Miami, FL; bUrology, University of Miami, Miami, FL; cUniversity of Miami, Miami Beach, FL; dUniversity of Miami / Department of Urology, Miami, FL; eUniversity of Miami Department of Urology, University of Miami Department of Urology, Miami, FL.

OBJECTIVE: The cause for aging related decline in reproductive function remains unclear. Based on recent findings which suggests the implications of S-nitrosylation on cell senescence and aging in mammals by controlling mitochondrial dynamics and mitophagy, we hypothesized that increased nitroso-redox imbalance could affect spermatogenesis as well as reproductive hormones and overcoming this could potentially reverse the adverse effects.

DESIGN: Animal study using GSNOR (S-nitrosoglutathione reductase) knockout mouse model.

MATERIALS AND METHODS: As the first step, we evaluated the reproductive parameters like-epididymal sperm concentration, motility, serum Luteinizing hormone (LH) and testosterone (T) in GSNOR KO mice at pre-pubertal, 3 months (young adults), and 12 months (senescent animals) of age. We compared these parameters to age-matched wild-type C57/BL6 mice. To study the impact of reversal of nitrosative stress in KO mice, we administered oral ascorbate (anti- oxidant) (10 mg/kg in water) in 5 GSNOR KO mice for 4 weeks and compared LH and testosterone levels to age-matched wild-type mice that were treated similarly.

RESULTS: With age, epididymal sperm concentration declined in WT mice (98.1 million/cc at 3 months, 80.5 million/cc at 6 months and 53.3 million/cc at 12 months). Interestingly, there was a greater reduction in sperm concentration in the young adult GSNOR KO mice (69.3 million/cc at 3 months to 32.9 at 12 months). We also observed a decline in sperm motility in both WT and GSNOR KO mice with aging. Additionally, we evaluated T and LH levels in pre-pubertal (less than 30 days), 3- and 12-months from GSNOR KO and WT mice. In pre-pubertal mice, both T (19.7 vs. 24.5 ng/dL) and LH (0.24 vs. 0.24 IU/mL) levels were similar between GSNOR KO and WT mice. Interestingly at 3 months, both the T (64.1 vs. 910.6 ng/dL) and LH levels (0.39 vs. 0.62 IU/mL) were lower in GSNOR KO compared to WT mice. We found similar trend at 12 months as well (T level 26.7 vs. 68 ng/dL and LH 0.24 vs. 1.56 IU/mL). Next, we evaluated the impact of gain of function (reversal of nitrosative stress) by oral administration of ascorbate. Importantly, ascorbate increased the T (644 vs. 674 ng/mL) and LH levels (0.84 vs. 0.51 IU/mL) in GSNOR KO mice similar to WT mice after 4 weeks of treatment.

CONCLUSIONS: Our findings suggest that age-related reproductive decline in a animal model of accumulating nitrosative stress is likely due to secondary hypogonadism. Antioxidant therapy with ascorbate appears to increase testosterone levels suggesting the effect of nitroso-redox imbalance on reproductive function is reversible. Further studies need to evaluate the mechanism of secondary hypogonadism and infertility in mice with nitroso-redox imbalance and can have implications in reproductive toxicology.

Supported by: Research Scholar Award from the Urology Care Foundation to RR.

**O-59 Monday, October 8, 2018 11:45 AM**

**SEMen PARAMETERS AMONG ADOLESCENT MALES UNDERGOING FERTILITY PRESERVATION IN AN INTERNATIONAL COHORT.**  J. Halpern, a N. Thirumavalavan, b T. P. Kohn, a A. Patel, d J. Leong, e D. J. Lamb, f R. Ramasamy. g aWeill Cornell Medicine, New York, NY; bBay- lor College of Medicine, Houston, TX; cJohns Hopkins, Baltimore, MD; dDepartment of Urology, University of Miami, Miami, FL; eSidney Kimmel College of Medicine, Thomas Jefferson University, Philadelphia, PA; fUrology, Weill Cornell Medical College, New York, NY; gUniversity of Miami Miller School of Medicine, Miami, FL.

OBJECTIVE: To determine the normal distribution of semen parameters among adolescent males presenting for fertility preservation compared to those of adults.

DESIGN: Retrospective, multi-institutional, multi-national cross- sectional cohort study.

MATERIALS AND METHODS: Adolescent males age 11-19 underwent semen analysis (SA) for fertility preservation at three centers across two countries (United States and United Kingdom). A comparison cohort was comprised of adults presenting for fertility preservation. Prevalence of azoospermia in adolescent versus adult males was compared using Chi-squared test. Median, interquartile range (IQR) and 4th and 95th percentile semen parameters (sperm volume, sperm concentration, motility) was compared between adolescents and adults using Wilcoxon rank-sum test.

RESULTS: A total of 197 adolescents and 95 adults underwent SA for fertility preservation. Azoospermia was present in 17 (8.6%) adolescents and 3 (3.2%) adults. There was a decline in the prevalence of azoospermia with increasing age among adolescents. After exclusion of patients with azoospermia, the adolescent and adult cohorts were comprised of 180 and 95 patients, respectively. Median age at presentation among adolescents and adults was 16.5 years (interquartile range [IQR] 15.2-17.6) and 30.8 years (IQR 22.7-43.8), respectively. Median semen volume was 1.0 mL (IQR 0.7-1.6) and 3.5 mL (IQR 2.4-5.0) for adolescents versus adults, respectively. Median sperm concentration was 30 million/mL (IQR 10-50) for adolescents versus 39 million/mL (IQR 14-57) for adults, <0.02. Median sperm motility was 39% (IQR 20-55) for adolescents versus 45% (IQR 35-55) for adults, p<0.01.

CONCLUSIONS: We present the first multi-national, multi-institutional comparison of adolescent and adult semen parameters in the setting of fertility preservation. Young adolescent males had a higher prevalence of azoospermia compared to adults, and the distribution of semen parameters

**O-58 Monday, October 8, 2018 11:30 AM**

**METHYLOME-WIDE ANALYSIS OF TESTICULAR FI- BROBLASTS IDENTIFIES NOVEL SITES THAT ARE HYPERMETHYLATED IN MEN WITH IDIOPATHIC NON-OBSTRUCTIVE AZOOSPERMIA.**  J. S. Gabrielsen, a D. J. Lamb, b aDepartment of Urology, Baylor College of Medicine, Houston, TX; bUrology, Weill Cornell Medical College, New York, NY.

OBJECTIVE: To identify epigenetic modifications and the potential underlying mechanisms in men with idiopathic non-obstructive azoospermia (NOA).

DESIGN: Hypermethylated DNA sites were identified in testicular fibroblasts from men with NOA compared to controls.

MATERIALS AND METHODS: Testicular fibroblasts were isolated and cultured from men with NOA (n=17) and men with proven fertility (n=5). Bisulfite conversion of unmethylated cytosines was performed. Methylation status was determined using the Illumina HumanMethylation450 Bead Chip. Highly differentially methylated sites were determined by setting the cutoff M-value to > 2 in subjects and the average of the controls to < -2 (β values of 0.8 and 0.2, respectively). All data analyses were performed using R. The highly associated methylated sites were then compared to the UCSC Genome Browser to determine the genomic location, associated SNPs and potential interactions with transcription factor binding sites.

RESULTS: Between 2 and 39 sites were found to be hypermethylated in each subject and while unmethylated in the controls, for a total of 123 unique sites. 34 were located upstream of genes, 50 within introns and 20 within exons. While several genes were identified that have been previously associated with male infertility (e.g, CDC42BPA, CYP2B1, FOXP1, HES1, HLA-B, FYN, LMS, WEE1), the majority of methylation sites and genes identified have not previously been associated with infertility. Using transcription factor ChIP data from the UCSC genome browser, 145 unique transcription factor associated sites were identified. Ten of the methylation sites were found within transcription factor consensus sequences. Additionally, a large number of the methylated sites were within Polycomb Group Protein-associated regions (e.g, YY1, REST and Ezh2). This data provide novel targets for investigation of the causes of NOA.

Supported by: JSG is supported in part by NIH K12 DK008301 Multidisciplinary K12 Urologic Research Career Development Program (to DIL).
was significantly lower in adolescents compared to adults. The current data establishes a frame of reference and clinical context for providers, patients, and families who are confronted with fertility preservation during adolescence.

Supported by: Ranjith Ramasamy received financial support from the Urology Care Foundation Award;

O-60 Monday, October 8, 2018 12:00 PM
TOTAL MOTILE SPERM COUNT TREND OVER TIME ACROSS TWO CONTINENTS: EVALUATION OF SEMEN ANALYSES FROM 119,972 INFERTILE MEN. A. W. Tieg, J. Hotaling, J. VTI-RMA NJ, Basking Ridge, NJ; N. Garrido, R. Scott, J. Landis, J. Kimmel Medical College, Philadelphia, PA; Foundation for Embryonic Competence, Basking Ridge, NJ; T. Wang, E. Seli, J. IVI Foundation, Valencia, Spain; Reproductive Medicine Associates of New Jersey, Saint Barthélemy, University of Utah School of Medicine, Salt Lake City, UT.

OBJECTIVE: While previous reports of declining sperm counts in the fertile and unselected population are concerning, the most reliable indicator of male fertility, the total motile sperm count (TMSC), has not been previously evaluated (1,2). Furthermore, the TMSC trend in the subfertile population remains unknown. We sought to characterize the TMSC trend over time in a large sample of men from infertile couples in two large fertility centers on separate continents to determine if TMSC was declining over time.

DESIGN: Retrospective cohort

MATERIALS AND METHODS: The first semen analysis (SA) of male patients from Reproductive Medicine Associates of New Jersey (RMANJ) and the Instituto Viciolano de Infertilidad (IVI) were identified: SAs from 2002-2017 and 2011-2017, respectively, were included due to robust sample size (n>2,000). SAs were excluded if collected retrograde, post-vasectomy, or if TMSC not available. SAs were categorized into 3 clinically relevant groups based on treatment strategy: TMSC >15 million (M) (Group 1), TMSC 5-15M (Group 2), and TMSC 0-5M (Group 3). Linear and logistic regression were used where appropriate to assess the impact of age and estimated TMSC group as a function of collection year.

RESULTS: A total of 41,809 SAs from RMANJ and 7,163 from IVI (129 countries of origin; 74% Spanish) were included. Analyses were performed on RMANJ and IVI data separately. In the RMANJ cohort, linear regression demonstrated a significant decrease in TMSC by 1.8% per year in Group 1 (p<2.2e-16), and the odds of belonging to Group 1 decreased over time (OR = 0.979; 95% CI = 0.974 - 0.985; p=2.8e-14). Age was associated with TMSC in Group 1. For every 1 yr increase in age, TMSC decreased by 1.1% (p=2.2e-16), and the odds of belonging to Group 1 decreased with age (OR = 0.977; 95% CI = 0.973 - 0.981; p=2.2e-16). Similar trends in groups were found in the IVI cohort.

CONCLUSIONS: Although TMSC was found to marginally decrease over time, the clinical significance of this finding is unclear. This trend may reflect a selection bias, in that more infertile men are presenting for treatment each year, or adverse effects of environmental factors. Whatever the underlying etiology, the shift in groups over time is clinically relevant, as treatment strategies differ by categorization. Longer follow up is necessary to confirm TMSC trends in the infertile population.

References:

Supported by: NIA

O-61 Monday, October 8, 2018 10:45 AM
EVALUATING MITOCHONDRIAL STRESS RESPONSE GENE CLPP-REGULATED DNA METHYLATION DYNAMICS IN FEMALE REPRODUCTIVE AGING. Z. Jiang, X. Tian, X. Seli, T. Wang, M. Zhang, X. Tian, E. Seli, Louisiana State University, Baton Rouge, LA; University of Connecticut, Storrs, CT; Yale School of Medicine, New Haven, CT; IVIRMA New Jersey, Basking Ridge, NJ.

OBJECTIVE: CLPP (caseinolytic peptidase P) mediates degradation of unfolded mitochondrial proteins to maintain protein hemostasis in response to metabolic and cellular stress. CLPP is required for oocyte and embryo development, and targeted deletion of Clpp results in female infertility and accelerated depletion of ovarian follicular reserve. The aim of the present study was to determine the effect of Clpp deletion on oocyte and cumulus cell DNA methylation in mature and older mice.

DESIGN: Experimental study.

MATERIALS AND METHODS: Cumulus oophorus complexes (COCs) were collected from 3- and 6-month-old Clpp knockout (Clpp-/-) and wild type (WT) mice (n = 3, per group). 48h after PMSG (5IU) injection Germlinal vesicle (GV) oocytes and cumulus cells were isolated, and 5 oocytes and approximately 50 cumulus cells were separately pooled from each mouse for analysis. Whole genome bisulfitite sequencing (WGBS) libraries were prepared and sequenced on Illumina’s HiSeq 4000 platform. Sequencing reads were pre-filtered and aligned to the mouse reference genome (mm10) using Bismark. DNA methylation levels were determined by the ratio of the number of reads supporting C (methylated) to that of total reads (methylated and unmethylated). Differentially methylated regions (DMRs) were called if DNA methylation level was greater than 80% in one group and less than 20% in the other group with FDR adjusted P <0.05.

RESULTS: Using WGBS, we found that genome-wide methylation level was significantly lower in 3-month Clpp-/-oocytes compared to WT (27.0% vs 52.0%, p<0.01). At 6 month, however, Clpp-/-oocytes had a higher methylation level compared to WT (45.5% vs 25.4%, p<0.001). At 3 months, a total of 4,918 DMRs were identified in Clpp-/- oocytes compared to WT. At 6 month, more DMRs (7,475) were found in Clpp-/- oocytes compared to WT. In cumulus cells, all treatment groups had a similar DNA methylation level, averaging 72.0%, however, the methylation of individual methylated regions was significantly different among different groups. In addition, we found that hyper-methylated regions in both oocytes and cumulus cells were enriched in repeat elements (e.g. LINEs, SINE, LTR), while CGIs, and promoter and enhancer regions were mainly demethylated. Finally, together with RNA-seq datasets (Wang et al., 2018), we revealed that promoter methylation was inversely correlated with gene expression of downstream targets that were regulated by Clpp and aging.

CONCLUSIONS: Clpp global deletion resulted in significant changes in genome-wide DNA methylation dynamics of GV oocytes and cumulus cells. Our findings provide new insight into the role of CLPP in reproduction, and may help understand the potential epigenetic mechanisms mediating infertility and reproductive aging associated with Clpp-deficiency.

O-62 Monday, October 8, 2018 11:00 AM
MFN1 IS REQUIRED FOR FOLLICULAR DEVELOPMENT, OOCYTE MATURATION, AND FEMALE FERTILITY. M. Zhang, M. B. Bener, X. Jiang, T. Wang, E. Esencan, R. Scott III, E. Seli, Yale School of Medicine, New Haven, CT; LSU, Baton Rouge, LA; IVIRMA New Jersey, Basking Ridge, NJ.

OBJECTIVE: Mitofusin 1 (MFN1), a member of the mitofusin family of GTPases, is highly expressed in the oocyte and cumulus in primordial and early small antral follicles. MFN1 is required for mitochondrial fusion and spindle formation during meiosis. MFN1 regulates the fusion of the mitochondrial outer membrane with the plasma membrane during fertilization and may be involved in the maintenance of the maternal mitochondrial genome in the oocyte.

DESIGN: Experimental study.

MATERIALS AND METHODS: 6 month male and female MFN1 knockout (MFN1-/-) and wild-type (WT) mice were mated. Germinal vesicle (GV) oocytes and cumulus cells were isolated, and 5 oocytes and approximately 50 cumulus cells were separately pooled from each mouse for analysis. Whole genome bisulfitite sequencing (WGBS) libraries were prepared and sequenced on Illumina’s HiSeq 4000 platform. Sequencing reads were pre-filtered and aligned to the mouse reference genome (mm10) using Bismark. DNA methylation levels were determined by the ratio of the number of reads supporting C (methylated) to that of total reads (methylated and unmethylated). Differentially methylated regions (DMRs) were called if DNA methylation level was greater than 80% in one group and less than 20% in the other group with FDR adjusted P <0.05.

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CONCLUSIONS: Clpp global deletion resulted in significant changes in genome-wide DNA methylation dynamics of GV oocytes and cumulus cells. Our findings provide new insight into the role of CLPP in reproduction, and may help understand the potential epigenetic mechanisms mediating infertility and reproductive aging associated with Clpp-deficiency.

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Proportions of males within Groups over time (RMA and IVI samples combined 2011-2017)

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<tr>
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<td>8,302</td>
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<td>60,077</td>
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<tr>
<td>Group 1 (TMSC &gt;15M)</td>
<td>84.7%</td>
<td>85.5%</td>
<td>81.0%</td>
<td>79.1%</td>
</tr>
<tr>
<td>Group 2 (TMSC 5-15M)</td>
<td>6.3%</td>
<td>6.0%</td>
<td>8.5%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Group 3 (TMSC 0-5M)</td>
<td>8.9%</td>
<td>8.9%</td>
<td>10.5%</td>
<td>11.6%</td>
</tr>
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OBJECTIVE: Mitochondria are dynamic organelles that continually adapt their shapes through fusion and fission in response to changes in energy demand and supply. Mitofusin-1 (MFN1) regulates mitochondrial dynamics by promoting mitochondrial fusion. The aim of the current study was to determine the role of mitofusin-1 in female reproductive competence using a mouse model with oocyte-specific deletion of Mfn1.

DESIGN: Experimental study.

MATERIALS AND METHODS: Mfn1floxed mice were crossed with Zp3-Cre mice to produce mice with oocyte-specific Mfn1 deletion (Mfn1floxed/cre). Fertility was assessed by mating 8-week-old Mfn1floxed/cre and wild type (WT) female mice (n=7 per group) with WT fertile males for 12 weeks. Serial ovarian sections were stained with hematoxylin and cosin. Ability to generate oocytes (germinal vesicle [GV] and metaphase II [MII]) and 2-cell embryos was assessed after injection with PMSG (5IU) or PMSG and hCG (5IU) and mating with WT males as indicated. Mitochondrial morphology and dynamics were assessed using electron microscopy. ATP levels were determined by bioluminescent assay. Mitochondrial DNA (mtDNA) copy number was measured in individual oocyte by cloning of mitochondria specific gene (Cox3) as a standard, followed by quantitative real-time PCR (qPCR). Finally, RNA sequencing analysis was performed using pooled Mfn1+/+ and WT preantral follicle oocytes (n=3 mice per group).

RESULTS: Mfn1+/+ female mice were fertile and did not produce any pups. Mfn1floxed/cre oocytes had similar number of primordial, primary, and secondary follicles compared to WT, but no antral follicles with or without PMSG stimulation. Mfn1floxed/cre mice generated a significantly lower number of GV oocyte (17±3.6 vs 40±3.0, p<0.01), no mature oocytes, and no 2-cell embryos (p<0.001). Electron microscopy revealed that Mfn1+/+ oocyte mitochondria were larger (5.4±1.9 vs 4.5±1.9 μm2; p<0.01) with lower aspect ratio (length/width; 1.23±0.01 vs 1.83±0.08; p<0.001). Mfn1floxed/cre oocytes had decreased ATP production (0.61±0.19 vs 0.43±0.19 μM; p<0.01) and mtDNA copy number (13.39±5.8 vs 99.10±15.1; p<0.001), and decreased expression of mitochondrial development factors (Gdf9 and Bnip3) (p<0.05). RNA-seq analysis revealed a total of 982 genes that were differentially regulated in Mfn1floxed/cre oocytes with a number of affected pathways including cell death (apoptosis) signaling and adhesion-junction signaling (p<0.01).

CONCLUSIONS: Targeted oocyte-specific deletion of Mfn1 results in impaired mitochondrial function and dynamics and female infertility, associated with defective follicle development, lack of oocyte maturation and embryo development. Future studies are required to determine how MFN1-dependent signaling pathways affect female reproductive potential.

CUMULUS CELLS HAVE LONGER TELOMERES THAN LEUKOCYTES IN REPRODUCTIVE AGE WOMEN. E. E. Lara Molina,1 J. M. Franasiak,2 D. Marin,3 X. Tao,4 P. Diaz-Gimeno,1 M. Florensa,2 M. Martin,1 E. Seli,1 A. Pellicer,4 IVI RMA, Barcelona, Spain;3 IVI RMA New Jersey, Basking Ridge, NJ;4 The Foundation for Embryonic Competence, Basking Ridge, NJ;4 IVI RMA Fundación IVI, Valencia, Spain;4 Yale School of Medicine, New Haven, CT;4 IVI RMA New Jersey, Basking Road, NJ;4 IVI RMA, Rome, Italy.

OBJECTIVE: Given that progressive shortening of telomeres has been linked with reproductive aging, we aimed to determine if telomere length (TL) in granulosa cells (GC) and cumulus cells (CC) are correlated with TL in leukocytes (L), so that TL measurements in blood could become useful indicators of follicular biology.

DESIGN: Prospective, non-interventional study.

MATERIALS AND METHODS: Thirty-five egg donors were included in the study. Following controlled ovarian hyperstimulation by using an antagonist protocol with standard doses of subcutaneous FSH, oocytes retrieval was done 36 hours after a bolus of GnRH agonist. CC were obtained after oocyte stripping, and GC were isolated from the pooled follicular fluid using a density gradient method. Genomic DNA (gDNA) from L, CC and GC from all donors was isolated for TL measurements. Relative TL was obtained using a SYBR green qualitative real-time PCR protocol. A Taqman assay for the multiplex gene 4F was used for normalization of measurements. Association between TL in L, CC and GC was primarily investigated and paired comparisons were performed. Age, smoking, confirmed fertility, anti-Müllerian hormone (AMH), antral follicular count (AFC) and number of mature oocytes were also analyzed against TL data. Paired t-tests and Pearson correlation coefficients were computed for TL comparisons and to determine associations between the TL and the aforementioned variables, respectively.

RESULTS: Mean age of subjects was 25.43±4.57 years, AMH levels were 1.90±0.92 ng/ml, AFC 23.29±5.11 and number of mature oocytes 25.29±9.13. No significant association between these variables, or confirmed fertility, and TL of GC, CC, or L was found. In addition, no correlation was observed between TL measurements of L vs CC (p=0.924), L vs GC (p=0.154) or between CC vs GC (p=0.512). Interestingly, TL of CC was significantly higher compared to L (1.54 fold, p<0.0001), while no significant differences were found between TL of GC vs CC (p=0.120), or GC vs L (p=0.114).

CONCLUSIONS: Cumulus cells from mature follicles have significantly longer telomeres than leukocytes, suggesting that the follicular environment could possess different and perhaps more effective mechanisms to cope against telomere shortening and therefore cellular aging than other somatic tissues. Further, these data do not support the utility of telomere DNA measuring in blood to estimate TL in follicular cells as an indicator of ovarian aging.
24,25(OH)2D3: A NOVEL ACCURATE INDICATOR OF OVARIAN VITAMIN D STATUS IN WOMEN AT REPRODUCTIVE AGE. E. E. Lara Molina, a J. M. Fransasiak,b A. Devesa-Perón,c M. Martin,a M. Florencia,d M. López,a P. Díaz-Gimeno,a A. Pellicer. bIVI RMA, Barcelona, Spain; cIVI RMA New Jersey, Basking Ridge, NJ; dIVI RMA Fundación IVI, Valencia, Spain; aInstituto de Investigación Sanitaria La Fe, Valencia, Spain; eIVI RMA, Rome, Italy.

OBJECTIVE: The impact of vitamin D in reproductive outcomes is still an unresolved issue, mainly because of lack of accuracy measuring vitamin D metabolites. 24,25-dihydroxyvitamin D (24,25(OH)2D) is the main product of the catabolism of 25-hydroxyvitamin D (25(OH)D), so it has been proposed as an effective systemic indicator of vitamin status. However, its presence and impact at reproductive level, especially in the follicular fluid, has not been studied yet. We aimed to determine the concentrations and correlations of 24,25(OH)2D3 with other vitamin D metabolites in serum (S) and follicular fluid (FF) from mature oocytes, in order to evaluate its potential implication in the ovarian physiology.

DESIGN: Prospective, non-interventional study.

MATERIALS AND METHODS: Thirty-five egg donors were included in the study. Following controlled ovarian hyperstimulation using an antagonist protocol and standard doses of subcutaneous FSH, oocytes retrieval was done 36 hours after a bolus of GnRH agonist. S samples and pooled FF from mature follicles were obtained. 24,25(OH)2D3, 25(OH)D3 and 1,25(OH)2D3 concentrations were measured through liquid chromatography-tandem mass spectrometry (LC-MS/MS) using a UPLC-TQ-S Xevo system with Waters Acquity BEH C18 (1.7µm, 2.1 x 100mm) column. A paired design was implemented in all statistical analyses performed. Pearson correlation test was used to evaluate S and FF vitamin D metabolites correlations. Mean differences between each vitamin D metabolite in S and FF were evaluated using Wilcoxon test.

RESULTS: Mean values for 25(OH)D3 concentrations were 91.56±39.01 nM in S, and 38.12±19.54 nM in FF. For 24,25(OH)2D3 the mean values in S concentrations were 156.16±109.96 nM, and 112.63±60.86 nM in FF. 1,25(OH)2D3 was not detected in any sample. 24,25(OH)2D3 and 25(OH)D3 concentrations were highly correlated (r=0.92, p-value=2.713e-14 for S and r=0.91, p-value=5.031e-14 for FF). After analyzing each metabolite separately, the strongest correlation between S and FF concentrations was observed for 24,25(OH)2D3 (r=0.77, p-value=1.121e-07), followed by 25(OH)D3 (r=0.69, p-value=6.902e-06).

CONCLUSIONS: This is the first study evaluating 24,25(OH)2D3 concentrations and correlations with other vitamin D indicators in FF and S. Our results suggest 24,25(OH)2D3 as an accurate indicator of vitamin D status in the ovary, and represents an important step in understanding the specific role of vitamin D in the ovarian physiology and reproductive outcomes.

Supported by: IVI RMA Fundación IVI

O-65 Monday, October 8, 2018 11:45 AM

PREDICTING BLASTOCYST FORMATION FROM OOCYTE MECHANICAL PROPERTIES: A COMPARISON OF A MACHINE LEARNING CLASSIFIER WITH EMBRYOLOGIST MORPHOLOGICAL ASSESSMENT. J. Kort,a D. Meyer,b N. Y. Chen,c V. L. Baker,c J. Y. Huang,c D. Camarillo,c B. Behr. aStanford Fertility and Reproductive Health, Sunnyvale, CA; bStanford University, Stanford, CA; cTaiwan IVF group, Hsinchu County 301 Zhubei City, Taiwan; dStanford University IVF/ART Program, Sunnyvale, CA.

OBJECTIVE: To determine if a machine learning algorithm incorporating mechanical properties of mature oocytes can predict blastocyst formation better than a senior lab director making predictions based on oocyte morphology.

DESIGN: Prospective split cohort study.

MATERIALS AND METHODS: After obtaining IRB approval, patients undergoing in vitro fertilization with intracytoplasmic sperm injection (IVF-ICSI) using ejaculated sperm at a single IVF clinic were prospectively enrolled if ≥ 10 mature oocytes were retrieved. At most half of a patient’s oocytes were measured with a micropipette device through which a stepwise aspiration pressure was applied. The aspiration depth over time was measured and applied to a Zener bulk mechanical model to obtain mechanical parameters: k0, k1, tau, eta0, and eta1. Oocyte fertilization, day 3 morphology, and blastocyst development were observed and compared between measured and unmeasured cohorts. A usable blastocyst was considered a 3CB/3BC or better by day 6 of culture. A support vector classifier was trained on a portion of the dataset while the remainder was used to test the classifier. A senior embryologist with ≥30 years experience was shown images of the same oocytes and gave the corresponding patient’s age and indication for IVF. Using this information and morphological assessment, they made a prediction whether the corresponding oocyte would develop into a blastocyst. The embryologist’s assessment and machine learning classifier were compared.

RESULTS: Thirty-four patients and their corresponding 773 oocytes—of which 213 oocytes underwent measurement and 560 did not—were included. Fertilization (74.2% vs. 78.0%, p=NS) and usable blastocyst development/ mature oocyte (48.8% vs. 45.5%, p=NS) were similar between measured and unmeasured oocytes. Using age, diagnosis and oocyte morphology, an embryologist predicted blastocyst development with a positive predictive value of 44% and a negative predictive value of 46%. The machine learning classifier using age, k1, and eta1 was able to correctly predict blastocyst development with a positive predictive value of 80% (95% CI 60.45% to 91.28%) and a negative predictive value of 63.8% (95% CI 53.42% to 73.18%).

CONCLUSIONS: A support vector classifier was able to employ mechanical parameters and patient age to predict mature oocytes’ developmental potential with greater accuracy than an experienced embryologist. While further improvements in oocyte assessments to predict reproductive potential are critically needed, this mechanical assessment can be performed without adversely affecting subsequent embryo culture outcomes, disrupting embryologist workflow, and may inform fertility preservation patients. Further analysis of a more diverse patient population is needed to validate these results and is underway.

Supported by: The Wallace H. Coulter Foundation

O-66 Monday, October 8, 2018 12:00 PM

A RANDOMIZED CONTROLLED TRIAL OF COMBINATION OF LETROZOLE AND CLOMIPHENE CITRATE VERSUS LETROZOLE ALONE FOR OVULATION INDUCTION IN WOMEN WITH POLYCYSTIC OVARY SYNDROME. R. Mejía,a K. M. Summers,b J. D. Kresowik,a B. J. Van Voorhis,b aOb-Gyn, Division of Reproductive Endocrinology & Infertility, University of Iowa, Iowa City, IA; bResearch Assistant, Iowa City, IA; cOb-Gyn, University of Iowa Hospitals and Clinics, Iowa City, IA; dOb-Gyn, University of Iowa College of Medicine, Iowa City, IA.

OBJECTIVE: To evaluate whether a combination of letrozole and clomiphene citrate results in higher ovulation rate than letrozole alone in infertile women with polycystic ovary syndrome (PCOS).

DESIGN: Open label randomized controlled trial.

MATERIALS AND METHODS: Setting: Academic medical center utilizing two clinic sites.

Patient(s): Eligible women were 18 to 40 years of age with a diagnosis of infertility and PCOS as defined by the Rotterdam criteria and no other known cause of infertility; the male partner had either fathered a pregnancy or a sperm concentration of at least 15 million per milliliter.

Interventions(s): Participants were stratified by age and body mass index and then randomized in a 1:1 ratio to either 2.5 mg letrozole alone on cycle days 3-7 or a combination of 2.5 mg letrozole and 50 mg CC on cycle days 3-7 for one cycle.

Main Outcome Measure(s): Ovulation measured by mid-luteal progesterone level. Serum progesterone concentration of ≥ 3 ng/mL indicated ovulation.

Sample size: The study was designed to have 80% power to detect an absolute difference 33 percentage points in ovulation rates between treatment groups with α of 0.05.

RESULTS: Seventy patients were randomized in this study, 35 to letrozole alone and 35 to the combination of letrozole and CC. There were no significant differences between the study groups for age, BMI, duration of infertility, parity, or prior exposure to either CC or letrozole. Results were
analyzed with the intent-to-treat principle. Women who received the combination of letrozole and CC had a higher ovulation rate compared to those who received letrozole alone (27 of 35 women [77%] vs. 15 of 35 women [43%], P < 0.007; rate ratio for ovulation, 1.80; 95% CI, 1.18 to 2.75). When comparing the combination of letrozole and CC to letrozole alone, there were no significant differences in clinical pregnancies (4/35 vs 2/35) or live births (4/35 vs 2/35), respectively. There were no serious adverse events or multiple gestation pregnancies in either group. The side effect profile was similar in the two treatment groups.

CONCLUSIONS: The combination of letrozole and CC was associated with a higher ovulation rate as compared to letrozole alone among women with infertility and PCOS. This suggests that larger studies of this promising new combination therapy should be conducted with live birth as the primary outcome.

Supported by: University of Iowa, Dept of Ob-Gyn: The Davis Foundation

O-68 Monday, October 8, 2018 11:00 AM

MATURE FOLLCLE COUNT AND MULTIPLE GESTATION RISK BASED ON PATIENT AGE IN OVULATION INDUCTION-INTRAUTERINE INSEMINATION (OI-IUI) CYCLES

OBJECTIVE: To evaluate risk factors for life-threatening complications in patients with severe OHSS with multiple follicles, and the multiple gestation rate does not substantially rise until 4 or more follicles are present. This large dataset can be used to guide patient counseling and clinical decision making.

References: N/A

O-69 Monday, October 8, 2018 11:15 AM

EPIDEMIOLOGY AND RISK FACTORS FOR LIFE-THREATENING COMPLICATIONS IN SEVERE OVARIAN HYPERSTIMULATION SYNDROME (OHSS) IN A NATIONWIDE SAMPLE

OBJECTIVE: To evaluate risk factors for life-threatening complications in patients with severe OHSS in a nationwide sample.

MATERIALS AND METHODS: Data were derived from the Nationwide Inpatient Sample (NIS) for OHSS admission for 2002-11. The NIS is a database containing information on 8 million hospital admissions yearly from more than 40 states and 1000 hospitals, and contains a weighting system that allows for calculation of population estimates. Patient (age, race, payer status, comorbidities, income) and hospital (region, bed-size, teaching status, location) variables were examined for association with life-threatening complications (deep vein thrombosis/pulmonary embolism [DVT/PE], acute respiratory distress syndrome [ARDS], renal failure [RF], intubation), non-routine discharge (discharge to skilled nursing facility, transfer hospital), length of stay (LOS), and total hospital charges. Survey-adjusted multivariable logistic regression models controlling for these factors assessed the primary exposure of comorbidities with complications.

RESULTS: A total of 11,562 patients were hospitalized with severe OHSS from 2002-2011. All admitted patients were pregnant. The majority were white (55.7%), with private insurance (87.7%), age 25-39 (84.6%), at an urban hospital (95%), 19.3% of patients had comorbidities (hypertension, diabetes, obesity, hypothyroidism, anemia). Death occurred in 9 patients. Life-threatening complications occurred in 4.4% of patients (DVT/PE 2.2%, RF 1.5%, ARDS 0.9%, intubation 0.5%). Older patients (> 40 years old (Odds Ratio [OR] = 3.4 95% CI: 1.1, 10.8 p<0.04), ones with comorbidities (OR = 2.1, 95% CI: 1.3, 3.3, p<0.01), and African American patients (OR = 2.1, 95% CI: 1.2, 3.7, p<0.01) were more likely to develop these life-threatening conditions. Patients with comorbidities (OR = 0.5, 95% CI: 0.3, 0.8, p<0.01), were also less likely to have routine discharge from the hospital. Adjusting for patient and hospital demographics, patients with comorbidities were more likely to develop DVT/PE (OR 2.5, 95% CI: 1.3, 4.8, p=0.01) and RF (OR = 2.3, 95% CI: 1.2, 4.2, p=0.01). Patients who developed life-threatening complications had longer LOS (OR = 3.7, 95% CI: 2.3, 6.1, p<0.01) and higher hospital cost (OR = 1.7, 95% CI: 1.2, 2.4, p<0.01).

CONCLUSIONS: Patients with common comorbidities have worse outcomes in severe OHSS. Furthermore, these complications are associated with high cost and hospital burden. Given the increasing number of IVF patients with comorbidities, these findings suggest that risk stratification and closer monitoring of patients who have these comorbid conditions may pre-

<table>
<thead>
<tr>
<th>Pregnancy Type</th>
<th>CP per IUI/Singleton per IUI/Twin per CP/ Triplet+ per CP</th>
<th>CP per IUI/Singleton per IUI/Twin per CP/ Triplet+ per CP</th>
<th>CP per IUI/Singleton per IUI/Twin per CP/ Triplet per CP</th>
<th>CP per IUI/Singleton per IUI/Twin per CP/ Triplet per CP</th>
<th>CP per IUI/Singleton per IUI/Twin per CP/ Triplet per CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 35 years, n=26,522</td>
<td>16.6% / 15.8% / 14.4% / 3.3%</td>
<td>14.3% / 13.5% / 5.5% / 0.9%</td>
<td>10.5% / 9.9% / 4.8% / 0.4%</td>
<td>5.7% / 5.5% / 3.9% / 0%</td>
<td>4.1% / 3.7% / 10.0% / 0%</td>
</tr>
<tr>
<td>35-37 years, n=11,317</td>
<td>20.1% / 17.3% / 13.2% / 1.0%</td>
<td>18.2% / 15.7% / 13.0% / 0.6%</td>
<td>13.9% / 11.8% / 13.9% / 1.1%</td>
<td>9.4% / 8.3% / 10.2% / 1.1%</td>
<td>4.2% / 3.7% / 10.5% / 0%</td>
</tr>
<tr>
<td>38-40 years, n=8,173</td>
<td>21.0% / 16.0% / 20.3% / 3.7%</td>
<td>20.1% / 16.7% / 15.2% / 1.8%</td>
<td>16.9% / 13.9% / 15.3% / 2.5%</td>
<td>11.1% / 10.2% / 6.8% / 1.4%</td>
<td>8.7% / 8.0% / 4.2% / 0%</td>
</tr>
<tr>
<td>41-42 years, n=3,054</td>
<td>22.1% / 15.7% / 23.6% / 5.7%</td>
<td>21.1% / 15.5% / 24.5% / 2.1%</td>
<td>19.5% / 15.8% / 15.1% / 3.8%</td>
<td>15.1% / 11.7% / 22.4% / 0%</td>
<td>8.3% / 6.8% / 18.2% / 0%</td>
</tr>
<tr>
<td>43-44 years, n=1,426</td>
<td>24.4% / 17.7% / 18.7% / 8.8%</td>
<td>21.9% / 13.3% / 27.9% / 11.6%</td>
<td>19.7% / 13.9% / 25.4% / 4.2%</td>
<td>19.6% / 16.1% / 15.2% / 3.0%</td>
<td>10.7% / 8.0% / 25.0% / 0%</td>
</tr>
</tbody>
</table>

TABLE 1: CP rates per IUI resulting in singleton, and CP per pregnancy for multiples
vent the development of severe OHSS and life-threatening complications. Additionally, utilizing freeze-all cycles to avoid pregnancy should be considered for these patients to decrease risk of OHSS and severe late complications.

O-70 Monday, October 8, 2018 11:30 AM

INDIVIDUALIZATION OF THE STARTING DOSE OF GONADOTROPIN REDUCES THE OVERALL OHSS RISK AND THE NEED OF PREVENTIVE INTERVENTIONS: CUMULATIVE DATA OVER THREE STIMULATION CYCLES. M. Fernandez-Sanchez,7 H. Visnova,5 A. A. Yuzpe,7 B. M. Klein,1 B. Mannaaerts,7 J. C. Arce.7 1IVIRMA Sevilla, Sevilla, Spain; 2IVF CUBE, SAR CGPS, Prague, Czech Republic; 3Olive Fertility Centre, Vancouver, BC, Canada; 4Ferring Pharmaceuticals, Copenhagen, Denmark; 5Ferring Pharmaceuticals, Parsippany, NJ.

OBJECTIVE: To evaluate the impact of individualized dosing with follitropin alfa in sequential controlled ovarian stimulation (COS) cycles as a preventive strategy for OHSS risk.

DESIGN: A combined analysis of two large comparative Phase 3 trials of follitropin delta.

MATERIALS AND METHODS: Secondary analysis of three stimulation cycles in IVF/ICSI patients included in a randomized, assessor-blinded trial comparing two recombinant FSH preparations (ESTHER-1, NCT01956110), and undergoing up to two additional COS cycles while maintaining the same treatment allocation and the assessor-blinded design (ESTHER-2, NCT01956123). A total of 1326 women were randomized in COS cycle 1 and treated with follitropin delta (Rekolve®) or follitropin alfa (Gonal-F®). Of these, 513 continued to cycle 2 and 188 to cycle 3. In COS cycle 1, the individualized follitropin delta dosing regimen was a fixed daily dose determined by serum AMH and body weight, and the conventional follitropin alfa dosing regimen was 150 IU for the first 5 days after which the daily dose could be adjusted. In COS cycles 2 and 3, the FSH doses were maintained or adjusted according to the ovarian response in the previous cycle.

RESULTS: Individualized dosing with follitropin delta resulted in a significant decrease in moderate/severe OHSS and/or preventive interventions (OR=0.59 [0.38; 0.92], p=0.018) compared to conventional dosing approach with follitropin alfa in patients undergoing up to three COS cycles. The greatest benefit was observed in the patients in the highest AMH quartile (≥ 25.5 pmol/L; OR=0.47 [0.26; 0.86]; p=0.012). When evaluating OHSS cases and the preventive interventions separately, individualized dosing with follitropin delta was associated with a significantly lower incidence of moderate/severe OHSS (OR=0.50 [0.26; 0.97], p=0.036) and a significantly lower incidence of preventive interventions (OR=0.56 [0.31; 0.99], p=0.044), mainly GnRH agonist triggering with no fresh transfer, compared to the conventional dosing approach with follitropin alfa. Across the three cycles, two women were hospitalized due to OHSS in the individualized follitropin alfa dosing group compared to eight in the conventional follitropin alfa dosing group.

O-71 Monday, October 8, 2018 11:45 AM


OBJECTIVE: To compare the cumulative live birth rate after treatment with highly purified-human menotropin (HP-hMG; Menopur®) or recombinant follicle stimulating hormone (rFSH; Gonal-F®) in predicted high responder women undergoing assisted reproductive technology.

DESIGN: Multicenter, randomized, open-label, assessor-blind, non-inferiority study.

MATERIALS AND METHODS: Ovulatory women aged 21-35y with BMI 18-30 kg/m² and serum anti-Müllerian hormone (AMH) ≥ 5 ng/mL (N=620) were randomized 1:1 to a 150 IU start dose of HP-hMG or rFSH in a GnRH antagonist cycle. Human chorionic gonadotropin (hCG) was used to trigger oocyte maturation (GnRH agonist if at high risk of ovarian hyperstimulation syndrome [OHSS]). Oocytes were fertilized by intracytoplasmic sperm injection. Day 5 trophectoderm biopsies were performed for preimplantation genetic screening (PGS), the results of which could be used to guide blastocyst selection for frozen transfers only. Fresh transfer of a single, best quality blastocyst selected by morphology was performed in hCG-triggered cycles; all embryos were frozen if the risk of OHSS was high. Live birth outcomes resulting from all fresh and any frozen transfers occurring within 6 months of randomization were collected.

RESULTS: Demographics for the HP-hMG and rFSH arms were similar (mean patient age: 30y for both; mean [SD] BMI: 24.4 [3.3], 24.3 [3.4] kg/m²; AMH: 7.8 [3.6], 7.5 [2.4] ng/mL; antral follicle count: 30.5 [15.5], 31.0 [12.2]). The average number of oocytes retrieved in the rFSH arm (22.2 [11.54]) was higher than in the hMG arm (15.1 [10.12]). However, the cumulative live birth rate was similar. This may be explained by higher early pregnancy loss rates in the rFSH arm in both fresh and frozen cycles, suggestive of differences in embryo quality between groups. The higher ovarian response in rFSH treated patients did not appear to confer benefit and was further associated with an increased incidence of ovarian hyperstimulation syndrome (OHSS).

CONCLUSIONS: MEGASET HR revealed key differences in treatment related outcomes in predicted high-responder patients creating an opportunity for improvement in care.

TABLE 1.

<table>
<thead>
<tr>
<th>Parameters, n (%) [95% CI]</th>
<th>HP-hMG</th>
<th>rFSH</th>
<th>Difference vs rFSH [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live birth rate, fresh transfer per cycle start</td>
<td>33.9% (105/310)</td>
<td>30.1% (93/309)</td>
<td>3.8% [-3.6, 11.1]</td>
</tr>
<tr>
<td>Live birth rate per fresh transfer</td>
<td>52.2% (105/201) [45.1, 59.3]</td>
<td>48.7% (93/191) [41.4, 56.0]</td>
<td>4.4% [-2.4, 11.2]</td>
</tr>
<tr>
<td>OHSS</td>
<td>9.7% (30/310)</td>
<td>21.4% (66/309)</td>
<td>-11.7% [-17.3, -6.1]</td>
</tr>
<tr>
<td>Live birth rate for frozen cycle 1</td>
<td>57.3% (47/82) [45.9, 68.2]</td>
<td>45.4% (59/130) [36.6, 54.3]</td>
<td>11.9% [4.2, 20.1]</td>
</tr>
<tr>
<td>Live birth rate for frozen cycle 2</td>
<td>62.5% (5/8) [24.5, 91.5]</td>
<td>50.0% (6/12) [21.1, 78.9]</td>
<td>-12.6% [-39.1, 13.9]</td>
</tr>
<tr>
<td>Cumulative live birth rate for frozen cycles</td>
<td>63.4% (52/82) [52.0, 73.8]</td>
<td>50.8% (66/130) [41.9, 59.6]</td>
<td>-12.6% [-32.3, 7.3]</td>
</tr>
<tr>
<td>Cumulative live birth rate (frozen + fresh)</td>
<td>50.6% (157/310) [44.9, 56.3]</td>
<td>51.5% (159/309) [45.7, 57.2]</td>
<td>-0.8% [-8.7, 7.1]</td>
</tr>
<tr>
<td>Early pregnancy loss, fresh cycle</td>
<td>42/121 (34.7%)</td>
<td>42/121 (34.7%)</td>
<td>-0.8% [-8.7, 7.1]</td>
</tr>
<tr>
<td>Early pregnancy loss frozen cycle 1</td>
<td>14.0% (8/57) [6.3, 25.8]</td>
<td>29.8% (25/84) [20.3, 40.7]</td>
<td>-15.0% [-29.2, -0.4]</td>
</tr>
<tr>
<td>Early pregnancy loss frozen cycle 2</td>
<td>16.7% (1/6) [0.4, 64.1]</td>
<td>22.2% (2/9) [2.8, 60.0]</td>
<td>-5.5% [-23.3, 12.3]</td>
</tr>
</tbody>
</table>

CI, confidence interval; hCG, human chorionic gonadotropin; OHSS, ovarian hyperstimulation syndrome. *Two positive β-hCG tests but no ongoing pregnancy 8-9 weeks after fresh transfer.

FERTILITY & STERILITY® e31
HIGH SERUM ESTRADIOL LEVEL ON THE DAY OF HCG TRIGGER IS ASSOCIATED WITH SMALL FOR GESTATIONAL AGE INFANTS: A RETROSPECTIVE COHORT STUDY.

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OBJECTIVE: Investigate whether high serum estradiol (E2) level on the day of HCG trigger is associated with small for gestational age (SGA) of singleton birth via IVF/ICSI.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: Patients with singleton pregnancies with delivered after transfer of fresh embryos, including Day-3 and Day-5 embryos, during the period of July 2008 to September 2016 at our center were included. Only patients aged 35 years or younger, cycle days -2/3 FSH<10 mIU/ml, AMH>1 ng/ml were included. The cycles with multiple births, vanishing twins, donor oocytes were excluded. A total of 2143 cycles met the criteria. According to E2 level on trigger day, we divided all patients into 6 groups. E2<2000 ng/l (referent group), E2:2001-3000 ng/l, E2:3001-4000 ng/l, E2:4001-5000 ng/l, E2:5001-6000 ng/l, E2>6000 ng/l. The primary outcome measure was SGA. The second outcome measures were low birthweight (LBW), preterm birth, full-term LBW. We compared the odds ratio of SGA, LBW, preterm birth and full-term LBW between the groups. Than multivariable logistics regression was used to analysis whether these outcome measures could be explained by the E2 level.

RESULTS: The median age, BMI, E2 level, neonatal birthweight for the cohort study was 28 (26-31) years, 22.0 (20.2-24.1) kg/m2, 3242 (2288-4662) ng/l, 3300 (3000-3600) g, respectively. SGA increased with increasing E2 levels. The incidence proportion of SGA, LBW, preterm birth and full-term LBW of singleton birth via fresh embryo transfer of increasing E2 levels. Odds of SGA,LBW and full-term LBW with increasing E2 levels were: OR(95%CI)=1 0.87 (0.46-1.66) 1.13 (0.59-2.18) 1.79 (1.13-3.33) 1.91 (1.06-3.54) 2.34 (1.36-4.02)


PREIMPLANTATION GENETIC TESTING 1

O-73 Monday, October 8, 2018 10:45 AM

COMPARISON OF TWO DIFFERENT NEXT GENERATION SEQUENCING (NGS) SYSTEMS, VERISEQ WITH WHOLE GENOME AMPLIFICATION AND FAST-SEQS WITH PCR FOR PREIMPLANTATION GENETIC TESTING FOR ANEUPLOIDY (PGT-A).


OBJECTIVE: VeriSeq with whole genome amplification (VeriSeq) and FAST-SeqS with PCR (FAST-SeqS) are two different methods of PGT-A and the former is reported as a more sensitive method for determination of aneuploidy including mosaicism. Here we compared the two PGT-A methods to determine if these would affect clinical outcome.

DESIGN: Retrospective study by a private IVF center.

MATERIALS AND METHODS: 2,121 blastocysts from 414 cases were biopsied and NGS performed by VeriSeq or FAST-SeqS method. Preimplantation genetic diagnosis (PGD) cycles were excluded. All blastocysts were vitrified after trophectoderm biopsy. Endometrial thickness was measured at day 12 of frozen embryo transfer (FET) cycle. For pregnancy outcome, 367 FET cycles were analyzed. The statistical analysis was performed using t-test, chi-square test or z-test. A p-value of <0.05 was considered statistically significant.

RESULTS: 1,200 blastocysts biopsy from 233 cases and 921 blastocysts biopsy from 181 cases were tested by VeriSeq and FAST-SeqS, respectively. Average age of patients was not significantly different. No call rate of biopsy was not different (1.4%). Euploid rate of VeriSeq was significantly lower than that of FAST-SeqS (50.7% vs 63.0%, p=0.0028) and mosaicism rate of VeriSeq was significantly higher than that of FAST-SeqS (8.8% vs 4.0%, p<0.0001). Partial (segmental) aneuploidy rate was not significantly different (8% vs 7%). Pregnancy outcomes were summarized in Table 1. The euploid rate was lower and the mosaicism rate was higher with VeriSeq. However, this had no effect on numerous markers of clinical success in IVF including ongoing pregnancy/live birth rates.
the result is not significantly different


OBJECTIVE: To analyze embryo culture metrics with regard to absolute measures (chromosome ploidy by NGS-PGS, age of oocyte) and trends (embryo age, embryo grade, egg donor recipient).

DESIGN: A single-center, retrospective, observational study.

MATERIALS AND METHODS: Oocyte retrieval was performed 34 hours after trigger under ultrasound guidance. After retrieval, the oocytes were denuded mechanically by pipetting with cumulase (Origio, enzyme activity 40-120 U/ml). ICSI was performed on all metaphase II oocytes. Fertilized oocytes were cultured in microdroplets of culture media (Vitrolife) overlaid with Ovol (Vitrolife), gassed with a blood gas mixture (WestAir Gases, 5% oxygen, 7.2% carbon dioxide, balanced nitrogen), until the day of assisted hatching (day 3 of embryo culture). Assisted hatching was performed and embryos were subsequently transferred to fresh culture medium. Embryos were assessed for blastocyst development, biopsy and cryopreservation criteria on days 5, 6, and 7. Blastocysts that met the criteria, either good (distinct inner cell mass (ICM)/numerous trophectoderm (TE) cells) or fair (ICM/TE cells) were biopsied and cryopreserved. All genetic analysis was performed by Ovation Fertility Genetics (Las Vegas) using Next Gen Sequencing.

RESULTS: 2557 blastocysts from 257 cycles were analyzed in the present study. A total of 1179 on Day 5, 1289 on day 6, and 89 blastocysts at day 7 were biopsied and analyzed by NGS-PGS. On day 5 of culture 64% of embryos tested were euploid, 34% aneuploid. On day 6 of culture 49% of embryos were euploid and 49% aneuploid, and day 7 of culture, 46% of embryos tested were euploid and 52% were aneuploid. The chi-square statistic is 58.1 and is significant at p < .01, indicating that ploidy and length of time in culture are dependent variables.

CONCLUSIONS: Our optimized culture system routinely yields blastocysts that are good and fair quality on day 7, which did not meet our biopsy and cryopreservation criteria on day 5 or 6 of culture. In the present study, we retrospectively analyzed PGS data from day 5, 6, and 7 blastocysts derived from IVF patients in our clinic during 2017-2018, and analyzed trends in embryo development and ploidy. Our results (46% euploid blaston day 7) agree with the small, but growing body of evidence that suggests that extended embryo culture to day 7 is clinically important for patients who do not have day 5 and/or day 6 blastocysts. Additionally, we believe for patients with day 5 and/or day 6 blastocysts, day 7 culture may still be necessary, considering the time and costs of IVF cycles, particularly when constructing an IVF cycle with donor eggs.

References:
A COMPARISON OF DIAGNOSTIC RESULTS OF PREEMPTIVE GENETIC TESTING FOR ANEUPLOIDY (PGT-A) FROM REFERENCE LABORATORIES DURING A PERIOD OF TRANSITION: TRENDS AND INHERENCES FOR PATIENT CARE.


OBJECTIVE: To evaluate how results from two different reference laboratories performing PGT-A compared, with regards to euploidy, multiple aneuploidies and no amplification/call rates across two patient cohort groups.

DESIGN: A retrospective study investigating trophectoderm biopsy cases where PGT-A was performed. Next generation sequencing (NGS) platforms were used by both reference laboratories to provide a diagnosis from the biopsy material sent. Patient groups were stratified based on the maternal or “oocyte” age (egg donors) into the following groups with the number of embryos biopsied analyzed by each laboratory: <38 (368 vs. 395) and ≥38 (345 vs. 291).

MATERIALS AND METHODS: All mature oocytes retrieved were injected, cultured, biopsied, and vitrified individually following the IVF laboratory’s standard operating procedures. Results from biopsies were reported by the reference laboratories as euploid, aneuploid, multiple aneuploidies or “no diagnosis”. Overall rates were calculated for each patient group cohort and compared between laboratories and published results. A chi-square test with Bonferroni correction for multiple comparisons was used to establish significance (p < 0.01).

RESULTS: A total of 1399 trophectoderm biopsies (659 vs.740 laboratories 1 and 2 respectively) were included in this study. The euploid rates for each patient age group were as follows: <38 (55% vs.36%), ≥38 (32% vs. 18%) depicting an increase in the rates reported from laboratory 1 for both patient groups. Multiple aneuploidies were reported at a lower rate from laboratory 1 for both patient groups <38 (3% vs.11%), ≥38 (4% vs. 24%). With regards to the no diagnosis category the overall cumulative rate (across patient cohort) was 2.3% from laboratory 1 compared to 12.3% from reference laboratory 2. The differences for all diagnostic categories between laboratory 1 and 2 were statistically significant (p <0.01).

CONCLUSIONS: Higher euploidy rates, in combination with lower multiple aneuploidies and “no result” rates reported by laboratory 1 provided a larger cohort of embryos available for transfer. Further analysis of outcome data is needed to demonstrate whether higher euploidy rates equate to higher delivery rates with concurrent lower pregnancy loss rates. The significant differences between the two reference laboratories highlight the need for external quality assessment of PGT-A platforms. Practitioners should be cautious about applying PGT-A clinically before the availability of comprehensive and convincing evidence.

A NOVEL NEXT-GENERATION SEQUENCING-BASED ANEUPLOIDY SCREENING TECHNOLOGY: CAPTURING SINGLE-NUCLEOTIDE POLYMORPHISM DATA TO REDUCE THE TRANSFER OF POLYPLOID AND HAPLOID EMBRYOS.


OBJECTIVE: To report the prevalence of polyploid and haploid embryos as detected by FAST-SeqS.

DESIGN: Recent changes to our FAST-SeqS aneuploidy screening (PGT-A) platform now allows for the capture of single-nucleotide polymorphism (SNP) genotype information enabling the detection of all forms of triploidy (e.g., 69,XXX), other forms of polyploidy (e.g., 92,XXX), haploid/whole genome uniparental isodisomy (WG-UPiD), and many instances of single-chromosome UPiD, in addition to whole-chromosome and segmental aneuploidies. FAST-SeqS allows for correct classification of abnormalities previously misclassified, which is essential for decreasing molar pregnancy and miscarriage rates. Here, we report our clinical experience since the addition of polyploidy and UPiD to our PGT-A offering.

MATERIALS AND METHODS: Trophectoderm biopsies from >15,700 embryos were analyzed using our recently refined assay. FAST-SeqS has been validated for detecting whole-chromosome and segmental aneuploidies (≥10 MB) and, more recently, validated to accurately capture and analyze data from ~10,000 polymorphic sites to identify WG-UPiD. All forms of triploidy, and many instances of single chromosome UPiD. Results were stratified by oocyte age, clinical indication, and fertilization type.

RESULTS: In 15,747 embryos tested, we identified 233 polyploid and WG-UPiD embryos (1.5% of all tested embryos) across all age groups (20-45 years old) and clinical indications. Interestingly, 18 patient cycles had more than one polyploid/WG-UPiD embryo, 4 of which were egg donor cycles.

There was an age-related increase in triploidy (n = 184), but not WG-UPiD (28) or tetraploidy (21). There was no correlation with clinical indication. Limited single-chromosome UPiD abnormalities were detected. Of the 184 triploid embryos, 51.1% were 69,XXX, 45.7% were 69,XXY, 1.6% were 69,XY, and 1.6% were sex chromosome mosaics. Of the tetraploid embryos 52% were 92,XXXX, 9 (4.3%) were 92,XXXY, and 1 (5%) was a sex chromosome mosaic. Twenty seven percent (63/233) of polyploid embryos had one or more additional copy number abnormalities. Without SNP-based ploidy calls, these additional aneuploidies would likely have been classified as mosaic. Of those cases where fertilization method was indicated, intracytoplasmic sperm injection was performed in 88.4% of the triploid and 100% of the tetraploid and WG-UPiD embryos.

CONCLUSIONS: Preventing transfer of chromosomally abnormal embryos is essential to improving PGT-derived pregnancy outcomes. Without our specific enhancements, in a ~3-month period, 127 embryos would have most likely been incorrectly classified as euploid or mosaic using other NGS-based technologies and if transferred, may have resulted in a miscarriage or molar pregnancy.

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A NOVEL NEXT-GENERATION SEQUENCING-BASED ANEUPLOIDY SCREENING TECHNOLOGY: CAPTURING SINGLE-NUCLEOTIDE POLYMORPHISM DATA TO REDUCE THE TRANSFER OF POLYPLOID AND HAPLOID EMBRYOS.


OBJECTIVE: To report the prevalence of polyploid and haploid embryos as detected by FAST-SeqS.

DESIGN: Recent changes to our FAST-SeqS aneuploidy screening (PGT-A) platform now allows for the capture of single-nucleotide polymorphism (SNP) genotype information enabling the detection of all forms of triploidy (e.g., 69,XXX), other forms of polyploidy (e.g., 92,XXX), haploid/whole genome uniparental isodisomy (WG-UPiD), and many instances of single-chromosome UPiD, in addition to whole-chromosome and segmental aneuploidies. FAST-SeqS allows for correct classification of abnormalities previously misclassified, which is essential for decreasing molar pregnancy and miscarriage rates. Here, we report our clinical experience since the addition of polyploidy and UPiD to our PGT-A offering.

MATERIALS AND METHODS: Trophectoderm biopsies from >15,700 embryos were analyzed using our recently refined assay. FAST-SeqS has been validated for detecting whole-chromosome and segmental aneuploidies (≥10 MB) and, more recently, validated to accurately capture and analyze data from ~10,000 polymorphic sites to identify WG-UPiD. All forms of triploidy, and many instances of single chromosome UPiD. Results were stratified by oocyte age, clinical indication, and fertilization type.

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CONCLUSIONS: Preventing transfer of chromosomally abnormal embryos is essential to improving PGT-derived pregnancy outcomes. Without our specific enhancements, in a ~3-month period, 127 embryos would have most likely been incorrectly classified as euploid or mosaic using other NGS-based technologies and if transferred, may have resulted in a miscarriage or molar pregnancy.

O-77 Monday, October 8, 2018 11:45 AM

VALIDATION OF SIMULTANEOUS DIAGNOSIS OF SINGLE GENE DISORDER (SGD) AND NEXT GENERATION SEQUENCING (NGS) - BASED COMPREHENSIVE CHROMOSOMAL ANEUPLOIDY SCREENING (CCS) FROM A SINGLE TROPHECTODERM (TE) BIOPSY.

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OBJECTIVE: We previously established a concurrent methodology of SGD pre-implantation genetic screening (PGD) and CCS using quantitative real-time (q)PCR from the same TE biopsies, which resulted in excellent clinical outcomes. To improve the accuracy of CCS and reduce the cost, we switched the CCS platform from qPCR to NGS. This study sought to validate our simultaneous testing SGD and CCS based on NGS from a single TE biopsy.

DESIGN: Blinded.
MATERIALS AND METHODS: Phase I-Reliability Analysis: Fibroblasts were isolated as 5-cell samples to mimic TE biopsies, and followed by multiplex-amplification with primers of NGS CCS and 40 SNPs with high minor allele frequencies. The allele drop out (ADO) and amplification failure (AF) rates were assessed by comparing to genotypes of isolated genomic DNA using Taqman genotyping assays. Phase II-Analysis of TE biopsies: Two TE biopsies were obtained from 10 aneuploid embryos, which were contributed by four patients with previous SGD and qPCR CCS results. Workups involved identifying informative SNPs in the parents using SNP arrays and phasing the markers using qPCR on family members.

RESULTS: Phase I: Twenty four 5-cell samples showed 0.74% ADO rate (8/1080), and 0% AF rate (0/1920), which demonstrated the reliability of the targeted amplification of the 40 SNPs with NGS CCS amplicons. Phase II: TE biopsies of 10 embryos from 4 cases, including autosomal or X-linked, recessive or dominant disorders, were tested with mutation and linkage asays with 0% ADO rate (0/176) and 0% AF rate (0/348). The SGD results were consistent with the previous PGD diagnosis.

CONCLUSIONS: This approach to combined CCS and SGD PGD provides the ability to reliably produce accurate SGD PGD results in parallel with NGS based CCS from the same biopsy.

O-78 Monday, October 8, 2018 12:00 PM

THE APPLICATION OF NEXT GENERATION SEQUENCING (NGS) FOR CLINICAL EXOMES WITHIN AN IN VITRO FERTILIZATION (IVF) SETTING. K. C. Cayton Vaughn, L. Pastore, M. S. Christianson, J. H. Segars, A. K. Dubey, W. G. Kearns. Department of Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Baltimore, MD; bStony Brook Medicine, Charlottesville, VA; cNorth Carolina IVF Labs, Fayetteville, NC; dGenetics, AdvanGenix and Johns Hopkins Med, Rockville, MD.

OBJECTIVE: To determine the clinical application of family-designed, whole exome sequencing (WES) for couples with a history of fetal or neonatal demise, within an IVF setting. To date, there are no reported studies investigating the role of NGS to identify potential pathogenic variants within embryos that could contribute to genetic disorders with high morbidity and mortality. We sought to determine the clinical validity of performing WES to identify pathogenic variants that may contribute to severe genetic disease in future offspring.

DESIGN: Prospective clinical WES study.

MATERIALS AND METHODS: In 5 couples undergoing IVF, clinical WES was first performed on their genomic DNA and then on amplified DNA from trophoderm cells from their embryos. The NGS technology employed for the Clinical Exome uses an S5 (Thermo-Fisher, South San Francisco, CA.) that provided over 75 million reads with a median sequencing fragment length of 191 bp. A molecular library was prepared from 50 to 100 ng of DNA. After quantification, a pool of primer pairs was used to amplify the coding sequences of all genes. A template-positive PCR. Additionally, LSC’s, upon treatment with Vismodigib and SAG signalling impact on graft differentiation, LSC’s in-vitro were treated with Vismodigib (Hedgehog inhibitor) and SAG (agonist). Expression of markers of DHH and LSC differentiation was evaluated by qRT-PCR. Additionally, LSC’s, upon treatment with Vismodigib and SAG were subsequently autografted in mice for 4 weeks.

RESULTS: Four weeks after subcutaneous autograft of LSCs in combination with Sertoli and myoid cells in castrate mice, the cells in graft expressed 3B-HSD, SOX-9 and α-SMA. Serum T levels were significantly higher in mice receiving grafts (22.4±1.9 VS 11.9±0.8 ng/DL, p<0.05). Importantly, mice receiving autograft maintained LH and FSH levels higher than mice that received T pellet implant (LH 3.09±1.47 VS 0.01±0.01 ng/ml) (FSH 102.6±28.1 VS 51.7±7.4ng/ml) respectively. Furthermore, T levels consistently increased at 15, 30 and 60 days following subcutaneous autograft (12.01±0.87ng/DL (neg CTL) vs 15.1±1.50ng/DL (15 days Autograft) vs 22.26±1.33ng/DL (30 days Autograft) vs 37.3±9.6ng/DL (60 days Autograft)), demonstrating differentiating LSC within the autograft. In addition, levels of 3BHS were induced upon SAG (DHH inducer) treatment in-vitro conditions. Immunostaining autografts (4 weeks), containing Sertoli and myoid cells, showed significant expression of SOX9, and α-SMA establishing Hedgehog signaling role in graft survival and LSC differentiation.

CONCLUSIONS: This study is the first to demonstrate that LSCs, when subcutaneously autografted in combination with Sertoli cells and myoid cells, can increase testosterone production without affecting HPG axis under the regulation of hedgehog signaling.

References: na

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FERTILITY & STERILITY®
O-80 Monday, October 8, 2018 11:00 AM
COMPARING THE CELLULAR PHENOTYPE OF NAÏVE AND PRIMED HUMAN EMBRYONIC STEM CELLS. 
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OBJECTIVE: Human embryonic stem cells (hESCs) exist in two different states of pluripotency, naïve and primed, which represent the earlier human blastocyst stage and the more advanced epithelial-like stage, respectively. Naïve hESCs differ from primed cells in their typical colonies morphology and their tolerance to single-cell passaging. These and other phenotypic differences may facilitate culture of naïve cells, conferring a practical advantage for their use in cell transplantation. The aim of the current study was to compare the cellular phenotype of naïve and primed hESCs.
DESIGN: A laboratory study using hESCs.
MATERIALS AND METHODS: Four hESC lines were included in this study: Lis 38_N, Lis 39_N, Lis 45_N and Lis 46_N, all of which were derived and cultured in naïve conditions. After 20 passages, half of the naïve cells were transferred to primed conditions, while the other half continued to grow under naïve conditions. After 10 additional passages, each sub-culture was confirmed as naïve or primed by the expression of naïve markers using qRT-PCR and immunofluorescence. Then each sub-culture was phenotypically characterized for cell proliferation using doubling time assay, cell cycle distribution using EdU incorporation during the S-phase and FACS analysis, and clonogenicity by low-density plating followed by alkaline-phosphatase staining.
RESULTS: All hESC lines were characterized as pluripotent by RT-PCR and immunofluorescence for pluripotency markers. Naïve hESCs that were converted to primed expressed significantly decreased mRNA levels of the naïve markers Klf4/17, TFCP2L1 and STELLA, compared to their naïve counterparts (p<0.05). While naïve cells exhibit nuclear staining for TFE3, converted primed cells displayed cytoplasmic staining. The doubling time of naïve cells (18.1±3.99) was significantly shorter than that of primed cells (33.7±7.15) (p=0.01). Respectively, significantly higher fraction of cells in S-phase was detected in naïve cells (45.3±2.1) compared with primed cells (35.4±2.9) (p<0.005). Additionally, naïve cells displayed a ~1.7-fold higher cloning efficiency from a single cell (39.8±3.5%) compared to primed cells (23.1±4.8) (p<0.05).
CONCLUSIONS: Our results indicate that naïve hESCs have higher proliferation rate and survived better under stress conditions compared to primed cells. These phenotypic characteristics suggest that naïve hESC may be favorable for practical applications than primed hESC.

O-81 Monday, October 8, 2018 11:15 AM
EVALUATION OF PARACrine FACTORS CRITICAL FOR HUMAN LEYDIG STEM CELL FUNCTION.
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OBJECTIVE: Impaired testosterone production as a result of Leydig cell loss or dysfunction can occur in men with testicular failure. Although several testosterone formulations are available, none are capable of replicating the physiological pattern of testosterone secretion. We have shown in our recent study conducted in murine models that, Leydig stem cell transplantation, along with peritubular myoid cells and Sertoli cells could be used to physiologically increase serum testosterone thereby potentially minimizing the adverse effects. However, in order to optimize the function of Leydig stem cells, we need to understand the paracrine factors released by myoid and Sertoli cells. In the present study we evaluated the significance of paracrine factors secreted by human peritubular myoid cells and Sertoli cells on Leydig stem cell function.
DESIGN: A total of 5 men with testicular failure underwent testis biopsies for sperm retrieval. Using an IRB approved protocol, about 10mg of testicular tissue from each of these men were processed for Leydig stem cell isolation, culture and characterized.
MATERIALS AND METHODS: The presence of Leydig stem cells (LSCs), Sertoli cells (SCs) and peritubular myoid cells (PMCs) in the harvested cellular pool was validated by immunofluorescence and quantitative real time PCR (qPCR) using PDGFR-α, 3βHSD and Sox-9, PZLF, respectively. Further stimulation by Luteinizing hormone (LH), the levels of 3βHSD mRNAs were increased. Additionally, the CD133 (+) cells representing LSCs were sorted using MACS kit and maintained along with unsorted cells in charcoal stripped medium. Condition media was collected from both the cell types and screened for secreted protein using RayBio Human Antibody Array for a total of 80 molecules.
RESULTS: We successfully isolated and cultured LSCs from all 5 testis biopsies. We were able to culture up to ~ 3 X 10^6 million cells / biopsy. Of the cells cultured, up to 70% of the cells were Leydig stem cells and 10% of them were Sertoli-cell in origin on day 14. IF and qPCR data showed as the majority of cell population was undifferentiated (PDGFR-α). Upon stimulation by LH, the expression of 3βHSD (mature Leydig cells) was increased and that of PDGFR-α was decreased. Importantly, human antibody protein array demonstrated increased expression of IL-6, CCL2 and TIMP2 in the media of LSC’s that were co-cultured with Sertoli cells and myoid cells compared to the media from purified LSCs cultures (CD133 positive).
CONCLUSIONS: Our results indicate that LSCs can be isolated and cultured from men with testicular failure. There are specific paracrine factors which are released by adjacent Sertoli and myoid cells which could be critical for LSC differentiation and testosterone production. Further studies are ongoing to validate the implications of these paracrine factors in terms of their role in LSCs function, differentiation and survival.

References: NA
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O-82 Monday, October 8, 2018 11:30 AM
BONE MARROW-DERIVED ENDOMETRIAL CELLS EXPRESS ANDROGEN RECEPTOR.
OBJECTIVE: An important role for androgens in regulating endometrial proliferation and decidualization has very recently emerged. In addition, recent data demonstrate that bone marrow (BM) is a long-term source of multiple parenchymal endometrial cell types. Whether endometrial cells of bone marrow origin express androgen receptor has not been previously studied. Thus, the objective of the current study was to determine whether bone marrow-derived endometrial cells express androgen receptor (AR).
DESIGN: Immunohistochemistry performed in uterine tissues from murine recipients of bone marrow transplant.
MATERIALS AND METHODS: The current study used tissues harvested in previously performed murine BM transplant experiments, in which BM cells harvested from transgenic mice which ubiquitously express Green Fluorescent Protein (GFP) were transplanted via tail vein into irradiated syngeneic female mice. BM recipients with successful hematopoietic reconstitution were hysterectomized at 12 months (n=5 animals). Immunohistochemistry was performed in uterine tissue sections of recipient mice using specific anti-AR, anti-GFP, and anti-CD45 primary antibodies. The pan-leukocyte marker CD45 was used to distinguish hematopoietic (CD45+) from nonhematopoietic (CD45-neg) endometrial cells of BM origin. Nuclei were stained with 4’,6-diamidino-2-phenylindole (DAPI). Confocal laser microscopy was used to localize and quantify BM-derived (GFP+) cells in the endometrial parenchymal cellular compartments and to determine whether BM-derived endometrial stromal and epithelial cells express AR. Three uterine sections from each recipient animal (n=5), using 4-5 high power fields per section, were assessed. Data are expressed as mean ± SEM cell number per animal.
RESULTS: In the endometrial stromal compartment, the mean number of cells counted was 4271.6 ± 178.4 (n=5 animals), of which 40.8% ± 3.5% express AR. BM-derived (GFP+) cells comprised 13.8% ± 2.8% of cells in this compartment, of which 92% ± 3.5% were nonhematopoietic (CD45-neg) stromal cells. 24.2% ± 12.7% of BM-derived, nonhematopoietic (CD45-neg) endometrial stromal cells expressed AR. In contrast to the
stromal compartment, BM-derived cells comprised only 0.3% ± 0.1% cells in the LE compartment and 1.0% ± 0.2% of cells in the GE compartment. Of the few epithelial compartment cells derived from BM, 11.2% ± 8.1% in the LE and 39.9% ± 17.9% in the GE were nonhematopoietic, BM-derived epithelial cells.

CONCLUSIONS: BM-derived cells engraft the endometrial stromal compartment to a much greater degree than the epithelial compartments, implicating a potential role for these cells in decidualization. That a substantial number of BM-derived endometrial stromal cells express AR supports a role for these cells in androgen-regulated endometrial functions, such as proliferation and/or decidualization.

Supported by: Funding for this work was provided by the American Association of Obstetricians and Gynecologists Foundation.

O-83 Monday, October 8, 2018 11:45 AM

BONE MARROW TRANSPLANTATION RESTORES DECIDUALIZATION IN INFERTILE HOXA11 KNOCKOUT MICE. R. Tul,a S. Shaikh,a R. Mamillapalli,a H. S. Taylor,b Obstetrics, Gynecology & Reproductive Sciences, Yale School of Medicine, New Haven, CT; Ob/Gyn, Yale University School of Medicine, New Haven, CT; Yale School of Medicine, New Haven, CT.

OBJECTIVE: The decidua is a transient uterine tissue shared by mammals with hemochorial placenta and is essential for pregnancy. Hoxa11 knockout (KO) mice are infertile having endometrial stromal cell defects resulting in lack of decidualization and implantation failure. Since bone marrow (BM)-derived cells (BMDC) were shown to differentiate into non-hematopoietic endometrial cells, we hypothesized that bone marrow transplantation from wild-type (WT) mice may rescue uterine defects in Hoxa11 KO mice.

DESIGN: Animal study.

MATERIALS AND METHODS: We utilized 5-fluorouracil-based non-gonadotoxic bone marrow transplant (BMT) regimen to transplant BM from either WT or Hoxa11 KO donors into Hoxa11 KO recipient mice. WT mice which underwent BMT from WT donors served as controls (n=12-15/group). Following 1 month of recovery post-BMT, transplanted mice were mated with proven males and reproductive performance was evaluated. Mice were sacrificed on ED5.5 and implantation sites were assessed for decidualization signs and markers by histology, immunohistochemistry, immunofluorescence and qPCR.

RESULTS: BMT from WT into KO mice (KO-WT) resulted in stromal expansion and gland formation, otherwise absent in KO mice receiving BMT from KO (KO-KO). Despite lack of normal implantation sites and no litters in the Hoxa11 KO mice, areas of increased swelling and vascularization in the uterus were observed on ED5.5 only in KO-WT mice. Histological analysis of uterine sections on ED5.5 from KO-WT revealed significant decidual reaction, while no reaction was observed in KO-KO. Immunohistochemical analysis of implantation sites for progesterone receptor revealed prominent expression in the decidua of KO-WT uteri similar in extent to the WT-WT mice. In contrast, PR expression was significantly reduced in the uteri of KO-KO, consistent with impaired decidualization. Immunostaining for PCNA demonstrated extensive cell proliferation in the KO-WT, in contrast to KO-KO uteri which were largely devoid of proliferation. In addition, CD31 staining revealed increased decidual blood vessel area (p<0.01) in KO-WT vs. KO-KO, consistent with increased decidualization. Western blot demonstrated Hoxa11 protein expression in uteri of KO-WT mice, but was absent in KO-KO mice. Moreover, the implantation-related genes MSX-1 (1.6-fold), prolactin (7.4-fold) and LIF (3.1-fold) were significantly upregulated in uteri of WT-KO as compared to KO-KO mice (p<0.05 for all genes). Immunofluorescence analysis of implantation sites demonstrated the presence of Hoxa11-expressing cells which were non-hematopoietic (CD45-negative) stromal cells in the KO-WT group but not the KO-KO group.

CONCLUSIONS: BMDCs can affect gene expression at the uterine implantation site leading to profound effects on decidualization as evidenced by promotion of decidual differentiation, cell proliferation and angiogenesis.

Supported by: NICHD R01HD076422; Ferring/New England Fertility Society grant; American Society for Reproductive Medicine.

O-84 Monday, October 8, 2018 12:00 PM

TRANSSCRIPTOME ANALYSIS OF ENDOMETRIAL STROMA-LIKE CELLS DERIVED FROM HUMAN INDUCED PLURIPOTENT STEM CELLS IDENTIFIES POTENTIAL ENDOMETRIAL STEM CELL MARKER. B. D. Yilmaz,* K. Miyazaki,* S. Bulun, Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine, Chicago, IL.

OBJECTIVE: The endometrium is known to undergo regeneration with each menstrual cycle, and stem cells are the source of this regeneration. Our group recently established a 14-day protocol, which enables in vitro differentiation of human induced pluripotent stem cells (hiPSC) into progesterone-responsive endometrial stroma-like cells. The objective of this study is to identify a novel cell surface marker for isolation and characterization of endometrial stromal endothelial cells based on our endometrial differentiation model.

DESIGN: Prospective experimental design.

MATERIALS AND METHODS: Transcriptome analysis was performed on RNA-Sequencing (RNA-Seq) data (unpublished data) to find differentially expressed cell surface markers during hiPSC differentiation. The results of RNA-seq at various differentiation points (day 0; hiPSCs, day 4: intermediate mesoderm, day 6: coelomic epithelium, day 8: Mullerian duct, day 14: endometrial stroma) were confirmed by RT-qPCR.

RESULTS: Analysis of RT-qPCR confirmed transcriptome data over the course of differentiation revealed that mRNA levels of FGFR2 peaked at day 8 and robustly decreased at day 14. This expression pattern was similar to that of typical endometrial mesenchymal stromal cell marker SUSD2, with maximal expression at Mullerian duct (MD) stage and a robust decline on day 14. The similarities in the mRNA expression profile, as well as the role of FGFR2 in embryonic development and stem cell maintenance, led us to hypothesize that FGFR2 could be a novel stem cell marker for the endometrial stroma. Immunohistochemistry staining showed that FGFR2 protein is located in the perivascular region of the endometrial stroma and is more frequently expressed in the basalis portion. FGFR2(+)-cells compose 2.35% (1.79-2.82%) of the stroma enhanced portion of the endometrium.

CONCLUSIONS: FGFR2(+) cells have a stem cell-like phenotype with decreased expression of mature tissue markers and increased expression of early differentiation markers. Isolation of FGFR2(+) cells can help characterization of endometrial stem cells and investigation of their role in gynecologic diseases such as endometriosis.

Supported by: National Institutes of Health grant R37-HD36891, USA.

REPRODUCTIVE SURGERY AND PROCEDURES

O-85 Monday, October 8, 2018 10:45 AM

IN VIVO AND EX VIVO ASSESSMENT OF THE VASCULAR SUPPLY TO THE FALLOPIAN TUBES DURING LAPAROSCOPIC HYSTERECTOMY FOR FUTURE APPLICATION IN UTERINE TRANSPLANTATION. S. Farag,* F. Prazzini Padilla,° K. A. Smith,* R. Flyckt,† M. L. Sprague,‡ S. E. Zimberg,* "Minimally Invasive Gynecologic Surgery, Cleveland Clinic Florida, Weston, FL; *Cleveland Clinic, Cleveland, OH.

OBJECTIVE: To evaluate the perfusion of the fallopian tubes using laser angiography with indocyanine green (ICG) in ex vivo and in vivo uteri at the time of total laparoscopic hysterectomy (TLH) with bilateral salpingectomy.

DESIGN: Pilot experimental study.

MATERIALS AND METHODS: This study was approved by the Institutional Review Board of Cleveland Clinic Florida. Fifteen women aged 18
years or greater underwent TLH with bilateral salpingectomy for benign indications. In five uteri, the uterine-ovarian artery was cannulated and injected with ICG. The fallopian tubes were imaged using laser angiography. The ten other participants underwent the ex vivo protocol. After transection of the mesosalpinx and the uterine vessels (partial protocol), laser angiography with ICG was utilized to image the fallopian tubes. Five patients underwent colpotomy prior to imaging (complete protocol).

RESULTS: Ex vivo, the fimbria of the ipsilateral fallopian tube had a 47% relative fluorescence as compared to the contralateral fallopian tube, which only had 2.4% relative fluorescence. In vivo, the post-ICG fluorescence intensity ratios were .61 ± .40 (about 61% of the tubal length) for the partial protocol, and .78 ± .30 (about 78% of the tubal length) for the complete protocol, with mean differences of .37 (95% CI 23.50, p < .0001) and .22 (95% CI 12.31, p < .0001), respectively. Most (60%, 12 of 20 individual tubes) fallopian tubes had greater than .75 fluorescence intensity ratios, or greater than 75% tubal length fluorescence.

CONCLUSIONS: The fallopian tubes may be perfused with the utero-ovarian vasculature alone, potentially allowing for future studies regarding tubal viability in recipients of uterine transplants.

GLDP Potential Uterus Transplant Donor Pool Evaluation

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<tr>
<th>Reproductive Age Female DBD Donor (n=94)</th>
<th>PHS</th>
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<th>Increased Risk (n=50)</th>
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<tr>
<td>Uterus in Place</td>
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O-87 Monday, October 8, 2018 11:15 AM

THE EFFECTS OF RESIDENT INVOLVEMENT IN OPEN AND LAPAROSCOPIC MYOMECTOMIES.

A. S. Garneau, a S. L. Lababidi, b K. McQuerry, Y. Li, Y. Qi, a J. W. Akin, a Obstetrics and Gynecology, University of Kentucky, Lexington, KY; bObstetrics & Gynecology, University of Kentucky, Lexington, KY; cStatistics, University of Kentucky, Lexington, KY; dBluegrass Fertility Center, Lexington, KY.

OBJECTIVE: The objective of this study was to investigate the rate of intraoperative and postoperative complications associated with resident involvement in open and laparoscopic myomectomies.

DESIGN: We performed a retrospective cohort study using the National Surgical Quality Improvement Program database.

MATERIALS AND METHODS: Patients who had open or laparoscopic myomectomies between January 1, 2006 and December 21, 2014 were included in analysis. Variables studied included resident participation, preoperative factors, surgical operative times, intraoperative complications, and postoperative complications. Cases were omitted if resident involvement was not specified in the database. Data analysis was performed using Chi square, T-test, and Fisher’s exact test with significance set at p<0.05. All analyses were completed in SAS 9.4.

RESULTS: A total of 1,152 cases were included in analysis. Patients were stratified by resident + attending vs attending-only surgeries. Of the cases included, 618 indicated resident involvement and 534 indicated attending-only cases. The two populations were similar in age, BMI, tobacco use and preoperative hematocrit. There was a difference in the incidence of diabetes between the groups, with an incidence of 4% in patients who had resident involvement in their case compared to 1.7% of patients who did not have a resident involved in their case, p=0.02. Procedures which included residents were noted to have longer operative times (129.2 mins) when compared to attending only (111.8 mins), p=0.0002. Bleeding events requiring transfusion occurred in 41 (6.6%) cases that included residents compared to 18 (3.4%) of cases that only included an attending, p=0.03. There was no significant difference in other peri-operative or post-operative complications, including superficial surgical site infections, deep surgical site infections, organ space surgical site infections, nerve injury, and wound healing.

CONCLUSIONS: Resident involvement in laparoscopic and open myomectomy was associated with an average 28 minute increase in operative time as well as a slight increase incidence of bleeding events requiring transfusion. Other peri-operative and post-operative complications, however, showed no significant difference with resident involvement. Given these overall similar operative outcomes regardless of resident involvement, the benefits of incorporating residents into myomectomy procedures, including resident education, may outweigh the potential risks. To our knowledge, this is the first study investigating resident involvement in myomectomies.

References:
1. SAS/STAT software, Version 9.4. SAS Institute Inc., Care, NC, USA.
- **OBJECTIVE:** To investigate the effectiveness of multifetal pregnancy reduction (MFPR) to twins and to singleton in trichorionic triplet (TCT) pregnancies after in vitro fertilization-embryo transfer.

- **DESIGN:** A retrospective cohort study.

- **MATERIALS AND METHODS:** 238 patients with TCT from January 2012 to December 2016 were enrolled. These patients were divided into group A (reduced to singleton, n = 12), group B (reduced to twins, n = 209) and group C (ongoing triplets without reduction, n = 17). The pregnancy outcomes were compared among these 3 groups.

- **RESULTS:** The characteristics including maternal age, infertility duration, BMI, infertility type and causes were similar among 3 groups (p > 0.05). Compared with group C, group A had significantly lower rates of premature delivery (0% vs. 82.4%, odds ratio (OR) 5.667; p < 0.001) and low birth weight (LBW, 0% vs. 80.0%, OR 5.000; P < 0.0001); the live birthweight (3100.0±435.0 vs. 2025.0±419.0, P < 0.0001) and gestational age (GA) at delivery (39.1±1.3 vs. 33.1±4.5, P < 0.0001) were significantly higher. Although the live birth rate was higher (100.0% vs. 88.2%) and perinatal mortality (0% vs. 11.8%) was lower in group A, no significant differences were found (p > 0.05). Compared with group C, group B had significantly lower risks of premature delivery (39.7% vs. 82.4%, OR 0.141; p = 0.001), perinatal mortality (4.7% vs. 11.8%, OR 0.369; p < 0.0001), gestational age at delivery (39.1±1.3 vs. 33.1±4.5, p < 0.0001), perinatal mortality (4.7% vs. 11.8%, OR 0.369; p = 0.048) and low birth weight (LBW, 43.3% vs. 80.0%, OR 0.191; P < 0.0001); the live birthweight (2475.0±480.0 vs. 2025.0±430.0, P < 0.0001) and GA at delivery (36.3±3.1 vs. 33.1±4.5, P < 0.0001) were significantly higher. Although the live birth rate was higher (100.0% vs. 88.2%) and perinatal mortality (0% vs. 11.8%) was lower in group A, no significant differences were found (p > 0.05). Compared with group B, group A had significantly lower rates of perinatal mortality (0% vs. 39.7%, OR 1.369; p = 0.004) and low birth weight (0% vs. 43.3%, OR 1.763; p = 0.003) and significantly higher live birthweight (3100.0±435.0 vs. 2475.0±480.0, P < 0.0001) and GA at delivery (39.1±1.3 vs. 36.3±3.1 weeks, p = 0.002). Higher live birth rate (100.0% vs. 95.7%) and lower perinatal mortality (0% vs. 4.7%) were observed in group A, but with no significance (p > 0.05) (Table).

- **CONCLUSIONS:** Both MFPR of TCT to twins and to singleton could lower the rates of premature delivery and LBW than MFPR to twins. While relative small sample size of group A and C was a limitation.

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**RCT: TOLERANCE OF CHLORHEXIDINE GLUCONATE VERSUS POVIDONE-IODINE VAGINAL CLEANSING SOLUTION.** J. Friedman, S. Rastogi, L. Glaser, C. Lis, J. Carter, M. Milad. Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine, Chicago, IL.

- **OBJECTIVE:** Although chlorhexidine gluconate has proven to be superior to povidone iodine for surgical site antisepsis, povidone iodine is the only FDA-approved antiseptic solution for surgical preparation of the vagina.-Many surgeons are hesitant to use chlorhexidine gluconate for preoperative vaginal cleansing due to the alcohol dissolvent present in the solutions that is implicated in a greater risk of irritation. Yet, there has been no randomized study to illustrate whether the risk of vaginal irritation is greater in 4% chlorhexidine gluconate versus 7.5% povidone iodine. Thus, the purpose of this study is to compare the tolerance of 4% chlorhexidine gluconate/4% isopropyl alcohol (CHG) versus 7.5% povidone-iodine (PI) vaginal cleansing solutions in adult women undergoing scheduled hysteroscopies, gynecologic dilation and curettage and endometrial ablations between July 2017 and April 2018.

- **DESIGN:** Single-blinded prospective randomized control trial.

- **MATERIALS AND METHODS:** All eligible patients were approached for enrollment. Consented patients underwent simple randomization into one of two groups: (1) PI or (2) CHG antiseptic as vaginal preparation. Patients completed a standardized survey evaluating vaginal symptoms (dryness, burning, itchiness, unusual discharge) and urinary symptoms (pain or burning with urination) at three time points: preoperatively (T0), immediately postoperatively (T1), and 24 to 48 hours postoperatively (T2). Adjusted odds ratios (aOR), controlling for age, menopause, catheterization, and T0 scores, were calculated.

- **RESULTS:** A total of 123 patients (PI n=63, CHG n=60) met inclusion criteria. At T1, patients treated with CHG were significantly more likely to experience dryness (aOR, 4.44; 95% CI 1.06-17.96; p=0.0416), vaginal burning (aOR 6.45; 95% CI 2.33-17.86; p=0.0003), and pain with urination (aOR 3.30; 95% CI 1.18-9.19; p=0.0224). In total at T1, 54.2% of CHG vs. 34.9% of PI patients had adverse symptoms. At T2, significantly more patients receiving CHG noted vaginal burning (aOR 5.05; 95% CI 1.85-13.78; p=0.0016), pain with urination (aOR 4.78; 95% CI 1.66-13.78; p=0.0037), and unusual discharge (aOR 3.56; 95% CI 1.13-11.26; p=0.0303). In total at T2, 68.8% CHG vs. 43.8% PI patients experienced adverse symptoms.

- **CONCLUSIONS:** The use of chlorhexidine vaginal preparation is associated with significantly worse vaginal and urinary symptoms when compared with povidone-iodine, both in the immediate postoperative period and 24 to 48 hours postoperatively. This is the first RCT comparing the tolerance of 4% chlorhexidine gluconate to 7.5% povidone-iodine using patient-reported outcomes. Patients undergoing procedures that require vaginal CHG prophylaxis should be warned about the high incidence of postoperative vaginal and urinary symptoms.

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**References:**


O-90 Monday, October 8, 2018 12:00 PM

TREATMENT EFFECT OF OIL-BASED CONTRAST AT HSG IS DEPENDENT ON PAIN AT HSG BUT NOT ON VOLUME OF CONTRAST. N. van Welie, a K. Dreyer,a N. van Rijsjwijk,b H. R. Verhoove,c M. Goddijn,c A. W. Nap,d J. M. Smeenk,d M. A. Traasd, B. W. Mol.e aReproductive Medicine, VU University Medical Center, Amsterdam, Netherlands; bObstetrics and Gynaecology, Rijnstate Hospital, Arnhem, Netherlands; cObstetrics and Gynaecology, Elisabeth-TweeSteden Hospital, Tilburg, Netherlands; dObstetrics and Gynaecology, Gelre Hospital, Apeldoorn, Netherlands; eObstetrics and Gynecology, Monash University, Melbourne, Australia.

OBJECTIVE: We recently showed in a randomized clinical trial (RCT) in 1,119 women that oil-based contrast during hysterosalpingogram (HSG) increases ongoing pregnancy rates as compared to water-based contrast. Here, we assess the impact of pain during HSG and used volume of contrast on the effectiveness of oil-based contrast.

DESIGN: Secondary analysis of a multicentre RCT.

MATERIALS AND METHODS: During the study, pain during HSG was measured in seven centres by means of the Visual Analogue Scale (VAS) (range 0.0 to 10.0 in cm, with higher scores indicating more severe pain). The used volume of contrast was recorded in 16 centres. We assessed the impact of pain and volume of contrast on ongoing pregnancy rates, as well as the interaction between each of these two and the treatment effect using logistic regression analysis. Data were analysed according to intention to treat principle.

RESULTS: Pain was measured in 400 women (overall median pain score of 5.0 (IQR 3.0-6.8), oil group 4.8 (IQR 3.0-6.4), water group 5.0 (IQR 3.0-6.7) (P=0.28)). There was significant interaction between pain and ongoing pregnancy (VAS cut-off 5.0, P=0.047). In women experiencing pain >5.0 HSG with oil contrast increased the ongoing pregnancy rate (oil versus water Relative Risk (RR) 1.7, 95% CI 1.1-2.5), while in women with a pain score ≤5.0 there was no effect of oil contrast compared to water contrast (RR 0.98, 95% CI 0.66-1.5). Volume of used contrast was recorded in 512 women (overall median volume of 8.3ml (IQR 5.8-14.0), 9.0ml (IQR 5.7-15.0) versus 8.0ml (IQR 5.9-13.0) (P=0.72)). There was no interaction between contrast volume and the type of contrast used. Also, pain and contrast volume were not related.

CONCLUSIONS: The treatment effect of oil-based contrast during HSG is dependent on pain experienced during the procedure. This points at a mechanistic pathway of the use of oil-based contrast, for example by flushing debris or dislodge of mucus plugs from the tubes.

 References:

Supported by: This study was not funded.

<table>
<thead>
<tr>
<th>TABLE 1. Ongoing pregnancies after the use of oil and water contrast during HSG stratified for pain</th>
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<tr>
<td><strong>Oil-based contrast (n=199)</strong></td>
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<td>VAS &gt;5.0</td>
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</table>
**O-91 Tuesday, October 9, 2018 10:45 AM**

**MALE FACTOR INFERTILITY AND RISK OF MORTALITY: A REGISTER BASED COHORT STUDY.** C. H. Glazer, a, 1 M. L. Eisenberg, 2 S. S. Toetterborg, a, 1 A. Giwercman, 2 E. Brauner, 2 D. Vassard, 3 A. B. Pinborg, 4 L. Schmidt, 3 J. Bonde, 4 a Department of Occupational and Environmental Medicine, Copenhagen NV, Denmark; 2 Stanford, Palo Alto, CA; 3 Molecular Reproductive Medicine, Malmö, Sweden; 4 Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark; 5 Social Medicine, Copenhagen, Denmark; Fertility Clinic, Rigshospitalet, Copenhagen University Hospital, Professor, Copenhagen, Denmark; 6 Occupational and Environmental Medicine, Bispebjerg Hospital, Copenhagen, Denmark.

**OBJECTIVE:** To determine whether men with male factor infertility are at increased risk of mortality in the years following evaluation for infertility.

**DESIGN:** A prospective cohort study.

**MATERIALS AND METHODS:** All men whose partner had undergone fertility treatment in all public and private fertility clinics in Denmark (n = 51,289) were identified from the Danish national IVF register between 1994-2015, which includes data on reasons for couple infertility. During the initial years of the register, male factor infertility was recorded as ‘yes’ or ‘no’ and from 2006 onwards as diagnosis codes (e.g. azoospermia, oligospermia). The reference group included men with male factor infertility = ‘no’ and those with diagnosis codes of normal semen quality or vasectomized men. All men were followed until death, emigration or end of follow-up on December 31st, 2015. Risk of death was assessed by Cox proportional hazard regression with age as an underlying timeline with adjustment for education as a proxy for socioeconomic status. In addition to analyzing the data for the entire IVF period, we analyzed data from 2006 onwards separately to assess the risks according to specific types of male factor infertility.

**RESULTS:** During a mean follow-up time of 7.8 years, 489 men died with cardiopulmonary disease (n = 380) and cardiovascular disease (n = 108) representing the most prevalent causes. Mean age of death was 48.8. For the entire IVF period, risk of death among men with male factor infertility compared with men with no male factor infertility was [OR 1.03, 95% CI 0.85-1.24]. When stratified by type of male factor infertility available from 2006 and onwards, men with azoospermia (n=1,722) had a two-fold increased mortality risk [OR 2.1, 95% CI 1.3-3.4], while men with oligospermia (n=12,815) and other reasons for male infertility (n=3,604) had corresponding risks of [OR 0.65, 95% CI 0.43-0.98] and [OR 1.0, 95% CI 0.62-1.6] when compared to men with normal semen quality or those vasectomized (n=18,340).

**CONCLUSIONS:** Men with azoospermia had increased risk of mortality during the years following assisted reproduction. Such association was not seen for oligospermic men but the use of an internal reference group implies a significant risk of misclassification and this result needs to be verified by comparison with an external control group, which we are presently working on establishing. Nonetheless, closer monitoring of azoospermic men after fertility treatment may be warranted.

**Supported by:** ReproUnion

**O-92 Tuesday, October 9, 2018 11:00 AM**

**PRECONCEPTION AND PRENATAL EXPOSURE TO ENVIRONMENTAL CHEMICALS AND THE RISK OF PRETERM BIRTH.** J. Yland, 1 A. L. Minguez-Alarcon, 1 J. B. Ford, 1 L. M. Williams, 1 A. Azvedo, 1 2 J. A. Attaman, 1 R. Hauser, 1 C. Messerlian. 1 1 Department of Epidemiology, Harvard Chan School of Public Health, Boston, MA; 2 Department of Environmental Health, Harvard Chan School of Public Health, Boston, MA; 3 Departments of Biostatistics and Epidemiology, Harvard Chan School of Public Health, Boston, MA; 4 Obstetrics & Gynecology, Massachusetts General Hospital Fertility Center, Boston, MA.

**OBJECTIVE:** Phthalate and phenol exposure during pregnancy has been associated with an increased risk of preterm birth. The potential effect of these environmental exposures during the preconception window of exposure is unknown. We examined the association of maternal preconception and prenatal phthalate and phenol exposure and preterm birth among singletons born to subfertile couples.

**DESIGN:** A prospective preconception cohort of subfertile women from an academic fertility center and their live born singletons.

**MATERIALS AND METHODS:** We averaged log-concentrations from multiple urine samples obtained in the preconception period and from each trimester of pregnancy from 364 women. Gestational age was abstracted from delivery records and validated using the American College of Obstetricians and Gynecologists guidelines for birth following medically assisted reproduction. We estimated the risk ratio (RR) of preterm birth (live birth before 37 completed weeks gestation) in relation to quartiles of urinary concentrations of bisphenol A (BPA), benzophenone-3, triclosan, the molar sum of parabens, and the molar sum of di-(2-ethylhexyl) phthalate metabolites (ΣDEHP) using log-binomial regression models, adjusted for covariates.

**RESULTS:** The mean gestational age among singletons was 39.3 weeks (SD: 1.4), mean 28.364 (8.6) born preterm. Among live births, 208 (57%) were conceived via in-vitro fertilization and the remainder via ovulation induction/intrauterine insemination or were non-medically assisted. In adjusted models, we observed a linear relationship across quartiles of preconception ΣDEHP metabolite concentrations and the risk of preterm birth: Q2, 2.4 (95%CI: 0.5, 12.0); Q3, 3.6 (95%CI: 0.75, 16.8); Q4, 6.3 (95%CI: 1.4, 27.6) (p-trend = 0.003). We also found evidence of increasing risk of preterm birth across quartiles of prenatal BPA concentrations: Q2, 6.1 (95%CI: 0.73, 51); Q3, 6.7 (95%CI: 0.83, 54); Q4, 9.1 (95%CI: 1.2, 68) (p-trend = 0.006). There was a suggestive association between women in the highest quartile of the sum of urinary paraben concentrations in pregnancy and preterm birth, with aRR = 2.8 (95%CI: 0.81, 10.0). We found no evidence of an association with triclosan and benzophenone-3 in either the preconception or prenatal window of exposure.

**CONCLUSIONS:** In this cohort of subfertile women, preconception DEHP and prenatal BPA exposure are associated with an increased risk of preterm birth. These results suggest that phthalates and phenols may have a different effect on preterm birth risk depending the exposure window and further point to the importance of the preconception period in adverse pregnancy outcomes.

**Supported by:** Work supported by grants R01 ES009718, R01 ES072408, and ES000002 from the National Institute of Environmental Health Sciences (NEIHS). CM was supported by an award from the Canadian Institutes of Health Research.

**O-93 Tuesday, October 9, 2018 11:15 AM**

**FSH SIGNALING IN HUMAN GRANULOSA CELLS IS AUGMENTED BY THE PKA REGULATORY II SUBUNIT AND RHO-GEF BINDING REGIONS OF A-KINASE ANCHORING PROTEIN 13 (AKAP13).** A. Sewdass, S. Ng, S. Su, P. H. Driggers, J. H. Segars. Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Baltimore, MD.

**OBJECTIVE:** Follicle stimulating hormone (FSH) signaling in granulosa cells requires Protein Kinase A (PKA) activation, which is regulated by PKA’s Regulatory II (RII) Subunit. AKAP13 binds to the RII subunit and sequesters PKA in specific subcellular locations to facilitate its activation. We have previously demonstrated that knockdown of AKAP13 decreased mRNA levels of key FSH-responsive genes in cultured granulosa cells, aromatase (CYP19A1) and LH-Receptor. Here, we sought to assess the PKA element binding (CREB) activation in order to identify the key regions of AKAP13 that are required for FSH signaling in human granulosa cells.

**DESIGN:** Basic Science Research

**MATERIALS AND METHODS:** COV434 cells, derived from a primary human granulosa cell tumor, were grown to 50% confluency and serum-starved overnight. Cells were then transfected for 24 hours with 0.9% sodium chloride) or 1.0 I.U. FSH/mL treatment with vehicle control (0.9% sodium chloride) or 1.0 I.U. FSH/mL for 24 hours, cells were lysed and assayed for CRE-luciferase activity and normalized to HSVtk-Renilla luciferase activity. Student’s t-tests were used to determine statistically significant differences.

**RESULTS:** Following FSH stimulation, COV434 granulosa cells demonstrated a 9.8-fold higher induction of CREB activation compared to vehicle control (p < 0.0001). COV434 cells coexpressing AKAP13 demonstrated an additional 6.9-fold CREB activation from 9.8-fold to 18.5-fold with the addition of 1.0 I.U. FSH/mL (p < 0.0006). COV434 cells coexpressing the AKAP13

**FERTILITY & STERILITY® e41**
EVALUATION OF A NOVEL, MINIMALLY INVASIVE TEST FOR FERTILITY HORMONES. E. Burke, S. Bequi, S. Luo. Modern Fertility, San Francisco, CA; Universal Diagnostic Laboratories, Van Nuys, CA.

OBJECTIVE: To develop and validate an at-home, self collection method for measuring eight reproductive hormones using minimally invasive fingerstick (FS) sampling on filter paper.

DESIGN: A prospective concordance study compared matched venipuncture and FS samples from 130 women ages 18 to 40 on menstrual cycle day three. All women provided written, informed consent. Precision, linearity, and accuracy studies were also conducted. Samples were measured for anti-Mullerian hormone (AMH), estradiol (E2), follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), testosterone (T), thyroid stimulating hormone (TSH), and free thyroxine (FT4).

RESULTS: Fetal weight was significantly different among the groups (p < 0.0001) [Nat-Nat 1.49 ± 0.15g (n=13); SO-Nat 1.55 ± 0.18g (n=23); Nat-SO 1.30 ± 0.17g (n=12); SO-SO 1.26 ± 0.25g (n=14)], with significantly lower fetal weights in SO compared to natural hosts with both the Nat and SO blasts. In contrast, placental weight was higher in embryos originating from SO blasts compared to Nat blasts (p = 0.02); this effect was greatest when transferred into an SO host [Nat-Nat 0.13 ± 0.02g; SO-Nat 0.15 ± 0.03g; Nat-SO 0.13 ± 0.02g; SO-SO 0.17 ± 0.05g]. There was no difference in litter size among groups. Placental architecture, assessed by junctional zone to labyrinth ratios, as well as global and site-specific DNA methylation in fetal liver were assessed with Luminometric Methylation Assay and bisulfite pyrosequencing. One-way ANOVA, Kruskal-Wallis, Student’s t-test, and Fisher’s Exact test were used to evaluate between-group differences.

CONCLUSIONS: These data suggest that the increased risk of fetal growth restriction following fresh embryo transfers result from exposure of the implanting embryo to an abnormal hormonal milieu. In addition, exposure of the developing oocyte to gonadotropin stimulation may affect placental growth, which can impact fetal health and long-term health and disease. Additional studies are necessary to determine the mechanism(s) by which the hormonal environment affects fetal and placental growth.

Supported by: This research was funded by Modern Health, Inc.
OBJECTIVE: This study aims to compare obstetric outcomes resulting from assisted reproductive technology (ART) in couples with a history of female sterilization compared to those with other infertility diagnoses.

DESIGN: Retrospective Cohort Study.

MATERIALS AND METHODS: All 760,705 fresh, autologous embryo transfer cycles with partner ejaculated sperm from 2004 to 2013 in the SART database were reviewed. Cycles in women with prior female sterilization were compared to cycles with other infertility diagnoses. After excluding cycles with male sterility, day of transfer >7, prior sterilization with an additional infertility diagnosis, and unknown method of ICSI or IVF, 4,174 cycles in patients with history of female sterilization were compared to 179,605 cycles in patients with other causes of infertility. Multiple linear regression analyses and generalized estimating equations were performed to assess whether gestational length and birthweight were significantly different between groups in singleton and twin pregnancies. Group comparison was performed after controlling for singleton and twin gestations except in birthweight for twins.

RESULTS: Previously sterilized women were older with significantly higher parity and body mass indices than women in couples with all other causes of infertility. Number of oocytes retrieved, timing of embryo transfer, pregnancy and live birth rates were not significantly different between the two groups. Women with a history of sterilization had significantly shorter gestations and lower birth weights than women with other causes of infertility. However, there was no significant difference between these two groups after controlling for singleton and twin gestations except in birthweight for twins.

CONCLUSIONS: Evidence has linked pregnancies resulting from ART with increased risk of adverse obstetric outcomes, including low birthweight; however, it is unclear if this is due to the ART procedures or to subfertility itself. This study provides a rare opportunity to evaluate the effects of ART in a population without an underlying infertility diagnosis. This analysis demonstrates no significant differences in neonatal birthweight or gestational age among ART births from women with infertility and tubal sterilization. The results suggest that differences in outcomes between ART and natural conceptions may be due to the procedures of ART itself.

OBJECTIVE: The risk of Hepatitis B (HBV) and Hepatitis C (HCV) transmission has been reduced by routine screening for Hepatitis B surface antigen (HBsAg), anti-Hepatitis B core antigen (anti-Hbc), and anti-Hepatitis C. However, these assays are prone to false positive (FP) results, and due to inherent test sensitivity and dependence on host response, are limited by a window period (WP) between infection and detection. Nucleic acid testing (NAT) offers improved sensitivity and specificity over antibody-based assays, decreasing the acute infection WP and improving detection of infections in late chronic phases. Concurrent NAT may be useful for differentiating serological FP results from true infected potential donors. Blood transfusion literature has shown that 2-16% of donors that tested positive for HBsAg were in fact HBV DNA negative after NAT. The aim of this study was to determine the true incidence of HBV and HCV in potential gamete donors, and evaluate the need for a re-entry protocol for suspected FP results with concurrent NAT.

DESIGN: Retrospective.

MATERIALS AND METHODS: The study included 1396 gamete donors screened for HBV and HCV from 2016-2018. HBsAg, anti-Hbc, HCV antibody, and triplex (HIV-1, HCV, HBV) NAT results were analyzed. Serologic and virologic results were compared.

RESULTS: Of 46 donors and 355 egg donors, 6 (0.6%) sperm donors and 4 egg donors (1.1%) were positive (+) for HBsAg or anti-Hbc. Two sperm donors had an active infection (+HBsAg and Anti-Hbc, confirmed on NAT). One egg donor had immunity from natural infection (positive anti-Hbc and anti-Hbs, negative(-) NAT). Three donors (2 sperm, 1 egg) were diagnosed with a resolved infection or FP (+Anti-Hbc but -HBsAg and -HBV NAT). Four donors (2 sperm, 2 egg) had a FP result (+HBsAg, -anti-Hbc and -NAT), yielding a 40% FP rate in this cohort. Five sperm donors had antibodies to HCV (0.5%) and were -HCV NAT, suggesting a 100% FP rate.

CONCLUSIONS: The true positive rate for HBV and HCV is low in a gamete donor population, whereas the FP rate is substantial (40% for HBV and 100% for HCV). Experts suggest that a combination of Triplex NAT and anti-Hbc is ideal, as it allows earlier detection of HBV infection, and captures individuals with chronic infections. Conversely, HBsAg testing has not been shown to provide additional information over NAT alone, and may be eliminated in donor screening programs. Given the current lack of a re-entry protocol for presumed FP results, current requirements for permanent deferral for any +screening test result leads to unnecessary donor loss. While patient safety is a priority, gamete donors are scarce, and deferral based on spurious values creates issues for donor supply. Given the many opportunities for retesting a sperm donor within the 6 month quarantine period, a rigorous re-entry process for gamete donors, similar to blood donors, should be considered.

References:

O-100 Tuesday, October 9, 2018 11:30 AM

TRANSFER OF COMPLETELY HATCHED EUPLOID BLASTOCYSTS RESULTS IN SIGNIFICANTLY LOWER PREGNANCY OUTCOMES COMPARED TO EUPLOID EXPANDED OR HATCHING BLASTOCYSTS. R. M. James, A. Picou, M. VerMilyea,

DESIGN: Retrospective analysis in a private reproductive technology program.

MATERIALS AND METHODS: Pregnancy rates between transfers of completely hatched blastocysts were compared to those of expanded or hatching blastocysts in 676 frozen single embryo transfer cycles occurring from January 2016 to December 2017. Blastocysts were tested for aneuploidy by NextGen Sequencing. The variable tested was completeness or degree of hatching status of the blastocyst at the time of transfer. Outcome measured was presence of fetal cardiac activity (FCA) via ultrasound at 7 weeks of gestation.

RESULTS: Of 676 euploid embryos in this analysis, 464 were expanded or hatching (Ex/HgBl) and 212 were completely hatched (CHBl) at the time of transfer. 248 of the 464 (53.45%) HgBl had positive FCA at 7 weeks compared to 93 of 212 (43.87%) CHBl. Statistical analysis by Chi-square demonstrated a significant difference (p=0.021) between clinical pregnancy rates of the two groups accordingly. Chi-square analysis also demonstrated a significant difference between these two groups with regards to both rates of positive β-HCG and presence of a gestational sac. Of the 464 Ex/HgBl, 60.56% developed a gestational sac, while 105 CHBl (49.53%) developed a gestational sac (p=0.01). Of the 464 Ex/HgBl transfers, 68.53% resulted in a positive β-HCG test, while 122 of CHBl transfers (57.55%) resulted in a positive β-HCG test (p=0.005). We further evaluated for differences in FCA in different subgroups and found no statistically significant difference between day 5 versus day 6 Ex/HgBl and CHBl (p=0.38). Similarly, there was no significant difference in FCA rates between Ex/HgBl and CHBl with morphologic grades greater than or equal to BB and less than BB (p=0.17).

CONCLUSIONS: In frozen embryo transfers with euploid, good morphologic quality embryos, completely hatched blastocysts at the time of transfer resulted in significantly lower pregnancy success compared to transfers of expanded or hatching blastocysts. These results suggest that completely hatched embryos may be more fragile due to the biopsy and vitrification/warming processes and thus more susceptible to potential cellular damage prior to transfer, resulting in lower implantation success. Further analysis...
OBJECTIVE: The objective of the study was to confirm whether administration of a single oral 900 mg dose of nolasiban, prior to day 3 or 5 (D3, D5) fresh single embryo transfer (SET) improves ongoing pregnancy rate.

DESIGN: Multinational, prospective, double-blind, randomized, parallel group, placebo-controlled, Phase 3 study assessing a single oral 900 mg dose of nolasiban or placebo (1:1), administered about 4 hours before ET following IVF/ICSI. The primary endpoint was an ongoing pregnancy defined as ultrasound observation of a fetal heartbeat at 10 weeks post-ET. Secondary endpoints included clinical pregnancy at 6 weeks post-ET and miscarriage.

MATERIALS AND METHODS: 778 subjects were recruited from 41 fertility clinics in Europe from Mar-Oct 2017. Eligibility criteria included age ≤ 36 years, ≤ 1 failed ART cycle, use of a GnRH antagonist, < 1.5 ng/mL serum progesterone on the day of hCG, and luteal support with vaginal micronized progesterone. One good quality embryo was transferred on either D3 (n=388) or D5 (n=390). The primary analysis was performed on the pooled D3/D5 population. Subgroup analyses were performed on the D3 and D5 populations separately. Data are reported up to 10 weeks post-ET. Follow-up of pregnancy, delivery including live birth, and neonatal and infant outcomes up to 6 months after birth is ongoing.

RESULTS: The ongoing pregnancy rates at week 10 in the pooled D3/D5 population were 29% for placebo and 36% for nolasiban (p=0.031); a 25% relative increase. The difference was more pronounced in the D3 subgroup (placebo 22%, nolasiban 25%; p=0.477, a 14% relative increase). Demographics were generally comparable between treatment groups (e.g. mean age 31; BMI 24; No. oocytes retrieved 9-10; No. good quality embryos 2.5-2.6, serum progesterone prior to ET). Sub-group analyses of these baseline factors did not show any significant interaction with the effect of nolasiban. Single dose administration of 900 mg nolasiban was well tolerated and did not result in increased occurrence of adverse events compared to placebo. The overall safety profile of nolasiban was similar to placebo.

CONCLUSIONS: A single oral dose of nolasiban taken before fresh SET resulted in a relative 25% increase in ongoing pregnancy rate compared to placebo. Nolasiban was well tolerated. The use of nolasiban has the potential to improve pregnancy and live birth rates following SET and potentially reduce the incidence of multiple pregnancies from ART by encouraging the use of elective SET.

References: ClinicalTrials.gov: NCT03081208.

Supported by: The study was funded by ObsEva SA.

O-101 Tuesday, October 9, 2018 11:45 AM

A PLACEBO-CONTROLLED, RANDOMIZED, DOUBLE-BLIND, PHASE 3 STUDY ASSESSING ONGOING PREGNANCY RATES AFTER SINGLE ORAL ADMINISTRATION OF A NOVEL OXYTOCIN RECEPTOR ANTAGONIST, NOLASIBAN, PRIOR TO SINGLE EMBRYO TRANSFER. H. Visnova,1 H. J. Tourmave, A. Humberstone,1 P. Terrill,1 L. Macgregor,1 E. Loumagne,1 IVF CUBE, SAR CPAS, Prague, Czech Republic; 2CRG, Brussels, Belgium; 3ObsEVA SA, Geneva, Switzerland; 4Cytel UK, London, United Kingdom.

Supported by: None to disclose.

O-102 Tuesday, October 9, 2018 12:00 PM

INTENT TO TREAT ANALYSIS REVEALS SIGNIFICANTLY IMPROVED CLINICAL OUTCOMES WITH ANEUPLOIDY TESTING IN AN AGE-MATCHED POPULATION. M. Katz-Jaffe,1 E. Surrey, R. L. Gustofson, L. A. Kondapalli, S. Barton, L. Erhart, S. McCormick, W. B. Schoolcraft, Colorado Center for Reproductive Medicine, Lone Tree, CO.

OBJECTIVE: Preimplantation genetic testing for aneuploidy (PGT-A) has been proposed as an improved embryo selection strategy to decrease pregnancy loss and increase live birth rates for infertility patients undergoing in vitro fertilization (IVF). In an intent to treat analysis, we investigated clinical outcomes with PGT-A, compared to patients who have freeze-all blastocyst cycles with embryo selection based on morphology alone.

DESIGN: Prospective cohort age-matched study.

MATERIALS AND METHODS: Infertility couples were identified during their IVF consult as intent to treat with either a freeze-all blastocyst cycle or IVF with PGT-A. Female patients were maternally age-matched between the two treatment groups (mean 32.5 ±3.7 years; n=40 per group). For the Freeze All group, blastocysts were vitrified using the Cryoprot method on cycle day four (D4) or day 5 (D5) or day 6 (D6) of development. In contrast, for the ‘PGT-A’ group, prior to vitrification, D5 or D6 blastocysts were biopsied and analyzed for chromosome enumeration using the VeriSeq™ platform (Illumina). Standard protocols for a hormone replacement frozen embryo transfer (FET) were utilized, with either blastocyst morphology alone (Freeze All) or euploid (PGT-A) embryo selection. Primary outcomes measured included implantation (fetal heart tone), ongoing clinical pregnancy, miscarriage, and live birth rates. Statistical analysis included Student’s t-test and Fisher’s exact test where appropriate, significance at P<0.05.

RESULTS: In each treatment group, 46 retrievals were performed with no significant differences in number of oocytes retrieved, fertilized or number of usable blastocysts between the two treatment groups (P>0.05; ns). Two retrievals (4.4%) resulted in no fertilization and four (8.7%) with no blastocyst development in the PGT-A group (P<0.05; ns). Additionally, following PGT-A, two (4.4%) cycles ended with all aneuploid blastocysts. Remaining patients underwent FET with significant clinical improvements for primary outcomes measured in the PGT-A group (P<0.05; Table 1).

CONCLUSIONS: From the prospective intent to treat analysis, at the time a clinical decision is made to proceed with IVF therapy, the inclusion of PGT-A resulted in significantly improved clinical outcomes in a younger maternally age-matched population. This data reflects that embryo selection incorporating PGT-A should be considered for infertility patients undergoing IVF.

CONTRACEPTION AND FAMILY PLANNING

O-103 Tuesday, October 9, 2018 10:45 AM


OBJECTIVE: To describe national trends in emergency department (ED) utilization for emergency contraception (EC) following the 2006 US Food and Drug Administration (FDA) approval of levonorgestrel EC without a prescription and coverage expansion for contraceptive services under the Affordable Care Act (ACA).

DESIGN: Retrospective cross-sectional study using a nationally-representative, all-payer database.

MATERIALS AND METHODS: ED utilization for EC was evaluated using the Nationwide Emergency Department Sample (NEDS), Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality (AHRQ; Rockville, MD). The database was queried for women aged 15-44 yo who presented to the ED with “encounter for emergency contraception counseling and prescription” listed as their primary ICD-09 diagnosis (V25.03). The primary outcome was the number of annual ED visits made between 2006-2014. Parameters assessed included age, payer

TABLE 1.

<table>
<thead>
<tr>
<th>FET Outcomes</th>
<th>Freeze All (n=40)</th>
<th>PGT-A (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implantation Rate (fetal heart tone)</td>
<td>48.2%</td>
<td>78.9%*</td>
</tr>
<tr>
<td>Ongoing Clinical Pregnancy Rate</td>
<td>60%</td>
<td>84.6%*</td>
</tr>
<tr>
<td>Miscarriage Rate</td>
<td>16.7%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Live Birth Rate per FET</td>
<td>50%</td>
<td>79.5%*</td>
</tr>
<tr>
<td>Live Birth Rate per Intent to Treat</td>
<td>43.5%</td>
<td>65.2%*</td>
</tr>
</tbody>
</table>

*P<0.05
status, income quartile, patient urban-rural designation, hospital geographic region and hospital teaching status. We compared data to visits by women in the same age range without an EC diagnosis. Z-tests were performed to assess any significant differences between groups.

The total number of encounters for EC in the ED decreased significantly during the study period. The steepest decline occurred from 2006 (15,039 visits; 95%CI: 11,270 - 18,902) to 2007 (4,370 visits; 95%CI: 3,523 - 5,217). After 2007, visits decreased steadily, reaching 685 visits in 2014 (95%CI: 488 - 881). Overall, this represented a 95% decrease in visits over time. Annual total ED charges decreased from $6.2M in 2006 to $0.65M in 2014. When compared to all other ED visits by women aged 15-44 yo in 2014, ED visits for EC were more likely to be by women aged 15-19 yo (30.7% vs 13.3%; p <0.001), who lived in the Northeast (53.7% vs 17.7%; p<.001), lived in large metropolitan areas (64.2% vs 48.1%; p=0.010), or presented to metropolitan teaching hospitals (64.0% vs 54.4%; p=0.011). The proportion of visits for EC by patients who lived in zip codes with average incomes in the lowest and second income quartiles was 29.9% (95%CI: 20.7%- 39.2%), and 36.2% (95%CI: 23.4%- 49.0%), respectively in 2014.

Trends by payer indicated that patients with private insurance or self-pay status experienced steeper declines in ED visit counts compared to patients with Medicaid, with estimated percent changes of -98.8%, -98% and -83% between 2006-2014 respectively.

CONCLUSIONS: ED utilization for emergency contraception decreased substantially between 2006-2014, demonstrating the influence of policy on these care seeking patterns. This decrease also led to cost-savings in the ED by reducing treatment. Nonetheless, trends by payer indicate a potential disparity in how women currently access ED (vs other outlets) and can pay for EC. Future policies should ensure that patients seeking care for unintended pregnancy are provided timely and cost-effective care.

Supported by: University of Michigan.

O-105 Tuesday, October 9, 2018 11:15 AM

PLASMA LEVONORGESTREL LEVELS IN NON-OBESE AND OBESE WOMEN USING A LEVONORGESTREL 52 MG INTRAUTERINE SYSTEM FOR UP TO 7 YEARS. M. D. Creinin, A. Gangestad, T. D. Kimble, B. Carr, A. Olariu, C. L. Westhoff. Obstetrics and Gynecology, University of California, Davis, Sacramento, CA; Obstetrics and Gynecology, Case Western Reserve University, Cleveland, OH; Obstetrics and Gynecology, Eastern Virginia Medical School, Norfolk, VA; UTSWMC, Dallas, TX; Medicines360, San Francisco, CA; Obstetrics and Gynecology, Columbia University, New York, NY.

OBJECTIVE: To evaluate levonorgestrel plasma concentrations for up to 7 years in non-obese and obese women using a levonorgestrel (LNG) 52mg intrauterine system (IUS). DESIGN: Prospective clinical trial. MATERIALS AND METHODS: Eligible women 16-45 years old received an LNG 52mg IUS (Liletta®) in a multicenter trial evaluating efficacy and safety for up to 10 years. A planned sub-study enrolled 40 participants (19 obese, 21 non-obese) to evaluate LNG concentrations over time at baseline, weeks 1 and 2, and months 1, 3, 6, 9, 12, 18, 24, 30 and 36. Additionally, all study subjects (219 obese and 670 non-obese) began blood sampling every 6 months at month 36. The liquid chromatography-tandem mass spectrometry assay had a lower limit of LNG detection of 25 pg/mL. We compared LNG concentrations in obese and non-obese women at each time point through 84 months (7 years) using an independent-samples t-test. RESULTS: Plasma LNG concentration was lower in obese compared with non-obese subjects at all time-points through 84 months (Table). All obese users had maximum levels <300 pg/mL at day 30 and thereafter. Maximum LNG concentrations in non-obese LNG 52mg IUS users were 603 pg/mL at week 1, 492 pg/mL at week 14, and <300 pg/mL by 1 year. From 3 to 84 months, LNG concentrations were 21-41% lower in obese subjects (p=0.01 for all months). Average BMI in the obese and non-obese sub-study participants was 38.5 ± 5.1 kg/m2 and 24.6 ± 2.9 kg/m2 respectively, with ranges of 30.4-49.2 kg/m2 and 18.9-29.5 kg/m2, respectively. Average BMI in the obese and non-obese study subjects beginning sampling at 36 months were similar, with 23.2% of obese subjects having a BMI ≥40 kg/m2.

CONCLUSIONS: Obese women demonstrate lower plasma LNG concentrations throughout seven years of LNG 52mg IUS use. The LNG concentrations in obese and non-obese women may be helpful for patient education.

O-104 Tuesday, October 9, 2018 11:00 AM

RETURN OF FERTILITY IN NULLIPAROUS AND PAROUS WOMEN AFTER LEVONORGESTREL 52 MG INTRAUTERINE SYSTEM DISCONTINUATION. B. R. Carr, M. A. Thomas, A. Gangestad, D. L. Eisenberg, A. I. Olariu, M. D. Creinin, UT SWMC, Dallas, TX; Obstetrics and Gynecology, University of California, Cincinnati, OH; Obstetrics and Gynecology, Case Western University, Cleveland, OH; Obstetrics and Gynecology, Washington University in St. Louis, St. Louis, MO; Medicines360, San Francisco, CA; Obstetrics and Gynecology, University of California, Davis, Sacramento, CA.

OBJECTIVE: Evaluate reproductive function in nulliparous and parous women after levonorgestrel 52mg IUS discontinuation based on time to pregnancy. DESIGN: Prospective clinical trial. MATERIALS AND METHODS: Eligible women 16-45 years old received an LNG 52mg IUS (Liletta®) in a multicenter trial evaluating efficacy and safety for up to 10 years. A planned sub-study enrolled 40 participants (19 obese, 21 non-obese) to evaluate LNG concentrations over time at baseline, weeks 1, and months 1, 3, 6, 9, 12, 18, 24, 30, and 36. Additionally, all study subjects (219 obese and 670 non-obese) began blood sampling every 6 months at month 36. The liquid chromatography-tandem mass spectrometry assay had a lower limit of LNG detection of 25 pg/mL. We compared LNG concentrations in obese and non-obese women at each time point through 84 months (7 years) using an independent-samples t-test. RESULTS: Plasma LNG concentration was lower in obese compared with non-obese subjects at all time-points through 84 months (Table). All obese users had maximum levels <300 pg/mL at day 30 and thereafter. Maximum LNG concentrations in non-obese LNG 52mg IUS users were 603 pg/mL at week 1, 492 pg/mL at week 14, and <300 pg/mL by 1 year. From 3 to 84 months, LNG concentrations were 21-41% lower in obese subjects (p=0.01 for all months). Average BMI in the obese and non-obese sub-study participants was 38.5 ± 5.1 kg/m2 and 24.6 ± 2.9 kg/m2 respectively, with ranges of 30.4-49.2 kg/m2 and 18.9-29.5 kg/m2, respectively. Average BMI in the obese and non-obese study subjects beginning sampling at 36 months were similar, with 23.2% of obese subjects having a BMI ≥40 kg/m2.

CONCLUSIONS: Obese women demonstrate lower plasma LNG concentrations throughout seven years of LNG 52mg IUS use. The LNG concentrations in obese and non-obese women may be helpful for patient education.

Mean Plasma Levonorgestrel Levels in Levonorgestrel 52mg IUS Users

<table>
<thead>
<tr>
<th>Time Point (months)</th>
<th>Obese</th>
<th>Non-Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25 (1 week)</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>1</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>3</td>
<td>1.25</td>
<td>1.25</td>
</tr>
<tr>
<td>6</td>
<td>1.50</td>
<td>1.50</td>
</tr>
<tr>
<td>12</td>
<td>1.75</td>
<td>1.75</td>
</tr>
<tr>
<td>24</td>
<td>2.00</td>
<td>2.00</td>
</tr>
<tr>
<td>36</td>
<td>2.25</td>
<td>2.25</td>
</tr>
<tr>
<td>48</td>
<td>2.50</td>
<td>2.50</td>
</tr>
<tr>
<td>60</td>
<td>2.75</td>
<td>2.75</td>
</tr>
<tr>
<td>72</td>
<td>3.00</td>
<td>3.00</td>
</tr>
<tr>
<td>84</td>
<td>3.25</td>
<td>3.25</td>
</tr>
</tbody>
</table>

*Chi-square test for trend

Pregnancy Rates by Parity After Levonorgestrel 52mg IUS Discontinuation

<table>
<thead>
<tr>
<th>Years of IUS Use</th>
<th>Parous</th>
<th>Nulliparous</th>
<th>Parous</th>
<th>Nulliparous</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11/12</td>
<td>3/3 (100%)</td>
<td>8/9 (89%)</td>
<td>0.29</td>
</tr>
<tr>
<td>2+</td>
<td>27/30</td>
<td>11/12 (92%)</td>
<td>16/18 (89%)</td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>36/41</td>
<td>17/21 (81%)</td>
<td>19/20 (95%)</td>
<td></td>
</tr>
<tr>
<td>4+</td>
<td>33/42</td>
<td>21/25 (84%)</td>
<td>12/17 (71%)</td>
<td></td>
</tr>
<tr>
<td>5+</td>
<td>25/27</td>
<td>18/19 (95%)</td>
<td>7/8 (85%)</td>
<td></td>
</tr>
</tbody>
</table>

P-value*
O-106 Tuesday, October 9, 2018 11:30 AM

POST HOC ANALYSIS OF A RANDOMIZED PLACEBO-CONTROLLED PHASE 3 STUDY ON THE EFFECT OF AMPHORA®, AN ACID-BUFFERING VAGINAL GEL, ON VAGINAL pH BY BASELINE VAGINAL pH LEVEL. J. Griffiss, a A. Avery, b S. Nayak, c D. R. Friend, d K. R. Culwell. e ClinicalRM, Hinckley, OH; f MetroHealth Medical Center, Cleveland, OH; g Johns Hopkins Bayview Medical Center, Baltimore, MD; h Evofem, Inc., San Diego, CA.

OBJECTIVE: High vaginal pH may increase a woman’s risk of bacterial vaginosis (Linhares et al. Am J Obstet Gynecol 2011). The objective of this study was to determine the change and duration of change in vaginal pH with intravaginal administration of single doses of an acid-buffering gel (Amphora) by baseline vaginal pH level.

DESIGN: This was a Phase 1, randomized, placebo-controlled, double-blind, multicenter study.

MATERIALS AND METHODS: The primary study randomized 105 women to receive a single intravaginal dose of one of three Amphora doses (3, 4 or 5 g), universal placebo gel (UPG 4 g) or no treatment. Subjects were admitted for overnight stay in the domiciliary unit. Vaginal pH measurements were taken prior to treatment (baseline) and 1, 6, 12 and 24 hours post-treatment. Subjects were then discharged and asked to measure vaginal pH daily on Days 2-6 post-treatment. On Day 7, subjects returned to the clinic and clinic staff measured patients’ vaginal pH. In this post-hoc analysis, the effect on vaginal pH was examined in women who were assigned to one of the following treatment groups: Amphora 5 g, UPG or no treatment. The mean change in vaginal pH was calculated at multiple intervals from baseline to Day 7 post-treatment. Change in vaginal pH and the duration of this change were determined according to baseline vaginal pH (pH <5 and pH ≥5).

RESULTS: Subjects in the Amphora treatment group experienced a decrease in vaginal pH at all time points from Day 0, 1 hour post-treatment, to Day 7, regardless of baseline vaginal pH (Table 1). When stratified by baseline vaginal pH (pH <5 and pH ≥5), significant decreases in pH from baseline were seen in both sub-groups at nearly all time points through Day 6, though the magnitude of the decrease was greater in women with higher baseline vaginal pH. When compared to UPG or no treatment, women with higher baseline vaginal pH had significantly greater decreases through Day 4 while in the lower vaginal pH group, these differences were only significant through the first 24 hours.

CONCLUSIONS: Amphora lowered the vaginal pH in subjects regardless of baseline vaginal pH levels, though this effect was most pronounced in subjects with baseline vaginal pH levels ≥5. This analysis will help guide future studies on the impact of Amphora on vaginal pH.


Supported by: This study was sponsored by Evofem, Inc. (San Diego, CA), a wholly owned subsidiary of Evofem Biosciences, Inc. Medical writing assistance was provided by PharmaWrite, LLC (Princeton, NJ), and was funded by Evofem, Inc.

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Table 1. Mean change (SD) in vaginal pH from baseline at each treatment timepoint

<table>
<thead>
<tr>
<th>Baseline pH</th>
<th>Amphora 5 g</th>
<th>UPG 4 g</th>
<th>No Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH &lt;5 (n=12)</td>
<td>pH ≥5 (n=10)</td>
<td>pH &lt;5 (n=10)</td>
<td>pH ≥5 (n=10)</td>
</tr>
<tr>
<td>Day 0 - 1 hr</td>
<td>-0.15 (0.25)</td>
<td>-0.80 (0.50)a</td>
<td>0.03 (0.31)</td>
</tr>
<tr>
<td>Day 0 - 12 hr</td>
<td>-0.57 (0.40)b,c, -0.97 (0.67)b,c</td>
<td>-0.05 (0.46)</td>
<td>0.01 (0.65)</td>
</tr>
<tr>
<td>Day 0 - 24 hr</td>
<td>-0.43 (0.35)b,c</td>
<td>-1.05 (0.55)b,c</td>
<td>-0.13 (0.33)</td>
</tr>
<tr>
<td>Day 2</td>
<td>-0.16 (0.25)</td>
<td>-0.52 (0.51)b,c</td>
<td>0.00 (0.31)</td>
</tr>
<tr>
<td>Day 3</td>
<td>-0.25 (0.27)b,c</td>
<td>-0.57 (0.52)b,c</td>
<td>-0.10 (0.29)</td>
</tr>
<tr>
<td>Day 4</td>
<td>-0.21 (0.26)b,c</td>
<td>0.57 (0.57)b,c</td>
<td>-0.05 (0.26)</td>
</tr>
<tr>
<td>Day 5</td>
<td>-0.25 (0.27)b,c</td>
<td>0.47 (0.56)b,c</td>
<td>-0.25 (0.33)b,c</td>
</tr>
<tr>
<td>Day 6</td>
<td>-0.44 (0.37)b,c</td>
<td>-0.47 (0.64)b,c</td>
<td>-0.13 (0.30)</td>
</tr>
<tr>
<td>Day 7</td>
<td>-0.18 (0.26)</td>
<td>-0.10 (0.68)</td>
<td>0.09 (0.72)</td>
</tr>
</tbody>
</table>

Note: aP<0.05 vs Baseline; bP<0.05 vs UPG; cP<0.05 vs No Treatment.

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O-107 Tuesday, October 9, 2018 11:45 AM


OBJECTIVE: To present data on product acceptability and genitourinary discomfort when using Amphora®, an investigational acid-buffering contraceptive vaginal gel, vs. nonoxynol-9 (Conceptrol®).

DESIGN: This was a multicenter, open-label, randomized phase 3 trial conducted over 6 months (representing 183 days or 7 menstrual cycles) assessing efficacy and safety of Amphora; women in the Amphora group could participate for an additional 6 cycles for a maximum of 13 cycles.

MATERIALS AND METHODS: Amphora, which was delivered in 5 mL doses, is a water-based, petroleum-free gel with active ingredients of citric acid, potassium bitartrate and L-lactic acid. Nonoxynol-9 (4% concentration) was delivered in 2.5 mL volume. Acceptability of study product and mild genitourinary discomfort (secondary endpoints) were measured by questionnaires. The acceptability questionnaire was administered at visits after Cycles 1, 7 and 13. P values were based on the CMH statistical test with the Row Mean Score Method using the numeric value of the response. The discomfort questionnaire was administered after Cycles 1, 3, 7, 10 and 13, and included the woman’s and her partner’s discomfort.

RESULTS: A total of 2,935 women were randomized and used at least once application of study drug (1,458 in the Amphora group and 1,477 in the nonoxynol-9 group). By Cycle 7, significantly more women in the Amphora group strongly liked or somewhat liked the product compared to those in the nonoxynol-9 group (83.5% vs. 79.8%, respectively; P=0.010) (Table 1). Acceptability remained high with Amphora users after Cycle 13 (88.2%). Approximately 11% of women reported mild genitourinary discomfort after Cycle 7 (10.9% Amphora; 11.8% nonoxynol-9), mostly due to itching, irritation and burning. Results were similar in the Amphora extension study with 11.6% and 6.6% of women reporting mild genitourinary discomfort after Cycles 10 and 13, respectively. Discomfort was reported in only 1.5% of partners at Cycle 7 (1.6% in the Amphora group and 1.5% in the nonoxynol-9 group) and in approximately 1% of partners of Amphora users after both Cycles 10 and 13. The most common adverse events in the Amphora and nonoxynol-9 treatment groups were similar and included bacterial vaginitis (11.0% and 11.5%, respectively), vulvovaginal mycotic infection (10.7% and 11.4%) and urinary tract infection (9.6% and 13.1%).

CONCLUSIONS: Amphora contraceptive vaginal gel was acceptable and comfortable to most women and their partners.

Supported by: This study was sponsored by Evofem, Inc. (San Diego, CA), a wholly owned subsidiary of Evofem Biosciences, Inc. Medical writing assistance was provided by PharmaWrite, LLC (Princeton, NJ), and was funded by Evofem, Inc.
**O-108** Tuesday, October 9, 2018 12:00 PM

**RANDOMIZED CONTROLLED TRIAL OF THE EFFECT OF A REPRODUCTIVE HEALTH SURVIVORSHIP CARE PLAN ON FERTILITY AND PREGNANCY CONCERNS, VASOMOTOR SYMPTOMS, SEXUAL HEALTH, AND CONCEPTION IN YOUNG BREAST CANCER SURVIVORS.** S. S. Stark, B. Kwan, E. Myers, L. Natarajan, H. Su. UCSD Moores Cancer Center, La Jolla, CA.

**OBJECTIVE:** Young breast cancer survivors (YBCS) have unmet reproductive health needs in managing fertility/pregnancy concerns, hot flashes, vaginal dryness, and contraception. Following development of an evidence-based, online educational intervention targeting YBCS and their healthcare providers (HCP), we hypothesized that YBCS who received the Reproductive Health Survivorship Care Plan (SCP-R) would be more likely to improve on fertility/pregnancy concerns, vasomotor symptoms, sexual health, or contraceptive practices, compared to waitlist controls (NCT02667626).

**DESIGN:** Randomized controlled trial.

**MATERIALS AND METHODS:** YBCS and their nominated HCP were recruited from cancer advocacy and physician referrals across the U.S. Eligible YBCS were aged 18-45 at diagnosis, 18-50 at enrollment, Stages I-III, able to read English, access the Internet and complete daily hot flash text messages. Participants had ≥ 1 of the following reproductive health needs: ≥ moderate fertility/pregnancy concerns, ≥ 4 hot flashes/day with > 1 of moderate severity, ≥ 1 moderate vaginal atrophy symptoms, not contraception/using less effective methods. YBCS underwent computer-generated, stratified randomization to the study arms and were followed for 24 weeks. The intervention group accessed the online SCP-R; the waitlist controls accessing/using less effective methods. YBCS underwent computer-generated, stratified randomization to the study arms and were followed for 24 weeks. A priori corrected using/accepting for age, AMH was not associated fetal weight percentile during the second trimester (%gestational timepointxAMH) did not differ by AMH level (P = 0.83).

**RESULTS:** Of the 522 pregnancies, 316 singleton live births were included in the analysis. Age adjusted mean AMH values did not differ between women with and without subchorionic hemorrhage (2.18ng/mL (95%CI 2.41, 3.4), P = 0.14). After adjusting for age, AMH was not associated fetal weight percentile during the second trimester (βln AMH = .0004, 95% CI -.03, 0.31), or change in percentile from second trimester to birth (βln AMH = .022, 95% CI -.066, 0.02), Fetal growth curves did not differ by AMH level (Pgestational timepointxAMH = 0.83).

**CONCLUSIONS:** MATernal AMH is not a predictor of fetal growth in naturally conceived pregnancies.

Supported by: NIH/NICHD R01 HD067683 and R21 HD060229.

**Table 1** Summary of Acceptability Questionnaire Results

<table>
<thead>
<tr>
<th></th>
<th>Amphora (n=1,458)</th>
<th>Nonoxynol-9 (n=1,477)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product acceptability (strongly/somewhat liked)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycle 1, n/N (%)</td>
<td>1,044/1,416 (73.7)</td>
<td>1,083/1,427 (75.9)</td>
<td>0.482</td>
</tr>
<tr>
<td>Cycle 7, n/N (%)</td>
<td>846/1,013 (83.5)</td>
<td>839/1,051 (79.8)</td>
<td>0.010</td>
</tr>
<tr>
<td>Cycle 13, n/N (%)</td>
<td>277/314 (88.2)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Would consider using product again (definitely/probably would)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycle 1, n/N (%)</td>
<td>1,180/1,417 (83.3)</td>
<td>1,188/1,426 (83.3)</td>
<td>0.946</td>
</tr>
<tr>
<td>Cycle 7, n/N (%)</td>
<td>891/1,014 (87.9)</td>
<td>884/1,050 (84.1)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cycle 13, n/N (%)</td>
<td>289/314 (92.0)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Figure 1** Improvement of individual reproductive health late effects by study arm (n=182)

**Table 1** Improvement of individual reproductive health late effects by study arm (n=182)

<table>
<thead>
<tr>
<th>Reproductive Health Late Effect</th>
<th>Treatment Arm N(%) (n=86)</th>
<th>Waitlist Control Arm N(%) (n=96)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy/fertility concerns ≤3</td>
<td>24 (53.3)</td>
<td>14 (30.4)</td>
<td>2.6 (1.1-6.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>50% decrease in hot flash score</td>
<td>26 (57.8)</td>
<td>24 (51.1)</td>
<td>1.3 (0.6-3.0)</td>
<td>0.52</td>
</tr>
<tr>
<td>50% decrease in vaginal atrophy symptoms</td>
<td>10 (25.6)</td>
<td>11 (23.9)</td>
<td>1.1 (0.4-3.0)</td>
<td>0.85</td>
</tr>
<tr>
<td>Reporting tier I/II contraception</td>
<td>23 (44.2)</td>
<td>21 (34.4)</td>
<td>1.5 (0.7-3.2)</td>
<td>0.29</td>
</tr>
</tbody>
</table>
PREGNANCY AND PERINATAL OUTCOMES OF FIRST-TRIMESTER CROWN-RUMP LENGTH DISCORDANCE IN DICHRIONIC TWIN PREGNANCIES AFTER IN VITRO FERTILIZATION. S. Xiao, M. Mo, H. Zhang, X. Hu, Y. Zeng. Shenzhen Zhongshan Urology Hospital, Shenzhen, China.

OBJECTIVE: To evaluate the association between first-trimester crown-rump length discordance and adverse pregnancy and perinatal outcomes in dichorionic twin pregnancies.

DESIGN: This was a retrospective cohort study of women with dichorionic twin pregnancies after in vitro fertilization (IVF) at our fertility center with two live fetuses scanned between 6 days and 8 weeks’ gestation during the perinatal study period (1st January 2015 and 1st January 2017).

MATERIALS AND METHODS: Study groups were defined by the presence or absence of ≥20% crown-rump length (CRL) discordance at the first-trimester ultrasound scans. Pregnancy outcomes including spontaneous abortion, stillbirth and live birth were compared between discordant and concordant twin pregnancies. Perinatal outcomes (preterm delivery, PTD), low birth weight (LBW), very low birth weight (VLBW), birthweight discordant, neonatal death and admission to neonate intensive care unit (NICU) were also assessed. Singleton live deliveries and twin deliveries were analyzed separately. Moreover, fetal anomalies were also evaluated.

RESULTS: During the study period we identified 1687 dichorionic twin pregnancies on first-trimester ultrasound, of which 1504 met the inclusion criteria. Of the 1504 dichorionic twin pregnancies included, 129 (8.58%) patients were identified as having CRL discordance of at least 20%. CRL discordant twins were more likely to end in one fetal loss before 12 weeks’ gestation (Relative risk= 15.073, 95% confidence interval, 10.128-22.431) than were concordant dichorionic twin pregnancies. Discordant twin pregnancies with twin deliveries were at significant higher risk of birthweight discordance (Relative risk= 2.192, 95% confidence interval, 1.054-4.558). There was no significant difference in perinatal outcomes including PTD, LBW, VLBW, neonatal death and admission to NICU in singleton or twin deliveries. No fetal anomalies were observed in discordant twin pregnancies.

CONCLUSIONS: Dichorionic twin pregnancies were at increased risk for one fetal loss prior to 12 weeks’ gestation and birthweight discordance, but were not associated with adverse perinatal outcomes and fetal anomalies.

A STUDY TO UNDERSTAND THE NEEDS OF A PREGNANCY LOSS COMMUNITY. S. Gavriz, W. Mak.

“Women’s Health, Dell Medical School, Austin, TX; 1RMA of Texas-Austin, Austin, TX.

OBJECTIVE: The purpose of this study is to evaluate the needs of families who have undergone pregnancy loss.

DESIGN: Observational, cross-sectional analysis.

MATERIALS AND METHODS: Families who were members of a Connecticut based peer support group for those who have experienced a pregnancy loss of unknown location were invited to participate in an online survey to assess their experience and evaluate their future needs. The short survey consisted of seven questions primarily as a needs assessment for families who have experienced pregnancy loss, questions included: immediately after your pregnancy loss, rank your most important need, 5 choices were given and these were, family support, bereavement counselling, peer support, why you lost your pregnancy and how to prevent another pregnancy loss; would you have wanted to be referred to a pregnancy loss specialist or team. 1000 families were sent a link to the online anonymous survey in May 2016 and 786 responses were obtained.

RESULTS: 78.2% of respondents experienced pregnancy loss at <12 weeks gestation with 55.0% of patients experiencing >1 pregnancy loss. The vast majority of patients (80.7%) sought care from their primary Ob/Gyn first. 45% of respondents ranked finding answers to why their pregnancy loss occurred as the most important need immediately after their pregnancy loss. 32% of respondents ranked how to prevent pregnancy loss from happening again as the second most important need. Other needs reported by respondents included family support, psychological support such as bereavement counseling, and peer support groups. The majority of patients (70.3%) did not ultimately find a cause for their pregnancy loss. 88.1% of respondents were never offered a consultation with a team or provider specializing in pregnancy loss. Of those patients, 55% of respondents would have desired a referral for a pregnancy loss specialist consult, while 40.6% said maybe they would have considered a referral.

CONCLUSIONS: Our study is the first needs assessment of a large population of families who have experienced pregnancy loss, the majority of whom had first trimester losses. Our results highlight the overwhelming importance to families experiencing pregnancy loss of finding answers of why it happened, and secondly how to avoid recurrence in the future. Furthermore, from our survey responses, all families affected by pregnancy loss could benefit from referral to a pregnancy loss specialist to address their needs.
regulates trophoblast differentiation and hCG production, a pathway which may support epidemiologic associations between VitD status and fetal growth. The goal of this study was to determine the relationship between preconception VitD status, hCG kinetics, and birthweight in women with polycystic ovary syndrome (PCOS) or unexplained infertility treated with ovulation induction.

**DESIGN:** Secondary analysis of the Reproductive Medicine Network randomized clinical trials PPCOSII (comparing efficacy of clomiphene citrate (CC) and letrozole in PCOS) and AMIGOS (comparing multiple birth Cyte following CC, letrozole, or gonadotropins in unexplained infertility).

**MATERIALS AND METHODS:** Total 25 (OH)D was measured with liquid chromatography-tandem mass spectrometry in banked sera collected before study medication initiation. Subjects were classified as VitD sufficient (25(OH)D ³ 30 ng/mL), VitD insufficient (25(OH)D 20-30 ng/mL) or VitD deficient (25(OH)D <20 ng/mL). ANOVA and x2 testing were used to assess differences in demographic characteristics by VitD status. Logistic and random effects linear regression models were used to determine the impact of preconception VitD status on hCG level, change over time (slope), and birthweight.

**RESULTS:** 114 women from PPCOSII and and 147 women from AMIGOS with viable singleton intrauterine gestations and available sera were studied. Only 20% of the women were VitD sufficient (n=52). Women with VDD were more likely to be obese (VDS 14.6% vs VDI 36.0% vs VDD 64%, p<0.0001), yet VitD status was not associated with age, race, ethnicity, infertility diagnosis, fetal sex, or gestational age at delivery. There was a two-fold increased risk of delivering a small for gestational age (SGA) infant in VDD compared to VDS/VDI women (a OR 2.3 [95% CI 1.15-5.2]). VitD status is an effect modifier in the relationship between hCG and birthweight, such that for every one standard deviation rise in log-hCG, there was a 75g reduction in birthweight amongst VitD insufficient/deficient women (adjusted for age, race, and body mass index, P=0.035). No association between hCG slope and birthweight was seen in VDS women.

CONCLUSIONS: Women with PCOS and unexplained infertility with preconception VitD deficiency may be particularly susceptible to abnormalities in placation. The observed relationship between VitD status and hCG kinetics suggests cell differentiation towards the villous/non-invasive rather than extravillous/invasive trophoblast phenotype in those with infertility and low VitD stores. Such an effect may impact fetal growth and supports the correlation between intrauterine growth restriction and VitD deficiency.

**References:**
3. Gernand AD, Simhan HN, Klebanoff MA, Bodnar LM. Maternal serum concentrations of E/P may alter endometrial gene expression and may elevate risk were observed in blastocyst FET cycles. While supraphysiologic concentrations of E/P during ovarian stimulation are associated with endometrial alterations in the tubal environment in most natural cycles, endometrial receptivity is the concern following IVF. Elevations in estradiol (E) and progesterone (P) during ovarian stimulation are associated with endometrial changes that may interfere with normal implantation, which may explain why risk of EP is greater after fresh compared to frozen ET (FET). Despite lower steroid hormone levels in a FET cycle, EP risk is still higher than in natural cycles. The study aimed to determine whether E/P levels during blastocyst FET cycles are associated with EP risk.

**DESIGN:** Retrospective.

**MATERIALS AND METHODS:** Patients who underwent IVF and blastocyst FET between 2002-2018 were included. Trophoderm biopsy and pre-implantation genetic testing for aneuploidy (PGT-A) were performed on select embryos. Patient age, body mass index (BMI), gravidity, parity, endometrial type/thickness at transfer, blastocyst morphologic grade, day of embryo biopsy for PGT-A were recorded. EP was defined as a pregnancy outside of the uterus. Cycles were grouped by pregnancy outcome (EP vs. no EP). Data was analyzed using a T-test, Chi square, and multivariate logistic regression.

**RESULTS:** A total of 4163 patients underwent 5968 FETs, of which 236 cycles resulted in EP (3.9%). Patients who had an EP resulting in EP had a higher BMI compared to those without an EP (24.7 ± 5.2, p=0.02). Patients in both groups were similar in age, gravidity, parity. All patients had comparable endometrial thickness/pattern at transfer, transferred embryos had similar morphologic grades. Peak E and P were comparable in study cohorts and not significantly associated with an EP outcome, before and after adjusting for confounders.

CONCLUSIONS: No association between steroid hormone levels and EP risk were observed in blastocyst FET cycles. While supraphysiologic concentrations of E/P may alter endometrial gene expression and may elevate EP rate in fresh ART cycles, this association is not found in cycles using frozen embryo transfer (FET). Despite changes that may interfere with normal implantation, which may explain why risk of EP is greater after fresh compared to frozen ET (FET). Despite lower steroid hormone levels in a FET cycle, EP risk is still higher than in natural cycles. The study aimed to determine whether E/P levels during blastocyst FET cycles are associated with EP risk.

Supported by: NIH-5K12HD001265 (SS), Penn Presbyterian George L. and Emily McMichael Harrison Fund for Research in Obstetrics and Gynecology (SFB), U10HD39005 (MPD), U10HD38992 (RLS)

**O-114 Tuesday, October 9, 2018 12:00 PM**

**SUPRAPHYSIOLOGIC LEVELS OF STEROID HORMONES DURING FROZEN EMBRYO TRANSFER CYCLES ARE NOT ASSOCIATED WITH ECTOPIC PREGNANCY RISK.**

T. G. Nazem, S. Chang, M. Oliva, J. Lee, A. B. Copperman.

**Objective:** The mechanism for ectopic pregnancy (EP) following an intrauterine embryo transfer (ET) is not fully understood. While EP result from alterations in the tubal environment in most natural cycles, endometrial receptivity is the concern following IVF. Elevations in estradiol (E) and progesterone (P) during ovarian stimulation are associated with endometrial changes that may interfere with normal implantation, which may explain why risk of EP is greater after fresh compared to frozen ET (FET). Despite lower steroid hormone levels in a FET cycle, EP risk is still higher than in natural cycles. The study aimed to determine whether E/P levels during blastocyst FET cycles are associated with EP risk.

**Design:** Retrospective.

**Materials and Methods:** Patients who underwent IVF and blastocyst FET between 2002-2018 were included. Trophoderm biopsy and pre-implantation genetic testing for aneuploidy (PGT-A) were performed on select embryos. Patient age, body mass index (BMI), gravidity, parity, endometrial type/thickness at transfer, blastocyst morphologic grade, day of embryo biopsy for PGT-A were recorded. EP was defined as a pregnancy outside of the uterus. Cycles were grouped by pregnancy outcome (EP vs. no EP). Data was analyzed using a T-test, Chi square, and multivariate logistic regression.

**Results:** A total of 4163 patients underwent 5968 FETs, of which 236 cycles resulted in EP (3.9%). Patients who had an EP resulting in EP had a higher BMI compared to those without an EP (24.7 ± 5.2, p=0.02). Patients in both groups were similar in age, gravidity, parity. All patients had comparable endometrial thickness/pattern at transfer, transferred embryos had similar morphologic grades. Peak E and P were comparable in study cohorts and not significantly associated with an EP outcome, before and after adjusting for confounders.

**Conclusions:** No association between steroid hormone levels and EP risk were observed in blastocyst FET cycles. While supraphysiologic concentrations of E/P may alter endometrial gene expression and may elevate EP rate in fresh ART cycles, this association is not found in cycles using synthetic preparation for FET. Given the increased EP rate in FET cycles compared to the general population, other mechanisms may be at play, including ET technique, altered uterine immune modulation, and inflammatory response.

With the use of big data and precision medicine, protocols can be optimized to enhance embryo and maternal selection for FET. Given the increased EP rate in fresh ART cycles, this association is not found in cycles using synthetic preparation for FET. Given the increased EP rate in FET cycles compared to the general population, other mechanisms may be at play, including ET technique, altered uterine immune modulation, and inflammatory response.
CULTURE MEDIA INCLUDING ANTIOXIDANTS COMPARED TO STANDARD MEDIA: A PROSPECTIVE RANDOMISED SIBLING STUDY. T. Hardarson, a,b aIVI RMA New Jersey, Basking Ridge, NJ;bThomas Jefferson University, Philadelphia, PA;cLivio Reykjavik, Reykjavik, Iceland; dLivio Gothenburg, Gothenburg, Sweden; eSkane Regionaljukhus, Malmo, Sweden; fUniversity of Melbourne, Melbourne, Australia.

OBJECTIVE: The purpose of this study was to compare blastocyst development on the same cohort of oocytes using a single-step medium with or without three antioxidants (α-lipoic acid, acetyl L-carnitine and acetyl L-cysteine).

DESIGN: A multicentre, prospective randomized, double blinded, sibling oocyte trial.

MATERIALS AND METHODS: Couples were enrolled in the study after fertilization check (day 1). A minimum of 6 normally fertilized oocytes were required for participation. Embryos were randomly allocated (1:1) into two study arms comparing embryo development on a time-lapse system (under 5% O2) using a single-step culture medium with (G-TLX) or without (G-TL) antioxidants. Percentage of good quality blastocysts (GQB) per fertilized oocyte on day 5 was the primary end-point in the study.

RESULTS: One hundred and twenty six patients participated in the study resulting in 1167 zygotes that were randomized into the two study arms. There were similar numbers of top quality embryos on day 3 in the G-TL (20.2%) and G-TLX (18.8%) groups, p=0.58. Percentage of day 5 good quality blastocysts was 29.8% (SD 28.2%) and 30.2% (SD 28.5%) in the G-TL and G-TLX groups, respectively. The mean difference 0.45 (95% CI -5.39; 6.29) between the two media systems was not significant (p=0.88). However, the ongoing clinical pregnancy rate was 41.5% vs 54.8% in G-TL (n=41) and G-TLX (n=49), respectively, p=0.38, although, the study was not powered for significance of clinical outcome data.

CONCLUSIONS: Addition of the combination of antioxidants (α-lipoic acid, acetyl L-carnitine and acetyl L-cysteine) to a single-step culture medium, there was a tendency towards a better development or blastocyst morphology grading by the addition of the antioxidants to a single-step culture medium containing the antioxidants, indicating possible positive effects of this combination of antioxidants on embryo viability when cultured in-vitro.

Supported by: The study received support from Vitrolife AB through culture media supplied by the company.

O-116 Tuesday, October 9, 2018 11:00 AM

ULTRA-LOW OXYGEN (O2) TENSION AFTER DAY 3 OF IN VITRO DEVELOPMENT DOES NOT ALTER BLASTOCYST TRANSCRIPTOME: A COMPARISON OF 2% VERSUS 5% O2 TENSION IN EXTENDED CULTURE. S. Morin, a,b T. Wang, a,b X. Tao, a M. Earnhardt, a E. Seli, a,b R. Scott, a,b 1IVI RMA New Jersey, Basking Ridge, NJ; 2Thomas Jefferson University, Basking Ridge, NJ; 3Yale School of Medicine, New Haven, CT; 4Foundation for Embryonic Competence, Basking Ridge, NJ; 5Rutgers Robert Wood Johnson Medical School, Morristown, NJ.

OBJECTIVE: Preliminary data suggest that reducing oxygen (O2) tension in embryo culture from 5% to 2% after day (d) 3 produces a greater number of blastocysts (blasts) compared to culture at 5% throughout. These findings fit with observations that 1) the embryo crosses the uterotubal junction on d3 in vivo, 2) the O2 tension in the uterus is lower than the oviduct, and 3) the embryo’s metabolic strategy shifts from oxidative phosphorylation to aerobic glycolysis around d3. However, modifications in the culture environment may induce untoward changes in the transcriptome that alter reproductive competence. This study sought to compare gene expression between human embryos cultured continuously at 5% versus embryos cultured at 5% from d1 - d3, then 2% through d6.

DESIGN: Experimental study.

MATERIALS AND METHODS: Patients were recruited as part of a randomized controlled trial comparing live birth rates between a sequential O2 tension culture system versus 5% O2 throughout. Aneuploidy screening (PGT-A) was performed on all blasts in the study. All embryos were vitrified while awaiting PGT-A results. Patients with aneuploid blasts were recruited for this subanalysis. After obtaining consent, blasts were warmed and additional biopsies were taken from the trophectoderm (TE) and inner cell mass (ICM). cDNA was amplified using the Smart-seq v4 Ultra Low Input RNA Kit (Clontech). RNA sequencing libraries were constructed using Nextera XT library preparation kit (Illumina) and were sequenced by Yale Center for Genome Analysis on Illumina’s HiSeq 2500 with paired-end 75 bp reads. Gene expression values were calculated as FPKM using Cufflinks 2.1.1. Genes were deemed differentially expressed between different conditions if they showed a FDR (adjusted p-value) of <0.05.

RESULTS: TE and ICM biopsies were obtained from 6 blasts cultured in 2% O2 and 5 blasts cultured at 5% O2. RNAseq analysis revealed significant differences in gene expression between the TE and ICM, with a total of 480 genes differentially expressed, including epigenetic regulatory histone modification genes (HIST1H1E, HIST1H4B, HIST3H3, HIST4H4). However, RNAseq analysis revealed no difference in gene expression between embryos cultured at 2% versus 5% (p>0.05) in either the TE or ICM.

CONCLUSIONS: Reducing O2 tension to 2% after d3 does not significantly alter the transcriptome in the ICM or TE. The increased efficiency in blast conversion previously observed appears related to different mechanisms mediating the biosynthetic activity and metabolic health of preimplantation embryos, potentially through translational and post-translational regulatory pathways. These findings also suggest that a culture system that decreases O2 levels after d3 does not result in significant perturbations in the expression of genes involved in mitochondrial function over standard 5% O2 systems.

References:

Supported by: Foundation for Embryonic Competence.

O-117 Tuesday, October 9, 2018 11:15 AM

THE USE OF ATMOSPHERIC OXYGEN (O2) CONCENTRATION DURING EMBRYO CULTURE UNTIL DAY 3 OF DEVELOPMENT DOES NOT AFFECT OBSTETRIC AND PERINATAL OUTCOMES. P. Gamiz, a M. Rendon, b J. M. de los Santos, c J. Remohi, d A. Navarro, e V. Serra, f M. J. De Los Santos. g IVF Laboratory, IVI-RMA, Valencia, Spain; hAndrology, Marques Barcelona, Barcelona, Spain; iMedical, IVI-RMA, Valencia, Spain; jUAGI, Fundacion IVI, Valencia, Spain.

OBJECTIVE: It is widely accepted that low O2 tension is necessary for optimization of blastocyst culture in IVF and pregnancy rates. However we previously published that when culturing embryos till day 3, pregnancy outcomes seem to be no affected. Long term effect on the use of atmospheric O2 till day 3 has not been described yet. Therefore we wanted further investigate the impact of culturing embryos at high O2 tension during in vitro culture in obstetric and perinatal outcomes.

DESIGN: Randomized clinical trial NCT 01532193 comparing embryo culture in a atmosphere 5.5% CO2, 6% O2, and 88.5% N2 versus a dual-gas system of 5.5% CO2 in air including a total 1125 eligible cycles for the study, which were all randomly allocated to one of the two study groups.

MATERIALS AND METHODS: After considering the different embryo transfer cancellation reasons, 1013 patients reached embryo transfer. After the publication of the primary end points that were pregnancy rates, Obstetrics and neonatal outcomes were also examined. Data presented are mean ± SD or numbers (%). The differences in outcomes between groups were tested by Student T-test for continuous variables and Fisher test for binomial variables. Risk Ratios with 95%IC were also calculated R based on standard error over Poisson regression estimation.

RESULTS: Culturing embryos under atmospheric O2 till day 3 of embryo development, did not impair live birth rates nor neonatal outcomes. No differences were found in terms of mean live births (1.32 +/- 0.494 vs. 1.26 +/- 0.438), birth weight (3196 +/- 654 vs. 3212 +/- 530), female/male ratio (41.23% vs. 38.78%), gestational age (GA) (38.9 +/- 2.94 vs. 39.1 +/- 2.25), percentage of preterm birth (1.75% vs. 2.04%), small for GA (7.02% vs. 8.84%), large for GA (14.04% vs. 12.24%), head circumference ratio (41.23% vs. 38.78%). gestational age (GA) (38.9 +/- 2.94 vs. 39.1 +/- 2.25), percentage of preterm birth (1.75% vs. 2.04%), small for GA (7.02% vs. 8.84%), large for GA (14.04% vs. 12.24%), head circumference ratio (41.23% vs. 38.78%).
CONCLUSIONS: The use of high O2 tension till day 3 of embryo development did not negatively affect the live birth rate nor the obstetric and perinatal outcomes in egg donation program.

O-118 Tuesday, October 9, 2018 11:30 AM

OBJECTIVE: Humidified incubators are widely used for culturing human embryos. However, the use of non-humidified benchtop incubators is becoming more common due to their smaller size and lower risk of fungal contamination. We previously reported that the osmotic pressure of culture media increased more than 20 mOsm/kg after continuous culture for five days in non-humidified incubators. Microdrops of culture medium are typically covered with mineral oil, which prevents changes in the medium’s osmotic pressure, pH and temperature. Although several types of mineral oils are commercially available, it is unknown how the different types affect culture conditions. In this study, we examined how different mineral oil viscosities influence the osmotic pressure of culture media in non-humidified incubators.

DESIGN: Basic Clinical Study.

MATERIALS AND METHODS: We prepared 18 culture dishes containing six 50-μl microdrops of single-step medium (265 ± 10 mOsM/kg). Dishes were divided into three groups: A, light oil (10.8 mPa/sec at 37°C); B, heavy oil (36.5 mPa/sec at 37°C); and C, washed oil (10.4 mPa/sec at 37°C), and placed in a non-humidified benchtop incubator for six days. The osmotic pressure of one dish per group was measured daily using an osmometer. Student t-tests were used for statistical analyses.

RESULTS: The osmotic values for each group are expressed as the mean ± S.D. In group A, the osmotic pressure increased from 268.4 ± 0.5 mOsM/kg (day 0) to 280.5 ± 0.5 mOsM/kg (day 3), and then 300.7 ± 2.4 mOsM/kg (day 6). The osmotic pressure in group B rose from 267.6 ± 0.5 mOsM/kg (day 0) to 275.6 ± 1.1 mOsM/kg (day 3), and then 286.8 ± 1.3 mOsM/kg (day 6). As with group B, the osmotic pressure in group C elevated from 267.6 ± 0.5 mOsM/kg (day 0) to 276.8 ± 0.8 mOsM/kg (day 3), and then 287.8 ± 0.4 mOsM/kg (day 6). These results showed that the osmotic pressure of microdrops covered by light oil significantly increased on day 3 onwards compared to that of microdrops covered by heavy oil (P < 0.01). Elevations in osmotic pressure are minimized by using heavy or washed mineral oils.

CONCLUSIONS: Low-viscosity mineral oil significantly increased the osmotic pressure of culture medium after three days in a non-humidified incubator. However, our results also showed that the osmotic pressure of culture media will inevitably increase in non-humidified incubators regardless of the viscosity of the mineral oil. Therefore, depending on the types of mineral oil, culture media, culture period and incubators used, it may be possible for the osmotic pressure of culture media to exceed the optimal culture environment for human embryos. Although in vitro culture is essential for ART programs, this system is unstable and insufficient compared to the in vivo situation. To more closely align the ART in vitro culture environment to that found in vivo, we must focus on optimizing the materials available to us.

O-119 Tuesday, October 9, 2018 11:45 AM
EFFECT OF DEGENERATED EMBRYOS ON GROUP CULTURED EMBRYOS IN A WELL OF THE WELL CULTURE SYSTEM. H. Watanabe,6 H. Kitasaka,6 T. Yoshimura,6 M. Kojima,6 N. Fukunaga,6 Y. Asada.6 6Asada Ladies Clinic, Nagoya, Japan; 5Asada Institute for Reproductive Medicine, Kasugai, Japan.

OBJECTIVE: Group culture has been demonstrated to improve mice, cattle, swine, and human embryonic development compared with individual culture. This positive effect of group culture may be attributed to paracrine interactions in which growth factors secreted from an embryo into the culture medium stimulate the development of other group-cultured embryos in the same medium. However, it was also reported to have effects such as increased metabolites in group culture and increased reactive oxygen species in degenerative embryos. To examine the influence of degenerative embryos on embryogenesis in group culture using a Well of the Well (WOW) culture system, we compared the blastocyst formation rate with or without degenerated embryos.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: For group culture of human embryos, WOW dish (LinKiD® culture dish; DNP, Japan) was used and 4-25 embryos per dish were cultured. We examined 1600 treated fresh embryo culture cycles between September 2014 and December 2016. Blastocyst formation rate and good blastocyst rate were retrospectively compared using a degenerate group (29 cycles), in which 1-2 degenerated embryos were present until Day 5 of culture, and a control group (1571 cycles) without degenerated embryos.

The average age and range of patients in each group were 33.5 (28-42) and 33.8 (24-44) years, respectively. Fresh embryos, which were obtained from either ICSI or conventional IVF, were cultured in a WOW dish with 60 μl of single culture medium for up to 7 days in a dry incubator. Embryos were evaluated by Gardner’s classification on Days 5, 6, and 7 of culture. A Mann-Whitney U test was used to compare results from the two groups.

RESULTS: Day 5 blastocyst formation rate was 56.2% and 56.9% in the degenerate and control group, respectively. Day 5 good blastocyst rate was 37.2% and 37.2% in degenerate and control group, respectively (not significant). The total blastocyst formation rate up to Day 7 was 65.5% and 68.7% in degenerate and control groups, respectively. The total good blastocyst rate up to Day 7 was 47.0% and 50.3% in degenerate and control groups, respectively (not significant).

CONCLUSIONS: In this study, there was no significant difference in the blastocyst formation rate between the degenerate and control groups. It was reported that the existence of degenerative oocytes or degenerative embryos inhibit the development of other embryos in group culture using conventional droplet culture system (Salahuddin et al. 1995, Tao et al. 2013). However, using the WOW culture system, it was shown that the effect of degenerated embryos is not necessarily adverse in group culture.

O-120 Tuesday, October 9, 2018 12:00 PM
HUMIDIFICATION OF A BENCHTOP IVF INCUBATOR: IMPACT ON CULTURE MEDIA PARAMETERS. R. Holmes1 J. E. Swain.2 1CCRM Boston, Newton, MA; 2CCRM IVF Network, Lone Tree, CO.

OBJECTIVE: Modern benchtop IVF incubators provide smaller/individualized culture chambers and advanced technology to improve environmental stability for gametes and developing embryos. However, many modern incubators are non-humidified. While lack of humidification may avoid some contamination concerns, a dry incubation environment can lead to media evaporation and harmful osmolality increase, even under mineral oil. This concern is especially relevant for labs that utilize single-step culture media with uninterrupted culture with no media replenishment. Recently, humidification of a dry incubator was reported to improve clinical outcomes (Fawzy et al. 2017). However, environmental parameters were not quantified and humidity level as a measure of a normally dry system could have unintended consequences. Humidification of a benchtop incubator was explored, assessing humidity, pH and media osmolality.

DESIGN: Prospective Study.

MATERIALS AND METHODS: In experiment 1, a dry benchtop incubator (G210; Ksystems) was humidified by placing 1 or 2 60mm dishes containing 6ml of water with their lids into a single chamber. Humidity was recorded over 6 days using a data logging hygrometer and compared to a chamber with no water added. The experiment was repeated with the lid removed from water dishes. For subsequent experiments, humidification was achieved using 1 60 mm dish containing 6ml of water and no lid. In experiment 2, pH of cleavage media (Sage) from 500ul microdrops under 1ml of oil in a 5-well dish was measured using a blood gas analyzer (iSTAT) following 24h of equilibration in a dry chamber and a humidified chamber. In experiment 3, osmolality of culture media from the same microdrop dish setup was compared between a dry and a humidified chamber. All experiments were repeated 3-times and data are presented as a mean ± SEM. Data were compared using Fisher’s Exact Test.

RESULTS: The dry incubator chamber maintained a relative humidity of 16%. Room humidity was 21%. Humidity with 1 dish or 2 dishes of water with lids was 23.5% ± 0.45 and 25.5 ± 0.63, respectively. With water, humidity levels were 40.3 ± 0.63 and 44.5 ± 0.59, respectively. pH of media after 24h was 7.23 ± 0.02 in the dry and 7.25 ± 0.01 in the humidified chamber and did not differ. Osmolality and pH of culture media significantly increased over 6 days of culture in both dry and humidified chambers, though less change occurred with humidification.

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CONCLUSIONS: Dry benchtop incubators can be humidified, though levels do not reach those of normally humidified “big box” incubators. Humidification requires additional dishes in the incubator, which takes away space in the culture chamber and presents other possible issues. Water condensed in the chamber at higher humidity and may also negatively impact internal incubator components. Despite achieving modest increases in humidity via addition of water dishes, evaporation of media still occurred, resulting in osmolality and pH increases; albeit less than that observed in a dry chamber.

References:

ENVIRONMENT AND REPRODUCTION
O-121 Tuesday, October 9, 2018 10:45 AM
OVARIAN TOXICITY FOLLOWING EXPOSURE TO POLychLORINATED BIPHENYL 126 IS MEDIATED BY THE ARYL HYDROCARBON RECEPTOR. V. Klenov, S. Flor, S. Ganesan, K. L. Clark, N. Eui, K. Iqbal, M. J. Soares, G. Ludewig, A. F. Keating, L. W. Robertson, Obstetrics and Gynecology, University of Iowa, Iowa City, IA; 2Occupational and Environmental Health, University of Iowa, Iowa City, IA; 3Animal Science, Iowa State University, Ames, IA; 4Pathology and Pediatrics, University of Kansas, Kansas City, KS.

OBJECTIVE: Polychlorinated biphenyls (PCBs) are persistent organic pollutants which adversely affect reproduction. The mechanisms underlying these adverse effects are unclear. We hypothesized the adverse reproductive effects of PCB 126 are mediated by the Aryl Hydrocarbon Receptor (AhR).

DESIGN: This exposure study used rats to investigate alterations in reproductive parameters following exposure to PCB 126.

MATERIALS AND METHODS: An AhR knock out (KO) rat model was developed using CRISPR/Cas9. Wild type (WT) and AhR KO rats received a single intraperitoneal injection of either corn oil (control) or PCB 126 dissolved in corn oil (exposure). After 28 days, animals were sacrificed, serum collected, and necropsy performed. Estrous cycles were synchronized prior to euthanasia. Statistical analyses were performed using one-way ANOVA.

RESULTS: Mean body weight was significantly lower in the WT-PCB group as compared to KO-Oil, KO-Oil and KO-PCB, p<0.001. Relative ovarian weight was significantly lower in the WT-PCB group compared to all other groups, p<0.001. There was no significant difference in relative uterine weight between the groups. Anti-mullerian hormone (AMH) was significantly higher in the WT-Oil group vs. all other groups, p<0.001. There was no significant difference in follicle numbers between each maternal lifestyle exposure and daughters' high (<3.5 ng/mL) versus normal (1.00-3.5 ng/mL) and low (<1.0 ng/mL) versus normal AMH.

CONCLUSIONS: 1202 women had information on their early exposures and current AMH data. Women who reported that their mothers breastfed (71.3%), consumed vitamins (88.3%) and worked while pregnant (32.6%) had relatively lower, but normal, AMH concentrations when adjusting for age and BMI. Caffeine use in mothers' pregnancy was associated with risk of low AMH of the adult offspring (RR1.7, 95% CI 1.1, 2.6), as was diethylstilbestrol (DES) use (RR4.13, 95% CI 1.8, 9.49) after adjustment for age and BMI. Other maternal lifestyle exposures were not associated with daughters' current AMH level.

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O-123 Tuesday, September 9, 2018 11:15 AM
DEVELOPMENTAL EXPOSURE TO ENDOCRINE DISRUPTING CHEMICALS INDUCE DNA DAMAGE IN MYOMETRIUM WHICH IS AMELIORATED BY VITAMIN D TREATMENT. H. E. Elkafas, O. A. Badary, E. A. ELmorsy, R. A. Kamel, A. Al-Hendy, Q. Yang. Obstetrics and Gynecology, Research Scholar, Chicago, IL; 2Pharmacology and Toxicology, The National Organization for Drug Control and Research, Cairo, Egypt; 3Pharmacology and Toxicology, Faculty of Pharmacy, Helwan University, Cairo, Egypt; 4University of Illinois at Chicago, Chicago, IL; 5Obstetrics and Gynecology, University of Illinois at Chicago, Chicago, IL.

OBJECTIVE: Uterine fibroids (UFs) are benign monoclonal tumor of the myometrium and considered the most common gynecologic tumor among reproductive-age women. An increasing body of evidence supports the hypothesis that UF origin from abnormal myometrial stem cells (MSCs). Previous studies showed that early life exposure to endocrine disrupting chemicals such as diethylstilbestrol (DES) increased the incidence of UF development. However, the underlying mechanism is largely unknown. The objective of this study was to determine the DNA damage repair (DDR) defect in myometrium developmentally exposed to DES, and characterize the role of Vitamin D3 in reversing DDR defect in MSCs.

DESIGN: Laboratory research studies were performed by using the Eker rat fibroid model (Tsc2-mutant Eker (Tsc2Eek+)) myometrium tissues as well as corresponding MSCs.

MATERIALS AND METHODS: Female newborn Eker rats (N=5 per group) were treated subcutaneously with vehicle (VEH) or 10 µg/kg of DES on postnatal days (PND) 10-12, a key period of uterine development. Myometrium tissues at age of 5 months were collected for immunohistochemical analysis (IHC) of RAD50, RAD51, and BRCA2. In addition, N. Perkins, R. Silver, E. Schisterman, Obstetrics and Gynecology, Walter Reed National Military Medical Center, Bethesda, MD; 2The Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD; 3NIH, Germantown, MD; 4NICHD, Bethesda, MD; 5NICHD, Bethesda, MD; 6Epidemiology Branch, Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Rockville, MD; 7University of Utah, Salt Lake City, UT.

OBJECTIVE: Anti-Müllerian hormone (AMH) is an established marker of ovarian reserve known to decrease with age and diminished ovarian reserve. Though the primordial follicle pool is established in fetal life, intergenerational effects of maternal health, medications, and other lifestyle exposures on AMH of daughters have not been thoroughly evaluated.

DESIGN: This report is a secondary analysis of the EAGeR trial, a multicenter, double-blind, block-randomized, placebo-controlled trial evaluating the effects of preconception-initiated, daily LDA on live birth among women with 1-2 prior pregnancy losses.

MATERIALS AND METHODS: At study enrollment, serum AMH concentrations were measured during menses and categorized using clinical thresholds. Women were also asked to report whether they were breastfed, their mother’s occupation during pregnancy, and whether their mothers were exposed to DES, vitamins, smoking, alcohol, and caffeine, during their pregnancy. Log binomial regression models were used to estimate associations between each maternal lifestyle exposure and daughters’ high (>3.5 ng/mL) versus normal (1.00-3.5 ng/mL) and low (<1.0 ng/mL) versus normal AMH.

CONCLUSIONS: Interuterine exposure to maternal DES use and caffeine intake may be associated with lower AMH in the offspring in adulthood. If replicated, these findings will link between maternal lifestyle factors and the establishment of the primordial follicle pool of daughters in fetal life.

Supported by: Intramural Research Program, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH.

References:
P42ES013661ES029280.
Support by: PRESTO received support from NIH grants R21-HD072326 and R01-HD086742.

O-125 Tuesday, October 9, 2018 11:45 AM

CHRONODISRUPTION IS ASSOCIATED WITH DELAYED TIME TO CONCEPTION. L. Wan, P. Zhao, R. McCarthy, E. Herzog, S. England, E. S. Junghaus. Washington University in St. Louis, St. Louis, MO.

OBJECTIVE: Circadian rhythms are important to normal physiologic function. Chronic misalignment between sleep timing and daily biologic rhythms is associated with a number of different diseases. We sought to determine associations between various measures of chronodiscruption and time to conception (TTC) in a cohort of pregnancy planners.

DESIGN: Prospective cohort.

MATERIALS AND METHODS: Women planning pregnancy were recruited from the local community. They were asked to wear actigraphy watches continuously for two weeks and followed for TTC. Women included in analysis had at least 7 days of usable actigraphy data and their conception date was confirmed. IVF patients were excluded. Participants who did not conceive were censored at one year. Actigraphy data was analyzed for sleep onset, sleep offset and sleep duration. Most women had set wake-up times due to alarm clock use, therefore day to day variability in timing of sleep was defined as the standard deviation of sleep onset change from one day to the next. This variability was stratified into quartiles as follows: Q1: <.67 minutes, Q2: 67-100 minutes, Q3: 100-138 minutes, and Q4: >138 minutes where Q1 was the most regular pattern, and Q4 was the most erratic pattern. Covariates included age, race, BMI, education, income, and smoking status. Our primary outcome was TTC. Log-rank tests and Cox regression models were conducted to generate unadjusted and adjusted hazard ratios for TTC.

RESULTS: 176 participants met criteria. 75 were pregnant, and 101 were not by the end of one year followup. In bivariate analysis the following covariates were associated with faster TTC: white, lower BMI, higher income and education. Smoking was associated with longer TTC. Participants with set, regular bedtimes had significantly faster TTC than women with more erratic onset of sleep. The association occurred in a dose-dependent with un-adjusted hazard ratios of 4.33 (95%CI: 2.05-9.15), 3.64 (95%CI: 1.20, 5.79), and 2.00 (95%CI: 0.89, 4.40) for Q1, Q2, and Q3 respectively when compared with Q4 group. After adjusting for BMI and income, this association remained significant for women with the most regular sleeping patterns (HR: 2.39, 95% CI 1.08-5.29). Obesity was negatively associated with TTC (HR 0.41, 95% CI: 0.2-0.84) whereas higher income was associated with faster TTC (HR 2.31, 95% CI: 1.01-5.3). These results remained significant for non-black women when the data was stratified by race, and trended similarly for black women. Sleep offset and duration were not associated with TTC.

CONCLUSIONS: Chronodisruption may be associated with a longer TTC. Further work is needed to determine if establishing set sleeping times would benefit women with subfertility.

O-126 Tuesday, October 9, 2018 12:00 PM


OBJECTIVE: Physicians and public health experts have been investigating whether there is evidence of deterioration in semen quality. Others have focused on increased exposure to environmental endocrine disruptors and changes in diet and BMI. One obstacle to understanding male fertility is possible geographic variations in semen quality, which may be due to differences in climate, pollution, occupational exposure, lifestyle, and social habits. This study sought to evaluate semen quality in geographically diverse US sperm donors.

RESULTS: 176 participants met criteria. 75 were pregnant, and 101 were not by the end of one year followup. In bivariate analysis the following covariates were associated with faster TTC: white, lower BMI, higher income and education. Smoking was associated with longer TTC. Participants with set, regular bedtimes had significantly faster TTC than women with more erratic onset of sleep. The association occurred in a dose-dependent with un-adjusted hazard ratios of 4.33 (95%CI: 2.05-9.15), 3.64 (95%CI: 1.20, 5.79), and 2.00 (95%CI: 0.89, 4.40) for Q1, Q2, and Q3 respectively when compared with Q4 group. After adjusting for BMI and income, this association remained significant for women with the most regular sleeping patterns (HR: 2.39, 95% CI 1.08-5.29). Obesity was negatively associated with TTC (HR 0.41, 95% CI: 0.2-0.84) whereas higher income was associated with faster TTC (HR 2.31, 95% CI: 1.01-5.3). These results remained significant for non-black women when the data was stratified by race, and trended similarly for black women. Sleep offset and duration were not associated with TTC.

CONCLUSIONS: Chronodisruption may be associated with a longer TTC. Further work is needed to determine if establishing set sleeping times would benefit women with subfertility.
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O-127 Tuesday, October 9, 2018 10:45 AM

VITRIFIED MACAQUE OVARIAN CORTICAL TISSUE TRANSPPLANTED TO HETEROTOPIC SITES PRODUCES FERTILIZABLE OOCYTES. M. B. Zelinski, A. Ting, A. C. Bishop, M. Lawson, L. Liang, T. Hobbs, D. Jacob, D. Lee, Oregon National Primate Research Center, Beaverton, OR; 2Department of Obstetrics & Gynecology, Oregon Health & Science University, Portland, OR; 321st Century Medicine, Fontana, CA; 4Department of Animal and Rangeland Sciences, Oregon State University, Corvallis, OR.

OBJECTIVE: To determine which heterotopic transplantation sites produce competent oocytes from vitrified ovarian cortical tissue.

DESIGN: Randomized, longitudinal, in vivo.

MATERIALS AND METHODS: Ovarian cortical pieces (3x6x0.5 mm³) from adult (n=4; 6-9 yrs) and peripubertal (n=4; 4-5 yrs) rhesus macaques were vitrified using glycerol:ethylene glycol containing non-permeating polymers, placed into straws and cooled in LN₂ with cryoprotectants removed in sucrose [1]. Within the same animal, pieces were transplanted to subcutaneous (sc) sites [2.3] in the arm (n=4); sc abdomen (n=4); sc abdomen + omental tissue (n=2) or retroperitoneal + omentum (n=2); and bilateral mesosalpinx sites (n=2). Serum was analyzed for estradiol (E) and progesterone (P) to determine ovarian cycling during one year post-transplantation. When E reached at least 100 pg/ml and the preovulatory follicle was >3-6 mm diameter, hCG (1000 IU, im) was given [3]. In alternate cycles, follicles were aspirated 30 hr later. Mature oocytes were inseminated in vitro.

RESULTS: All animals resumed cyclic ovarian cycling based on midcycle E rise and luteal phase P. There was no difference in the time to the first cycle post-transplantation between adult (5.9±0.8 mos) and peripubertal (6.0±0.8 mos), or the number of ovarian cycles displayed during the year (7.2±1 vs 6±1, respectively). The total number of preovulatory follicles seen in the sc arm (2) and sc abdomen (2) was less than those seen in the sc abdomen + omentum (14), retroperitoneal + omentum (10) and mesosalpinx (11). A single preovulatory follicle typically developed at a single site within each animal during a given month despite the presence of multiple transplants. The numbers of preovulatory follicles observed and oocytes collected were similar between adults and peripubertal animals. Of 38 total follicles that developed, 31 were aspirated yielding 21 oocytes (68%); 52% metaphase II, 24% metaphase I, 24% degenerated and no immature oocytes. Three oocytes fertilized, and two cleaved to the 4-cell (from mesosalpinx) and 8-cell stage (retroperitoneal + omentum), and one developed to a morula (sc abdomen + omentum).

CONCLUSIONS: Vitrified ovarian cortical tissue transplanted to retroperitoneal or sc abdominal sites containing omentum and in the mesosalpinx consistently developed a single preovulatory follicle and produced steroid hormones typical of normal ovarian cycles. A competent oocyte was retrieved from each of these sites and efforts to produce offspring are ongoing. Heterotopic transplantation of vitrified ovarian tissue is promising for cancer survivors seeking fertility who sustain extensive ovarian damage after cancer therapy that may preclude re-vascularization to support orthotopic transplantation.

References:

Supported by: R01HD083930 (MZ), P51OD011092 (ONPRC).

O-128 Tuesday, October 9, 2018 11:00 AM

CONSERVATIVE TREATMENT FOR ENDOMETRIAL CANCER AND COMPLEX ATYPICAL HYPERPLASIA: RISK OF INTRATUMORAL SYNECHIA. A. C. N. Cordeiro Mitchell, J. Y. Maher, K. Hunkler, R. A. Garbose, L. J. Collins, M. S. Christianson. Johns Hopkins University School of Medicine, Department of Gyn/Ob, Division of Reproductive Endocrinology, Johns Hopkins, Lutherville, MD; Gyneecology and Obstetrics, Johns Hopkins School of Medicine, Lutherville, MD; Johns Hopkins University School of Medicine, Baltimore, MD; Johns Hopkins School of Medicine, Baltimore, MD; Population, Family, and Reproductive Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; Reproductive Endocrinology and Infertility, John Hopkins University School of Medicine, Lutherville, MD.

OBJECTIVE: To determine what proportion of endometrial adenocarcinomas and complex atypical hyperplasias (CAH) had intratumoral synechiae and to determine potential risk factors.

DESIGN: A single center cross-sectional study.

MATERIALS AND METHODS: A total of 152 consecutive histologically verified endometrial adenocarcinomas and CAHs were included in the study.

RESULTS: Intratumoral synechiae were found in 67% of adenocarcinomas (n=101) and 66% of CAHs (n=12). Most synechiae (59%) were found in the lower uterine segment (LUS), and 37% were found in the lower posterior LUS. The size of synechiae was large in both groups (mean size of synechiae, adenocarcinomas: 2.3 cm, CAH: 2.7 cm). The median number of synechiae was 1 in both groups.

CONCLUSIONS: Intratumoral synechiae are common in endometrial adenocarcinomas and CAHs. Larger studies are needed to determine the clinical significance of synechiae and their potential association with adverse outcomes.

References:
OBJECTIVE: Intrauterine synechiae (IS) are a complication of repetitive dilation and curettage (D&C) procedures. Patients treated conservatively for complex atypical endometrial hyperplasia (CAH) or early endometrial cancer (EC) are at risk for IS and thus impaired fertility. We aimed to identify whether progestin treatment type or number of D&C’s were associated with development of IS or ability to conceive in this group.

DESIGN: Retrospective analysis.

MATERIALS AND METHODS: We evaluated patients undergoing conservative treatment for CAH or EC from 2000 to 2017 at an academic center. We calculated proportions for diagnosis, treatment type, number of D&C’s, method to achieve pregnancy and outcomes (IS, pregnancy, livebirth), IS were identified by hysteroscopy, Pearson chi-squared and Fisher’s exact tests were used to test associations between D&C number, treatment type, and outcomes. Post-hoc power analysis indicated low power to detect pregnancy (power <80%), and sufficient power to detect live birth (power >80%).

RESULTS: We analyzed 54 patients—15 with CAH (27.8%), 39 with EC (72.2%). Mean age was 35 ± 1.3 years. Treatment modalities included megestrol acetate (MA) alone (n=24) and levonorgestrel intrauterine device (LngIUD) (n=19)—either following MA (n=3), with MA (n=10), or alone (n=6). The remaining patients (n=3) received a different oral progestin. Mean number of D&Cs was 3.9 ± 0.9. Women who received MA underwent the most D&C’s (n=24, mean 5.1), followed by those with MA plus LngIUD (n=10, mean 3.4). The uterine cavity was evaluated in 53 subjects; 10 (18.8%) were diagnosed with IS. There was a trend between more D&C’s and IS. LngIUD was associated with a significantly lower rate of IS (15.8% with LngIUD vs. 25.9% without, p<0.001). There were 15 pregnancies and 9 livebirths: 5 spontaneous, 2 with intrauterine insemination, 4 with IVF and 1 with a gestational carrier. Pregnancy was significantly associated with fewer D&C’s. There was no association between livebirths and number of D&C’s (p=0.16) or number of pregnancies or livebirths and LngIUD (p=0.68, 0.97 respectively).

CONCLUSIONS: Among 54 patients undergoing conservative treatment for EC and CAH, nearly 20% developed IS. Treatment with LngIUD was associated with a significantly lower chance of IS, and a higher number of D&C’s was associated with a significantly lower pregnancy rate. Further study is needed to determine whether LngIUD also affects pregnancy outcomes. The risk of IS should be included in counseling.

Supported by: Dr. Edward E. Wallach Research Award

O-130 Tuesday, October 9, 2018 11:30 AM

C-ABL IS NOT ACTIVATED IN GENOMIC DAMAGE INDUCED AND TAP63 MEDIATED OOCYTE APOTOPSIS IN HUMAN. O. Oktam, a G. Bildik, a K. Yakin, a B. Urman. a Obstetrics and Gynecology, The Division of Reproductive Endocrinology and Infertility, Koc University School of Medicine, Istanbul, Turkey; bGraduate School of Health Sciences, Koc University, Istanbul, Turkey.

OBJECTIVE: There is a controversy in literature as to whether c-Abl is crucial for the induction of Tap63-mediated apoptosis and that inhibition of c-Abl with imatinib, which was designed to inhibit the oncogenic kinase BCR-ABL and c-kit, protects oocytes from chemotherapy-induced apoptosis in mice (1-3). We previously showed in an in-vitro model that imatinib did not confer any protection against cisplatin induced follicle loss in human ovary; rather, it accelerated follicle loss mainly via its c-kit blocking actions (4). In this follow-up study we generated a human ovarian xenograft model in nude mice to assess in-vivo ovarian effects of imatinib and explore if Tap63 mediated oocyte apoptosis after chemotherapy-induced genomic damage involves c-Abl activation.

DESIGN: A human ovarian xenograft model.

MATERIALS AND METHODS: Human ovarian tissue samples (0.5 x 0.5 cm) were xenografted subcutaneously to the right flank region of the 8 week-old nude mice (n=4 per group). At 6th weeks post-transplantation, the animals received a single intra-peritoneal injection of cisplatin, imatinib or cisplatin-imatinib. The animals were euthanized and the xenografts were removed at 24h.

RESULTS: Treatment of the animals with a single IP injection of cisplatin (5 mg/kg) resulted in a significant decrease in the number of healthy primordial follicles along with a reciprocal increase in the number of atretic primordial follicles in the xenografts at 24 h post-injection compared to control xenografts. Imatinib administered (7.5 mg/kg) prior to (2 hours) or concurrent to cisplatin did not prevent follicle loss. Interestingly, the magnitude of the gonadotoxicity after imatinib was similar to cisplatin when a comparison was made based on the degree of follicle loss and the reduction in AMH levels. Notably, bizarre shaped primordial follicles lacking oocytes and unclassifiable small follicles possessing atretic oocytes without granulosa cells were much more frequently observed in the samples exposed to imatinib in comparison to control xenografts and those exposed to cisplatin (33% vs. 8% respectively, p<0.01). Cisplatin exposure induced genomic damage and activated SAPK/JNK and TAP63 pathways and triggered apoptosis in the oocytes as evidenced by increased expressions of the phosphorylated forms of γ-H2AXSer139, Chk-1Ser345 and Chk-2Thr68, JNKThr183/Tyr185, JNKpEm183/Thr185 p63Ser190 and cleaved form of caspase-3 on immunoblotting and immunofluorescence. However, Tap63 activation was not associated with any notable change in the protein expression of c-Abl.

CONCLUSIONS: Our findings suggest that Tap63 mediated oocyte apoptosis after chemotherapy does not require c-Abl activation and provide evidence for gonadotoxic effects of imatinib on human ovary, which is also consistent with the observation of Kerr et al in mouse ovary (2) and two anecdotal case reports in human (5,6).

References:
O-131 Tuesday, October 9, 2018 11:45 AM

DYNAMIC VASCULAR CHANGES IN VITRIFIED, WARMED PRIMATE OVARIAN CORTICAL TISSUE IN HETERTROPIC SITES POST-TRANSPLANTATION. C. V. Bishop, a,b A. Ting, c J. Stanley, c M. Lawson, c M. B. Zelinski. d

Division of Reproductive & Developmental Sciences, Oregon National Primate Research Center/Oregon Health & Science University, Beaverton, OR; 3Animal and Rangeland Sciences, College of Agriculture, Oregon State University, Corvallis, OR; 21st Century Medicine, Fontana, CA.

OBJECTIVE: To quantify vascular dynamics in theus macaque ovarian cortical tissue transplanted into heterotropic sites using dynamic contrast-enhanced ultrasound (CEUS).

DESIGN: Repeated measures, longitudinal cohort.

MATERIALS AND METHODS: Adult (n=4) and peri pubertal (n=4) macaque females underwent ovariectomy in the early follicular phase of the menstrual cycle. Ovarian cortical tissue was cryopreserved in 3x6x0.5 mm³ pieces by vitrification using established techniques [1]. Pieces of cortical tissue were transplanted back into heterotropic subcutaneous (sc) sites in these same females similar to previous studies [2] in the arm, abdomen, sc abdomen + omentum and retroperitoneally + omentum. Some pieces were also transplanted into the mesosalpinx below the oviducts. A selected cohort of peripubertal females had additional graft support [n=2; SIS collagen matrix]. At weeks 1, 2, 4, 12, and 16 the vasculature of the arm, abdomen, and omental sites was imaged by contrast-enhanced ultrasound (CEUS) [3]. Very little vascular flow was imaged in most abdominal sites and those in the mesosalpinx were not reliably detected by CEUS, so video clips of arm (n=4-2 females/group) and omental sites (n=4 females/group) were quantified for blood volume (BV) and vascular flow (VF) by custom software (iMCE) and analyzed by novel microbubble assay for blood flow. Fertility and Sterility, 2012, 98(3): p.869.

Supported by: R01HD083930 (MZ), P51OD011092 (ONPRC).

O-132 Tuesday, October 9, 2018 12:00 PM

DOES OXYGEN TENSION INFLUENCE IN VITRO MATURATION OF HUMAN OOCYTES IN A FERTILITY PRESERVATION PROGRAM? PRELIMINARY RESULTS OF A PROSPECTIVE AUTO-CONTROLLED STUDY. C. Herbemont, a M. Dahoun, a N. Sermondade, b I. Cedrin-Durnerin, b M. Grynb erg, c Sifer, c IVF Unit Jean Verdier, Bondy, France; 2Reproductive Biology, Jean Verdier University Hospital, Bondy, France; 3Hospital Antoine Beclere, Clamart, France.

OBJECTIVE: O2 tension within the mammalian female genital tract is low (2-8%), contrary to conditions applied in most of Assisted Reproductive Technology laboratories (20% O2). Hypoxia might reduce oxidative stress commonly triggered by atmospheric O2 tension, further allowing a more physiological process. Besides, the latest recommendations state that embryos should be cultured under hypoxia. However, several randomized studies in mammals have reported controversial findings concerning in vitro maturation rate (MR) and subsequent embryo development when oocytes were matured under either 5% O2 or 20%. To date, no study has ever evaluated the impact of O2 tension on human oocyte matured in vitro.

DESIGN: This prospective, observational, monocentric, auto-controlled study on sibling oocytes was performed from 11/2016 to 07/2017. Fifty-nine patients candidates for fertility preservation (FP) using vitrification of metaphase 2 (M2) oocytes from in vitro maturation (IVM) cycles were included when ≥2 cumulus-oocyte complexes (COCs) were retrieved. Each COC cohort was randomly split into two equal groups: group 1=culture under 20% O2; and group 2=culture under 5% O2.

MATERIALS AND METHODS: COCs were incubated for 48h using an appropriate media, in similar benchtop incubators (G-210, K-Systems®), either under 5 or 20% O2. After 24h and 48h of culture, every oocyte was assessed for maturity and morphology, using 6 parameters (shape, size, ooplasm, perivitelline space, zona pellucida and polar body characteristics) each graded as 1, 0 or +1, giving a total oocyte score (TOS) ranging from -6 to +6. MR and TOS were compared using paired-sample analysis.

RESULTS: We analyzed our preliminary data. Briefly, patients' mean age was 30.6 years. Their mean serum AMH levels and antral follicle count were 3.62 ng/mL and 33.2 follicles, respectively. On average, 13.13 COCs per cycle were retrieved, leading to 7.5 M2 oocytes vitrified (global MR=58.01% (449 M2/774 COCs)). Respectively 383 and 391 COCs were included in groups 1 and 2. In group 1 (20% O2), MR after 48h of culture yielded 56.14% of M2 oocytes (215/383), which was comparable to MR achieved in group 2 (5% O2) (59.85%; 234/391; p=0.21). Considering M2 oocyte morphology, the mean TOS was significantly higher under low O2 tension (3.44 per oocyte in group 2 versus 3.16 in group 1; p=0.014). Finally, a subgroup analysis outlined a significantly higher number of high-grade oocytes (TOS ≥ 4) in group 2 than in group 1 (2.24 versus 1.64, respectively; p=0.032).

CONCLUSIONS: Although these preliminary results failed to highlight any increase in MR under hypoxia, oocyte morphology has been improved. Therefore, further analysis is needed to investigate whether oocyte maturation under 5% O2 increases the chances of pregnancy after warming.

GENETIC COUNSELING

O-133 Tuesday, October 9, 2018 10:45 AM

INTRODUCTION OF EXPANDED CARRIER SCREENING BY A LARGE SPERM BANK IMPROVES PRECONCEPTUAL CARE WITHOUT ALTERING ACCEPTABILITY OF SPERM DONORS. T. G. Nazem, a M. D. Gounko, a S. Chang, a J. Lee, b P. Callum, c N. Bar-Chama, c J. M. Shamonki, a A. B. Copperman, a

Supported by: KUTTAM, equally funded by the Republic of Turkey Ministry of Development Research Infrastructure Support Program.

References:

Supported by: R01HD083930 (MZ), P51OD011092 (ONPRC).
Children conceived with anonymous sperm donors are increasingly choosing to use the donor’s expanded carrier screening (ECS) as a criterion for donor selection. To examine donor characteristics and cycle outcomes among SLOS mutation carriers and controls, a retrospective cohort study was undertaken.

O-134 Tuesday, October 9, 2018 11:00 AM

SMITH-LEMLI-OPITZ DISEASE CARRIERS HAVE NORMAL OVARIAN RESERVE, AND RESPONSE TO STIMULATION DESPITE REDUCED CHOLESTEROL BIOSYNTHESIZING ABILITY. L. Sekhon, a,b Z. Luscher, a D. Aharon, a J. Lee, b T. Mukherjee, b,a A. B. Copperman. b,a Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY; bReproductive Medicine Associates of New York, New York, NY.

OBJECTIVE: Smith-Lemli-Opitz (SLOS) syndrome is an autosomal recessive disease caused by a mutation in 7-dehydrocholesterol reductase (DHCR7), and is involved in cholesterol biosynthesis. Homozygous patients have severe cholesterol deficiency and increased collections of toxic cholesterol precursors. Heterozygotes have partially reduced enzyme deficiency compared with non-carriers (Shefer et al., 1997). Given that cholesterol is a precursor of sex steroid hormones, it is conceivable that partially reduced DHCR7 activity could affect reproductive function. The objective of the study was to examine the effect of SLOS disease heterozygosity on ovarian reserve, response, and ART outcome.

DESIGN: Retrospective, cohort study.

MATERIALS AND METHODS: Patients underwent expanded carrier screening and IVF from 2012-2018. Demographics and cycle outcomes number of recipients are incorporating genetic compatibility in the donor selection process. Perhaps future screening including ancestry and hereditary panels will further improve the donor gamete selection process and ensure optimal health for the next generation.

REFERENCES:

Cycle characteristics and outcomes among SLOS mutation carriers and controls

<table>
<thead>
<tr>
<th></th>
<th>SLOS Mutation Carriers</th>
<th>Controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oocyte age</td>
<td>36.1 ± 6.2</td>
<td>36.1 ± 6.2</td>
<td>0.64</td>
</tr>
<tr>
<td>AMH</td>
<td>4.0 ± 5.2</td>
<td>3.4 ± 4.1</td>
<td>0.48</td>
</tr>
<tr>
<td>Oocytes retrieved</td>
<td>13.3 ± 8 (371)</td>
<td>12.7 ± 9 (8828)</td>
<td>0.76</td>
</tr>
<tr>
<td>Fertilization Rate</td>
<td>80.9% (250/309)</td>
<td>72.3% (638/8828)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Blastulation rate</td>
<td>65.6% (164/250)</td>
<td>63.8% (4071/6381)</td>
<td>0.56</td>
</tr>
<tr>
<td>Embryos biopsied for PGT</td>
<td>4.9 ± 4.1 (102)</td>
<td>4.1 ± 3.6 (2361)</td>
<td>0.36</td>
</tr>
<tr>
<td>Aneuploidy Rate</td>
<td>48.0% (49/102)</td>
<td>45.6% (1077/2361)</td>
<td>0.63</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>43.5% (10/23)</td>
<td>58.8% (257/437)</td>
<td>0.15</td>
</tr>
<tr>
<td>Ongoing pregnancy rate</td>
<td>39.1% (9/23)</td>
<td>53.3% (233/437)</td>
<td>0.18</td>
</tr>
<tr>
<td>Clinical pregnancy loss rate</td>
<td>10.0% (1/10)</td>
<td>9.3% (24/257)</td>
<td>0.54</td>
</tr>
<tr>
<td>Live birth rate</td>
<td>45.5% (5/11)</td>
<td>41.3% (93/225)</td>
<td>0.79</td>
</tr>
</tbody>
</table>
were compared between SLOS carriers and controls. A sub-analysis restricted to single euploid FETs was done. Student’s t-test, chi-square test, and multivariate linear and binary logistic regression models were used.

RESULTS: SLOS mutation carriers (n = 55) were compared to non-carriers (n = 1214) (Table). Controlling for age, SLOS heterozygosity did not impact AMH (β = −0.54, p = 0.4) or BAFC (β = 0.74, p = 0.05). Controlling for age and AMH, oocyte yield (β = −0.2, p = 0.9), fertilization (β = 0.07, p = 0.2), blastulation (β = −0.002, p = 0.98) and embryonic aneuploidy (β = −0.05, p = 0.47) were not impacted in carriers. Controlling for age, BMI, endometrial thickness, and day of trophectoderm biopsy, SLOS carriers (n = 23) had similar implantation (OR 1.2 [0.4-3.3], p = 0.7), ongoing pregnancy (OR 0.9 [95% CI 0.3-2.6], p = 0.9), live birth (OR 0.5 [95% CI 0.1-2.3], p = 0.4), and clinical pregnancy loss (OR 1.6 [95% CI 0.2-14.1], p = 0.6) compared to controls (n = 437).

CONCLUSIONS: Our results demonstrate that SLOS carriers have ovarian reserve and ART outcome similar to that of non-carriers, despite having reduced cholesterol to support steroidogenesis. It is possible that perturbations in genes related to lipid metabolism may be needed for clients have not had screening on themselves so that they can make informed decisions when selecting donors because there is likely to be an increased number of donors screened by this methodology in the future.

O-136 Tuesday, October 9, 2018 11:30 AM

GONADOTROPHIN RECEPTOR POLYMORPHISMS (FSHR N680S AND LHCGR N312S) ARE NOT PREDICTIVE OF CLINICAL OUTCOME AND LIVE BIRTH IN IVF CYCLES. P. Pirtea,a,b D. Marin, b L. Sun, b K. Hong, b Y. Zhan, a X. Tao, c R. Scott, c “Hospital FOCCH, Suresnes, France; bIVI RMA, Basking Ridge, NJ; cFEC, Basking Ridge, NJ.

OBJECTIVE: Recent studies reported that women with homozygous alleles for serine (S) in both FSHR (rs 6166) and LHCGR (rs 2293275) polymorphisms had a 40% higher chance of live birth compared to those with other genotypes after in vitro fertilization (IVF) cycle. Given the major repercussions that these findings might bring to clinical practice, this study aimed to investigate any association between different polymorphism combinations of both FSHR and LHCGR and clinical outcomes in IVF cycles with preimplantation genetic testing for aneuploidy (PGT-A), therefore controlling for the embryo ploidy status.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: All women age 18-40 undergoing their first IVF cycle with aneuploidy screening between 2006-2017 with body mass index <40 were included. All patients received both recombinant FSH and hMG. Genomic DNA was isolated from patient’s blood. For the genotyping of the aforementioned variants, allelic discrimination for the FSHR and LHCGR receptor polymorphisms were performed using TaqMan genotyping assays. Associations between both receptor genotypes and clinical

| TABLE 1. Clinical outcomes for different polymorphism combinations of both FSHR and LHCGR. |
|----------------------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
| FSHR/LH | Number of patients: 1183 | Oocyte yield | Mean MII rate | Usable Blastocyst rate | Successful discharge | Implantation rate | Live birth |
| NN/NN  | 44 | 17.36 +/- 10.03 | 76.4% (73.3-79.4) | 40.6% (36.9-44.7) | 59.1% (43.2-73.7) | 53.4% (39.9-66.7) | 56.8% (41.0-71.7) |
| NN/NS  | 169 | 17.33 +/- 9.79 | 77.4% (75.8-78.9) | 44.5% (42.5-46.6) | 70.4% (62.9-77.2) | 60.1% (53.3-66.6) | 68.0% (60.4-75.0) |
| NN/SS  | 132 | 17.61 +/- 10.57 | 79.1% (77.4-80.7) | 46.2% (43.9-48.5) | 71.2% (62.7-78.8) | 63.6% (55.9-70.8) | 69.7% (61.1-77.4) |
| NS/NN  | 93 | 16.97 +/- 10.96 | 73.1% (70.9-75.3) | 42.7% (39.9-45.6) | 62.4% (51.7-72.2) | 57.6% (48.2-66.7) | 60.2% (49.5-70.2) |
| NS/NS  | 258 | 17.10 +/- 10.75 | 74.5% (73.2-75.8) | 44.9% (43.2-46.6) | 65.9% (59.8-81.7) | 60.8% (55.3-66.0) | 62.8% (56.6-66.7) |
| SS/NN  | 230 | 16.54 +/- 10.63 | 75.4% (74.0-76.8) | 42.8% (41.0-44.6) | 67.8% (61.4-73.8) | 61.6% (55.8-67.1) | 64.8% (58.2-70.9) |
| SS/NS  | 117 | 17.21 +/- 10.84 | 73.3% (70.1-76.3) | 42.1% (38.1-46.1) | 70.2% (55.1-82.7) | 65.1% (52.0-76.7) | 68.1% (52.9-80.9) |
| SS/SS  | 94 | 17.29 +/- 12.47 | 77.1% (75.0-79.1) | 42.1% (39.3-44.8) | 53.2% (42.6-63.6) | 50.4% (41.1-59.7) | 51.1% (40.5-61.5) |

P value 0.2082 0.070 0.118 0.234 0.344 0.237
outcomes was assessed using generalized regression and ANOVA. Live birth rate was the primary outcome. Secondary outcomes included: oocyte yield, mature oocytes (MII) rate, blastocyst rate, usable blastocyst rate, and implantation rate.

RESULTS: 1183 patients met the inclusion criteria and generated reliable genotype calls. The overall genotype frequencies in the study population for the FSHR gene were: 21.7% homozygous for S in codon 680, 29.2% homozygous for N680 and 48.1% heterozygous (N680S). As for the LHCRG, 15.6% were homozygous for N312, 45.9% heterozygous (N312S) and 38.5% homozygous for S312. Our study population consisted of 53.8% white non-Hispanic, 6.1% white Hispanic, 4.1% Afro-American, 20.6% other or unknown. No significant association was found with any of the studied variables (oocyte yield, usable blastocyst rate, implantation rate, live birth) when genotypes were analysed per receptor or in combination with one another (Table 1). There was a statistically significant but clinically insignificant difference in the rate of MII across different variants combinations.

CONCLUSIONS: Our findings suggest that the presence of gonadotrophin receptor polymorphisms is not associated with assisted reproductive technique (ART) outcomes, therefore these variants should not be considered as reproductive predictors.

References:

Supported by: Foundation of Embryonic Competence.

O-137 Tuesday, October 9, 2018 11:44 AM


OBJECTIVE: To compare the rate of abnormal and actionable results on products of conception (POC) testing from women with and without recurrent pregnancy loss (RPL).

DESIGN: Retrospective analysis of results on POC samples.

MATERIALS AND METHODS: Fresh POC samples were shipped with maternal blood samples to a reference lab for analysis. Genotyping was performed using Illumina CytoSNP-12b microarrays and bioinformatics. Diagnosis codes were reviewed and grouped by RPL vs RPL not indicated (non-RPL). Cases with fetal results, in which maternal cell contamination was ruled out, were categorized as normal or abnormal and included aneuploidy, triploidy, deletions (dels), duplications (dups), single chromosome UPD, or full paternal UPD. Results warranting parental studies or maternal medical management were termed actionable (dels/dups, triploidy and full paternal UPD); those with no follow-up indicated were labeled non-actionable.

RESULTS: 2044 fetal POC results were reviewed. RPL was identified in 491 cases and non-RPL was found in 1553 cases. The binomial confidence interval was calculated for each group.

CONCLUSIONS: Two categories of actionable results were highlighted in this study. The first, triploidy and full paternal UPD, may be associated with molar pregnancy and a risk of gestational trophoblastic disease (GTD) warranting maternal medical follow-up. The second, dels/dups, indicate a risk of parental balanced chromosome rearrangement and possible higher risk for miscarriage and/or offspring with chromosomal imbalances. Guidelines set forth by ACOG as well as other professional societies only recommend POC studies after the second consecutive pregnancy loss.1,2 This study demonstrates no statistical difference in the rates of abnormal and actionable results between patients with or without RPL, calling into question the currently established guidelines. Our results underscore the benefit of offering POC chromosome analysis to all patients, to provide an explanation for the loss, direct recurrence risk counseling and impact medical management.

This study demonstrates that RPL alone is not a reliable indication for determining when POC testing is medically appropriate.

References:

O-138 Tuesday, October 9, 2018 12:00 PM

ABSENCE OF AGG INTERRUPTIONS IS A RISK FACTOR FOR A FULL MUTATION EXPANSION AMONG ISRAELI FMRI PREMUTATION CARRIERS. N. Domniz, a L. Ries-Levavi,b L. Marom Ha-ham, a M. Berkenstadt,b R. Orvietoa, c S. E. Elizura, c Y. Cohen, d Department of Obstetrics Gynecology and Fertility, Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel; e The Genetic Institute, Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel.

OBJECTIVE: To assess the role of AGG interruptions as a risk factor for a full mutation expansion among Israeli FMRI premutation carriers.

DESIGN: A cohort population-based study.

MATERIALS AND METHODS: All FMRI premutation carriers who underwent chorionic villus sampling (CVS) or amniocentesis (AC) at Sheba Medical Center during the period of 2011-2017 were included in this study. FMRI PCR assay was performed using the Asuragen Kit in order to determine the number of CGG repeats and AGG interruptions in all women and fetuses. General distribution and data analysis were calculated using SPSS 18.0 and Microsoft Excel.

RESULTS: 406 FMRI premutation carriers underwent CVS or AC. 193 carriers within the range of 55-90 CGG repeats were included in this study.

Results of cases with RPL vs. non-RPL:

<table>
<thead>
<tr>
<th></th>
<th>RPL Cases</th>
<th>non-RPL Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Maternal Age (years)</td>
<td>34.5 (range 21-45)</td>
<td>34.4 (range 17-47)</td>
</tr>
<tr>
<td>Average Gestational Age (days)</td>
<td>64.2 (range 34-192)</td>
<td>69.7 (range 16-284)</td>
</tr>
<tr>
<td>Normal</td>
<td>208/491 (42.4% +/- 4.37%)</td>
<td>694/1553 (44.7% +/- 2.47%)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>283/491 (57.6% +/- 4.37%)</td>
<td>585/1553 (55.3% +/- 2.47%)</td>
</tr>
<tr>
<td>Actionable results: total</td>
<td>65/491 (13.2% +/- 2.97%)</td>
<td>176/1553 (11.3% +/- 1.57%)</td>
</tr>
<tr>
<td>Actionable results: dels/dups</td>
<td>19/491 (3.9% +/- 0.94%)</td>
<td>58/1553 (3.7% +/- 1.57%)</td>
</tr>
<tr>
<td>Actionable results: triploidy/UPD</td>
<td>46/491 (9.4% +/- 2.6%)</td>
<td>118/1553 (7.6% +/- 1.3%)</td>
</tr>
<tr>
<td>Non-actionable results</td>
<td>426/491 (86.8% +/- 2.97%)</td>
<td>1377/1553 (88.7% +/- 1.57%)</td>
</tr>
</tbody>
</table>

Supported by: Foundation of Embryonic Competence.
Among fetuses, 58% of all full mutation expansions occurred from maternal alleles with no AGG interruptions. The risk for a full mutation expansion was 5 times higher in premutation alleles with no AGG interruptions compared to 2 AGG interruptions. Moreover, unstable expansions (increase of 1 CGG or more) occurred in 87% of alleles with no AGG interruptions whilst this number was reduced to 58% when the allele contained a single AGG interruption, and further diminished to 35% in 2 AGG-containing alleles.

CONCLUSIONS: The absence of AGG interruptions is a major risk factor for allele instability and full mutation expansion among Israeli FMR1 premutation carriers with 55 - 90 CGG repeats. Therefore, it is a valuable and fundamental tool and should be part of the genetic and fertility counseling for FMR1 premutation carriers.

LEIOMYOMAS

O-139 Tuesday, October 9, 2018 10:45 AM

Efficacy and Safety of Elagolix in a Sub-Group of Women With Uterine Fibroids and Adenomyosis: Results from a Phase 2 Trial. H. S. Taylor,1 M. A. Bediaye,1 A. S. Lukes2, K. Chwalisz2, C. Owens1, L. B. Welsh2. 1Yale School of Medicine, New Haven, CT; 2University of British Columbia, Vancouver, BC, Canada; 3Carolina Women’s Research & Wellness Center, Durham, NC; 4AbbVie Inc., North Chicago, IL; 5Cleveland Clinic, Cleveland, OH.

OBJECTIVE: Adenomyosis is characterized by benign endometrial tissue growth within the myometrium and is associated with heavy menstrual bleeding (HMB) and dysmenorrhea. Elagolix, an oral, gonadotropin-releasing hormone receptor antagonist, reduces dysmenorrhea in women with endometriosis and HMB in women with uterine fibroids (UF). We evaluated the efficacy and safety of elagolix in a subgroup of women with both UF and adenomyosis.

DESIGN: This 6-month, randomized, double-blind, placebo-controlled, phase 2b clinical trial evaluated the safety and efficacy of elagolix in premenopausal women with HMB (>80 mL, menstrual blood loss [MBL]/cycle) with imaging confirmed UF in 2 cohorts: 300mg twice daily (BID) in cohort 1 and 600 mg once daily [QD] in cohort 2. Each cohort had 4 arms: placebo, elagolix alone, and 2 elagolix with hormonal add-back arms (0.5mg estradiol [E2]/0.1mg norethindrone acetate [NETA]) and 1.0 mg E2/0.5 mg NETA.

MATERIALS AND METHODS: Patients were evaluated with ultrasound and a subset were also evaluated by MRI (both read centrally). Women were to be excluded if they had evidence of diffuse or segmental adenomyosis as a dominant condition (>50% of the myometrium via ultrasound/MRI). Efficacy and safety were evaluated in a post hoc defined subgroup of women who had confirmed adenomyosis (ultrasound/MRI) at baseline (BL). The primary endpoint was the proportion of women who had a ≥50% reduction from BL in menstrual blood loss (MBL) and <80mL MBL in the last 28 days. Safety data was collected from sanitary pads (using the alkaline hematin method). Adverse events (AEs) were recorded.

RESULTS: Of the 567 women treated, 86 (Cohort 1=32; Cohort 2=54) had confirmed adenomyosis at BL; the majority (87%) of these women had a BL BMI ≥25 kg/m2. In Cohort 1, the proportion of women who met the primary endpoint was 40% (4/10) for placebo, 80% (8/10) for elagolix 300mg BID, 83% (10/12) for elagolix 300 mg BID+0.5 mg E2/0.1 mg NETA, and 100% (5/5) for elagolix 300mg BID+1.0mg E2/0.5mg NETA; in Cohort 2 the proportions were 13% (2/16) for placebo, 92% (12/13) for elagolix 600mg QD, 93% (13/14) for elagolix 600mg QD+0.5mg E2/0.1mg NETA, and 89% (8/9) for elagolix 600mg QD+1.0mg E2/0.5mg NETA. At least 1 AE was reported in 90% of the placebo group (n/N=9/10) and 77% of elagolix-treated groups (n/N=17/22) in Cohort 1 and 88% of the placebo group (n/N=14/16) and 67% of the elagolix-treated groups (n/N=25/38) in Cohort 2.

CONCLUSIONS: A higher proportion of elagolix-treated (with or without add-back) women who had UF with HMB and adenomyosis at BL had a reduction in MBL compared to placebo, suggesting that further studies evaluating elagolix treatment in women with adenomyosis are warranted.

Supported by: AbbVie.

O-140 Tuesday, October 9, 2018 11:00 AM

Neuronal Tumor Suppressor NAV3 Decreased in Leiomyomas. I. M. Aly1, T. D. Lewis,2,3 T. Parikh,2,3 J. Pilgrim,2,3 J. Britten-Webb2, M. Malik, W. Catherino,4 Uniformed Services University of the Health Sciences, Bethesda, MD; 5Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD; 6Obstetrics and Gynecology, Uniformed Services University of the Health Sciences, Bethesda, MD.

OBJECTIVE: NAV3 is a tumor suppressor of unknown function in fibroids. The objective of this study is to assess NAV3 expression and its potential role in human uterine fibroids. NAV3 gene silencing induces an upregulation in the GnRH receptor (GnRHr) in other tissues, and fibroids express both GnRH and GnRHr. We hypothesize that NAV3 expression is decreased in fibroids compared to patient-matched myometrium, and that exposure to GnRH agonist would increase NAV3 expression, providing a direct mechanism for GnRH regulation of fibroid growth.

DESIGN: Evaluation of NAV3 mRNA and protein expression in human leiomyoma and patient-matched myometrium, and leuprolide acetate-treated leiomyoma cells.

MATERIALS AND METHODS: RNA sequence (RNAseq) analysis was performed on placebo treated patient matched leiomyoma and normal myometrium samples from a prospective, randomized, placebo-controlled clinical trial. These results were confirmed with qPCR, and quantitative immunohistochemistry (IHC). qPCR results are reported as mean ± SEM. IHC data was quantitated using the H score, and analyzed using the student t-test.

RESULTS: RNAseq analysis of placebo-treated fibroids compared to myometrium unexpectedly demonstrated the presence of transcripts encoding for several neuronal proteins. For NAV3, RNA sequence analysis demonstrated decreased expression in leiomyoma as compared to myometrium (0.81 fold). Presence of NAV3 mRNA was also decreased in surgical samples (0.43±0.05, p=0.026). Confirmatory qPCR results on immortalized fibroid and myometrial cell lines similarly demonstrated a decrease in expression of NAV3 in fibroids (0.28±0.02, p=0.00075). IHC demonstrated a qualitative decrease in NAV3 protein in fibroids as compared to myometrium by visual examination in morphologic appearance and staining intensity and demonstrated a quantitative decrease by H score (H score 154.7±6.2 vs 312.5±14.7, P<0.0001). qPCR on Lupron treated leiomyoma showed an increase in NAV3 mRNA expression (1.53 ± 0.13, p= 0.00037). Similarly, western blot analysis on Lupron treated leiomyoma cells showed an increase in NAV3 protein expression (1.26 ±0.09, p= 0.063).

CONCLUSIONS: NAV3, a tumor suppressor in numerous cancers, is decreased in leiomyoma cells compared to myometrium, and increased by GnRH agonist treatment, suggesting that NAV3 may mediate hormone-independent fibroid regulation by GnRH analogues.

Supported by: Intramural Research Program, NICHD, NIH.

O-141 Tuesday, October 9, 2018 11:15 AM

Effectiveness of Letrozole Combined with Cabergoline on Uterine Myoma Regression in Comparison to the Effect of Cabergoline Alone. A. M. Elbareg, Obstetrics and Gynecology, Associate Professor, Al-Amal Hospital, Misurata University, Misurata, Libyan Arab Jamahiriya.

OBJECTIVE: Uterine myoma is a very common pelvic tumor in premenopausal women. Therapeutic options include medical treatments, which aims to control symptoms in order to replace or delay surgery. Various medical therapies are available, among them, letrozole (LE) & Cabergoline (CE). Aim of this work is to evaluate the effect of LE combined with CE, on regression of symptomatic uterine myomas in women of reproductive age compared to CE alone.

DESIGN: Prospective controlled clinical trial.

MATERIALS AND METHODS: Thirty six patients with symptomatic myomas of >5 cm in diameter were enrolled in a hospital based trial over a period of one year and divided randomly and equally into 2 groups of 18
each: group (A) received 5 mg LE daily & CE 0.5 mg once weekly from first day of menstrual cycle for 6 weeks. Those in group (B) were prescribed only CE for the same dose & duration of trial. Regular follow-up visits were arranged, and changes in uterine & myoma size, volume and number were recorded at each patient. Adverse effects were recorded if any. Data analyzed and P-value considered to be significant if < 0.05. All analyses were performed using SPSS software.

RESULTS: Treatments well tolerated in both groups with minor side effects. Five patients lost during follow-up period, three from (A) & two from (B) groups. Compared with baseline values, mean uterine volume was reduced significantly (P < 0.05) in both groups and with significant difference between groups. Uterine volume in group (A) than (B) (P < 0.016). Total number of myomas was reduced significantly in both groups (P < 0.023). Group (A) patients expressed more myoma shrinkage in comparison to those in group (B) (P < 0.05). Reduction rate of tumor nodule varied from 43-78% in (A) group, while that in group (B) was between 38 to 58%. One patient in (A) group discontinued treatment because of headache, none in the other group.

CONCLUSIONS: Combination of LE and CE in management of uterine myomas is safe and more effective than CE alone, leading to symptomatic improvements, and might be considered for short term treatments before surgery along with the opportunity to preserve fertility.

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A.M. Elbarag et al: Effectiveness of dopamine agonist, Cabergoline (Dostinex), treatment on uterine myoma regression in comparison to effect of gonadotrophin-releasing hormone analogue (Zoladex). Fertility and Sterility, 2013, 100, 3 Supplement, S33.

O-143 Tuesday, October 9, 2018 11:30 AM

EFFICACY AND SAFETY OF THE SELECTIVE PROGESTERONE RECEPTOR MODULATOR (PRM) VI-LAPRISAN: A SUB-ANALYSIS OF THE ASTEROID 1 TRIAL BY ETHNICITY.

L. D. Bradley,4 E. Groeßrup-Wolfers,3 M. Zvolanek,3 K. Petersdorf,3 C. Seitz.3 3Ob/Gyn, Cleveland Clinic, Cleveland, OH; 4Pharmacovigilance, Bayer, Global Safety Leader, Berlin, Germany; 3Medical Affairs Physician, Berlin, Germany; 4Clinical Development, Bayer AG, Employee of Bayer AG, Berlin, Germany; 3GMA Womens Health, Bayer AG, Berlin, Germany.

OBJECTIVE: In ASTEROID 1, 12 weeks’ treatment with the selective PRM vilaprisan (VPR) stopped heavy menstrual bleeding (HMB), induced amenorrhea, and reduced uterine fibroid (UF) volume. Here, we present the efficacy and safety of VPR over 24 weeks in women with UF.

DESIGN: ASTEROID 2 is a randomized, placebo- and active-controlled phase 3, multicenter study. Women with UF > 3 cm and hematocrit (Hct) > 34; the remaining women received placebo during parts of the treatment phase and were not considered here. At 24 weeks, amenorrhea rates were 65.7%, 80.0% and 75.7% for women receiving VPR 6/2, VPR 3/1 and UPA 3/2, respectively. Mean number of bleeding days during treatment periods and treatment breaks normalized to 365 days (standard deviation [SD]) was 23.0 (22.1) days for VPR 6/2, 17.9 (7.7) for VPR 3/1, and 27.1 (14.1) for UPA 3/2. Pronounced reductions in UF volume (-64.8, -50.2 and -33.7 mL) were observed after 24 weeks for VPR 6/2, VPR 3/1 and UPA 3/2, respectively, and were partially maintained at the end of follow-up with VPR (-61.1, -38.0 and 18.5 mL, respectively). Women self-reported decreases in symptom severity beyond bleeding and improvements in quality of life. No unexpected safety signals were observed. Evaluation of endometrial biopsies did not reveal any critical safety findings. Evaluation of expected PRM-associated endometrial changes (PAEC) did not indicate any significant difference in occurrence or reversibility of PAEC between women randomized to VPR 6/2 and VPR 3/1.

CONCLUSIONS: In ASTEROID 2, 24 weeks of VPR 2 mg treatment in 6/2 and 3/1 regimens effectively induced amenorrhea and decreased UF volume. Treatment was well tolerated and there were no unexpected endometrial safety findings. The treatment regimens explored here will be further investigated in phase 3 studies.

Supported by: This study was funded by Bayer Pharma AG.

O-143 Tuesday, October 9, 2018 11:45 AM

EFFICACY AND SAFETY OF THE SELECTIVE PROGESTERONE RECEPTOR MODULATOR (PRM) VI-LAPRISAN: A SUB-ANALYSIS OF THE ASTEROID 1 TRIAL BY ETHNICITY.

L. D. Bradley,4 E. Groeßrup-Wolfers,3 M. Zvolanek,3 K. Petersdorf,3 C. Seitz.3 3Ob/Gyn, Cleveland Clinic, Cleveland, OH; 4Pharmacovigilance, Bayer, Global Safety Leader, Berlin, Germany; 3Medical Affairs Physician, Berlin, Germany; 4Clinical Development, Bayer AG, Employee of Bayer AG, Berlin, Germany; 3GMA Womens Health, Bayer AG, Berlin, Germany.

OBJECTIVE: This subgroup analysis of the ASTEROID 1 trial aimed to assess the efficacy and safety of the highly selective PRM vilaprisan (VPR) in women of different ethnicities with uterine fibroids (UF).

DESIGN: ASTEROID 1 is a multicenter, randomized, double-blind, multi-arm, phase 2 study of women with at least one UF ≥ 3 cm and heavy menstrual bleeding (>80 mL). Women were randomized to receive VPR 0.5 mg, 1 mg, 2 mg or 4 mg once daily or placebo for 12 weeks.

MATERIALS AND METHODS: Amenorrhea (<2 mL per 28 days), and controlled bleeding (menstrual blood loss <80 mL during the third 28-day reference period of the treatment period) were measured by menstrual pictogram. Time to onset was defined as the first day at which controlled bleeding (through to all subsequent 28-day periods) started. The change in volume of the three largest fibroids from baseline to the end of treatment period was assessed by ultrasound. Here, we report outcomes with VPR 2 mg, for Black and African-American women.

RESULTS: 300 patients were included in the full analysis set for ASTEROID 1, of whom 66 (22%) were Black or African American. At baseline, mean UF volume was 173.2 mL in the overall population and 179.0 mL for Black and African-American women. Median volume of the three largest fibroids at baseline was higher for Black and African-American women (78.5 mL) compared with the overall population (57.6 mL). After 12 weeks’ treatment with VPR 2 mg, the amenorrhea rate was 88.5% in the overall population (54 of 61 patients) compared with 76.9% of Black and African-American women (10 of 13 patients). Time to next bleeding was 8 days for Black and African-American women and 6 days in the overall population. For both the overall population and for Black and African-American women, 100% of women achieved controlled bleeding with VPR 2 mg, with a median time to onset of 2 days in both groups (interquartile range [IQR] 1-3 and 1-4, respectively). At the end of treatment, a median reduction in the volume of the three largest fibroids was 42.0% was observed overall, compared with 45.5% for Black and African-American women. Mean hemoglobin levels increased with VPR 2 mg treatment by 0.85 g/dL in the overall population, compared with a 0.27 g/dL increase for Black and African-American women.

CONCLUSIONS: The results from this sub-analysis highlight the disproportionate burden of UF on women of Black or African-American ethnicity. VPR 2 mg treatment induced amenorrhea and controlled bleeding, and reduced fibroid volume in UF overall, similar to the effects observed in the overall population in ASTEROID 1. The VPR 2 mg dose has been selected as the dose for further clinical development in phase 3.

Supported by: This study was funded by Bayer Pharma AG.
IDENTIFICATION OF TARGETABLE MUTATIONS FOR DIFFERENTIAL MOLECULAR DIAGNOSIS OF UTERINE LEIOMYOMAS VersUS LEIOMYOSARCOMAS USING NEXT GENERATION SEQUENCING. A. Mas, a R. Alonso, a J. Jimenez Almanzar, a J. Martin, a G. L. Ayala, a N. Pellicer, a J. Monleon, a C. Simon. b Igenomix Foundation/Institute of Health Research, La Fe Hospital, Valencia, Spain; c Igenomix Foundation, Paterna, Spain; d Bioinformatics, Igenomix Foundation, Paterna, Spain; e Igenomix Foundation, Paterna-Valencia, Spain; f Obstetrics and Gynecology, Institute of Heath Research, La Fe Hospital, Valencia, Spain; g Institute of Health Research La Fe Hospital, Valencia, Spain; h Valencia University, Igenomix, Paterna, Spain.

OBJECTIVE: Although uterine leiomyomas (LM) and leiomyosarcomas (LMS) are considered biologically unrelated tumors, both share morphological and histological characteristics that complicate their differential diagnosis. The development of accurate and non-invasive differential diagnostic methods in patients with surgical indication is urgently needed. Here, we aim to identify targetable mutations in LMS vs LM using Next Generation Sequencing (NGS) to advance our knowledge in their differential diagnosis.

DESIGN: Research clinical study analysing tumour specimens (n=21) from patients diagnosed with uterine LM and/or LMS.

MATERIALS AND METHODS: Targeted sequencing of DNA and RNA coding regions for 170 solid tumours associated-genes (TST170, Illumina, USA) was performed on formalin-fixed, parafin-embedded (FFPE) samples from LM and LMS specimens. DNA sequencing data were assessed by TST170 DNA analysis workflow to identify copy number variations (CNVs), single nucleotide variants (SNVs) and small insertions/deletions (indels). TST170 RNA analysis workflow was also used to get gene expression profile as well as gene fusions and splice variants.

RESULTS: Tumor mutation burden was higher in terms of CNVs, SNVs, indels, and gene fusions in LMS vs LM specimens. For CNVs, 17 genes were affected by deletions in LMS samples, compared to 5 observed losses in LM. Gains (duplications) were also more frequently identified in LMS, present in 13 genes vs 1 gene with duplication within LM cohort. The most common mutations (SNVs and indels) for LMS were identified in 88 of 159 genes in 70% of LMS samples, while mutations in 21 of 55 genes were the most frequent in 64% of LM samples. Finally, specific transcriptomic profile was observed for 15 genes of 55 in LMS samples while 8.5% of LMS showed high confidence gene fusions associated with these tumors for the first time.

CONCLUSIONS: Through an integrated genomic and transcriptomic analysis, we identified novel differential mutations in LMS vs LM tumor driver genes, providing a new insight into their genomic instability and ultimately, increasing the possibilities for a differential diagnosis that, may result in the creation of test to prevent unwanted LMS dissemination prior to surgery.

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Supported by: Sara Borrell Program Fellowship CD15/00058 from Spanish Carlos III Institute (A.M.).

MALE REPRODUCTION AND UROLOGY: CLINICAL

REAL LIFE OUTCOMES OF INTRACYTOPLASMIC SPERM INJECTION (ICSI) CYCLES UTILIZING SPERM AND SPERMATIDS OBTAINED BY MICRO-SURGICAL TESTICULAR SPERM EXTRACTION (MTESE). J. E. Elliott, a C. Labos, b J. S. Meriano, c E. Greenblatt, d K. Jarvi. e Department of Obstetrics and Gynecology, Mount Sinai Fertility - University of Toronto, Toronto, ON, Canada; f Groupe Medicole Jean Talon, Montreal, QC, Canada; g Embryology, TRIO Fertility, Toronto, ON, Canada; h Department of Surgery, Mount Sinai Hospital – University of Toronto, Toronto, ON, Canada.

OBJECTIVE: To assess the operative outcomes from a large number of mTESE procedures performed on men with non-obstructive azoospermia in a single centre, with analysis of subsequent ICSI cycles at 2 fertility clinics using these samples.

DESIGN: Retrospective, single-center chart review.

MATERIALS AND METHODS: 291 mTESE procedures performed at Mount Sinai Hospital, Toronto, Canada between January 2004 and December 2017 were linked to embryology laboratory and outcome data of ICSI cycles utilizing sperm and spermatids from these surgical samples performed at two affiliated fertility clinics in Toronto. A descriptive statistical analysis and logistic regression of selected results was performed.

RESULTS: 256 men underwent a total of 291 mTESE procedures during the 14 year period, with 63% (n=184) resulting in 251 total ICSI cycles. Average male age at time of mTESE procedure was 36.7 years. Average serum FSH and testosterone prior to the mTESE procedure were 21.4 IU/L and 8.4 mmol/L, respectively. Mature sperm were identified intraoperatively by the urologist in 37% (n=109), and in the embryology lab in 33% (n=96) of cases. Spermatids only were found in the embryology lab in 57% (n=166) of mTESE cases. Twenty-nine (10%) mTESE procedures failed to retrieve sperm or spermatids. Sperm was used in 97 ICSI cycles (38.6%), while spermatids were used in 154 (61.4%). Fresh mTESE samples were used in 57 cycles (23%) and frozen samples in 194 (77%). Embryo transfer (ET) occurred once in 133 ICSI cycles (53%), while 22 cycles (9%) had additional frozen embryo transfers. No embryo transfer occurred in 39% (n=97) of cycles started. Eighteen live births occurred in the entire cohort. Of live births, 83% (n=15) resulted from use of mature sperm and only 17% (n=3) from elongated spermatids.

CONCLUSIONS: Sperm retrieval rates from mTESE procedures performed on men with non-obstructive azoospermia at this single urology-center used in 2 affiliated fertility clinics were lower than previous reports in the literature. Similarly, live birth rates (per embryo transfer) utilizing either fresh or frozen mTESE samples were lower than reported US and Canadian in vitro fertilization data. Outcome data such as in this study facilitates more effective counselling of men/couples contemplating conception using surgically retrieved sperm or spermatids.

LIVE BIRTH RATES

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Live Birth Rates (%)</th>
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<td>Overall by:</td>
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O-146 Tuesday, October 9, 2018 11:00 AM

THE ACCEPTABILITY, SAFETY, AND EFFICACY OF NEEDLE-FREE JET ANESTHETIC TECHNIQUE (MAJET) VersUS CONVENTIONAL NEEDLE INJECTION FOR SPERM RETRIEVAL. K. D. Le. a Q. N. Tran, b T. D. Pham, a L. M. Nguyen, a D. T. Nguyen, a V. Q. Dang, a V. N. Ho, a B. W. Mol, a D. J. Handelsman, b IVFMD, My Duc Hospital, c Department of Obstetrics and Gynecology, My Duc Hospital, d Department of Laboratory, My Duc Hospital.
O-148 Tuesday, October 9, 2018 11:30 AM

SPERM RECOVERY RATE FROM CONVENTIONAL TESTICULAR SPERM EXTRACITION (TESE) AND MICRODISSECTION-TESE AMONG THREE HISTOLOGICAL SUBTYPES OF NONOBSTRUCTIVE AZOO-SPERMIA: A META-ANALYSIS. C. Doungkhamchan, a,b E. O. Talbott, c T. Chu, b K. E. Orwig. a,b aObstetrics Gynecology and Reproductive Sciences, University of Pittsburgh, Pittsburgh, PA; bMagee-Womens Research Institute, Pittsburgh, PA; cEpidemiology, University of Pittsburgh, Pittsburgh, PA.

OBJECTIVE: Microdissection-Testicular Sperm Extraction (microTESE) is a preferred technique to retrieve sperm from the testes of patients with non-obstructive azoospermia (NOA) due to high sperm retrieval rates (SRR) in overall uncategorized NOA patients (1-3). However, microTESE cannot be provided to every NOA case due to requirement of expertise, special equipment and long procedure time (4-5). We used meta-analyses to help prioritize patients for microTESE by identifying which NOA histological subtypes, among Sertoli cell only (SCO), Maturation arrest (MA) or hypospermatogenesis (HP) is more likely to benefit from microTESE over conventional TESE.

MATERIALS AND METHODS: We included the studies that performed conventional and/or microTESE in NOA patients with either SCO, MA or hypospermatogenesis subtypes who had no prior TESE. SRRs were reported as the outcome. Studies that performed conventional and microTESE on the same testis were excluded. Meta-analyses based on a random-effects model were performed using STATA software.

RESULTS: Overall 35 studies between 1996 and 2017 were included in this analysis with total 6,335 patients. The pooled SRRs for conventional TESE for SCO, MA and hypospermatogenesis subtypes were 26% (95% confidence interval [CI] 20.59-31.41), 21% (95% CI 16.93-25.07) and 17% (95% CI 13.23-20.77), respectively. The pooled SRRs for microTESE were 73% (95% CI 69.69-76.31), 62% (95% CI 56.36-67.64) and 54% (95% CI 48.74-59.26) for SCO, MA and HP, respectively. The mean difference between the SRRs of conventional and microTESE was statistically significant for all subtypes (p < 0.001).

CONCLUSIONS: Microdissection-Testicular Sperm Extraction is more likely to be successful in patients with hypospermatogenesis subtypes, while patients with Sertoli cell only and Maturation arrest have higher chances to benefit from conventional TESE. Further studies are needed to confirm these findings.
confidence interval (CI) = 20-33%) 44% (95% CI = 35-53%) and 84% (95% CI = 76-91%), respectively. While the pooled SRRs for microTESE in SCA, MO and hypospermatogenesis were 33% (95% CI = 27-39%), 47% (95% CI = 38-56%) and 94% (95% CI = 90-98%), respectively. To directly compare SRR from micro-TESE and conventional TESE among histological subtypes, we calculated SRR ratios (SRR from microTESE divided by SRR from conventional TESE) from the studies that performed both conventional and micro-TESE in the same studies. The pooled SRR ratio for SCO was 1.67 (p = 0.003), meaning that microTESE had significantly superior SRR by 1.67-fold. However, the pooled SRR ratios for MA and hypospermatogenesis were 1.38 (p = 0.21) and 1.14 (p = 0.12), respectively, which were not statistically different.

CONCLUSIONS: The pooled SRRs for microTESE or conventional TESE in each NOA subtype provide insight into the success rate of each technique and will serve as a reference point for new studies. The pooled SRR ratio enables direct comparison of SRRs by micro-TESE and conventional TESE within each histological subtype. We found that SRR using micro-TESE was superior to conventional TESE in patients with SCO but not significantly different in patients with MA or hypospermatogenesis subtypes.

This finding may help clinicians prioritize surgical approach based on NOA histological subtype.

References:

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O-150 Tuesday, October 9, 2018 12:00 PM

OBJECTIVE: To characterize the spermatogenic function of NOA men based on their testicular biopsy samples and create a profile of those likely to have a successful testicular sperm extraction (TESE).

DESIGN: Surgical samples were collected over 1 year from NOA men undergoing TESE. Samples were assessed for spermatozoa by stage-specific germ cell markers and analyzed by microfluidics to identify viable germ cells and meiotic-stage germ cells, respectively, while the lecin PNA was used to identify the acrosome of meiotic-stage cells. RNA was sequenced using Illumina HiSeq 2500 with a 2x150bp configuration per sample.

RESULTS: Comparing the Ej-ICSI with the TESE-ICSI group, 2PN rates were 17% vs. 47% (p = 0.001). Blastocyst formation rate was significantly (P < 0.01) higher following TESE-ICSI (47.0%) compared to Ej-ICSI (30.8%). Clinical pregnancy rate was significantly (P < 0.05) higher following TESE-ICSI (30.7%) compared to Ej-ICSI (13.9%). Significantly more motile sperm were found in the fresh TESE-ICSI group compared with the frozen-thawed TESE-ICSI group (17.6% vs. 73.7%, p < 0.001). Between fresh and cryopreserved testicular sperm, clinical pregnancy rates were 44% vs. 30.8%. Significantly more motile sperm were found in both groups compared to Ej-ICSI (17.6% vs. 73.7%, p < 0.001). Blastocyst formation rate was significantly (P < 0.01) higher following TESE-ICSI (47.0%) compared to Ej-ICSI (30.8%). Clinical pregnancy rate was significantly (P < 0.05) higher following TESE-ICSI (30.7%) compared to Ej-ICSI (13.9%). Significantly more motile sperm were found in the fresh TESE-ICSI group compared with the frozen-thawed TESE-ICSI group (17.6% vs. 73.7%, p < 0.001). Between fresh and cryopreserved TESE-ICSI groups rates of 2PN, blastocyst formation, good-blastocyst, and clinical pregnancy were all comparable (51.5% vs. 53.4%, 49.3% vs. 43.2%, 21.3% vs. 19.2%, and 32.5% vs. 27.7%, respectively).

CONCLUSIONS: From the viewpoint of blastocyst formation rate and clinical pregnancy rate, we recommend the option of testicular sperm retrieval procedure when the outcome of fertilization by ejaculated sperm is not favorable.

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OBJECTIVE: Cryptozoospermia is a situation in which spermatozoa cannot be observed in a fresh semen sample unless an extended centrifugation and microscopic search are performed. Several investigators have performed ICSI using testicular sperm in men with cryptozoospermia and have reported high pregnancy and live birth rates in these couples. However, to use ejaculated (Ej) sperm or testicular sperm retrieved through testicular sperm extraction (TESE) is a difficult question faced when deciding on treatment for cryptozoospermia because of the invasiveness and cost of surgical treatment. In this study we compared the ICSI outcomes using Ej sperm or frozen-thawed testicular sperm in cryptozoospermia cases.

DESIGN: A retrospective study in a reproductive center.

MATERIALS AND METHODS: We have suggested our patients an option of testicular sperm retrieval procedure when the outcome of fertilization is not favorable or no clinical pregnancy is achieved after multiple attempts with Ej sperm. This study investigated 66 cryptozoospermic couples that failed with Ej-ICSI and subsequently underwent TESE between September 2013 and January 2018. One hundred fifty-eight ICSI cycles were performed, in which 883 oocytes were ICSI inseminated with testicular and 273 oocytes with Ej sperm. TESE-ICSI cases were further subdivided into fresh and cryopreserved sperm groups. Fifty-three cycles (503 oocytes) with fresh and 63 cycles (380 oocytes) with cryopreserved testicular sperm were examined. Rates of 2PN, blastocyst formation, good-blastocyst, and clinical pregnancy, were compared according to the sperm derivation.

RESULTS: Comparing the Ej-ICSI with the TESE-ICSI group, the clinical pregnancy rates were 52% and 52.3%, and good-blastocyst rates (11.5% and 20.5%), were not different. Blastocyst formation rate was significantly (P < 0.01) higher following TESE-ICSI (47.0%) compared to Ej-ICSI (30.8%). Clinical pregnancy rate was significantly (P < 0.05) higher following TESE-ICSI (30.7%) compared to Ej-ICSI (13.9%). Significantly more motile sperm were found in the fresh TESE-ICSI group compared with the frozen-thawed TESE-ICSI group (17.6% vs. 73.7%, p < 0.001). Between fresh and cryopreserved TESE-ICSI groups rates of 2PN, blastocyst formation, good-blastocyst, and clinical pregnancy were all comparable (51.5% vs. 53.4%, 49.3% vs. 43.2%, 21.3% vs. 19.2%, and 32.5% vs. 27.7%, respectively).

CONCLUSIONS: Identifying germ cells stages may help determine the spermatogenic profile of azoospermic men and predict the presence of spermatozoa. This is useful for TESE specimens in which the ability to retrieve spermatozoa may be adversely affected by a technical processing error or a spermatogenic arrest.

OBJECTIVE: Cross-sectional data reveal an increased prevalence of depressive symptoms in women with polycystic ovary syndrome (PCOS). The trajectory of symptoms over time has not been described due to a lack of longitudinal studies. We sought to describe the course of depressive symptoms over time and to identify predictors of enduring depression risk in PCOS using a longitudinal design.

DESIGN: Longitudinal cohort study

MATERIALS AND METHODS: Rigorously characterized women with PCOS-Rotterdam ages 16-44 were enrolled in a cohort study between 2006 and 2017 following a visit to a multi-disciplinary clinic. The Beck Depression Inventory Fast Screen (BDI-FS) was self-administered to identify depression risk using a cut-off score of 3-4 at the baseline visit. A follow-up survey was distributed via email in 2017 to determine interval changes and the BDI-FS was repeated. Women with positive depression risk at baseline were divided into two groups on the basis of whether they screened positive or negative for depression risk at follow-up. Kruskall-Wallis, chi-square and Fischer’s exact testing compared parameters between groups. Multivariate logistic regression modeling evaluated factors associated with odds of enduring depression during the study period.

RESULTS: A 24% response rate (170/423) yielded 163 women with complete BDI-FS data at baseline and follow-up. At baseline, median age was 29.0 years (IQR 25.2, 32.2) and BMI was 28.3 kg/m2 (IQR 24.1, 35.2). Follow-up interval was 5.5 years (IQR 2.4, 8.1). 59/163 women screened positive for depression risk at baseline (36%); 52 women (32%) screened positive at follow-up. Median change in BDI-II score was 0 (IQR -2, 1) over the study period. Of the 59 women with depression risk at baseline, 37% were not depressed at follow-up (Resolved group), while 63% had enduring depressive symptoms (Enduring group). For subjects with depression risk at baseline, participants with enduring depression had higher total and LDL cholesterol, lower HDL and a trend toward higher BMI at baseline compared to subjects with resolved depression risk. Serum androgens and hirsutism scores did not differ between groups. In a multivariate logistic regression model controlling for baseline age, baseline BDI-FS score and follow-up interval, each additional unit of BMI at baseline increased odds of enduring depression by 9% (aOR 1.09, 95% CI 1.00, 1.18, p=0.05). Similarly, compared to women with normal body weight, women in the obese range at baseline (BMI ≥30 kg/m2) had a five-fold increased risk of enduring depression at follow-up (aOR 4.81, 95% CI 0.94, 24.6, p=0.058).

CONCLUSIONS: Women with PCOS are at high risk of mood disorders. We found that the prevalence of depression was relatively stable over time in a cohort of women followed longitudinally, and that elevated BMI is a hallmark of enduring depression risk. These results may assist providers in developing targeted intervention strategies to reduce the prevalence of women with long-term depressive symptoms.

O-152 Tuesday, October 9, 2018 11:00 AM

EXAMINATION OF BEHAVIORAL DIFFICULTIES AND ATTENTION DEFICIT HYPERACTIVITY DISORDER AMONG CHILDREN CONCEIVED BY INFERTILITY TREATMENT. E. Yeung,1 R. Sundaram,2 T. Lin,1 A. Ghassabian,3 J. E. Stern,4 E. Bell.5 NICHD, Bethesda, MD; 1New York University, New York, NY; 2Ob/Gyn, Dartmouth-Hitchcock, Lebanon, NH; 3University at Albany, Rensselaer, NY.

OBJECTIVE: To evaluate whether children conceived with infertility treatment differ in behavioral difficulties and attention deficit/hyperactivity at 7-8 years of age from children not conceived with infertility treatment. To determine whether there are differences by type of infertility treatment (i.e., assisted reproductive technologies (ART) or ovaulation induction (OI)).

DESIGN: The Upstate KIDS Study is a matched exposure birth cohort which recruited newborns based on birth certificate indication of infertility treatment use. For every singleton conceived with treatment, three singletons who were not conceived with treatment were recruited (between 2008-2010 frequency matched on region of birth in New York State (excluding New York City).

MATERIALS AND METHODS: Mode of conception was based on maternal report at 4 months postpartum. Linkage of the cohort to the Society for Assisted Reproductive Technology Clinic Outcome Reporting System was conducted to verify ART use. Behavioral difficulties were assessed using the Strengths and Difficulties Questionnaire (SDQ) at 7 years (n=946) and hyperactivity/inattention using the Vanderbilt questionnaire at 8 years of age (n=1041). Maternal questionnaires were scored and clinical cut-points used to define difficulties. Maternal report at 7 or 8 years of age of physician diagnoses or medication use for ADHD was also evaluated (n=1301). Logistic regression estimated adjusted odds ratios (aOR) and 95% confidence intervals (95% CI) for having difficulties/hyperactivity adjusting for socio-demographic factors, smoking and parity.

RESULTS: Thirty-three percent of children were conceived by infertility treatment, with 15% by ART and 18% by OI. Children conceived with infertility treatment did not exhibit any more behavioral difficulties than their peers at age 7 (aOR: 1.17; 95% CI: 0.70-1.94). Neither inattention or hyperactivity at age 8 were associated with infertility treatment (aOR: 0.84; 95% CI: 0.43-1.64 and 0.65; 95% CI: 0.30-1.38, respectively). Their combination based on the Vanderbilt questionnaire (attention deficit hyperactivity disorder, ADHD) did not differ (aOR: 1.06; 95% CI: 0.46, 2.45). Maternal report of a history of ADHD of their children (10%) also did not differ by infertility treatment use (aOR: 1.21; 95% CI: 0.77, 1.90). Results were similar in the ART and OI subgroups.

CONCLUSIONS: Despite concerns that children conceived with infertility treatment are at risk for health issues, our findings show that behavioral difficulties and inattention/hyperactivity did not differ at 7-8 years of age.

References:

Supported by: Supported by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (Contracts HHSN275201200005C, HHSN276200700001C, HHSN275201400013C, HHSN275201300026D/27500004).

O-153 Tuesday, October 9, 2018 11:15 AM

PARENT-INFANT RELATIONSHIP QUALITY IN FAMILIES CREATED BY EGG DONATION. S. Imrie, V. Jaldou, S. Golombek. Centre for Family Research, University of Cambridge, Cambridge, United Kingdom.

OBJECTIVE: In recent years there has been an increase in the number of children born through egg donation. This study examined the quality of mother-infant and father-infant relationships in families created through egg donation.

DESIGN: Eighty-five egg donation families and a comparison group of 65 IVF families (who had conceived using their own gametes) with an infant (M = 11 months) were compared on standardised interview and observational measures assessing parent-infant relationship quality. Families were recruited through UK fertility clinics and all families were heterosexual two-parent families.

MATERIALS AND METHODS: Participants were visited at home by trained researchers. Mothers and fathers were administered the Parent Development Interview (PDI: Abey et al., 1985; Slade et al., 1999) which was coded using a scheme developed by Henderson et al. (2007). Mothers and fathers were interviewed separately. The PDI assesses parental representations of the parent-infant relationship and yields codes assessing parents’ representations of themselves, their representations of the child, reflective functioning, and the coherence and richness of their narratives.

Parents and infants were also administered 10-minute free play tasks, which were filmed and coded using the Emotional Availability (EA) scales (Biringen, 2008) to obtain observational assessments of mother-infant and father-infant interactions. The EA scales consist of four parent dimensions (sensitivity, structuring, nonintrusiveness, nonhostility) and two infant dimensions (responsiveness to the parent, involvement of the parent). Outcomes were examined between family types using multivariate ANOVAs.

RESULTS: Very few differences were found between egg donation and IVF parents in their representations of the parent-infant relationship. Egg donation and IVF fathers did not differ in the quality of their interactions with their infants. Differences were found between family types in the observational assessment of mother-infant relationship quality, indicating less optimal interactions in egg donation families. Egg donation mothers were...
less sensitive ($p = .02$), and less optimally structuring ($p = .01$) than IVF mothers, and egg donation infants were less optimally responsive to their mothers ($p = .01$) and less optimally involving of their mother ($p = .01$) than IVF infants. These differences were of a medium effect size. CONCLUSIONS: The findings suggest that egg donation families function well in infancy overall, but there may be subtle yet meaningful differences in mother-infant interaction quality.

References:

Supported by: The study was supported by the Wellcome Trust [097857/Z/11/Z] and the ESRC (CHESS-ESRC studentship).

O-154 Tuesday, October 9, 2018 11:30 AM

IMPACT OF YOGA- AND MEDITATION-BASED LIFESTYLE INTERVENTION ON DEPRESSION, QUALITY OF LIFE, AND CELLULAR AGING IN INFERTILE COUPLES. M. R. Tolahunase, B. R. Sagar, P. Chaurasia, R. Dada. "Lab for Molecular Reproduction and Genetics, Department of Anatomy, All India Institute of Medical Sciences, New Delhi, India. 2Department of Psychiatry, All India Institute of Medical Sciences, New Delhi, India.

OBJECTIVE: Nearly half of the cases of infertility are of unknown origin comprising both idiopathic and unexplained infertility. Depression, accelerated biological aging, and decreased quality of life are associated with this group. Modern lifestyle plays a critical role in both infertility and depression. The goal of this study was to evaluate the effect of yoga- and meditation-based lifestyle intervention (YMLI) on depression, quality of life and cellular aging in couples with infertility of unknown origin.

DESIGN: A randomized controlled trial.

MATERIALS AND METHODS: Seventy-four couples diagnosed with infertility of unknown origin were randomized into YMLI group (n = 37 couples) and routine expectant management (REM) group (n = 37 couples). All couples were assessed both pre- and post-intervention using Beck Depression Inventory-II scale (BDI-II), 26 item brief version of the World Health Organization Quality-of-Life Scale (WHOQOL-BREF), and assay kits for the peripheral blood biomarkers of cellular aging that included 8OHdG, telomere length, telomerase activity, ROS, TAC, Cox-II activity, cortisol, β-endorphin, DHEAS, IL-6, TNF-α, LL-37, sirtuin-1, BDNF, melatonin, and serotonin. Morphological and functional parameters of semen were also evaluated in the male partners. WHOQOL-100 criteria were used for morphological semen analysis. Functional assessment of the semen included cardinal markers of cellular aging: Sperm DNA damage by DNA fragmentation index (DFI); oxidative stress in semen by reactive oxygen species (ROS), and total antioxidant capacity (TAC); and telomere metabolism in sperm by telomere length and telomerase activity.

RESULTS: Intention-to-treat analysis demonstrated that there was a significant reduction in depression severity [difference between means, (95% CI)] in BDI-II score [-4.73 (-8.13, -3.47), p < 0.001] after YMLI compared to REM group. The study also showed significantly decreased cellular aging and improved quality of life (in all four domains of WHOQOL-BREF scale - physical, psychological, social, and environmental) in YMLI group in comparison to REM group (all p < 0.05). Semen analysis in male partners showed a significant decrease in DNA damage and a significant optimization of oxidative stress in YMLI group compared to REM group (all p < 0.01).

CONCLUSIONS: The results showed that YMLI has an important role in decreasing depression, delaying/reversing cellular aging, and increasing quality of life in couples with infertility of unknown origin. In addition, improvement in the morphological and functional semen parameters of male partners in YMLI group suggest that cellular aging and depression are closely related and, therefore, yoga and meditation may have important effects on both of these variables. Both depression and aggravation may change long-term biological processes and can potentially have significant effects on the quality of life in these couples.

Supported by: This study was supported by the Ministry of AYUSH, Government of India.

O-155 Tuesday, October 9, 2018 11:45 AM


OBJECTIVE: Women undergoing infertility treatment have increased levels of depression and anxiety compared to the general population. We wanted to compare anxiety and depression in oocyte donors to IVF patients, specifically controlling for those who have never undergone an IVF or donor cycle.

DESIGN: Prospective case control study

MATERIALS AND METHODS: 86 oocyte donors and 208 IVF patients undergoing IVF were enrolled. The State-Trait Anxiety Inventory (STAI) and Beck’s Depression Inventory (BDI-II) were used to assess anxiety and depression respectively at cycle day (CD) 2 and time of retrieval (ToR). A score ≥40 on the State Anxiety scale (S-Anxiety) was used to detect clinically significant anxiety. BDI-II scores of ≥14 were used to detect mild depression and ≥20 for moderate depression. Nonparametric tests, student t-tests and Chi-squared tests were used where appropriate and a p < 0.05 was considered to be significant.

RESULTS: The IVF patients had a mean age of 37.5 (±0.34) and 1.26 (±0.115) prior IVF cycles. Donors had a mean age of 26.3 (±0.44) and 1.05 (±0.195) prior donor cycles. 51 IVF patients (24.5%) were receiving psychological therapy and 17 (8.2%) were on psychiatric medications at the time of treatment. No donors were being treated with therapy or psychiatric medications. Overall, IVF patients had higher Trait Anxiety compared to donors (mean 40.0 vs 30.0, p < 0.001). 98 IVF patients (54.7%) had a S-Anxiety ≥40 at CD 2 compared to 7 donors (13%) (p < 0.001). IVF patients had higher S-Anxiety compared to donors at CD2 (mean 41.3 vs 30.5, p < 0.001) and at ToR (mean 42.6 vs 36.0, p < 0.05). There was no difference in the S-Anxiety of IVF patients at CD2 and ToR (p = 0.579) but S-Anxiety of donors increased significantly from CD2 to ToR (mean 30.0 vs 36.4, p < 0.001). 32.1% of donors that were not clinically anxious at CD2 became anxious at ToR. At CD 2, IVF patients and donors had a significant difference in S-Anxiety regardless of their history of previous cycles (p < 0.001) but at ToR, S-Anxiety was only different in patients and donors with prior cycles (p < 0.001). In terms of depression, 48 IVF patients (26.4%) were depressed overall compared to 1 donor (1.9%). Of the depressed IVF patients, 23 (52.1%) were mildly depressed and 23 (47.9%) were moderately to severely depressed. IVF patients had higher BDI-II scores compared to donors at CD2 (mean 10.5 vs 2.1, p < 0.001) and ToR (mean 11.3 vs 2.6, p < 0.001). This difference was still significant when controlled for history of prior cycles (p < 0.001). From CD2 to ToR, there was no change in IVF patient depression or donor depression.

CONCLUSIONS: IVF patients have higher anxiety and depression compared to donors at CD2 and ToR. While levels of anxiety and depression of IVF patients remained constant throughout, donors had a significant increase in anxiety at the ToR compared to the cycle start.

O-156 Tuesday, October 9, 2018 12:00 PM


OBJECTIVE: As assisted reproductive technology (ART) gains popularity, concerns regarding the potential health and developmental consequences of techniques used including controlled ovarian hyperstimulation and manipulation of embryos remain. The aim of this study is to determine if mode of conception has an influence on the risk of autism spectrum disorders (ASD). We hypothesize that the use of ART and other fertility treatments may be associated with increased ASD risk.

O-058 Tuesday, October 9, 2018 11:00 AM

ABC TRIAL: APPRAISAL OF BODY CONTENT. FROZEN EMBRYO CYCLES ARE NOT IMPACTED BY THE NEGATIVE EFFECTS OF OBESITY SEEN IN FRESH CYCLES. J. G. Kim, S. Morin, G. Patounakis, C. Juneau, S. A. Neal, A. W. Tiegs, R. Scott. IVF/IVM/RMA-FL, Lake Mary, FL; College of Medicine, University of Central Florida, Orlando, FL.

OBJECTIVE: Prior research on over 200,000 SART IVF cycles has noted that implantation rate, clinical pregnancy rate, pregnancy loss rate, and live birth rate are all negatively impacted by obesity as defined by BMI (Provoost et al 2016). While these findings are compelling, only fresh transfers were included in this study. This analysis seeks to determine if the negative impact of obesity may be ameliorated by frozen embryo transfer. Moreover, as BMI is derived from an individual’s weight and height alone, the measurement does not account for age, gender, or body composition. These limitations expose BMI as an inexact metric for conferring negative effects of poor metabolic health on fertility. This analysis also explores use of bioelectric impedance analysis (BIA) and its estimation of adiposity as a more precise method of defining obesity.

DESIGN: Prospective cohort study

MATERIALS AND METHODS: Females and their male partners at a single center undergoing IVF from June 2016 - April 2018 were offered utilization of the InBody 770 BIA scale at time of vaginal oocyte retrieval to determine their body composition. Participant demographics, BMI, percent-body fat (%BF), IVF cycle outcome, and pregnancy data were recorded prospectively. Participants’ %BF were analyzed to determine if increased adiposity impacted cycle outcome. Statistical analysis in this evaluation was performed using a mixed effects model accounting for female age and correlation among oocytes derived from the same cohort. An alpha error of 0.05 was accepted and a piecewise approximation was used to adjust for female age.

RESULTS: Data for 1248 females was collected during this study period. Neither female BMI nor %BF was significantly associated with rates of fertilization, blastulation, euploidy, or sustained implantation after adjusting for female age (Table 1).

Adjusted OR of FET Cycle Outcomes

<table>
<thead>
<tr>
<th>Fertilization Rate</th>
<th>Blastulation Rate</th>
<th>Euploidy Rate</th>
<th>Sustained Implantation Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI 0.994 [0.984-1.004] p=0.211</td>
<td>1.002 [0.993-1.011] p=0.606</td>
<td>0.993 [0.982-1.005] p=0.247</td>
<td>1.062 [0.920-1.228] p=0.407</td>
</tr>
<tr>
<td>%BF 0.999 [0.993-1.005] p=0.788</td>
<td>1.000 [0.994-1.005] p=0.886</td>
<td>0.998 [0.992-1.005] p=0.648</td>
<td>1.000 [0.987-1.014] p=0.967</td>
</tr>
<tr>
<td>Visceral Fat Area 1.000 [0.991-1.010] p=0.974</td>
<td>0.994 [0.985-1.002] p=0.125</td>
<td>0.998 [0.998-1.000] p=0.756</td>
<td>0.996 [0.977-1.017] p=0.726</td>
</tr>
<tr>
<td>Mismatch: Normal BMI, High %BF 0.964 [0.826-1.112] p=0.625</td>
<td>1.072 [0.892-1.288] p=0.459</td>
<td>0.885 [0.610-1.282] p=0.517</td>
<td></td>
</tr>
<tr>
<td>Mismatch: High BMI, Normal %BF 1.244 [0.962-1.609] p=0.96</td>
<td>0.838 [0.671-1.047] p=0.119</td>
<td>1.220 [0.929-1.602] p=0.152</td>
<td>1.187 [0.669-2.105] p=0.557</td>
</tr>
</tbody>
</table>

Thomas Jefferson University, Philadelphia, PA; University of Pennsylvania, Pennsylvania State University, Hershey, PA.
CONCLUSIONS: Frozen embryo transfer appears to mitigate the negative effects of obesity seen in fresh cycles. BMI and %BF measurements determined by BIA do not appear to influence rates of fertilization, blastulation, or clinical pregnancy, even when BMI and %BF are controlled. The poor outcomes seen in earlier studies may be attributed to a preexisting suboptimal endometrial milieu in obese patients that is exacerbated by effects of stimulation during fresh cycles.

References:

O-159 Tuesday, October 9, 2018 11:15 AM

OBESITY AFFECTS ENDOMETRIAL RECEPTIVITY BY INDUCING A DISPLACEMENT OF THE PERSONALIZED WOI THAT AFTER CORRECTION BY PERSONALIZED EMBRYO TRANSFER NORMALIZE

CLINICAL RESULTS. J. Bellver, a R. B. Lathi, b E. Labarta, c Vidal, c J. Giles, c S. Cabanillas, a Armaral, a D. Galliano, a C. Marin, a Ruiz-Alonso, a C. Simon, c D. Valbuena. a Medical Department, IVIRMA, Valencia, Spain; bStanford University Medical Center, Sun- nyside, CA; cIgenomix S.L, Valencia, Spain; dMedical Department, Igenomix S.L, Valencia, Spain; eValencia University, Igenomix S.L, Valencia, Spain.

OBJECTIVE: Accumulated evidences demonstrated that higher body mass index (BMI) decreases implantation rate (IR), clinical pregnancy rate (PR) while increasing miscarriages (Bellver 2013; Provost 2016). We aim to investigate the effect of BMI in endometrial receptivity by comparatively assessing the displacement of the window of implantation (WOI) and the clinical impact of personalized embryo transfer (pET) in obese vs non-obese patients.

DESIGN: This is a prospective cohort study involving 176 infertile patients from different BMI (kg/m2) categories: normal weight: 18.5-24.9 (n=80), overweight: 25-29.9 (n=29) and obese: ≥ 30 (n=99).

MATERIALS AND METHODS: Endometrial biopsies were collected using a pipelle catheter in hormone replacement therapy (HRT) cycles at progesterone P+5. Endometrial receptivity analysis (ERA) was performed to diagnose the personalized WOI in each patient. Normal and overweight groups were clustered as non-obese versus obese categories to identify the displacement of their WOI and to compare their clinical outcome after performing pET guided by ERA.

RESULTS: We identified an increase in displacement of the WOI rate as BMI increases: 4.2% for normal weight, 17.2% for overweight and 24.2% for obese patients with a significant difference (p<0.01) between normal weight and obese groups, as well as between non-obese (normal weight and overweight) versus obese categories (9.1% and 24.2% respectively) (p<0.01). The correlation between BMI and displaced WOI is also observed inside the obese category, being highest for patients with BMI ≥ 40 (38.5%) (Table 1). Interestingly, after the clinical correction of the displaced WOI using pET, no significant differences for clinical outcome in terms of pregnancy and implantation rates as well as similar pregnancy loss rate (6.7% versus 13.2%), were observed between non-obese and obese categories (Table 1).

CONCLUSIONS: Our results demonstrate that higher BMI is associated to an increase displacement of the personalized WOI. However, after their correction by performing pET, no significant differences in the clinical outcome in obese vs non-obese patients can be found. Although the metabolic consequences of higher BMI remains to be understood, endometrial assessment for obese women might play a relevant role to increase their reproductive success in ART.

References:

O-160 Tuesday, October 9, 2018 11:30 AM

NLRP1 INFLAMMASOME MEDIATES IMMUNOMETABOLIC DYSFUNCTION IN FOLLICULAR NICHIE OF PCOS. Y. Lai, L. Mu, Y. Zhao, J. Qiao. Center for Hu- man Reproduction, Peking University Third Hospital, Beijing, China.

OBJECTIVE: Investigating mechanism of chronic inflammation in PCOS ovary regulated by NLRP inflammasome.

DESIGN: To determine whether NLRP expression is associated with inflammatory status in follicular niche of PCOS patients, we analyzed expres- sion level of NLRP genes in ovarian granulosa cells isolated from 35 women with PCOS and 32 healthy adult female controls undergoing in vitro fertiliza- tion and embryo treatment (IVF-ET) at the Reproductive Center of Peking University Third Hospital. PCOS patients were diagnosed by Rotterdam-PCOS criteria.

MATERIALS AND METHODS: Ovarian Granulosa cells was isolated by Ficoll density gradient centrifugation and gene expression was detected by Real-time RT-PCR analysis. Furthermore, we tested IL18 and IL 1B protein level in follicular fluids from these patients by ELSA.LCMS/MS was applied to quantify long-chain fatty acids in in follicular fluid. Human ovarian granu- losa cell line KGN was used for in vitro cell tests. Activation of NLRP infla- mmasome and MMP-9 production was detected by western blotting.

RESULTS: Our results showed that IL18 level in follicular fluid of PCOS patients is significantly higher than female controls, besides, IL18 protein level is positively correlated with BMI, which indicated potential link be- tween inflammation and lipid metabolic aberration in follicular microenvi- ronment of PCOS. We also found that NLRP1 transcription level is higher in follicular fluids than healthy women. Inflammasome-activating stimulus induced phosphorylation of caspase-1 in granulosa cell line KGN. Long- chain fatty acids from abnormal lipid metabolism is significantly elevated in follicular fluids from PCOS patients.

CONCLUSIONS: Based on existing results, we infer that up-regulation of NLRP1 in ovarian granulosa cells may be related to lipid metabolic dysfunc- tion in PCOS and result in elevated IL18 secretion in follicular fluid of PCOS women, possibly through NLRP1 inflammasome assembly and activation.

References:

Supported by: National Natural Science Funds for general program 81571400, 31501201, 81771580, 81570101, and 31371521.

O-161 Tuesday, October 9, 2018 11:45 AM

THE ASSOCIATION OF EUPLOID MISCARRIAGE WITH OBESITY. J. C. Lee, a L. Bernardi, b C. E. Boots, b aObstetrics and Gynecology, Northwestern University, Chi- cago, IL; bNorthwestern University, Chicago, IL.

OBJECTIVE: To calculate the rate of structural chromosome abnormalities in products of conception collected at the time of miscarriage and determine the association with maternal obesity.

DESIGN: Retrospective cohort study in an academic medical center.

MATERIALS AND METHODS: All patients with spontaneous pregnancy loss less than 20 weeks gestation with available cytogenetic results from products of conception were included. Institutional Review Board approval was obtained. Obesity was defined as body mass index (BMI) ≥ 30kg/m2. Chi square and binary logistic regression was performed using SPSS.

RESULTS: A total of 2,661 women with a mean age at time of loss of 34.8 years (+/- 4.95) and mean BMI of 25.3 kg/m2 (+/-5.57) were included in final analysis. Within the cohort, 63.8% of the losses were aneuploid, of which 8% were monosomies, and 7% were polyploidies. Of the euploid losses, 18.1% were 46,XX and 18% were 46,XY, which suggests that the rate of maternal cell contamination was low. After adjusting for age and race, obese women were 59.2% more likely to have a euploid
CONCLUSIONS: Obesity is linked to a wide range of negative health outcomes including decreased fertility and pregnancy loss. Our data shows that elevated maternal BMI is associated with a higher rate of pregnancy loss before 20 weeks gestation that cannot be explained by structural chromosomal abnormalities. Existing data in the recurrent early pregnancy loss population suggests a correlation between obesity and higher rates of euploid miscarriage. Our cohort included all patients who requested cytogenetic evaluation and is not limited to those with recurrent loss. Potential pathophysiologic effects of obesity on early pregnancy loss include hormonal dysregulation, changes to the endometrium, and influence on oocyte function and early embryo development. Continued research is needed to better understand the mechanisms for pregnancy loss in this population. Though miscarriage can be a difficult experience for patients, interventions aimed to encourage lifestyle modifications and weight loss in the obese population before subsequent conception could influence reproductive health outcomes including repeat miscarriage.

References:
Boots CE, Bernardi LA, Stephenson MD Frequency of euploid miscarriage is increased in obese women with recurrent early pregnancy loss. Fertil Steril 2014;102:455-9
Supported by: The Northwestern university Enterprise data warehouse (EDW) and EDW pilot grant program were used to support this research.

Preimplantation Genetic Testing 2

O-163 Tuesday, October 9, 2018 10:45 AM

BIRTH RATES FOLLOWING EUPLOID BLASTOCYST TRANSFER DECLINES RAPIDLY WITH PREVIOUS UNSUCCESSFUL TRANSFERS OF EUPLOID BLASTOCYSTS. J. Zolton, 1 K. S. Richter, 1 B. C. B. J. R. Graham, 2 M. J. Hill, 2 A. H. DeCherney, 2 M. J. Tucker, 2 C. Kallen, 2 K. Devine, 2 E. A. Widra, 2, I. Sasson, 2 "Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD; 3 Shady Grove Fertility Reproductive Science Center, Rockville, MD.

OBJECTIVE: To evaluate outcomes of vitrified euploid blastocyst transfers according to the number of previous consecutive unsuccessful cryopreserved euploid blastocyst transfer cycles

DESIGN: Retrospective cohort study

MATERIALS AND METHODS: All patients undergoing autologous transfer of cryopreserved blastocysts diagnosed as euploid by preimplantation genetic testing for aneuploidy (PGT-A) from 2012-2016 at a large assisted reproduction center. Clinical pregnancy was defined by ultrasound confirmation of an intrauterine gestational sac.

RESULTS: A total of 1489 patients underwent one or more transfers of PGT-A euploid cryopreserved blastocysts during the study period. 387 of these patients underwent 1 to 5 additional attempts after initial failures. While age and BMI did not differ by attempt number, the number of embryos per transfer increased with increasing numbers of previous failures. The likelihood of pregnancy outcomes declined progressively with additional attempts following initial failures. Live birth declined from 52% in first time euploid transfers to only 20% in the fifth transfer cycle after failed euploid blastocyst transfers. Compared to first transfers of euploid blastocysts, the relative reductions in birth rate per transfer was 22%, decreasing from 52% to 41%, for second attempts after one failed euploid blastocyst transfer. After two prior unsuccessful transfers of euploid blastocysts, birth per transfer decreased by an additional 33%, from 41% to 35%. Moreover, this decline in success was observed despite transferring a greater number of embryos in subsequent cycles. The cumulative result was that the number of live born children per transferred euploid blastocyst declined from 49% to 18% from the first to the fifth attempts.

CONCLUSIONS: Birth rates from euploid blastocyst transfers declined rapidly with an increasing number of previous unsuccessful transfers of euploid blastocysts. Patients who fail to achieve live birth after multiple euploid blastocyst transfers have a poor prognosis and warrant further clinical investigation.
A comparison of twin rates and pregnancy outcomes with and without PGT-A

<table>
<thead>
<tr>
<th>SET with PGT-A</th>
<th>DET/SET without PGT-A</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPR</td>
<td>7/992 (0.7%)</td>
<td>15/546 (2.7%)</td>
</tr>
<tr>
<td>MZTR</td>
<td>7/992 (0.7%)</td>
<td>1/546 (0.2%)</td>
</tr>
<tr>
<td>SABR</td>
<td>91/675 (13.5%)</td>
<td>52/233 (22.3%)</td>
</tr>
<tr>
<td>OPR/LBR</td>
<td>576/992 (58.0%)</td>
<td>166/546 (30.4%)</td>
</tr>
</tbody>
</table>

**SET with PGT-A**

**DET without PGT-A**

**p-value**

| TPR | 7/992 (0.7%) | 1/288 (0.3%) | 0.7 |
| MZTR | 7/992 (0.7%) | 1/288 (0.3%) | 0.7 |
| SABR | 91/675 (13.5%) | 28/149 (18.8%) | 0.12 |
| OPR/LBR | 576/992 (58.0%) | 120/188 (64.7%) | 0.0001 |

**References:**


**O-165 Tuesday, October 9, 2018 11:15 AM**

**COMPARISON OF THE TIMES TO ACHIEVE AN ONGOING PREGNANCY IN ADVANCED MATERNAL AGE PATIENTS WITH PGS AND YOUNG IVF PATIENTS WITHOUT PGS.** M. Cetinkaya, C. Pirkevi Cetinkaya, S. Kahraman. Assisted Reproductive Technologies and Reproductive Genetics Center, Istanbul Memorial Hospital, Istanbul, Turkey.

**OBJECTIVE:** To evaluate using a Kaplan-Meier survival analysis whether young IVF patients achieve an ongoing pregnancy earlier than older patients applying for PGS.

**DESIGN:** This retrospective cohort study includes 2400 frozen-thawed embryo transfer cycles (FET) of 1956 couples whose embryos were frozen, thawed and transferred between August 2011 and December 2017. Blastocysts of young patients with a good ovarian reserve were frozen and transferred later (freeze-all group; n=1456). Aneuploidy screening was routinely applied for advanced maternal age (above 37), patients with an history of abnormal fetal karyotype and with repeated implantation failures (above 2) (PGS group; n=954).

**MATERIALS AND METHODS:** The mean female age was 29.8±4.2 and 35.1±4.9 for the freeze-all and the PGS groups, respectively (p below 0.0001). The mean number of cumulus oocyte complexes and metaphase II oocytes was 21.6±10.5 and 17.3±8.7 for the freeze-all group and 14.6±9.7 and 12.1±7.9 for the PGS group, respectively (p below 0.0001). The mean number of frozen blastocysts was 6.7±3.9 and 4.9±3.5 for the freeze-all and the PGS groups, respectively (p below 0.0001). PGS was done either with aCGH or NGS. Evaluation of the time between pick-up and transfer as days may be influenced by many patient and clinical factors, thus misrepresenting the interpretation of survival analysis. To overcome this bias, each embryo transfer cycle is used as a time unit.

**RESULTS:** In the Kaplan-Meier survival analysis performed, at most four subsequent FET cycles were taken into consideration for each patient. However, once a patient reached an ongoing pregnancy, any further FET cycles were not cumulatively counted since the purpose of the study was to determine the number of FET cycles required to obtain an ongoing pregnancy. When survival curves were compared in the Kaplan-Meier analysis, it revealed that achieving an ongoing pregnancy was one cycle earlier in the PGS group than the freeze-all group (p below 0.0001). The overall ongoing pregnancy rate of FET cycles with PGS was significantly higher when compared to transfers without PGS (49.3% vs. 44.1%, respectively (p below 0.05)), despite a higher average age in PGS cycles (29.8±4.2 and 35.1±4.9, respectively) and a significantly lower AMH level in the PGS group (5.6±3.9 and 3.2±2.9, respectively). Additionally, FET cycles with PGS were 1.19 (1.0589 to 1.3275 95% CI) fold more likely to result in an ongoing pregnancy when compared to non-PGS FET cycles with significantly less frozen embryos (6.7±3.9 and 4.9±3.5, respectively) (*number before aneuploidy screening*).

**CONCLUSIONS:** PGS may be offered to young IVF patients with a good ovarian reserve to decrease the time to achieve an ongoing pregnancy.
Comparison of euploid rates in D5 vs. D6 expanded blastocysts by sex

<table>
<thead>
<tr>
<th>Day of blastocyst expansion</th>
<th>Male</th>
<th>Female</th>
<th>p-value</th>
<th>Male</th>
<th>Female</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euploid</td>
<td>63%</td>
<td>41%</td>
<td>0.02</td>
<td>55%</td>
<td>60%</td>
<td>0.59</td>
</tr>
<tr>
<td>Aneuploid</td>
<td>37%</td>
<td>59%</td>
<td>0.02</td>
<td>45%</td>
<td>40%</td>
<td>0.65</td>
</tr>
</tbody>
</table>

References:
2. Lin PY, Huang FJ, Kung FT, Wang LJ, Chang SY, Lan KC. Comparison of sex-ratio imbalances in blastocyst transfer with some studies suggesting an altered ratio in favor of male offspring following blastocyst embryo transfer. Previous studies are limited by only fresh embryo transfer cycles and sex determination from live birth data, with all studies retrospective in design. It has also been suggested that embryos with delayed blastulation are more likely to be aneuploid, however it remains unknown whether this relationship is affected by the sex of the embryo. The objectives of the study were (1) to evaluate the sex ratio in blastocyst embryos undergoing preimplantation genetic testing (PGT-A) and (2) to ascertain differences in euploid rates between Day 5 and Day 6 expanded blastocysts within male and female cohorts.

DESIGN: This was a retrospective study of IVF patients who underwent PGT-A at a single IVF center.

MATERIALS AND METHODS: Blastocysts were graded using the Gardner grading system and embryos with a score of >2 were considered expanded and suitable for trophectoderm biopsy. All PGT-A was performed using next-generation sequencing. A chi-squared analysis was performed.

RESULTS: A total of 465 embryos were included from 81 patients between 2017-2018. The average age of patients was 35.2 years (range 22-44), BMI was 23.6 kg/m2, and average CD3 FSH was 6.2 mIU/mL. The overall aneuploidy rate in this cohort of embryos was 44%. The male-to-female ratio of blastocysts was (258/207) 55%/45% (p = 0.03). The euploid rate was 55% vs 57% among male and female embryos, respectively. 60% of embryos were euploid on day 5 compared to 50% on day 6 (p = 0.03). Male embryos were more likely to be euploid on day 5 versus day 6 (63% vs 41%, p < 0.05) compared to female embryos which had a similar euploid rate on day 5 versus day 6 (55% vs 60%, p = 0.48).

CONCLUSIONS: To our knowledge, this is the first study to assess sex imbalances and ploidy in IVF-PGT-A cycles as it relates to blastocyst expansion on day 5 versus day 6 at an individual center. We observed a sex-ratio imbalance among blastocysts undergoing PGT-A, in favor of males. Similar to other studies, we found a higher euploid rate among day 5 blastocysts versus day 6, in both male and female embryo cohorts. Overall, the euploid rate was higher in day 5 male embryos versus day 6 male embryos, while in female embryos the euploid rates were similar. These results might suggest differences in morphokinetics and blastocyst expansion of male and female embryos as it relates to ploidy status.
without PGT-A (control group) were compared. This enabled a single donor to serve as her own control. GEE models accounted for multiple transfer cycles within the same recipient and paired for cycles both with and without PGT-A from the same donor. PGT-A was performed by array comparative genomic hybridization. DNA microarray or next generation sequencing. PGT-A cycles with no euploid embryos were included in the primary analyses, making it a per oocyte retrieval/haw analysis. The primary outcome was live birth when available or ongoing pregnancy.

RESULTS: 1291 recipient cycles from 223 donors were available for analysis, including 262 cycles with PGT-A and 1029 without PGT-A. The average number of blastocysts available for testing per PGT-A cycle was 2.9. On average 0.97 embryos were transferred in the PGT-A group compared to 1.38 in the group without PGT-A (P < 0.01). The median aneuploidy rate per recipient was 25%. 43% of PGT-A cycles had 100% euploid embryos, whereas only 12.7% of cycles had no euploid embryos for transfer. For 82% more than half their embryos tested as euploid. Live birth/ongoing pregnancy occurred in 53.8% of egg thaw cycles with PGT-A versus 55.8% in the no PGT-A cohort (P = 0.14). Similar findings persisted when all subsequent transfers from one egg thaw cycles were analyzed (Table 1). When excluding the 12% all aneuploidy cycles from the PGT-A cohort, PGT-A resulted in a 61.3 versus 55.8% live birth/ongoing pregnancy rate (P = 0.14).

CONCLUSIONS: Aneuploidy is relatively uncommon in blastocysts generated from donor oocytes. This study was unable to adequately assess time to pregnancy. PGT-A did not improve the likelihood of live birth nor decrease miscarriage for recipients of vitrified donor oocytes. Therefore, PGT-A may indicate overall cost without demonstrable benefit in the donor recipient population. Time to pregnancy studies are needed.

Vitrified donor egg IVF with no PGT-A versus PGT-V

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PGT-A</th>
<th>No PGT-A</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First thaw</td>
<td>n=231</td>
<td>n=849</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth/ongoing (%)</td>
<td>53.8 (47.3-59.7)</td>
<td>55.8 (52.4-59.2)</td>
<td>0.79 (0.45-1.42)</td>
<td>0.44</td>
</tr>
<tr>
<td>Miscarriage loss (%)</td>
<td>9.7 (6.0-15.5)</td>
<td>11.1 (8.9-13.8)</td>
<td>0.86 (0.47-1.55)</td>
<td>0.61</td>
</tr>
<tr>
<td>Chemical loss (%)</td>
<td>9.6 (5.8-15.6)</td>
<td>11.0 (8.8-13.7)</td>
<td>0.86 (0.49-1.55)</td>
<td>0.63</td>
</tr>
<tr>
<td>Total loss (%)</td>
<td>19.5 (14.4-26.5)</td>
<td>22.1 (19.0-25.5)</td>
<td>0.85 (0.54-1.32)</td>
<td>0.48</td>
</tr>
<tr>
<td>Total twins</td>
<td>n=262</td>
<td>n=1029</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth/ongoing (%)</td>
<td>51.5 (45.7-47.3)</td>
<td>52.8 (49.5-56.1)</td>
<td>0.95 (0.73-1.23)</td>
<td>0.70</td>
</tr>
<tr>
<td>Miscarriage loss (%)</td>
<td>10.0 (6.1-16.0)</td>
<td>13.1 (10.7-16.0)</td>
<td>0.73 (0.41-1.31)</td>
<td>0.30</td>
</tr>
<tr>
<td>Chemical loss (%)</td>
<td>11.7 (7.5-17.9)</td>
<td>13.5 (11.1-16.2)</td>
<td>0.85 (0.50-1.46)</td>
<td>0.56</td>
</tr>
<tr>
<td>Total loss (%)</td>
<td>21.6 (15.9-28.6)</td>
<td>26.6 (15.9-28.6)</td>
<td>0.76 (0.50-1.14)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Supported by: PREG, NICHD, NIH

REPRODUCTIVE BIOLOGY: ANIMAL STUDIES

O-169 Tuesday, October 9, 2018 10:45 AM

HUMAN PLATELET-RICH PLASMA IMPROVES ENDOMETRIAL REGENERATION AND PREGNANCY OUTCOMES IN A MURINE MODEL OF ASHERMAN SYNDROME. J. Kim, J. Hwang, S. Lyu, J. Kim. Department of Obstetrics and Gynecology, Fertility Center of CHA Gangnam Medical Center, CHA University, Seoul, Korea, Republic of.

OBJECTIVE: AS is characterized by intrauterine adhesion or fibrosis, which are usually sequelae from damage to the endometrium, and is often associated with infertility. There are few therapeutic options that are not practically effective. The efficacy of autologous PRP including several cytokines and growth factors was recently suggested for patients with impaired endometrium. We investigated whether PRP administration could restore endometrial function and increase pregnancy outcomes in a murine model of AS.

DESIGN: Experimental study

MATERIALS AND METHODS: Under IRB approval, humans PRP were donated from 6 patients. We have established a murine model of AS by injected into the unilateral horn or bilateral horns of AS group by intrauterine injection at day 7 after injury. The cellular and molecular fibrosis was analyzed by histology and immunofluorescence staining and comparative expression of fibrosis-related factors at day 7 after PRP treatment. Female mice were individually bred to males with proven fertility to evaluate embryos on day 12 and the live birth rate.

RESULTS: The histologic evidence of regeneration in damaged horn after PRP treatment was confirmed by hematoxylin and eosin, and Masson’s trichrome staining. The expression of COL1A1 was lower in the PRP treated AS horn in comparison with the untreated AS horn on immunofluorescence staining. The result RT-PCR and real-time RT-PCR of fibrosis-related factors (Tgfβ1, Timp1, and Coll1a1) revealed that intrauterine infusion of PRP was effective to recuperate traumatized horn (5.9 vs. 2.6, 3.1 vs. 1.0; 4.4 vs. 1.0, p < 0.01). The number of implantation site of AS horn was improved by PRP treatment (2.1 vs. 4.6, p < 0.01). The live birth rate in the untreated AS group and in the PRP treated AS group was 0% and 83.3%, respectively (p < 0.01). On average, litter size were 6.3 in the PRP-treated AS group and 11 in the sham group (p < 0.01). The weight of the pups born to PRP-treated mice was similar to that of sham mice on day 7 to 28 after birth.

CONCLUSIONS: This is the first study so far to show that human PRP is able to regenerate impaired endometrium and to enhance pregnancy outcomes in a murine model of AS. In previous studies, endometrial development was assessed by ultrasound to confirm the effect of PRP treatment in humans. These data provide evidence for histological alteration and changed expression of fibrosis-related factors. We believe that our studies support the potential value of using PRP for endometrial regeneration in clinical settings with compromised endometrial growth.

References:
O-170 Tuesday, October 9, 2018 11:00 AM

MULTIPLE EFFECTS OF INTERLEUKIN-10 ON OSTEOPOROSIS IN OVARIECTOMIZED MICE. Z. Yan,† L. Gao,† Y. Cui.† The First Affiliated Hospital, Nanjing Medical University, Nanjing, China; ‡State Key Laboratory of Reproductive Medicine, Clinical Center of Reproductive Medicine, First Af-fil, Nanjing, China; §Basic Research in Reproductive Medicine, Nanjing, China.

OBJECTIVE: Estrogen is a key protective factor of bone mineral density (BMD). Osteoporosis can be induced in the ovariectomized mice. The previous study showed that the expression of interleukin-10 (IL-10) in the osteoblasts was positively correlated with estrogen receptors.

DESIGN: This study was designed to explore the possible effect of IL-10 on osteoporosis in the ovariectomized mice.

MATERIALS AND METHODS: 60 ICR mice were divided into three groups: control group, model group (OVX group) and IL-10 treatment group (IL-10 group), each group with 20 mice. Bilateral ovaries were removed to setup the model. In the IL-10 treatment group, the ovariectomized mice were followed by the IL-10 injection (80 mg/kg) for 12 weeks in a row (2 times per week). Only a piece of fat tissue, the size same as ovary around the ovary, was removed in the control group. After 12 weeks, bone-related parameters and alkaline phosphate (BALP) were tested. The levels of serum IL-1β, IL-6 and tumor necrosis factor (TNF)-α were measured by ELISA.

RESULTS: The bone mineral density (BMD), bone volume fraction (BV/TV), trabecular thickness (Tr.BTh) and trabecular number (Tr.BN) were significantly decreased, and trabecular separation (Tb.Sp) was increased in the OVX group, and that IL-10 treatment had a significant rescued effect. The levels of serum BALP, IL-1β, IL-6 and TNF-α were significantly increased in the OVX group when compared with the control group (all P < 0.01), suggesting that osteoporosis was successfully induced in the OVX group. The BMD, BV/TV, Tr.BTh and Tr.BN in the IL-10 treatment group were significantly increased, and Tr.Sp decreased, when compared those parameters in the OVX group (P < 0.05 or P < 0.01). Micro-CT images showed that the trabecular number was obviously decreased in the OVX group, and that IL-10 treatment had a significant rescued effect. Meanwhile, these volumes were significantly decreased in the IL-10 treatment group when compared with the OVX group (P < 0.05 or P < 0.01).

CONCLUSIONS: IL-10 treatment can increase BMD and alleviate the osteoporosis in the ovariectomized mice, which is related with the suppressions of serum BALP, IL-1β, IL-6 and TNF-α.

O-172 Tuesday, October 9, 2018 11:30 AM

ANGIOGENIC FACTORS IN EARLY AND MID-GESTATION ARE ALSO BEING FOLLOWING SUPEROVA-LIZATION WITH HUMAN CHORIONIC GONADOTROPIN (hCG) TRIGGER AND GONADOTROPIN RELEASING HORMONE AGONIST (GNRHA) TRIGGER IN A MOUSE ART MODEL. T. Segal,† V. R. Libby,† K. Van Heertum,† P. Amini,† M. Maimgi,† J. Goldfarb,† S. Mesiano,‡ R. Weinerman.† University Hospitals Cleveland Medical Center, Cleveland, OH; †Case Western Reserve University School of Medicine, Cleveland, OH; ‡Hospital of the University of Pennsylvania, Philadelphia, PA.

OBJECTIVE: Gonadotropin releasing hormone agonists (GnRHa) are used clinically as an alternative to human chorionic gonadotropin (hCG) to trigger ovulation and decrease the risk of ovarian hyperstimulation syndrome. GnRHa is less potent at inducing ovarian vascular endothelial growth factor (VEGF), but may also affect endometrial angiogenesis and early placental development. In this study we explore the effect of superovulation (induced with hCG or GnRHa) on endometrial angiogenesis during critical periods of gestation in a mouse ART model.

DESIGN: Laboratory research

MATERIALS AND METHODS: Female mice were assigned to 3 protocols: 1) GnRHa trigger: 5 IU of chorion gonadotropin (eCG) followed 48 h later by GnRHa; 2) hCG trigger: 5 IU eCG, followed 48 h later by hCG; 3) Control group, naturally mated. All mice (n = 5-11 per group) were mated to fertile males. Females were killed prior to implantation (E3.5), post-implantation (E7.5), and at midgestation (E10.5) and maternal serum, uterus and ovaries were collected. Total RNA was extracted followed by qRT-PCR. Immunohistochemistry was performed with antibodies to VEGF, VEGF Receptor 1 (VEGFR1), and VEGF Receptor 2 (VEGFR2), to localize expression. Serum was analyzed via ELISA for progesterone (P), VEGF and soluble VEGFR1 (sVEGFR1). Placental microvessel density was quantitated. Data was analyzed with non-parametric tests including the Kruskal-Wallis and Mann-Whitney test.

RESULTS: Females exposed to superovulation induced with hCG and GnRHa trigger had elevated serum P levels, increased ovarian LH-R and VEGF expression in the more vascularized endometrial tissue, compared to naturally mated mice (p < 0.05). During the perimplantation period, endometrial VEGFR1 and VEGFR2 mRNA were significantly increased in the GnRHa trigger group (p < 0.02) relative to the hCG group and there was no difference in uterine VEGF expression between the groups (p = 0.4). VEGFR1 is highly expressed in the endometrial lining and secretary glands immediately prior to implantation. At E7.5, ectoplacental cone mRNA expression of VEGF and VEGFR2 were significantly higher in the hCG trigger group compared to the GnRHa group (p < 0.05). Midgestational serum sVEGFR1, bioavailable VEGF and local VEGF expression in the placenta were much higher in mice exposed to the hCG trigger relative to GnRHa group (p < 0.02). Although placental microvessel density was similar, Thy1, a transcription factor for spiral artery remodeling was significantly lower in the superovulated groups compared to controls.

CONCLUSIONS: GnRHa and hCG triggers differentially disrupt endometrial expression of key angiogenic factors during critical periods of
A NOVEL GREMLIN-2 MUTATION FROM A PATIENT WITH PRIMARY OVARIAN INSUFFICIENCY IS PREDICTED TO AFFECT BONE MORPHOGENETIC PROTEIN BINDING AND MAY ALTER THE OVARIAN RESERVE.

OBJECTIVE: Determine how GREM2, a bone morphogenetic protein (BMP) antagonist, alters the ovarian reserve and contributes to primary ovarian insufficiency (POI).

DESIGN: Basic Research Study

MATERIALS AND METHODS: Patients with POI were recruited at Baylor College of Medicine and The University of Pittsburgh with IRB approval, and DNA samples were obtained for whole genome exome sequencing. Prediction software was used to analyze the effect of the variant on GREM2 protein function (PolyPhen-2 v.2.2.2 and SIFT algorithms). In order to study the function of GREM2, we generated mice null for Grem2 using CRISPR/Cas9 engineering. We verified complete loss of Grem2 by quantitative PCR in multiple tissues, including the ovary and lung, where it is normally highly expressed. We tested fertility in 8-month continuous mating trials (n=3 females, 3 males per genotype). Estrous cycles were evaluated with daily vaginal lavage. Serum levels of FSH, estradiol, and AMH were evaluated by enzyme linked immunosorbent assay (ELISA).

RESULTS: In human studies, we identified a novel nonsynonymous mutation in GREM2 within the GREM2-BMP interface in a POI patient sample that is predicted to be disruptive. In our murine model, we found that while Grem2−/− females had normal litter sizes, they showed a statistically significantly reduction in the numbers of litters per month compared to the controls (0.65 litters per month for the mutant versus 1.0 for the control, P<0.05). Initial histologic analysis of newborn Grem2−/− ovaries showed they are grossly normal. By 12 weeks of age Grem2−/− mice have fewer estrous cycles per month than wild type (P<0.05). No expression of Grem2 was found in the pituitary of either the wild type or Grem2−/− mice. In preliminary data, AMH levels at 6 weeks trended higher in the Grem2−/− mice (P=0.0593) with no difference in FSH or estradiol levels.

CONCLUSIONS: Our fertility data coupled with reduced estrous cycles in the Grem2−/− mice is indicative of dysfunction in the hypothalamic-pituitary-gonadal axis consistent with early reproductive senescence. We did not find expression of Grem2 in the mouse pituitary, suggesting the defect is intraovarian. Elevation of AMH levels at 6 weeks could suggest greater numbers of growing follicles due to lack of BMP antagonism, which may lead to early depletion or dysfunction of the ovarian reserve. In total, our data indicate that GREM2 has a key role in adult ovarian function and fertility and is a new candidate gene for POI.

Supported by: These studies were supported by NIH/NICHD R01 HD085994 (to S.A.P. and the University of Virginia Ligand Core (PS0-HD28934)

SPERM BIOLOGY

EVALUATION OF SPERM MITOCHONDRIAL DNA COPY NUMBER AS A PREDICTOR OF IN VITRO FERTILIZATION/ INTRACYTOPLASMIC SPERM INJECTION (IVF/ICSI) CYCLE OUTCOMES IN A LARGE CLINIC POPULATION

OBJECTIVE: Male factor accounts for approximately half of infertility diagnoses, however, few prognostic tests of sperm quality or function exist. Recent evidence suggests that sperm mitochondria may serve as a biomarker for sperm health and fertility potential (1,2). The present study sought to determine whether sperm relative mitochondrial DNA copy number (mtDNA CN) influenced fertilization, blastulation, blastocyst euploidy, and live birth rates in an infertile population.

DESIGN: Prospective cohort study

MATERIALS AND METHODS: Consent was prospectively obtained for use of de-identified, otherwise discarded whole sperm material. Random sampling identified 2100 unique sperm samples used to create transferred embryos (2007-2013); 1718 cycles utilizing intracytoplasmic sperm injection (ICSI) were analyzed. Cycles using frozen sperm were excluded. mtDNA CN was evaluated using several TaqMan assays targeting different sites around the circular mitochondrial genome, and normalized to a multi-copy nuclear control (ALU). Linear regression and mixed effects logistic regression models were used to explore relationships between sperm mtDNA CN and the various parameters of interest.

RESULTS: Lower relative sperm mtDNA CN was associated with increased pre-wash sperm motility (p<0.001). No association was identified between relative sperm mtDNA and paternal age, days of abstinence prior to sample collection, fertilization (p=0.40), blastulation (p=0.36), euploidy (p=0.10) (preimplantation genetic testing was used in 490 cycles), or live birth rates (p=0.42) when accounting for maternal age (mean 34.3 years), paternal age (mean 37.1 years) and pre-wash motility.

CONCLUSIONS: Lower sperm relative mtDNA copy number was associated with increased sperm motility, consistent with observations from other investigators. However, once a high quality euploid blastocyst was obtained, sperm relative mtDNA copy number did not add any additional prognostic

Supported by: IntegraMed Innovation-In-Research Grant
value with regard to transfer outcome in this sample of patients undergoing IVF/ICSI.

References:

Supported by: Foundation for Embryonic Competence

O-176 Tuesday, October 9, 2018 11:00 AM
CHARACTERIZATION OF PROTAMINE MODIFICATIONS USING NEWLY GENERATED MODIFICATION SPECIFIC ANTIBODIES. S. B. Schon, C. Sultan, G. Manske, S. Hammoud. Division of Reproductive Endocrinology & Infertility, Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI; Human Genetics, University of Michigan, Ann Arbor, MI.

OBJECTIVE: Protamines have traditionally been considered inert nuclear proteins serving as passive structural elements that condense the paternal genome. However, emerging evolutionary, developmental, and biochemical evidence calls for a need to revisit protamine protein’s presumed biological function. Importantly, in 2014 mass spectrometry analysis revealed that mouse protamines bear a number of post-translational modifications (PTMs). This raises the possibility that these modifications may bear a “protamine code” analogous to the “histone code”, however, to date none of these novel modifications have been further explored. Our objective was to generate modification specific antibodies to a subset of protamine modifications and begin to explore their functional significance.

DESIGN: Laboratory experiments utilizing murine testes and sperm.

MATERIALS AND METHODS: Modification specific antibodies were generated through Genemed Synthesis Inc using a rabbit host. Specificity of polyclonal antibodies were tested via western blot, testing of pre-blot serum, peptide competition and phosphatase treatment. The validated antibodies were subsequently tested with immunofluorescence (IF) on cross-sections of C57BL6 mouse testes and mature sperm.

RESULTS: Antibodies to Protamine 1 K50 acetyl (P1K50Ac) and Protamine 1 S43, T45 Phosphorylation (P1S43/T45Ph) are both efficient and specific for the modified form of protamine 1. P1S43/T45Ph was noted in high abundance on acid extracted protamines, and throughout the testes, however, did demonstrate some stage-specific staining. P1K50Ac was found in lower abundance and was also detected in a stage-specific manner.

CONCLUSIONS: We provide validation of previously described post-translational modifications on mouse protamine 1 using newly generated modification-specific polyclonal antibodies. Furthermore, we report the first histologic description of these modified proteins in testes and sperm.

Supported by: 5K12HD065257-07 (SBS) and 1DP2HD091949-01 (SSH)

O-177 Tuesday, October 9, 2018 11:15 AM
IN VITRO CULTURE OF NEONATAL MOUSE TESTICULAR CELLS MAINTAINED ON DECELLULARIZED SEMINIFEROUS TUBULE. P. Xie, Z. Rosenwaks, G. D. Palermo, Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medicine, New York, NY.

OBJECTIVE: To propose a culture method utilizing an adult decellularized testicular matrix (DTM) as a scaffold to sustain neonatal mouse testicular cells and induce differentiation of spermatogonial stem cells in conditioned medium.

DESIGN: We tested the ability of a modified culture system, based on a bioreactor concept and supported by a biological scaffold, to sustain and induce differentiation of neonatal testicular cells.

MATERIALS AND METHODS: Testicular cells from 7-day-old B6D2F1 neonatal mice with or without DTM were loaded with DMEM in a culture dish equipped with a 0.4-m pore size mesh inlet treated with gelatin. B6D2F1 14-week-old adult male mice were sacrificed for DTM and conditioned medium. Scaffolds were prepared by exposure to 1% sodium dodecyl sulfate for 24 hours. Germ cell characteristics were analyzed by immunofluorescence on an H&E-stained background.

RESULTS: Isolated cells from the germinal epithelium were derived from three testicles of three adult mice and layered on the mesh of nine bioreactors. Seminiferous tubules, sectioned approximately 3 mm in length and isolated from the contralateral testicles of these adult mice following decellularization, were placed below the mesh in the bioreactor. Isolated cells collected through the dissection and digestion of 10 testicles retrieved from five neonatal mice were seeded around the scaffold on the bottom of the bioreactor. Following incubation, recellularization of the scaffold started to appear between 7 and 10 days, as observed by optic microscopy. A small portion of the isolated cells obtained from biopying the recellularized tubules from the bioreactors followed by digestion showed positivity of OCT4, indicating stemness; cytoplasmic staining of DAZL showed maturational progression. Positive vimentin staining of some cells derived from the scaffolds showed propagation of nurturing pre-sertoli cells.

CONCLUSIONS: Attempting to maintain neonatal testicular cells in a 3D biocompatible scaffold within a bioreactor system appears to be an effective way to reconstitute the architectural structure of the seminiferous tubule. Cell migration and proliferation occurred as early as day 7 of incubation. Once the ability of a 3D biocompatible scaffold to induce maturational meiosis is confirmed, it will be possible to study spermatogenesis in vitro, which may prove beneficial for men with spermatogenic arrest.

Supported by: Supported in part by the Urology Care Foundation Russell Scott Jr., MD, Resident Research Award (AWP), a Urology Care Foundation Research Scholars Award (AEP), as well as NIH grants K12 DK098304 (CJJ, DJL), the Multidisciplinary K12 Urologic Research (KURe) Career Development Program (CJJ, DJL), and by P01HD036289 from the Eunice Kennedy Shriver National Institute for Child Health and Human Development, NIH (DJL).

O-178 Tuesday, October 9, 2018 11:30 AM
THE GLUCOSE TRANSPORTER GLUT3 MODULATES MALE FERTILITY. A. W. Pastuszak, A. C. Cengiz, C. J. Jorgez, L. I. Lipshtultz, D. J. Lamb, C. Scott Department of Urology, Baylor College of Medicine, Houston, TX; Center for Reproductive Medicine, Baylor College of Medicine, Houston, TX; Urology, Baylor College of Medicine, Houston, TX; Center for Reproductive Medicine, Baylor College of Medicine, Houston, TN; Urology, Weill Cornell Medical College, New York, NY.

OBJECTIVE: Approximately 15% of couples have fertility problems, with a 50% male factor contribution. In many of these men, a genetic cause is suspected. While numerous known genetic alterations cause male infertility, many other genetic etiologies likely exist. Glucose transporters (GLUTs) may be involved in sperm motility, though their role in this process is unclear and no genetic studies exist supporting a role for GLUTs in fertility. Here, we present genomic and animal data associating GLUT3 with male infertility.

DESIGN: Genetic study comparing infertile and fertile men, with validation in a mouse model.

MATERIALS AND METHODS: Genomic DNA from 22 men with non-obstructive azoospermia (NOA) and normal Y-chromosome microdeletion and karyotype analyses, as well as 4 fertile controls, was used for array comparative genomic hybridization (aCGH) to assess for copy number variations (CNVs). Candidate fertility genes were selected based on frequency of CNVs in a gene, magnitude of the CNV, and available gene expression data. CNVs were validated using qPCR, and sequencing performed for genes of interest. Immunohistochemical staining of human and mouse testis sections used commercially available antibodies and standard protocols.

RESULTS: Copy number gains were identified using aCGH in GLUT3 in 2/22 NOA men, and in CASPR5 in 1/22 men and in no controls, and confirmed using qPCR copy number assays (CNAs). Subsequent CNAs of DNA from 56 NOA men yielded 5 more men with GLUT3 gains. The frequency of GLUT3 CNVs in the general population (including fertile and infertile individuals) is approximately 0.06%, whereas our gain frequency is 13% (p<0.001). Sequencing of GLUT3 yielded benign SNP's in exons 2, 6, and 10. GLUT3 staining in testis of a male with 3 copies and hypospermogenesis demonstrated cytoplasmic Leydig cell and spermatocyte staining. A testis-specific GLUT3 knockout mouse was generated, which demonstrated maturation arrest and azoospermia.

CONCLUSIONS: CNVs in GLUT3 were identified in infertile males more frequently than in fertile males or the general population, and a testis-specific GLUT3 knockout mouse model demonstrated maturation arrest and azoospermia. Future work will assess the molecular role of GLUT3 on fertility-related cellular signaling pathways and will further elucidate the role of GLUT3 in male fertility.

Supported by: Supported in part by the Urology Care Foundation Russell Scott Jr, MD, Resident Research Award (AWP), a Urology Care Foundation Research Scholars Award (AEP), as well as NIH grants K12 DK098304 (CJJ, DJL), the Multidisciplinary K12 Urologic Research (KURe) Career Development Program (CJJ, DJL), and by P01 HD036289 from the Eunice Kennedy Shriver National Institute for Child Health and Human Development, NIH (DJL).
NON-RANDOM ORGANIZATION OF HISTONE-BOUND DEVELOPMENTAL GENES WITHIN THE HUMAN SPERM NUCLEUS. H. G. Tempest D. Ioannou. Human and Molecular Genetics, Florida International University, Miami, FL.

OBJECTIVE: The contribution of spermatozoa to embryogenesis is often overlooked. The oocyte is considered the controlling force for embryogenesis, providing the environment and various factors for initial cleavage divisions. However, evidence suggests that epigenetic perturbations in sperm contribute to infertility and aberrant embryogenesis. Sperm chromatin undergoes significant changes, 85-95% of histones are replaced with protamines. Histone retention is enriched at promoters of embryonic developmental genes, microRNAs and imprinted genes. Furthermore, histone-removed regions carry unique epigenetic modifications suggesting the paternal genome provides an epigenetically “poised” set of developmentally important genes. Chromatin organization plays an integral role in epigenetic mechanisms, however we have a poor understanding of the higher order chromatin organization of these important loci in spermatozoa.

DESIGN: Transversal study in a laboratory environment.

MATERIALS AND METHODS: This study was approved by the FIU IRB. Semen samples were obtained from five normozoospermic sperm donors. Fluorescence in-situ hybridization was utilized to investigate the topology of ten histone-bound developmentally important genes. The nuclear localization of each gene radially and longitudinally was assessed (e.g. interior - periphery and head - tail position, respectively). A minimum of 100 cells per gene, per subject was analyzed for radial and longitudinal organization. Chi-squared goodness-of-fit test was utilized to identify whether non-random organization existed (p<0.05).

RESULTS: In this study all 10 investigated genes demonstrated a statistically significant nonrandom radial and longitudinal organization that was reproducible in all five sperm donor samples. The radial distribution of these genes demonstrated a preferential interior/intermediate localization. Furthermore, a significant nonrandom longitudinal organization was observed with 25%, 50%, and 27% of these 10 genes localizing in head, mid and tail regions, respectively.

CONCLUSIONS: Our data demonstrates that these developmentally important genes, which preferentially contain unique epigenetic modifications and retain a more open chromatin configuration (histone-bound) tend to have a more interior and mid localization in the sperm cell. We postulate, given the lack of DNA repair in spermatozoa that this localization could confer protection from DNA damage, with densely packaged protamine-bound chromatin enveloping and protecting these regions. Thereby, allowing the “safe delivery” of these important genomic regions to the oocyte and the propagation of unique epigenetic cues to the developing embryo. We will expand this study to target more genes and to investigate whether perturbations in this organization is observed in infertile men, particularly in men with high levels of DNA fragmentation, failed fertilization, arrested embryogenesis and recurrent pregnancy loss (with no attributable female factor).

References: NA

Supported by: This investigation was supported by the University of Utah Study Design and Biostatistics Center, with funding in part from the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant UL1TR001067-02 (formerly UL1TR000105 and UL1RR025764).

ART OUTCOMES

O-181 Wednesday, October 10, 2018 10:45 AM

EVALUATING IVF AND PERINATAL OUTCOMES FOLLOWING REPEAT TROPHECTODERM BIOPSY. L. Sekhon, a, b B. McAveeney, c L. Lee, c C. Briton-Jones, c M. Duke, e E. Flisser, a, b A. B. Copperman, a, b Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY; c Reproductive Medicine Associates of New York, New York, NY; c Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai West, New York, NY.

OBJECTIVE: Failed DNA amplification and other technical limitations of preimplantation genetic testing (PGT) can result in a non-diagnostic result leaving patients to choose whether to have their embryos biopsied. While the safety of TB has been widely demonstrated, there is limited data regarding repeated TB and possible downstream effects on placentation. The purpose of our study was to evaluate the impact of repeat TB on IVF and perinatal outcome.

DESIGN: Retrospective cohort

MATERIALS AND METHODS: Patients underwent frozen embryo transfer (FET) of euploid blastocysts after double vs. single TB (2013-2018). The double TB group underwent transfer of a euploid frozen-thawed blastocyst after warming, rebiopsy and re-vitrification due to a non-diagnostic PGT result after initial TB. The single TB group had previously vitrified unscreened embryos that were warmed, biopsied once and re-vitrified, prior to FET. Perinatal outcomes included gestational age, infant
results showed no impact of the number of biopsies on pregnancy outcomes.

The study also aimed to determine if the risk of reduced implantation must be balanced against the potential benefits gained from obtaining a clinically impactful PGT diagnosis. Patients whose embryos underwent double TB (n = 81) were compared to 56 controls. Controlling for oocyte age, BMI, endometrial thickening, hatching status, and day of biopsy, ongoing pregnancy was reduced in the double TB group (OR 0.4 [0.15-0.95], p = 0.04). The odds of pregnancy loss were not modified by double TE biopsy (OR 3.5 [0.77-15.8], p = 0.11). Controlling for age, gestational age at delivery was not impacted by the number of TB biopsies (b = 0.7, p = 0.2). Controlling for age and gestational age at delivery, double TB biopsy did not significantly impact infant birthweight (b = -1.44, p = 0.4).

CONCLUSIONS: While repeat embryo vitrification and thawing can be safely performed in the modern IVF laboratory, our findings suggest that double TB decreases implantation potential, but does not lead to impaired placentation. As the capability of PGT technology expands, patients may request their embryos undergo repeat testing for conditions for which these embryos were not originally tested, warranting further studies to confirm our findings. When counseling patients regarding their decision to rebiopsy, the risk of reduced implantation must be balanced against the potential benefits gained from obtaining a clinically impactful PGT diagnosis.

Cycle characteristics and outcome after transfer of a single vs. double biopsied, euploid blastocyst

<table>
<thead>
<tr>
<th></th>
<th>Single TB</th>
<th>Double TB</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oocyte age</td>
<td>32.9 ± 4.1</td>
<td>36.1 ± 4.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Proportion of embryos that underwent first TE biopsy on day 5</td>
<td>42.9% (24/56)</td>
<td>53.1% (43/81)</td>
<td>0.239</td>
</tr>
<tr>
<td>Proportion of embryos that underwent first TE biopsy on day 6</td>
<td>50.0% (28/56)</td>
<td>43.2% (35/81)</td>
<td>0.433</td>
</tr>
<tr>
<td>Proportion of hatched (expansion grade 6) embryos</td>
<td>25.0% (14/56)</td>
<td>51.9% (42/81)</td>
<td>0.001673</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>66.1% (37/56)</td>
<td>40.7% (33/81)</td>
<td>0.003548</td>
</tr>
<tr>
<td>Ongoing pregnancy rate</td>
<td>62.5% (35/56)</td>
<td>35.8% (29/81)</td>
<td>0.002077</td>
</tr>
<tr>
<td>Early pregnancy loss rate</td>
<td>7.5% (3/40)</td>
<td>18.2% (8/44)</td>
<td>0.14723</td>
</tr>
<tr>
<td>Live birth rate</td>
<td>45.9% (17/37)</td>
<td>31.0% (13/42)</td>
<td>0.1706</td>
</tr>
<tr>
<td>Gestational age at delivery</td>
<td>37.8 ± 1.7</td>
<td>38.5 ± 1.1</td>
<td>0.2027</td>
</tr>
<tr>
<td>Preterm delivery rate</td>
<td>11.8% (2/17)</td>
<td>7.7% (1/13)</td>
<td>0.8923</td>
</tr>
<tr>
<td>Infant birthweight</td>
<td>3400.2 ± 524.6</td>
<td>3365.1 ± 378.5</td>
<td>0.8562</td>
</tr>
</tbody>
</table>

O-183 Wednesday, October 10, 2018 11:15 AM
HEALTH OUTCOMES FOR MASSACHUSETTS INFANTS FOLLOWING FRESH VERSUS FROZEN EMBRYO TRANSFER

O-182 Wednesday, October 10, 2018 11:00 AM
INCREASED RISK OF INCIDENT CHRONIC DISEASE IN INFERTILE WOMEN: ANALYSIS OF US CLAIMS DATA

OBJECTIVE: To investigate if the diagnosis of infertility is associated with increased risk of developing non-malignant chronic health conditions.

DESIGN: Retrospective analysis

MATERIALS AND METHODS: We analyzed the Optum® insurance claims database covering data from 2003-2016. Infertile women were identified through diagnosis and testing codes and compared to a control group of women seeking routine gynecologic care including contraceptive management. Development of a non-malignant chronic health condition was identified using ICD-9/ICD-10 codes. Women with a prior diagnosis of an outcome of interest, cancer, or with such a diagnosis within one year of data collection were excluded. The risk of developing a chronic health condition was assessed using a Cox proportional hazards model while adjusting for age, index year, nulliparity, race, smoking, obesity, number of visits per year and education. Analyses were performed using SAS (version 9.4, SAS Institute, Inc., Cary, NC, USA).

RESULTS: A total of 59,513 women with a diagnosis of infertility or who underwent infertility testing were identified with an average age of 34.9. 2,424,374 women comprised the control group with an average age of 33.4. The majority of patients were followed for at least 4 years from diagnosis. 21% of women with an infertility diagnosis were obese compared to 14% of the control group. 16% of women with an infertility diagnosis were smokers compared to 10% of the control group. The majority of women in both cohorts were Caucasian (>60%). Women with an infertility diagnosis were at increased risk of developing diabetes (5.0% v 2.7%, HR 1.34, CI 1.28-1.39), liver disease (4.4% v 2.6%, HR 1.28, CI 1.23-1.34), cerebrovascular disease (2.6% v 0.6%, HR 1.18, CI 1.08-1.29), and ischemic heart disease (2.2% v 1.3%, HR 1.19, CI 1.12-1.27) compared to controls. Women with an infertility diagnosis were also at increased risk of developing bipolar disorder (1.5% v 0.9%, HR 1.14, CI 1.06-1.23) and drug abuse (1.7% v 0.9%, HR 1.33, CI 1.24-1.42) compared to controls while the risk of depression was similar between groups (11.9% v 9.4%, HR 1.07, CI 1.04-1.10).

The low absolute risks observed in both cohorts were Caucasian (60%). Women with an infertility diagnosis had a higher frequency of underlying pathology or if the emotional or medical impact of infertility influences the development of chronic disease. Long-term follow up as well as controlling for additional potential confounders are warranted to better understand the etiology of the association.
and for infants ≥ 35 weeks, prolonged hospital stay (> 2 days for vaginal delivery, > 4 days for cesarean).

CONCLUSIONS: When compared with infants conceived from fresh embryo transfer, those born by FET have higher birthweight but increased odds of infectious disease, hematologic, respiratory and neurologic abnormalities. These risks should be considered when making decisions on fresh versus frozen embryo transfer. Further studies are needed to elucidate the biologic mechanisms underlying these relationships and the potential long term impact on infant health and development.

Supported by: NIH R01HD067270

O-184 Wednesday, October 10, 2018 11:30 AM

THE IMPACT OF LOW DOSE ASPIRIN ON THE MODE OF DELIVERY: SECONDARY ANALYSIS OF THE EFFECT OF ASPIRIN IN GESTATION AND REPRODUCTION (EAGER) TRIAL. A. Ebanks, a C. J. Noble, b S. Mumford, c M. J. Hill, d A. H. DeCherney, e L. A. Sjaarda, f N. Perkins, f R. Silver, f E. Schisterman, f Walter Reed National Military Medical Center, Bethesda, MD; b Epidemiology Branch, Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD; c The Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD; d NIH, Germantown, MD; e NICHD, Bethesda, MD; f University of Utah, Salt Lake City, UT; g NICHD, Bethesda, MD.

OBJECTIVE: Given the increasing use of low-dose aspirin (LDA) therapy for prevention of pre-eclampsia in at-risk women, we sought to examine whether use of LDA throughout pregnancy impacted risk of vaginal versus cesarean delivery, an important outcome that impacts maternal and neonatal health complications.

DESIGN: This is a secondary analysis of the EAGeR trial, a multicenter, double-blind, block-randomized, placebo-controlled trial evaluating the effects of preconception-initiated, daily LDA on live birth among women with 1-2 prior pregnancy losses.

MATERIALS AND METHODS: Women were randomized to 81 mg daily aspirin with 400 mcg folic acid or placebo with folic acid beginning preconception and continued to 36 weeks gestation if they became pregnant. Reproductive history (e.g. prior cesarean delivery) was collected through self-report at enrollment and mode of delivery in the current pregnancy was abstracted from medical records. This study used intent-to-treat analysis. Log-binomial regression was used to calculate the risk of vaginal versus cesarean delivery, applying inverse probability weights to account for selection bias potentially introduced by excluding women without a live birth.

RESULTS: A total of 1228 women were enrolled, with 597 having a live birth (309 assigned to LDA and 288 assigned to placebo). No difference was observed between the group taking LDA and those taking placebo for risk of vaginal versus cesarean delivery, an important outcome that impacts maternal and neonatal health complications.

O-185 Wednesday, October 10, 2018 11:45 AM

NEONATAL OUTCOMES AMONG TWIN PREGNANCIES STRATIFIED BY MODE OF CONCEPTION IN THE UNITED STATES (2014-2016). S. Arias, a H. Erfani, c C. Valdes, a W. Gibbons, b A. Shamsuddin, a Reproductive Endocrinology and Infertility, Baylor College of Medicine, Houston, TX; b Maternal-Fetal Medicine, Baylor College of Medicine, Houston, TX.

OBJECTIVE: To compare neonatal outcomes among twin pregnancies conceived as a result of fertility treatments, including Assisted Reproductive Technology (ART), ovulation induction (OI), intrauterine insemination (IUI) and twin pregnancies conceived spontaneously.

DESIGN: A retrospective population-based study

MATERIALS AND METHODS: This is a population-based analysis of neonatal outcomes in twin pregnancies in the United States based on their mode of conception: 1) Fertility enhancing drugs for OI/IUI, 2) ART (including in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), and 3) spontaneous conception (SC). We used “Natality” files from the National Center for Health Statistics from 2014-2016. All twin gestations with reported variable for mode of conception were included. The primary outcome was the rate of composite neonatal morbidity (CNM) and was defined by presence of at least one of the following: gestational age (GA) at delivery < 28 weeks, 5 min Apgar score < 7, assisted ventilation > 6 hours, neonatal intensive care unit (NICU) admission, antibiotics administration or seizure. Statistical analysis was performed using R-3.4.1.

RESULTS: Included in this study were 388,045 twin deliveries of which 334,677 (86.2%) resulted from SC, 36,883 (9.5%) from ART and 16,485 (4.2%) were conceived by OI/IUI. CNM was positive in 134108/334677 (40.1%; 95%CI 43.4-44.7) of ART and 7108/16485 (43.1%; 95%CI 42.4-43.9) of OI/IUI fertility treatments. The differences between these 3 groups were statistically significant before and after adjustment for potential covariates. Parameters of CNM are reported in the table. Variables are presented as n (%). P-Value is calculated based on Multinomial Logistic Regression with Mode of Conception as dependent variable and the following covariates: maternal age, body mass index (BMI), race/ethnicity, marital status, gestational hypertension and diabetes.

CONCLUSIONS: In this retrospective study, we observed that the rate of neonatal morbidity was slightly higher in twins conceived by IVF/ICSI and OI/IUI compared to SC. This slightly increased rate however, is not clinically significant and overall reassurance can therefore be provided regarding neonatal outcomes to the patients undergoing fertility treatments.

Composite neonatal morbidity and its parameters based on mode of conception

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>SC</th>
<th>ART (IVF/ICSI)</th>
<th>OI/IUI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 28 w</td>
<td>14151 (4.2)</td>
<td>1619 (4.4)</td>
<td>785 (4.8)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>5 min Apgar &lt; 7</td>
<td>19772 (5.9)</td>
<td>1962 (5.3)</td>
<td>895 (5.4)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Assisted Ventilation &gt; 6h</td>
<td>20217 (6.0)</td>
<td>3315 (9.0)</td>
<td>1477 (9.0)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>NICU Admission Antibiotic Administration</td>
<td>124719 (37.3)</td>
<td>15298 (41.5)</td>
<td>6657 (40.4)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Seizure 0.01</td>
<td>137 (0.0)</td>
<td>18 (0.0)</td>
<td>11 (0.1)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Composite Neonatal Morbidity (CNM)</td>
<td>134108 (40.1)</td>
<td>16283 (44.1)</td>
<td>7108 (43.1)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

References:
2. Helmerhorst FM, Perquin DA, Donker D, Keirse MJ. Perinatal outcome and for infants conceived by IVF/ICSI and OI/IUI compared to SC. This slightly increased rate however, is not clinically significant and overall reassurance can therefore be provided regarding neonatal outcomes to the patients undergoing fertility treatments.

O-186 Wednesday, October 10, 2018 12:00 PM

CLINICAL, OBSTETRICAL AND PERINATAL OUTCOMES OF FREEZE-ALL CYCLES: SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS. M. Roque, a T. Haahr, b S. Geber, c S. C. Esteves, d P. Humaidan, e ORIGEN - Center for Reproductive Medicine, Rio de Janeiro, Brazil; b Department of Clinical Medicine - Aarhus University, Skive, Denmark; e ORIGEN - Center for Reproductive Medicine, Belo Horizonte, Brazil; d Androfert, Campinas, Brazil.

O-187 Wednesday, October 10, 2018 12:15 PM

FERTILITY & STERILITY®, e79
OBJECTIVE: To determine whether the freeze-all strategy offers better clinical, obstetrical, and perinatal outcomes than fresh embryo transfer to patients undergoing in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) treatment.

DESIGN: Systematic review and meta-analysis

MATERIALS AND METHODS: We conducted a systematic review using PubMed/MEDLINE, EMBASE, and the Cochrane database to identify all relevant studies published from their inception to March 2018. Only randomized clinical trials were included in the meta-analysis. Participants were infertile couples undergoing IVF/ICSI with or without preimplantation genetic testing (PGT). The primary outcome was the live birth rate (LBR). The secondary outcomes were the rates of implantation, ongoing pregnancy, miscarriage, multiple pregnancy, OHSS, ectopic pregnancy, preterm birth, pregnancy-induced hypertension, preeclampsia, birth weight, and congenital anomalies. Subgroup analysis included normal- and hyper-responder patients, embryo development stage on day transfer (cleavage vs. blastocyst), and freezing method (slow-freezing vs. vitrification). We also conducted sensitivity analyses to verify the leverage of individual studies on the pooled results.

RESULTS: Eleven studies involving 5,379 patients fulfilled the inclusion criteria for this meta-analysis, and were subjected to qualitative and quantitative analysis. There was an increase in LBR when comparing freeze-all to fresh embryo transfer in the overall IVF/ICSI population (Relative Risk [RR] 1.07; 95% CI 1.01-1.14; I² =46%; P = 0.02). Subgroup analyses indicated higher LBR with freeze-all than fresh ET in hyper-responders (RR 1.78; 95% CI 1.04-2.72; I²= 0%; P = 0.005) and PGT cycles (RR 1.55; 95% CI 1.14-2.10; I²= 0.005). However, there was no differences in LBR in normal responders (RR 1.00; 95% CI 0.93-1.08; I²= 34%; P = 0.94). Sensitivity analyses demonstrated that the benefit of the freeze-all strategy in LBR became no significant by the removal of the PGT study (RR 1.06; 95% CI 1.00-1.12; I²= 22%; P = 0.07). The overall risk of preeclampsia was higher in the freeze-all group (RR 1.78; 95% CI 1.11-2.84; I²= 13%; P = 0.02), mainly due to an increased risk observed in hyper-responders (RR 3.12; 95% CI 1.26-7.73; P = 0.01). There were no statistical differences in all the other outcomes in the overall population.

CONCLUSIONS: Although many practitioners have advocated the use of freeze-all strategy, to either the overall IVF population or a specific subset of patients, the benefit of this strategy is only observed in some particular groups of patients, such as hyper-responders and those submitted to PGT. Moreover, the freeze-all policy and subsequent FET may be associated with an increase in the risk of preeclampsia.

EMBRYO BIOLOGY

O-187 Wednesday, October 10, 2018 10:45 AM
DNA METHYLATION IS ASSOCIATED WITH FLODDY STATUS AND PATIENT AGE IN HUMAN EMBRYOS. X. Tao, Y. Zhan, K. L. Scott, R. Scott, E. Sei. TEC, Basking Ridge, NJ; 2IVIRMa Southern California, Los Angeles, CA; 3IVIRMa New Jersey, Basking Ridge, NJ; 4Yale School of Medicine, New Haven, CT.

OBJECTIVE: During pre-implantation embryo development, DNA methylation (DNAm) is a fundamental epigenetic regulatory mechanism that guides differentiation of cells into their future lineages. As its accuracy and efficiency is essential for embryo viability, DNAm has the potential to be a maker for embryonic reproductive competence. This study aims to establish whole genome-wide DNA methylome analysis for embryo trophoectoderm (TE) biopsies.

DESIGN: Experimental study.

MATERIALS AND METHODS: Two TE biopsies from each of the previously diagnosed euploid (n=10) and aneuploid (n=20) embryos were analyzed using Whole Genome Bisulfite Sequencing (WGBS). Bisulfite conversion was performed using EZ DNA Methylatino-Direct Kit (Zymo). Methylome sequencing libraries were constructed using TruSeq DNA Methylation Library Prep (Illumina) with 18 cycles of amplification. Sequencing was performed on Illumina HiSeq 2500 with paired-end 150 bp reads, and sequencing reads were aligned to human genome reference using Bismark software. Duplicates were removed, unconverted reads were filtered, and genome-wide cytosine methylation at single base resolution was determined. Statistical analysis was carried out using a linear model to assess the relationship of DNAm levels with ploidy status, maternal age (range 29.5 to 41.1), and time of blastulation (day 5 [n=16] vs. day 6 [n=14]).

RESULTS: The average CpG coverage achieved by WGBS in TE samples was 30% of the sites predicted in the genome. Analysis revealed that 20%–50% CpGs in TE samples were methylated, consistent with previous studies using animal models. The two TE samples from the same embryo showed significantly higher similarity of overall methylation rate compared to the unrelated embryos (p<0.0001), which demonstrated the reproducibility and feasibility of assessing DNAm from blastocyst TE biopsies. Aneuploid embryos showed significantly higher DNAm levels compared to euploid embryos (p<0.0001), and increased patient age was associated with elevated DNAm levels in blastocysts (p<0.0001). Whole chromosomal aneuploidy was predicted by calculating the fraction of read count from each chromosome, and all the karyotypes showed 100% consistent with previous aneuploidy screening. The chromosomes involved in monosomy embryos (-4,-13,-16, -17, -21, and -22) showed reduced methylation rates compared to the other chromosomes.

CONCLUSIONS: DNA methylation levels detected in trophoectoderm biopsies from human blastocysts correlate with ploidy status and maternal age, and may provide a foundation for the development of epigenetic biomarkers of reproductive competence.

O-188 Wednesday, October 10, 2018 11:00 AM

OBJECTIVE: Embryos are diagnosed as mosaic if their chromosomal copy number falls within a range between euploid and aneuploid. Copy number cutoffs are largely determined by bioinformatic and software settings. The objective was to determine if mosaic embryos are distinct in terms of gene expression or if they resemble euploid or aneuploid embryos.

DESIGN: Descriptive study.

MATERIALS AND METHODS: 39 blastocysts that underwent pre-implantation genetic testing for aneuploidy (PGT-A) with either NGS or array comparative genome hybridization (aCGH) and had been donated for IRB approved research were included in the study. Fifteen blastocysts were diagnosed as mosaic with NGS including 7 full mosaic monosomies, 5 partial mosaic monosomies, 2 full mosaic trisomies, and 1 partial mosaic trisomy. Three of the mosaic embryos were replicates of each other in order to confirm sequencing results. Three NGS diagnosed euploid embryos, 6 NGS diagnosed aneuploid embryos, and 15 aCGH diagnosed aneuploid embryos were used as comparisons. Aneuploid embryos were chosen if their aneuploidy was classified as one of the major monosomies or disomies. Mosaic embryos were thawed and complementary DNA was created using the SMARTer v4 Ultra Low Kit. RNA-seq library preparation followed by sequencing on the Illumina HiSeq 2500 with 50 nucleotide length paired end reads was performed. The STAR/2.5 aligner was used to align the reads against the hg19 ensemble reference transcriptome. Differentially expressed genes (DEGs) were calculated using DESeq2/3.5, and p values <0.05 were considered significantly differentially expressed.

RESULTS: The 15 mosaic embryos had transcriptomic profiles which were distinct from full aneuploid embryos involving the same chromosome. Mosaic embryos had fewer DEGs compared to aneuploid embryos when using euploid embryos as controls. Mosaic embryos were grouped on principal component analysis (PCA) and distinguishable from euploid and aneuploid embryos, but there were no significant differences seen between full mosaic and partial mosaic embryos. The number of significant DEGs within the mosaic embryos varied from 26 to 3388. Mosaic monosomy X had the fewest DEGs considered significantly differentially expressed.

CONCLUSIONS: Mosaic cell lines within human embryos result in changes in global gene expression. This is reflected by transcriptomic profiles which are distinct from euploid or aneuploid embryos. Altered gene expression is likely to account for the reduced viability of mosaic embryos after embryo transfer. Transcriptomic profiles within mosaic embryos may be more reliable in determining the mosaic embryos by the number of DEGs. Embryos with fewer DEGs or those that express genes more associated with normal development may be more likely to implant. These results provide some evidence that the diagnosis of mosaicism is not due to the frailties of the NGS technique.
were thawed and recovered in culture medium for 2 h. Embryos were established in vitro trophoblast model generated from stem cells. The present study was to determine the transcriptomic profile of early human pre-implantation embryos. Here, we adopted a novel in vitro system to culture human embryos through interventions for a large number of pregnancy disorders are constrained.

OBJECTIVE: To isolate and characterize exosomes secreted from human embryos.

DESIGN: Prospective experimental study

MATERIALS AND METHODS: Spent IVF culture media was collected prospectively and pooled from 50 embryos at two different stages of early embryonic development on day 3 and at blastocyst. The 4 groups assessed were: control media without protein supplement (plasmanate), control media with plasmanate, day 3 embryo media, and blastocyst media. Exosome size and number were measured using nanosight tracking analysis (NTA). Characterization of embryonic exosome cargo was performed through mass spectrometry proteomic analysis. Exosomal protein cargo unique to embryos was submitted to bioinformatic analysis for molecular pathways and biological processes.

RESULTS: NTA identified exosomes in control media with plasmanate, pooled day 3 embryo media, and pooled blastocyst media, which had significantly higher concentrations compared to control media without plasmanate. The particle size distribution for all 3 groups showed isolated peaks in the known exosome size range of 50-150 nm. Moreover, day 5 embryo media had significantly higher protein amount per mL media and per exosome compared to day 3 media and control media with plasmanate. Mass spectrometry proteomic analysis identified 273 distinct proteins in the control with plasmanate, day 3, and day 5 embryonic exosomes, of which 193 were shared by all groups. We identified 30 unique proteins with increased expression in day 3 and/or day 5 exosomes. These proteins were enriched in components of the WNT and p53 pathways, which have been shown in mouse and human models to play vital roles in embryonic development and implantation. Importantly, 11 of these genes have been shown previously via knockout models to play roles in embryonic development and implantation. Furthermore, 10 of these unique embryonic proteins are involved in biological processes of immune cell activation and vesicle mediated exocytosis, which further supports their potential immune function and packaging of these proteins into exosomes.

CONCLUSIONS: By analyzing spent IVF media, we have shown that pre-implantation embryos secrete exosomes with unique cargo that may serve potential roles in implantation, early embryogenesis and immune regulation. Future directions include molecular functioning studies with isolated embryonic exosomes as well as correlating exosome proteomic profile to embryonic outcomes such as blastocyst morphology and aneuploidy.

O-191 Wednesday, October 10, 2018 11:45 AM
IDENTIFICATION OF NOVEL TROPHOBLAST MARKERS IN SELF-ORGANIZING HUMAN EMBRYOS IN VITRO.

M. Logsdon, D. M. Logsdon, R. Kile, W. Schlenkrafft, R. L. Krisher, Y. Yuan. Colorado Center for Reproductive Medicine, Lone Tree, CO.

OBJECTIVE: The recently developed system to culture human embryos in vitro through the implantation period has provided a unique opportunity to obtain human early trophoblast cells that were previously inaccessible by other means. The objective of this study is to identify the presence and localization of several novel early trophoblast markers that have only been described in a trophoblast cell model derived from embryonic stem cells (ESC) by BMP4 exposure.

DESIGN: Research study

MATERIALS AND METHODS: Vitriated day (ED) 5 human blastocysts were warmed using the Kitazato protocol, and blastocysts recovered for two hours at 37 °C in IVC1 (Cell Guidance Systems) before they were demembranated using Acid Tyrode’s solution. Embryos were then plated onto optical-grade outgrowth plates coated with fibronectin. Embryos were cultured in IVC1 for 48 h when attachment was assessed and medium exchanged with IVC2 (Cell Guidance Systems). Media was exchanged daily until fixation on ED 10 or 11. Embryos were then fixed and selectively stained with antibodies against F-actin, POU5F1, novel trophoblast markers VTCN1, WFDC2, DIO3, and GABARP (known trophoblast markers CBG, KRT7, and GATA3. Cell nuclei were identified by DAPI staining. Images were obtained by 3D confocal microscopy and analyzed by Image J software.

RESULTS: The trophoblast cell lineage in outgrowth embryos was confirmed by positive KRT7 and GATA3 staining. Syncytiotrophoblast was further confirmed by the formation of multinucleated structures and positive CGB staining on the periphery of the colony. Novel trophoblast marker VTCN1 showed a homogenous cytoplasmatic distribution throughout the trophoblast area, while WFDC1 also demonstrated cytoplasmatic distribution in the same area but was more abundant toward the peripheral syncytiotrophoblast. GABARP demonstrated peculiar filamentous formation and strong positive staining close to the epiblast cells, which were POU5F1 positive. ACTC1 also had strong positive staining co-localized with nuclei throughout the entire trophoblast area.

CONCLUSIONS: We have identified the expression and localization of four trophoblast markers in implantation stage human embryos in extended culture.
outgrowth culture that were previously reported in trophectoderm cells differentiated from human ESC by BMP4 exposure. Importantly, this work demonstrates the potential of this newly developed extended in vitro culture system to characterize and study early trophectoderm cell differentiation and examine the earliest events of pregnancy in humans that has previously been inaccessible to investigators.

O-192 Wednesday, October 10, 2018 12:00 PM

THE MORULA STAGE TRANSCRIPTOME IS CHARACTERIZED BY MARKED UPREGULATION OF GENES THAT MEDIATE KEY MITOCHONDRIAL FUNCTIONS. L. Sekhon, a,b,c E. Ellis, c Y. Wang, d J. Lee, e C. Briton-Jones, f E. Schadt, d R. P. Sebra, d A. B. Copperman, d,a,b,d aObstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY; bDepartment of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY; cReproductive Medicine Associates of New York, New York, NY; dGenetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY; eSema4, Medicine Associates of New York, New York, NY; fProgram in Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY; gQuantitative and waste disposal have been shown to be key at this transition.

OBJECTIVE: RNA sequencing may uncover the transcriptional programs mediating embryogenesis. Compaction involves cellular polarization/differentiation, in preparation for blastulation. Genes involved in energy mobilization and waste disposal have been shown to be key at this transition.

RESULTS: Of the 20,553 protein-coding transcripts, 3 were found to have significant differential expression (POLR1D, SULT2A1, CSAG3) between January-June, 2016 were collected from day 3 to 7. Embryos had ~2-4 cells were removed for aneuploidy screening by next generation sequencing (NGS), prior to RNA Sequencing. Differential gene expression between embryo cohorts was calculated using DESeq2 (adjusted significance, p < 0.05). A likelihood ratio test was used to account for heterogeneity due to patient, batch, and ploidy and growth status.

CONCLUSIONS: Transcripts mediating major mitochondrial functions play an important role in compaction prior to blastulation. Enrichment in processes related to mitochondrial function may reflect the switch from anaerobic glycolysis to aerobic metabolism at the morula stage. A deeper understanding of the molecular pathways that drive the cleavage-to-blastocyst transformation may facilitate future advances in embryo culture technique to optimize energy generation, minimize stress, and ultimately improve blastulation rates.

Table 1.

<table>
<thead>
<tr>
<th>Pathways</th>
<th>Genes</th>
<th>Log2 Fold Change</th>
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<tbody>
<tr>
<td>Mitochondrial function</td>
<td>CISD1/ISCA1//</td>
<td>3.3/3.3/</td>
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<tr>
<td></td>
<td>MFN2//MRPL42//</td>
<td>-5.4</td>
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<tr>
<td>Anti-apoptotic</td>
<td>FBXL2</td>
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<td>Lysosomal function</td>
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<tr>
<td>Transcription mediating</td>
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<tr>
<td>Post-translational modification</td>
<td>NMT2</td>
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Differentially expressed genes in morula vs. cleavage/blastocyst stage with p < 0.05

ENDOMETRIOSIS, ADENOMYOSIS, PELVIC PAIN

O-193 Wednesday, October 10, 2018 10:45 AM

ELAGOLIX REDUCED DYSpareunA AND IMPROVED HEALTH-RELATED QUALITY OF LIFE IN PREMENOPAUSAL WOMEN WITH ENDOMETRIOSIS-ASSOCIATED PAIN. N. Leyland, h,a,b D. F. Archer, b,c D. F. Archer, b,c P. M. Pelosi, d,b,e B. Schwefeld, c,a, M. Soliman, d,a M. Martinez, c,a, M. S. Abrao, c,a, McMaster Univ., Hamilton, ON, Canada; b,a,Yale School of Med., New Haven, CT; eEastern Virginia Med. School, Norfolk, VA; c,a,AbbVie, North Chicago, IL; c,a,Univ. of Sao Paulo & Hospital Beneficiencia Portuguesa, Sao Paolo, Brazil.

OBJECTIVE: We analyzed the effect of elagolix, an oral, GnRH antagonist, on dyspareunia (DYSP) in >1600 women with endometriosis-associated pain.

RESULTS: Efficacy data from two 6-month (M), randomized, placebo-controlled trials (Elaris EM-I and EM-II) of elagolix (150mg QD or 200mg BID) in women with endometriosis were pooled (N=1686). MATERIALS AND METHODS: Women assessed DYSP in a daily pain impact diary (none, mild, moderate, severe, not applicable) and the impact of endometriosis on pain with sexual intercourse (30-item Endometriosis Health Profile [EHP-30] questionnaire sexual intercourse dimension [never, rarely, sometimes, often, always] with monthly recall; normalized to 0-100 scale [best to worst]). DYSP responders had stable/decreased rescue analgesic use and a clinically meaningful decrease from baseline (BL) to M6 in DYSP score; differences vs. placebo were based on a logistic regression model. Differences vs. placebo for the mean change from BL in EHP-30 sexual intercourse dimension score were based on an ANCOVA model. Adverse events were recorded.

RESULTS: Most women were white (88%) with a mean age of 32 years (range=18-49). Of the 1384 women who reported sexual activity (≥1 day of none, mild, moderate, severe DYSP) in the 35-day BL interval, 94% reported ≥1 day of any DYSP and 48% reported ≥1 day of severe DYSP; the mean number of days women reported severe DYSP ranged 3.5-4.1 days across groups. Of the women who reported ≥1 day of severe DYSP at BL and sexual activity during M6, ≥1 day of none/mild DYSP and zero days of moderate/severe DYSP (M6) was reported by 21% of placebo (n=197), 33% of 150mg QD elagolix (n=141) and 54% of 200mg BID elagolix (n=134). Of the women who reported sexual activity at BL and M6, the proportion of DYSP responders were 36% for placebo (n=526), 40% for 150mg QD elagolix (n=350,p<0.272), and 53% for 200mg BID elagolix (n=326; p<0.001). Mean [SD] EHP-30 scores on the sexual intercourse dimension were similar at BL (placebo=61.9[25.4]; 150mg QD elagolix=60.3[26.7];
200mg BID elagolix=62.0(24.6)). The least-squares mean (SE) changes from BL to M6 EHP-30 scores on the sexual intercourse dimension were -12.8(1.3) for placebo (n=322), -16.6(1.6) for 150mg QD elagolix (n=239; p=0.004), and -28.7(1.6) for 200mg BID elagolix (n=234; p=0.001). Elagolix-treated women had hypoestrogenic events consistent with the mechanism of action, though few discontinued due to these events.

CONCLUSIONS: Nearly half of the women who reported sexual activity at BL had ≥1 day of severe DYSP, confirming the importance of assessing changes in DYSP. Compared to placebo, the 200mg BID elagolix dose significantly improved DYSP in women with endometriosis-associated pain, which was accompanied by improvement in the health-related quality of life for sexual intercourse dimension.

Supported by: AbbVie

O-194 Wednesday, October 10, 2018 11:00 AM
ULIPRISTAL ACETATE IMPROVES HEALTH-RELATED QUALITY OF LIFE AND REDUCES IMPACT OF SYMPTOMS DUE TO UTERINE FIBROIDS: RESULTS FROM VENUS I AND II. L. Shulman, A. Lysy, D. Denner, E. Seiper, A. Harrington, V. Smialek, Y. Mo, P. Gillard, Feinberg School of Medicine, Northwestern University, Northbrook, IL; Carolina Women’s Research and Wellness Center, Durham, NC; Medical University of South Carolina, Charleston, SC; Allergan Plc, Irvine, CA; Allergan Plc, Madison, NJ.

OBJECTIVE: Investigate ulipristal acetate (UPA) effects on health-related quality of life (HRQoL) and symptom severity in women with uterine fibroids (UF) and abnormal uterine bleeding (AUB).

DESIGN: Women were randomized to UPA (5 mg, 10 mg) or placebo in two Phase 3, multicenter, double-blind, placebo-controlled trials (VENUS I and II). HRQoL and symptom severity were assessed at baseline and over one (VENUS I) and two (VENUS II) 12-week treatment courses (TCs), using the Uterine Fibroid Symptom and Health-Related Quality of Life questionnaire (UFS-QOL).

MATERIALS AND METHODS: In the pooled VENUS I and II data, change from baseline to end of TC1 for each UFS-QOL scale was analyzed. The proportion of women achieving meaningful change (≥20-point improvement) in physical and social activities, as measured by the Revised Activities subscale, was also calculated. In VENUS II data, change from baseline to end of TC1 and TC2 in each UFS-QOL scale, including the Revised Activities subscale, was analyzed for each treatment arm.

RESULTS: Pool: intent-to-treat (ITT) population comprised 589 patients (TC1: UPA 5 mg, n=215; 10 mg, n=205; placebo, n=169). Significantly greater improvements from baseline in all UFS-QOL scale scores were observed with both UPA doses vs placebo (p<0.0001). Least-square mean differences (95.7% confidence interval) in UFS-QOL subscale scores with UPA 5 mg and 10 mg vs placebo were: HRQoL Total: 29.5 (23.8, 35.3), 37.7 (31.8, 43.6); Symptom Severity: -22.9 (-28.0, -17.6), -30.2 (-35.5, -24.9); Revised Activities: 33.98 (27.56, 40.40), 42.15 (35.57, 48.73) (all p<0.0001). A meaningful change in physical and social activities was achieved by 73.5%, 80.6%, and 34.9% of patients receiving UPA 5 mg, 10 mg, and placebo, respectively. VENUS II - ITT population, TC1/TC2, placebo/UPA 5 mg, n=55; placebo/UPA 10 mg, n=58; UPA 5/5 mg, n=107; UPA 5 mg/placebo, n=55; UPA 10/10 mg, n=110; UPA 10 mg/placebo, n=47. At end of TC1 and TC2, both UPA doses demonstrated significant improvements from baseline vs placebo for all UFS-QOL scale scores (p<0.005). Mean Revised Activities subscale scores also showed that beneficial UPA effects were maintained in TC2. Furthermore, improvements on this subscale occurred on switching to UPA: placebo/UPA 10 mg: baseline, 32.2; end of TC1, 42.8; end of TC2, 81.5; results with UPA 5 mg and the other UFS-QOL scales were similar.

CONCLUSIONS: UPA was associated with significant improvements in HRQoL and symptom severity vs placebo in women with UF and AUB. Beneficial UPA effects were maintained in TC2 and improvements occurred on switching to UPA.

Supported by: Allergan plc, Dublin, Ireland. Editorial assistance: Complete HealthVizion.

O-195 Wednesday, October 10, 2018 11:15 AM
PROGESTIN ONLY MEDICATIONS FOR CHRONIC PELVIC PAIN: USE PATTERNS AND CAUSES OF DISCONTINUATION. N. Alsowayan, P. Yong, C. Allaire, H. Noga, M. A. Bediawy, C. Williams, Obstetrics and Gynecology, University of British Columbia, Vancouver, BC, Canada; BC Women’s Hospital, Vancouver, BC, Canada; Clinical Professor, UBC Department of ObstGyn, Vancouver, BC, Canada; Research Coordinator, Vancouver, BC, Canada; Obstetrics and Gynecology, University of British Columbia, Vancouver, BC, Canada; BC Women’s Health Center, Vancouver, BC, Canada.

OBJECTIVE: To evaluate patterns of progestin only therapy in patients with chronic pelvic pain referred to a tertiary care facility and to determine the causes of treatment discontinuation due to ineffectiveness or intolerable side effects.

DESIGN: Retrospective review of a prospective registry (Endometriosis Pelvic Pain Interdisciplinary Cohort-EPPI-ClinicalTrials.gov#NCT 02911090) between December 2013-April 2015.

MATERIALS AND METHODS: 656 patients who were prospectively consented and included. Patients were were surveyed via online questionnaire at baseline. For hormonal treatments, they report current or past use, discontinuation due to ineffectiveness or side effects. Patients are reporting on use of a single or more methods as a multivariate response. Statistical analysis performed via SPSS software, frequency analysis was performed to calculate the number in each group and subgroup followed by student T-test.

RESULTS: Total of 354 (54%) patient used any form of progestin only medication at baseline. Mirena Intrauterine device (IUD) is the most frequently utilized progestin therapy by 138 (39%) participants. 57 (42.5%) discontinued due to ineffectivity in treating their symptoms, while 50 (37.3%) discontinued due to side-effects intolerability. Followed by denogest, which was reported by 97 (27.4%), 32 of them (36.3%) reported discontinuation due to treatment ineffectiveness and 28 (31.8%) due to side-effects intolerability. Then, 73 (20.6%) participants reported prior use of depot-provera of whom 26 (30.2%) stated it was ineffective and 46 (48.8%) discontinued due to intolerable side effects. Finally, 46 (13%) participants reported prior use of northingdrome, 20 participants (42.5%) of this group reported inefficacy, while 21 (44.7%) discontinued because of side-effects intolerability. Patients reported discontinuation due to intolerable side effects are similar to discontinuation due to ineffectiveness. The subgroups of patients who discontinued due to ineffectiveness are significantly more likely to have worse dyschezia and back pain in the past three months with dinogest and nothendrine group (P<0.04). While discontinuation due to intolerable side effects was significantly associated with worse chronic pelvic pain and quality of life in the past three months with deinoestog and depro provera group (P< 0.05).

CONCLUSIONS: Mirena IUD is the most commonly used progesterone treatment. Discontinuing progestin therapy due to ineffectiveness or intolerability of side-effects is common in our population. Further research is needed to identify the risk factors of medical treatment discontinuation and identify patients who are more likely to fail medical treatment.

Supported by: This work was supported by the Canadian Institutes of Health Research (CIHR), Operating Grant Priority Announcement (Reproductive & Child Health Start-up grant) from the Institute of Human Development, Child and Youth Health and CIHR Transitional Operating Grant.

O-196 Wednesday, October 10, 2018 11:30 AM
A CONTROLLED TRIAL ON UTERINE ADENOMYSIS TREATMENT COMPARING AROMATASE INHIBITOR PLUS GnRH ANALOGUE VERSUS DIENOGEST IN WOMEN UNDERGOING IVF. M. Sbracia, F. Scarpellini, CERM, Rome, Italy; Hungary, CERM, Roma, Italy.

OBJECTIVE: Adenomyosis is a benign gynecological disease affecting women of childbearing age, characterized by infiltration of endometrial tissue into the myometrium leading to dysmenorrhea, pelvic pain and subfertility. Furthermore, it has a detrimental effect on IVF clinical outcomes. In this study we compared in women with adenomyosis undergoing IVF the aromatase inhibitor plus GnRH analog combined treatment versus Dienogest.

Supported by: Allergan plc, Dublin, Ireland. Editorial assistance: Complete HealthVizion.
OBJECTIVE: To evaluate the efficacy and safety of elagolix as compared to placebo in the management of endometriosis-associated pain using a dataset of >1600 women. The efficacy of elagolix was also evaluated in pre-specified subgroups of women with different baseline characteristics.

DESIGN: Data were pooled from two 6-month (M), placebo-controlled, phase 3 studies (Elaris Endometriosis [EM]-I and II) evaluating two doses of elagolix (150mg once daily [QD] and 200mg twice daily [BID]).

MATERIALS AND METHODS: Participants were 18-49 year old women with surgically diagnosed endometriosis and moderate/severe endometriosis-associated pain. Efficacy endpoints included the proportion of responders (controlled for rescue analgesic use) at M3 and M6 in the pooled dataset (Table) and across all subgroups. The efficacy of elagolix was also evaluated in pre-specified subgroups of women with different baseline characteristics.

CONSISTENT ACROSS A RANGE OF BASELINE CHARACTERISTICS.

CONCLUSIONS: Adenomyosis on 3D US is associated with clinical loss following FET. However, this association is only present when five independent reviewers unanimously agree on the diagnosis, suggesting that the increased risk of clinical loss is restricted to the most obvious cases of adenomyosis. Further refinement of the ultrasound criteria for adenomyosis is needed to enhance the discriminatory ability of this imaging modality.

References:

O-198 Wednesday, October 10, 2018 12:00 PM

REDUCTIONS IN ENDOMETRIOSIS-ASSOCIATED PAIN AMONG ELAGOLIX-TREATED WOMEN ARE CONSISTENT ACROSS A RANGE OF BASELINE CHARACTERISTICS. S. Singh,a B. A. Lessey,b M. Martinez,c P. Peloso,c B. Schwefel,c E. Surrey,d H. S. Taylor.e aOttawa Hospital, Ottawa, ON, Canada; bSidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA; cRMA Pennsylvania, Allentown, PA; dColorado Center for Reproductive Medicine, Lone Tree, CO; eYale School of Medicine, New Haven, CT.

OBJECTIVE: To compare placebo to undergo surgery for adenomyosis, and showed pain symptoms. The mean age of women was 35.8 ± 2.2 (range 25/39). The women were assigned to the study group or to the control group by a computer generated sequence. 27 women of the study group were treated for 3 months with Anastrazole 1 mg/die plus Goserelin 3.6 mg/month. 29 women of the control group were treated for 3 months with Dienogest 2mg/die orally. The women of the two groups were followed up during the treatment. After treatment all patients underwent IVF. The patients underwent during follow-up to the assessment for the pain levels with Visual analogue scale (VAS), and 3D ultrasound scan. Primary outcome were pregnancy rate and pain reduction by VAS assessment.

RESULTS: The two groups of patients did not show statistical significant differences for any of epidemiological data. The time of pain symptom disappearance was shorter in the group treated with the combined therapy than in the control group (1.2±0.9 vs 2.1±1.0, P<0.01). After the end of treatment the levels of pain assessed by VAS was statistically significant lower in women treated with the combined therapy than in the control group (P<0.01). The pregnancy rate after treatment was 48.1% in combined treatment whereas in dienogest group was 20.7% (P<0.05).

CONCLUSIONS: The combined treatment for uterine adenomyosis with Anastrozole plus GnRH analog showed better results than dienogest treatment with a higher reduction of symptoms and a higher pregnancy rate. The combined treatment seems to be the treatment of choice in these women. These data should be confirmed in larger study.

O-197 Wednesday, October 10, 2018 11:45 AM

ONLY PATIENTS WITH OBVIOUS ADENOMYOSIS ON THREE-DIMENSIONAL ULTRASOUND (3D US) ARE AT INCREASED RISK OF CLINICAL LOSS FOLLOWING FROZEN EMBRYO TRANSFER. S. A. Neal,a,b L. R. Goodman,a S. Morin,a,b M. D. Werner,a N. Gueye,a A. W. Tieg,a,b P. Pirtea,a R. Scott.a aIVI/RMA, Basking Ridge, NJ; bSidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA; cRMA Pennsylvania, Allentown, PA.

OBJECTIVE: Traditionally, the diagnosis of adenomyosis has been reserved for histologic specimens, making it challenging to evaluate its association with reproductive outcomes. MRI has emerged as a non-invasive diagnostic tool, but it remains expensive and impractical for routine use. Given its low cost and widespread availability, ultrasound has been proposed as an alternative imaging modality but its interpretation is subjective. The aim of this study is to determine if adenomyosis as diagnosed by 3D US is associated with clinical loss following frozen embryo transfer (FET).

DESIGN: Prospective observational study

MATERIALS AND METHODS: Between April and December 2017, patients planning to undergo FET of a single euploid embryo were recruited to undergo 3D US examination on the day prior to scheduled FET. Images were independently reviewed by five physicians and evaluated for adenomyosis on the basis of seven criteria: 1) increased myometrial thickness, 2) asymmetry of the uterine walls, 3) heterogeneous echotexture, 4) irregular endometrium-myometrium interface, 5) intramyometrial cysts, 6) linear striations, and 7) presence of an adenomyoma. Fulfillment of any one criterion was sufficient to screen positive for adenomyosis. Patients with obvious adenomyosis, defined as those who were unanimously classified by the five reviewers as having adenomyosis, were identified and compared to those patients who were unanimously deemed to be free of adenomyosis. Analyses were also performed on patients for whom at least 4/5 reviewers agreed. Pregnancy outcomes were recorded prospectively and compared using chi square analysis or Fisher’s exact test as appropriate.

RESULTS: Six-hundred-ninety-nine patients were enrolled in the study. Forty-eight were excluded on the basis of poor quality 3D US images. Reviewers reached a unanimous conclusion regarding 258 patients, 21 (8.1%) of whom were deemed to have adenomyosis. There was no difference in sustained implantation rates between the two groups. Patients with obvious adenomyosis were more likely to experience a clinical loss when compared to those without adenomyosis (23.8% vs. 6.3%, P=0.03). When expanding the groups to include all patients for whom at least 4/5 reviewers agreed, there were 461 patients. The prevalence of adenomyosis was significantly higher (15.4% vs. 8.1%, P<0.01) but the association with clinical loss was no longer present.

CONCLUSIONS: Adenomyosis on 3D US is associated with clinical loss following FET. However, this association is only present when five independent reviewers unanimously agree on the diagnosis, suggesting that the increased risk of clinical loss is restricted to the most obvious cases of adenomyosis. Further refinement of the ultrasound criteria for adenomyosis is needed to enhance the discriminatory ability of this imaging modality.
FERTILITY PRESERVATION 2

O-199 Wednesday, October 10, 2018 10:45 AM

EGG FREEZING FOR FERTILITY PRESERVATION AND FAMILY PLANNING: A SURVEY OF OB/GYN RESIDENTS ACROSS UNITED STATES. N. Esfandiari, a J. K. Sayler, a J. F. Lizkay, b P. Zagadaiova, a K. E. George, c L. R. DeMars. a "OB-GYN, Dartmouth Hitchcock Medical Center, Lebanon, NH; b Geisel School of Medicine at Dartmouth, Lebanon, NH; c OB-GYN, The GW Medical Faculty Associates, Bethesda, MD.

OBJECTIVE: Our aims were twofold, to evaluate OB/GYN residents’ views on elective egg freezing for fertility preservation and postponement of pregnancy, and to determine whether formal education on egg freezing affects views on fertility preservation and ability to discuss egg freezing with patients.

RESULTS: Of those surveyed, 101 residents and 7 fellows (98 female) completed the survey with all required information. Three quarters of female respondents reported postponing pregnancy due to residency. Among women, primary non-exclusive reasons for this choice included career plans (56.1%), concern over childcare (54.1%), and concern for fellow residents and their program (51.0%). Only 27.6% of female respondents thought that egg freezing should be considered by all female residents and less than half said that they would consider it for themselves (44.9%). Many residents were unsure whether their employer offered egg freezing as a benefit (37.0%), and whether their IVF program (if there was one at their institution) offered on-site egg freezing (31.1%). Almost three quarters (72.4%) of female residents indicated that they would consider egg freezing if it was offered as a benefit or covered by insurance. More than half of respondents reported having received education on egg freezing for fertility preservation at the time of the study (56.5%). Of those who did, almost all (96.7%) received this in an REI rotation.

CONCLUSIONS: Female OB/GYN residents are choosing to delay pregnancy during residency for career and social support reasons. Although they are likely to be one of the primary contact points for providing information to patients on egg freezing to preserve fertility or to postpone pregnancy, few residents feel comfortable providing this information. Appropriate curricular content on egg freezing during residency could improve residents’ knowledge of egg freezing or comfort counseling patients.

O-200 Wednesday, October 10, 2018 11:00 AM

CAN WE PERFORM FLEXIBLE ANTAGONIST PROTOCOL FOR LUTEAL PHASE OVARIAN STIMULATION FOR BREAST CANCER PATIENTS SEEKING FERTILITY PRESERVATION?. M. Grynberg, a M. Cometet, b M. Presse, c J. Raad, c C. Sifer, c C. Sonigo. a "Hopital Antoine Beclere, Clamart, France; b Hopital Jean Verdier, Bondy, France.

OBJECTIVE: Evidence indicates that luteal phase ovarian stimulation may represent an efficient option for women seeking FP, leading to comparable results as those obtained with early follicular phase stimulation. Currently, GnRH antagonists are simultaneously administered with FSH in order to induce early luteolysis and prevent premature LH surge. The feasibility of postponing GnRH antagonist initiation during luteal phase stimulation has not been studied. Therefore, we wondered if the timing of GnRH antagonist initiation during the luteal phase could impact the outcome of fertility preservation (FP) cycles?

RESULTS: Chi-square tests were used to evaluate the relationship between educational exposure regarding egg freezing and personal feelings about egg freezing (p=0.014) but there were no other associations between exposure to and education on egg freezing and personal feelings about egg freezing or comfort counseling patients.

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administration on stimulation day 1 (S1) or flexibly. In the flexible group, GnRH antagonist was started when the leading follicle reached 12 mm in diameter. Stimulation outcomes were compared between both groups.

RESULTS: As expected, both groups were comparable in terms of age, body mass index, and AMH level. Despite different timing in GnRH antagonist initiation, the duration of ovarian stimulation and total amount of gonadotropins were comparable between S1 and flexible groups (11.0±2.5 vs 11.0±2.2 days and 3530.6±1357.0 vs 3446.3±1207.7IU, respectively). Finally, the mean number of recovered oocytes and vitrified oocytes at metaphase 2 stage were similar in both groups (12.9±3.0 vs 14.3±8.6 and 10.3±9.9 vs 10.2±6.9 respectively). The mean day of antagonist introduction in the flexible group was the 6.7th day.

CONCLUSIONS: Flexible GnRH antagonist initiation during luteal phase ovarian stimulation may not impact negatively FP outcome when compared with simultaneous administration with exogenous FSH.

O-201 Wednesday, October 10, 2018 11:15 AM
CURRENT RESIDENCY PROGRAMS IN WOMEN’S HEALTH LACK ADEQUATE TRAINING IN FERTILITY POTENTIAL AND GAMETE PRESERVATION. N. R. Kalakota, a V. Moy, b M. A. Thomas, b J. Sroga-Rios, c S. S. Thakore. aObstetrics and Gynecology, OB/GYN Resident, Cincinnati, OH; bObstetrics and Gynecology, University of Cincinnati, West Chester, OH; cObstetrics and Gynecology, University of Cincinnati College of Medicine, West Chester, OH.

OBJECTIVE: Increasing trends of delayed childbearing in industrialized countries have not been associated with an increased awareness of age-related decline in fertility. Although obstetrics and gynecology (OBG) physicians provide care to the majority of women who experience fertility issues, family medicine (FM) physicians see up to 20% of these patients and are more likely to provide care in underserved areas. Our objective was to assess and compare the attitudes and knowledge of OBG and FM residents concerning female fertility potential and elective oocyte cryopreservation (EOC).

DESIGN: Questionnaire-based observational study.

MATERIALS AND METHODS: An IRB-approved survey was electronically distributed to all ACGME-accredited OBG and FM residency programs from January to April 2018. The questionnaire assessed attitudes and knowledge of age-related decline in fertility, reproductive potential, and EOC; satisfaction with education on these topics was also evaluated. Surveys were anonymous and completed voluntarily. Descriptive data was analyzed as percentages. Comparisons between groups were evaluated using chi-square tests with significance defined as p < 0.05.

RESULTS: One-hundred and fifty six surveys were completed (OBG: n=62, FM: n=94). Compared to OBG residents, FM residents had a lower comfort level when discussing age-related decline in fertility with patients (OBG 93.5%, FM 76.5%; p=0.005) and evaluating fertility potential (OBG 64.5%, FM 30.8%; p<0.001). This reported discomfort was most commonly due to a perceived lack of training (OBG 60%, FM 48.7%; p=0.89). Both groups agreed providers should routinely initiate conversations with patients about age-related decline in fertility (OBG 82.2%, FM 65.9%; p=0.025). However, residents who felt comfortable discussing fertility decline reported conversations were largely patient-initiated (OBG 46.5%, FM 65.2%; p=0.011). Similarly, both specialties would refer patients for EOC, but only if the patient expressed interest (OBG 68%, FM 85%; p=0.017). Only 58% of OBG and 46.8% of FM residents were aware that a marked decrease in fertility occurs between the ages of 35-39 years old (p=0.02). Residents in both groups reported inadequate training by their programs on educating patients regarding age-related decline in fertility (OBG 67.7%, FM 97.8%; p<0.0001).

CONCLUSIONS: Our study demonstrates that residents caring for reproductive-aged women have inadequate training and significant knowledge gaps in fertility potential and gamete preservation. Understanding appropriate patient education and counseling regarding age-related fertility decline is a critical aspect of women’s health care. Therefore, resident training programs should include targeted education regarding these important topics that affect a large portion of their patient base.

References:
3. Cohen D, Coco A. Trends in the provision of preventative women’s health services by family physicians. Family Medicine 2011;43:166-71

O-202 Wednesday, October 10, 2018 11:30 AM
A NURSE NAVIGATOR DRAMATICALLY IMPROVES AN ESTABLISHED FERTILITY PRESERVATION PROGRAM. P. M. Kennedy, E. Ginsburg, P. Whitney, S. Stroj, R. Ashby, R. N. Gramolini, R. H. Goldman. Obstetrics & Gynecology, Brigham & Women’s Hospital and Harvard Medical School, Boston, MA.

OBJECTIVE: To determine the impact of a dedicated nurse navigator on fertility preservation referrals and utilization of services.

DESIGN: Retrospective cohort study of a fertility preservation program at a tertiary referral center.

MATERIALS AND METHODS: Fertility preservation for women has been performed at our institution since the 1990s. Since 2007, fertility preservation referrals and procedures (oocyte/embryo cryopreservation and ovarian tissue freezing) have been tracked using a prospectively maintained database. A dedicated nurse navigator, a registered nurse with 19 years’ infertility experience, was hired in 10/2013, and in 2014 an internal computerized referral service was implemented allowing oncolologists to send electronic requests for urgent fertility preservation consultation. Within 24h, the nurse navigator explained treatment options including side effects, risks, and logistics of treatment. Interested patients were offered formal consultation with a physician within 24h. The nurse navigator maintained email communication among the referring team, fertility team, and patient throughout treatment to enable prompt initiation of oncologic treatment after completion of fertility preservation. Two-sided Fisher’s exact tests were used to compare referral patterns and rates of fertility preservation before and after hiring a dedicated nurse navigator; p<0.05 defined statistical significance.

RESULTS: The average patient age at referral was 31.2 years and the most common diagnoses were breast cancer (47%), hematologic malignancies (19%) and malignant brain tumors (6%). These stayed consistent over time. There were 198 referrals for fertility preservation between 10/2007-9/2013 and 638 between 10/2013-4/2018, a referral rate increase of 323% (Table). Before and after 10/2013, 57% and 39% of patients referred utilized fertility preservation services, respectively, and 53% and 37% of patients specifically underwent oocyte/embryo cryopreservation. While the percent of patients who utilized treatment decreased, this is likely a result of the higher volume of patients successfully referred and counseled; the rate of treatment in fact increased by 194%. There were statistically significant increases in the rates of fertility preservation referrals and treatments after 10/2013 (p<0.01 for both).

CONCLUSIONS: An experienced infertility nurse navigator facilitates fertility preservation referrals, dramatically improves communication and utilization of services, and is an invaluable resource for fertility preservation programs.

Referral Patterns and Fertility Preservation Utilization Before and After Hiring a Nurse Manager

<table>
<thead>
<tr>
<th></th>
<th>2007-10/2013</th>
<th>2013-4/2018</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referrals</td>
<td>N=198</td>
<td>N=638</td>
<td></td>
</tr>
<tr>
<td>Referral Rate</td>
<td>2.73 per 30 days</td>
<td>11.55 per 30 days</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Utilization of Fertility Preservation Service</td>
<td>N=112 (57%)</td>
<td>N=251 (39%)</td>
<td></td>
</tr>
<tr>
<td>Rate of Fertility Preservation</td>
<td>1.55 per 30 days</td>
<td>4.54 per 30 days</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Fisher’s exact test, 2-tailed

O-203 Wednesday, October 10, 2018 11:45 AM
IMPACT OF BREAST CANCER PROGNOSTIC FACTORS ON THE RESPONSE TO CONTROLLED OVARIAN STIMULATION PATIENTS UNDERGOING FERTILITY PRESERVATION. F. Zeghari, a C. Sonigo, b J. Raad, a N. Sermondade, a M. Gryenberg, c Jean Verdier Hospital, Bondy, France; cInserm U1185, Le Kremlin Bicetre, France; cGynecologist Obstetrician -Reproductive Medicine, Paris, France; cReproductive Biology, Jean Verdier University Hospital, Bondy, France; cHôpital Antoine Beclere, Clamart, France.
OBJECTIVE: The objective is to know if breast cancer (BC) prognostic factors influence ovarian function and response to controlled ovarian stimulation (COS) in patients seeking fertility preservation (FP)?

RESULTS: A total of 151 BC patients undergoing COS for FP were prospectively included between November 2013 and December 2016. COS was initiated regardless of the phase of the cycle, with or without letrozole supplementation. Matured oocytes and/ or embryos obtained were vitrified. COS characteristics and outcomes were analyzed in all women.

MATERIALS AND METHODS: BC prognostic factors considered in the present study were Scarff-Bloom-Richardson (SBR) SBIII grade, Ki 67> 20%, HER2 overexpression and “triple negative” tumor. Univariate and multivariately analyzed between performed to determine their impact on ovarian reserve markers (serum Anti-Müllerian Hormone (AMH) and antral follicle count (AFC)) as well as on ovarian response to exogenous FSH. Less than 8 mature oocytes vitrified, maturation rate under 70% or Follicle Output Rate (FORT) under 35% were considered as poor COS outcomes.

RESULTS: A total of 154 COS cycles were performed and analyzed in BC patients 33.4±4.1 years of age were analyzed. Mean AMH and AFC were 3.2±4.5 ng/mL and 20.2±14.3 follicles, respectively. HER2 overexpression was observed in 18.9% and 34.7% of tumors expressed estrogen or progesterone receptors. Triple negative status characterized 25% of tumors. BRCA1/2 mutation was found in 22.4% of patients. A mean of 9.2±7.4 mature oocytes were cryopreserved per cycle. After multivariate analysis, only serum AMH levels, AFC and smoking status were significantly associated with the number of mature oocytes obtained following COS. BC prog nostic factors did not appear to have a significant influence on ovarian reserve markers, number of retrieved oocytes, maturity rate or on ovarian response to exogenous FSH assessed by FORT index, defined as the ratio of the number of pre-ovulatory follicle (16-22 mm) count on the triggering day X100 to the antral follicle (3-8 mm) count at baseline.

CONCLUSIONS: BC prognostic factors probably have no or low impact on ovarian function in terms of ovarian reserve and response to COS. Further analysis in particular on oocyte thawing will be needed to clarify a possible impact on egg quality.

FERTILITY & STERILITY® e87

O-204 Wednesday, October 10, 2018 12:00 PM

FERTILITY PRESERVATION IN PREPUBERTAL BOYS: FOLLOW-UP DATA AFTER 13 YEARS OF CLINICAL EXPERIENCE. C. Wyns,b F. de Michele,a,b,c Clinkes Universitaires Saint Luc, Brussels, Belgium; aInstitut de Recherche Expérimentale et Clinique (IRES), Université Catholique de Louvain, Brussels, Belgium.

OBJECTIVE: The objective is to report the experience of fertility preservation in pre- and peripubertal boys before gonadotoxic therapies at Cliniques universitaires Saint Luc.

METHODS: Prospective cohort of 127 boys that underwent a testicular biopsy for cryopreservation of immature testicular tissue (ITT) within a pilot program started in 2005. Patients’ characteristics, tissue content and follow-up data on fertility after gonadotoxic therapy are presented.

RESULTS: All patients underwent ITT cryobanking in our center between May 2005 and April 2018 were included in the study. The residual fertility of boys after therapy was assessed via sperm analysis.

RESULTS: The mean age at cryopreservation was 7 ± 4.15 years (y). 41.7% of boys were affected by hematological malignancies, 22.8% by soft tissue cancers, 16.5% by nervous system tumors, 14.1% by benign diseases (thalassemia, sickle cell anemia, Hurler’s disease) and other malignancies. 23.6% had bone marrow transplantation. 83.5% of patients were at Tanner stage P1G1, 1.5% at P1G2, 7% at P2G2/P2G1, 6.2% at P2G3-P3G3 and 1.5% at P4G4. The mean Johnsen score of tissues was 3.3±1.2 and spermatogonia were present in 96% of patients. 11 patients performed an evaluation of their residual fertility. Their mean age at cryopreservation was 12 ± 2 y and the mean Johnsen score was 4.2 ± 1.9. Five patients were azoospermic (1 had no sperm in peripheric testicular tissue (ITT) 3 prenatally collected oocyte (OAT) and 2 were normozoospermic. Azoospermic patients were affected by rhabdomyosarcoma (2/5), osteosarcoma (1/5), Hodgkin lymphoma (1/5) and sickle cell anemia (1/5) and their chemotherapy was administered after testicular biopsy at a mean age of 11 ± 2 y. Two of them underwent bone marrow transplantation. The mean Johnsen score at cryopreservation was 4.2 ± 1.9 including 2 patients with scores at 8 and 5 indicating onset of spermatogenic alterations. Nevertheless, all patients allowed freezing of motile sperm. Mean age and Johnsen score were 14 ± 3.2 and 5.1 ± 1.8, and 11 ± 1.5 and 3.3 ± 0.5, respectively for the OAT and normozoospermic patients.

CONCLUSIONS: While ITT cryopreservation is spreading, our preliminary results underline the need of a more extensive application and suggest that, besides a drug specific toxicity effect, there might be a correlation between tissue maturation at chemotherapy and fertility recovery. Further evaluation of ITT content at cryopreservation and follow-up data on reproductive potential after prepubertal gonadotoxic therapy could lead to more robust data and clinical recommendations for ITT cryopreservation.

LABORATORY PROCEDURES 2

O-205 Wednesday, October 10, 2018 10:45 AM


OBJECTIVE: Time-lapse technology allows timing of the most relevant events in embryo development. This increases the probability of selecting the highest quality embryo. However, not all seemingly good quality embryos lead to implantation raising the need of defining new selection variables. A precise morphokinetic evaluation was conducted with the high optical quality incubator Embryoscope Plus®. In order to improve the embryologists’ parameters, but also to introduce new variables, which have not been evaluated so far.

RESULTS: A retrospective analysis, including 242 patients, was conducted. 253 embryos transferred were evaluated out of 530 viable embryos. Single embryo transfer (SET) was performed for 211 of them, known as KID embryos (Known Implantation Data). All of them were cultured in a time-lapse incubator (Embryoscope Plus®).

MATERIALS AND METHODS: All the embryos were evaluated with the Embryoviewer®. Drawing tools were used to measure new variables, including: the distance travelled by the pronuclei from their syngamy up to their disappearance, the speed of this migration, blastocyst expanded diameter, inner cell mass (ICM) area and the trophoderm cell cycle length. Data obtained was assessed in terms of clinical outcome and score analyzed with ANOVA test and Chi-squared test (SPSS software).

RESULTS: New variables analyzed showed values associated with different clinical outcomes. Implantation rate improved significantly (p<0.05) as the blastocyst expanded diameter increased (48.8% for 161-177μm vs. 64.4% for 178-190μm vs. 77.80% for >190μm). According to our data, embryos with ICM area between 2500-3264μm² reached a better implantation rate than smaller and larger ones. The same happens with the distance travelled by pronuclei, which showed better results between 9-17μm (72.7%) than out of range (57.6%). In terms of speed of pronuclear migration, the fastest displayed the highest implantation rates (70.8% for >1.6 μm/h vs. 62.3% for <1.6 μm/h). Trophoderm cell cycle length was shorter than blastomere cell cycle. Nevertheless, our data suggest, embryos with longer trophoderm cell cycle tend to achieve higher implantation rates (68.3% for >8.27 h vs. 53.6% for <8.27h).

CONCLUSIONS: Our novel analyzed variables show a clear influence over the implantation rate. However, a larger sample size would be necessary to confirm our observations. A possible subsequent consolidation of our variables in embryo selection could lead to the development of new algorithms improving the selection of the best quality embryo.

O-206 Wednesday, October 10, 2018 11:00 AM

TROPHODERM (TE) BIOPSY PROTOCOLS CAN AFFECT CLINICAL RESULTS, TIME TO FOCUS ON THE BIOPSY TECHNIQUE. P. Rubino,a R. Ruiz de Assin Alonso,b L. Pagliardini,b L. Hernandez,a L. Guan,a K. N. Mazmanian,a L. Dearden,a A. Thiel,a J. Wilcox,a T. Tan,a HRC fertility, Pasadena, CA; bSan Raffaele Scientific Institute, Milano, Italy; cHRC Fertility, Pasadena, CA.

OBJECTIVE: Comprehensive Chromosome Screening-based analysis of TE biopsies at the blastocyst stage is presently the most used approach to conduct preimplantation genetic testing for aneuploidies (PGT-A). While the testing technique has been refined over the years, there is no data available about the most efficient TE biopsy method. The purpose of our study is to compare two TE biopsy protocols in terms of clinical outcomes.

DESIGN: Retrospective, single-center cohort study

MATERIALS AND METHODS: Protocol 1: a 30 μm hole is laser-drilled in the ZP of day 3 embryos; the embryos are further cultured to blastocyst
TABLE 1. Clinical outcome comparison of the two TE biopsy protocols.

<table>
<thead>
<tr>
<th></th>
<th>TE biopsy performed with day 3</th>
<th>TE biopsy performed without day</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pre-hatching (protocol 1)</td>
<td>3 pre-hatching (protocol 2)</td>
<td></td>
</tr>
<tr>
<td>N° FET Cycles</td>
<td>835</td>
<td>835</td>
<td></td>
</tr>
<tr>
<td>N° ET</td>
<td>834</td>
<td>834</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>38.1±6.2</td>
<td>38.3±6.6</td>
<td>0.46</td>
</tr>
<tr>
<td>N° of embryos thawed</td>
<td>1.4±0.6</td>
<td>1.3±0.5</td>
<td>0.0003</td>
</tr>
<tr>
<td>Survival rate after thawing (SR)</td>
<td>95.1%</td>
<td>99.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N° of embryos transferred</td>
<td>1.3±0.5</td>
<td>1.3±0.5</td>
<td></td>
</tr>
<tr>
<td>Clinical pregnancy rate (CPR)</td>
<td>55.1%</td>
<td>63.5%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Implantation rate (IR)</td>
<td>46.8%</td>
<td>58.4%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Abortion rate (AR)</td>
<td>9.6%</td>
<td>11.7%</td>
<td>0.31</td>
</tr>
</tbody>
</table>


CONCLUSIONS: The incidence of clinical pregnancy is superior in embryos exposed to a single biopsy and vitrification-warm cycle, compared to embryos that have undergone two vitrification-warm cycles. While transferring a euploid embryo is thought to improve reproductive outcomes, patients should be counseled on the possibility of diminishing returns due to excess embryonic micromanipulation. Our study is ongoing to identify which, if any, patients benefit from undergoing more than one thaw/biopsy cycle.

References:

O-207 Wednesday, October 10, 2018 11:15 AM

DO MULTIPLE CRYOPRESERVATION-WARM CYCLES COUPLED WITH BLASTOCYST BIOPSY IMPACT IVF OUTCOMES? A. Aluko, a D. Vaughan, a A. Modest, a L. Murphy, b E. Seidler, b D. Duval, b M. Hacker, a A. S. Penzias, a, b T. L. Toth, a, b D. Sakkas, a Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Boston, MA; bBoston IVF, Waltham, MA.

OBJECTIVE: Pre-implantation genetic testing for aneuploidy (PGT-A) improves implantation and live birth rates in select patient groups. a PGT-A biopsy is typically performed on fresh blastocyst trophectoderm followed by immediate cryopreservation. Many patients request PGT-A of cryopreserved embryos. This requires thaw, biopsy, and re-freezing (TBR) of embryos. Few studies have examined the impact of this additional manipulation of the embryo on IVF outcomes. a, 2 We sought to investigate reproductive outcomes resulting from transfer of embryos that have undergone TBR.

DESIGN: Retrospective cohort study

MATERIALS AND METHODS: We analyzed all homologous frozen embryo transfers at a university-affiliated IVF center in 2017. All embryos were cryopreserved by vitrification. Cycles were grouped by degree of embryo manipulation: fresh biopsy, vitrified once (PGT-A/Vit); vitrified once (Vit); biopsied once and vitrified twice (TBR). The primary outcome was clinical pregnancy. Secondary outcomes included biochemical pregnancy and first-trimester miscarriage. PGT-A/Vit was the reference group. We compared proportions with chi-square or Fisher’s exact tests and used log-binomial regression to calculate adjusted risk ratios (aRR), controlling for age at retrieval, number of oocytes retrieved, and embryo quality.

RESULTS: We included 469 PGT-A/Vit, 1008 Vit, and 21 TBR cycles. The PGT-A/Vit group had a significantly higher incidence of clinical pregnancy (67.2%) than the Vit (59.5%, p<0.005) and TBR (38.1%, p<0.006) groups. Miscarriage was less likely in the PGT-A/Vit group (11.7%), compared to the Vit (18.5%; p=0.008) and TBR (37.5%; p=0.006) groups. When adjusted for age, embryos retrieved and embryo quality, the incidence of clinical pregnancy was significantly higher in the PGT-A/Vit group than the Vit (aRR 0.87, 95% CI 0.80-0.95) and TBR aRR 0.48, 95% CI 0.23-0.98) groups. See Table 1.

CONCLUSIONS: The incidence of clinical pregnancy is superior in embryos exposed to a single biopsy and vitrification-warm cycle, compared to embryos that have undergone two vitrification-warm cycles. While transferring a euploid embryo is thought to improve reproductive outcomes, patients should be counseled on the possibility of diminishing returns due to excess embryonic micromanipulation. Our study is ongoing to identify which, if any, patients benefit from undergoing more than one thaw/biopsy cycle.

References:

O-208 Wednesday, October 10, 2018 11:30 AM


OBJECTIVE: The aim of this study was to validate the Spindle Transfer (ST) technique in human donor oocytes and explore its feasibility for clinical application in the treatment of infertility associated with poor oocyte quality.

DESIGN: Experiments were licensed by the Greek National Authority of Assisted Reproduction and approved by the IRB of IASO Maternity Hospital. Informed consent was obtained from the 20 donors participating in the study. We first aimed to compare the efficiency of two fusion protocols. In a second
set of experiments, we evaluated an optimized protocol using donor fresh or vitrified oocytes with different morphological/developmental characteristics.

MATERIALS AND METHODS: Micromanipulation was performed on an inverted microscope (Olympus IX71) equipped with polarized light. Karyoplast-cytoplasm fusion was induced by exposure of the reconstructed oocytes to either a chemical solution or an inactivated protein extract (HVJ-E). The same donor’s sperm sample was used in all experiments. Embryos underwent conventional culture (Embryoscope®, Vitrolife) in single medium (LifeGlobal) and were biopsied for assessing aneuploidy and mitochondrial DNA (mtDNA) carryover. Statistical significance was assessed by Students’ t-test or Fisher’s exact test.

RESULTS: We initially compared two fusion protocols using 63 MII donor oocytes. HVJ-E-mediated fusion rates were significantly higher (98.1%) than those obtained in the chemical method (76.8%, p<0.01), while fertilization and blastocyst formation rates were similar (p>0.05) between the control (70.2%-78.7%), HVJ-E (75.5%-76.3%) and chemical-fusion (60.5%-60.2%) groups. In the second set of experiments, ST was performed in 118 donor oocytes. Overall, results varied greatly depending on the quality of the recipient cytoplasm. When spindles were transferred from in vitro matured or morphologically “abnormal” oocytes into good quality cytoplasts, individual cohorts showed fertilization (66.7%-71.4%) and blastocyst rates (75.0%-60.0%) significantly improved (p<0.05) compared to non-manipulated controls (50.0%-33.3% and 0.0%-0.0%, respectively) or reciprocally reconstructed (25.0%-0.0% and 37.5%-33.3%, respectively) oocytes. From a total of 36 blastocysts analysed, aneuploidy rates were statistically equivalent (p=0.53) between controls (41.2%, n=17) and ST (52.6%, n=19) embryos. mtDNA carryover levels were estimated to be ≈1%.

CONCLUSIONS: This study shows that cytoplasm replacement by ST can enhance the potential of developmentally compromised oocytes to develop up to the blastocyst stage without compromising euploidy rates. This opens up the possibility of providing new treatment options for patients with certain forms of infertility refractory to current clinical strategies.

Supported by: This study was financially supported by the Institute of Life (Athens, Greece).

O-209 Wednesday, October 10, 2018 11:45 AM

ASSESSING HUMAN BLASTOCYST QUALITY USING ARTIFICIAL INTELLIGENCE (AI) CONVOLUTIONAL NEURAL NETWORK (CNN) (CNN), N. Zaninovic,1 P. Khosravi,1 I. Hajirassouliha,1 J. E. Malmsten,1 E. Kazemi,1 Q. Zhan,1 M. Toschi,1 O. Elemento,1 Z. Rosenwaks,1 aCRM, Reproductive Facilities, New Haven, CT; bColorado Center for Reproductive Medicine, Lone Tree, CO, cCRM IVF Network, Lone Tree, CO.

OBJECTIVE: The objective of this study is to classify blastocyst (BL) quality by applying an AI system that uses time-lapse (TLM) images. We postulated that our unbiased AI method would learn to predict embryo quality without relying on human judgment.

DESIGN: We utilize a computational method based on convolutional neural networks (CNN) to build a stand-alone framework to accurately predict the morphological quality of human blastocysts based on raw time-lapse digital images.

MATERIALS AND METHODS: This study included a total of 50,392 images from 10,148 embryos cultured in the TLM system (EmbryoScope, Vitrolife, Sweden) at 110 hours post-insemination/ICSI. We applied deep neural networks on blastocyst images to analyze them using Google’s Inception (V1) architecture by fine-tuning the parameters for all layers and without pre-training the network. We compared the AI outcome data to the standardized BL grading system and the clinical outcomes.

RESULTS: We first classified blastocyst quality into three grades: good, fair, and poor, based on statistically different implantation outcomes (p =< 0.0001). Next, we trained the Inception-V1 algorithm on the three quality grades by using 18,000 images and then evaluated the algorithm’s performance by using the remaining images as a blind test set. Our results showed an average predictive accuracy of 74.95% for all three BL grades (92.34% for poor, 53.88% for fair, and 69.81% for good BL). As the fair BL group is a mix of poor and good grades and is influenced by additional factors like maternal age, we focused on identifying the poor and good BL groups. Our results showed 97.52% accuracy for discriminating between poor and good BL groups. When we compared AI output data for BL classification with known implantation data (KID), we obtained 90.6% accuracy for true positive (implanted and good quality BL) and 89.6% accuracy for true negative (non-implanted and poor quality BL). The accuracy of good quality with a negative outcome was 14.63%, while that of poor quality with a positive outcome was 44.78%.

CONCLUSIONS: We successfully applied AI to predict BL quality with high accuracy based on BL grading and implantation. Our data-driven approach provides a novel way to assess embryo quality and uncovers a new strategy for identifying embryos, which is likely to increase the chance of pregnancy.

O-210 Wednesday, October 10, 2018 12:00 PM

IMPACT OF A CONTROLLED TEMPERATURE GRADIENT FROM 35.0° - 37.5°C ON MOUSE EMBRYO DEVELOPMENT AND MORPHOKINETICS. E. Walters,1 J. Brown,1 R. L. Krisher,1 J. E. Swain,1 S. Voelkel,1 aCCRM Atlanta, Atlanta, GA; bColorado Center for Reproductive Medicine, Lone Tree, CO, cCRM IVF Network, Lone Tree, CO.

OBJECTIVE: To examine the impact of different in vitro culture temperatures on mouse embryo development and morphokinetic timings.

DESIGN: Prospective study

MATERIALS AND METHODS: An embryo culture incubator with 6 individual chambers and time-lapse imaging (ESCO MIRI TLM™) was set to vary the temperature between chambers by 0.5° to give a gradient that ranged from 35.0-37.5°C. Gas concentration was consistent between chambers (6% CO₂, 5% O₂, 89% N₂). Frozen-thawed 1-cell mouse embryos (B)(C)F₁xBxDxF₁, Embryotech™) were thawed, pooled and randomly distributed between 6 culture dishes in Global culture medium + 10% SPS. One dish containing individually cultured embryos was placed into each culture chamber/temperature for simultaneous culture and assessment. Embryos were cultured over 96h, recording blastocyst formation as well as morphokinetic timings for time to 2-cell, 3-cell, 4-cell, compaction and blastocoele formation. Experiments were repeated 3-times. Data were analyzed using ANOVA and Fisher Multiple-Comparison Test and are presented as the mean ± SEM. Statistically significance was measured at p<0.05.

RESULTS: Changes in temperature during mouse embryo culture significantly impacted blastocyst formation and morphokinetic timings. Blastocyst formation rates were highest at 37.0°C and decreased at other temperatures examined. Cell division timings became more rapid as temperature increased and significantly differed between temperature treatments for most endpoints examined.

CONCLUSIONS: New incubator technology offers the opportunity to examine the impact of temperature on embryo development while controlling for other culture variables. Changes in incubation temperature as little as 0.5°C have a significant impact on mouse embryo development, affecting blastocyst formation and morphokinetic timings. This data has potential implications for application of morphokinetic selection algorithms between facilities, as temperature between labs must be tightly controlled.

Mouse morphokinetic timings and blastocyst development at different culture temperatures

<table>
<thead>
<tr>
<th>Temperature</th>
<th>t-2cell</th>
<th>t-3cell</th>
<th>t-4cell</th>
<th>t-Compaction</th>
<th>t-Blastocyst</th>
<th>% Blastocyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>35.0°C</td>
<td>8.7±0.6</td>
<td>33.6±1.0a</td>
<td>34.9±1.1a</td>
<td>61.2±1.6a</td>
<td>80.5±5.1a</td>
<td>31.2%a</td>
</tr>
<tr>
<td>35.5°C</td>
<td>9.1±0.5a</td>
<td>34.1±0.8a</td>
<td>35.4±0.8a</td>
<td>61.4±0.8a</td>
<td>81.5±1.1a</td>
<td>52.7%b</td>
</tr>
<tr>
<td>36.0°C</td>
<td>8.6±0.4</td>
<td>31.7±0.9ab</td>
<td>33.4±0.7</td>
<td>57.9±1.3a</td>
<td>77.5±1.6a</td>
<td>55.5%b</td>
</tr>
<tr>
<td>36.5°C</td>
<td>7.7±0.4</td>
<td>30.3±0.7a</td>
<td>31.1±0.6</td>
<td>53.1±0.8a</td>
<td>69.1±1.2a</td>
<td>52.7%b</td>
</tr>
<tr>
<td>37.0°C</td>
<td>7.3±0.4</td>
<td>28.6±0.4a</td>
<td>30.5±0.7</td>
<td>53.5±1.3a</td>
<td>70.7±3.0a</td>
<td>65.5%c</td>
</tr>
<tr>
<td>37.5°C</td>
<td>6.8±0.4a</td>
<td>28.0±0.8a</td>
<td>28.6±0.7</td>
<td>49.2±0.9a</td>
<td>62.1±0.6a</td>
<td>56.7%bc</td>
</tr>
</tbody>
</table>

Different superscripts within a column represent statistically significant differences between temperatures p<0.05.

FERTILITY & STERILITY®
**LUTEAL PHASE AND IMPLANTATION**

**O-211 Wednesday, October 10, 2018 10:45 AM**


OBJECTIVE: To investigate differences in implantation rate among Japanese patients with repeated implantation failure (RIF) undergoing transfer at the blastocyst stage in their first IVF/ICSI cycle randomized to deferred embryo transfer or personalized embryo transfer (pET) after endometrial receptivity array (ERA) test.

DESIGN: Prospective randomized controlled trial that started in April 2016, with preliminary outcome evaluated in March 2018. Japanese patients with RIF were allocated through computer-generated randomization into deferred embryo transfer (DET) or pET groups. Sample size calculated for the endpoint of the implantation rate per embryo transfer was 253 patients per arm.

MATERIALS AND METHODS: We investigated the implantation rate of Japanese infertile women with RIF (mean age: 36.6 years old) in their first IVF/ICSI cycle with elective blastocyst transfer randomly allocated to DET group or pET group. The primary outcome in the present study was the implantation rate. Statistical analyses were conducted using univariate and multiple regression analyses. Significance was defined as p < 0.05. All patients gave informed consent. The present study was approved by institutional review board.

RESULTS: Our results have been analyzed after recruiting 506 patients of the 550 planned. The implantation rate was 8.7% in the DET group and 19.0% in the pET group. Therefore, pET was associated with significant improvement in the implantation rate versus regular DET (P = 0.0004). Furthermore, multiple logistic regression analysis showed that pET (P = 0.001) and blastocoele stage (P = 0.025) were significantly associated with the implantation rate but that patient age (P = 0.39), estradiol (E2; pg/mL) value (P = 0.77), progesterone (P, ng/mL) value (P = 0.64), trophoectoderm grade (P = 0.94) and inner cell mass grade (P = 0.73) were not.

CONCLUSIONS: The pET after ERA test and blastocoele stage are significantly correlated with the implantation rate for Japanese infertile women with RIF.

References: "None"

Supported by: "None"

**O-212 Wednesday, October 10, 2018 11:00 AM**

**USE OF ORAL DYDROGESTERONE FOR LUTEAL PHASE SUPPORT IN FRESH IVF CYCLES IS ASSOCIATED WITH AN INCREASE IN LIVE BIRTH RATE: AN INTEGRATED INDIVIDUAL PATIENT DATA ANALYSIS OF THE LOTUS PHASE III TRIAL PROGRAM.** G. Griesinger, a C. Blockeel, e E. Kahler, c C. Pexman-Fieth, d "Department of Gynecological Endocrinology and Reproductive Medicine, University Hospital of Schleswig-Holstein, Lübeck, Germany; bCenter for Reproductive Medicine, Universität Zürich, Zürich, Switzerland; cAbbott Laboratories GmbH, Hannover, Germany; dAbbott GmbH & Co. KG, Wiesbaden, Germany.

OBJECTIVE: To synthesize the data from two recent large, randomized phase III trials comparing oral dydrogesterone with micronized vaginal progesterone for luteal phase support in fresh embryo transfer IVF cycles.

DESIGN: Data from two randomized phase III trials (NCT01850030 and NCT02491437) performed according to GCP standards with a total of 1,957 patients in the full analysis sample were integrated on an individual patient data level with key design factors.

MATERIALS AND METHODS: Oral dydrogesterone (DYD) was administered to a total of 991 subjects and micronized vaginal progesterone (MVP) was administered to a total of 966 subjects who underwent fresh embryo transfer after ovariian stimulation followed by IVF or ICSI. Oral DYD 30 mg daily was compared to either 600 mg MVP capsules (NCT01850030) or MVP gel 90 mg daily (NCT01850030) for luteal phase support. The key outcome measures were pregnancy rate at 12 weeks of gestation, live birth rate and incidence of adverse events of the fetus or newborn coded to “congenital, familial, and genetic disorders”. Logistic regression was applied to come to the best prognostic model for the main dichotomous outcome measures of efficacy and safety.

RESULTS: For all efficacy outcome measures, preliminary results show that treatment was a significant prognostic factor. The administration of DYD versus MVP is associated with an increased likelihood of pregnancy at 12 weeks of gestation (OR = 1.3, 95% CI: 1.1 to 1.6; p < 0.05, ongoing pregnancies/1000 women: 381 DYD vs. 341 MVP) and an increased likelihood of mothers having a live birth (OR = 1.3, 95% CI: 1.0 to 1.6; p < 0.05, live births/1000 women: 344 DYD vs. 312 MVP). In addition, maternal age, site and day of embryo transfer were independent significant predictors for the efficacy outcome measures. No significant impact of treatment could be found regarding the incidence of “congenital, familial, and genetic disorders” adverse events.

CONCLUSIONS: The LOTUS trial program data indicate higher rates of ongoing pregnancy and live birth in women receiving oral dydrogesterone for luteal phase support in fresh IVF cycles as compared to micronized vaginal progesterone, while no significant difference in the incidence of “congenital, familial, and genetic disorders” adverse events was observed.

Supported by: This study was sponsored by Abbott.

**O-213 Wednesday, October 10, 2018 11:15 AM**

**A COMPARISON OF OUTCOMES WITH INTRAMUSCULAR PROGESTERONE AND 17-ALPHA HYDROXYPROGESTERONE CAPROATE IN WOMEN UNDERGOING FROZEN EMBRYO REPLACEMENT TRANSFER CYCLES.** S. Seshadri, a A. Al Chami, b R. Oidia, c X. Vinals Gonzalez, b W. Saab, e P. Serhal. b CRGH, LONDON, United Kingdom; cCRGH, London, United Kingdom.

OBJECTIVE: To assess if luteal support with intramuscular (IM) 17 alpha hydroxyprogesterone caproate (17OHPC) (Lentogest, AMSA, Italy) improves the pregnancy outcome in comparison to natural intramuscular progesterone (Prontogest, AMSA, Italy) when administered to recipients of vitrified blastocysts in a frozen embryo transfer cycle.

DESIGN: A retrospective comparative analysis of the outcomes of the two different intramuscular regimens used as luteal support in frozen embryo transfer cycles of autologous and donor egg IVF and ICSI patients (906 IVF cycles) who had a blastocyst transfer from February 2014 to April 2017.

MATERIALS AND METHODS: This retrospective study was carried at Centre for Reproductive and Genetic Health (CRGH) between 1st February 2014 and 1st April 2017. Nine hundred and six (906) cycles were available for analysis (466 cycles with IM natural progesterone and 440 cycles with IM 17 OHPC were identified).

RESULTS: The Live birth rate were significantly higher in women who received 17OHPC (Lentogest) group compared to the natural IM progesterone (Prontogest) group (39.5% versus 32.6%, p = 0.05). The miscarriage rate was found to be lower in the 17OHPC (Lentogest) group compared to the natural IM progesterone (Prontogest) group (14.5% vs 22.9%, p = 0.04). It is well known that, both intramuscular and vaginal progesterone preparations are considered the standard of care for luteal phase support in women having frozen embryo transfer cycles. However, there is no clear scientific consensus with regards to the optimum luteal support in such cycles. Also there are no studies in the literature comparing the use of artificial versus natural intramuscular progesterone in frozen embryo transfer cycles. The one indication where synthetic intramuscular progesterone 17OHPC (this vaginal one)(Lentogest) has been approved by the FDA is in the prevention of preterm birth.

CONCLUSIONS: Live birth rates are significantly higher in women who received artificial progesterone (Lentogest) compared to women who received natural progesterone (Prontogest) in frozen embryo transfer cycles.


**O-214 Wednesday, October 10, 2018 11:30 AM**

**GM-CSF (SARGRAMOSTIM) TREATMENT IN WOMEN WITH RECURRENT IMPLANTATION FAILURE UNDERGOING TRANSFER OF SINGLE HEALTHY BLASTOCYST AFTER PGS: A RANDOMIZED CONTROLLED TRIAL.** F. Scarpellini, a M. Sbracia, a Hungaria, CERM, Roma, Italy; bCERM, Roma, Italy.

OBJECTIVE: The GM-CSF is a cytokine promoting leukocyte growth as well as trophoblast development. We described that this cytokine may be
used in the treatment of recurrent abortion. We tested in this randomized controlled trial the use of GM-CSF (sargramostim) in the treatment for recurrent implantation failure in women undergoing IVF.

DESIGN: A controlled randomized study conducted on women with recurrent implantation failure.

MATERIALS AND METHODS: The study was conducted to the CERM, Rome, Italy, from the January 2016 to December 2017 on 73 women with recurrent implantation failure after IVF cycles. This study was approved by IRB. Inclusion criteria were: at least 9 good embryos previously transferred, women less than 38 years old, absence of systemic diseases. These women underwent IVF cycle and PGS on developed blastocysts. Single hatched blastocyst was transferred. The next cycle used only chromosomally healthy blastocysts. Patients were randomly divided in two groups: one (36 women) treated with subcutaneous GM-CSF 1.5mg/kg/daily (60-100) from the day of embryo transfer to the day of β-hcg day and if it was positive the treatment was continued for other 40 days: the control group (37 women) was treated with subcutaneous saline solution infusion in the same way of the study group. Primary outcome was the pregnancy rate.

RESULTS: Epidemiological data of the two groups did not show statistically significant differences. Pregnancy rate in the group treated with GM-CSF was 75.0% (27/36) whereas in the control group was 43.2% (16/37), P= 0.0087. No side effects were observed.

CONCLUSIONS: The clinical use of GM-CSF in women experienced implantation failure may be useful, even though more studies are needed to confirm these findings.

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LACTOBACILLUS NON-DOMINANT (LBND) MICROBIOME (MB) IS ASSOCIATED WITH DECREASED VITAMIN D RECEPTOR (VDR) EXPRESSION IN THE ENDOMETRIUM OF WOMEN WHO FAIL EUPLOID FROZEN EMBRYO TRANSFERS (FET). A. K. Masbou,a J. A. Grifo,a F. Wang,b S. Brown,c C. Oh,d Y. Hao,e Y. Xia,e D. L. Keefe,f NYU Fertility Center, New York, NY; bNYU Langone Health, New York, NY.

OBJECTIVE: Growing evidence supports the role of chronic endometritis (CE) in implantation failure (IF), yet the factors which contribute to CE remain poorly understood. Perturbation of the endometrial immune system and the endometrial MB, inflammatory cytokines and the evolutionary-ancient and the endometrial MB have been implicated in CE. We studied the effects of the endometrial MB, inflammatory cytokines and the evolutionary-ancient immune system provided by vitamin D and its receptor on CE in women failing single, euploid FET.

DESIGN: Prospective, observational, IRB approved study of women undergoing in vitro fertilization with preimplantation genetic testing who failed ≥1 single euploid FET at a university-based fertility center.

MATERIALS AND METHODS: Consenting patients meeting criteria underwent endometrial biopsy (EMB) by Tao brush™ and Pipelle® to analyze the MB and rule out CE. CE was defined by the presence of CD-138 positive plasma cells in the endometrial stroma. Pts also underwent saline infusion sonography (SIS) to rule out uterine defects. DNA was extracted from EM Bucks and SIS sample aspirates. Microbial composition was defined by 16S ribosomal RNA gene sequencing and analyzed for α and β diversity. For gene expression, RNA was isolated and cDNA synthesized by commercial kits. TaqMan gene expression assays measured inflammatory cytokines (LIF, TNFα, IL6, IL1β), GAPDH (housekeeping gene), and VDR. Quantitative PCR was performed and relative gene expression was normalized to GAPDH and analyzed by comparative CT method. Serum vitamin D was measured by chemiluminescence immunoassay. Mann-Whitney U test was used to analyze values of the mRNA expression, comparing lactobacillus dominant (LBD) vs LBND samples. Expression of endometrial VDR and p’s of serum vitamin D levels, as well as cytokines pre- and post-antibiotic treatment were assessed using Spearman’s Rank-Order Correlation Coefficient. For group comparison, ANOVA was used for normal variables, Kruskal-Wallis for non-normally distributed variables.

RESULTS: 79 pts enrolled and 28 completed the study. 54% had CE on first EMB. 80% of these tested negative after antibiotics. MB profile in cells extracted from SIS did not differ from EMB (non-significant α and β diversity tests). VDR gene expression was significantly decreased in pts with LBND vs LBD profiles in pts with CE prior to antibiotic treatment (p=0.04). Serum vitamin D levels were positively correlated with VDR at time of FET and IVF but failed to achieve statistical significance (p=0.57, p=0.4, respectively).

CONCLUSIONS: LBND MB, which has been implicated in IF, is associated with decreased VDR gene expression in the endometrium of women who failed euploid FET. The MB in cells lavaged from the endometrium during SIS closely resembles that obtained by EMB, and thus provides a less invasive approach to analyzing endometrial MB. Additional studies should clarify the roles of VDR expression in inflammatory cytokine expression and IF.

References:

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CONCENTRATION OF COLONY-STIMULATING GROWTH FACTOR (CSF) IN UTERINE FLUSHING AS PROGNOSTIC CRITERION OF IVF CYCLE OUTCOME IN PATIENTS WITH RECURRENT IMPLANTATION FAILURE. D. Obidnik,a A. Ggzyb, A. Kalugina,a D. Niauir. aAssisted Reproductive Technology, Ava-Peter, Saint-Petersburg, Russian Federation; bMedical Faculty, St.Petersburg State University, Saint-Petersburg, Russian Federation.

OBJECTIVE: To investigate if colony-stimulating growth factor can be used as reliable prognostic criterion of clinical pregnancy in “fresh” IVF cycles.

DESIGN: Study type: Interventional; Design: randomized controlled pilot study; Intervention Model: Parallel Assignment; Masking: open-label; Size: 83 patients; Duration: 12 months

MATERIALS AND METHODS: After obtaining board approval 83 women aged 22 - 39 years were recruited. Matching criteria: recurrent implantation failure, normal karyotype, absence of uterine factors of infertility. The patients were randomized into study group (N = 43) and control group (N = 40): no intervention. At the day of oocyte retrieval the uterine flushing was collected using insufflation catheter (CCD). CSF concentration in uterine flushing was determined using ELISA with following calculation per gram of protein.

RESULTS: As a primary assessed outcome the clinical pregnancy rate was analysed: there was no significant difference comparing between groups (X²=0.018, p=0.05, CC=0.015). Thus the method of collection of uterine flushing doesn’t affect IVF cycle outcome and can be used routinely. The CSF concentration in uterine flushing was significantly higher in women with clinical pregnancy. The ROC-curve showed sensitivity of 87.5% and specificity of 94.3% with cut-off value of CSF being 0.151.

CONCLUSIONS: The concept of recurrent implantation failure (RIF) in assisted reproductive technology has been enlarged and the tactics for such patients have included searching prognostic criteria of IVF outcome with the aim to minimize the number of unsuccessful attempts and the risk of patient’s drop-out. These data prove the necessity for further research of CSF role in implantation process and need for consideration the lack of CSF as a possible cause of recurrent implantation failure.

MALE FACTOR

O-217 Wednesday, October 10, 2018 10:45 AM

OLIGOSPERMIA, ASTHenOZOOSPERMIA, AND TERATOZOOSPERMIA ARE NOT ASSOCIATED WITH MORPHOLOGICAL TROPHOCYTEDERM SCORE. T. G. Nazem,a,c A. Fernandez-Nieto,a J. Lee,a C. Briton-Jones,a,b N. Bar-Chama,a A. B. Copperman,a,b,c Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY; bReproductive Medicine Associates of New York, New York, NY.

OBJECTIVE: The paternal and maternal genomes differentially express developmental genes during embryogenesis. In mouse studies, the
trophectoderm (TE) is unable to proliferate in the absence of the paternal genome despite normal inner cell mass (ICM) formation. This finding suggests a significant male contribution to TE development, which may be impacted by defective spermatogenesis. The study aimed to evaluate whether TE morphologic grade is affected by quantitative/qualitative deficiencies in semen function.

**DESIGN:** Retrospective

**MATERIALS AND METHODS:** Patients who underwent IVF stimulation from 2006-2016 were included. TE biopsy and pre-implantation genetic testing for aneuploidy (PGT-A) were performed on select blastocysts. Female age and body mass index (BMI), male age, days of abstinence preceding semen analysis (SA), type of ejaculate, SA parameters, type of oocyte insemination, number of blastocysts biopsied, and number of euploid embryos were collected. Embryos were grouped by TE quality—"high" quality embryos were assigned grades of A or B, "low" quality embryos were assigned grades of C or D. Data were analyzed using a Student’s T-test, Chi-square, and multivariate logistic regression.

**RESULTS:** A total of 64,937 embryos were included. Embryos with a high TE grade were from younger patients (female: 34.7±4.4 y, p<0.0001, male: 39.1±5.2 y, p=0.04). High TE grade embryos were more likely to have an expansion grade of 5 (28.7%, p<0.0001), an ICM grade of A (51.6%, p<0.0001), undergo biopsy for PGT-A (42.2%, p<0.0001), and have a euploid result (55.8%, p<0.0001). Low TE grade embryos were more likely to result from intracytoplasmic sperm injection (ICSI) (76.5%, p<0.0001). SA parameters (morphology, concentration, motility, TMC) days of abstinence, type of ejaculate and rate of re-biopsy were similar between groups. When adjusting for confounders and after sub-analysis of severe male factor cases utilizing testicular sperm, TE grade was not associated with SA parameters.

**CONCLUSIONS:** TE development is not impaired in embryos created using sperm from oligospermic, asthenozoospermic or teratozoospermic males. While presence of the paternal genome is essential for oocyte fertilization and initiation of embryo development, poor sperm quality/quantity do not impede this process. Genome-wide association studies are needed to uncover genes associated with male factor infertility that impact oocyte activation, fertilization and early embryo development.

**References:**

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**Objective:** The aim of this study was to: 1. evaluate clinical outcomes after ICSI cycles using surgically recovered sperm, and 2. to assess the influence of maternal age on those outcomes.

**Design:** Retrospective cohort study of 24,763 IVF cycles of fresh autologous oocytes and ICSI using surgically recovered sperm reported to SART CORS database from 2004-2015.

**Materials and Methods:** The data were stratified into five groups based on maternal age: <30 years, 30-34 years, 35-37 years, 38-42 years, and >42 years. The primary outcome measure was live birth rate per cycle initiated. Additional outcomes included proportion of normal fertilization, embryo cleavage, embryo grading, proportion of spontaneous miscarriages, clinical pregnancies, gestational age at delivery, births with PTD (<37 weeks gestational age) and the proportion of neonates with LBW (<2500g). Results were compared to the 2014-2015 SART CORS registry for ICSI for male factor and to the non-male factor ICSI and male factor ICSI 2008-2012 National Surveillance System database.

Mean and standard deviation were calculated for continuous variables, and frequencies and percentages for categorical variables. T-test was used for continuous variables and chi-square analysis was used for categorical variables. We used Analysis of variance to determine whether the means of the maternal age groups were significantly different in each variable. Post hoc pairwise comparisons were performed when maternal age groups differed significantly. Welch’s test for unequal variances was employed when variances of each group differed significantly. Chi-square was further used to determine the odds of variables occurring with each maternal age group in comparison to women aged <30.

**Results:** There was no significant association between fertilization rate and maternal age. Compared to other older age groups, women <30y had significantly higher embryo grading, higher clinical pregnancy rates, and lower miscarriage rate. However, live birth rates, gestational age at delivery, number of preterm deliveries, neonatal birth weight, and low birth weight were not different. For twin pregnancies, but not for singleton pregnancies, women <30y had significantly higher number of live births, term deliveries, and lower preterm deliveries than older women. When compared to the 2014-2015 SART CORS registry for ICSI for male factor and to the non-male factor ICSI and male factor ICSI 2008-2012 National Surveillance System (NASS) database, pregnancy outcomes with surgically recovered sperm were reassuring and comparable to those of ejaculated sperm.

**Conclusions:** Overall pregnancy outcomes with surgically recovered sperm are reassuring and comparable to those of ejaculated sperm.

**References:**

O-219 Wednesday, October 10, 2018 11:15 AM

**HUMAN ZYGOTES RESPOND TO SPERM DNA DAMAGE BY DELAYING EMBRYONIC DEVELOPMENT.** M. Eibert, S. R. Soares, A. Pacheco, A. Ballesteros, M. Florensa, M. Meseguer. IVF Laboratory, IVIRMA Barcelona, Barcelona, Spain; Gynecological Unit, IVIRMA Lisboa, Lisboa, Portugal; Andrology Laboratory, IVIRMA Madrid, Madrid, Spain; Gynecological Unit, IVIRMA Barcelona, Barcelona, Spain; IVF laboratory, IVIRMA Barcelona, Barcelona, Spain; IVF Laboratory, IVIRMA Valencia, Valencia, Spain.

**Objective:** The aims of this study were: 1. to evaluate clinical outcomes after ICSI cycles using surgically recovered sperm, and 2. to assess the influence of maternal age on those outcomes.
OBJECTIVE: Time-lapse monitoring (TLM) technology has been implemented in the clinical setting for the culture and selection of human embryos. Little is known about the effect of male gamete on the embryo division timings, but some experiments performed on mouse zygotes showed that sperm DNA fragmentation (DFI) plays a toxic role in early embryonic progression (1). The main goal of this study was to evaluate the correlation between sperm DNA fragmentation (sDNAf), male age and embryo kinetics parameters.

MATERIALS AND METHODS: Embryonic TLM data was obtained for 631 embryos from 61 couples undergoing ART at an academic fertility center. To minimize the effect of any female factor infertility, only couples enrolled in an oocyte donation program were included. Fresh ejaculated samples were evaluated according to the WHO criteria and processed through density gradients. The aliquot used to perform the ICSI was analyzed by flow cytometry TUNEL assay to measure the level of sperm DNA fragmentation. The fertilization process and embryo development were assessed through an Embryoscope® (VitroLife) time-lapse system until D+5 of development. Association between sDNAf, male age and morphokinetic parameters was investigated using the Pearson correlation coefficient.

RESULTS: Mean age of males was 41.10 (95% CI 39.40-42.80) and mean sDNAf was 14.13 (95% CI 11.68-16.58). When the effect of DNA damage was analyzed, we found a significantly positive correlation between sDNAf and both time of second polar body extrusion (pPB2) (r = 0.02, p = 0.015) and time of pronuclear appearance (PNa) (r = 0.09, p = 0.034). The remaining morphokinetic variables were not related with sperm DNA damage. Regarding paternal age, we did not find any relationship between paternal age and any morphokinetic parameters but observed a clear positive relationship with sDNAf (r = 0.303, p < 0.0001).

CONCLUSIONS: According to our study, sperm DNA fragmentation is affecting the timing necessary to resume meiosis (defined by 2PB extrusion) and the initiation of S-phase of first embryo cell cycle (defined by the PNa). Further basic studies may be necessary to understand the molecular processes that may condition our observations.


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THE ATTRACTIVE EFFECT OF DNA FRAGMENTATION INDEX ON ASSISTED REPRODUCTIVE TREATMENT OUTCOME: A LARGE SAMPLE SIZE AND WELL-CONTROLLED RETROSPECTIVE STUDY. C. Deng, T. Li, Y. Xie, M. Cai, X. Liang, G. Liu. Reproductive Medicine Research Center, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; Department of Urology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.

OBJECTIVE: To study the impact of sperm DNA fragmentation index (DFI) on the assisted reproductive treatment (ART) outcome, including the rate of good quality embryos, clinical pregnancy and miscarriage.

DESIGN: Retrospective cohort study

MATERIALS AND METHODS: We conducted a retrospective analysis of infertile couples undergoing IVF or ICSI treatments at our reproductive center from May 2012 to April 2018. Only infertile couples caused by cervical factors, male factors, pelvic factors, fallopian tube factors or sexual disturbances were included in the study. Inclusive couples are divided into four subgroups according to the age of the female, including the subgroup less than 30 years old, the 30 to 35 year old subgroup, the 35 to 40 year old subgroup, and the subgroup more than 40 years old. The sperm DNA fragmentation was evaluated by SCSA assay and flow cytometry. With DFI ≥ 30 as the threshold, each subgroup was divided into low DFI group and high DFI group and the ART outcome were respectively compared.

RESULTS: 4841 cycles were included, 4117 of which in low DFI group and 724 in high DFI group. The average age of female and male in high DFI group was slightly higher than low DFI group subgroup less than 30 years old (30.22 ± 2.34 vs. 31.69 ± 2.84, p < 0.005), but the slight age difference, the baseline factors, including the level of FSH (P > 0.05), number of sinus follicles (P > 0.05), were not different between low DFI group and high DFI group of four subgroups. There was no statistically significant difference in oocyte number, 2PN fertilization rate, cleavage rate, number of available embryos (P > 0.05) of all 4 subgroups. There were no significant differences in biochemical pregnancy rate (41/7676 vs 33/61, P > 0.05), clinical pregnancy rate (36/412 vs 32/33, P > 0.05), miscarriage rate (4/386 vs 4/32, P > 0.05) between low DFI group and high DFI group in four subgroups. The good quality embryo rate of high DFI group were significantly lower than low DFI group in couples received both IVF and ICSI in the subgroup less than 30 years old (IVF: 0.27 ± 0.40 vs 0.16 ± 0.33, P < 0.05; ICSI: 0.05 ± 0.20 vs 0.16 ± 0.35, P < 0.05), the 30 to 35 year old subgroup (IVF: 0.28 ± 0.41 vs 0.15 ± 0.35, P < 0.05; ICSI: 0.05 ± 0.20 vs 0.16 ± 0.34, P < 0.05). In the subgroup more than 40 years old, high scores blastocyst rate in high DFI group is significantly lower than in the low DFI group (IVF: 0.18 ± 0.58 vs 0.03 ± 0.18, P < 0.05; ICSI: 0.17 ± 0.38 vs 0.00 ± 0.00, P < 0.05).

CONCLUSIONS: This is a well-controlled and large size retrospective study assessing whether DFI affect the ART outcome. By strictly controlled the confounding female factors, we concluded that DFI had adverse impacts on embryo quality in both IVF and ICSI. Interestingly, unlike previous studies, we found that DFI does not affect biochemical pregnancy rate, the clinical pregnancy rate and miscarriage rate after strict control of the woman’s factors.

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SPERM TRANSCRIPTS AND GENOMIC INTEGRITY: ROLE IN IMPLANTATION AND EMBRYO VIABILITY IN IVF CYCLES. V. Dhawan, M. Kumar, V. Vadhwal, N. Singh, R. Dada. Anatomy, All India Institute of Medical Sciences, New Delhi, India; Anatomy, Lab for Molecular Reproduction and Genetics, New Delhi, India; Obstetrics & Gynecology, All India Institute of Medical Sciences, New Delhi, India; Professor, New Delhi, India; Lab for Molecular Reproduction and Genetics, Anatomy, AIIMS, N Delhi, India.

OBJECTIVE: The current male infertility diagnosis has a limited value in selecting the optimum treatment and predicting birth success in IVF cycles. Spermatozoa are not just the vehicle for contributing a structured and epigenetically marked genome to the oocyte at fertilization but they also provide a host of RNAs and proteins. The critical role of sperm RNA in embryonic development and as a prognostic indicator of live birth has already been shown. The present study is focussed on assessing the levels of such transcripts as well as genomic integrity and overwhelming oxidative stress to address this tenet.

DESIGN: A case-control study of 50 male partners of females experiencing recurrent implantation failures in IVF cycles and 50 healthy fertile controls at AIIMS, New Delhi, India.

MATERIALS AND METHODS: Semen samples were obtained from the cases and controls and semen analysis was done by WHO (2010) criteria. RNA was isolated from the semen samples and reverse transcribed. The gene expression of was analysed using quantitative real-time PCR and the relative quantification of target genes was done after normalization to β-actin. The level of genes critical for embryonic development (FOXG1, SOX17, RPL10A, RPS6, RPS9) and oxidative stress (RPL10A, RPS6) have been analysed by DNA fragmentation index (DFI) and chemiluminescence assay to measure reactive oxygen species (ROS) levels (RLU/sec/million sperm).

RESULTS: The relative gene expression of FOXG1 (p = 0.02), RPS6, RPL10A and RPL108 (p < 0.001) was seen to differ significantly between cases and controls. The mean ROS level in the cases was seen to be significantly higher (>25) in RIF patients (45.04±12.38) with respect to controls (18.6±7.6) (p = 0.002). The mean percentage DFI was significantly higher (>28) in RIF cases (38.61±8.91) as compared to controls (40.32±8.6) (p < 0.001). The odds of occurrence of RIF was 4.2 times greater, whose ROS>25 RLU/sec/million sperm (OR 4.2, 95% CI: (1.14-15.3), and was statistically significant (p = 0.03). No association of RIF was found with DFI>28% (p = 0.989).

CONCLUSIONS: The functional significance of these selective transcripts is invaluable for assessing the paternal contributions in implantation and embryonic development. The defects in genomic integrity, mitochondrial dysfunctions or abnormal delivery of paternal transcripts are “carried over” to the embryo, compromising embryo viability and also produce transgenerational effects adversely affecting the progeny.


OBJECTIVE: To evaluate the validity of sperm morphology as a predictor of male factor infertility through analysis of andrology laboratory proficiency statistics collected and reported by the American Association of Biostatisticians (AAB) Proficiency Testing Service (PTS).

MATERIALS AND METHODS: Andrology laboratory proficiency statistics reported by the AAB PTS over a twelve year period (2002-2013) were reviewed. A total of 48 sperm specimens were evaluated by over 200 laboratories during this time period as a measure of diagnostic proficiency. Laboratories evaluated each sample in accordance with the standard methodology of semen analysis used at each site and reported the results. The statistics reported by the AAB PTS included the values assessed in traditional semen analysis aggregated from all participating laboratories. However, for the purposes of this analysis, only the values regarding sperm morphology using strict Kruger criteria were included. These statistics included the mean percentage of normal morphology per specimen, the "grading range", and the standard deviation. The grading range is defined by AAB PTS as three times the standard deviation above and below the mean. This range includes the acceptable values for a passing proficiency score.

RESULTS: Six of the 48 specimens had a mean normal morphology score of less than 4%. The grading range for these six specimens all had an upper limit exceeding 4%. 46 of the 48 total specimens (95.8%) had grading ranges with a lower limit less than 4%. Of these 46 specimens, 40 (87.0%) had reported mean normal morphology values greater than or equal to 4%. 0% of the specimens had a mean normal morphology score greater than 14%.

CONCLUSIONS: Sperm morphology has long been considered an important component of semen analysis for prediction of fertilization rates. The study by Kruger et al. in 1988 states that normal morphology scores of less than 4% are predictive of severe fertilization impairment, while values greater than 14% are indicative of normal fertilization rates.1 However, the current testing for laboratory proficiency allows for a wide range of acceptable values when assessing sperm morphology, 87% of samples with mean normal morphology values greater than 4% had a grading range with a lower limit below 4%. This indicates that a laboratory could report a value that is not associated with AMH overall (β= -0.03, 95% CI -0.14, -0.08, per 1% change), when examined by tertile, in the second tertile range of SFA were found to have a statistically significant decrease in AMH (-1.8 mg/L, 95% CI -1.0, -0.6) compared to the first tertile. There were no associations between PUFA and AMH.

CONCLUSIONS: Our data suggest that micronutrients and fatty acids are not associated with AMH levels in women with proven fecundity. Additional research in infertile populations is needed to understand whether potential lifestyle factors are associated with AMH levels.

Supported by: Intramural Research Program, NICHD, NIH

Wednesday, October 10, 2018 11:00 AM

RECURRENT PREGNANCY LOSS IN FOOD DESERTS IN THE MID-SOUTH USING GEOGRAPHIC INFORMATION SYSTEM ANALYSIS

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OBJECTIVE: Evaluate the association between United States Department of Agriculture (USDA) Food Deserts and recurrent pregnancy loss.

DESIGN: Retrospective cohort study

MATERIALS AND METHODS: Retrospective cohort study was performed among women diagnosed with pregnancy in the outpatient clinic at our academic institution from 2015 to 2018. Patients with recurrent pregnancy loss (RPL) were identified utilizing the International Classification of Diseases (ICD) codes. RPL was defined as two or more failed clinical pregnancies. The primary exposure was "low income, low access to a supermarket (LLA)", more commonly known as a "food desert". A low-income area was defined by the Department of Agriculture’s !986 Tax Credit (NMTCC) program as having greater than 20% of the poverty rate or a median family income of less than 80% of the state-wide or metropolitan area median. Low access was defined the number of households without access to a vehicle and live in an urban area that is half a mile from a supermarket or within a rural area that is twenty miles from the nearest grocery store. Chi-squared analysis was performed with statistical significance (p<0.05). RPL was diagnosed in 236 of the 2996 patients (7.9%) included in our study. The demographics of the cohort were 70% African American, 20% Caucasian and 2% Asian American. The majority of the patients (89%) were characterized as living in an urban setting. In our cohort, 61.5% of patients diagnosed with RPL in the outpatient clinic lived in a food desert compared to 47% of patients who continued their pregnancy during the same time period (p-value of 0.008). According to the 2010 Census of

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NUTRITION
Population and Housing Report, 4.2% of the United States population live in a food desert, compared to 13% of Tennessee residents. Food deserts demonstrate a disparity in the availability of resources among varying communities. From our analysis, patients with recurrent pregnancy loss were more likely to live in a food desert compared to the general population.

CONCLUSIONS: The incidence of RPL in our patient population was higher than the national average of 2.5%. Patients with RPL are more likely to live in a food desert compared to the general population. This effect is likely a reflection of racial and socioeconomic disparities, and this may be a good marker for patients requiring additional treatment or earlier intervention. In the Mid-South, environmental factors may be more influential than previously thought in the setting of RPL.

References:

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OBJECTIVE: To evaluate prospectively the association between glycemc load (GL), dietary fiber (DF), and added sugars fecundability. Total GL reflects quantity and quality of carbohydrates in the diet; DF and added sugars are related to total GL. Diets with high GL have been linked with adverse health outcomes, including polycystic ovary syndrome and diabetes. Sugar-sweetened beverages, a high-GL food, have been associated with reduced fertility in many studies. Studies of the association between DF intake and reproductive function have been mixed, with one study showing a positive association between high fiber intake and anovulation and another reporting little association between fiber intake and ovulatory infertility.

DESIGN: Prospective cohort study

MATERIALS AND METHODS: Pregnancy Online Study (PRESTO) is a web-based prospective preconception cohort of pregnancy planners living in North America. At baseline, female participants, aged 21-45 years, complete a web-based questionnaire on demographic, lifestyle, medical and reproductive factors. After enrollment, participants complete a validated food frequency questionnaire (FFQ). National Dietary History Questionnaire II. We calculated GL (sum of glycemic index (GI) times portion size); total DF, soluble fiber, insoluble fiber (grams/day); and added sugars (teaspoons (tsp)/day), based on reported frequencies for individual foods, standard recipes for mixed foods, and average serving size. The analysis included 3,295 couples attempting to conceive for 6 cycles at study entry and not using contraception or fertility treatments. We adjusted for energy intake, healthy eating index score (HEI 2010), and lifestyle and demographic factors.

RESULTS: Compared with an average daily GL ≤ 75, FRs for an average daily GL of 76-100, 101-125, and >125 were 1.03 (CI: 0.91-1.16), 0.95 (CI: 0.84-1.09), and 0.80 (CI: 0.65-0.99), respectively. Compared with consuming ≤ 12 grams/day of fiber, FRs for 13-16, 17-21, and >21 grams/day were 1.04 (CI: 0.89-1.22), 1.06 (CI: 0.89-1.26), and 1.00 (CI: 0.82-1.22), respectively. Similar results were observed for soluble and insoluble fiber. Compared with consuming ≤ 6 tsp/day of added sugars, FRs for 7-9, 10-13, and >13 tsp/day were 0.93 (CI: 0.83-1.03), 0.87 (CI: 0.78-0.98), and 0.80 (CI: 0.70-0.93), respectively. Results for GL, total fiber, soluble fiber, and added sugars did not appreciably differ by BMI. However, among women with BMI ≥25 kg/m2, higher intake of insoluble fiber was associated with reduced fecundability while among women with BMI <25 kg/m2, it was associated with improved fecundability.

CONCLUSIONS: Dietary change to higher GL and added sugars was associated with reduced fecundability.

References:

Supported by: This research was supported by R01 HD086742.
Supplementation with omega-3 fatty acids has been suggested as an intervention to improve ovarian function into advanced reproductive age. We hypothesized that omega-3 fatty acid supplementation to HFD would restore HFD-induced ovulatory dysfunction.

**DESIGN:** Prospective laboratory animal study.

**MATERIALS AND METHODS:** 5 wk old C57BL/6J mice were randomly assigned to receive 60% HFD (N = 45) or chow (N = 10) for 10 weeks. After 10 weeks, HFD mice were assigned to continue HFD (N = 15), or were switched to chow (N = 10), DHA enriched chow (N = 10, chow+DHA), or DHA enriched HFD (N = 10, HFD+DHA) for 10 weeks. Chow mice remained on chow. Estrus cycle was evaluated daily for the last two weeks of each diet and mice were sacrificed in diestrous. Chi-square and Kruskal-Wallis (Dunn’s post-hoc) tests were used for statistical analysis.

**RESULTS:** As expected, mice fed HFD weighed more than chow controls after 10 weeks of dietary intervention. Diet reversal to chow or to chow+DHA restored body weight to that of chow-fed mice, while adding DHA to HFD had no effect (table). After 10 weeks on diet, more HFD mice had abnormal estrous cycles compared to chow controls (table). A high prevalence of irregular cycles continued in mice fed HFD for additional 10 weeks and adding DHA to HFD did not have a benefit. However, switching to chow or chow+DHA after HFD restored estrous cyclicity to that of controls (table).

<table>
<thead>
<tr>
<th>Diet weeks 0 to 10</th>
<th>Chow</th>
<th>HFD</th>
<th>HFD</th>
<th>Chow+DHA</th>
<th>HFD+DHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight week 10 (g) (mean ± SEM)</td>
<td>21.8 ± 0.5; 28.8 ± 1.4b; 29.6 ± 1.2; 21.2; 29.5 ± 1.3; 0.0003</td>
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<tr>
<td>Body weight week 20 (g) (mean ± SEM)</td>
<td>24.5 ± 0.9; 40.9 ± 2.1b; 24.6 ± 0.5; 24 ± 1.7; 40.0 ± 1.9; &lt;0.0001</td>
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</tr>
<tr>
<td>Irregular cycle week 10 (% of mice)</td>
<td>20.0%a 80.0%b 90.0%b 88.8%b 80.0%b 0.002</td>
<td></td>
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<tr>
<td>Irregular cycle week 20 (% of mice)</td>
<td>20.0%a 80.0%b 30.0%a 33.3%a 60.0%ab 0.02</td>
<td></td>
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</table>

**CONCLUSIONS:** Our data suggest that adding DHA to diet has no additional benefit to diet-induced weight loss in restoring ovulatory dysfunction. Our pre-clinical model suggests that supplementation with omega-3 fatty acids cannot be recommended as the only intervention without concurrent switch in diet.

**References:**


**OFFICE AND PRACTICE MANAGEMENT**

O-229 Wednesday, October 10, 2018 10:45 AM

**ART CENTER PROCESS FLOW ANALYSIS: A QUALITATIVE ANALYSIS OF HOW AN ART CENTER DELIVERS EFFECTIVE PATIENT CARE EVERY TIME.** B. Singh, J. H. Segars, P. Xia. *Gynecology & Obstetrics, Johns Hopkins School of Medicine, Baltimore, MD; Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Baltimore, MD; OB/GYN, Johns Hopkins Medicine, Lutherville, MD.

**OBJECTIVE:** There are 464 fertility clinics in operation, performing 231,936 total ART cycles in the U.S. (CDC ART National Summary Report, 2015). Laboratory errors in ART must be avoided, and improved efficiency has been associated with error reduction. Process Flow Analysis has been used in other disciplines but has not been reported for ART clinics. Here we sought to apply Process Flow Analysis Tools to identify bottleneck areas in the efficient delivery of services for an ART center.

**DESIGN:** Prospective quality assessment/improvement study.

**MATERIALS AND METHODS:** The study was approved by the Institutional Review Board at Johns Hopkins School of Medicine. Process Flow Analysis is an operations management tool used to study the inputs and outputs of a procedure/practice. To create these multi-dimensional complex flowcharts, 14 individuals from the ART centers (both clinical and non-clinical staff) were interviewed to evaluate their experiences as related to their daily activities and responsibilities. Based on the information gathered, process flow diagrams were generated by the research team using Microsoft Office Professional Plus 2016 Flowchart Tools. The flowcharts generated were reviewed with the ART clinic and lab members to verify the process validity. The capacity and flow rate of the system were established using clinic data from the last 3 years (2014-2017).

**RESULTS:** Our multifaceted flowchart analysis revealed that the ART center operated at moderate efficiency. The research identified niche areas with the potential to elevate the overall experience for both patients and providers. Process flow charting identified a few critical bottle-neck areas in the

**OFFICE AND PRACTICE MANAGEMENT**
O-230 Wednesday, October 10, 2018 11:00 AM

PATIENT-CENTERED CARE: FACTORS ASSOCIATED WITH REPORTING A POSITIVE EXPERIENCE AT U.S. FERTILITY CLINICS. L. Shandley,\textsuperscript{a} L. J. McKenzie,\textsuperscript{b} H. Hipp,\textsuperscript{c} J. Anderson-Bialis,\textsuperscript{d} D. Anderson-Bialis,\textsuperscript{b} J. F. Kawwass.\textsuperscript{a} Emory Reproductive Center, Atlanta, GA;\textsuperscript{a} FertilityIQ, San Francisco, CA.

OBJECTIVE: To identify factors associated with patients having a positive experience (PE) at a fertility clinic using data from a nationwide questionnaire.

DESIGN: FertilityIQs is an open access website (https://www.fertilityiq.com/) with a voluntary questionnaire for individuals and couples pursuing fertility treatment. Data gathered include type of treatment(s), review of doctors and clinics, and personal preferences regarding infertility treatment experience.

MATERIALS AND METHODS: Deidentified surveys from women who completed the FertilityIQ questionnaire, reviewing the only or first clinic visited, between July 2015 and January 2018 were included (n = 4698). A PE was defined as a score of 9 or 10 of 10 on the question, “Would you recommend this fertility clinic to a best friend?” Descriptive statistics were used to characterize the population, comparing patients who reported a PE to those who reported a non-positive experience (response of 1-8). Logistic regression was used to estimate the odds ratios (OR) for various predictor associated with reporting a PE. A sub-analysis, stratified by whether or not a woman conceived, was also performed.

RESULTS: Of the 4698 respondents who met inclusion criteria, 63.4% reported a PE. Those who reported positive and non-positive experiences were similar with regards to age at survey, age at treatment, geographic location, race, and income. The variables most strongly associated with a PE were related to physician personality, with a PE associated with physician trustworthiness (OR 58.1, 95% confidence interval [CI] 41.2, 82.0), communication (OR 35.2, 95% CI 28.1, 44.0), and compassion (OR 23.2, 95% CI 18.9, 28.4). Clinics with shorter wait times to speak with a doctor or nurse (within 24 hours: OR 18.6, 95% CI 11.8, 29.3; referent: 24 hours) and shorter wait times to be seen by a doctor (within a week: OR 4.9, 95% CI 4.1, 5.9; referent: more than a week) were more likely to be seen positively. Clinics with direct phone lines to nurses or doctors were three times more likely to be reported as being rated positively. Clinics with additional on-site ancillary resources were more likely to be rated positively (OR 2.4, 95% CI 2.1, 2.7) as were those reporting satisfaction with the billing department (OR 6.3, 95% CI 7.2, 9.6). In a sub-analysis stratified by whether or not a woman got pregnant following treatment, there were differences in satisfaction amongst those not reporting a pregnancy based on fertility diagnosis, with those with diminished ovarian reserve (OR 0.7, 95% CI 0.6, 0.8) and unexplained infertility (OR 0.7, 95% CI 0.6, 0.8) being less likely to report a PE while those with polycystic ovary syndrome (OR 1.5, 95% CI 1.2, 1.8) and tubal factor infertility (OR 1.7, 95% CI 1.2, 2.3) being more likely to report a PE.

CONCLUSIONS: There are many modifiable predictors of a patient reporting a positive experience at a fertility clinic, the majority of which did not differ by whether or not pregnancy was achieved.

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FERTILITY PRACTICE ADVERTISING -ASSESSMENT OF FERTILITY PRACTICE WEBSITES’ ADHERENCE TO SOCIETY FOR REPRODUCTIVE TECHNOLOGY PRACTICE GUIDELINES. S. B. Schoen,\textsuperscript{a} P. Masson,\textsuperscript{b} E. Wang,\textsuperscript{c} M. D. Pisarska,\textsuperscript{d} J. L. Chan.\textsuperscript{b} OB/GYN, UCLA, Los Angeles, CA;\textsuperscript{a} OB/GYN, University of Michigan, Ann Arbor, MI;\textsuperscript{b} Urology, University of Pennsylvania, Philadelphia, PA;\textsuperscript{d} OB/GYN, Cedars-Sinai Medical Center, Los Angeles, CA.

OBJECTIVE: Our objective was to evaluate the information that is advertised on fertility practice websites and objectively quantify how well fertility practice websites are following SART advertising guidelines.

DESIGN: Cross-sectional evaluation

MATERIALS AND METHODS: Between 3/2017-4/2017, SART fertility practice websites were systematically examined and categorized by size (<500 cycles/year vs. ≥500 cycles/year) and type of practice (academic vs. private). Websites were surveyed for a variety of advertising content. Additionally, we assessed and scored practice websites’ adherence to the SART 2018 required advertising guidelines: following Federal Trade Commission’s (FTC) guidelines, no claims of superiority and not using SART data to rank itself to other practices. While advertising success rates are not mandatory, if reported, must include: a link to their summary report on SART.org, data to support success claims and a disclaimer statement. Chi-square tests were used to evaluate differences between groups and Wilcoxon Ranksum tests were used to evaluate differences in scores. P < 0.05 was considered statistically significant.

RESULTS: 96% of practices had a unique, active website of which 79% were private practices. 30% of practices performed <500 cycles/year. Table 1 lists fertility practice characteristics. 77% followed FTC guidelines, 93% made no claims of superiority over other practices and 95% did not use SART data to compare themselves to other practices. The average score of practices following these guidelines was 2.64 out of 3 points. There were

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GENDER INEQUALITY IN SALARIES AMONG REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY SPECIALISTS IN THE US. S. B. Gilbert,\textsuperscript{a} A. Allshouse,\textsuperscript{a} M. Skaznik-Wickel.\textsuperscript{b} Obstetrics and Gynecology, University of Colorado School of Medicine, Aurora, CO;\textsuperscript{c} Department of Biostatistics and Informatics, Colorado School of Public Health, Aurora, CO.

OBJECTIVE: Current literature, including a recent commentary published in the journal of the American College of Obstetricians, identifies a gender-based pay gap among physicians in the US, and specifically in the field of Obstetrics and Gynecology (Ob/Gyn), where female gender is associated with lower pay when compared to male gender.\textsuperscript{1} Since differences in pay in the general population have been shown to widen with higher education and additional professional degrees, we sought to determine whether and by how much pay among board certified or eligible Reproductive Endocrinology and Infertility (REI) specialists at both private and academic institutions in the US differs by gender.

DESIGN: Cross-sectional web-based survey

MATERIALS AND METHODS: A REDcap survey was emailed to all board certified and board eligible members of the Society for Reproductive Endocrinology and Infertility (SREI) using the SREI distribution list two times between 12/18/17 and 1/27/2018. The survey instrument included demographics (gender, age) and practice characteristics (practice type, location, years in practice, salary included bonuses, marital and dependent status, additional practice specifics and days of work per week). Income was calculated using the mid-point to categorical responses for income and annual bonuses, analyzed on the log scale, and summarized as geometric mean and 95% confidence interval. Age and practice characteristics were summarized as frequency and percentage by gender, and differences tested with a chi-square. Gender-based differences in log-scale income were modeled using linear regression to adjust for age, days of work per week, practice type and years in practice.

RESULTS: Among 215 responses (27% response rate), 49% were female and 95% were full SREI members. Significantly more males reported being in private practice than females (64% vs. 45%, p = 0.008). No differences by gender were significant for regional location or practice specifics. Male gender was associated with an income gap of 27% in unadjusted comparisons. When adjusted for years in practice and type of practice (private vs. other), the gap diminished in magnitude to 21% but remained significant with almost twice the pay among reporting higher incomes than females.

CONCLUSIONS: The gender pay gap seen among physicians and Ob/Gyns more widely persists among REI specialists even when accounting for characteristics related to differences in pay. Acknowledging the pay gap among REI specialists is a first step in working toward gender-neutral compensation for equivalent work.

References:

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no differences in scores between practice type or size. Overall, 46% of practices advertised success rates with 92% of them having data to support success claims, 80% had a SART link present and 49% had a disclaimer statement. The average score of practices following success rate reporting was 3.2 out of 4 points. Large practices were more likely to mention success rates (38% vs. 70%, p < 0.001), as well as publish the required disclaimer statement regarding success rates (41% vs. 58%, p = 0.026). There were no differences between academic and private practices regarding any of the success rate advertising guidelines.

CONCLUSIONS: There is significant heterogeneity in the advertised content on fertility practice websites, as well as a significant difference in how practice sizes advertise their success rates. This study suggests that there is still significant work to be done on how practices are reporting success.

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COMPARING MALE AND FEMALE ENROLLMENT IN A REPRODUCTIVE BIOREPOSITORY: THE IMPORTANCE OF BALANCED PARTICIPATION. S. B. Schon,a M. Xu,a H. G. Cameron,b N. Mazur,b R. Hershock,d J. M. Dupree,e E. E. Marsh,a A. Catherino,a B. Hayward,a F. Sharara,b J. Bromer,c W. Catherino,d aEMD Serono, Inc., Rockland, MA; bVirginia Center for Reproductive Medicine, Reston, VA; cShady Grove Fertility, Rockville, MD; dUniformed Services University of the Health Sciences, Bethesda, MD.

OBJECTIVE: Biorepositories provide a critical resource for the expansion and development of clinical and translational reproductive research. However, it’s unknown if male fertility patients are willing to participate in biorepositories at rates similar to female patients. We have recently established a comprehensive reproductive biorepository targeting both male and female partners presenting for fertility services. Herein, we report our differential experience recruiting male and female patients as well as a significant difference in how practice sizes advertised their success rates. This study suggests that there is still significant work to be done on how practices are reporting success.

DESIGN: Prospective, interventional, cohort study.

MATERIALS AND METHODS: Beginning in December 2017, all men and women presenting for consultation and/or semen analysis at the University of Michigan Center for Reproductive Medicine were approached separately for informed consent. Following enrollment, patients completed a reproductive and medical history questionnaire. For male patients undergoing semen analysis, semen that would have otherwise been discarded following analysis was collected for immediate biorepository processing and storage. Semen samples were aliquoted for storage into neat samples, seminal fluid, and isolated sperm. We compared scores of male and female participation using chi-squared tests.

RESULTS: As of April 2018, 437 patients have been approached for participation in the biorepository, including 262 men and 175 women. 58% of men (152/262) agreed to participate compared with 44% of women (77/175) (p<0.004). Among enrolled men, 113 semen samples were processed and stored as 400 vials of whole semen, 964 vials of sperm, and 466 vials of seminal fluid. Semen from 12 men were found to be insufficient for biorepository storage, as the lab required the entire specimen for analysis. 27 men enrolled but have yet to present for a semen analysis.

CONCLUSIONS: We report the successful establishment of a reproductive biorepository at an academic reproductive endocrinology and urology practice. Over 50% of men approached agreed to enrollment. In fact, men were significantly more likely to participate in the study when compared to women. Biorepositories enable the ability to answer important clinical and translational questions. However, their success depends on the willingness of patients to participate. These results suggest a need to establish interventions that support equal participation among men and women presenting for infertility care.

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interactions. Ongoing training of nurses should be prioritized as emerging science becomes standard of care.

Supported by: The research was conducted in partial fulfillment of a Doctorate in Health Education; no financial support was received.

OVARIAN FUNCTION

O-235 Wednesday, October 10, 2018 10:45 AM

RAPAMYCIN PARITIALLY RESCUES OOCYTE DYSFUNCTION IN MICE DEFICIENT FOR MITOCHONDRIAL STRESS RESPONSE PROTEIN CLPP. T. Wang,1 E. Babayev,1 Z. Jiang,1 M. Zhang,1 E. Esencan,2 E. Seli,1 OB&GYN, Yale School of Medicine, New Haven, CT; 3Feinberg School of Medicine, Northwestern University, Chicago, IL; *Louisiana State University, Baton Rouge, LA; 4IVIRMA New Jersey, Basking Ridge, NJ.

OBJECTIVE: CLPP (caseinolytic peptidase P) is a key regulatory protein for mitochondrial unfolded protein response (mUPR) and helps maintain homeostasis in response to metabolic and cellular stress. CLPP is required for oocyte and early embryonic development, and global germline knockout of Clpp results in female infertility and accelerated follicular degeneration, associated with mTOR pathway activation. The aim of the current study was to determine whether rapamycin, a known inhibitor of mTOR pathway, could rescue oocyte competence in Clpp-knockout (Clpp-/-) mice.

DESIGN: Experimental study.

MATERIALS AND METHODS: Rapamycin rescue experiments were performed in vivo (2mg/kg rapamycin or saline injected intraperitoneally daily for 14 days) and in vitro (1μM rapamycin added to the culture medium vs media alone). Clpp-/- mice/oocytes treated with rapamycin [KO-RAP] were compared to untreated Clpp-/- mice/oocytes [KO-CON] and to wild type [WT]. Western blotting (WB) and immunofluorescence (IF) were used to determine protein expression in oocytes and oocytes, respectively. Ability to generate germinal vesicle (GV) and metaphase II (MII) oocytes was assessed after injection with PMSG (5IU) or PMSG and hCG (5IU), respectively. Spindle morphology was determined by staining with α-tubulin and DAPI. ANOVA, student’s t-test, and Chi Square analysis were used for statistical analysis as appropriate.

RESULTS: KO-RAP mice produced significantly higher number of GV (20.3 ± 3 vs 15 ± 2.6%, p<0.05) and MII (13.3 ± 2.5 vs 6.5 ± 1.3%, p<0.05) oocytes compared to KO-CON. In addition, GV oocytes obtained from KO-RAP mice showed higher germinal vesicle breakdown (GVBD) (60 ± 8.7 vs 24.5 ± 9.2%, p<0.05) and normal spindle formation (60 ± 17.4% vs. 24.5 ± 18.4%, p<0.05) rates compared to KO-CON, although lower than that observed in WT (79.5±5.2% GVBD, 79.5±5.5% spindle formation, both p<0.0001). In vitro rapamycin treatment also resulted in improved GVBD (69 ± 1.3 vs 39.5 ± 5.85%, p<0.05), and normal spindle rates (56.84 ± 8.73 vs 30.71 ± 6.58%, p<0.01). mTOR pathway downstream regulatory proteins (p-S6, p-S6K, p-4EBP1, p-aktG73, p-mTOR2481) detected by WB were significantly up-regulated in Clpp-/- oocytes (p<0.05). Similarly, IF staining showed p-S6 and p-AKTG73 expression to be higher in Clpp-/- GV oocytes (p<0.001). After in vivo rapamycin treatment, p-S6, p-S6K, p-4EBP1, p-AKTG73, and p-mTOR2481 expression were significantly decreased in KO-RAP oocytes compared to KO-CON, confirming mTOR pathway suppression in response to rapamycin.

CONCLUSIONS: Our findings demonstrate that rapamycin can partially rescue the reproductive dysfunction in Clpp-/- oocytes by suppressing mTOR pathway. The potential benefit from rapamycin treatment in other mitochondrial dysfunction models and potentially in human subfertility remains to be investigated.

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OOCYTE SECRETED FACTORS REGULATE AROMATASE EXPRESSION IN HUMAN PRIMARY CUMULUS GRANULOSA CELLS. E. Hoibeika,1 M. Armoult,1 M. Fiero,1 N. Winston,2 H. Scoccia,2 A. M. Zamah,1 C. Stocco,2 Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Illinois at Chicago, Chicago, IL; 3Department of Physiology and Biophysics, University of Illinois at Chicago, Chicago, IL.

OBJECTIVE: The role of oocyte secreted factors (OSFs) in human folliculogenesis is poorly understood. The purpose of this study is to determine the role of the OSFs growth differentiation factor 9 (GDF9) and bone morphogenetic protein 15 (BMP15) on aromatase expression and estradiol production in human primary cumulus granulosa cells (hGC).

DESIGN: Prospective in vitro studies using human primary cumulus granulosa cell cultures.

MATERIALS AND METHODS: Follicular aspirates from 41 women undergoing in vitro fertilization at a University clinic were used. Cumulus cells were mechanically separated from the oocyte, seeded on culture dishes precoated with extracellular matrix at a density of 6×10⁴ cells/mL and cultured for 24-72 hours in serum-free media. After this preincubation, cells were treated with a combination of GDF9, BMP15, recombinant follicle stimulating hormone (FSH), dbcAMP and SMAD inhibitors for 48 hours. Cells and supernatants were collected for analysis. Aromatase mRNA and protein levels were quantified using real-time PCR and Western blot, respectively. Estrogen levels were measured by ELISA. Data was analyzed by two-way ANOVA and P<0.05 was considered significant.

RESULTS: As we have previously demonstrated, FSH (F) treatment strongly stimulated the expression of aromatase in hGCs when compared to non-treated controls (C). Strikingly, cotreatment with FSH in the presence of GDF9+BMP15 (G+B) potentiated the stimulatory effect of FSH (aromatase mRNA relative expression: C: 0.6±0.1; F: 3.4±1.6; F+G+B: 9.2±1.5, P<0.0001). In contrast, treatment with GDF9 or BMP15 separately did not increase FSH stimulation of aromatase. Finally, treatment with G+B in the absence of FSH had no effect on aromatase mRNA expression. A 5-fold increase in protein expression (P<0.05) was seen in the F+G+B group compared to the F group, which matches findings observed when estradiol levels were quantified in the cultured media (pg/ml): C: 2.0±0.7, F: 25.9±5.2, F+G+B: 66.3±8.0, and G+B: 3.0±0.9, P<0.0001). The effect of G+B on aromatase appears to be at the transcriptional level as the stimulation of aromatase promoter activity by FSH was also significantly increased by G+B cotreatment by 31-fold relative to control (P=0.0006). Addition of SMAD2/3 and SMAD3 inhibitors prevented G+B potentiation of aromatase mRNA (P<0.05), promoter activity (P<0.01), and protein (P<0.05). Finally, G+B potentiated the stimulatory effect of dbcAMP, an analog of cAMP (P<0.0001).

CONCLUSIONS: We show, for the first time, that the oocyte actively participates in aromatase regulation in primary hGC. The findings establish that the combination of G+B, via SMAD2/3 and SMAD3 mediated signaling pathways, strongly potentiates the stimulation of aromatase by FSH downstream of cAMP.

Supported by: NIH grant R56HD86054 and RO1HD057110 (CS)

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RESULTS: RNA sequencing revealed 1,079 and 623 differentially expressed genes in KO CCs compared to WT in 3- and 6-month-old mice, respectively. Among them, 163 genes were commonly differentially expressed at both age groups. Pathway analysis revealed apoptosis and phagosome-associated pathways to be uniquely affected at 3- and 6-month-old KO CCs, respectively. IF microscopy for apoptotic and cell proliferation markers in ovarian sections and COCs confirmed RNAseq findings with increased immunoreactivity for TUNEL and decreased expression of Ki67 and PCNA (p < 0.05). Electron microscopy revealed significant impairment of mitochondrial dynamics in Clpp-deficient cumulus cells with lower aspect ratio (length/width: 1.92 ± 0.04 vs. 1.64 ± 0.04, p < 0.0001). qRT-PCR showed a significant decrease in expression of genes involved in mitochondrial dynamics, Mfn1, Mfn2 and Opa1 (p < 0.05).

CONCLUSIONS: Impaired mitochondrial stress response in cumulus cells with targeted deletion of Clpp is associated with significant changes in CC transcriptome and mitochondrial dynamics that culminate in increased apoptotic cell death and accelerated follicular depletion. The relevance of these parameters in women undergoing IVF and whether they can be exploited to improve treatment outcomes remain to be investigated.

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OCYTOE SECRTE FACTORS REGULATE INSULIN GROWTH FACTOR 2 (IGF2) EXPRESSION IN HUMAN PRIMARY CUMULUS GRANULOSA CELLS. E. Hobeika,a M. Armouti,b M. Fierro,a N. Winston,a PRIMARY CUMULUS GRANULOSA CELLS. GROWTH FACTOR 2 (IGF2) EXPRESSION IN HUMAN OOCYTE SECRETED FACTORS REGULATE INSULIN pathway.

RESULTS: Treatment with GDF9 or BMP15 alone, or in combination (G+B) had no effect on IGF2 mRNA levels. Interestingly, FSH-stimulation of IGF2 mRNA expression was significantly potentiated in the presence of G+B (P < 0.01) and higher baseline estradiol levels (0.307). Of note, women with diminished ovarian reserve (defined as antral follicle count <5.7 and AMH < 0.5-1.1), 43 patients with who were identified as a comparison group and further categorized into: 1) unexplained infertility (24 patients) and 2) controls (19 patients with tubal or male factor). H19 total RNA was isolated from discarded serum collected on cycle day 2, and cDNA was synthesized by reverse transcription. RNA levels were analyzed using quantitative real-time PCR. H19 levels were normalized to β-actin and presented as relative expression levels using the comparative Ct method. Statistical analysis was performed using one-way ANOVA.

CONCLUSIONS: Our data are the first to show that the oocyte actively regulates IGF2 expression observed in the presence of dbcAMP, an analog of cAMP that G+B actions target mechanisms downstream of cAMP in the FSH pathway.

Supported by: NIH grant R56HD086054 and RO1HD057110 (CS)

O-240 Wednesday, October 10, 2018 11:45 AM

SERUM H19 EXPRESSION IS DECREASED IN WOMEN WITH DIMINISHED OVARIAN RESERVE. X. Xiaa,b A. N. Kallen.b "Reproductive Medicine Center, Peking University Shenzhen Hospital, Shenzhen, Guangdong, China; "Obstetrics, Gynecology and Reproductive Sciences, Yale School of Medicine, New Haven, CT.

OBJECTIVE: The Anti-müllerian hormone (AMH) is an informative marker for the assessment of ovarian reserve, but its regulation remains poorly understood. We previously demonstrated that AMH is a novel target of the microRNA let-7, which itself is regulated by the long noncoding RNA H19, and that H19 knockout mice have decreased AMH, accelerated follicular recruitment, and diminished fertility. In this study we sought to determine whether alterations in serum H19 might be associated with diminished ovarian reserve in a sample of patients undergoing fertility treatment.

DESIGN: Experimental study

MATERIALS AND METHODS: Serum was collected from women (n=69) presenting for baseline assessment prior to initiation of a controlled ovarian hyperstimulation/in vitro fertilization cycle. 26 women were categorized as having diminished ovarian reserve (defined as antral follicle count <5.7 and AMH < 0.5-1.1), 43 patients with who were identified as a comparison group and further categorized into: 1) unexplained infertility (24 patients) and 2) controls (19 patients with tubal or male factor). H19 total RNA was isolated from discarded serum collected on cycle day 2, and cDNA was synthesized by reverse transcription. RNA levels were analyzed using quantitative real-time PCR. H19 levels were normalized to β-actin and presented as relative expression levels using the comparative Cт method. Statistical analysis was performed using one-way ANOVA.

RESULTS: Women with DOR had significantly lower serum H19 expression levels as compared to control women and women with unexplained infertility and normal ovarian reserve (P < 0.001). Of note, women with DOR were significantly older than their counterparts (39.6 years vs 35.0 and 35.2 years, P < 0.01), with lower AMH levels (as expected; 0.4 ng/mL vs 2.5 ng/mL and 2.5 ng/mL, P < 0.01) and higher baseline estradiol levels (69.9 pg/mL vs 50.9 and 35.2 pg/mL, P < 0.01). BLM serum progesterone, and FSH and LH did not differ among groups. Serum H19 was positively correlated with serum AMH (r = 0.09). The addition of G+B also potentiated the increase in IGF2 expression observed in the presence of dbcAMP, an analog of cAMP (P < 0.03). To determine whether G+B controls IGF2 mRNA transcription, the promoter 3 of the IGF2 gene was cloned into a luciferase reporter. Using this reporter, we observed that although FSH stimulated IGF2p-Luc activity, treatment with FSH+G+B had no additive effect on promoter activity. Moreover, inhibition of insulin-like growth factor 1 receptor partially blocked G+B potentiation of FSH actions, suggesting other mechanisms of action in addition to IGF2 positive feedback (P < 0.009).

CONCLUSIONS: Our data are the first to show that the oocyte actively participates in the regulation of IGF2 expression in primary hGCs. We demonstrated that the specific combination of G+B potently synergized FSH actions on IGF2 via a SMAD2/3 and SMAD3 receptor pathway and that G+B actions target mechanisms downstream of cAMP in the FSH pathway.

Supported by: NIH grant R56HD086054 and RO1HD057110 (CS)
in the human ovary remains unknown. The purpose of our study was to determine the role of hMSC secretome on immortalized unutilized gonadotropin dependent human granulosa cell line (GC).

DESIGN: Prospective in vitro studies using immortalized unutilized gonadotropin dependent human granulosa cell line.

MATERIALS AND METHODS: GCs were seeded on culture dishes precoated with extracellular matrix at a density of 6x104/ml and cultured for 24 hours before treatment. Media was then collected, and either replaced by control media (C) or conditioned media (Cm). Cm was previously prepared by collecting the media of hMSC when those reached 90% confluence in their culture plate. A subset of those two groups was treated with recombinant follicle stimulating hormone (FSH) at a concentration of 50 ng/ml. Forty eight hours after media change and FSH treatment, cells and supernatant were collected for analysis. Proliferation assay based on Ki67 analysis with flow cytometry was performed. Genes mRNA and protein expression levels were quantified by real-time PCR and Western blot, respectively. Estradiol levels were measured by ELISA.

RESULTS: Human GCs cultured in hMSC Cm showed significantly higher proliferation rates when treated with Cm compared to the control group based on the percentage of gated Ki67+cells (4.02% ± 0.78 vs 30.9 ± 4.62, P < 0.001). The addition of FSH to both groups showed a trend of increased proliferation in the Cm group, however this did not reach statistical significance (52.7 ± 2.45 vs 53.1 ± 2.6, P > 0.05). Human aromatase mRNA expression was 20 fold increased with Cm compared to the C group (P < 0.05), and 30 fold increase with CmF compared to the CF group (P < 0.05). This was also shown at the level of human STAR mRNA without FSH (14 fold increase, P < 0.05), and with FSH (30 fold increase, P < 0.05). Protein studies and other gene expression profiles, in addition to results with molecular pathway inhibitors are being analyzed and will be presented during the meeting in October 2018.

CONCLUSIONS: These findings show, for the first time, that hMSC secretome promotes human granulosa cell proliferation and regulates gene expression involved in folliculogenesis, such as aromatase. Further investigation, including co-culture and analysis of Cm is warranted to fully understand the effect of hMSC on human granulosa cells.

Supported by: UIC start-up fund

OVARian STIMULATION 2

O-241 Wednesday, October 10, 2018 10:45 AM

MOLECULAR STIMULATION FOR PROMOTING GROWTH OF EARLY STAGE FOLLICLES BY IGF-1. L. Man, L. Park, Z. Rosenwaks, D. J. James. CRM1 Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medicine, NYC, NY.

OBJECTIVE: Most of the follicles in human ovaries remain dormant, and only a fraction are mobilized into the growing pool. The growth of these follicles is mediated in part by upregulation of Akt signaling. Insulin-like growth factor 1 (IGF-1) is a potent physiological activator of the AKT pathway. Using our unique xenograft model, we co-transplanted endothelial cells (ECs) that overexpress IGF-1 and achieved both restoration of vascular perfusion and the direct paracrine delivery of IGF-1 in the vicinity of human ovarian tissue. We investigated the potential for ECs expressing IGF-1 to promote human granulosa cell proliferation and regulates gene expression profiles, in addition to results with molecular pathway inhibitors.

DESIGN: Xenograft of human ovarian tissue into NSG mice with co-transplantation of ECs that overexpress IGF-1.

MATERIALS AND METHODS: To test the modulation of follicles in grafts, we have generated lentiviral vectors expressing human IGF-1. ECs modified by the adenoviral gene fragment E4-ORF1 were transduced with these particles. Xenograft of human ovarian tissue into NSG-oophorectomized mice with co-transplantation of IGF-1 ECs served as the study group. Patient-matched ovarian tissue co-transplanted with non-IGF-1-producing ECs served as controls. We co-transplanted multiple grafts and harvested at 3 (Ctrl, n=10; study, n=9), 8 (Ctrl, n=2; study, n=2), and 14 (Ctrl, n=7; study, n=9) weeks. The ratio of follicles in each treatment was assessed in histologic sections.

RESULTS: The study group demonstrated at 3 and 8 weeks a higher proportion of secondary follicles (35.38±9.78 vs. Ctrl 21.36±8.16; p=0.035) and a lower proportion of primary follicles (42.86±5.6 vs. Ctrl 55.49±6.63; p=0.017); no difference was found between the ratios of primordial follicles. Interestingly, at 14 weeks, the proportion of primordial follicles was reduced in the study group (4.73±4.72% vs. Ctrl 22.63±7.04%); p=0.03), while the primary follicle rate was increased (64.27±9.16 vs. Ctrl 50.55±5.29; p=0.05). While there was no difference in the short term, the total number of follicles per mm² in the study group was lower in the long-term grafts (4.2±3.6 vs. 7.5±2.05; p=0.05).

CONCLUSIONS: In this distinct xenograft model, we have measured the effect of IGF-1 on the growth and development of early-stage follicles that are not responsive to gonadotropins and, therefore, cannot be influenced using conventional in vitro fertilization stimulation protocols. Importantly, long-term exposure resulted in a “burn out” phenotype. Nevertheless, a short-term “molecular stimulation” approach could provide a means of promoting the growth of early stage follicles and fostering their survival to more advanced stages. This approach would benefit patients with unmet need (e.g., poor responders) by optimizing the growth and survival of residual follicles that typically undergo atresia before maturing to the hormone-responsive stages.

References: NA

Supported by: Internal CRM1

O-242 Wednesday, October 10, 2018 11:00 AM

ADJUVANT RECOMBINANT LH(rLH) OR GROWTH HORMONE (GH) TO THE ANTAGONIST PROTOCOL IN POOR RESPONDERS UNDERGOING IVF.


OBJECTIVE: To evaluate the effectiveness of the addition of recombinant LH(rLH) or Growth hormone (GH) to the antagonist protocol cycles in poor responders undergoing IVF. In Vitro Fertilisation)

DESIGN: Single centre prospective randomised control trial at a tertiary care infertility centre from 1st April 2017 to 30th March 2018.

MATERIALS AND METHODS: One hundred and twenty poor responder patients selected as per Psoedion Group 3 and 4 for IVF were enrolled the study and were randomly divided into two groups. Group A (n = 64) received rLH (75 IU)+rFSH (225 IU) from Day 2 (D 2) of cycle with addition of GnRh antagonist from D 6 and group B (n = 56) received GH (4 IU)+FSH (225 IU) from D 2 with addition of GnRh antagonist from D 6 . The primary outcome measured was pregnancy rate. The secondary outcomes measured were number of oocytes retrieved, number of embryos formed and miscarriage rates.

RESULTS: The number of retrieved oocytes was significantly higher in rLH/rFSH/GnRH antagonist group (Gp A) than GH/rFSH/GnRH antagonist group (Gp B), 9.35 ± 3.09 vs. 6.58 ± 2.91 (p = 0.002) and the number of obtained embryos was also significantly higher in rLH/rFSH/GnRH antagonist group than GH/rFSH/GnRH antagonist group, 6.96 ± 2.82 as compared to 4.08 ± 1.72 (p < 0.001). There were no significant differences between these group A & B regarding implantation, clinical pregnancy and miscarriage rate.

Comparison of means for number of oocytes retrieved and number of embryos formed

<table>
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<th>Variables</th>
<th>Therapy</th>
<th>Number of patients</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Std. Error</th>
<th>Unpaired t-test p-value</th>
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<tr>
<td>Number of oocytes retrieved</td>
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<td>9.35</td>
<td>3.098</td>
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<td>GH</td>
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<td>0.572</td>
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<td>2.821</td>
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<tr>
<td>GH</td>
<td>56</td>
<td>4.08</td>
<td>1.719</td>
<td>0.337</td>
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</tbody>
</table>

CONCLUSIONS: Addition of recombinant LH in antagonist protocol in poor responder patients significantly increased number of oocytes retrieved and embryos formed when compared to addition of Growth hormone but there was no difference in pregnancy rates between the two groups.

INDUCTION OF OVULATION USING CLOMIPHENE CITRATE PLUS N-ACETYL CYSTEINE VERSUS LUTROZOLE IN INFERTILE PATIENTS WITH POLYCYSTIC OVARIAN DISEASE: A RANDOMIZED CLINICAL TRIAL. T. Farghaly, A. Abbas, M. A. Kamel, E. Badran, A. F. Amin. Assiut University, Assiut, Egypt; Faculty of Medicine, Assiut University, Assiut, Egypt; Reproductive Endocrinology, Assiut, Egypt; 04BGYN, Assiut University, Assiut, Egypt.

OBJECTIVE: Polycystic ovarian disease (PCOD), a common endocrine disorder with multisystem affection, is the most common cause of anovulatory infertility. Our objective is to evaluate the effect of using clomiphene citrate (CC) plus N-Acetyl cysteine (NAC) versus letrozole in ovulation induction in infertile patients with PCOD.

DESIGN: Randomized controlled open-labeled trial.

MATERIALS AND METHODS: Reproductive-aged infertile women either primary or secondary diagnosed as PCOD according to Rotterdam criteria, 2003 were considered for enrollment. Patients with male factor abnormalities, unhealthy tubes, endocrinopathies, those received prior induction of ovulation and patients with previous laparoscopic ovarian drilling were excluded. Eligible women for were recruited and randomized (1:1) to receive either CC 100 mg plus NAC 600 mg (CC+NAC arm) or letrozole 5 mg (NCT03241472, clinicaltrials.gov). All medications were started from day 3 of the menstrual cycle for 5 days. Transvaginal ultrasound was carried-out for follow up of the follicular growth, the number of follicles and the endometrial thickness. All patients were followed-up for 3 months.

RESULTS: One hundred ten patients were enrolled and randomized to CC+NAC arm (n=55) or letrozole (n=55). Both arms were comparable in age, parity, BMI, type and duration of infertility. The ovulation rate in patients in letrozole arm was significantly higher than CC+NAC arm (71.8% vs. 53.2%, p=0.01). Additionally, endometrial thickness was higher in letrozole arm (mean±SD: 11.46±1.61 vs. 9.0±1.13, p=0.031). However, no statistical significant difference with regarding the ovarian hyperstimulation rate (1.8% vs. 3.6%, p=0.157), clinical pregnancy rate (3/19 patients [15.8%] vs. 5/15 patients [33.3%], p=0.109) and miscarriage rate (4/15 patients [26.7%] vs. 9/15 [60.0%], p=0.137) in CC+NAC versus letrozole groups respectively.

CONCLUSIONS: Addition of NAC to CC in ovulation induction leads to comparable pregnancy rate as letrozole. However, letrozole produces high ovulation rate and the better mid-cyclic endometrial thickness.


OBJECTIVE: MVT-602 is a kisspeptin analog being developed as a trigger agent to promote oocyte maturation and ovulation in infertile women undergoing controlled ovarian stimulation. As a kisspeptin analogue, MVT-602 is expected to stimulate the release of endogenous gonadotropin releasing hormone resulting in a more physiologic pre-ovulatory LH surge than current trigger agents, potentially reducing the risk of ovarian hyperstimulation syndrome. This study assessed the effect of MVT-602 on luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), and progesterone (P) in healthy premenopausal women during the follicular phase.

DESIGN: Randomized, single-blinded, placebo-controlled, dose-ranging study of MVT-602 in healthy premenopausal women.

MATERIALS AND METHODS: Twenty-four subjects were randomized equally to receive a single-dose subcutaneous MVT-602 (0.3, 1, or 3 μg) or placebo. The dose was administered between days 1 to 6 of the menstrual cycle. Serum concentrations of LH, FSH, E2, and P were evaluated at baseline and for up to 72 hours postdose. Pharmacokinetic (PK) samples for MVT-602 were collected. Maximum change from baseline (peak), area under the
hormone concentration-time curve, and MVT-602 PK parameters were determined.

RESULTS: The median (minimum, maximum) change from baseline for peak serum LH response were 3.5 (1.1, 25.5), 10.0 (2.9, 75.4), and 8.1 (3.0, 27.6) iU/L. Compared to stimulating MVT-602 doses (0.1, 0.3, or 3 µg, respectively) with little change observed in the placebo group, 3.6 (0.0, 6.1) iU/L. The peak LH response generally occurred 24 hours postdose and returned to baseline approximately 72 hours postdose. An area-under-the-serum LH curve also showed a plateauing, albeit less variable, dose-response relationship. The day of dosing relative to menstrual start and baseline LH concentration appeared to positively correlate with response. Increases in serum E2 appeared to correlate with LH response. Little dose-dependent changes in FSH or P were observed. The peak plasma MVT-602 concentration was observed ~30 minutes post-dose, suggesting rapid absorption from the injection site; the plasma half-life was <3 hours. MVT-602 was well tolerated; no serious adverse events (AEs) or severe AEs were reported. The most frequent treatment-emergent AE was headache (placebo was well tolerated; no serious adverse events (AEs) or severe AEs were reported. The most frequent treatment-emergent AE was headache (placebo n=3; 0.3 µg n=3; 1 µg n=3; 3 µg n=4). No dose response was observed for any AE.

CONCLUSIONS: MVT-602 stimulated the release of LH and was well-tolerated when administered to healthy premenopausal women in the follicular phase. The dose-dependent changes in serum LH suggest MVT-602 is a promising agent to stimulate the hypothalamic-gonadotropin axis and trigger oocyte maturation and ovulation.

Supported by: Sponsored by Myovant Sciences GmbH.

O-246 Wednesday, October 10, 2018 12:00 PM


OBJECTIVE: The kisspeptin analogue, MVT-602 (previously known as TAK-448), has a longer half-life (1/1/2 108min) than native kisspeptin-54 (KP54, t 1/2 28min). MVT-602 is known to stimulate LH release in men, but its effects in women are unknown. We sought to determine the effect of MVT-602 in healthy women on gonadotropin release and compare it to KP54.

DESIGN: Two-phase prospective randomized dose-finding study.

MATERIALS AND METHODS: Healthy women with regular cycles (<35d, n=7) attended during the early follicular phase (D1-4). Participants (n=3) received a single subcutaneous bolus of either KP54 (9.6nmol/kg), or one of five doses of MVT-602 (0.003, 0.03, 0.1, 0.3, or 1.0nmol/kg). Reproductive hormones were measured every 30min for 14hrs post-MVT-602, and then subsequently at 24hrs and 48hrs post-injection. Following interim analysis, a further 4 women underwent regular blood sampling for 24hr post-MVT-602 (0.01 and 0.03nmol/kg). Hormone levels were compared by paired t test vs baseline, and interventions by one-way ANOVA with post hoc Tukey’s test.

RESULTS: Serum LH increased by 10.4±4.7iU/L at 4-6hr post-KP54, whereas peak serum LH occurred later between 14hrs and 24hrs post-MVT-602. Regular blood sampling over 24hr revealed: (i) Peak serum LH was 8.0±2.1iU/L post-MVT-602 0.01nmol/kg (P=0.43 vs KP54) and 9.6±3.1iU/L post-MVT-602 0.03nmol/kg (P=0.72 vs KP54). (ii) Serum LH at 24hr post-injection: KP54 3.6±2.0iU/L; MVT-602 0.01nmol/kg 5.0±1.0iU/L (P=0.30 vs KP54); MVT-602 0.03nmol/kg 8.9±3.3iU/L (P=0.01 vs KP54). (iii) Area under curve for change in LH over 24hr: KP54 56.0±15.0iU/hr/L; MVT-602 0.01nmol/kg 59.7±14.0iU/hr/L (P=0.30 vs KP54); MVT-602 0.03nmol/kg 76.5±16.0iU/hr/L (P=0.03 vs KP54); (iv) MVT-602 0.03nmol/kg increased serum FSH by 4.9±1.4iU/L (P=0.024 vs baseline), sufficient to induce a rise in serum estradiol of 207±186pmol/L (P=0.016 vs baseline).

CONCLUSIONS: MVT-602 resulted in a more prolonged LH-surge compared to that induced by KP54 during the follicular phase in healthy women. The greatest rise in serum LH occurred following MVT-602 0.03nmol/kg at 20-24hr to a similar amplitude as KP54. This same dose of KP54 has been demonstrated to safely induce oocyte maturation during IVF treatment. Thus, further studies are now indicated to determine whether the longer duration of action of MVT-602 may confer additional utility for treating women affected by disorders of reproductive health.

Supported by: SC, PCE & WSD: NIHR Research Professorship. AA: Imperial Clinician Fellowship. CI-E & LY: MRC Clinical Research Training Fellowships. JP: NIHR Imperial Biomedical Research Centre. EM: Imperial College Healthcare Charity Fellowship. DP: NIHR CLRN. MVT-602 was provided by Myovant Sciences Inc.

PREIMPLANTATION GENETIC TESTING 3

O-247 Wednesday, October 10, 2018 10:45 AM


OBJECTIVE: Report the 24-chromosome preimplantation genetic testing for aneuploidy (PGT-A) results for trophectoderm (TE) re-biopsy samples that had an initial inconclusive result due to uninformative SNP data.

DESIGN: Retrospective analysis.

MATERIALS AND METHODS: Study cohort included TE biopsy samples from in vitro fertilization (IVF) patients from multiple clinics that were subsequently referred for PGT-A; reasons for referral included prior failed IVF cycle, recurrent pregnancy loss, and/or advanced maternal age. TE biopsies were performed according to each clinic’s standard procedures; samples were shipped to a single reference laboratory for genotyping using Illumina Cytot12 SNP-based microarray and an informatics technique. Samples with an inconclusive result due to uninformative SNP data were offered the option to re-biopsy for PGT-A. Re-biopsied samples with results were classified as either ‘euploid’ (if no chromosome abnormality was detected), ‘aneuploid’ (if monosomy, trisomy/polysomy, haploidy, triploidy, large deletions/duplications, and/or unparental disomy were detected) or discordant (if the re-biopsy sample was not a genetic match to the original embryo sample). Statistical analysis was performed using binomial confidence intervals.

RESULTS: Of the initial 104,345 TE samples submitted for PGT-A, 469 (0.4%) had an inconclusive result due to uninformative SNP data; day of embryo biopsy breakdown: 389 (82.9%) Day 5, 60 (12.8%) Day 6, 2 (0.4%) Day 7, and 18 (3.8%) Day unknown. Embryonic stage was provided for 375 samples: morula (4), early blastocyst (7), blastocyst (98), expanded blast (91), hatching blast (150), hatched blast (25). Of the samples that had an uninformative result, 158 (33.7%) underwent TE re-biopsy for reanalysis. At the time of re-biopsy, the samples spanned all stages of embryonic development except morula. The average maternal age for this patient cohort was 35.3 years (range 24–44). Re-biopsy sample results revealed: 102 (64.6%) euploid, 45 (28.5%) aneuploid, 7 (4.4%) inconclusive due to insufficient DNA for analysis, and 4 (2.5%) discordant. For maternal age-matched samples, 59% of embryos are euploid on initial biopsy.

CONCLUSIONS: Sixty-five percent of embryos that underwent TE re-biopsy with an initial inconclusive result due to uninformative SNP data were euploid allowing for an additional embryo to be considered for transfer. Though uninformative SNP data can result from DNA degradation, insufficient biology of the sample, and sample contamination, these findings suggest that samples receiving an inconclusive result during PGT-A due to uninformative SNP data can be considered for re-biopsy. Interestingly, this euploid rate was not statistically different than the euploid rate on initial biopsy for the maternal age-matched patients that did not have embryos with uninformative SNP results. Follow-up data on transfer decisions and pregnancy outcomes is ongoing.

References:
1 Natera internal data
Supported by: Natera, Inc.

O-248 Wednesday, October 10, 2018 11:00 AM


OBJECTIVE: The World Health Organization estimates that 15–25% of the population will die prematurely from non-communicable diseases, which
predominantly originate in polygenic disorders. Population-level whole-genome biobanking has increasingly made genomic prediction of polygenic disorder risk viable in practice. This study develops and validates a combined method, capable of conventional testing for PGT-A, PGT-M, as well as concurrent PGT-P of polygenic disorders, in a precedent-setting first.

DESIGN: Training sample set calibration, followed by blinded 7-cell/trophectoderm sample set validation.

MATERIALS AND METHODS: PGT-A was validated using a variety of Coriell Cell Repository cell lines with known chromosomal abnormalities (n=348), and rebiopsies of blastocysts with prior aneuploid test results (n=32 embryos, 123 rebiopsies). PGT-M was validated using cell lines with known cystic fibrosis delta F508 status (n=110). PGT-P was validated using a UK Biobank validation cohort (n=5000), and WGA genotyping of cell lines with known genotype status (n=55). Samples were tested using a gSEQ amplification and library preparation kit (Genomic Prediction), and next generation sequencing with a MiSeq (Illumina), combined with Axiom genotyping microarray analyses (Affymetrix). Data analysis was performed using the gSEQ analysis suite (Genomic Prediction).

RESULTS: 7-cell samples from cell lines with known karyotypes were 96.5% concordant. Full karyotype concordance was obtained in 95% (118/123) of trophoderm rebiopsies; well within the expected range when considering the potential impact of embryonic mosaicism. Cystic fibrosis status was accurately predicted on all 7-cell samples (100%) by both direct mutation testing on the array, as well as linkage-based analysis using informative SNPs within 1 MB of the mutation locus. Diabetes status on the UK Biobank validation cohort reached an AUC of 0.66, consistent with expected genetic contribution levels. All 7-cell samples were genotyped at concordance with known genotype in excess of 0.995.

CONCLUSIONS: This study provides a precedent-setting proof-of-principle that aneuploidy, monogenic, and polygenic disorders can be accurately predicted, using material from a single, 7-cell biopsy. Expanding preimplantation testing to include polygenic disorders may result in broader use of IVF.

O-250 Wednesday, October 10, 2018 11:30 AM SEGMENTAL ANEUPLOIDY IN BLASTOCYSTS: WHEN THE CHROMOSOMES BREAK. M. Insua, a M. Escerba,a X. Vendrell,a V. Peinado,a T. Viloria.a aIVI Valencia, Valencia, Spain; bReproductive Genetics Unit, Sistemas Genomics, Paterna, Spain; cPGD Molecular Cytogenetics, GENIMOX, Valencia, Spain; dIVF-Laboratory, IVIRMA Valencia, Valencia, Spain.

OBJECTIVE: Our objective is to describe quantitatively and qualitatively segmental aneuploidies (SA) in trophoderm samples, defined as a loss or gain of a chromosomal fragment and its relationship with clinical and embryological parameters.

DESIGN: Clinical retrospective historical study

MATERIALS AND METHODS: 3628 blastocysts were studied of 844 cycles of PGT-A. Trophoderm samples were analyzed by NGS (next generation sequencing). SA was considered if the lost/gained fragment was higher than 5 Mb. The diagnosed aneuploidies were classified as: complete chromosome, single segmentals (only a segmented chromosome, with or without complete chromosome aneuploidy) and pure segmentals (SA, segmented chromosome unique without additional aneuploidy).

RESULTS: 8.6% (314/3628) of blastocysts showed SA associated or not with complete chromosome aneuploidy: 7.9% (288/3628) exhibited unique SA, and 4.4% (161/3628) PSA. The incidence of PSA was not related to clinical or embryological parameters, except for the quality of the trophectoderm. Chromosomes 19, 22, and Y did not exhibit PSA. PSA were more frequent in the q arm of the metacentric and submetacentric chromosomes. Its size was greater in q than in p. The PSA/q chromosome ratio was constant. The PSA in q was greater than in p. The ratio PSA / arm was lower in arm q. The description of the PSA only relates to intrachromosome topographic parameters.

CONCLUSIONS: PSA is chromosome-dependent with clear topographic effect. In addition, it does not vary with maternal age, but it does vary with the morphology of the blastocyst, as a possible indicator of chromosomal instability in the trophectoderm.

Supported by: IVIRMA Private Grant.

O-251 Wednesday, October 10, 2018 11:45 AM TOWARDS UNDERSTANDING HUMAN EMBRYO MOSAICISM: REGIONAL AND DEVELOPMENTAL GENETIC CONCORDANCE BY SINGLE CELL SEQUENCING. G. D. Smith,a L. Yan,b Y. Ren,b L. Keller,a Z. Yan,b J. Qiao,a aOb/Gyn, University of Michigan, Ann Arbor, MI; bOb/Gyn, Peking University, Beijing, China; cPeking University Third Hospital, Beijing, China.

OBJECTIVE: Knowledge of human preimplantation embryonic genetic concordance at a single cell level is essential, and significantly wanting, to fully appreciate the incidence of human embryo mosaicism and interpretation of preimplantation genetic testing for aneuploidy (PGT-A) in relation to offspring genetic normalcy. We asked the question: how does the ploidy status compare between neighboring trophectoderm (TE) cells, neighboring...
inner cell mass (ICM) cells, and ICM-derived human embryonic stem cells (hESCs) at a single cell level?

DESIGN: Prospective single cell genetic analysis and comparison of human embryo TE, ICM, and resulting hESCs.

MATERIALS AND METHODS: Human blastocysts no longer needed for reproduction or unsuitable for implantation were donated with informed consent to an IRB-approved study for hESC derivation. Warmasted blastocysts underwent laser dissection of the ICM for hESC derivation and resulting TE was collected for single cell isolation. ICMs were plated on human foreskin fibroblasts in xeno-free media with knock-out serum replacement at 5%O2/5%CO2/95%N2; 37°C. After 3-4 days of culture half of the ICM was harvested for single cell isolation. Remaining ICMs were used to derive hESCs. TE, ICM, and hESC single cells were isolated with trypsin/accutase treatment, confirmed to be single cells, placed individually into tubes for lysis, and whole genome DNA amplification was performed by multiple annealing and looping based amplification cycles. Single cell amplicons were confirmed by gel electrophoresis, used to make sequencing libraries, and subjected to next generation sequencing to compute copy number variance (CNV) for single cell aneuploidy detection. hESCs were also assessed by single cell G-banding. Differences in genetic concordance (%) within specific embryonic regions and/or during development of hESCs were statistically compared by $\chi^2$ with p-values $< 0.05$ considered significant.

RESULTS: To date 252 single cell CNVs have been measured, comprised of 182 single cell-TEs from 19 embryos (9.6±0.8, ave±se cells/embryo), 37 single cell-ICMs from 3 embryos (12.3±3.3 cells/embryo), and 33 single cell-hESCs from 3 embryos (11.0±2.3 cells/embryo). Collectively, significantly less single cell genetic concordance ($p<0.001$) existed in TE (69%) compared to ICM (89%) and hESCs (94%). In the only 2 sample sets with TE, ICMs, and hESCs per embryo, the per embryo/per region concordance rates were TE - (50%, n=10 and 50%, n=10), ICM - (95%, n=19 and 89%, n=9), and hESCs (100%, n=11 and 100%, n=12), respectively.

CONCLUSIONS: These data suggest that single cell genetic concordance is lower in the human TE compared to the ICM and/or resulting hESCs. These findings may have significant relevance on understanding: i) human embryo mosaicism, ii) PGT-A results obtained from multiple unknown embryonic regions and/or during development of hESCs were statistically compared by $\chi^2$ with p-values $< 0.05$ considered significant.

REPRODUCTIVE ENDOCRINOLOGY

O-253 Wednesday, October 10, 2018 10:45 AM

MULLERIAN-INHIBITING SUBSTANCE AUGMENTS OVARIAN RESPONSE TO SUPEROVULATION IN MICE WITH DIMINISHED OVARIAN RESERVE. J. Y. Hsu, M. Kano, P. K. Donahoe, D. Pepin.

OBJECTIVE: To determine whether pretreatment with Mullerian-inhibiting substance (MIS) affects the oocyte yield of superovulation in a mouse model of diminished ovarian reserve (DOR).

DESIGN: Preclinical placebo-controlled animal study.

MATERIALS AND METHODS: The DOR mouse model was created by giving intraperitoneal (IP) injections of 4-vinylcyclohexene diepoxide (VCD) to 6-week old nu/nu mice (n=3) at 160 mg/kg daily for 5 days. Control mice (n=3) were injected IP with vehicle control (corn oil). Mice were euthanized 14 days later. Dissected ovaries were fixed in 4% paraformaldehyde, embedded in paraffin blocks in an automated tissue processor, cut into 8-um sections, and mounted onto glass slides, which were stained with hematoxylin and eosin. Under light microscopy, ovarian follicles were classified into five groups - primordial, primary, secondary, antral, and atretic - and counted.

A cohort of DOR mice was subsequently treated with subcutaneous recombinant human MIS protein (750 ug/kg, n=3) or saline (n=4) twice daily for 40 days. After 30 days of observation, superovulation was performed in standard fashion with pregnant mare serum gonadotropin 7.5 IU IP, followed by human chorionic gonadotropin (hCG) 7.5 IU IP 49 hours later to trigger ovulation. 16 hours after hCG, oocytes were dissected from the oviducts of euthanized mice and were counted. Morphologic assessment of collected oocytes was performed under a stereo microscope, and the percentage of degenerated oocytes collected from each mouse was noted.

Oocyte yields and percentage of degenerated oocytes of MIS-treated and saline control mice were compared using student’s t-test. A p-value of $< 0.05$ was considered significant.

RESULTS: VCD administration as described above creates a DOR phenotype in mice, by depleting primordial follicle reserve by 73%, while maintaining ovulatory function.

DOR mice treated with MIS produced, on average, 29 oocytes through superovulation compared to saline control mice who produced only 11 oocytes (p = 0.038). Furthermore, more oocytes were morphologically abnormal in controls compared to MIS-treated mice (52.2% versus 30.1%, p = 0.026).

CONCLUSIONS: In the setting of DOR, treatment with MIS protein significantly enhances oocyte yield following superovulation and leads to a lower proportion of degenerated oocytes. These findings suggest a future clinical application of MIS in IVF protocols, particularly for patients with DOR.

O-254 Wednesday, October 10, 2018 11:00 AM


OBJECTIVE: Due to conflicting evidence on the effect of low dose aspirin (LDA) on menstrual cycle length and the increasing study of aspirin’s effects
when initiated while attempting pregnancy, we evaluated the effect of taking daily LDA on menstrual cycle length.

DESIGN: Secondary analysis of the Effects of Aspirin on Gestation and Reproduction (EAGeR) trial, a multi-site, block-randomized, double-blind, placebo-controlled clinical trial evaluating the effect of daily LDA (81 mg) on live birth among women with 1-2 prior pregnancy losses.

MATERIALS AND METHODS: We included 1,078 women who had at least one menstrual cycle of follow-up in which pregnancy did not occur. Participants were randomized on days 3-4 of their first menstrual cycle of follow-up to LDA (n=535) or placebo (n=543), and were followed for up to 6 menstrual cycles or throughout pregnancy for those who became pregnant. The beginning of menses and ovulation date was recorded each cycle (with Clearblue Easy fertility monitors). Menstrual cycle length was calculated as the number of days from the beginning of menses to the beginning of menses in the next cycle. Follicular phase length was calculated as the number of days from menses start to ovulation, and luteal phase as the number of days from ovulation to the beginning of menses in the next cycle. Total cycle length was defined as short (<25th percentile: <27 days) and long (>75th percentile: >30 days) vs. moderate (25th to 75th percentile: 27-30 days). Short, moderate, and long follicular length were defined as <13, 13-18, and >18 days, respectively. Short, moderate, and long luteal length was defined as <11, 11-15, and >15 days, respectively. Generalized estimating equations accounted for dependence among cycles in the same woman, weighting by total number of cycles per woman to adjust for fecundability differences among women contributing multiple cycles.

RESULTS: The LDA vs. placebo group revealed no difference in age (28.9 vs. 28.7, p = 0.68), BMI (26.2 vs 26.5 kg/m², p = 0.54), ethnicity (white vs. non-white, p = 0.16), and history of menstrual regularity (p = 0.41). No differences were found in total cycle, follicular, or luteal phase length between LDA and placebo groups. In unadjusted models, LDA was not associated with either short (OR 1.09; 95% CI: 0.71, 1.66, p = 0.70) or long (OR 1.02; 95% CI: 0.70, 1.50, p = 0.91) follicular phase length. Results were similar for follicular and luteal length.

CONCLUSIONS: In women aged 18-40 with 1 or 2 prior pregnancy losses and no subfertility history, LDA was not associated with differences in total cycle, follicular, or luteal phase length. Thus, patients receiving preconception, daily LDA will likely have no change in menstrual cycle patterns.

O-255 Wednesday, October 10, 2018 11:15 AM
ASSOCIATION OF ANTI-MULLERIAN HORMONE WITH COGNITIVE FUNCTION IN UK BIOBANK: A MENDELIAN RANDOMIZATION STUDY. S. M. Nelson,1 S. Ilhoodrom,2 J. Pell,3 D. Lyall.4 1School of Medicine, University of Glasgow, Glasgow, United Kingdom; 2Obstetrics and Gynaecology, University of Glasgow, Glasgow, United Kingdom; 3Institute of Health and Wellbeing, University of Glasgow, Glasgow, United Kingdom; 4Institute of Health and Wellbeing, University of Glasgow, Glasgow, United Kingdom.

OBJECTIVE: To use Mendelian randomization to assess whether anti-mullerian hormone (AMH) was causally associated with cognitive function in men.

DESIGN: Cross-sectional baseline data from a population-based cohort study including 162,217 male UK Biobank participants with complete phenotypic (medical and sociodemographic) and genetic data.

MATERIALS AND METHODS: Participants attended 1 of 22 assessment centers across the United Kingdom between 2006 and 2010. We focussed on six cognitive tests which were included in UK Biobank at various time points with number of participants ranging from 34,006 to 162,217 per test. All tests were administered via computerised interface. Participants self-reported sociodemographic information pertaining to confounders. A genetic risk score comprising 3 single-nucleotide polymorphisms associated with AMH from the most recent, largest genome-wide association study was constructed, and the AMH-weighted genetic risk score applied to derive causal estimates using a mendelian randomisation approach.

RESULTS: Mendelian randomisation analysis showed significant positive associations between genetically instrumented higher AMH concentrations and reduced reasoning scores (standardised β per 1-SD higher AMH -0.09, 95% CI -0.112, -0.070, P<0.001), poorer reaction time (β (0.051; 95% CI 0.039, 0.064, P<0.001), poorer episodic memory (β 0.047 95% CI 0.033, 0.060, P<0.001) but no effect on executive function as assessed by the trail making test (part A β 0.025 95% CI -0.002, 0.053, P=0.074; part B β 0.020 95% CI -0.007, 0.047, P=0.14) or complex processing speed/executive (β -0.005 95% CI -0.030, 0.020, P=0.69). These associations were independent of age, baseline assessment centre, genotypic array, Townsend deprivation score, education, smoking, cardiovascular disease and diabetes.

CONCLUSIONS: Our Mendelian randomization study provides evidence to suggest that AMH may be causally associated with male cognitive function, in particular the cognitive domains that control simple processing speed, episodic memory and fluid intelligence.

References: This analysis was undertaken under the auspices of UK Biobank application 17689.

O-256 Wednesday, October 10, 2018 11:30 AM
HOW DOES ANTIMULLERIAN HORMONE DOWN-REGULATE STEM CELL FACTOR IN GRANULAR CELLS? INHIBITING THE PHOSPHORYLATION OF CREB. Y. Fu,1 R. Hu,2 S. Iliodromiti,3 J. Pell,4 D. Lyall.5 1Department of Obstetrics and Gynaecology, University of Glasgow, Glasgow, United Kingdom; 2Ningxia Medical University, Yinchuan, China; 3General Hospital of Ningxia Medical University, Yinchuan, China.

OBJECTIVE: To determine whether antimullerian hormone (AMH) regulates stem cell factor (SCF) expression via effecting the activity of SCF promoter, and investigate the molecular regulatory mechanism of AMH, SCF and CREB in human granular cells.

DESIGN: Prospective experimental study

MATERIALS AND METHODS: Firstly, we proved the combination of CREB and SCF promoter by Chromatin Immunoprecipitation (ChIP) and Electrophoretic mobility shift assay (EMSA). Next, to test the effect of CREB to SCF promoter and the binding sites of CREB in SCF promoter, different truncations and mutations of SCF promoter and CREB were transduced into human granular cells and detected the luciferase activity. Futher more, AMH was stably over-expressed or knocked down in GCs and confirmed by western blot, quantitative real-time PCR. The luciferase activity was analysed when pGL-Basic-SCF+ CREB was transected into GCs with overexpressed AMH, low expressed AMH and the normal to confirm the relationship among AMH, SCF promoter and CREB in human granular cells. Finally, the SCF expression and the phosphorylation of CREB were observed in the GCs, AMH-high GCs and AMH-low GCs by immunofluorescence and double immunostaining to test AMH regulated SCF expression and inhibited the the phosphorylation of CREB.

RESULTS: 1. CREB could combine with SCF promoter and enhanced the transcription of SCF and the best binding site was 318bp-321bp in SCF promoter (P<0.05). 2. When pGL-Basic-SCF+ CREB were transected into the granular cells,cells with high AMH and cells with low AMH respectively, the luciferase activity is the lowest in AMH-high group (P<0.05) and there is no statistical significance between the GCs group and AMH-low group (P>0.05). 3. The expression of SCF in AMH-high group was lower than the control (P<0.01) and AMH-low group (P<0.01) in immunofluorescence. 4. The phosphorylation of CREB and SCF was statistically significant lower in AMH-high group than the control (P<0.05)in double immunostaining.

CONCLUSIONS: We confirmed AMH inhibited the SCF through decreasing the phosphorylation of CREB in GCs. This breakthrough will help to better understand the molecular mechanism of AMH suppressing follicle growth, and that will promote to devise a new therapy for infertility of ovulation failure.

References: No

Supported by: This work was supported by the National Natural Science Foundation of China (No. 81660257), the Ningxia Natural Science Foundation (NZ16125), Personnel Agency Overseas talent Project . 2016 Autonomous Region Leader in Science and Technology Innovation.

O-257 Wednesday, October 10, 2018 11:45 AM
GLOBAL TRANSCRIPTIONAL PROFILING CORRO- DATES AN ENDOMETRIAL DEFECTIVE DECIDUALIZATION PATTERN IN SEVERE PREECLAMPSIA. T. Garrido-Gomez,1 A. Amador,1 J. Jimenez Almazan,1 P. Mateos,1 D. Blesa,2 L. Rubert,2 A. Perales,3 C. Simón.4 1Research, Igenomix Foundation, INCLIVA, Valencia, Spain; Bioinformatics Department, Igenomix SL, Paterna, Spain; 2Bioinformatics, Igenomix Foundation, Paterna, Spain; 3Igenomix SL, Paterna, Valencia, Spain; 4Development, Igenomix Foundation, Igenomix SL, Valencia, Spain; 5Hospital Universitario La Fe, Valencia, Spain; 6Valencia University, Igenomix, Paterna, Spain.

Supported by: This work was supported by the National Natural Science Foundation of China (No. 81660257), the Ningxia Natural Science Foundation (NZ16125), Personnel Agency Overseas talent Project . 2016 Autonomous Region Leader in Science and Technology Innovation.
OBJECTIVE: Our previous work demonstrates a defective in vitro decidualization of endometrial stromal cells isolated from patients with a previous severe preeclampsia (sPE) affecting the expression of 129 genes. To corroborate in vivo these previous findings, here we performed a global and targeted RNA sequencing to identify this decidual endometrial defect during the secretory phase of the menstrual cycle in patients that have previously suffered sPE.

DESIGN: Prospective research trial where endometrial biopsies were obtained in the secretory phase from patients with a previous sPE pregnancy (n=16) versus controls with normal pregnancies outcomes that included preterm (n=10) and term (n=8) deliveries.

MATERIALS AND METHODS: We carried out both global gene profiling and targeted RNA sequencing using a custom panel designed for the 129 genes dysregulated in our previous work. RNA was extracted using RNEasy mini-kit (Qiagen) and quality-checked by Fragment Analyzer (AATI, USA). Gene expression was analysed using a TrueSeq Stranded mRNA in a NexSeq 500 platform (Illumina, USA) for global RNAseq and Ion AmpliSeq RNA in an Ion S5 system (Life Tech, USA) for our custom panel. All the sequences were pre-processed, normalized and analyzed comparing sPE vs control specimens. Differentially expressed genes (DEGs) were determined by statistical analysis of FDR <0.05 and fold change ≥2.

RESULTS: Global RNAseq analysis revealed 36 DEGs in the endometrium of patients with a prior sPE vs control pregnancies. Specifically, sample comparisons of sPE vs preterm control and sPE vs term control presented 15 and 24 DEGs, respectively. Interestingly, comparison between term and preterm control pregnancies failed to detect any difference in the gene profile. Principal component analysis (PCA) showed a separation between sPE vs control groups based on their transcriptional profiles. Strikingly, global and targeted RNAseq approaches obtained similar distribution of all the samples in the PCA. Correlation analysis revealed a strong gene expression association between the 129 DEGs targeted and those genes detected by global transcriptomic analysis (Pearson’s value = 0.89).

CONCLUSIONS: Our results using global gene profiling and targeted RNA sequencing corroborates the existence of an altered in vivo decidualization transcriptional profile in sPE patients. These findings further reinforce a possible maternal cause for sPE opening new directions to find strategies for early diagnosis and possible treatment.

References:
Supported by: Sara Borrell Programme (CD14/00229) from Spanish Carlos III Institute

O-258 Wednesday, October 10, 2018 12:00 PM
IS ANTI-MULLERIAN HORMONE (AMH) REALLY JUST A NUMBER? LONGLATUDINAL AMH AND ITS CORRELATION WITH PUBERTAL MILESTONES.
M. B. Smith, a J. Ho, a L. Ma, a M. Lee, a S. Czerwinski, a T. Glenn, a D. R. Cool, a F. Stanczyk, a S. R. Lindheim. a aObstetrics and Gynecology, Fellow, University of Southern California, Los Angeles, CA; aObstetrics and Gynecology, University of Southern California, Los Angeles, CA; aUniversity of Texas Health Science Center at Houston, Brownsville, TX; aEpidemiology, The University of Texas Health Science Center at Houston, Brownsville, TX; aObstetrics and Gynecology, Wright State University, Boonshoft School of Medicine, Dayton, OH; aObstetrics and Gynecology, Wright State University, Boonshoft School of Medicine, Dayton, OH; aWright State Integrated OB/GYN Residency Program, Dayton, OH.

OBJECTIVE: AMH has been well established as a tool to evaluate ovarian reserve and predict response to ovarian stimulation in adult infertile females. Knowledge regarding longitudinal changes in AMH and its relationship with reproductive milestones is not well understood. Our aim was to examine longitudinal change in AMH over time in females and to analyze the relationship of AMH levels with pubertal milestones.

DESIGN: Secondary analysis of a prospective, longitudinal study

MATERIALS AND METHODS: Ninety-one participants from the Fels Longitudinal Study, a prospective study of child growth and development, between the ages of 7.7 to 16.9 years (mean 11.7 years) were included. Demographics, pubertal development by Tanner staging, and blood samples were collected at 228 serial study visits between 1990 and 2015. Stored frozen serum samples were analyzed for AMH using ultrasensitive ELISA (Ansh Labs, Webster, TX). A generalized mixed effect linear model with a random intercept was used for analysis between longitudinal log-transformed AMH (AMHlog) levels and milestones of pubertal development. Milestones were defined as: thelarche at Tanner Stage II or beyond; pubarche at Tanner Stage II or beyond; menarche.

RESULTS: Overall, the mean AMH level from all visits was 5.3 ng/ml (SD ± 3.7). Mean age at menarche was 12.5 (SD ± 1.2) years and about 7% reported early menarche (<11 years). AMHlog appeared to be in non-linear relationship (quartic) with age. AMH decreased slightly between 10 and 14 years, increased until 16 years old then slowly declined over time. An increase in abdominal adiposity (Waist/Height ratio, WHR) was significantly associated with changes in AMHlog levels (β=-1.37, p = 0.035). Tanner stages for breast development (p = 0.031) and for pubic hair development (p = 0.064) were inversely associated with AMHlog while adjusting for age and WHR. Similarly, thelarche (β=-0.20, p = 0.044) was associated with changes in AMHlog. Pubarche and early menarche were not significantly related to AMHlog.

CONCLUSIONS: In this study, we observed significant non-linear relationships between changes in mean AMH over time, suggesting that the overall change in AMH levels vary with age. Changes in AMH were influenced by abdominal adiposity, and a decline in AMH was seen during progression through Tanner stages. It appears that AMH is predictive of thelarche milestones.

Supported by: Goldhirsh-Yellin Foundation Research Grant, Dayton Area Graduate Medical Education Community Research Grant, National Institutes of Health (R01HD12522).

THE OLDER PATIENT

O-259 Wednesday, October 10, 2018 10:45 AM
CUMULUS CELL ACETYL-CoA ENRICHMENT FROM ACETATE FOUND TO DECREASE WITH MATERNAL AGE USING A NOVEL APPROACH TO MEASURE METABOLISM IN INDIVIDUAL CUMULUS CELL COMPLEXES. S. Anderson, a,b N. Snyder, a A. Bloom, a,b D. Brasile, a,b B. Gocial, a,b J. J. Orris, a,b M. J. Glassner. a,b aMain Line Fertility Center, Bryn Mawr, PA; bOb/Gyn, Drexel University College of Medicine, Philadelphia, PA; cAJ Drexel Autism Institute, Drexel University, Philadelphia, PA.

OBJECTIVE: Cumulus cells possess cytoplasmic projections that penetrate through the zona pellucida to form an intimate association with the oocyte in the ovarian follicle. In our preliminary research, and utilizing methodology established for other cell types, we found that cumulus cells metabolize acetate into acetyl-CoA. This is important because acetyl-CoA controls key cellular processes, including energy metabolism and mitosis. The objective of this study was to determine if this enrichment of acetyl-CoA from acetate in cumulus cells is affected by maternal age.

DESIGN: Prospective, controlled, and blinded study at a private fertility center and collaborating university biochemistry research laboratory.

MATERIALS AND METHODS: Patients pursuing in vitro fertilization were screened using strict inclusion/exclusion criteria, and all patients received a standardized controlled ovarian stimulation protocol. Cumulus cell complexes (CCC) were removed from oocytes after oocyte retrieval procedure and then transported to the research laboratory, where they were individually analyzed. CCC were incubated with stable isotope 13C-labeled acetate substrate. The % relative enrichment of acetyl-CoA was determined using liquid chromatography-high resolution mass spectrometry, which maintains a quantitative substrate to product relationship. To control for the total number of cells in the CCC, which varies between oocytes, did not factor into the metabolic analysis. Acetyl-CoA enrichment from acetate was measured in 403 individual sets of CCC from 36 patients. Statistical significance was set at p<0.05. Maternal age

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e107
was a binary variable, and % acetyl-CoA was a continuous variable. Data were analyzed by an independent statistician using a two sample t-test with JMP Pro 13.0 software.

RESULTS: The mean % enrichment of acetyl-CoA in CCC from women \<34 years of age (49.06±0.76) was significantly higher (p=0.0004) than in those CCC from women \>34 (43.38±1.46). We can say with 95% confidence that the average % acetyl-CoA enrichment in women \>34 is between 2.3 and 8.8% lower than in women \<34.

CONCLUSIONS: The % acetyl-CoA enrichment from acetate, which is indicative of active metabolism, was found to be lower in individual CCC from women over 34 years of age. This stable isotope tracing methodology indicative of active metabolism, was found to be lower in individual CCC may be a promising new non-invasive approach to study how aging affects metabolism of cumulus cells and competency of associated oocytes.

Supported by: EMD Serono

O-260 Wednesday, October 10, 2018 11:00 AM

ADVANCED PATERNAL AGE DOES NOT AFFECT EMBRYO ANEUPLOIDY IN EGG DONOR CYCLES. R. J. Carraquillo,a C. Rubio,b T. P. Kohn,c C. Simon,d R. Ramasamy,c N. Al-Asmar,b aUrology, University of Miami, Miami, FL; bIgenomix, Paterna, Spain; cJohns Hopkins, Baltimore, MD; dSART, Boston, MA.

OBJECTIVE: The impact of advanced maternal age on a couple’s fertility and reproductive outcomes is well-understood, but the influence of advanced paternal age has been less studied and remains controversial. The purpose of this study was to evaluate whether advanced paternal age affects prevalence of embryo aneuploidy in egg donor cycles, as a means of controlling for female partner age.

DESIGN: Retrospective, multi-center cohort study.

MATERIALS AND METHODS: 1,202 IVF/ICSI cycles (6,934 embryos) with egg donor in conjunction with preimplantation genetic testing for aneuploidy (PGT-A) performed between January 2016 and April 2018 in a global population across all Igenomix centers were included in this study. All embryos included were biopsied days 5 and 6 (blastocyst) according to institutional protocol. All of the aneuploidy testing on trophectoderm biopsies was performed using next-generation sequencing. Only cycles with ejaculated sperm were included. Chi-square test was used to assess p-value and statistical significance was set at p<0.05. Analysis of variance (ANOVA) was used to assess differences in mean sperm concentration, for which data was available only for a subset of patients in the cohort.

RESULTS: Results from 6,934 embryos are tabulated according to paternal age groups (see table). CONCLUSIONS: To our knowledge, this is the largest study of its kind to evaluate the effect of advanced paternal age on embryo aneuploidy using egg donor cycles. No significant association was found between advancing paternal age and embryo aneuploidy. Limitations of this study include lack of outcomes such as pregnancy and live birth rate, smaller N for the oldest subset of men age 60+, as well as absence of data regarding sperm aneuploidy, specifically. Further studies are needed to assess the degree to which embryo aneuploidy is a consequence of the additive effect of advanced age in both parents.

<table>
<thead>
<tr>
<th>Male age group</th>
<th>Euploidy Rate</th>
<th>Female age</th>
<th>Cycles/ embryos</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>31.62%*</td>
<td>40.1</td>
<td>42/ 136</td>
</tr>
<tr>
<td>35-40</td>
<td>34.68%</td>
<td>40.0</td>
<td>419/ 1416</td>
</tr>
<tr>
<td>&gt;40</td>
<td>30.71%*</td>
<td>40.5</td>
<td>475/ 1498</td>
</tr>
</tbody>
</table>

CONCLUSIONS: Increased aneuploidy rate is associated with males over 40 years old. Male age, although not as much as female age, may have an impact on the embryo aneuploidy rate. A further analysis about the type of aneuploidies and the chromosomes involved is currently undergoing.

O-262 Wednesday, October 10, 2018 11:30 AM

PUBLIC PERSPECTIVES ON PLACING AGE LIMITS ON MEN AND WOMEN SEEKING FERTILITY TREATMENT. M. S. Lee,a L. V. Farland,b A. M. Thomas,c E. Ginsburg,d aObstetrics and Gynecology, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA; bObstetrics & Gynecology, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA; cObstetrics & Gynecology, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA; dSART, Boston, MA.

OBJECTIVE: While the ASRM recommends that fertility treatments of women over the age of 55 should be discouraged, there are no suggested age guidelines for men. The objective of this study was to assess the US
general public’s opinion regarding the upper age limit of parenthood and attitudes toward placing age limits on both men and women seeking fertility treatment.

### MATERIALS AND METHODS

A nationally representative sample of adult US residents (balanced on gender, race, and ethnicity, and age) completed an online questionnaire in February 2016. Demographic characteristics associated with support for age limits on men and women seeking fertility treatment, as well as with discordant responses (supporting age limits for one gender but not the other), were evaluated. Respondents who support age limits were compared with those who were neutral or in opposition using chi-squared tests and log binomial regression, adjusted a priori for age and gender, to calculate ratio RR) and 95% confidence intervals (CI).

RESULTS: Of the 1,574 respondents, 1,427 (91%) completed the survey. 46% of respondents felt that the oldest age a woman should carry a pregnancy was 45-54 years. 32% respondents felt that the oldest age a woman should become a non-biological mother (such as adoptive, or using a gestational carrier with donor egg) was 55-64. Similarly, 473 (33%) respondents felt that the oldest age a man should become a father (biological or adoptive) was 55-64. Support for placing age limits on women and men seeking fertility treatments were 70% and 57% of respondents, respectively.

While 55% supported placing age limits on both men and women, 213 (15%) answered discordantly, with 12% supporting age limits on women but not men, and 3% supporting age limits on men but not women (p<0.0001). Male survey respondents were more likely to answer discordantly when compared to female respondents (RR: 1.45; CI: 1.08-1.95).

Individuals older than 50, who lived in the Western US, or had a personal knowledge of someone who used ART were more likely to support age limits on both women and men seeking fertility treatments. Republicans (compared to Democrats) were more likely to support age limits on women. Sexual minorities (compared to heterosexuals), people without biological children, and single, long-term partnered and divorced/widowed respondents (compared to married respondents) were less likely to support age limits on men or women seeking fertility treatments.

CONCLUSIONS: 55% of respondents in a nationally representative sample support upper age limits on both men and women seeking fertility treatments. Support was associated with various demographic characteristics.

Men were more likely than women to support age limits only on women.

Supported by: Supported by the Expanding the Boundaries Grant from the Dept. of Obstetrics, Gynecology & Reproductive Biology, Brigham and Women’s Hospital.

### CAN A HIGH AMH OVERCOME ADVANCING REPRODUCTIVE AGE? THE ASSOCIATION BETWEEN AMH AND LIVE BIRTH RATE AMONG WOMEN OVER AGE 40. B. S. Harris,* K. S. Acharya,* T. Truong, R. Lerebours, C. F. Pieper,* J. L. Eaton. *Division of Reproductive Endocrinology and Infertility, Duke University, Durham, NC; *Department of Biostatistics & Bioinformatics, Duke University Medical Center, Durham, NC.

OBJECTIVE: Serum antimullerian hormone (AMH) levels are routinely used to predict an individual patient’s response to controlled ovarian stimulation [1]. It is controversial, however, whether AMH predicts live birth, particularly in older patients [2]. We hypothesized that among women age ≥41 undergoing IVF, high AMH is associated with increased odds of live birth.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: We utilized the Society for Assisted Reproductive Technologies-Clinical Outcomes Reporting System (SART-CORS) to identify all first, fresh, autologous IVF cycles performed between 2012 and 2014 in women ≥41 years old. Cycles with preimplantation genetic testing were excluded. Women were assigned to the “high AMH” or “low AMH” group based on AMH ≥90th percentile for the study cohort (2.7 ng/mL), or <90th percentile, respectively. Differences between the groups were compared using the Student’s t-test or Wilcoxon rank sum test for continuous variables, or the Chi-square test for categorical variables. Logistic regression models were created to test the association between high AMH and live birth while adjusting for the following covariates: age, race, body mass index (BMI), gravidity, parity, smoking status, infertility diagnosis, intracytoplasmic sperm injection (ICSI), assisted hatching, blastocyst transfer, total follicle-stimulating hormone (FSH) dose, and the number of embryos transferred.

RESULTS: Of the 7,820 women included in the analysis, 796 had high AMH and 7024 had low AMH. Women with high AMH had more oocytes (6.4 vs. 6.0, p<0.0001), required less FSH (2.475 IU vs. 4.275 IU, p<0.0001), and were less likely to have a cancelled cycle (5% vs. 23%, p<0.0001) than women with low AMH. After adjusting for covariates, however, there was no significant association between high AMH and live birth (OR 1.15; 95% CI 0.88 - 1.50; p=0.31).

CONCLUSIONS: Among women age ≥41 years undergoing IVF, high AMH confers decreased cancellation rates and higher oocyte yield but does not improve live birth rates. Women over age 40 can be counseled that a high AMH level does not overcome the negative impact of advancing reproductive age on IVF outcomes.

References:

### EPGENETIC DYSREGULATION IN BLASTOCYSTS DERIVED FROM ADVANCED PATERNAL AGED FATHERS INCLUDE AUTISM SPECTRUM CANDIDATE GENES. M. Denomone Tignanelli, B. McCallie, J. Parks, N. I. McCubbin, W. B. Schoolcraft, M. Katz-Jaffe. Colorado Center for Reproductive Medicine, Lone Tree, CO.

OBJECTIVE: Advanced paternal age (APA) has been associated with adverse outcomes including birth defects and childhood neurodevelopmental diseases, like autism spectrum disorder. Epigenetic dysregulation, such as inherited DNA methylation errors from aged fathers, may lead to permanent altered gene expression in offspring resulting in a clinical phenotype. The aim of this study was to investigate the methylome and subsequent transcriptome of human blastocysts in association with advanced paternal age.

DESIGN: Research study.

MATERIALS AND METHODS: Cryopreserved, transferrable quality, human blastocysts were donated with IRB approval and patient consent. Normozoospermic aged fathers (APA; ≥50 years) were compared to normozoospermic younger fathers (Young; ≤35 years) with only donor oocytes to eliminate known female factors. Blastocyst DNA (n=12) was bisulfite converted and sequenced using Methyl-MaxiSeq (Zymo Research), while blastocyst RNA (n=12) underwent small cell number RNA-seq (Illumina). Results were analyzed in conjunction with pathway analysis (DAVID 6.8). Transcription validation (n=12) was performed using qPCR with REST 2009 and methylation validation (n=10) utilized the PyroMark Q24 Advanced system (Qiagen). Statistical analysis included Student’s t-test, ANOVA in R, Fisher’s Exact Test and Pair Wise Fixed Reallocation Randomization Test where appropriate, with significance at p<0.05.

RESULTS: An overall shift towards hypomethylation was observed in APA blastocysts (34% APA vs. 40% Young; p<0.05), with 57,286 hypomethylated and 49,709 hypermethylated CpG sites (p<0.05). RNA sequencing revealed 751 genes with significantly decreased, and 195 genes with significantly increased expression (p<0.05). Combining the methylome and transcriptome datasets, 319 genes were significantly and directionally altered in both (p<0.05). Pathway analysis identified “disease mutation” as a highly significant key functional annotation category that includes intellectual disability, tumor suppressor genes, neurodegeneration, and autism spectrum disorder. To date, validation of methylation increase for the autism spectrum candidate genes SHANK2 (45% APA vs. 33% Young; p<0.05) and ANKRD11 (75% APA vs. 43% Young; p<0.05), and the observed decreased effects on their gene expression have been confirmed (p<0.05).

CONCLUSIONS: This novel study investigated the impact of APA on epigenetic events during embryogenesis. Our results reveal an overall hypomethylated shift in blastocysts derived from aged fathers, in accordance with literature on APA sperm, resulting in significantly altered transcription. Interestingly, however, autism spectrum candidate genes were primarily hypermethylated with subsequent decreased gene expression, providing a mechanistic link between the advanced paternal age effect and childhood neurodevelopmental disorders.
POSTER SESSION

PEDIATRIC AND ADOLESCENT GYNECOLOGY

P-1 Tuesday, October 9, 2018 6:30 AM

OVARIAN STIMULATION IS A SAFE AND EFFECTIVE FERTILITY PRESERVATION (FP) OPTION IN THE ADOLESCENT POPULATION. S. L. Manuel, M. B. Moravec, R. Contino, K. Smith, S. Klock, A. K. Lawson, M. Pavone. Obstetrics & Gynecology, Northwestern University, Chicago, IL; University of Michigan, Ann Arbor, MI; Obstetrics and Gynecology, Northwestern University, Chicago, IL; Northwestern Medicine, Chicago, IL; Saint Barthslemy, OB/GYN & Psychiatry, Northwestern University, Chicago, IL.

OBJECTIVE: Describe the multi-disciplinary approach and stimulation outcomes in adolescent patients (ages 13-21) who underwent oocyte cryopreservation for FP.

DESIGN: Multi-site retrospective cohort study

MATERIALS AND METHODS: Data were collected from patients aged 13-21 who underwent ovarian stimulation for FP from 2006-2017. Chi-square analysis was used to compare characteristics between the two groups, ages < 18 and 18-21 years, in which all p values were two-sided, and a p value of <0.05 was considered statistically significant.

RESULTS: 30 patients underwent controlled ovarian stimulation (COH) for FP for diagnoses including cancer (n=14), of which n=4 were recurrent cancer), gender dysphoria (n=4), Turner’s syndrome (n=2), and other (n=10). Median age at beginning the process, each patient met with a psychologist or social worker to design the process and wanted to move forward. Patients <18 years gave assent in addition to written consent from the parents/guardians. Transabdominal ultrasound monitoring was available for those that could not tolerate vaginal exams. Anesthesiologists who were comfortable sedating minors were made part of the treatment team. All patients successfully underwent COH and oocyte retrieval, with mature oocytes obtained and cryopreserved without any adverse outcomes. When dividing the group by ages <18 vs 18-21, the median doses of FSH used were 2326 and 1950 IU, the median number of mature oocytes cryopreserved were 7 and 10, and median number frozen oocytes were 10 and 13 respectively. The median days of stimulation were 10 and median number of total oocytes retrieved were 13 for both groups. There was no statistical difference in BMI, AMH, peak E2, total FSH dosage, days stimulated, antagonist start date, total oocytes retrieved, mature oocytes retrieved, and oocytes frozen between the two groups.

CONCLUSIONS: COH and oocyte cryopreservation is a feasible FP option for adolescents and young adults who may not have other alternatives if a multi-disciplinary approach and appropriate precautions are taken, such as proper counseling and a support team in place. These promising outcomes in adolescent patients (ages 13-21) who underwent oocyte cryopreservation for FP with and without OT had abdominal pain, whereas only 56% of patients without OT had abdominal pain (P<0.01). Nausea and/or emesis were more common symptoms in premenarchal patients with OT (82% versus 33%, P<0.01). Thirteen of 33 cases of OT (39%) did not have an adnexal mass apparent on imaging. Patients with OT and no distinct mass on imaging were younger (average age of 7.9 years, IQR 7.0 - 9.7) than those with OT and an adnexal mass (average age of 10.5 years, IQR 9.3 - 11.7, P < 0.01). Decreased Doppler flow was noted in 15/25 patients (60%) in the OT group and 1/9 patients (11%) in the control group (P < 0.01). Patients with OT and a mass were more likely to undergo an oophorectomy (40%) when compared to patients with OT and no distinct adnexal mass (8%) (P < 0.05). There were two cases of malignancy in each group. Four patients had recurrent episodes of OT; three had OT on the same side and one on the contralateral side.

CONCLUSIONS: While there were no distinct characteristics that clearly differentiated premenarchal girls with and without OT, patients with OT had significantly more nausea, emesis and abdominal pain, as well as decreased ovaries. Doppler flow on imaging. Within the torsion group, patients without a mass were significantly younger than those with a mass. In contrast to other studies 50% of malignancies were found in patients with OT.

ANDROGEN EXCESS

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OBJECTIVE: Current practice defines Hispanic women with hyperandrogenism as high risk for non-classical congenital adrenals hyperplasia (NCCAH).1 This recommendation stems from research that was conducted in New York City demonstrating that women with Hispanic ethnicity have a high prevalence of NCCAH (1:40).2 However, clinical experience suggests that the disease frequency of NCCAH in the Hispanic population in South Texas is lower. Here, we determine the prevalence of NCCAH in our patient population to evaluate whether Hispanic ethnicity should be considered a high risk factor.

DESIGN: Retrospective Chart Review

MATERIALS AND METHODS: We reviewed six hundred and sixty-eight female patients ages eight to fifty with irregular menses and/or clinical or laboratory hyperandrogenism whose evaluation included 17-hydroxy progesterone (17-OHP) measurements between the years 2007 and 2017 from University Heath System in San Antonio, Texas. Demographic data, screening and diagnostic testing, and the final diagnoses were collected using RedCap. Statistical analysis was performed utilizing ANOVA, Fisher’s exact test, and Tukey’s HSD test and adjusted for hirsutism, irregular menses, and polycystic ovaries by ultrasound.

RESULTS: The prevalence of NCCAH in all patients is 0.9% (6 out of 668), and in the South Texas Hispanic population is 1.4% (3 out of 210). Hispanic ethnicity in our patient population is not associated with NCCAH diagnosis (OR 2.18, 95%CI [0.35;13.67], p=0.40) nor is it associated with elevated 17-OHP levels (OR 1.39, 95%CI [0.79;2.4], p=0.34). Hispanic ethnicity is associated with hirsutism (p=0.01).

CONCLUSIONS: The prevalence of NCCAH in the South Texas Hispanic population is lower than previously reported. The prevalence of NCCAH diagnosis is similar among all ethnicities in our patient population. Screening of Hispanic hyperandrogenic women in South Texas for NCCAH should be individualized.

References:

Supported by: NIH KL2 TR001118 (JK)
EFFECT OF ANDROGEN LEVEL ON THE ABORTION RATE IN CHINESE WOMEN AFTER ASSISTED REPRODUCTION TECHNOLOGY.

**OBJECTIVE:** To determine the effect of androgen level on the abortion rate during in vitro fertilization embryo transfer (IVF-ET).

**MATERIALS AND METHODS:** Total 7374 infertile women who received IVF-day 3 embryo transfer fresh cycles with autologous oocytes from January 2009 to December 2016 at the Center for Reproductive Medicine, Peking University Third Hospital, Beijing, China; & Human Reproduction Medicine Center, Peking University Third Hospital, Beijing, China.

**RESULTS:** A total of 6290 women resulted in live births and gave birth to 4471 live birth singletons and 1819 twins. 1070 women ended with abortion and 14 women ended with stillbirth. Live-birth rates in HA group was significantly lower than that in non-HA group. The abortion rate in HA group was significantly higher than that in non-HA group (17.18% vs. 13.95%, P=0.003). The risk ratio suggested a 27.9% increase in abortion with HA women compared with non-HA group. The increased risk of abortion rate was largely driven by high risks associated with late abortion rate in HA group than that in non-HA group (36.5% vs. 27.03%, P=0.006). There was no significant difference in the preterm rate, caesarean section (CS) rate, and live-birth rate between groups stratified by androgen level.

**CONCLUSIONS:** Androgen level was significantly influential factors on the abortion rate in Chinese women after assisted reproduction technology.

<table>
<thead>
<tr>
<th>Effect of androgen level on the abortion rate in Chinese women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-HA (n=6099)</strong></td>
</tr>
<tr>
<td>Number of embryos transferred</td>
</tr>
<tr>
<td>Number of high-quality embryos transferred</td>
</tr>
<tr>
<td>Live-birth sex ratio (M/F)</td>
</tr>
<tr>
<td>Abortion rate</td>
</tr>
<tr>
<td>Early abortion rate</td>
</tr>
<tr>
<td>Late abortion rate</td>
</tr>
<tr>
<td>Multiple pregnancy rate</td>
</tr>
<tr>
<td>Live-birth rate</td>
</tr>
<tr>
<td>Preterm rate (Live-birth singleton)</td>
</tr>
<tr>
<td>Caesarean section rate (Live-birth singleton)</td>
</tr>
</tbody>
</table>

**References:**
EXERCISE BEHAVIORS BY ETHNIC GROUP AMONG PATIENTS WITH POLYCYSTIC OVARY SYNDROME. D. Huang, E. Greenwood, C. Kao, M. Quinn, M. Cedars, H. Huddleston. Department of Ob-Gyn&RS, UCSF, San Francisco, CA.

OBJECTIVE: To characterize exercise behavior of patients with polycystic ovary syndrome (PCOS) by ethnicity.

DESIGN: This was a cross-sectional assessment of women who attended a multidisciplinary PCOS clinic.

MATERIALS AND METHODS: Participants were recruited consecutively from 2006-2018 from a PCOS specialty clinic at a tertiary academic institution and systematically evaluated for demographic and anthropometric data. Exercise data were ascertained by the validated International Physical Activity Questionnaire in which we calculated metabolic equivalents (METs) as the unit of energy expenditure. Threshold for adequate physical activity was defined by the guidelines published by the US Department of Health and Human Services (DHHS), either as 150 minutes a week of moderate-intensity, or 75 minutes a week of vigorous-intensity aerobic activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity. Patients were divided into three groups based on their self-reported ethnicity (White, Hispanic, or East/Southeast Asian). Statistical analysis was performed with SAS 9.4, 32-bit edition. All testing was performed at the 0.05 level of significance.

RESULTS: Of the 375 women evaluated, 71.7% (n = 269) were White, 17.6% (n = 66) were Hispanic, and 10.7% (n = 40) were East/Southeast (SE) Asian. The study population was notable for Hispanic patients having higher BMI (p < 0.01). Analysis of exercise data revealed differences in mean METs from vigorous activity (METvig) as well as mean total METs (moderate plus vigorous activity) between the 3 groups. These differences appear, but do not reach, statistical significance when controlled for age (p = 0.08 for METvig and p = 0.12 for METtotal). This trend is mainly attributed to differences in METvig and METtotal between East/SE Asian and White patients (paired t-values of 0.16 and 0.15, respectively), where East/SE Asian patients have less METvig and METtotal. The three ethnic groups also differ significantly in frequency of METtotal between East/SE Asian and White patients (paired t-values of 0.16 and 0.15, respectively), where East/SE Asian patients have less METvig and METtotal. Most residents were aware of the menstrual irregularity and hirsutism criteria, but fewer were aware of serum androgens and ultrasound criteria (see table). Most residents (98%) were screened for diabetes, but fewer (70%) screened for dyslipidemia. Less than 50% were aware of mood disorders associated with PCOS. Overall, 47% of residents prescribed letrozole as first line therapy for infertility. Residents who completed an REI rotation had increased odds (aOR: 1.9, 95% CI: 1.0-3.5, P = 0.038) of using letrozole after adjusting for seniority status.

CONCLUSIONS: Although senior residents were more likely to apply Rotterdam criteria in the diagnosis of PCOS, the overall number of residents identifying all components of the criteria was very low. Increased resident education is needed regarding PCOS diagnosis and long-term management, in order to improve the patient experience and provide more comprehensive care.

References:

Supported by: Dickens Fellowship Fund, University of Pennsylvania Department of Obstetrics and Gynecology
OBJECTIVE: To evaluate the stability over time of recently identified gonadotropin-releasing hormone receptor autoantibodies (GnRHR-AAbs) in the serum of infertile patients with polycystic ovary syndrome (PCOS). Our assay may hold promise in future diagnostic testing for PCOS, however currently no data exists regarding antibody level stability.

DESIGN: Case series.

MATERIALS AND METHODS: Serum samples from a convenience sample of seven women with PCOS and infertility were assessed for GnRHR-AAbs levels over multiple time points (17 total) spanning, on average, a two year timeframe for all patients. All time points represent baseline AAb levels as the patients were not on hormonally modulating medications at the selected times. The initial identification of AAbs were screened by enzyme-linked immunosorbent assay (ELISA) for GnRHR-AAbs using a synthetic 28-mer peptide (LifeTein, Somerville, NJ) from the second extracellular loop (ECL2) of human GnRHR as coating antigen and evaluated for optical density (OD) values. Statistical analyses were performed with paired t-tests using all sequential pairs of GnRHR values for evaluation of GnRHR AAb level total absolute change over time (TAC/T).

RESULTS: There was a non-significant difference between GnRHR AAb level values over time for each patient, p=0.39. Additionally, increased variation in AAb level over time (higher TAC/T) was not associated with higher GnRHR AAb levels, p=0.23. Lastly, when evaluating the relationship of AAb level variation and other measures also averaged over time (estradiol level, age, body mass index (BMI), and antimullerian hormone level), only estradiol was found to have a significant association with higher estradiol levels and GnRHR AAb TAC/T, p=0.048.

CONCLUSIONS: Our initial investigations have shown that most patients in our study with PCOS have activating AAbs to GnRHR compared to ovulation controls (1). In this case series we have demonstrated that GnRHR AAb levels are stable over time and AAb level consistency does not vary by baseline AAb level. Additionally, there may be an association between higher estradiol levels and GnRHR AAb level TAC/T.

Supported by: Oklahoma University College of Medicine Alumni Association (COMAAA) Grant

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THE EFFECT OF BMI AND LIPID METABOLISM ON PREGNANCY OUTCOME OF PCOS PATIENTS UNDERGOING IVF/ICSI USING GnRH ANTAGONIST PROTOCOL.

X. Huang*a F. Diao.

aCenter of Clinical Reproductive Medicine, State Key Laboratory of Reproductive Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; bFirst Affiliated Hospital with Nanjing Medical University, Nanjing, China.

OBJECTIVE: To explore the effect of body mass index (BMI) and lipid metabolism on ovarian response, embryo quality and pregnancy outcome of polycystic ovary syndrome (PCOS) patients, who undergoing their first oocyte retrieval cycle using GnRH antagonist protocol and following fresh/frozen-thawed embryo transfer cycles.

DESIGN: Retrospective, single-center clinical cohort.

MATERIALS AND METHODS: From January 2013 to June 2016, 762 infertile PCOS patients, younger than 40 years old, undergoing their first IVF/ICSI oocyte retrieval cycle using GnRH antagonist protocol were recruited to the research. Among these PCOS patients, 244 patients undergoing their fresh embryo transfer cycles. Those patients didn’t get pregnancy in fresh embryo transfer cycles, or who used a freeze-all strategy after oocyte retrieval undergoing 758 fresh-frozen thawed embryo transfer cycles. The values of BMI, total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL) and low-density lipoprotein (LDL) was collected to analyze their effects on ovarian response and embryo quality. Binary Logistic regression analysis was using to investigate the influence of BMI and lipid metabolism on clinical pregnancy outcome.

RESULTS: 1. There was a positive correlation between BMI and TG/LDL and negative correlation between BMI and HDL (P<0.05). 2. BMI and LDL negatively correlated with the index of ovarian response and embryo quality, while HDL positively correlated with the ovarian response and embryo quality (P<0.05). For those PCOS patients with BMI less than 28, the BMI showed no correlation with the clinical pregnancy rate. 3. In fresh embryo transfer cycles, Binary Logistic regression analysis showed that for each additional unit of HDL, the chance of clinical pregnancy rate increased by 3.86 times (P=0.011, OR=3.856), which means HDL was the protective factor in clinical pregnancy outcome. Even in frozen-thawed embryo transfer cycles, LDL/TC still were the risk factors in clinical pregnancy outcome, for each additional unit of LDL/TC, the chance of clinical infertility increased by 1.33 times/1.59 times (P=0.040, OR=0.753; P=0.015, OR=0.628).
CONCLUSIONS: Excessive BMI and abnormal lipid metabolism adversely affected PCOS patient’s ovarian response, embryo quality and clinical pregnancy outcome in GnRH antagonist protocol. For improve the clinical pregnancy results of PCOS patients, pretreatment before IVF / ICSI will not only include weight losing, but also need attach great importance to the lipid metabolism screen and management. In particular, re-evaluation and treatment of abnormal BMI and lipid metabolism before frozen-thawed embryo transfer could improve the cumulative pregnancy rate.

Supported by: State Key Lab of Reproductive Medicine Funding for Innovation, SKLRM-GC201804.

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THE CORRELATION BETWEEN MENTAL HEALTH AND NUMBER OF SYMPTOMS ENDORSED on A REVIEW OF SYSTEMS FORM IN POLYCYSTIC OVARY SYNDROME. V. Sundaram, a E. Greenwood, b H. Huddleston, a UCSC, San Francisco, CA; aObstetrics, Gynecology & Reproductive Sciences, UCSF, San Francisco, CA; aREI, UCSF, San Francisco, CA.

OBJECTIVE: (1) To determine if a relationship exists between the number of items endorsed on a review of systems (ROS) and depressive symptoms as measured by the Beck Depression Index Fast Screen (BDI-FS) in a cohort of women with polycystic ovary syndrome (PCOS). (2) To further quantify the relationship between various mental health scores to number of symptoms endorsed on the ROS.

DESIGN: Cross-sectional cohort

MATERIALS AND METHODS: All patients diagnosed with polycystic ovary syndrome by Rotterdam criteria at the multidisciplinary PCOS clinic at the University of California, San Francisco Center for Reproductive Health between August 2005 and April 2018 were offered participation in a cohort study. Patients completed the ROS and Beck Depression Index (BDI-FS) prior to their initial visit. The number of items endorsed on the ROS was correlated to depression scores using Spearman’s correlation coefficient; linear regression models further evaluated the relationship while controlling for age, body mass index (BMI), and education. Additionally, in a smaller cohort with further mental health data, the Generalized Anxiety Disorder (GAD7), PCOS Quality of Life assessment, Eating Disorder Questionnaire, and Patient Health Questionnaire (PHQ-9) scores were correlated to symptoms endorsed on ROS.

RESULTS: 425 patients were identified with a diagnosis of PCOS by Rotterdam criteria and had completed ROS data prior to their initial visit. The Spearman’s correlation coefficient between endorsed symptoms on ROS and BDI score was 0.2075 (p < 0.001). Positive correlations were noted between ROS symptoms endorsed and PHQ-9, GAD7, and Eating Disorder Exam Questionnaire scores. A negative correlation was noted with PCOS QOL scores.

Validated Questionnaires Scores Correlated with Total ROS Score in Smaller Cohort of PCOS Patients

<table>
<thead>
<tr>
<th>Validated Questionnaire</th>
<th>Sample Size</th>
<th>Correlation Coefficient (r)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Health Questionnaire (PHQ-9) Score</td>
<td>47</td>
<td>0.3794</td>
<td>0.001</td>
</tr>
<tr>
<td>Generalized Anxiety Disorder (GAD7) Score</td>
<td>46</td>
<td>0.3024</td>
<td>0.001</td>
</tr>
<tr>
<td>Eating Disorder Exam Questionnaire Score</td>
<td>24</td>
<td>0.1780</td>
<td>0.040</td>
</tr>
<tr>
<td>PCOS Quality of Life</td>
<td>41</td>
<td>0.1932</td>
<td>0.004</td>
</tr>
</tbody>
</table>

CONCLUSIONS: Due to the suggested significant relationship between number of symptoms endorsed on an ROS and BDI-FS scores, the ROS itself may serve as a screen for depression in the PCOS population. A score >8 on ROS should lead to formal screening for depression. ROS may be significantly correlated to additional mental health disorders, though further evidence is required to confirm the relationship.

Demographics and Scores for Women with PCOS versus Controls

<table>
<thead>
<tr>
<th></th>
<th>PCOS (n=55)</th>
<th>Controls (n=121)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (years)</td>
<td>28 (19-44)</td>
<td>31.5 (20-49)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Median BMI (kg/m²)</td>
<td>36.5 (19.3-52.6)</td>
<td>26.5 (17.3-54.4)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Race, n (%): white</td>
<td>37 (67%)</td>
<td>39 (33%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Race, n (%): black</td>
<td>11 (20%)</td>
<td>64 (53%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Prevalently pregnant (Preceding Preg)</td>
<td>12 (22%)</td>
<td>85 (71%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Median HADS depression score</td>
<td>5.0 (0-13)</td>
<td>3.0 (0-13)</td>
<td>0.10</td>
</tr>
<tr>
<td>Median HADS anxiety score + SD</td>
<td>9.6 ± 3.4</td>
<td>8.1 ± 4.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Median MBSRQ appearance evaluation score (range)</td>
<td>2.4 (1-5)</td>
<td>3.7 (1.4-5)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Median MBSRQ overweight preoccupation score (range)</td>
<td>3.5 (1-5)</td>
<td>2.5 (1-4.5)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Median MBSRQ appearance orientation score + SD</td>
<td>3.8 ± 0.6</td>
<td>3.4 ± 0.6</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Median MBSRQ body areas satisfaction score + SD</td>
<td>2.8 ± 0.6</td>
<td>3.5 ± 0.8</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Median MBSRQ weight classification score + SD</td>
<td>4.2 ± 0.9</td>
<td>3.4 ± 0.8</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

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BODY IMAGE DISTRESS (BID) CONTRIBUTES TO INCREASED RISK OF ANXIETY AND DEPRESSIVE SYMPTOMS IN WOMEN WITH POLYCYSTIC OVARY SYNDROME (PCOS). S. Alur-Gupta, a A. Chemerinski, a C. Liu, a J. Lipson, a M. D. Sammel, a K. Allison, a D. Dokras, a Hospital of the University of Pennsylvania, Philadelphia, PA; bUniversity of Pennsylvania, Philadelphia, PA; cPennsylvania Hospital, Philadelphia, PA; bBiostatistics & Epidemiology, University of Pennsylvania, Philadelphia, PA; aCenter for Weight & Eating Disorders, University of Pennsylvania, Philadelphia, PA.

OBJECTIVE: To evaluate differences in BID scores in women with PCOS compared to controls, and examine associations between BID and anxiety, depression and quality of life.

DESIGN: Cross-sectional survey

MATERIALS AND METHODS: From January-April 2018, non-pregnant women aged 18-50 presenting to an academic PCOS center and gynecology clinic were surveyed. The Multidimensional Body Self Relations (MBSRQ-AS), and Hospital Anxiety and Depression Scale (HADS) questionnaires were used for both groups and Health-Related Quality of Life survey (HRQOL) was used in women with PCOS. The 5 MBSRQ subscales evaluated are shown in the table. Multivariable linear regression modeling was used to evaluate whether the association between PCOS/control status and depression anxiety and distress scores were mediated by MBSRQ subscales.

RESULTS: The table shows elevated depressive anxiety and body image distress scores in women with PCOS. In multivariate regression models, PCOS was associated with higher anxiety (p = 0.08) and depression (p = 0.051) scores. The association between PCOS/control status and higher anxiety scores was strongly mediated (72-78%) by appearance evaluation (p = 0.003) and body areas satisfaction (p = 0.004) while accounting for founders. The association between PCOS/control status and depressive symptoms was also strongly mediated (88-92%) by appearance evaluation (p = 0.001) and body areas satisfaction (p = 0.001) and partly mediated (33%) by overweight preoccupation (p = 0.043). Appearance orientation and self-classified weight subscales were not significant mediators. In women with PCOS, MRSRQ subscales were significantly correlated with...
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POLYCYSTIC OVARY SYNDROME (PCOS) PROTECTS AGAINST THE NATURAL DECLINE IN FERTILITY WITH ADVANCING REPRODUCTIVE AGE: FINDINGS OF A LARGE RETROSPECTIVE COHORT ANALYSIS.

W. Huber, III,a V. Mensah,b Y. Zhang,c M. Sauerbrun-Cutler,a Y. Huang,d,e R. Alvero,a S. Wang,a Obestetrics and Gynecology, War- ren Alpert Medical School of Brown University/Women and Infants Hospital, Providence, RI; bReproductive Science Center, Eatontown, NJ; cBiostatistics, Brown University School of Public Health, Providence, RI; dInstitute of Statistical Sciences Academia Sinica, Taipei, Taiwan.

OBJECTIVE: To assess the impact of PCOS on live birth rate and age-related decline in fertility based on peak estradiol among women <37 years old (yo) and ≥37yo

DESIGN: Retrospective cohort study

MATERIALS AND METHODS: Utilizing the eIVF® database, we analyzed 20,848 autologous fresh IVF cycles from 2000-2016 in women ages 21-55. Cycles were categorized as PCOS and non-PCOS in the eIVF® database by the primary clinic and further stratified by age (<37 and ≥37yo). We applied generalized additive modeling (GAM) with penalized smoothing splines to estimate the effects of peak serum estradiol concentrations on our primary outcome, live birth rate. The data was adjusted for possible confounders including age.

RESULTS: In women <37yo, PCOS had no impact on live birth rates across all estradiol levels, with both PCOS and non-PCOS patients ranging from 40-50% live birth rate at peak E2 levels above 3000 pg/ml. Conversely, in women ≥37yo, the peak live birth rate was higher in the PCOS group (30-35%) compared with the non-PCOS (20%) patients at peak estradiol levels ranging from 2000-4000 pg/ml. Lastly, the age-related decline in fertility was lower for PCOS patients than non-PCOS patients across E2 levels of 2000pg/ml-4000 pg/ml. For example, the difference in peak live birth rate in PCOS patients <37 yo compared to ≥37yo was approximately 5%. However, in non-PCOS patients this age related decline in peak live birth rate was 20%, which was statistically significant utilizing GAM. The ≥37yo PCOS group was younger (39 +/-1.9 vs 40 +/-2.3 years, p<0.05), had more oocytes retrieved (11.8 +/- 7.3 vs 8.5 +/- 6.0, p<0.05) and 2pn embryos (6.3 +/-5.2 vs 4.0 +/- 4.1, p<0.05) than the non-PCOS group; however, the increase in live birth rate and lower decline in age-related fertility seen in the PCOS group remained significant after controlling for age.

CONCLUSIONS: As expected, increasing age has a detrimental impact on overall live birth rate; however, PCOS appears protective against this natural decline in fertility. Younger women, with or without PCOS, have similar

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PCOS IVF. L. G. Cooney,a I. Lee,b M. A. Clapp,b S. Bjerkan,c M. Goldsammler,c M. Sammel,d B. Fisher,d A. Dokras,a bObGyn, University of Pennsylvania, Philadelphia, PA; cMontefiore Medical Center, Bronx, NY; dYale School of Medicine, New Haven, CT; aPerelman School of Medicine, Philadelphia, PA.

OBJECTIVE: To derive a prediction model for cumulative live birth (cLB) per egg retrieval cycle in women with polycystic ovary syndrome (PCOS) undergoing in-vitro fertilization (IVF).

DESIGN: Multi-center retrospective cohort study

MATERIALS AND METHODS: Women aged 18-45 years with a diagnosis of PCOS by Rotterdam criteria who underwent their first IVF cycle at the University of Pennsylvania, Montefiore Medical Center, or Yale School of Medicine between 2009-2016 were included. A multivariable logistic regression model was derived to predict cumulative live birth (cLB) per egg retrieval. Outcomes from the first fresh transfer and all subsequent frozen transfers were included. The final model was chosen based on maximization of the area under the ROC (AUROC) with the minimum number of predictors. Predictors including demographic characteristics, medical history, and baseline laboratory tests of metabolic and androgen status were considered. Bootstrap resampling was used to compute 95% confidence intervals (CI). Adjusted odds ratios (aORs) and predicted probabilities (PP) were calculated.

RESULTS: 176 women, representing 226 cycles were included (Penn: 105 women /139 cycles, Montefiore: 49/61, Yale: 22/26). 40.9% had cLB. The final model (Table 1) included age <35, normal weight, resistance to clomiphene citrate or letrozole (defined as failure to ovulate at max dose), history of depression, polycystic ovaries on ultrasound (PCOM) and current use of metformin. AUROC was 0.71 (95% CI: 0.64-0.79). Table 1 shows potential uses of this model to predict PP of cLB for sample patients with different combinations of characteristics. Additional variables associated with cLB in univariate analysis but not included in the final model due to missing data include impaired glucose tolerance (elevated Hgb A1c or 2hr GTT)
CONCLUSIONS: Patients with PCOS have significantly higher serum BCAA levels compared to controls. This suggests a potential role of BCAA in the pathophysiology of PCOS, supporting further studies to investigate the association between BCAA and PCOS.

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OBJECTIVE: Polycystic ovary syndrome (PCOS), traditionally known as a common reproductive disorder with a variety of clinical manifestations such as menstrual irregularities, signs of androgen excess, and infertility, is now considered not only as an endocrine disorder but also as a heterogeneous syndrome due to fallopian tube or male factors into PCOS group. Besides, the localization of AQP7 and AQP9 in ovarian tissues and oocytes was investigated.

MATERIALS AND METHODS: This study divided the infertile women due to fallopian tube or male factors into PCOS group (n=20) and control group (n=20). The expression level of AQP7 and AQP9 mRNA and protein in mural granulosa cells and follicular granulosa cells was measured by the real-time polymerase chain reaction (RT-PCR) and Western blotting. Immunofluorescence was used to detect the localization and expression of AQP7 and AQP9 in oocytes at different developmental stages. Immunohistochemical method was used to detect the localization and expression of AQP7 and AQP9 in ovarian tissues. The expression of AQP7 and AQP9 in ovarian tissues and oocytes was investigated.

RESULTS: The expression of AQP7 and AQP9 in ovarian tissues of PCOS group were significantly higher than that of control group (P < 0.05). The expression of AQP7 and AQP9 in mural granulosa cells and follicular granulosa cells were measured by the real-time polymerase chain reaction (RT-PCR) and Western blotting. Immunofluorescence was used to detect the localization and expression of AQP7 and AQP9 in mural granulosa cells at different stages of follicular development. Immunohistochemical method was used to detect the localization and expression of AQP7 and AQP9 in mural granulosa cells. The expression of AQP7 and AQP9 in mural granulosa cells was investigated.
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OBJECTIVE: Polycystic ovary syndrome (PCOS), a common reproductive disorder with a variety of clinical manifestations such as menstrual irregularities, signs of androgen excess, and infertility, is now considered not only as an endocrine disorder but also as a complex, multifaceted syndrome with substantial long-term health implications and several adverse metabolic, cardiovascular alterations including metabolic syndrome, obesity, dyslipidemia, insulin resistance, diabetes mellitus and coronary artery disease risks in the life span. Insulin resistance (IR) is suggested to have a critical role in the metabolic and cardiovascular consequences of PCOS. Human zonulin which is a biomarker for gut permeability is suggested to be related with insulin resistance and metabolic disturbances; however, to our knowledge there is only one study evaluating zonulin levels in PCOS subjects. The aim of the study is to investigate zonulin as a novel biomarker in women with PCOS.

DESIGN: Case-control study

MATERIALS AND METHODS: A total of 90 women with PCOS and 45 age and body mass index (BMI) matched healthy controls were enrolled. Clinical, hormonal and metabolic parameters in addition to serum zonulin levels were determined by ELISA and compared between the groups. Insulin resistance, defined by the homeostasis model assessment of insulin resistance (HOMA-IR), was calculated. Student’s t-test or Mann-Whitney U-test was used for comparisons of the mean between the two groups, as appropriate. Correlation analyses were performed by using Pearson’s and Spearman’s correlation methods.

RESULTS: Zonulin levels were significantly higher in the PCOS group compared with the control (32.51±32.48 ng/ml vs 18.72±16.07 ng/ml, respectively; p<0.01). There was no statistically significant difference between the groups in terms of age, BMI, waist/hip ratio, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride levels, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride levels, and free androgen index. HOMA-IR and Ferriman Gallwey score and systolic blood pressures were significantly higher in the PCOS group compared with the controls. GPC4, YKL-40 and NRG4 levels were all significantly higher in the PCOS group compared with the control (20.50±20.35 ng/ml vs 7.91±4.65 ng/ml for GPC4; 142.08±141.62 ng/ml vs 21.56±20.35 ng/ml for YKL-40; and 2.53±2.35 ng/ml vs 1.13±0.58 ng/ml for NRG4, respectively; p<0.01). GPC4, YKL-40 and NRG4 levels were positively correlated with each other and with BMI, WHR and HOMA-IR in women with PCOS.

CONCLUSIONS: Women with PCOS have significantly higher serum zonulin levels than the controls. The significant correlation between zonulin levels and HOMA-IR in PCOS subjects suggests zonulin as a key pathogenic, novel biomarker in women with PCOS.

References:

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OBJECTIVE: Insulin resistance (IR) which affects 50-70% of women with polycystic ovary syndrome (PCOS) is suggested to be an important feature that has critical role in the metabolic and cardiovascular consequences of the syndrome. Glypican-4 (GPC-4) is an adipokine which affects insulin sensitivity and in a pilot study its serum levels were found to be higher in PCOS subjects compared to the controls. Moreover, GPC-4 levels were reported to be correlated with cardiovascular disease risk parameters. Human cartilage glycoprotein-39 (YKL-40) is suggested to be a marker of inflammation and endothelial dysfunction and also is reported to play an important role in IR and diabetes. To our knowledge, there is only one study comparing YKL-40 levels in PCOS subjects with controls.

Neuregulin-4 (NRG4) is an epidermal growth factor like signaling molecule and a novel adipokine, which is found to be associated with metabolic disorders including type 2 diabetes. The only study evaluating NRG4 levels in women with PCOS reported higher levels of NRG4 in PCOS subjects compared with the controls. Since studies evaluating GPC4, YKL-40 and NRG4 in women with PCOS do not provide sufficient information to make general recommendations, further studies are needed. The aim of the study is to investigate GPC4, YKL-40 and NRG4 levels as novel biomarkers in women with PCOS.

DESIGN: Case-control study

MATERIALS AND METHODS: A total of 110 women with PCOS and 40 age and body mass index (BMI) matched healthy controls were enrolled. Clinical, hormonal and metabolic parameters in addition to serum GPC4, YKL-40 and NRG4 levels were compared between the groups. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated. Student’s t-test or Mann-Whitney U-test was used for comparisons of the mean between the two groups, as appropriate. Correlation analyses were performed by using Pearson’s and Spearman’s correlation methods.

RESULTS: There was no statistically significant difference between the groups in terms of age, BMI, waist to hip ratio (WHR), diastolic blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride levels and free androgen index. HOMA-IR and Ferriman Gallwey score and systolic blood pressures were significantly higher in the PCOS group compared with the controls. GPC4, YKL-40 and NRG4 levels were all significantly higher in the PCOS group compared with the control (20.50±20.35 ng/ml vs 7.91±4.65 ng/ml for GPC4; 142.08±141.62 ng/ml vs 21.56±20.35 ng/ml for YKL-40; and 2.53±2.35 ng/ml vs 1.13±0.58 ng/ml for NRG4, respectively; p<0.01). GPC4, YKL-40 and NRG4 levels were positively correlated with each other and with BMI, WHR and HOMA-IR in women with PCOS.

CONCLUSIONS: Women with PCOS have significantly higher serum GPC4, YKL-40 and NRG4 levels than the controls. GPC4, YKL-40 and NRG 4 levels were positively correlated with each other and with BMI, WHR and HOMA-IR in women with PCOS. GPC4, YKL-40 and NRG4 may be promising novel biomarkers in women with PCOS.

References:

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PODOCALYXIN A NEW BIOMARKER IN POLYCYSTIC OVARY SYNDROME. G. Anik Ilhan B. Yildizhan. Obstetrics and Gynecology, Reproductive Endocrinology and Infertility, Marmara University, Istanbul, Turkey.

OBJECTIVE: Polycystic ovary syndrome (PCOS) is a common endocrine disorder with long-term health implications in addition to the short-term reproductive consequences with an increase in the prevalence of metabolic syndrome; a cluster of risk factors that increase the risk of cardiovascular disease (CVD) and diabetes mellitus. Podoalyxin, a podocyte-specific protein is expressed in not only glomerular podocytes but also in vascular endothelial cells. Podoalyxin levels were found to be associated with carotid intima thickness, implicating its potential role as a novel marker for atherosclerosis. Podoalyxin levels were also found to be elevated in preeclampsia and reported as a marker of endothelial cell dysfunction. Since PCOS is considered not only as a reproductive disorder but also as a multifaceted syndrome with substantial long-term health implications, including metabolic syndrome and CVD, special attention should be given for detection of target subjects with a high cardiometabolic risk. The aim of the study is to evaluate podoalyxin levels in women with PCOS and to our knowledge, it is the first in literature that evaluates serum podoalyxin levels in PCOS subjects.
MATERIALS AND METHODS: A total of 120 women with PCOS and 50
age and body mass index (BMI) matched healthy controls were enrolled.
Clinical, hormonal, metabolic parameters and serum podocalyxin levels
were compared between the groups. PCOS subjects were further divided
into two groups according to the presence of metabolic syndrome as
MetS+ and MetS-. Clinical, hormonal, metabolic parameters and podoca-
lyxin levels were compared between the groups in PCOS subjects. Student’s
t-test or Mann-Whitney U-test was used for comparisons of the mean be-
tween the two groups.
RESULTS: Podocalyxin levels were significantly higher in the PCOS
group compared with control (15.36±15.01 ng/ml vs 9.37±3.90 ng/ml,
respectively; p<0.05). There was no statistically significant difference be-
tween the groups in terms of BMI, diastolic blood pressures (DBP), total
cholesterol, LDL cholesterol, HDL cholesterol, triglyceride levels, homoeco-
status model assessment of insulin resistance (HOMA-IR) and free androgen
index. Waist to hip ratio (WHR) and systolic blood pressures (SBP) were
significantly higher in the PCOS group compared with controls. Of the 110
PCOS subjects, 32 were diagnosed as MetS+. There was no statistically sig-
ificant difference between the Met S+ and MetS- groups in terms of age,
BMI, LDL cholesterol and total cholesterol levels. WHR, SBP, DBP,
HOMA-IR, triglyceride and podocalyxin levels were significantly higher in the
MetS+ group compared with the MetS- one (29.16±8.43 ng/ml vs
9.70±8.43 ng/ml, respectively; p<0.001).
CONCLUSIONS: Women with PCOS have significantly higher podoca-
lyxin levels than controls. In addition, podocalyxin levels were significantly
higher in the MetS+ group compared to the MetS- one. Podocalyxin may be
a promising biomarker in women with PCOS.

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early-onset preeclampsia and may represent a novel marker of maternal
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late with carotid intima media thickness, implicating its role as a novel

P-22 Tuesday, October 9, 2018 6:30 AM
TELOMERE LENGTH AND TELOMERASE ACTIVITY IN
REPRODUCTIVE CELLS OF WOMEN WITH POLY-
CYSTIC OVARY SYNDROME. D. C. Pedroso, C. L. Miranda-
Furtado, M. C. Picinato, V. P. Santana, B. A. Santana, R. N. Pimentel,
R. L. Keefe, R. T. Calado, R. A. Ferriani, R. M. Reis. Reproductive
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Ribeirao Preto, Brazil; *Internal Medicine, Ribeirao Preto School of Medi-
cine, University of Sao Paulo, Ribeirao Preto, Brazil; †Gynecology and Ob-
stetrics, NYU Langone Medical Center, New York, Saint Barthelmy.

OBJECTIVE: Infertility is commonly observed in women with polycystic
ovary syndrome (PCOS) and these women there is often a low oocyte quality.
Telomeres and telomerase activity play a key role in the maintenance of
genomic stability and are considered important markers of cell viability,
and may be indicative of oocyte quality. Thus, the aim of the present study
was to evaluate telomere length and telomerase activity in the immature oo-
cytes and cumulus cells of women with PCOS.

MATERIALS AND METHODS: A total of 110 volunteers were recruited,
43 women with PCOS and 67 controls, from September 2015 to June 2017.
Age, body mass index (BMI), luteinizing hormone (LH), follicle stimulating
hormone (FSH), sex hormone binding globulin (SHBG), prolactin, estradiol,
insulin, total testosterone, androstenedione, free androgen index (FAI), ho-
mocysteine and c-reactive protein was evaluated. The telomere length in
the cumulus cells of immature oocytes (CCI), cumulus cells of mature oo-
cytes (CCM), immature oocytes in germinal vesicle stage (GV) and in meta-
phase I (MI), and in leukocytes was measured by the quantitative polymerase
chain reaction (qPCR) method. The telomerase activity of the CCI, CCM,
GV and MI oocytes were evaluated by the TRAPeze® XL Kit. The statistical
analysis was determined by the Mann-Whitney test, multiple linear regres-
sion and Spearman’s correlation.

RESULTS: The BMI (p=0.011), LH (p=0.015), estradiol (p=0.004), insulin
(p=0.002), testosterone (p=0.001), androstenedione (p=0.001). FAI
(p=0.001) and c-reactive protein (p=0.003) were greater in the PCOS group.
FSH (p=0.0002) was lower in the PCOS group. Prolactin and homocysteine
did not differ between the groups. The telomere length in the CCI and in the
CCM did not differ between the PCOS and control groups. However, in the
leukocytes, the telomere length was smaller in the PCOS group (p=0.02).
Telomerase activity in the CCI and the CCM was higher in the PCOS group in
relation to the control group (p<0.003), as well as the telomerase activity in
the CCM (p=0.02). The telomere length and telomerase activity in the GV and
MI oocytes did not differ between the groups. There was a positive correla-
tion of the telomere length between leukocytes, CCI and CCM in both groups.
CONCLUSIONS: The data suggest that PCOS does not affect telomere length in CCI and CCM, only in the leukocytes. However, increased telomerase activity in CCI and CCM may be necessary to maintain telomere length at reproductive level in women with PCOS.

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ASSOCIATION BETWEEN POLYCYSTIC OVARY SYNDROME AND THE POLYMORPHISMS OF ARYL HYDROCARBON RECEPTOR REPRESSOR, GLUTATHIONE-S-TRANSFERASE T1, AND GLUTATHIONE-S-TRANSFERASE M1 GENES. Y. Choi, a Y. Chung, b J. Kim, a M. Hong, c S. Chae, c K. Hwang, a S. Yoon. 1Department of Obstetrics and Gynecology; The Institute of Reproductive Medicine and Population, Seoul National University College of Medicine, Seoul, Korea, Republic of; 2Department of Obstetrics and Gynecology, National Cancer Center, Goyang-si, Gyeonggi-do, Korea, Republic of; 3Department of Obstetrics and Gynecology, Healthcare System Gangnam Center, Seoul National University Hospital, Seoul, Korea, Republic of; 4Department of Obstetrics and Gynecology, Maria Fertility Hospital, Seoul, Korea, Republic of; 5Department of Obstetrics and Gynecology, Seoul Metropolitan Government- Seoul National University (SMG-SNU) Boramae Medical Center, Seoul, Korea, Republic of; 6Department of Obstetrics and Gynecology, Dongguk University Ilsan Hospital, Goyang-si, Gyeonggi-do, Korea, Republic of.

OBJECTIVE: It is well known that genetic polymorphisms are also involved in the development of polycystic ovary syndrome (PCOS), but currently there is no study about the polymorphism of detoxification enzymes in PCOS patients. We examined whether genetic polymorphisms of aryl hydrocarbon receptor repressor (AhRR), glutathione-S-transferase M1 (GSTM1) and glutathione-S-transferase T1 (GSTT1) are associated with susceptibility to polycystic ovary syndrome.

DESIGN: Case-control study
MATERIALS AND METHODS: DNA samples from 478 patients with PCOS and 376 controls were genotyped for AhRR codon 185 polymorphism (CCC to GCC, Pro to Ala), GSTM1 deletion, and GSTT1 deletion.

RESULTS: There was no significant difference in the genotype distribution of AhRR codon 185 C/G polymorphism between women with PCOS and controls. Also, there was no significant difference in the genotype distribution of GSTM1 or GSTT1 genes between patients with PCOS and controls. However, there was a trend for an association of CG+GG genotypes of GSTM1 (CC and non-CC frequencies were 37.1% and 62.8% for the PCOS group and 43.6% and 56.4% for the controls, respectively, \( P = 0.06 \)). And using the wild-type CC genotypes as the references, the odds ratio (OR) that a woman has PCOS was 1.30 (95% confidence intervals (CIs) 0.99-1.72) for the non-CC genotype.

Analyzing AhRR and GSTT1 together, we found that patients with variant allele genotype combinations have increased risk of PCOS, compared with controls. Using the wild allele genotype combination as the reference, the odds ratios that a woman has PCOS were 1.54 (95% CIs 1.04-2.29) for the non-CC/GSTT1 null mutation combination (\( P = 0.03 \)). Also, analyzing GSTT1 and GSTT1 together, combined GSTM1/GSTT1 null genotypes were associated with the presence of PCOS (\( P = 0.016, OR=1.48, 95\% \text{CIs}=1.08-2.04 \)).

CONCLUSIONS: The polymorphisms of AhRR, GSTM1 and GSTT1 genes are associated with the development of PCOS.

Supported by: a grant from the Seoul National University Hospital Research Fund (04-2017-0370).

P-24 Tuesday, October 9, 2018 6:30 AM
ROLE OF SENP3 IN THE AUTOPHAGY OF GRANULOSA CELLS IN POLYCYSTIC OVARY SYNDROME. X. Zeng W. Chai. Department of Assisted Reproduction, Shanghai Ninth People’s Hospital, Shanghai, China.

OBJECTIVE: Studies have found that autophagy is activated in granulosa cells (GCs) in polycystic ovary syndrome (PCOS), but regulatory mechanism of this phenomenon has not been reported. Post-translational SUMOylation and de-SUMOylation are newly discovered regulatory mechanisms of autophagy, and under oxidative stress status, SUMO-specific protease SENP3 mediates de-SUMOylation and plays a key role. Therefore, the aim of this study was to investigate the role of SENP3 in the autophagy of GCs in PCOS.

DESIGN: Basic science project
MATERIALS AND METHODS: Patients treated by IVF/ICSI with the same controlled ovarian stimulation protocol were divided into two groups between January 2015 to January 2016. Group A included 75 PCOS -factor infertile patients and group B included 75 male-factor infertile patients. GCs were isolated from the follicle fluid discarded after oocyte retrieval in the process of IVF/ICSI. Before and after transflocation of SENP3 expression vector and small interfering RNA (siRNA) in both groups, western blotting and quantitative PCR analysis were used to detect the SENP3 and LC3-II levels, quantitation of autophagosomes was observed with transmission electron microscopy (TEM), and the accumulation of microtubule-associated protein light chain 3 (LC3)-II and ubiquitin-binding protein p62 were measured for examining autophagic flux.

RESULTS: In group A, expression of SENP3, LC3-II and mRNA levels, as well as the amount of autophagosomes were higher than group B. After SENP3 overexpression, siRNA and mRNA levels increased while p62 decreased. On the contrary, LC3-II declined after the transfection of siRNA.

CONCLUSIONS: SENP3 and cell autophagy may play a role in PCOS and increased SENP3 level is relevant to the activation of autophagy of GCs.

References:

Supported by: None.

P-25 Tuesday, October 9, 2018 6:30 AM
THE INSULIN SIGNALING PATHWAY IS DYSREGULATED IN CUMULUS CELLS FROM OBESE, INFERTILE WOMEN WITH POLYCYSTIC OVARIAN SYNDROME WITH AN ABSENCE OF CLINICAL INSULIN RESISTANCE. L.C. Cherrin,a A. R. Loreznos,a T. C. Bonetti,a P. C. Serafini,a E. L. Motta,a,c 1Clinical Medicine, Huntington Medicina Reprodutiva, São Paulo, Brazil; 2Department of Gynecology, Federal University of São Paulo, São Paulo, Brazil; 3Department of Gynecology, Santo Amaro University - UNISA, São Paulo, Brazil; 4Scientific Coordinator, Huntington Medicina Reprodutiva, São Paulo, Brazil; 5Clinical Director, Huntington Medicina Reprodutiva, São Paulo, Brazil; 6Department of Gynecology and Obstetrics, University of São Paulo, São Paulo, Brazil.

OBJECTIVE: The aim of the present study was to evaluate granulosa cumulus cell gene expression in the insulin signaling pathway in polycystic ovary syndrome (PCOS) patients undergoing in vitro fertilization (IVF) treatment and to compare the cumulus gene expression between eutrophic and obese women without clinical insulin resistance.

DESIGN: This study was a cross-sectional study.
MATERIALS AND METHODS: This study was conducted at a university-based reproductive medicine center and private reproductive medicine center. Fifteen patients, nine eutrophic patients and six obese patients presenting normal HOMA IR (Homeostasis Model Assessment - Insulin Resistance), participated. Patients underwent oocyte retrieval for IVF. After the procedure, granulosa cumulus cells were removed from the oocytes for RNA extraction. Quantitative PCR array analysis of insulin signaling pathway gene expression was conducted. The results were expressed as fold up- or fold down-expression in obese patients compared to that in eutrophic patients. Any fold-change \( \geq 3 \) or \( \leq 3 \) and any p \( \leq 0.05 \) were considered statistically significant.

RESULTS: There were 11 genes that were overexpressed in obese compared to those in eutrophic women. BCL2 L1, BRAF, CBL, DOK1, FBP1, FRS2, GAB1, MTO1, PKC2, RPS6KA1 and SORBS1, that had a fold change \( \geq 3 \) or \( \leq 3 \) and p \( \leq 0.05 \) were consid-

CONCLUSIONS: In the obese group, the overexpressed genes are mainly responsible for the proliferation and differentiation of cumulus cells during oocyte maturation, insulin resistance, apoptosis regulation, and glucose metabolism during early embryogenesis, suggesting that in the follicular environment, insulin resistance is present even in the absence of clinical signs.
bjective: PCOS is a common, complex disease, with severe long term sequelae such as ovulatory infertility, endometrial carcinoma, heart attack and stroke. Despite its public health importance, PCOS is inconsistently diagnosed due to both its clinical heterogeneity and the use of multiple diagnostic definitions. An innovative approach to identify PCOS cases is to repurpose data routinely collected into the EMR, using the standardized International Classification of Diseases, Ninth and Tenth Revision (ICD-9 and ICD-10) coding system. The present study aimed to validate the ICD-9 and ICD-10 codes for PCOS and associated diagnostic features in order to develop an algorithm that accurately identifies PCOS cases.

Design: Retrospective chart review study.

Materials and methods: Women aged 18-40 years old, seen at the clinics of Northwestern Memorial Hospital between 01/01/2011-01/01/2016, were identified from the Northwestern Medical Enterprise Data Warehouse (n=26,711). We specifically identified patients with ICD codes for the following diagnoses: Polycystic ovary syndrome, menstrual disorders, acne, alopecia, hirsutism, female infertility and androgen excess. An initial algorithm included only the codes for PCOS (n=1,330 women) and subsequent algorithms included one or more features of the syndrome (n=1,408 women). We selected 150 charts (~10%) at random in each algorithm group for manual review (V.C.) using the gold standard of the Rotterdam PCOS definition (2 of 3 of the following: biochemical or clinical hyperandrogenism, irregular menses, polycystic ovary morphology). The positive predictive value (PPV) for each algorithm was then calculated.

Results: 25 of the 150 charts examined in the group with PCOS codes had a confirmed PCOS diagnosis (PPV 17%). In the group with a PCOS code and a code for an individual PCOS feature, the PPVs ranged from 28% to 66%. The highest and lowest PPVs were alopecia and androgen excess, respectively. Requiring a PCOS code and any one or more PCOS features codes had a PPV of 52%.

Conclusions: The accuracy of a primary code alone for predicting PCOS is very low (PPV 17%). It is improved by the use of additional codes specific for PCOS features (PPV 52%) but requires additional refinement to more accurately identify PCOS cases. Future improvements to test include: increasing required count of PCOS features from ≥1 to ≥2, or even higher; natural language processing of the clinical notes; limiting the specialty of treating physician to reproductive or endocrine clinics. If successful, using an EMR-based algorithm to identify large numbers of PCOS cases will facilitate large scale population based studies (e.g. genotype-phenotype associations) to better predict and prevent this syndrome.

Supported by: V.C. was supported by Ruth L. Kirschstein National Research Service Award T32 DK007169 from NIDDK.

P-26 Tuesday, October 9, 2018 6:30 AM

Using the Electronic Medical Record (EMR) for Identifying Women with Polycystic Ovary Syndrome (PCOS). V. Conoscenti, A. N. Kho, G. Hayes. Northwestern University, Chicago, IL.

Objective: PCOS is a common, complex disease, with severe long term sequelae such as ovulatory infertility, endometrial carcinoma, heart attack and stroke. Despite its public health importance, PCOS is inconsistently diagnosed due to both its clinical heterogeneity and the use of multiple diagnostic definitions. An innovative approach to identify PCOS cases is to repurpose data routinely collected into the EMR, using the standardized International Classification of Diseases, Ninth and Tenth Revision (ICD-9 and ICD-10) coding system. The present study aimed to validate the ICD-9 and ICD-10 codes for PCOS and associated diagnostic features in order to develop an algorithm that accurately identifies PCOS cases.

Design: Retrospective chart review study.

Materials and methods: Women aged 18-40 years old, seen at the clinics of Northwestern Memorial Hospital between 01/01/2011-01/01/2016, were identified from the Northwestern Medical Enterprise Data Warehouse (n=26,711). We specifically identified patients with ICD codes for the following diagnoses: Polycystic ovary syndrome, menstrual disorders, acne, alopecia, hirsutism, female infertility and androgen excess. An initial algorithm included only the codes for PCOS (n=1,330 women) and subsequent algorithms included one or more features of the syndrome (n=1,408 women). We selected 150 charts (~10%) at random in each algorithm group for manual review (V.C.) using the gold standard of the Rotterdam PCOS definition (2 of 3 of the following: biochemical or clinical hyperandrogenism, irregular menses, polycystic ovary morphology). The positive predictive value (PPV) for each algorithm was then calculated.

Results: 25 of the 150 charts examined in the group with PCOS codes had a confirmed PCOS diagnosis (PPV 17%). In the group with a PCOS code and a code for an individual PCOS feature, the PPVs ranged from 28% to 66%. The highest and lowest PPVs were alopecia and androgen excess, respectively. Requiring a PCOS code and any one or more PCOS features codes had a PPV of 52%.

Conclusions: The accuracy of a primary code alone for predicting PCOS is very low (PPV 17%). It is improved by the use of additional codes specific for PCOS features (PPV 52%) but requires additional refinement to more accurately identify PCOS cases. Future improvements to test include: increasing required count of PCOS features from ≥1 to ≥2, or even higher; natural language processing of the clinical notes; limiting the specialty of treating physician to reproductive or endocrine clinics. If successful, using an EMR-based algorithm to identify large numbers of PCOS cases will facilitate large scale population based studies (e.g. genotype-phenotype associations) to better predict and prevent this syndrome.

Supported by: Authors are employees of, and study funded by: SPD Development Company Ltd.

Obesity and Metabolism

P-28 Tuesday, October 9, 2018 6:30 AM


Objective: To evaluated the effect of female body mass index (BMI) on IVF/ICSI pregnancy outcomes in a large population

Design: Prospective cohort

Materials and methods: A total of 3740 cycles of couples who underwent IVF/ICSI treatment and fresh embryo transfer were included. Only one cycle per couple was considered. Exclusion criteria included abnormal karyotype, uterine defects, evidence of hydrosalpinx, infections, endocrine problems, coagulation defects or thrombophilia and autoimmune defects. Couples were stratified into four groups by female BMI: <18.5 kg/m² (underweight); 18.5-24.9 kg/m² (normal weight); 25-29.9 kg/m² (overweight); ≥30 kg/m² (obesity). Clinical pregnancy, miscarriage and live birth rates were the primary outcomes analysed. Variables such as age, duration/type of infertility, previous embryo transfers, etiology, endometrial thickness, type of ovarian stimulation, and number/quality/development stage of embryo transferred were included as potential confounding factors. For group comparisons, the t-test and chi-square test were used. Logistic regression analyses were performed to evaluate the associations between BMI and the probabilities of clinical pregnancy (CP), miscarriage and live birth (LB). Normal-weight patients were considered the reference group.

Results: Overall prevalence of PCOS in a population of women seeking to conceive naturally was 16.4%. There was a slight decline in self-reported PCOS with age; 19.1% for age 18-24, 16.6% for age 25-34, 12.3% for age 35-40, 9.9% for age 41+. There was a striking increase in prevalence with length of time trying to conceive (table).CONCLUSIONS: Although it is unsurprising that women with PCOS would take longer to conceive, it was saddening to see that many women with PCOS were still trying to conceive naturally after 1, or even 3 years without success. It indicates that these women need more support to understand and manage their condition.

Relationship between PCOS prevalence with time trying to conceive

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<th>Length of time trying to conceive</th>
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<th>% reporting PCOS</th>
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<tr>
<td>Not yet</td>
<td>878</td>
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<tr>
<td>&gt;3 years</td>
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</tbody>
</table>

Supported by: Authors are employees of, and study funded by: SPD Development Company Ltd.

Obesity and Metabolism

P-27 Tuesday, October 9, 2018 6:30 AM

Prevalence of PCOS Amongst Women Seeking to Conceive. S. Johnson, S. P. Bond, S. J. Bench-Capon. *SPD Development Company Ltd, Bedford, United Kingdom; **Clinical, Clearblue, Bedford, United Kingdom; ***SPD Swiss Precision Diagnostics GmbH, Bedford, United Kingdom.

Objective: Polycystic ovarian syndrome (PCOS) is a relatively common condition associated with infertility, but most women can be treated successfully to achieve pregnancy. This analysis examined the prevalence of PCOS in women seeking to conceive naturally.

Design: Women were invited to complete a screening survey in order to enrol in a large, UK based, seeking to conceive study (NCT03424590). Social media platforms and websites popular with women seeking to conceive were used to recruit women aged 18-40 who were trying to conceive naturally, which collected basic demographics and also asked whether the applicant had been diagnosed with PCOS.

Materials and methods: Of 11788 surveys completed between January 2 2018 and May 2 2018, 11487 indicated whether they had PCOS or not.

Results: Overall prevalence of PCOS in a population of women seeking to conceive naturally was 16.4%. There was a slight decline in self-reported PCOS with age; 19.1% for age 18-24, 16.6% for age 25-34, 12.3% for age 35-40, 9.9% for age 41+. There was a striking increase in prevalence with length of time trying to conceive (table).CONCLUSIONS: Although it is unsurprising that women with PCOS would take longer to conceive, it was saddening to see that many women with PCOS were still trying to conceive naturally after 1, or even 3 years without success. It indicates that these women need more support to understand and manage their condition.
TABLE 1. Results

<table>
<thead>
<tr>
<th>GROUP COMPARISONS</th>
<th>Total</th>
<th>Underweight</th>
<th>Normal Weight</th>
<th>Overweight</th>
<th>Obesity</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical pregnancy rate</td>
<td>29.2%</td>
<td>26.6%</td>
<td>31.0%^a,b</td>
<td>27.3%^a</td>
<td>23.1%^b</td>
<td>&lt;0.04;0.001</td>
</tr>
<tr>
<td>Miscarriage rate</td>
<td>21.3%</td>
<td>40%^a</td>
<td>17.8%^a,b,c</td>
<td>25.9%^b</td>
<td>30.8%^a</td>
<td>&lt;0.01;0.007;0.004</td>
</tr>
<tr>
<td>Live birth rate</td>
<td>22.4%</td>
<td>13.8%^a</td>
<td>25.0%^a,b,c</td>
<td>19.8%^b</td>
<td>15.5%^a</td>
<td>&lt;0.01;0.002;&lt;0.0001</td>
</tr>
</tbody>
</table>

LOGISTIC REGRESSION ANALYSES

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical pregnancy</td>
<td>1(Ref.)</td>
<td>——</td>
</tr>
<tr>
<td>-Normal Weight</td>
<td>0.78</td>
<td>0.48-1.27</td>
</tr>
<tr>
<td>-Underweight</td>
<td>0.83</td>
<td>0.70-0.98</td>
</tr>
<tr>
<td>-Obesity</td>
<td>0.68</td>
<td>0.52-0.87</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>1(Ref.)</td>
<td>——</td>
</tr>
<tr>
<td>-Normal Weight</td>
<td>3.7</td>
<td>1.56-8.82</td>
</tr>
<tr>
<td>-Underweight</td>
<td>1.7</td>
<td>1.18-2.38</td>
</tr>
<tr>
<td>-Obesity</td>
<td>2.3</td>
<td>1.40-3.84</td>
</tr>
<tr>
<td>Live birth</td>
<td>1(Ref.)</td>
<td>——</td>
</tr>
<tr>
<td>-Normal Weight</td>
<td>0.44</td>
<td>0.24-0.81</td>
</tr>
<tr>
<td>-Underweight</td>
<td>0.73</td>
<td>0.60-0.88</td>
</tr>
<tr>
<td>-Obesity</td>
<td>0.55</td>
<td>0.41-0.74</td>
</tr>
</tbody>
</table>

CONCLUSIONS: Higher BMI (overweight and obesity) and lower BMI (underweight) in women have a detrimental effect on ART outcomes. Both high BMI and low female BMI are associated with decreased clinical pregnancy and live birth rates and increased miscarriage rate.

P-29 Tuesday, October 9, 2018 6:30 AM

THE INCREASED COST OF SUCCESS OF IVF IN OBESE WOMEN. J. Jackman, C. Chatzicharalampous, M. Saketo, J. Stelling, L. Sung, R. Robertazzi, M. Bray. The Brooklyn Hospital Center, Brooklyn, NY; Obstetrics and Gynecology, Wayne State University, Detroit, MI; Reproductive Specialists of New York, Mineola, NY; SUNY Stony Brook, Commack, NY; Reproductive Specialists of New York, Mineola, NY.

OBJECTIVE: In our program where obese women have similar live birth rates (LBR) to non-obese women, we sought to determine which cycle-related variables helped them to achieve this outcome equivalence.

DESIGN: We retrospectively analyzed a database of 778 first or second autologous, fresh IVF cycles in women under age 38 who did not have polycystic ovary syndrome (PCOS) for gonadotropin dosage and days of stimulation who were dichotomized as: Controls: 593 with BMI below 30 (18.5-29.9 kg/m.2) and Obese: 185 with BMI 30+ (30.0-63.4).

MATERIALS AND METHODS: Women under age 38 who underwent fresh IVF, day 5 blastocyst transfer of fewer than 3 embryos from 2010 to 2015, with less than two prior IVF retrievals, were included in the study. The primary outcome was the amount of Gn needed per mature egg, with secondary outcomes of CPR and LBR. We compared age, FSH, AMH, diagnoses, days of stimulation, total Gn dosage, number oocytes retrieved, number of mature follicles and number of embryos transferred. Exclusions: PCOS, age above 37, BMI below 18.5, more than one prior IVF cycle. We calculated dose of Gn per mature egg, clinical pregnancy rate (CPR), and LBR.

RESULTS: Women in the two groups did not differ in mean age and had comparable CPR and LBR. However, the lower BMI group had significantly less favorable FSH and AMH levels. Yet the obese women required significantly higher doses of Gn despite only slightly longer stimulation protocols. This resulted in a higher Gn/Mature Egg ratio. There was no difference in the other variables above aside from the obese women having significantly more tubal factor (non-hydro) and more uterine factor.

CONCLUSIONS: Obese women had more favorable FSH and AMH and maintained equivalent CPR and LBR at the expense of higher Gn requirements. The additional 153 IU per mature egg would result in an extra medication cost in excess of $1800 per woman per cycle. In aggregate, the 185 obese women spent $350,000 more for medications than the lower BMI group.

P-30 Tuesday, October 9, 2018 6:30 AM

HUMAN MESENCHYMAL STEM CELL THERAPY OF POLYCYSTIC OVARY SYNDROME (PCOS) ENHANCES ADIPOGENETIC EXPRESSION IN THE FAT AND PROTECT AGAINST BROWN FAT WHITENING. A. El Andaloussi, N. Ismail, A. Al-Hendy. University of Illinois at Chicago, Chicago, IL; Pathology, Professor, Chicago, IL.

OBJECTIVE: PCOS is associated with low level of serum adiponectin and brown fat whitening. Exogenous adiponectin treatment of PCOS mice decreases circulating androgen and glucose levels, and reduce body mass. Recently, the key role of ovarian chronic inflammation in pathogenesis of PCOS is more realized. This inflammation leads to induction of androgen production by theca cells which in turn causes the metabolic and reproductive aberrations of PCOS. The utility of human mesenchymal stem cells (hMSCs) as a potential therapy for PCOS is yet to be verified. Additionally, no previous studies have evaluated associations between adiponectin and brown fat activation in PCOS.

DESIGN: Preclinical study of PCOS treatment with hMSC.

MATERIALS AND METHODS: The PCOS animal model was developed in presexual (3 weeks old) C57BL6 female mice by implanting letrozole (LTZ) pellet subcutaneously in the neck area (5 mg/pellet, 90 days release). The control group received placebo pellet. Our study was composed of three groups: 1- Placebo control, 2- LTZ and 3- LTZ treated with hMSCs. Human References:

bone marrow MSCs were collected from a healthy female donor by flow cy-
tometry using standard surface markers. After 5 weeks of LTZ treatment, hMSCs (25x10^5 cell per ovary) were injected into the ovaries using limited laparotomy. The control mice received sham surgery and were injected with PBS model. In this study, we investigated the impact of hMSC implanted into ovaries on adiponectin expression level in white and brown fat, and fat homeostasis in PCOS induced by LTZ. Statistical analysis was done using paired t-test. Values were considered statistically significant when P was less than 0.05 (p<0.05).

RESULTS: The Hematoxylin and eosin stain data of brown fat was marked by the store of lipid droplets in LTZ group compared to LTZ treated with hMSC group due to metabolic rearrangement and significant decrease in the energy expenditure rescued by hMSC. This data was supported by PD-L1 and UCP-1 BAT immunohistochemistry staining. Our results also show that LTZ exposure alters brown adipose tissue (BAT) gene expression PGC-1α, UCP-1 and Cidea-1, including adiponectin. However, the treatment with hMSC induces significantly the expression level of adiponectin mRNA in the white gonadal fat (0.046 ± 0.0002) compared to the matched control (0.035 ± 0.0003) and in the BAT (treated group: 3.2 ± 1.3; control: 0.452057 ± 0) (P < 0.005). In addition, leptin mRNA expression was significantly induced in BAT by LTZ (0.071452 ± 0.005) compared to treated group with hMSC (0.011 ± 0.001) (P < 0.05). In addition, hMSC-adiponectin induced was able to regulate the plasticity of resident beige fat cells in gonadal white fat, into brown fat cell. This discovery represent new original model to dissect the mystery of this phenomena using PCOS model.  

CONCLUSIONS: Stem cell therapy might potentially be a novel tool for effective treatment of PCOS-related morbidities.  

Supported by: UIC start-up fund

Tuesday, October 9, 2018 6:30 AM

OVARIAN RAGE EXPRESSION CHANGES WITH FOLLICULAR DEVELOPMENT AND SUPEROVULATION. M. Goldsammler, Z. Merhi,\textsuperscript{a} K. Thornton, M. J. Charron, E. Buyuk.\textsuperscript{b} \textsuperscript{a}Albert Einstein College of Medicine/Montefiore Institute for Reproductive Medicine and Health, Bronx, NY; \textsuperscript{b}New York University School of Medicine, New York, NY; \textsuperscript{c}Albert Einstein College of Medicine, Bronx, NY.  

OBJECTIVE: The pro-inflammatory molecules Advanced Glycation End products (AGEs), formed endogenously or absorbed endogenously through unhealthy diets, bind to their cell membrane receptor RAGE leading to systemic inflammation (1,2). Elevated AGEs and up-regulation of ovarian RAGE have been implicated in ovarian dysfunction. Granulosa cell (GC) RAGE activation in vitro causes alterations in folliculogenesis and steroidogenesis (3,4); however, localization of RAGE expression in the ovary and follicular development and steroidogenic gene expression by granulosa cells: an effect partially mediated by superovulation on ovarian RAGE expression.  

DESIGN: Laboratory-based research in a university setting  

MATERIALS AND METHODS: In the 1st experiment, the ovaries of 18- 20 weeks old C57Bl/6J female mice (n=10) were harvested and subjected to immunofluorescence for RAGE expression. In the 2nd experiment, mice were sacrificed before (n=5) or after (n=5) superovulation with gonadotropins. Follicles were stratified based on their stage of development: primordial, primary, secondary, preantral, and corpus luteum. RAGE intensity was semi-quantified by a blinded observer. Wilcoxon rank test, Kruskal Wallis and Spearman rank correlation were used for statistical analyses.  

RESULTS: RAGE expression was localized to GCs with minimal expression within theca cells. GC RAGE expression significantly decreased as follicles progressed from early (primordial) to advanced stages (antral) of development with minimal staining in corpora lutea (CL). Oocytes in early stages of folliculogenesis had intense RAGE staining, which was lost by the preantral stage. CL had significantly lower RAGE expression compared to preovulatory follicles (p<0.001). Superovulation caused significantly lower RAGE expression in both primary follicles and CL (p=0.0004 and p<0.001; respectively) compared to no superovulation.  

CONCLUSIONS: RAGE expression declines as follicular development progresses until very minimal expression in CL. These results, along with the localization of RAGE in GCs, may indicate a role for RAGE in early follicular development and steroidogenesis. RAGE downregulation caused by superovulation indicates that RAGE expression is affected by gonadotropins. Understanding the factors that affect ovarian RAGE expression is critical, and the development of RAGE blockers/activators could represent future therapeutic modalities for improving ovarian health and response to gonadotropins in assisted reproductive technologies.  

Supported by:  

References:  
3. C19  

Supported by: ASRM and SRI grants

Tuesday, October 9, 2018 6:30 AM

IMPACT OF BARIATRIC SURGERY ON OVARIAN RESERVE MARKERS AND ITS CORRELATION WITH NUTRITIONAL PARAMETERS AND ADIPOKINES. G. Casals, S. Ventosa, L. Flores, S. Peralta, A. Ibarzabal Olano, F. Torres, G. Casals, D. Manau, J. Vidal. Assisted Reproduction Unit, Hospital Clinic de Barcelona. Univer-
sitat de Barcelona, Barcelona, Spain; Obesity Unit, Hospital Clinic de Bar-
celona, IDIBAPS, Universitat de Barcelona, Barcelona, Spain; Department of Gastrointestinal Surgery, Hospital Clinic de Barcelona, Barcelona, Spain; Medical Statistics Core Facility, Hospital Clinic de Barcelona, Barcelona, Spain; Biochemistry and Molecular Genetics Service, Hospital Clinic de Barcelona, Barcelona, Spain; Obesity Unit, Hospital Clinic de Bar-
celona, IDIBAPS, Universitat de Barcelona, Barcelona, Spain.  

OBJECTIVE: A reduction in anti-Mullerian hormone (AMH) levels after bariatric surgery (BS) has been recently described. This may be related to decreased ovarian reserve, metabolic changes or a lack of precursors for the synthesis of the AMH. This study includes for the first time a simultaneous analysis of reproductive hormones, adipokines, nutritional parameters and ultrasound ovarian reserve markers.  

DESIGN: A prospective cohort study of 20 women followed postopera-
tively for 12 months.  

MATERIALS AND METHODS: Women aged 19-40 years with a mean body mass index (BMI) 43.9 (CI 41.6; 46.1) kg/m2 with indication of BS were studied baseline (BL), 1 month after BS (BS1), 4 months after BS (BS2) and 12 months after BS (BS3). Antropometrical parameters were measured and blood samples were obtained in each point of study to determine: 1) reproductive hormones (AMH, FSH, LH, estradiol, testosterone, SHBG, androstenedione); 2) metabolic parameters (adiponectin, leptin, ghrelin, insulin); 3) nutritional data (vitamins and salts). We also performed a 2D/3D ultrasound to assess the antral follicular count (AFC) and the ovarian volume. Mixed models were used for analysis of longitudinal data using SAS 9.2 software (SAS Institute, Cary, NC, USA).  

RESULTS: The mean AMH level was 3.9 ng/ml (95% CI 2.6;5.2) at BL and decreased significantly 12 months after BS (mean: 2.6 ng/ml, CI 1.3;3.9) (p=0.034). We also observed a nonsignificant decrease in AFC: mean 24.2 at BL (CI 17.9;30.5), mean 16.8 at BS3 (CI 10.5;23.1) (p=0.095). A longitudinal analysis using mixed models revealed the following associations: (a) a change in 10 kg was associated with a change in AMH (95% CI) change of 0.357 (0.074,0.639) ng/ml in AMH, p=0.014; (b) a change in 1 BMI point was associated with an average (95% CI) change of 0.109 (0.035,0.184) ng/ml in AMH, p=0.005; (c) a change in 1 microg/ml adiponectin was associated with an average (95% CI) inverse change of 0.091 (0.009,0.173) ng/ml in AMH, p=0.041.  

CONCLUSIONS: This study confirms the reduction of AMH levels after BS and demonstrates, for the first time, a non-significant tendency in AFC reduction. We also found an association between reproductive and metabolic changes. Our investigation has allowed us to study new parameters related to the origins and clinical effects of AMH reduction after BS.  

Supported by: The authors received an Emilii Letang grant from the Hos-
pital Clinic de Barcelona to support the present research.
BODY MASS INDEX (BMI) IS NOT CORRELATED WITH BLASTULATION RATE. K. Van Heertum,a D. Epstein,b V. R. Libby,b T. Segal,b A. C. Bouchelon,b J. Goldfarb,b R. Weinerman.b Reproductive Endocrinology and Infertility, University Hospitals Fertility Center, Beachwood, OH; cCase Western Reserve University, Beachwood, OH; dOB/GYN, University Hospitals-Case Western Reserve University, Cleveland, OH; eUniversity Hospitals of Cleveland, Beachwood, OH.

OBJECTIVE: To assess the effect of BMI on blastocyst (blast) formation rate.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: All fresh cycles from 4/2014 through 3/2017 in our institution were reviewed. Embryos included resulted from IVF or ICSI and had 2 pro-nuclei on the day following oocyte retrieval. Embryos transferred or frozen prior to day 5 were excluded. Day 2 and 3 morphology was assessed by blastomere number. Blast stage excluded cavitating/early blast. Chi-square and logistic regression were used for analysis. A power analysis found that the sample sizes of this study provided 80% power to detect a 6% difference in blastulation rate with an alpha of 0.05.

RESULTS: A total of 3719 embryos were included in the analysis. The mean BMI, age and AMH in our cohort were 26 kg/m² (SD 5.79), 33 years (SD 4.42), and 4.18 ng/ml (SD 3.63), respectively. An initial chi-square analysis showed no difference in blastulation rate between patients with a BMI of < 30 (48.3%) versus those with a BMI >= 30 (44.3%) (P = 0.07). Logistic regression was then performed, using log transformation of BMI for normalization, and controlling for age, AMH and day 2 and day 3 morphology. While age (P = 0.01), day 2 morphology (P < 0.001) and day 3 morphology (P < 0.001) were significantly correlated with blastulation rate for a given embryo, there was no statistically significant correlation with either AMH (P = 0.24) or BMI (P = 0.26) and blast formation rate. An additional logistic regression was performed assessing blastulation rate per normally fertilized embryo per patient, again controlling for BMI, age, and AMH. Again, the same relationships were seen: no significant correlation was seen between blast formation rate and AMH (P = 0.49) or BMI (P = 0.64), but age continued to show a significant relationship with blastulation rate (P < 0.001).

CONCLUSIONS: Our previous research confirmed that day 2 and day 3 morphology are highly predictive of blastocyst formation rate (1). This study aimed to assess how BMI affects blastulation, specifically, whether early embryo morphology continues to be predictive of blastulation across all BMI’s. We found that BMI did not correlate with blastulation rate when controlling for age, AMH and early embryo morphology. However, day 2 and day 3 morphology continued to be highly predictive of blast formation when controlling for the above factors, including BMI, as did age. These findings may help clinicians in reassuring obese patients that their BMI does not appear to affect the rate of blast formation following normal fertilization.

References:

Variation in placental morphology by BMI category.

<table>
<thead>
<tr>
<th>Placental morphology</th>
<th>Normal weight</th>
<th>Overweight</th>
<th>Obese</th>
<th>P-value</th>
<th>Overweight aOR</th>
<th>Obese aOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomic</td>
<td>236 (50%)</td>
<td>146 (53%)</td>
<td>64 (55%)</td>
<td>0.449</td>
<td>1.20 (0.86, 1.68)</td>
<td>1.05 (0.66, 1.69)</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>60 (13%)</td>
<td>49 (18%)</td>
<td>22 (19%)</td>
<td>0.072</td>
<td>1.45 (0.93, 2.26)</td>
<td>1.69 (0.95, 3.02)</td>
</tr>
<tr>
<td>Infectious</td>
<td>104 (22%)</td>
<td>74 (27%)</td>
<td>27 (23%)</td>
<td>0.283</td>
<td>0.69 (0.48, 1.00)</td>
<td>0.71 (0.41, 1.22)</td>
</tr>
<tr>
<td>Vascular/thrombotic</td>
<td>261 (55%)</td>
<td>150 (55%)</td>
<td>71 (61%)</td>
<td>0.441</td>
<td>1.02 (0.74, 1.40)</td>
<td>1.32 (0.84, 2.05)</td>
</tr>
</tbody>
</table>

OBJECTIVE: Controversy exists regarding if and how BMI impacts anti-mullerian hormone (AMH) levels in women with and without polycystic ovary syndrome (PCOS) (1). An understanding of the BMI-AMH relationship has implications for the clinical interpretation of lab values and could shed light on underlying ovarian physiology. We sought to test the hypotheses: 1) BMI is associated with reduced AMH in PCOS and controls and 2) the reduced AMH seen with increased BMI relates to reduced production of AMH by the follicle unit.

DESIGN: Cohort study

MATERIALS AND METHODS: This is a secondary analysis of women ages 25-40 with PCOS-Rotterdam enrolled in a clinical trial (PPCOSII, placebo and ovulatory community controls in the Ovarian Aging cohort (OVA, n=923). Multivariate linear regression models assessed the relationship between BMI or waist circumference (WC) (predictors) and ovarian
reserve markers (outcomes), including AMH, antil follicle count (AFC) and AMH per follicle, controlling for age and study site. We tested for interactions between cohort (PPCOS vs OVA) and BMI in its effect on AMH. Body surface area (BSA), which unlike BMI is proportional to plasma volume, was added to the models to investigate a potential dilutitive effect of body size on AMH serum concentrations.

RESULTS: In both cohorts, increasing BMI, BSA and WC were associated with reductions in AMH and AMH per follicle, after adjusting for age and study site (Table). In a model controlling for BSA, BMI and WC retained independent negative relationships with AMH (both cohorts) and with AMH:AFC (OVA), while the association of BSA with AMH and AMH:AFC was no longer significant. No statistically significant association between BMI and AFC was observed in either cohort. An interaction between cohort (PCOS vs OVA) and BMI was noted: a 1-km/m² increase in BMI had a greater negative impact on AMH in PCOS (coefficient -0.09, 95% CI -0.16, -0.03, p < 0.01).

CONCLUSIONS: Markers of adiposity, but not body size, are associated with reduced AMH and AMH:AFC suggesting that the observed effect of BMI on AMH is due to an absolute decrease in AMH hormone, rather than hemo-dilution. Markers of adiposity were not associated with reduced AFC, suggesting that the lower AMH seen with increased BMI is due to decreased AMH production by the follicle unit rather than a reduction in follicles. These findings suggest granulosa cells may be sensitive to a toxic effect of adipose tissue and that this effect may be amplified in PCOS ovaries.

References:

Supported by: OVA: R01HD044876; PPCOS: U10 HD27049 (NICHD)

P-36 Tuesday, October 9, 2018 6:30 AM
HEPARIN INDUCED LIPOLYSIS INCREASES CIRCULATING FREE FATTY ACIDS AND MODULATES SERUM GONADOTROPPINS. S. Black, K. Kuhn, K. Jones, A. Bradford, I. Schauer, N. Santoro. University of Colorado School of Medicine, Aurora, CO.

OBJECTIVE: Heparin induces lipoprotein lipase and causes elevation in circulating free fatty acids (FFAs). We have previously shown that a lipid + heparin infusion results in a small increase in FSH in women, compared to a saline control, and that the combination of lipid + heparin infusion with added insulin reduced both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (1). We sought to determine whether a saline + heparin infusion, in the absence of exogenous insulin or insulin, would result in altered gonadotropin secretion or circulating FFAs compared to saline alone.

DESIGN: A comparison study was performed of LH, FSH and FFAs among 19 regularly cycling, normal-weight women (NW) in the early follicular phase of the menstrual cycle, who received a 4-hour infusion of either 0.9% normal saline or saline with heparin.

RESULTS: Compared to saline alone, only mean FSH was significantly increased with heparin infusion p = 0.002. Saline and heparin increased FFAs by 1.5 ± 0.2-fold, whereas women who received saline alone demonstrated a 0.8 ± 0.1 fold change in FFAs (one sided p = 0.045).

CONCLUSIONS: Heparin’s role as an activator of lipoprotein lipase may be sufficient to account for increased FSH secretion, and increases circulating free fatty acids in normal individuals undergoing short-term experimental infusion.


Supported by: Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD); grant number R01 HD 087314 (to NS), University of Colorado School of Medicine Research Track (for SB)

P-37 Tuesday, October 9, 2018 6:30 AM
GUT MICROBIOTA PLAYS A ROLE IN THE DEVELOPMENT OF POLYCYSTIC OVARY SYNDROME AND ITS METABOLIC DISORDERS. Z. Liang, N. Di, L. Li, D. Yang. Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China.

OBJECTIVE: Exploring the associations between PCOS metabolic disorders and its composition of gut microbiota.

DESIGN: We compared the gut microbiota of 20 PCOS patients (lean PCOS individuals, PL, n = 10; overweight/obese PCOS individuals, PO, n = 10) with 20 healthy controls (lean control individuals, CL, n = 10; overweight/obese control individuals, CO, n = 10) by collecting their fecal samples. We compared the metabolic markers between PCOS patients and the controls by collecting their blood samples, hoping to find out metabolites that connect gut microbiota with the development of PCOS and its metabolic disorders.

MATERIALS AND METHODS: 40 women in reproductive stage were recruited at the Sun Yat-Sen Memorial Hospital. Fecal samples were stored at -80°C within 20 minutes of collection for 16S rRNA Amplicon Sequencing. After an overnight fast, all participants underwent an oral glucose tolerance test. Blood was sampled frequently for measurement of blood glucose and plasma insulin, blood cholesterol, triglyceride, HDL-C and LDL-C. Plasma inflammatory factors such as hsCRP, LBP, TNF-α, IL-1, IL-6, IL-8 and basal hormone such as FSH, LH, PRL, estradiol and total testosterone were also detected. Statistical analyses were performed using IBM SPSS statistics 20.0 for clinical data. QIIME(v1.8.0) and Metastats for gut microbiota sequence data.

RESULTS: Women with PCOS had higher levels of fasting insulin levels as well as higher homeostasis model assessment of insulin resistance (HOMA-IR) values and triglyceride level. Inflammatory biomarkers such as hsCRP, LBP, IL-6 and IL-8 all showed a higher trend in PCOS group, but the difference was not statistically significant. Metabolic disorders in PCOS were associated with reduced biodiversity in gut microbiota. Women with PCOS had less OTUs number compared to healthy
OBJECTIVE: Despite well publicized campaigns in the UK encouraging women to take folic acid supple-ments prior to conceiving, and the trend of improved pregnancy outcomes, the proportion of women taking folic acid has remained stable over the years. The objective of the study was to assess the current trend of folic acid usage and to determine if age and other demographic factors influence the usage of folic acid.

METHODS: A large scale online survey was carried out, recruiting women who were planning to try for conception. The survey was advertised and encouraged on social media platforms and websites popular with women seeking to conceive. The adverts allowed women to click through to the screening survey, which invited women aged 18-40 who were wishing to become pregnant to apply. The adverts were placed on social media and online platforms popular with younger conceivers. A total of 2018 women consented to participate in the study.

RESULTS: Only 58.9% of women interested in participating in a seeking to conceive study were taking folic acid. Prevalence of usage varied with age; 46.7% for 18-24 (n=22), 45.1% for 25-34 (n=6913), 68.7% for 35-40 (n=1833), 58.9% for >40 (n=72). Women who were planning to begin trying in the next couple of months were lowest users of folic acid (36.2%, n=878), but for those women actively trying, there was no relationship between length of time trying and folic acid use; 61.7% (n=2453) for <3 months, 63.3% (n=2595) for 3-6 months, 59.2% (n=1879) for 7-12 months, 59.6% (n=1890) for 1-2 years, 62.5% (n=915) for 2-3 years and 54.7% (n=877) for >3 years.

CONCLUSIONS: Despite well publicized campaigns in the UK encouraging women to take folic acid pre-conception, over 40% of women seeking to conceive are not taking supplements. This is especially true of younger women, suggesting that different media may be required to get the message to younger conceivers.

Supported by: Authors are employees of, and study funded by: SPD Development Company Ltd.

P-39 Tuesday, October 9, 2018 6:30 AM

SUGAR-SWEETENED BEVERAGE CONSUMPTION AND INFERTILITY AMONG PARTICIPANTS OF THE MEXICAN TEACHERS’ COHORT. M. Arvizu Boy,a A. Cortes,b M. Lajous-Loazaa, J. E. Chavarro,c,d Nutrition, Doctoral Student, Boston, MA; aCenter for Research on Population Health, Cuernavaca, Mexico; bEpidemiology and Global Health, Center for Research on Population Health, Cuernavaca, Mexico; cHarvard T.H. Chan School of Public Health, Boston, MA.

OBJECTIVE: To evaluate whether consumption of sugar-sweetened beverage is related to risk of infertility among Mexican women.

DESIGN: Nested case-control study

MATERIALS AND METHODS: Between 2006 and 2008, a total of 115,346 Mexican teachers employed by the Public Sector, were enrolled in the Mexican Teachers’ Cohort (MTC), an ongoing prospective cohort study. Participants have completed lifestyle and dietary surveys in 4-year cycles thereafter. For the present study, we followed 11,317 pre-menopausal women in a stable relationship, aged <40 years, who attempted a pregnancy or became pregnant between 2008 and 2011. Infertility was defined as a pregnancy attempt lasting 12+ months. Beverage consumption was assessed in 2008 with a food frequency questionnaire (FFQ) that included coffee, tea, sodas, salas, diet sodas, juices, atole and fruit-infused waters in servings/day (8 fl. Oz. = 1 serving). The relative risk of infertility in relation to beverage intake was estimated using log-binomial regression. Multivariable-adjusted models included terms for age, healthcare coverage, physical activity, smoking status, parity, history of diabetes, use of birth control in 2008, indigenous heritage and summary measures of quality of diet.

RESULTS: We identified 1,156 (10%) incident cases of infertility among 11,317 women whose mean (SD) age was 35(3) years. The mean intake of total sugar-sweetened beverages (sodas, coffee, tea, atole, juice and fruit waters) was 3.9(3.1) servings/day. The relative risk (RR, 95%CI) of infertility comparing the highest category of intake with the lowest, for total sugar-sweetened beverages was RR 1.11 (95%CI, 0.96,1.29). When specific beverages (sodas, colas, diet sodas and coffee/tea) were separately examined, we found that women in the highest category of intake of coffee and tea consumption (≥ 1.2 servings/day) had a 18% (95% CI: 4%-35%) higher risk of infertility than women in the lowest category of intake (< 0.07 servings/day; p-linear trend =0.001) and women with highest consumption of sodas (sodas and colas) had a 10% (95% CI: 4%-75%) higher risk of infertility than women in the lowest category. We did not find any significant association between risk of developing infertility and categories of fruit-infused water, juice or atole consumption.

CONCLUSIONS: The consumption of sugar-sweetened beverages is associated to higher risk of infertility among Mexican women. Women that were highest consumers of either coffee/tea or sodas, yielded increased risk of developing infertility, with coffee and tea having the strongest association. Nevertheless, when sodas and coffee/tea consumption are combined, pregnancy attempt lasting 12+ months appears to be lower among these group of women. Further studies to confirm the results from our study are warranted.

P-40 Tuesday, October 9, 2018 6:30 AM

THE ASSOCIATION OF DIETARY ANTIOXIDANTS AND ANTRAL FOLLICLE COUNTS AMONG WOMEN UNDERGOING INFERTILITY TREATMENTS. I. Souter,a M. Li,b M. Arvizu Boy,a,y Chiu,c L. Miguez-Alarcón,d P. L. Williams,e R. Hauser,e J. E. Chavarro,f Nutrition, Doctoral Student, Boston, MA; aCenter for Research on Population Health, Cuernavaca, Mexico; bHarvard T.H. Chan School of Public Health, Boston, MA; cDepartments of Biostatistics and Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA.

OBJECTIVE: To examine the relation between dietary intake of antioxidants and antral follicle count (AFC).

DESIGN: Prospective cohort study with single AFC measure per participant.

MATERIALS AND METHODS: AFCs were determined via ultrasound among 344 women undergoing infertility treatments at an academic institution and participating in an ongoing study on environment and reproductive health outcomes (EARTH study). Antioxidant intakes (Vitamins: A, C, and E; Carotenoids: a-carotene, b-carotene, lycopene, lutein and zeaxanthin) from food and supplements were assessed within one year of ovarian reserve evaluation using a validated food frequency questionnaire (FFQ).

We used Poisson regression models to evaluate the relation between antioxidant intake (dietary and supplemental) and AFC while adjusting for the
other antioxidants, age, body mass index (BMI), smoking, total calorie intake, dietary patterns (Western and Prudent), intakes of folate and vitamin B12, and treatment protocol.

RESULTS: Mean (SD) age and BMI were 35.0 (4.2) years and 24.3 (4.6) kg/m². Vitamin A, C, and E significantly correlated with carotenoid, folate, and B12 intakes, positively associated with the Western and inversely related to the Prudent diet patterns. Intakes of vitamins A, C, and E were not associated with AFC.

There was a suggestion of a positive association between β-carotene from supplements and AFC (p, trend: 0.09). Adjusted mean (95% CI) AFC in the top quartile (Q4 > 1800 mcg/day) was significantly higher than that in the bottom quartile of intake (Q1 < 150.0 mcg/day): (14.1 (13.1-15.1) vs. 12.4 (11.5-13.3), for Q4 vs. Q1, respectively, p = 0.03). Intake of β-carotene from food sources was unrelated to AFC.

A similarly suggestive positive association between lycopene intake and AFCs was noted, albeit weaker in magnitude (Q4 > 5870.5 mg/day) vs. Q1 < 3017 mg/day); 13.7 (12.9-14.6) vs. 13.1 (12.3-13.9), respectively, p, trend = 0.03. Intake of other carotenoids was unrelated to AFC.

CONCLUSIONS: We found no association between intakes of vitamins A, C, and E and AFCs. We found suggestive positive associations between β-carotene from supplements and total lycopene intake with AFCs, suggestive of a possible beneficial effect of certain antioxidants on ovarian reserve.

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Supported by: National Institutes of Health: P30ES000002, R01ES009718, R01ES022955 and P30DK046200.

P-41 Tuesday, October 9, 2018 6:30 AM
Department of Obstetrics and Gynecology, Uniformed Services University of the Health Sciences (USUHS), Bethesda, MD; Division of Intramural Population Health Research, NICHD, NIH, Bethesda, MD; University of Utah, Salt Lake City, UT; Program in Reproductive Endocrinology and Gynecology, NICHD, NIH, Bethesda, MD.

OBJECTIVE: Prior studies demonstrate that obese women have a lower ovarian reserve than normal weight women which is reflected by their lower serum AMH. The mechanism by which this occurs has not yet been elucidated. Additionally, studies have found that increased adipokines produced in the adipose tissue, such as leptin, can directly inhibit ovarian function. Specifically, when cumulus granulosa cells were exposed to leptin vs control, leptin treatment suppressed AMH, follicle stimulating hormone, and progesterone, caloric intake, and physical activity.

RESULTS: Mean (SD) age and BMI were 35.0 (4.2) years and 24.3 (4.6) kg/m². There was a suggestion of a positive association between leptin and serum AMH in healthy women, providing evidence of a potential mechanism for the association between obesity and ovarian reserve. Supported by: Intramural Research Program, NICHD, NIH

P-42 Tuesday, October 9, 2018 6:30 AM
Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai West, New York, NY; Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY; Reproductive Medicine Associates of New York, New York, NY.

OBJECTIVE: Obesity is a worldwide epidemiologic and negatively impacts reproductive health. Studies demonstrate conflicting results on the effect of obesity on in vitro fertilization (IVF) outcomes with potentially deleterious effects on oocyte quality and endometrial receptivity. Oocyte donation (OD) cycles provide an opportunity to isolate the effect of increased body mass index (BMI) on the endometrium. The aim of the study was to determine if overweight/obese patients had similar pregnancy outcomes to normal weight patients after a frozen single blastocyst transfer (FET) with donated oocytes.

DESIGN: Retrospective

MATERIALS AND METHODS: Oocyte recipients who underwent single blastocyst FET between 2004-2018 were included. Patients were categorized by BMI (Normal 18.5-24.99; Overweight 25-29.99; Obese ≥ 30.0 kg/m²). Underweight patients (< 18.49 kg/m²) and those with an endometrial thickness < 7 mm at transfer were excluded. Clinical pregnancy (CP) was defined as sonographic evidence of a gestational sac. Data were analyzed using an ANOVA, Chi Squared/Fisher’s Exact Test and multivariate logistic regression.

RESULTS: A total of 564 patients were included. Obese patients were older than normal weight or overweight patients (45.4 ± 3.9, p = 0.0003).
Patients in all BMI groups had similar gravidity, parity, and cycle characteristics, including endometrial thickness, percent of embryos biopsied for pre-implantation genetic testing for aneuploidy (PGT-A), day of embryo biopsy, and blastocyst morphology. CP rate did not differ among BMI groups. There were also no differences in OP/LB, EPL, and CPL rates (p = 0.88) among BMI groups, before and after adjusting for confounders.

CONCLUSIONS: While the maternal metabolic environment adversely affects IVF outcomes in obese women, the mechanism of action is not fully understood. Following transfer of a single, frozen blastocyst in OD cycles, overweight and obese patients had similar CP, OP/LB, EPL, and CPL rates compared to controls. This study is the first to evaluate the impact of obesity on implantation, independent of oocyte quality, and confirms that maternal obesity exhibits minimal effect on the endometrium. Future studies of the endometrial transcriptome and metabolome may improve our understanding of the impact of nutritional status and obesity on endometrial receptivity.

**P-43 Tuesday, October 9, 2018 6:30 AM**


OBJECTIVE: Patients with significantly elevated or diminished BMI may exhibit a variety of health consequences and decreased fecundity. The reproductive impact of elevated BMI has been well studied, but few studies have convincingly quantified the effects of low BMI on oocyte/embryo quality and implantation efficacy. This study aimed to determine the impact of low BMI on ovarian response to controlled ovarian stimulation (COS) for IVF.

DESIGN: Retrospective

MATERIALS AND METHODS: This study included patients who underwent COS for IVF between 2002-2018. Trophoectoderm biopsy and preimplantation genetic testing for aneuploidy (PGT-A) were performed. BMI was categorized as underweight (< 18.5 kg/m²), normal weight (18.5-24.9 kg/m²), and obese (≥ 25.0 kg/m²). Patient age, gravidity, parity, AMH (ng/mL) and E2 (2279 ± 1175 pg/mL, p < 0.01) level, and P4 (0.99 ± 1.1 ng/mL, p < 0.01) level, but lower total GND dose (3572 ± 1559 IU, p < 0.01) than normal weight women. Gravidity, parity and trigger type used were similar between groups. While the number of MII oocytes (11.3 ± 8.1, p < 0.01) and fertilized oocytes (8.3 ± 6.6, p < 0.01) were greater in underweight vs. normal weight women, BMI and fertilization rates did not differ between groups, before and after adjusting for confounders. Blastulation and euploidy rates were not significantly different between BMI groups after accounting for covariates.

CONCLUSIONS: Extreme alterations in body composition and decreased energy availability associated with a low BMI may result in serious health consequences, but ART outcome does not appear to be affected. With the use of IVF, women can overcome the detrimental effects of ovulatory dysfunction associated with a low BMI and achieve successful reproductive outcomes. While this study provides reassurance to underweight patients undergoing IVF, providers are encouraged to discuss nutritional and exercise guidelines that may optimize preconception health.

**References:**

**REPRODUCTIVE IMMUNOLOGY**

**P-44 Tuesday, October 9, 2018 6:30 AM**

**HIGH PREVALENCE OF ALLERGY IN PATIENTS UNDERGOING ASSISTED REPRODUCTIVE TECHNOLOGY: A CONUNDRUM.** N. Esfandiari, D. Dela Cruz, J. F. Litzky, S. H. Gibson, L. R. DeMarx, N. Esfandiari, Health Sciences, McMaster University, Hamilton, ON, Canada; Obstetrics and Gynecology, Dartmouth Hitchcock Medical Center,
OBJECTIVE: A possible association between allergy and infertility has not been investigated. Our aim was to determine whether female allergy correlates with infertility treatment outcomes.

DESIGN: Retrospective cohort study in an academic medical center.

MATERIALS AND METHODS: Patient data from July 2010 through January 2017 was compiled from medical records. Mixed effects models were used to evaluate the relationship between presence of female allergy and type (fresh or FET) and cycle outcomes, controlling for type of procedure, number of embryos transferred, female patient age, BMI, smoking status, gravidity, parity, and Caucasian race.

RESULTS: After exclusions for missing data, the cohort contained 493 patients with a total of 935 cycles. Of these, 90.7% identified as Caucasian with a mean age of 34.8 (SD = 4.6) at the time of each cycle initiation. Over half of the female patients had allergy (54.0%). Nonexclusively, among all female patients, allergy to antibiotics was most common (29.2%), followed by allergy to non-antibiotic prescription medications (22.3%). Allergies to pollen and dust (5.7%), foods (6.5%), latex (4.4%) and other substances (9.7%) including cat and dog allergens were less common. Among cycles with fresh embryo transfer (581 cycles from 408 patients), having an allergy to pollen and/or dust was significantly associated with having a negative beta-hCG test (p = 0.02). Pollen/dust allergy was not associated with SAB, biochemical pregnancy, or ectopic pregnancy alone; however, it was associated with whether an infant was born at the end of the cycle (p = 0.04), with only 15.4% of those with a pollen/dust allergy having a cycle which resulted in a live-born infant compared with 34.7% of those without such allergy. Overall, the presence of any allergy was not associated with negative beta-hCG or pregnancy outcomes, nor was another sub-classes of allergies.

CONCLUSIONS: The high rates of allergy among patients seeking infertility treatment, as compared to the general population, are surprising. Female allergy to pollen and/or dust is associated with a greater chance of failed fertility treatment and a lower chance of a successful pregnancy resulting in a live-born infant. The reproductive performance of allergic patients needs further investigation using a larger dataset.

P-46 Tuesday, October 9, 2018 6:30 AM

ENDOMETRIUM INFECTION BY HUMAN HERPESVIRUS-6A: IMPLICATION IN FEMALE IDIOPATHIC INFERTILITY. R. Rizzo D. Di Luca. University of Ferrara, Ferrara, Italy.

OBJECTIVE: We first reported HHV-6A DNA presence in 43% of endometrial cells from women with idiopathic infertility, whereas no fertile controls harbored the virus. Growing evidence confirms this implication. We investigated the effect of HHV-6A infection on the immunological status of the endometrium.

DESIGN: This is a case-control study. The sample size guarantees to achieve a 0.8 power with 5% alpha error in detecting differences between groups.

MATERIALS AND METHODS: Endometrial biopsies, uterine flushing and whole blood samples were collected during the implantation (mid secretory phase) window in 67 idiopathic infertile women. The presence of HHV-6A infection was evaluated by DNA and mRNA analysis (U22, U42, U94 genes) on endometrial cellular subsets. We analyzed the endometrial immunological status evaluating: i) the levels of immune-regulatory HLA-G and HLA-E molecules, innate inflammatory (IL-6, IL-8, TNF-alpha), Th1 pro-inflammatory (IFN-gamma, IL-1alpha, IL-1beta, IL-12) and Th2 anti-inflammatory (IL-4, IL-10) cytokines by multiplex ELISA in uterine flushing samples; ii) endometrial receptivity to cytotoxicphoblasts in an endometrial 3D in vitro model; iii) natural killer (NK) cells and regulatory T cells percentage and immune-phenotype in endometrial biopsies and peripheral blood by flow cytometry.

RESULTS: We confirmed the presence of HHV-6A infection in a 40% of idiopathic infertile women. We observed increased levels of IFN-gamma, IL-1beta and IL-12 (p < 0.001; Student t test), decreased levels of both IL-4 and IL-10 (p < 0.001) in uterine flushing samples from HHV-6A positive women. HLA-G and HLA-E molecules were not expressed on the surface of endometrial epithelial cells from HHV-6A positive women. As a proof of principle, endometrial biopsies positive for HHV-6A infection presented a lower permissivity to cytotoxicphoblasts invasion. We observed a lower amount of endometrial (e)NK cells in the endometrium of women positive for HHV-6A infection compared with endometrium negative for HHV-6A (p < 0.0001; Student T test). In particular, when we analyzed (e)NK subpopulations, we observed a lower percentage of CD56dimCD16 (e)NK cells in women positive for HHV-6A infection (p < 0.0001). When we looked at peripheral blood cell subsets, we observed a decrease in CD4+CD25+CD127dim– regulatory T cells in women positive for HHV-6A infection (p = 0.016).

CONCLUSIONS: The identification of an effect of HHV-6A infection on endometrial immune status opens new perspectives in idiopathic infertile women care management. In addition, it would be possible to select antiviral therapies as novel therapeutic approaches to those idiopathic infertile women characterized by the presence of endometrial HHV-6A infection, to increase their pregnancy rate.

References:
decrease in mRNA RBP7, Notch1 and Hey1. Ishikawa cells with silenced RBP7 failed to upregulate CD94 expression in NK cells in contrast to a control co-culture. Corresponding experiments with endometrial stromal cells are in progress.

CONCLUSIONS: The endometrium from women with either RPL or RIF is characterized with significantly lower expression of RBP7 than in fertile women. Our data indicate that deregulated Notch signaling could contribute to reproductive failures and provide important insight into potential biomarkers related to endometrial receptivity.

Supported by: Clinical Immunology Laboratory at Rosalind Franklin University of Medicine and Science, North Chicago, IL.

P-47 Tuesday, October 9, 2018 6:30 AM

UTERINE NATURAL KILLER CELL DENSITY AS A PREDICTOR FOR IMPLANTATION SUCCESS OR FAILURE IN FERTILE SURROGATES AND IN WOMEN WITH IMPLANTATION FAILURE. D. P. Shivalingegowda, V. Rao, K. Rathnam, G. T. Pranesh, M. Dwarkanath, S. Mummadi, K. A. Rao, a Reproductive Medicine, Milann, Bangalore, India; b Reproductive Medicine, Milann, The fertility center, Bangalore, India; c Laboratory Medicine, Milann, Bangalore, India; d Reproductive Medicine, Milann The Fertility Centre, Bangalore, India; e Milann, Bangalore, India.

OBJECTIVE: To assess the uterine NK(uNK)cell subpopulation in the peri-implantation endometrium in prospective surrogate and in women with implantation failure

To correlate uterine NK cell density with implantation failure or success

DESIGN: A prospective observational study

MATERIALS AND METHODS: The study was conducted over a period of 1 year at Milann-the fertility center, Bangalore. Total of 21 prospective surrogates and 87 women with implantation failure were studied. Patients with uterine abnormalities and/or endocrine disorders were excluded. Trans-vaginal ultrasound was done on day 2/3 of the menses. Natural cycle or Hormone Replacement Therapy (HRT) cycle was followed. Diagnostic hysteroscopy with endometrial biopsy for uNK cell was done on day 5 after ultrasound documentation of ovulation in natural cycle or after 5 days of progesterone therapy in HRT cycle. Flow cytometry was used to assess CD56 and CD3 NK cells in the endometrial biopsies and the percentage was identified by immunocytochemistry. Embryo transfer or Frozen embryo transfer was performed in the subsequent menstrual cycle either in stimulated cycle or HRT cycle. Primary outcome was to find the percentage of uterine NK cells in prospective surrogate with proven fertility so as to create a normogram. Secondary outcome measured was the reproductive outcome in surrogates and in women with implantation failure in relation to percentage of uterine NK cell.

RESULTS: The 10th and 90th percentile cut offs for NK cells in surrogates was determined to be 19.58% and 44.3% respectively. Patients with history of implantation failure had a wider distribution of NK cells. 10.5% (versus 9.5% in surrogates) of implantation failure patients had NK cells below the 19.58% cut off. 17.5% (versus 9.5% in surrogates) were found to have NK cell values above 44.3%. However there was no statistically significant difference in terms of implantation failure or success in relation to uNK cell density, both in surrogates and in women with implantation failure.

CONCLUSIONS: Previous studies have implicated both low NK cell activity and high NK cell activities to be associated with implantation failure. The data from our study did not find this correlation. This study proves that increased uterine NK cell number in the secretory phase may not be the sole reason that affects embryo implantation. There is some evidence regarding relationship between maternal uterine natural killer cell immunoglobulin receptor (KIR) genotype and trophoblastic HLA-C (human leukocyte antigen) genotype. Further studies are required to evaluate maternal KIRs along with trophoblastic HLA-C, so the effect of various KIR/HLA-C combinations on miscarriage risk/implantation failure can be analysed.

References:
development might be compromised. Inflammation could, thus, also serve as a causative factor for the substantial proportion of miscarriages that reveal normal karyotypes after analysis of products of conception (POCs). To evaluate in infertile women the relationship between pre-pregnancy CRP levels and karyotype, and for the objective of this study.

**DESIGN:** Retrospective cohort study in academically affiliated private fertility center.

**MATERIALS AND METHODS:** One hundred infertile women who presented with missed abortions and underwent D&C with cytogenetic analysis of POCs were included in this study. A normal female fetus cannot be differentiated from maternal cell contamination (MCC) in conventional chromosomal analyses. POC testing at our center was, therefore, exclusively performed by chromosomal microarray analysis, featuring single nucleotide polymorphism technology (Anora®, Natera, San Carlos, CA). POC analyses that revealed MCC were excluded. The proportion of elevated serum CRP levels in women with normal and abnormal karyotypes in their POCs was the main outcome measure. CRP levels were compared using the Mann-Whitney U test.

**RESULTS:** Women were 39.2±6.3 years old, 36.2% were parous, 52.9% had no prior pregnancy losses, 39.7% had 1-2 miscarriages and 7.4% had 3 or more. POCs revealed normal karyotypes in 23 (23%) women, abnormal karyotypes in 53 (53%) patients and MCC in 23 (23%) cases, while validation failed in one test (1%). Elevated CRP levels were more frequently observed in women with normal than with abnormal POC karyotypes (82% vs. 20%, P<0.001). CRP levels were 3.1±3.6 ng/L in women with normal and 1.2±2.4 ng/L in those with abnormal POC results, respectively (P=0.006), while other baseline characteristics were comparable.

**CONCLUSIONS:** As women with elevated CRP levels were more likely to demonstrate normal POC karyotypes, this study offers further evidence for a possible causal relationship between subclinical systemic inflammation and miscarriages in infertile women.

**References:**

**Support by:** Intramural funds from The Center for Human Reproduction and grants from The Center for Reproductive Medicine.

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**P-51** Tuesday, October 9, 2018 6:30 AM

**SEVERE HSV PREDICTS ONGOING PREGNANCY FOLLOWING IVF.**

**E. Minis, a M. Irani, b A. Athanasiou, c S. S. Witkin, a S. Spandorfer. a Weill Cornell Medicine, New York City, NY; bCenter for Reproductive Medicine and Infertility, Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medicine, New York, NY; cObstetrics and Gynecology, Weill Cornell Medicine, New York, NY; dRonald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medicine, NYC, NY.

**OBJECTIVE:** Previous smaller studies have indicated that an elevated serum level of interleukin-1β (IL-1β) at baseline (day 2 of IVF cycle) is potentially predictive of an ongoing intrauterine gestation/live birth following IVF treatment. The aim of this study was to confirm and extend these findings on a larger study population.

**DESIGN:** Prospective cohort study

**MATERIALS AND METHODS:** Sera from 273 women were prospectively collected on day 2 of their IVF cycle (prior to stimulation) and tested for levels of IL-1β by ELISA. Associations between levels of IL-1β and IVF outcomes were calculated by Student’s t-test and Mann-Whitney test as appropriate.

**RESULTS:** The mean age of the study subjects was 37.7±4.3 years, mean BMI was 24.2±4.2 kg/m², and the mean number of harvested oocytes was 10.2±4.4. Thirty-four patients (12.5%) had a cycle cancellation, 8 (2.9%) did not undergo embryo transfer (ET), while 228 (82.7%) underwent an ET. Of women with an ET 112 had a positive initial pregnancy test (49.1%), 93 of whom (83%) achieved a clinical pregnancy and 64.2% had an ongoing pregnancy. Of women with detectable serum IL-1β, those who achieved an ongoing pregnancy/live birth had a higher mean serum level of IL-1β at baseline than those who did not (28.8±10.2 vs 12.2±3.1 pg/ml, p=0.049). In addition, if IL-1β was detectable, patients who had an ongoing pregnancy/live birth had higher levels of this cytokine than women who suffered a pregnancy loss (49.4±17.1 vs 11.5±5.4 pg/ml, p=0.045).

**CONCLUSIONS:** Elevated serum IL-1β prior to stimulation is indicative of a subsequent live birth and ongoing pregnancy. This could suggest a potential role for inflammation and IL-1β in embryo development and implantation.

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**P-52** Tuesday, October 9, 2018 6:30 AM

**CLINICAL UTILITY OF PERIPHERAL BLOOD IMMUNOPHENOTYPE: CORRELATIONS WITH ENDOMETRIAL BIOPSY ASSESSMENT.**

**K. Marron, a D. Walsh, b C. Harrity, a ZentraLab, Sims IVF Clinic, Dublin, Ireland; bClinical, Sims IVF Clinic, Dublin, Ireland; Obstetrics & Gynaecology, Royal College of Surgeons, Dublin, Ireland.

**OBJECTIVE:** The immune system is intimately involved in the process of implantation and alloimmune acceptance. With early pregnancy loss or recurrent implantation failure, and in the absence of other rational explanations, both the physician and the patient, naturally look for causative mechanisms. Over the years many attempts have been made to correlate peripheral blood immunophenotype findings with outcomes in failed cycles, but with limited acceptance among the wider scientific community. Endometrial biopsies are considered the best tool available for the assessment of the uterine immunophenotype both pre- and post-transfer, but it is an invasive technique not without its own associated risks. Does the non-invasive peripheral blood immunophenotype correlate in any way with biopsy findings?

**DESIGN:** A comprehensive panel was used to simultaneously investigate peripheral blood and endometrial immunophenotype in the same patient. MATERIALS AND METHODS: 53 blood and biopsy samples simultaneously obtained were immunophenotyped and correlations between markers were established.

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**CONCLUSIONS:** CMV past infection had an adverse effect on live birth rate, and TOXO past infection increased the incidence of malformation in offspring after IVF/ICSI-ET. Our study provides the first evidence of a correlation between past exposure to TORCH and the pregnancy and neonatal outcomes after IVF/ICSI-ET, which may shed new lights on the ART clinical practice.

**Supported by:** Grant support was provided by the National Key Research and Development Programme of China (2017YFC0100103), and the National Natural Science Foundation of China (No. 81471421,81270664).
RESULTS: Median percentage expression for the various markers employed are illustrated in the table below. Pearson correlations show natural killer T cells (NK-T), CD57 positive natural killer and natural killer T-cells, and CD4+ Th1+ T-cells are significantly positively correlated with each other. All other markers show no association between blood and biopsy

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Biopsy (%)</th>
<th>Blood (%)</th>
<th>p Value</th>
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<td>NK-T</td>
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<tr>
<td>CD4+</td>
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<td>CD4:CD8 Ratio</td>
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</table>

CONCLUSIONS: Endometrial biopsies are considered the gold standard technique to assess uterine immunophenotype but there may yet be still a place for peripheral blood evaluation with several significant immune markers showing positive correlations across the two methods. Given the invasive nature of biopsies and the necessity to take in the late luteal phase this information may prove useful.

Supported by: This project was entirely funded by Sims IVF and Virtus Health. There are no conflicts of interest.

P-53 Tuesday, October 9, 2018 6:30 AM

ENDOMETRIAL CYTOKINE LEVELS IN RECURRENT PREGNANCY LOSS AND IMPLANTATION FAILURE. K. Marron, a D. Walsh, b C. Phillip, c C. Harrity. a Zentra Lab, Sims IVF Clinic, Dublin, Ireland; b Clinical, Sims IVF Clinic, Dublin, Ireland; c Obstetrics & Gynaecology, Royal College of Surgeons, Dublin, Ireland.

OBJECTIVE: Serum specific cytokine levels have been controversially proposed as indicators of immunological related pregnancy loss or implantation failure, but suffer from poor acceptance among the wider scientific community. Endometrial assessment is a more specific evaluation, the available cellular markers are diverse. Potentially coupling cytokine measurement with a thorough assessment of immunophenotype. This pilot aims to determine if selected cytokines are resident within the endometrium of recurrent pregnancy loss (RPL) and repeated implantation failure (RIF) patients, and if there are differing levels of expression.

DESIGN: A pilot study of 28 cases was performed to correlate the levels of total measurable cytokines (ng/ml) using a sensitive non-multiplexed ELLA platform (R&D Systems). Patients were divided into RIF (n=18, >2 unsuccessful blastocyst ETs and primary infertility) and RPL (n=10, >2 miscarriages).

MATERIALS AND METHODS: Cytokines CXCL10, TNFa, INFg, IL1b, IL 5, IL-6, IL 8 and IL-10 were measured and correlated with clinically defined reproductive outcomes in weight and BCA protein level matched endometrial biopsies.

RESULTS: CXCL10, TNFa, INFg, IL1b, IL 5, IL-6, IL 8 and IL-10 were all within detectable levels in the analysed endometrium. Population means, SDs and ranges are displayed (Table 1). Statistical analysis demonstrated no significant differences in cytokine levels between the RIF and RPL groups.

CONCLUSIONS: We have previously established that flow cytometric endometrial evaluation of patients with RIF or RPL can yield differing immunophenotypes. In this pilot study, specific cytokine evaluation shows that these markers are detectable locally in the endometrium. Further study is required to determine if this correlates with outcomes. Taken together, greater understanding of the underlying disease process may be gained from the combination of these two types of analysis.

Supported by: This project was entirely funded by Sims IVF and Virtus Health. There are no conflicts of interest.

P-54 Tuesday, October 9, 2018 6:30 AM

OVARIAN STIMULATION DOESN’T INFLUENCE THE UTERINE IMMUNE ENVIRONMENT IN HEALTHY INFERTILE WOMEN. D. Aleksandru, a A. Pacheco, a A. Fabris, a A. Barrio, b P. Aparicio, b J. Garcia Velasco, c IVI RMA Global, Madrid, Spain; b Pilar Aparicio, Madrid, Spain.

OBJECTIVE: There is a controversy about the impact of the OS on the immune cell composition and behavior in women undergoing to IVF. Our aim was to determine whether OS has any impact on the mothers immune uterine cells in healthy infertile patients undergoing to IVF.

DESIGN: Prospective cohort study.

MATERIALS AND METHODS: Sixty-five patients at IVI RMA Madrid who experienced RM or RIF and were undergoing IVF were included between November 2016 and November 2017. Endometrial biopsies were taken on LH+7 in a natural cycle or hCG+7 after OS. Twenty-five healthy oocyte donors were included as a control group, and they underwent similarly two endometrial biopsies in a natural cycle and stimulated cycle on the same day. Patients included in the study had a normal karyotype, pelvic ultrasound, serum TSH, fasting glucose and insulin, inherited thrombophilia tests (factor V Leiden, prothrombinG20210A, homocysteine, protein C and S and anti-thrombin III) and were negative for anticardiolipin and anti-β2-glycoprotein (IgG and IgM) antibodies and lupus anticoagulant. They had a normal cervical cytology and were negative for HPV, Chlamydia, Ureaplasma and Mycoplasma. The immune cell populations were analyzed by 3 techniques: flow cytometry, immunohistochemistry and gene expression. An “artificial embryo” as HLA-C tetramer molecule was used to investigate immune cells binding. We analyzed the gene expression of the main proinflammatory TNF alpha and anti-inflammatory IL-10 cytokines in all samples.

RESULTS: We compared the number, % and gene expression of CD56high (uNK), CD56+CD16+, CD16+, TregCD25+CD4+FoxP3+ cells, the uNK binding to HLA-C tetramer (“artificial embryo”), TNFalpha and IL-10 expression and no differences were observed in natural cycles between groups (patients and oocyte donors). Similarly, we did not find any differences when the immune cells were analyzed in endometrial biopsies obtained during OS between both groups. When biopsies from natural cycles and from OS cycles were compared, again we could not detect any significant differences in the immune cell populations.

CONCLUSIONS: OS does affect the uterine immune cells populations or the HLA-C binding capacity in healthy women undergoing OS. Further studies are undergoing to investigate if women with previous autoimmune disorders may have different responses.

Supported by: CTI. Spain
OBJECTIVE: To study the accuracy of diffusion weighted MRI & dynamic contrast enhanced MRI in pre-operative differentiation between benign & malignant ovarian masses for optimum possible surgical strategies.

DESIGN: This study was a prospective study included twenty female patients (including twenty four lesions as four patients had bilateral lesions & sixteen one had one lesion) referred with ovarian lesions based on ultrasound examination. They were divided into purely solid, purely cystic & complex solid/cystic lesions.

MATERIALS AND METHODS: Twenty patients with ovarian masses underwent conventional MRI then diffusion -weight imaging (DWI) including apparent diffusion coefficient (ADC) value calculation & dynamic contrast enhanced MRI before surgery. Correlation of the pathological specimen with lesion morphology, signal characteristics, enhancement criteria including dynamic contrast-enhanced MRI, DWI followed by ADC value measurement were obtained.

RESULTS: All solid malignant lesions showed diffusion restriction as well as the wall & septations of most malignant cystic lesion except one case. Most benign lesions did not display diffusion restriction in DWI. The best cut off value of ADC to discriminate between benign & malignant lesions was 1.2 x 10⁻³ mm²/s (after exclusion of mature cystic teratoma, endometrioma & tubo-ovarian abscess) which show restricted diffusion & low ADC value due to mixed cellularity of the lesion. Diffusion shows higher sensitivity of 88.8% than conventional MRI.

CONCLUSIONS: For optimum possible surgical strategies, DWI & ADC value measurement & dynamic contrast enhanced MRI increases the sensitivity of conventional MRI in differentiating benign from malignant ovarian lesions.

References:
6- Park HJ, Nam EJ and Rha SY. A new prognostic index model using-meta-analysis in early-stage epithelial ovarian cancer. Gynecol Oncol 2012;126(3):357-63.


P-55 Tuesday, October 9, 2018 6:30 AM

EFFECT OF TRANSCERVICAL EMBRYO TRANSFER ON PLACENTAL LOCATION IN PATIENTS UNDERGOING ASSISTED REPRODUCTIVE TECHNOLOGY. R. Roman, a I. Peregrin-Alvarez, b N. Van De Velde, a M. Christiansen, a J. C. Gordon, a L. Detti, a Obstetrics and Gynecology, University of Tennessee Health Science Center, Memphis, TN; aUniversity of Tennessee Health Science Center, Memphis, TN; aUniversity of Tennessee Health Science Center, University of Tennessee Health and Science Center, Memphis, TN; aUTHSC, Memphis, TN.

OBJECTIVE: IVF pregnancies have been associated with an increased risk of placenta previa a, which can be associated with adverse maternal-fetal outcomes. Previous studies by our group have shown that placental location can be diagnosed as early as 5 weeks’ gestation b. In our study, we sought to determine whether there is a difference in placental location between IVF- FET cycles and spontaneous conceptions using first trimester ultrasound.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: Review of 276 ultrasounds performed at 5-6 weeks’ gestation in an academic center between 2014-2017. Ultrasound reports and images were reviewed for placental location, categorized as ante- rior, posterior, fundal, lateral, or previa in spontaneous/intrauterine insemination and IVF-FET. Nonparametric tests were used, with significance determined with p < 0.05.

RESULTS: Of the 276 patients reviewed, of which 177 singletons, 97 twin gestations, and 2 triplet gestations, 150 were spontaneous/intrauterine insemination conceptions and 126 IVF-FET conceptions. In spontaneous concep- tions, placental location was noted to be anterior in 63 patients (42%), posterior in 35 patients (23.3%), fundal in 29 patients (19.3%), lateral in 15 patients (10%), and previa in 8 patients (5.3%). In IVF-FET conceptions, placental location was anterior in 41 patients (32.5%), posterior in 42 pa- tients (33.3%), fundal in 23 patients (18.25%), lateral in 14 patients (11.1%), and previa in 6 patients (4.76%). Chi square test showed no statisti- cal difference in placental location between the groups (p = 0.37), and the results did not differ in twin (p = 0.89) and singleton pregnancies (p = 0.66), respectively.

CONCLUSIONS: Placenta previa was equally frequent in spontaneous and IVF-FET pregnancies using first trimester ultrasound. There was no differ- ence in placental location between transcervical catheter embryo transfer and spontaneous pregnancies.

Supported by: None.

P-58 Tuesday, October 9, 2018 6:30 AM

ENDOMETRIOSIS IS A RISK FACTOR FOR INCORRECTLY DIAGNOSED LATERALITY OF ECTOPIC PREGNANCY ON PELVIC ULTRASOUND.

J. A. Gingold, a L. Gemmell, b I. Janney, b T. Falcone, c Women’s Health Institute, Cleveland Clinic Foundation, Cleveland, OH; cCase Western Reserve University School of Medicine, Cleveland, OH; cCleveland Clinic, Cleveland, OH.

OBJECTIVE: Pelvic ultrasound is a key tool for diagnosing and localizing ectopic pregnancy. The frequency of discordance in laterality between ultra- sound and surgery in surgically proven tubal ectopic pregnancy is unknown, as are risk factors for laterality discordance. This study attempts to measure the frequency of discordant laterality of tubal ectopic pregnancy and associ- ated risk factors.

DESIGN: Retrospective case-control study

MATERIALS AND METHODS: Patients with surgically confirmed tubal ectopic pregnancy between 2006 and 2017 within a single health system were identified from chart review. Data set included 166 (of 693 identified) cases (n=156 patients) primarily managed with surgery as well as 94 cases (n=94 patients) who required surgery after failing methotrexate. The laterality of the ectopic pregnancy on the ultrasound report (if known) was compared with the laterality at the time of surgery and classified as discordant, discordant or not applicable (if sonographic laterality was unknown).

Patient demographic parameters, ectopic risk factors, hCG levels and addi- tional sonographic or surgical findings were compared across the groups by ANOVA of logistic regression for categorical variables or t-test for contin- uous variables.

Study was powered at 80% with p<0.05 to detect a difference between risk factors with 5% prevalence in concurrent laterality cases and 50% preva- lence in discordant laterality cases.

RESULTS: We identified 223 cases (79%) with concordant sonographic laterality, 54 (19%) with discordant laterality, and 9 (3.2%) with uncertain laterality.

We used the frequency of discordant laterality of tubal ectopic pregnancy as the primary outcome measure and compared the concordant and discordant laterality groups. Three ectopic pregnancies with discordant laterality groups and 156 cases with concordant laterality were identified from chart review. Data set included 166 (of 693 identified) cases (n=156 patients) primarily managed with surgery as well as 94 cases (n=94 patients) who required surgery after failing methotrexate. The laterality of the ectopic pregnancy on the ultrasound report (if known) was compared with the laterality at the time of surgery and classified as discordant, discordant or not applicable (if sonographic laterality was unknown).

Chi square test showed no statisti- cal difference in placental location between the groups (p = 0.37), and the results did not differ in twin (p = 0.89) and singleton pregnancies (p = 0.66), respectively.

CONCLUSIONS: Placenta previa was equally frequent in spontaneous and IVF-FET pregnancies using first trimester ultrasound. There was no differ- ence in placental location between transcervical catheter embryo transfer and spontaneous pregnancies.

References:

Supported by: None.
CONCLUSIONS: Approximately 1.7% of confirmed ectopic pregnancies have a misdiagnosed laterality on ultrasound. Endometriosis is an independent risk factor for discordant laterality and may stem from distorted pelvic anatomy.

OBJECTIVE: To determine changes in utero-ovarian artery blood flow following robotic-assisted laparoscopic myomectomy (RALM).

MATERIALS AND METHODS: Patients between ages 18-45 with regular menstrual cycles who were candidates for laparoscopic approach to myomectomy were included. Patients with history of prior abdominal surgery or open hysterectomy were excluded. A total of 44 consecutive patients underwent robotic-assisted laparoscopic myomectomy. Blood flow velocity waveforms were then obtained and a minimum Doppler range gate was applied across an arterial vessel in the utero-ovarian ligament. Blood flow velocity waveforms were then obtained and a minimum Doppler range gate was applied across an arterial vessel in the utero-ovarian ligament. Blood flow velocity waveforms were then obtained and a minimum Doppler range gate was applied across an arterial vessel in the utero-ovarian ligament. Blood flow velocity waveforms were then obtained and a minimum Doppler range gate was applied across an arterial vessel in the utero-ovarian ligament. Blood flow velocity waveforms were then obtained and a minimum Doppler range gate was applied across an arterial vessel in the utero-ovarian ligament.

RESULTS: Of the 44 patients, 15 patients had a statistically significant postoperative increase in RI and PI on the ipsilateral side of the fibroids without significant change on the contralateral side. A further subset analysis examining left vs right-sided location of fibroid resection did not reach statistical significance.

CONCLUSIONS: In this pilot study, statistically significant impairment in flow was associated with ipsilateral location of fibroid, and with higher total fibroid specimen mass. Non-significant decrease in AMH was observed. Completion of our 6-month measurements of utero-ovarian artery blood flow and AMH will allow determination of longer term changes.

REFERENCES:

P-60 Tuesday, October 9, 2018 6:30 AM

EXPLORATORY ANALYSIS OF MOLECULAR PHARMACODYNAMIC EFFECTS OF VILAPRISAN IN THE ENDOMETRIUM. A. Wagenfeld, A. Schulz, M. Schultz-Mosgau, B. Schuett, M. K. Machens, B. Rohde, Bayer AG, Berlin, Germany; Bayer AG, 13353 Berlin, Germany; Clinical Pharmacology, Bayer AG, Berlin, Germany; Bayer AG, Pharmaceuticals, Physician, Dept. Clinical Sciences, Berlin, Germany.

OBJECTIVE: Investigation of the mRNA expression profile in endometrial tissue of healthy women treated with different doses of the Selective Progestosterone Receptor Modulator Vilaprisan (VPR).

MATERIALS AND METHODS: Endometrial biopsy samples were obtained from 163 healthy tubal-ligated women enrolled in a double blind, parallel-group study, randomized to VPR doses of 0.1, 0.5, 1, 2 and 5 mg/d or placebo and treated over 84 days. Biopsy specimen were taken before treatment (d9±2), end of treatment (d84±2) and after start of next menstrual bleeding (d9±2).

RESULTS: Treated with VPR exerts strong effects on the endometrial gene expression which are almost all reversible or reduced after first bleeding post-treatment. Gene ontology analysis revealed that the majority of affected genes were highly down-regulated and involved in processes that are directly related to the cell cycle regulation/progression or control of cell growth, like AURKA, CDK2, CCNB1, DLG7, MELK and Kif6. This indicates VPR’s strong inhibitory effect on endometrial proliferation. These genes are also known to be overexpressed in endometrial carcinoma and other malignant tumors. In addition, genes playing a specific role in endometrial decidualisation

LEIOMYOMA

P-59 Tuesday, October 9, 2018 6:30 AM

UTERO-OVARIAN ARTERIAL BLOOD FLOW IS IMPAIRED AT 1 MONTH FOLLOW-UP AFTER ROBOTIC-ASSISTED LAPAROSCOPIC MYOMECTOMY. A. M. Mahesan, a S. Sadek, a R. Sabouni, a L. Stadtmuera, a Jones Institute for Reproductive Medicine, Norfolk, VA; aEastern Virginia Medical School, Norfolk, VA; aObstetrics and Gynecology, Jones Institute for Reproductive Medicine, Norfolk, VA.

OBJECTIVE: To examine changes in utero-ovarian artery blood flow following robotic-assisted laparoscopic myomectomy (RALM).

MATERIALS AND METHODS: Patients between ages 18-45 with regular menstrual cycles who were candidates for laparoscopic approach to myomectomy were included. Patients with history of prior abdominal surgery or open hysterectomy were excluded. A total of 44 consecutive patients underwent robotic-assisted laparoscopic myomectomy. Blood flow velocity waveforms were then obtained and a minimum Doppler range gate was applied across an arterial vessel in the utero-ovarian ligament. Blood flow velocity waveforms were then obtained and a minimum Doppler range gate was applied across an arterial vessel in the utero-ovarian ligament. Blood flow velocity waveforms were then obtained and a minimum Doppler range gate was applied across an arterial vessel in the utero-ovarian ligament. Blood flow velocity waveforms were then obtained and a minimum Doppler range gate was applied across an arterial vessel in the utero-ovarian ligament. Blood flow velocity waveforms were then obtained and a minimum Doppler range gate was applied across an arterial vessel in the utero-ovarian ligament.

RESULTS: Of the 44 patients, 15 patients had a statistically significant postoperative increase in RI and PI on the ipsilateral side of the fibroids without significant change on the contralateral side. A further subset analysis examining left vs right-sided location of fibroid resection did not reach statistical significance.

CONCLUSIONS: In this pilot study, statistically significant impairment in flow was associated with ipsilateral location of fibroid, and with higher total fibroid specimen mass. Non-significant decrease in AMH was observed. Completion of our 6-month measurements of utero-ovarian artery blood flow and AMH will allow determination of longer term changes.

REFERENCES:
and receptivity (e.g. FOXM1, HOXA10) are also found to be repressed under VPR treatment.

CONCLUSIONS: Endometrial gene expression is strongly affected by VPR treatment. The majority of genes were down-regulated and involved in cell growth suggesting an antiproliferative effect of VPR on the endome-

rrium. A dedicated mechanism of action study of VPR has been recently initi-

ated in fibroid patients to further investigate the effect of VPR on menstrual bleeding and fibroid shrinkage.

Supported by: All authors are full-time employees of Bayer AG.

P-61 Tuesday, October 9, 2018 6:30 AM

EFFICACY AND SAFETY OF THE SELECTIVE PRO-

GESTERONE RECEPTOR MODULATOR (PRM) VI-

LAPRISAN: INTEGRATED ANALYSIS OF PHASE 2

ASTEROID 1 AND 2 STUDIES. K. Genuzli Danielsson,a L. D. Bradley,b C. Ahlers,c T. Faustmann,d K. Petersdorf,a M. Zvolanek,e E. Groettrup-Wolters,a C. Seitzf, Karolinska Institutet, Stockholm, Sweden; bOb/Gyn, Cleveland Clinic, Cleveland, OH; cBayer AG, Wuppertal, Germany; dBayer AG, Berlin, Germany.

OBJECTIVE: This integrated analysis of ASTEROID 1 and 2 aimed to assess the efficacy and safety of the highly selective PRM vilaprisan (VPR) in women with uterine fibroids (UF), using an extended patient dataset.

DESIGN: ASTEROID 1 and 2 are multicenter, randomized, double-blind, multi-arm, phase 2 studies conducted in women with at least one UF ≥ 3 cm and heavy menstrual bleeding (HMB) > 80 mL. In ASTEROID 1, women were randomized to VPR 0.5 mg, 1 mg, 2 mg or 4 mg once daily (OD) or placebo for 12 weeks. In ASTEROID 2, women were randomized to VPR 2 mg, ulipristal acetate (UPA) 5 mg, or placebo OD for one/two 12-week treatment periods.

MATERIALS AND METHODS: An integrated analysis of women randomized to VPR 2 mg, UPA and placebo treatment for 12 weeks in ASTEROID 1 and 2 was performed. Amenorrhea (<2 mL per 28 days), HMB response (<80 mL and >50% reduction in bleeding from baseline during the third 28-day reference period of the treatment period) and controlled bleeding (<30 mL) were measured by menstrual pictogram. Time to onset was the first day at which the parameter of interest (through to all subsequent 28-day periods) started. Change in volume of the three largest fibroids from baseline to the end of treatment period was assessed by MRI. Health-related quality of life and symptom severity were measured by patient questionnaires. Adverse events and laboratory parameters were monitored, and endometrium was assessed by biopsy.

RESULTS: 267 women completed 12 weeks of treatment (VPR n=128; UPA n=68; placebo n=71). Amenorrhea, HMB response and controlled bleeding rates have been reported previously. Median time to onset of amenorrhea was 6 (interquartile range [IQR] 5-10) and 7 (IQR 5-10) days for VPR and UPA, respectively. Median time to onset of both HMB response and controlled bleeding was 3 days (IQR 2-4 and 1-4, respectively) for both VPR and UPA. No median values could be calculated for placebo. At 12 weeks, for the three largest fibroids, mean reductions in volume (standard deviation [SD]) of 28.9% (27.9) with VPR 2 mg and 23.8% (29.1) with UPA 5 mg were observed, and an increase of 6.9% (34.5) for placebo. VPR treatment was associated with clinically meaningful decreases in symptom severity and improvements in health-related quality of life. No unexpected safety issues were identified, no critical endometrial findings or findings indicative of liver toxicity were observed.

CONCLUSIONS: VPR 2 mg rapidly induced amenorrhea and controlled bleeding, and decreased UF size. VPR was well tolerated, with no unexpected findings observed during monitoring of hepatic and endometrial safety. This integrated analysis considers a larger patient dataset to support existing evidence from ASTEROID 1 and 2 and reports on additional parameters.

Supported by: This study was funded by Bayer Pharma AG.

P-63 Tuesday, October 9, 2018 6:30 AM

A MEANINGFUL RESPONSE ON THE UTERINE

FIBROID SYMPTOM AND HEALTH-RELATED

QUALITY OF LIFE QUESTIONNAIRE (UFS-QOL).

K. S. Coyne,a A. Harrington,a B. M. Currie,c Y. Mo,d P. Gillard,e J. Spies,e aEvidera, a PPD Business Unit, Bethesda, MD; bAllergan Plc, Irvine, CA; cEvidera, Bethesda, MD; dAllergan Plc, Madison, NJ; eMedstar Georgetown University Hospital, Washington, DC.

OBJECTIVE: Evaluate responsiveness of the 1-month recall version of the UFS-QOL among women with uterine fibroids (UF) and abnormal uterine bleeding (AUB) treated with ulipristal acetate (UPA).

DESIGN: Analyses were conducted using data from two Phase 3, randomized, placebo (pho)-controlled trials (VENUS I and II) in women with UF and AUB.

MATERIALS AND METHODS: The 1-month UFS-QOL was administered at baseline and after 12 weeks’ therapy (Visit [V] 2) in VENUS I/II. Vaginal bleeding was assessed via a daily diary in both studies. The Patient Global Impression of Menstrual/Vaginal Bleeding Improvement scale (PGI-I) was completed in VENUS II. Anchor- and distribution-based methods, with clinically relevant analyses, were used to evaluate responsiveness of the UFS-QOL. Symptom Severity and Health-Related Quality of Life (HRQoL) Total scales, HRQoL subscales (Concern, Activities, Energy/Mood, Control, Self-Consciousness, Sexual Function), and a Revised Activities subscale.

RESULTS: 483 women completed the UFS-QOL at baseline and V2. In VENUS I/II, mean (standard deviation) age was 41.1 (5.4) and 41.0 (5.6) years, respectively; most women were black (VENUS I, 68.8%; VENUS II, 50.6%).
WOMEN WITH SYMPTOMATIC UTERINE FIBROIDS

P-64 Tuesday, October 9, 2018 6:30 AM

DEVELOPMENT OF A SCREENING TOOL FOR WOMEN WITH SYMPTOMATIC UTERINE FIBROIDS (UF): A DELPHI PANEL APPROACH


University of Michigan Medical School, Ann Arbor, MI; Allergan plc, Irvine, CA; Endpoint Outcomes, Long Beach, CA; Endpoint Outcomes, Boston, MA; Women’s Health Practice, Champaign, IL; MedStar Washington Hospital Center, South Washington, DC; Baylor University Medical Center, Dallas, TX; University of California, San Francisco, San Francisco, CA; Carolina Women’s Research and Wellness Center, Durham, NC; Wayne State University School of Medicine, Detroit, MI; Johns Hopkins Hospital, Baltimore, MD; Johns Hopkins University School of Medicine, Baltimore, MD.

OBJECTIVE: To develop a screening tool to identify women with symptomatic UF. Symptoms of UF negatively impact on quality of life yet often women remain undiagnosed or unaware that their symptoms arise from UF.

MATERIALS AND METHODS: A targeted qualitative literature review was conducted using the MEDLINE database (2007-2017) to understand UF symptoms and impacts from a patient perspective, and identify existing patient-reported outcome instruments. A conceptual framework including key symptoms, impacts, and risk factors, alongside an item bank of potential screening questions from existing instruments, was developed. Items on therapies and results of testing were excluded. A 2-round modified Delphi panel was used to gain consensus among 9 expert clinicians on concepts and items to include in the tool, which was tested on 15 women with symptomatic UF through qualitative cognitive interviews.

RESULTS: The literature review and consultation with a clinical expert produced 21 concepts and 42 items for inclusion in a conceptual framework. Review of the framework by the Delphi panel identified 28 concepts and 27 items (>77.8% panel agreement [PA]) for further consideration; the second review determined 11 items for inclusion in the draft screening tool. Seven items met a 55.6% PA threshold: heavy menstrual bleeding (2 menstrual hygiene use items, volume of bleeding); prolonged periods; dysmenorrhea; race; and family history of UF. The concept of anemia met the threshold, although a related item did not; the panel thus recommended inclusion of a modified anemia item. The age item was included as it was identified as an important UF risk factor in the literature. Panelists also recommended inclusion of a bulk symptoms item. In a final review, all items had concurrence of >8 panelists. The draft tool was then revised based on cognitive interview feedback of relevancy to patients’ experience and patients’ ability to interpret instructions, items, and recall period as intended.

CONCLUSIONS: The draft UF screening tool could facilitate earlier identification of women suffering from symptomatic UF, improving time to treatment and quality of life. Research is planned to validate the tool.

Supported by: Allergan plc, Dublin, Ireland. Editorial assistance: Complete HealthVizion.

P-65 Tuesday, October 9, 2018 6:30 AM

ULIPRISTAL ACETATE (UPA) TREATMENT OF UTERINE FIBROIDS (UF): INTEGRATED LIVER SAFETY RESULTS FROM VENUS I AND II


University of Illinois at Chicago, Chicago, IL; Medical University of South Carolina, Charleston; Allergan SpA, Roma, Italy; Allergan plc; Madison, NJ; University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, OH.

OBJECTIVE: Investigate liver safety in women receiving UPA therapy for UF and abnormal uterine bleeding (AUB).

MATERIALS AND METHODS: In the Phase 3, multicenter, double-blind, placebo (pbo)-controlled VENUS I and II trials, premenopausal women (18-50 years) with ≥1 UF and AUB were randomized to UPA (5 or 10 mg) or pbo once daily treatment course; UPA, ulipristal acetate; Pbo, placebo; ALT, alanine transaminase; ULN, upper limit of normal; AST, aspartate transaminase; ALP, alkaline phosphatase.

Supported by: Allergan plc, Dublin, Ireland. Editorial assistance: Complete HealthVizion.

Table 1.

<table>
<thead>
<tr>
<th>TC1 and following off-treatment period:</th>
<th>UPA 5 mg (N1=203)a</th>
<th>UPA 10 mg (N1=189)a</th>
<th>Pbo (N1=162)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT ≥ 2 × ULN</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>ALT ≥ 3 × ULN</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>2 (1.2)</td>
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<tr>
<td>AST ≥ 2 × ULN</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>ALP ≥ 2 × ULN</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Bilirubin ≥ 2 × ULN</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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</table>

<table>
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<tr>
<th>TC2 and second off-treatment period:</th>
<th>UPA 5 mg/pbo (N1=39)b</th>
<th>UPA 10 mg/pbo (N1=32)b</th>
<th>UPA 5/5 mg (N1=81)b</th>
<th>UPA 10/10 mg (N1=78)b</th>
<th>Pbo/UPA 5 mg (N1=42)b</th>
<th>Pbo/UPA 10 mg (N1=41)b</th>
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<tr>
<td>ALT ≥ 5 × ULN</td>
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<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<tr>
<td>ALT ≥ 3 × ULN</td>
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<tr>
<td>AST ≥ 2 × ULN</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
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<tr>
<td>ALP ≥ 2 × ULN</td>
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<tr>
<td>Bilirubin ≥ 2 × ULN</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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aN1 = number of patients who received ≥1 dose in TC1 and had ≥1 post-baseline value in the specific category within the periods of interest.

bN1 = number of patients who received ≥1 dose in TC2 and had ≥1 post-baseline value in the specific category within the periods of interest.
for 12 weeks (one treatment course [TC] for VENUS I and two TCs for VENUS II, separated by a drug-free interval of two membes), with a 12-week drug-free follow-up. Patients with abnormal liver chemistries at screening were excluded, i.e., ≥2 × upper limit of normal (ULN) for alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), or total bilirubin.

MATERIALS AND METHODS: Liver tests were conducted at screening, baseline, end of TC1 (VENUS I and II), 10-18 days after first membes following TC2 (VENUS II), and end of study (or early withdrawal), and were assessed in the safety population, comprising all randomized patients who received ≥1 UPA dose. Cases of Hy’s Law were defined as post-base-line elevation of ALT or AST ≥3 × ULN, with bilirubin ≥2 × ULN and ALP <2 × ULN. Liver chemistry discontinuation rules were: 1) ALT ≥3 × ULN and bilirubin ≥2 × ULN; 2) ALT ≥5 × ULN; 3) ALT ≥3 × ULN plus symptoms; 4) ALT ≥3 × ULN for ≥4 weeks; 5) ALT ≥3 × ULN without weekly monitoring for 4 weeks. To further assess UPA effects on the liver, international criteria for drug-induced liver injury were applied, defined as any one of the following: 1) ALT ≥5 × ULN; 2) ALP ≥2 × ULN; or 3) ALT ≥3 × ULN and total bilirubin >2 × ULN [1].

RESULTS: The analysis population comprised 554 patients in TC1 and 313 in TC2. Liver test data following TC1 and following TC2 are presented in Table 1. No patients met liver chemistry discontinuation criteria or Hy’s Law criteria. No patients had ALT or AST in TC2. Liver test data following TC1 and following TC2 are presented in Table 1. No patients met liver chemistry discontinuation criteria or Hy’s Law criteria. No patients had ALT or AST ≥3 × ULN and ALT or AST ≥3 × ULN at end of treatment; however, this abnormality was present at baseline. One patient receiving pbo also had ALT ≥2 × ULN at the end of treatment in VENUS II.

CONCLUSIONS: In VENUS I and II, there was no evidence for UPA-induced liver injury.

References:

Supported by: Allergan plc, Dublin, Ireland. Editorial assistance: Complete HealthVizion.
IMPACT OF RACE, BODY MASS INDEX, AND CO-MORBIDITIES ON UTERINE FIBROID TREATMENT SELECTION: FINDINGS FROM THE FIRST 1,000 WOMEN ENROLLED IN A NATIONAL US REAL-WORLD STUDY. T. Jackson-Bey, A. Al-Hendy, L. D. Bradley, H. S. Taylor, J. H. Liu, K. Moon, M. Kerolous, University of Illinois at Chicago, Chicago, IL; Cleveland Clinic, Cleveland, OH; Yale School of Medicine, New Haven, CT; University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, OH; Mapi, an ICON plc Company, Dundas, ON, Canada; Allergan plc, Madison, WI.

OBJECTIVE: Collect real-world data on women with uterine fibroids (UF) and understand their clinical course and experience.

DESIGN: Capture-US is a prospective, observational, non-interventional national registry of pre-menopausal women with UF in the US.

MATERIALS AND METHODS: Pre-menopausal women, aged ≥18 years, with a clinician-confirmed UF diagnosis were enrolled. Demographics and UF management plans were collected at baseline for the initial 200 enrollees. Data were analyzed descriptively and presented as mean ± standard deviation or as frequency counts and percentages for continuous and categorical variables, respectively.

RESULTS: The mean age was 40.2 ± 6.8 years and mean body mass index (BMI) was 29.9 ± 6.8 kg/m². Of our study population, 50.0% (n=98) identified as black, 43.4% (n=85) as white, and 6.6% (n=13) as other/mixed race. Black women had higher BMI vs white or mixed race women (31.4±7.6, 28.5±5.7, 27.5±5.5 kg/m², respectively). Overall, black (26.5%, n=26) and other/mixed race (30.8%, n=4) women were more likely to choose treatment compared to white women (20%, n=17) at baseline. Among women who chose treatment, race was not equally distributed between treatment choices (p=0.0467). Black women were more represented in those who chose medication compared to those who chose procedure only (69.6%, n=16 vs 33.3%, n=6). Mean BMI was significantly higher in those who selected medication (33.5±10.2 kg/m², n=24) compared to those who selected procedure only (28.3±6.1 kg/m², n=19; p=0.0459). Among those who chose treatment, more women had non-UF-related co-morbidities (medication: 73.7%, n=19; procedure: 70.8%, n=14; procedure with medication: 58.8%, n=4) were women more likely to choose treatment compared to white women (20%, n=17) at baseline. Among women who chose treatment, race was not equally distributed between treatment choices (p=0.0467). Black women were more represented in those who chose medication compared to those who chose procedure only (69.6%, n=16 vs 33.3%, n=6). Mean BMI was significantly higher in those who selected medication (33.5±10.2 kg/m², n=24) compared to those who selected procedure only (28.3±6.1 kg/m², n=19; p=0.0459). Among those who chose treatment, more women had non-UF-related co-morbidities (medication: 73.7%, n=19; procedure: 70.8%, n=14; procedure with medication: 83.3%, n=5) compared to those who chose watchful waiting (asymptomatic: 18.8%, n=3; symptomatic: 54.8%, n=74). The most common co-morbidities among women seeking treatment for UF included hypertension (20.4%, n=10), iron deficiency anemia (18.4%, n=9), and hyperlipidemia (10.2%, n=5). There were more black women with each of the indicated co-morbidities than white or other/mixed race.

CONCLUSIONS: Results from this preliminary analysis demonstrate that race, BMI, and medical co-morbidities may play a role in the selection and type of management plans for women living with UF.

Supported by: Allergan plc, Dublin, Ireland. Editorial assistance: Complete HealthVizion.


OBJECTIVE: Prior studies have demonstrated that estrogen exposure increases the myometrial expression of neurotrimin (NTM/HNT-1), a member of the immunoglobulin IgLON family of cell adhesion molecules that regulates late neurite outgrowth and cellular adhesion. We hypothesize that NTM will be increased in leiomyoma tissue as estrogen-rich environments promote its expression.

MATERIALS AND METHODS: RNA sequence (RNAseq) analysis was performed on placebo and matched UPA (10mg or 20mg) treated patient leiomyoma and myometrium samples from a prospective, randomized, placebo-controlled clinical trial. Results were performed in triplicate with qRT-PCR and results reported as mean ± SEM. For western blot analysis, calculations were done using software from Bio-Rad. Data is presented as fold difference between leiomyoma and myometrium (L/M) relative density units that was corrected for internal control using COX IV. Immunohistochemistry was also performed.

RESULTS: Alterations of NTM mRNA transcripts by RNAseq in human uterine leiomyoma specimen demonstrated increased expression of transcripts in leiomyoma as compared to myometrium (5.22±0.03 fold, p=0.0005) and a reduced expression of NTM following UPA treatment (0.75 fold, p=0.134), when UPA treated leiomyoma is compared to placebo. In untreated patient samples, qRT-PCR showed an increased expression of NTM in leiomyoma compared to myometrium (1.95±0.03 fold, p=0.037). However, qRT-PCR results on immortalized leiomyoma and myometrial cell lines demonstrated a reduced expression of NTM in leiomyoma (0.13±0.02 fold, p=0.005). Western blot analysis in immortalized leiomyoma and myometrial cell lines demonstrated an up-regulation of NTM protein expression (2.4±0.04 fold, p=0.003). Following UPA treatment of an immortalized cell line (10⁻⁷ M UPA for 72 hours), there is reduced expression of NTM in treated versus untreated leiomyoma (0.67±0.04 fold, p=0.003) change in protein expression. A significant increase in intensity of staining in leiomyoma as compared to myometrium was seen following immunohistochemistry, supporting an increased cytoplasmic expression of NTM in leiomyoma.

CONCLUSIONS: NTM, a neural cell adhesion molecule highly expressed within brain tissues, is identified for the first time in leiomyoma tissue. NTM is increased in leiomyoma as compared to myometrium in both cell line and patient tissue and similarly down-regulated following treatment with UPA. Prior studies have demonstrated an up-regulation of NTM protein expression (2.4±0.04 fold, p=0.003) change in protein expression. A significant increase in intensity of staining in leiomyoma as compared to myometrium was seen following immunohistochemistry, supporting an increased cytoplasmic expression of NTM in leiomyoma.
expression of PD-L1, and, strikingly, we also observed persistent upregulation of PD-L1 in MED12mutant UFs compared to autologous MM.

CONCLUSIONS: our data demonstrate that UF-DC cooperate with UF-SC through PD-L1/PD-1 interaction and NF-Kb- dependent inflammatory cytokines to promote UF tumor growth.

Supported by: UIC start-up fund

P-71 Tuesday, October 9, 2018 6:30 AM
HORMONAL AND EPIGENETIC CONTROL OF PRICKLE1 - REST PATHWAY IN UTERINE FIBROIDS, J. Herzberg, M. McWilliams, F. Koohestani, C. J. Williams, W. N. Jefferson, S. Gunewardena, K. Swan, V. M. Chennathukuzhi. Obstetrics and Gynecology, University of Kansas Medical Center, Kansas City, MO; bCharles River Labs, Reno, NV; cKame, Kansas City, KS; dNH/NIEHS, Research Triangle Park, NC; eNIEHS, Research Triangle Park, NC; fUniversity of Kansas Medical Center, Kansas City, KS; gUniversity of Kansas SOM, Shawnee, KS; hMolecular and Integrative Physiology, KU, Medical Center, Kansas City, KS.

OBJECTIVE: Pre-pubertal exposure to environmental estrogens resulting in developmental reprogramming of the uterus is implicated as one of the leading risk factors for uterine leiomyoma (UL). Our objective is to determine the molecular pathways that link pre-pubertal exposure to environmental estrogens and the development of UL, with intention of developing targeted drug therapy for women who experience adverse symptoms related to UL.

DESIGN: A retrospective design was used in which UL and myometrial tissue samples were obtained from women 21-50 years of age undergoing hysterectomy at the University of Kansas Medical Center who had not had hysterecomy in the 6 months preceding surgery. Additionally, the short- and long-term effects of environmental estrogen exposure on PRICKLE1 and REST expression were analyzed prospectively using rodent models treated with estrogenic compounds. Data were analyzed by two-tailed t-test.

MATERIALS AND METHODS: Forty matched myometrial and UL samples were analyzed by TaqMan qRT-PCR, western blotting, immunohistochemistry and chromatin immunoprecipitation (ChIP) assays.

RESULTS: We have previously shown that the loss of REST (RE-1 Silencing Transcription factor) in UL promotes tumorigenesis through the activation of PI3K/AKT-mTOR pathway, a pathway well known to cause cell proliferation and survival. This pathway is activated via GPR-10, a G-protein coupled receptor that, outside of UL, is only found in the central nervous system. Loss of REST correlates with significant downregulation of PRICKLE1 and REST expression were analyzed prospectively using rodent models treated with estrogenic compounds. Data were analyzed by two-tailed t-test.

CONCLUSIONS: Collectively, our results identify a novel link between environmental estrogen exposure and PRICKLE1, a protein that regulates REST nuclear localization. PRICKLE1 is transcriptionally repressed in the myometrium by estrogen induced ERα activity. Crucially, mice exposed neonatally to environmental estrogens express significantly lower levels of PRICKLE1 and REST and develop increased sensitivity to estrogen after puberty. Our data also indicate that UL express increased levels of EZH2, a transcriptional repressor that inversely correlates with the expression of REST. Lastly, data from ChIP assays indicate that EZH2 and ERα mediated silencing of PRICKLE1 plays a critical role in the pathogenesis of UL.

P-73 Tuesday, October 9, 2018 6:30 AM

OBJECTIVE: Assessment of a potential proarrhythmic risk of vilaprisan (VPR), a highly selective progesterone receptor modulator (PRM).

DESIGN: Integrated evaluation of clinical electrocardiogram (ECG) interval measurements including QTcF (Heart rate corrected QT interval - Fridericia equation), ECG waveform analysis, cardiac magnetic resonance imaging (CMR) imaging, and VPR plasma concentration - QTc effect analysis based on Phase 1 clinical studies.

MATERIALS AND METHODS: Three Phase 1, placebo-controlled safety and pharmacokinetic studies in healthy postmenopausal women were conducted including an analysis of repeated, high quality ECG recordings following oral VPR administration of up to 30 mg/kg given on average every 2 days. On the basis of guidance on the use of concentration-QTc relationship to classify the risk for QTc prolongation [ICH Guideline, Questions & Answers (R3), 2017], a concentration-QTc effect analysis using a linear mixed-effect model was performed for VPR using Phase 1 study data with the aim to obtain a waiver for a thor-ough QT(TQT) study.

RESULTS: Based on the clinical ECG evaluation, the ECG interval measurements including QTcF values, ECG waveform analysis and outlier evaluation of the single studies, no risk for QT prolongation was identified following VPR administration. In the integrated VPR concentration-QTc effect analysis, there was no indication that the mean difference in QTc from baseline (ΔQTc) and placebo (ΔΔQTc) exceeds the 10 ms threshold at systemic drug exposures up to 193 μg/L, which is approximately 17-fold above the steady state geometric mean maximum drug concentration (Cmax,ss) at the intended therapeutic dose of 2 mg. A negative slope of -0.05 ms/L/μg was estimated for the concentration-QTcF relationship. Based on these data, the FDA granted a waiver for a QT study.

CONCLUSIONS: Applying a model-based analysis of the relationship between the VPR plasma concentration and ΔQTc, no clinically relevant effect of VPR on the QTc interval was found. The integrated analysis of all nonclinical and clinical data led to the FDA acceptance and granting of a waiver for a dedicated QT study.

Supported by: All authors are full-time employees of Bayer AG or Bayer Healthcare.

FERTILITY & STERILITY®
P-74 Tuesday, October 9, 2018 6:30 AM

EPIDEMIOLOGY AND RECENT TREATMENT OF LEIOMYOMAS IN KOREAN WOMEN. J. Namkung, M. Kim, H. Hwang. "Department of Obstetrics and Gynecology, St. Paul’s Hospital, The Catholic University of Korea College of Medicine, Seoul, Korea, Republic of; 2Department of Obstetrics and Gynecology, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea, Republic of.

OBJECTIVE: The purpose of this study is to investigate epidemiology of uterine leiomyoma in general population.

DESIGN: Retrospective cohort study using administrative data provided by the Korean National Health Insurance Service (NHIS).

MATERIALS AND METHODS: Korean National Health Insurance Service (KNHIS) sample cohort dataset which were collected during 2002-2013. Patients with uterine leiomyoma were identified by ICD-10 and intervention codes for the Korean health insurance.

RESULTS: A total of 50,884 women aged 15-54 were selected from the NHIS cohort database, which included approximately 1 million individuals.

The incidence had increased all over the age. The age group 45-49 showed highest incidence for the years. In 2012, the incidence of age group 45-49 was 2.97%. The total number of surgical treatment and intervention was increased from 561 in 2002 to 1137 in 2011. The treatment percentage of all diagnosed patient was decreased (28.51% in 2002 to 13.81% in 2013). Only the treatment percentage of 20-24 age group was increased (5.00% in 2002 to 7.10% in 2013). Of all treatment, the proportion of myomectomy was increased 2.22 fold (22% in 2002 to 49% in 2013) while the proportion of hysterectomy was decreased 0.57 fold (78% in 2002 to 45% in 2013) constantly.

CONCLUSIONS: This study showed a significant trend towards an increase in diagnosis for uterine leiomyoma in Korean women with time. Particularly, we found that the trend of surgical treatment moved to preservation fertility among Korean women. This study has meaningful in regard of general population based epidemiology study in asian women.

References:

P-75 Tuesday, October 9, 2018 6:30 AM

ROBOT ASSISTED LAPAROSCOPIC ADENOMYOMECTOMY IS A FEASIBLE OPTION FOR PATIENTS WHO WANT TO PRESERVE FERTILITY: COMPARISON WITH LAPAROTOMY. M. Kim, H. Hwang, J. Namkung. "Department of Obstetrics and Gynecology, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea, Republic of; 2Department of Obstetrics and Gynecology, St. Paul’s Hospital, The Catholic University of Korea College of Medicine, Seoul, Korea, Republic of.

OBJECTIVE: To evaluate feasibility of robot assisted laparoscopic adenomyomectomy for fertility preservation comparing with laparotomy

DESIGN: Retrospective chart review

MATERIALS AND METHODS: We performed a retrospective chart review of 58 women who underwent adenomyomectomy by a single surgeon at Seoul St. Mary’s Hospital between January 2011 and December 2017. Of all treatment, the proportion of myomectomy was increased 2.22 fold (22% in 2002 to 49% in 2013) while the proportion of hysterectomy was decreased 0.57 fold (78% in 2002 to 45% in 2013) constantly.

RESULTS: A low proliferation index, limited period of cell death and ECM main in vivo mechanisms identified. Compared to controls and non-responders, as UPA clinically reduces myoma size in 75-80% of cases. In 20-25% of women, myomas fail to respond to UPA therapy.

CONCLUSIONS: The correlation found between MMP expression and clinical response (defined as a reduction in volume of more than 25%). Myomas were then accordingly classified into responsive (n = 15) or nonresponsive (n = 18). Proliferation, apoptosis, and extracellular matrix (ECM) volume were evaluated by immunohistochemistry. Matrix metalloproteinase (MMP) expression and that of its tissue inhibitor (TIMP) were assessed by immunohistochemistry and zymography.

RESULTS: A low proliferation index, limited period of cell death and ECM remodeling concomitant with stimulation of MMP-2 expression were the main in vivo mechanisms identified. Compared to controls and non-responders, as UPA clinically reduces myoma size in 75-80% of cases. In 20-25% of women, myomas fail to respond to UPA therapy.

DESIGN: Prospective study in an academic research unit.

MATERIALS AND METHODS: Uterine biopsies were obtained from 47 patients with symptomatic myomas undergoing myomectomy, 33 of whom were ≥4-operative during 2-4 courses of 3 months with UPA therapy, and 14 not given any hormone therapy to serve as controls. Myoma volume was individually monitored during UPA therapy to determine any significant clinical response (defined as a reduction in volume of more than 25%). Myomas were then accordingly classified into responsive (n = 15) or nonresponsive (n = 18). Proliferation, apoptosis, and extracellular matrix (ECM) volume were evaluated by immunohistochemistry. Matrix metalloproteinase (MMP) expression and that of its tissue inhibitor (TIMP) were assessed by immunohistochemistry and zymography.

RESULTS: A low proliferation index, limited period of cell death and ECM remodeling concomitant with stimulation of MMP-2 expression were the main in vivo mechanisms identified. Compared to controls and non-responders, as UPA clinically reduces myoma size in 75-80% of cases. In 20-25% of women, myomas fail to respond to UPA therapy.

CONCLUSIONS: The correlation found between MMP expression and volume fold change supports the notion that MMPs play a key role in UPA-induced myoma shrinkage. MMP and ECM remodeling mechanisms can explain the difference between good and poor responders.

References:
P-77  Tuesday, October 9, 2018 6:30 AM

REGULATION OF A KEY DNA REPAIR GENE RAD50 IN HUMAN UTERINE FIBROIDS. Q. Yang, A. Laknau, M. Ali, L. Prusinski Fernung, T. Boyer, A. Al-Hendy. OB/GYN, University of Illinois at Chicago, Chicago, IL; Biochemistry and Molecular Biology, Augusta University, Augusta, GA; Molecular Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX.

OBJECTIVE: Uterine fibroids (UFs) are benign smooth muscle neoplasms with genetic abnormalities affecting up to 80% of women. The objective of this study was to investigate the expression and regulation of RAD50 encoding a key protein for initial processing of double-strand DNA breaks (DSB) prior to repair, and to determine if vitamin D3 can restore the DNA damage response (DDR) defect.

DESIGN: Laboratory research studies using human normal and UF tissues as well as corresponding Stro-1/CD44 stem cells (SCs).

MATERIALS AND METHODS: Surgically removed fresh human UF tissues and adjacent myometrial tissues were collected, and subjected to myometrial and UF SC isolation using dual Stro-1 and CD44 surface markers. Immortalized human UF cells (HuLM) were transduced with Ad-Ezh2 (Adenovirus expressing Ezh2 under CMV5 promoter) to introduce the exogenous expression of Ezh2. Nuclear-cyttoplasmatic fractionation was conducted for subcellular localization of RAD50. Statistical analysis was done using a single factor analysis of variance (ANOVA) and the standard two-sample Student’s t-test.

RESULTS: Western blot and immunohistochemistry analysis demonstrated that RAD50 protein expression levels were significantly downregulated in UF tissues compared to matched myometrium (N=10; p<0.05), which negatively correlated with estrogen receptor expression. The UF SCs also exhibited downregulation of RAD50 protein expression vs myometrial SCs (p<0.05). Since the polycomb repressive complex 2 (PRC2), the mammalian polycomb group protein EZH2 impairs the catalytic subunit of PRC2 regulated RAD50 expression. Ectopic introduction of Ezh2 by viral infection decreased the expression of RAD50 in both cytoplasm and nucleus. The decreased expression of RAD50 was correlated with increased expression of Ezh2. Notably, treatment of UF SCs with vitamin D3 was capable of increasing the expression of RAD50 significantly (p<0.05).

CONCLUSIONS: Our studies provide the first evidence showing that the expression of the key DSB repair protein RAD50 is downregulated in both fibroid tumors and SCs compared to matched adjacent myometrial tissues and SCs, respectively. Importantly, polycomb protein EZH2 regulates RAD50 through epigenetic marker H3K27me3. Notably, vitamin D3 treatment is capable of restoring the DDR suggesting that vitaminD3/receptor axis links to DNA damage repair.

References:

Supported by: This work was supported in part by NIH grant R01 HD094378-01

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OBJECTIVE: Mitotic errors that occur during post-zygotic cell division lead to mosaicism in human embryos. Research suggests a higher incidence of mosaicism in day 3 embryos, suggesting that embryos with complex mitotic-derived aneuploidy are more likely to arrest. Mosaicism may have been initially overestimated in day 3 cleavage stage embryos due to technical limitations (i.e. FISH on single blastomeres). Few studies have evaluated mosaicism throughout embryo development, using NGS—which allows for high resolution copy number variant (CNV) analysis. The purpose of the study was to characterize the degree of mosaicism according to embryo developmental stage, day of development, viability, and morphology.

DESIGN: Prospective cohort study

MATERIALS AND METHODS: Patients who donated fresh embryos, during IVF, from January-June 2016. Embryos were collected from day 3 to 7 and biopsied, with ~4 cells removed for aneuploidy screening by NGS using the ReproSeq assay. Samples with <100,000 reads and with Metadata of the absolute values of all Pairwise Differences (MAPD) >0.3 were excluded. Mosaicism was identified based on intermediate position CNV (between disomy and aneuploidy, 1.2-1.3 or 2.2-2.8). Student’s t-test, chi-square and linear regression was used for analysis.

RESULTS: Of the 78 embryos (41 blastocyst/29 cleavage), 63 were aneuploid, with 92% displaying varying degrees of mosaicism. The number of mosaics did not vary according to embryo stage (p=0.6). Mosaicism was most often absent in blastocysts (26.8% vs. 5.2%, p=0.03). Mosaics were not modified by developmental arrest (β=1.6, p=0.2), number of cells on day 3 (β=0.4, p=0.2), or ICM grade (β=0.06). Controlling for day of development mosaicism increased in blastocysts with poor expansion (β =7.3, p=0.001) and low trophectoderm grade (β =-7.9, p=0.001).

CONCLUSIONS: Given the consistent level of mosaicism detected from the cleavage to blastocyst stage and the lack of association with developmental arrest, our findings refute the hypothesis that complex mitotic errors lead to negative selection. This is the first report of an association between increasing degree of mosaicism and poor expansion and trophectoderm grade. This finding supports the theory of progressive clonal depletion as a compensatory mechanism against postzygotic mitotic errors, which could translate into limited proliferation and increased apoptosis within the trophectoderm. Future research is required to: 1) overcome technical and biological limitations to the accurate assessment of mosaicism, 2) understand the diverse molecular mechanisms contributing to mitotic error, and 3) define the impact of mitotic errors in preimplantation embryogenesis.

References:

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OBJECTIVE: Hereditary cancer syndrome carriers require vigilant screening to prevent cancer-associated morbidity and mortality. Women who have not completed childbearing may undergo oocyte/embryo cryopreservation, particularly prior to risk-reducing surgery. Preimplantation genetic testing for monogenic disorders (PGT-M) may be used to select unaffected embryos to prevent cancer risk to offspring. The purpose of the study was to survey BRCA carriers’ knowledge and opinions on fertility preservation and PGT-M to identify key factors that impact decision-making.

DESIGN: Prospective survey study

MATERIALS AND METHODS: A 33-question online survey was conducted between April-May 2018. The survey was publicized to women with hereditary cancer syndromes who subscribed to newsletters/social media posts from a non-profit advocacy group. The survey assessed demographics and reproductive status and investigated respondent knowledge/attitudes regarding diminished ovarian reserve, oocyte/embryo cryopreservation, and PGT-M. Descriptive statistics and binary logistic regression were used.
RESULTS: Of the respondents who completed the survey (n=140), 50% were reproductive aged. The majority were college educated (89%) and married (73%), with 20% desiring future children. BRCA 1 (36.2%) and BRCA 2 (46.9%) carriers were most prevalent. Mean age at mutation testing was 41.3 ± 12.8y. Of those that underwent risk reducing surgery (70%), 67% had ovaries removed. PGT-M awareness was higher in younger patients (p=0.02) without cancer (p=0.04). Of those familiar with PGT-M (43.6%), few (17%) stated they would consider using it. Most respondents (69%) were unaware that oocytes cannot undergo PGT-M. Only 16% had consulted with a reproductive endocrinologist (RE) for family planning. Despite this, 44% were aware of fertility preservation and would freeze oocytes/embryos proactively. Top concerns included financial burden (69.8%) and psychological distress (48.7%).

CONCLUSIONS: Individuals with cancer-predisposing mutations are faced with complex challenges that require counseling regarding medical implications, fertility preservation, and PGT-M to prevent transmission to offspring. Our findings show a need for earlier mutation screening to maximize the opportunity for fertility preservation and PGT-M. There is an opportunity to increase patient awareness about reproductive options, particularly by OB/GYNs and geneticists who could implement early referral to a RE for counseling. Potential barriers to patients’ accessing available options may be alleviated by promoting access to ART (including IVF-PGT) and by a multidisciplinary approach involving psychological support.

P-80 Tuesday, October 9, 2018 6:30 AM
GAUCHER’s DISEASE CARRIERS DEMONSTRATE IMPROVED ART OUTCOME. L. Sekhon, a,b Z. Luscher, a T. G. Nazem, a,b J. Lee, b L. Grunfeld, b A. B. Copperman. a,b Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY; bReproductive Medicine Associates of New York, New York, NY.

OBJECTIVE: Gaucher’s disease is an autosomal recessive glycolipid storage disorder, caused by a mutation in the gene coding for the lysosomal enzyme, glucocerebrosidase (GBA). Homozygous females have delayed menarche/puberty, impaired fertility, adult pregnancy outcomes, suggesting that Gaucher cell infiltration affects reproduction. Enzyme replacement therapy can reduce risk of early pregnancy loss in women with the full mutation. Data on the effect of a single GBA mutation on female reproduction therapy can reduce risk of early pregnancy loss in women with the full mutation. Data on the effect of a single GBA mutation on female reproduction is limited. The study objective was to examine ovarian reserve/ART outcome of Gaucher’s carriers.

RESULTS: GBA mutation carriers (n=1214) (Table 1). Controlling for age, GBA heterozygosity did not impact AMH (β =0.9, p=0.19) or BAFC (β =0.9, p=0.37). After controlling for age and AMH, GBA carriers had increased oocyte yield (β =3.3, p=0.006). Carriers had lower fertilization rate, greater mean number embryos, more blastocysts, and lower rate aneuploid embryos. Controlling for age and AMH, carrier status did not impact fertilization (β =0.016, p=0.74), blastulation (β =0.04, p=0.45) or aneuploidy (β =0.05, p=0.4).

After adjusting for confounders, carriers (n=21) compared to controls (n=437) had no difference in implantation (OR 0.8 [0.3-2.1], p=0.6), ongoing pregnancy (OR 2.8 [0.9-8.8], p=0.08), live birth (OR 0.7 [0.2-2.1], p=0.5), or clinical pregnancy loss (OR 1.4 [0.2-11.3], p=0.8).

CONCLUSIONS: Gaucher’s carriers were demonstrated to have similar ovarian reserve and embryo aneuploidy rates compared to non-carriers. However, carriers had more eggs in response to ovarian stimulation and more embryos available than non-carriers. This may prove to be an example of ‘heterozygote advantage’. The advantage in carriers is likely limited to folliculogenesis and oocyte and embryo development, as the presence of euploid embryos at transfer were shown to have similar odds of implantation and live birth as compared to non-carriers. Large scale studies are required to further elucidate the paradoxical relationship between GBA carrier status and ovarian response to COH.

References:

Table 1: Cycle characteristics and outcomes for GBA carriers and controls.

<table>
<thead>
<tr>
<th></th>
<th>GBA Mutation Carriers</th>
<th>Controls</th>
<th>p value</th>
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</thead>
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<tr>
<td>Oocyte age</td>
<td>35.1 ± 5.6</td>
<td>36.1 ± 4.8</td>
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<td>AMH</td>
<td>4.5 ± 7.6</td>
<td>3.4 ± 4.1</td>
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<td>Oocytes retrieved</td>
<td>17.1 ± 15.5 (937)</td>
<td>12.7 ± 9.0 (8828)</td>
<td>0.05</td>
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<td>Fertilization Rate</td>
<td>60.3% (518/859)</td>
<td>72.3% (6381/8828)</td>
<td>&lt;0.0001</td>
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<td>Blastulation rate</td>
<td>77.2% (400/518)</td>
<td>63.8% (4071/6381)</td>
<td>&lt;0.0001</td>
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<td>Aneuploidy Rate</td>
<td>35.8% (85/237)</td>
<td>45.6% (1077/2361)</td>
<td>0.004</td>
</tr>
<tr>
<td>Single euploid FET cycles</td>
<td>21</td>
<td>437</td>
<td></td>
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<td>Implantation rate</td>
<td>66.7% (14/21)</td>
<td>58.8% (257/437)</td>
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<td>Ongoing pregnancy rate</td>
<td>61.9% (13/21)</td>
<td>53.3% (233/437)</td>
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<tr>
<td>Clinical pregnancy loss rate</td>
<td>7.1% (1/14)</td>
<td>9.3% (24/257)</td>
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<tr>
<td>Live birth rate</td>
<td>53.8% (7/13)</td>
<td>41.3% (93/225)</td>
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</table>

P-81 Tuesday, October 9, 2018 6:30 AM
PHYSICIAN KNOWLEDGE, ATTITUDES, AND PRACTICE REGARDING EXPANDED CARRIER SCREENING. S. Chang, a,b L. Sekhon, a,b T. G. Nazem, a,b J. Friedenthal, a,b J. Lee, a A. B. Copperman, a,b Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY; aReproductive Medicine Associates of New York, New York, NY.

OBJECTIVE: The number of disorders detected by expanded carrier screening (ECS) has increased dramatically over the past few years. Traditionally, carrier screening for single-gene disorders was limited to a few severe diseases in populations with a high prevalence. Modern advances in sequencing technology and decreases in cost have made universal screening of many diseases viable. Given the expansion of genetic testing platforms, understanding the knowledge base and attitudes of the physicians who will be employing these tools will be increasingly important. The study aimed to understand individual and practice-related factors that influence physician use of ECS.

DESIGN: Prospective

MATERIALS AND METHODS: A 20-question online survey was conducted between November 2017-February 2018. Obstetrician/gynecologists (OB/GYNs) from a single institution participated in a survey assessing knowledge and use of ECS. Descriptive statistics were computed, and chi square tests were performed to compare frequencies according to demographics and practice characteristics.

RESULTS: A total of 42 responses were collected. Nearly half of respondents (46%) were generalist OB/GYNs (25% practiced GYN only). Respondents were roughly split between university hospitals (44%) and private...
settings (56%). The majority of respondents (76%) routinely recommended ECS to patients. Eighty five percent of respondents believed that all patients should be offered ECS, ideally prior to pregnancy. ECS knowledge base was not influenced by provider age or years from training. Compared to providers in an academic setting, providers in the private setting were more likely to know the correct technology used for ECS (82.6% vs. 61.1%, p = 0.12) and the number of diseases screened (91.3% vs. 66.7%, p = 0.04). Compared to generalists, subspecialists were also more likely to answer these questions correctly (81.8% vs. 70%, p = 0.44; 100% vs. 76.7%, p = 0.07). The top 3 concerns limiting the use of ECS were time spent on counseling patients about results (56%), financial burden to patients (54%), and time spent on follow-up on patient results (44%).

**POLYMORPHIC VARIANTS OF CHROMOSOMES DECREASE CLEAVED EMBRYOS RATE IN VITRO FERTILIZATION AND EMBRYO TRANSFER TREATMENT.**

S. Li, D. Zhou, Y. Zhang, J. Yang, W. Xu. *Reproductive Medical Center, Renmin Hospital of Wuhan University, Wuhan, China; Renmin Hospital of Wuhan University, Wuhan, China.*

OBJECTIVE: This retrospective study comprehensively explore effect of chromosomal polymorphisms on IVF-ET outcomes.

DESIGN: 1415 infertile couples who had received their first IVF-embryo transfer treatment cycle in our hospital were selected for this retrospective study, and divided into four groups: 1182 couples with normal chromosomes (Group 1), 233 couples with chromosomal polymorphism were divided into three subgroup as their polymorphism types: 129 couples with (1qh+, 9qh+, and 16qh+/-) visualized polymorphic variations in the length of the centromeric heterochromatin on the long arms of chromosomes 1, 9, and 16 (Group 2); 36 couples with distinct polymorphic variants of the size of satellites (ps+) and lengths of stalls(ps)+ of the acrocentric chromosomes (Group 3); And 48 couples with pericentric inversion of chromosomes 9 (Group 4).

MATERIALS AND METHODS: The clinical outcomes include fertilized rate, embryo cleaved rate, good quality embryos rate, clinical pregnancy rate, implantation rate and early stage miscarriage rate after IVF-embryo transfer treatment were compared.

RESULTS: There were no statistically significant differences among the four groups in patient’s fertilization rate, good quality embryos rate, clinical pregnancy rate (CPR) and implantation rate. But the chromosomal polymorphism groups (Group 2, Group 3 and Group 4) had lower cleaved embryos rate comparing with control group (Group 1) (95.83, 95.05, 89.90 and 97.5% respectively, P < 0.05). The first trimester pregnancy loss rates in Group 4 patients were higher than in control group (25% versus 4.4%, P < 0.05), but not in Group 2 and Group 3.

CONCLUSIONS: Chromosomal polymorphism carrier could decrease cleaved embryos rate, chromosomal pericentric inversion may increase first trimester pregnancy loss and impact IVF outcomes. We should afford individual genetic counseling suggestion according to the polymorphism types.

**REFERENCES:**


**FERTILITY & STERILITY**

P-83 Tuesday, October 9, 2018 6:30 AM

**FAMILY HISTORY MATTERS: A CASE SERIES OF ALLELE RECLASSIFICATIONS ON EXPANDED CARRIER SCREENING SECONDARY TO PRIOR MOLECULAR DIAGNOSES.**

L. J. Isley R. Mar-Heyming, Counsyl, South San Francisco, CA.

OBJECTIVE: Counsyl uses internal criteria adapted from the American College of Medical Genetics and Genomics (ACMG) guidelines to classify alleles associated with autosomal recessive and X-linked diseases on an expanded carrier screening panel. Significant enrichment of the allele frequency in cases vs. controls is a key line of evidence used in variant classification. This study uses a case series to explore whether knowledge of patient family history—even in the prenatal/preconception carrier screening setting—may be useful for variant curation and interpretation of carrier screening results by the testing laboratory.

DESIGN: Manual database search to identify relevant cases.

**MATERIALS AND METHODS:**

- Cases were identified via a manual database search using key phrases pertaining to allele reclassifications that were based on family history.
- **RESULTS:** Three cases were identified in which a confirmed molecular diagnosis of a family member resulted in the reclassification of an allele from variant of uncertain significance (VUS) to likely pathogenic. Alleles included variants in SGSH, NPC, and PAH; all three were rare with a lack of functional data in the literature. At the time of the initial classification, the case count of affected individuals carrying these variants was insufficient to meet statistical significance, thus the variants were classified as VUS. However, upon receipt of a confirmed diagnosis in an affected family member, the respective increments in case counts triggered a change in classification of the variants. The individuals pursuing carrier screening were subsequently reported as having a positive result for the condition in question.

**CONCLUSIONS:** Knowledge of patient family history and established familial mutations may be useful for variant classifications in the carrier screening setting. The laboratory’s knowledge of additional cases may lead to reclassification of an allele, which may help to define a plan for carrier screening of the reproductive partner to assess risk of an affected offspring. Providers should be aware of the importance of gathering a detailed family history in the preconception/prenatal screening, which is critical not only for being able to offer appropriate carrier screening, but also to guide appropriate variant interpretation by the laboratory.

**References:**


**Supported by:** This study was supported internally by Counsyl.
using a standard morphological grading system prior to trophectoderm biopsy for PGT (mean blastocysts biopsied 10.1±6.0). Chi-Square analysis for independence was performed to determine the relationship between the highest grade, monogenic, unaffected blastocyst in an embryo cohort and its chromosomal constitution, with significance at P<0.05.

RESULTS: Overall, 41.9% of blastocysts biopsied were affected with the monogenic disorder tested. Aneuploidy was observed in 58.6% of blastocysts biopsied, independent of the monogenic mutation. The highest grade, monogenic, unaffected blastocyst was identified as aneuploid in 54% of embryo cohorts representing 37.5% of the PGT cycles. Therefore, over a third of the PGT-M cycles would have resulted in the transfer of an aneuploid, monogenic, unaffected embryo based on blastocyst morphology alone without aneuploidy screening. Even younger women (≤34 years) would have transferred an aneuploid, monogenic, unaffected embryo in 31.8% of PGT-M cycles. Errors for all 23 pairs of chromosomes, including both losses and gains, were observed in these highest grades, aneuploid, monogenic, unaffected blastocysts. However, since PGT-A was performed in all these PGT-M cycles a euploid, unaffected blastocyst was transferred, resulting in a 62.2% live birth rate.

CONCLUSIONS: Analysis of this consecutive large cohort of PGT-M cycles revealed that an aneuploid, monogenic, unaffected blastocyst would have been selected and transferred in 37.5% of frozen embryo transfers if the criteria were based on blastocyst morphology alone without additional aneuploidy screening. Aneuploid embryos result in implantation failure, miscarriage or a chromosomally aneuploid fetus. The ability to select euploid, monogenic, unaffected blastocysts in a PGT-M cycle allows for the highest chance of a chromosomally normal, monogenic unaffected live birth.

P-85 Tuesday, October 9, 2018 6:30 AM

PREVALENCE OF FRAGILE X PREMUTATION CARRIERS AMONG FEMALE PATIENTS SEEKING FERTILITY TREATMENTS. R. Allen,* K. Owens,* C. Terhaar,* C. Settler,* J. Omark,* F. Fernandes,* N. Resetkova,* Medical Affairs, Progenity, Inc., Ann Arbor, MI; bGenetic Counseling Program, University of Texas, Houston, TX; cLaboratory Affairs, Progenity, Inc., Ann Arbor, MI; dBoston IVF, Waltham, MA.

OBJECTIVE: The association between fragile X premutations and infertility due to primary ovarian insufficiency has previously been well-defined, and current societal guidelines recommend fragile X testing for women with this history. However, it is unclear whether the prevalence of fragile X alleles is higher in general among women with fertility issues than the general population. This study compares the prevalence of fragile X premutation and/ or gray zone allele carriers among females seeking fertility treatments to rates in a general referral population.

DESIGN: A retrospective review was conducted of fragile X carrier testing results for over 200,000 female samples referred for testing at a large commercial laboratory. Results were grouped by type (premutation and gray zone) and practice type (reproductive medicine vs. other).

MATERIALS AND METHODS: The prevalence of premutation and gray zone alleles in samples ordered by reproductive medicine clinics were compared to the prevalence among samples ordered by non-fertility clinics. Binomial confidence intervals (CI) for both groups were approximated using Agresti-Coull intervals and compared using A/B (split-run) testing.

RESULTS: The prevalence of premutation carriers within the general population was 1 in 211, and the prevalence within the reproductive medicine population was 1 in 141. This difference was statistically significant (p<0.005). The prevalence of gray zone alleles within the general population was 1 in 50, compared to 1 in 44 in the fertility population. This difference was not statistically significant (p=0.089).

CONCLUSIONS: Our results from a large clinical testing laboratory indicate that there is a statistically significant difference in the prevalence of premutation alleles in the reproductive medicine group versus the general population, but not for gray zone alleles. This data adds to the previous literature on the prevalence of fragile X premutation alleles among females seeking fertility treatments. Current societal guidelines recommend fragile X testing for women with a history of ovarian insufficiency. This study suggests that expanding those recommendations to include testing for any women with a fertility indication will help identify more fragile X carriers, allowing for critical counseling and family planning discussions for these patients.

VALUE AND USAGE OF SEMEN DONORS’ ECS RESULTS BY PROSPECTIVE RECIPIENTS. S. Melnick. Genetics, California Cryobank, Los Angeles, CA.

OBJECTIVE: Expanded carrier screening (ECS) involves pan-ethnic carrier screening for 50+ recessively inherited disorders. This testing is has been performed with greater frequency on gamete donors to aid prospective recipients in their donor selection process. This study aimed to examine how semen donor recipients valued and used this information in selecting respective donors.

DESIGN: An ECS panel of over 260 diseases was performed on semen donor applicants. Applicants who screened positive for mutations in the CF, ATM, SMN1, FH, and NBN genes were excluded from the program. Vials from 123 donors who had ECS were available for use between May 2017- April 2018; 57% percent of donors were identified as carriers for at least one autosomal recessive condition. Vials from ~500 other donors who had limited, ethnic-based carrier screening, with negative results, were also available during this time.

MATERIALS AND METHODS: Online survey of clients who ordered semen vials between October 5, 2017 and April 5, 2018

RESULTS: Responses were received from 1138 clients, including 139 who ordered vials from donors with a positive result on ECS, 201 who ordered vials from donors with a negative result on ECS, and 798 who ordered vials from donors without ECS. The donor feature that the most clients considered to be “very important” was the donor’s family medical history (88.94%). Thirteen percent of clients reported that they either did not consider the donor’s genetic testing at all in the selection process (Table 1). Notably, 44.07% of clients who ordered vials from donors who did not have ECS had stated that it was “very important” to them to choose a donor who had ECS performed. Additionally, 3.75% of clients who chose a donor with a positive result on ECS indicated “I wanted a donor with negative results regardless of whether the donor had basic screening or ECS.”

CONCLUSIONS: Results indicate that the availability of ECS results did not necessarily factor into the decision-making process for clients when selecting a sperm donor. A higher percentage of clients valued a donor’s family medical history, ethnicity, and other features as very important compared to the percentage who considered ECS to be very important. The study demonstrates that while expanded genetic testing of donors may be important to some clients when selecting a sperm donor, there are many other factors that influence their selection. Given the contradictory responses identified, additional support or client education may be beneficial to help donor recipients identify donors that meet their preferences.

| TABLE 1. Value of Donor Characteristics to Clients’ Donor Selection Process |
|---------------------------------|-----------------|-----------------|
| Height                          | 49.21%          | 46.12%          | 4.67%           |
| Donor had Psychological Screening | 75.31%          | 20.59%          | 4.10%           |
| Donor had a Criminal Background Check | 68.77%          | 21.92%          | 9.32%           |
| Ethnicity                       | 72.66%          | 24.78%          | 2.56%           |
| Family Medical History          | 88.94%          | 10.71%          | 0.35%           |
| Donor Type (ID Disclosure, Open, or Anonymous) | 53.23%          | 36.96%          | 9.81%           |
| Donor had expanded genetic testing for 260+ recessive conditions | 49.34%          | 32.27%          | 18.39%          |

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ASRM Abstracts
P-87 Tuesday, October 9, 2018 6:30 AM

POSITIVE CLASSIC GALACTOSEMIA CARRIER STATUS DOES NOT IMPACT OVARIAN RESERVE. T. A. Caccinone, a L. Sekhon, a,b T. G. Nazem, a,b D. Gounko, a J. Lee, a L. Grunfeld, a,b A. B. Copperman, a,b Reproductive Medicine Associates of New York, New York, NY; Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY.

OBJECTIVE: Classic galactosemia is an inherited disorder of galactose metabolism caused by mutations in the galactose-1-phosphate uridylyltransferase (GALT) gene. Even with early adoption of the recommended galactose-restricted diet, over 80% of affected females develop Premature Ovarian Insufficiency (POI). In a study by Cramer et al, female carriers were observed to demonstrate an increased likelihood of infertility and early menopause. Conversely, a Dutch study by Knauff et al. found no difference in ovarian reserve when comparing classic galactosemia carriers and controls. Thus, we explored the relationship between classic galactosemia carrier status and ovarian reserve in the context of a more ethnically diverse group of patients undergoing fertility treatments.

DESIGN: Retrospective

MATERIALS AND METHODS: The study included patients who underwent fertility assessment and completed expanded carrier screening between June 2012-March 2018. Day 3 Follicle Stimulating Hormone (FSH), Anti-Mullerian Hormone (AMH), and antral follicle count (AFC) were compared between female heterozygote carriers for classic galactosemia and negative controls. Student’s t-test and a multivariate linear regression model were used for data analysis.

RESULTS: Female heterozygous carriers for classic galactosemia (n = 43) were compared to non-carriers (n = 7,777). Baseline demographic factors and measures of ovarian reserve are shown in Table 1. When controlling for age, positive classic galactosemia carrier status was not correlated with Day 3 FSH (β =-0.7, p =0.22), AMH (β =-0.04, p =0.95), or BAFC (β =-1.3, p =0.18).

Comparison of mean age and ovarian reserve markers between galactosemia carriers and controls

<table>
<thead>
<tr>
<th>Galactosemia carriers</th>
<th>Negative Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=43)</td>
<td>(n=7777)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>35.8 ± 4.4 (21.7-43.4)</td>
<td>35.7 ± 5.0 (20.7-49.5)</td>
</tr>
<tr>
<td>Day 3 FSH</td>
<td></td>
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<tr>
<td>7.9 ± 3.6</td>
<td>7.2 ± 3.7</td>
</tr>
<tr>
<td>AMH</td>
<td></td>
</tr>
<tr>
<td>3.6 ± 3.9</td>
<td>3.5 ± 4.7</td>
</tr>
<tr>
<td>BAFC</td>
<td></td>
</tr>
<tr>
<td>12.3 ± 7.0</td>
<td>10.9 ± 6.8</td>
</tr>
</tbody>
</table>

CONCLUSIONS: In a large, single center, ethnically diverse population of women presenting for fertility evaluation and treatment, classic galactosemia carrier status does not demonstrate diminished ovarian reserve. Our study provides additional support to the findings published by Knauff et al and offers further reassurance to female carriers of classic galactosemia. Future studies should aim to: 1) Confirm our findings and those of Knauff et al. with a larger sample size and 2) investigate whether specific GALT variants confer differential effects on ovarian reserve given the considerable allelic heterogeneity observed for this gene. In addition, further studies to help elucidate the causative mechanism of POI in affected females is crucial in order to facilitate better treatment options for these patients.

References:

P-88 Tuesday, October 9, 2018 6:30 AM

FERTILE PATIENTS UNDERGOING IVF FOR PGT-M REQUIRE MORE OOCYTE RETRIEVALS THAN INFERTILE COUNTERPARTS, BUT ACHIEVE COMPARABLE OUTCOMES. T. A. Caccinone, a N. Hertlihy, a T. G. Nazem, a,b D. Gounko, a J. Lee, a A. B. Copperman, a,b Reproductive Medicine Associates of New York, New York, NY; Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY.

OBJECTIVE: Couples at risk of having a child with a genetic disorder often use preimplantation genetic testing for monogenic disorders (PGT-M). PGT-M requires IVF even though most of these couples do not suffer from infertility. Many assume their lack of infertility confers higher success rates than those of women with infertility. However, due to the exclusion of affected embryos, couples using PGT-M have fewer embryos available for transfer than infertile counterparts. Thus, predicting outcomes for fertile patients using PGT-M is challenging, particularly regarding the number of cycles needed to achieve pregnancy with concurrent testing for aneuploidy (PGT-A). This study aimed to determine outcomes for couples who underwent IVF with PGT-M/PGT-A.

DESIGN: Retrospective

MATERIALS AND METHODS: Infertile patients who did IVF/PGT-A and patients who did IVF with PGT-M/PGT-A between 2014-2018 were included. Patient age, anti-mullerian hormone (AMH), basal antral follicle count (BAFC), number of oocytes retrieved, blastocysts biopsied, euploid embryos, affected/unaffected/carrier embryos, vaginal oocyte retrieval (VOR) cycles, and frozen embryo transfer (FET) cycles needed to achieve pregnancy were examined. Clinical pregnancy (CP) (defined as sonographic evidence of a gestational sac), ongoing pregnancy (OP) and early pregnancy loss rates were determined. Patients who did PGT-A/PGT-M were compared to those who did PGT-A alone. Data was analyzed with a T-test, chi square and multivariate logistic regression.

RESULTS: A total of 992 patients underwent IVF with PGT-A: 90 without an infertility diagnosis did PGT-M/PGT-A and 902 with infertility did PGT-A alone. Patients who did PGT-M/PGT-A were significantly younger than those who did PGT-A only. Both groups had comparable AMH, BAFC, number of oocytes retrieved and fertilized, and number of blastocysts biopsied (Table). Patients who did PGT-M/PGT-A required more VOR cycles than those who did PGT-A alone (1.5 ± 0.85 vs. 1.2 ± 0.27, p =0.002) but both groups underwent a similar number of FET cycles. The rate of CP and OP per FET was comparable between groups before and after adjusting for confounders.

CONCLUSIONS: Due to the growth of expanded carrier screening, PGT-M will likely become a routine part of treatment for the modern IVF patient. In this study, patients who sought IVF for PGT-M had comparable IVF and pregnancy outcomes to their counterparts who underwent similar procedures for infertility. While these patients pursuing PGT-M/PGT-A may require 20% more VOR cycles to obtain euploid, unaffected embryos, they can be reassured that IVF/PGT-A success rates for their age bracket are representative of their probability of success. With targeted counseling, clinicians can equip couples for the emotional and financial undertakings of IVF with PGT-M/PGT-A and guide them to realizing their goals of conceiving a healthy child.

References:
sample size of 93 patients per group was needed to detect a 20% difference in aneuploidy rate with 80% power (\(\alpha=0.05\)).

RESULTS: Of 6,249 cycles, a 11% prevalence of polymorphism was found on the entire population. Of the 748 patients included in the analysis, the prevalence of any MTHFR mutation was 75.9%, (n=568). Controls consisted of patients without a MTHFR polymorphism (n=180). Most common mutated alleles were C677T 46.3% (n=263), A1298C 35.2% (n=200), and the compound mutation (A1298C+C677T) 18.4% (n=105). Overall the aneuploidy rate was similar among non-MTHFR carrier patients (49%) as compared with all MTHFR mutation carriers (50%, \(p=0.69\)). After the data was evaluated using a Generalized Estimating Equation (GEE) model; no association was found with the presence of any MTHFR variant and the odds of aneuploidy (L’Beta 0.83, C95% 0.50-1.14, \(p=0.26\)). There was a positive association with increasing oocyte age with the odds of aneuploidy OR 0.19, (C95% 0.15-0.24, \(p<0.0001\)). After the data was evaluated using multivariate logistic regression; no association was found with the odds of aneuploidy when analyzing the different allele types ((A1298C, OR 1.22 (0.74 - 1.99, \(p=0.42\)); C677T, OR 0.87 (C95% 0.54 - 1.40, \(p=0.53\))).

CONCLUSIONS: Personalized and genomic medicine is expanding the understanding of how genetic variants can impact human condition and healthcare. By using big data and a systems-based approach, this study demonstrated the presence of the most common MTHFR genotype variants are not associated with the rate of embryo aneuploidy. Even after controlling for age and other potential confounders, patients who have a MTHFR polymorphism did not experience increased odds of embryo aneuploidy.

OBJECTIVE: Research demonstrates that the internet is widely utilized by individuals with infertility to provide information and support, including decision-making support. Despite a growing body of research into the benefits, and drawbacks, of internet use among individuals with infertility, there are no in-depth studies of the experience of internet use among those considering preimplantation genetic testing (PGT). This qualitative study investigated the ways individuals utilize the internet, and particularly social media, as they navigate their decision about whether or not to use PGT.

DESIGN: In-depth, qualitative interview study

MATERIALS AND METHODS: Individuals who recently considered or had undergone PGT (<6 months) were recruited. A total of 11 women and 4 men, representing 6 states participated (mean age 37.6±6.2 years). The video conference interviews lasted approximately 1 hour, and explored the decision to undergo, or not, PGT, including support resources. PGT-aneuploidy screening was the test considered by all, though the study was open to any PGT decision.

RESULTS: The internet, and particularly social media, emerged as an important resource for participants, especially women. (91%, vs. 25% of men) described broad involvement in on-line support networks, including local interest groups, national groups, social media, as well as following and/or creating podcasts, blogs, and Instagram accounts documenting the infertility treatment experience. Participants utilized the social media resources primarily to: (1) Identify reliable factual resources and narrative tales in order to navigate what they perceive as unclear or evolving medical information (e.g., whether PGT does or does not increase their chances of IVF success; feasibility and acceptability of transferring mosaic embryos); (2) Exchange support with peers who “get it”; (3) Use social media updates to relieve the burden of continually sharing their infertility treatment status with friends, relatives, “fertility friends,” and followers; and (4) De-stigmatize infertility through openness and visibility. Participants actively engaged in these platforms, even as they simultaneously expressed ambivalence about the biases inherent to the anecdotal information they gathered, as well as privacy concerns.

CONCLUSIONS: Social media has transformed the experience of infertility treatment decision-making. Individuals with infertility are informed and interconnected through social media, using it to seek information, support and understanding from others who share their experience. Assessing patients’ internet and social media use, and helping them sort through and interpret conflicting information available online may alleviate patient distress and enable more informed decision-making.

REPRODUCTIVE GENETICS

P-91 Tuesday, October 9, 2018 6:30 AM

NAVIGATING PREIMPLANTATION GENETIC TESTING DECISIONS IN THE AGE OF SOCIAL MEDIA: A QUALITATIVE STUDY. L. Rubin,\(^a\) L. Pastore,\(^b\) S. Subramony,\(^c\) M. Lobel,\(^d\) J. Stelling.\(^e\) Psychology, New School for Social Research, New York, NY;\(^b\) Stony Brook Medicine, Charlottesville, VA;\(^c\) New School for Social Research, New York, NY;\(^d\) Stony Brook University, Stony Brook, NY;\(^e\) SUNY Stony Brook, Commack, NY.

OBJECTIVE: To assess incidences and referral trends of XLD for PGT-M at a single genetic testing laboratory.

DESIGN: Retrospective Cross-Sectional Study

MATERIALS AND METHODS: Patient data including ethnicity, previous pregnancy outcomes, disease, referral reason (family history, affected child, expanded carrier screening - ECS), mutation identification method, and genetic testing results was recorded for patients who underwent PGT-M for an XLD from 1/2011-6/2017. Temporal changes in referral reasons and genetic testing results was recorded for patients who underwent PGT-M.

CONCLUSIONS: Benefited from broad screening of X-linked diseases (XLD). The average maternal age was 33.67 ± 4.42. The proportion of carrier screening was 53.85% (n=1163), family history 23.08% (n=510), affected child 15.38% (n=344), and affected child & family history 6.45% (n=144). The increase between 2011 and 2012 is likely due to the increase in awareness of the need for wide screening. The referral rate increased from 14% to 79% over the study period.

CONCLUSIONS: Benefited from broad screening of X-linked diseases (XLD). The average maternal age was 33.67 ± 4.42. The proportion of carrier screening was 53.85% (n=1163), family history 23.08% (n=510), affected child 15.38% (n=344), and affected child & family history 6.45% (n=144). The increase between 2011 and 2012 is likely due to the increase in awareness of the need for wide screening. The referral rate increased from 14% to 79% over the study period.

P-92 Tuesday, October 9, 2018 6:30 AM

PATERNAL MITOCHONDRIAL DNA PRESENT IN HUMAN EMBRYOS. C. Fischer,\(^a\) R. Prosser,\(^b\) R. Lobo,\(^d\) D. Egli.\(^c\) "Columbia University Medical Center, New York, NY;\(^b\)Ob/Gyn, Columbia University, New York City, NY;\(^d\) Saint Barthelémy.

OBJECTIVE: Mitochondrial DNA (mtDNA) is maternally inherited. Several mechanisms might account for the loss of paternal mtDNA, which
is introduced into the egg at fertilization: a bottle-neck effect during preimplantation development, active degradation of sperm mitochondria, or lack of replication competence of paternal mtDNA. Recent advances in MR have brought new attention to the significance of maternal inheritance of mtDNA. Mitochondria play a role in the transmission of mtDNA diseases, but an inherent consequence is the introduction of small numbers of a different mtDNA genotype. Concerns about MR as a form of treatment center on questions regarding the significance of this heteroplasm and acceptable levels of mtDNA heteroplasm is in resulting embryos, and whether haplotype matching donors is required. To this end, our objective was to assess the population of mtDNA in human pre-implantation embryos after parthenogenesis, fertilization, and spindle transfer in both preimplantation embryos and in ES cells.

DESIGN: Research protocol

MATERIALS AND METHODS: Healthy oocyte donors underwent ovarian stimulation with subsequent oocyte retrieval. All donors, including sperm donors, had mitochondrial genome and haplotype analysis. Donor oocytes either underwent MRT or ICSI with no other manipulation. All oocytes were enucleated, then nuclear transfer, ICSI, and fusion occurred. Embryos were evaluated the following day for fertilization and cultured up to 6 days. Embryos were used for ESC derivation and mtDNA analysis. Both embryos and ESC lines underwent deep DNA sequencing for mtDNA identity. Sequence reads were compared to reference sequences of genomes to identify source using SNP analysis. Sanger sequencing was used as another measure of mtDNA heteroplasm. ESC lines were karyotyped.

RESULTS: 9 out of 11 MRT pre-implantation embryos contained sperm mtDNA. The level ranged from 0-0.035%. 4 out of 7 MRT ESC lines contained sperm mtDNA in multiple passages. The level ranged from 0.002-0.0044%. In the ESC lines with no manipulation, sperm mtDNA was found in all lines. The median level was 0.003%.

CONCLUSIONS: We have found sperm mtDNA remains in pre-implantation embryos and ESCs. This finding suggests sperm mtDNA are replication competent and are not actively eliminated during embryogenesis. Our findings show that replication is inherently associated with low-level heteroplasmy between different mtDNA genotypes. An acceptable level of heteroplasmy after MRT may be close to that introduced by sperm.

Supported by: Supported by a grant from the American Society for Reproductive Medicine

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DIFFERENCES IN CORD BLOOD DNA METHYLATION IN WOMEN WITH PREECLAMPSIA VERSUS NORMOTENSIVE WOMEN. O. J. Carpintiel, C. J. Nobles, W. Guan, S. Mumford, M. J. Tsai, L. Sjarda, M. J. Hill, A. H. DeCherney, R. Silver, E. F. Schisterman, E. Yeung. "Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD; University of Minnesota, Minneapolis, MN; University of Utah, Salt Lake City, UT.

OBJECTIVE: Offspring of women with preeclampsia may have increased rates of neurodevelopmental disorders, hypertension and cardiovascular disease. This observation suggests fetal in utero epigenetic modifications in the setting of preeclampsia. We evaluated whether differences in DNA methylation in newborns of mothers with preeclampsia versus those without preeclampsia may partially explain the biological mechanisms of these associations.

DESIGN: An epigenome-wide association study was performed to examine DNA methylation in cord blood samples of infants born to women with and without preeclampsia.

MATERIALS AND METHODS: Cord blood samples were obtained from 391 singletons in the EAGeR Trial. Systolic and diastolic maternal blood pressures at 12 weeks gestation were evaluated as continuous variables and diagnosis of preeclampsia was determined by clinical record abstraction. DNA methylation was measured at over 50,000 CpG sites using the Infinium MethylationEPIC BeadChip. Linear mixed models were used to evaluate the association of preeclampsia, systolic and diastolic blood pressure with DNA methylation while accounting for batch effects, estimated cell counts and other confounding factors.

RESULTS: Of the 391 singletons, 36 (9.2%) had mothers with preeclampsia. After adjusting for maternal age, parity, smoking status, and mode of delivery, maternal systolic and diastolic blood pressures were associated with 6 CpG sites (p<1x10^-7) that were identified. Hypermethylation of the site associated with the SZRDI gene and hypomethylation associated with HYDIN, RALGDS2, PIK3R6, and SLC9A8 were observed among newborns of mothers with preeclampsia. As week 12 systolic and diastolic blood pressures increased, differences in DNA methylation were observed at 8 sites: hypermethylation was associated with the ARL13B gene, while hypomethylation was observed at the ARHGEP16, KCNMA1, NAV2 and GFR13 associated CpGs. None of these genes is known to be associated with preeclampsia or hypertension. However, SZRDI and ARL13B are highly expressed in the endometrium. KCNMA1, which helps regulate smooth muscle tone, is highly expressed in both the endometrium and brain. NAV2 plays a roll in neuronal cell growth and migration and is highly expressed in both brain and placenta.

CONCLUSIONS: These data demonstrate novel genes expressed in the endometrium and placenta that are differentially methylated in infants whose mothers had preeclampsia. These are candidate genes for further investigation of the potential associations with preeclampsia and developmental origins of health and disease.

Supported by: Supported by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health.

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FAMILY HISTORY OF GYNECOLOGICAL DISORDERS, TIME TO PREGNANCY AND PREGNANCY OUTCOMES. L. A. Bishop, K. Kim, S. Mumford, L. Sjarda, N. Perkins, R. Silver, E. Schisterman, A. H. DeCherney, M. J. Hill, NIH, Arlington, VA; NICHHD, Bethesda, MD; Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD; Epidemiology Branch, Div Intramural Pop Health Res, NIH, Bethesda, MD; University of Utah, Salt Lake City, UT; NIH, Germantown, MD.

OBJECTIVE: To determine if women with a family history of infertility have a longer time to pregnancy.

DESIGN: Cohort study of women enrolled in the EAGeR trial, which included 1228 healthy women with no known infertility or gynecologic disorders and ages 18-40 years. Participants had a history of 1-2 prior pregnancy losses and were followed for up to 6 menstrual cycles while attempting pregnancy and throughout pregnancy if they became pregnant.

MATERIALS AND METHODS: 1173 women completed a detailed questionnaire regarding family history of gynecological disorders. Reproductive disorders included ovarian cysts, endometriosis, uterine fibroids and polyps, ovulatory dysfunction, infertility, and other or unknown conditions. Pregnancy was detected with hCG and confirmed by ultrasound at 6-7 weeks gestation. Fecundability odds ratios (FOR) and 95% confidence intervals (CI) were determined using Cox proportional odds regression models for discrete survival time, accounting for left truncation and right censoring. For live birth and pregnancy loss, log-binomial regression models were used to estimate relative risk (RR) and 95% CI. All models were adjusted for age, BMI, and treatment arm.

RESULTS: Approximately 3% of participants had first-degree biological family members with a history of any reproductive disorder. Ovarian cysts and endometriosis were the most commonly reported conditions. Participants who denoted a family history of reproductive disorders had a longer time to pregnancy compared to those with no history [FOR 0.83, 95% CI 0.69, 1.00]. Accordingly, live birth rate was lower in women with a family history of reproductive disorders [RR 0.88, 95% CI 0.78, 0.99]. There were no associations between a family history of reproductive disorders and risk of pregnancy loss (RR 1.08, 95% CI 0.83, 1.42).

CONCLUSIONS: Women with first-degree relative with known gynecologic disorders have a longer time to pregnancy and lower birth rate than those without a family history of reproductive disorders. These findings suggest early intervention may be beneficial in women with a family history of reproductive disorders attempting pregnancy without success.

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OBJECTIVE: Among couples identified as at-risk by expanded carrier screening (ECS) during the preconception period, describe the impact of ECS results on planned and actual pregnancy management.

DESIGN: Retrospective survey of couples at increased risk for having an affected pregnancy.
MATERIALS AND METHODS: Couples who elected ECS and were found to be at increased risk of having a pregnancy affected by at least one of 176 genetic conditions were invited to complete a survey about the impact of ECS results on planned and actual pregnancy management.

RESULTS: Two hundred and thirty-five at-risk couples (ARCs) tested preconceptionally completed the survey. Sixty-six percent reported that they were altering or planning to alter pregnancy management to reduce the risk of having an affected pregnancy, including in-vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD), use of donated gametes, adoption, or avoidance of pregnancy altogether. Subsequent to preconception ECS, nearly half of ARCs had at least one pregnancy, resulting in 111 pregnancies. 39% of these pregnancies were achieved through IVF with PGD, reducing the risk of the pregnancy being affected. Prenatal diagnosis was pursued in one-third of pregnancies, with 36% of pregnancies found to be affected; more than half of affected pregnancies were terminated. In couples who chose not to pursue prenatal diagnosis, common reasons cited were to avoid risk to the pregnancy, a perception that it was not necessary because the couple had undergone IVF with PGD, a perception that the risk of an affected pregnancy was low, and that it “would not make a difference” in the management of the pregnancy. In those that did not undergo prenatal diagnosis, more than half of couples tested or planned to test the baby after birth. In babies tested after birth, 27% were found to be affected.

CONCLUSIONS: In a majority of couples surveyed, preconception ECS led to altered pregnancy management that reduced the risk of an affected pregnancy. In addition, ECS facilitated diagnosis and ruled out disease after birth. Supported by: This study was funded by Counsyl. All authors are employees of Counsyl. being used

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DETECTION OF COPY-NUMBER VARIANTS IN EXPANDED CARRIER SCREENING MAXIMIZES IDENTIFICATION OF CYSTIC FIBROSIS CARRIERS.
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OBJECTIVE: Cystic fibrosis is one of the most common autosomal recessive conditions. The disease is caused by mutations to the CFTR gene that include single-nucleotide variants (SNVs), short insertions or deletions (indels), and large copy-number variants (CNVs). Guidelines recommend routine carrier screening via targeted genotyping of 23 frequent variants, including SNVs and indels, but not CNVs; CNV screening is recommended only when a reproductive partner is a known carrier. Here we assess the performance and clinical impact of routinely screening for SNVs, indels, and CNVs in a next-generation sequencing (NGS)-based expanded carrier screen (ECS).

DESIGN: Retrospective analysis of pathogenic variants observed in a large deidentified cohort of ECS patients.

MATERIALS AND METHODS: Pathogenic variants in CFTR from a cohort of 103,718 patients were discovered via a validated NGS-based ECS. A custom algorithm identified CNVs via statistically significant relative deviations in NGS read depth, with downward depth deflections signifying deletions and upward deflections indicating duplications. Approximate CNV breakpoints were inferred from the NGS-depth profile across the gene. Positive CNVs were orthogonally assessed via multiplex ligation-dependent probe amplification (MLPA). 

RESULTS: The observed carrier rate for cystic fibrosis was 3.3% (N=3,394). The 23 commonly screened variants accounted for approximately 60% of observed carriers, and 98.7% of carriers had pathogenic SNVs or indels in the CFTR gene. Critically, the remaining 1.3% of carriers harbored a pathogenic CNV spanning at least one exon. We observed a diversity of breakpoints (25 unique CNVs in total), suggesting that a bioinformatics pipeline must have the flexibility to detect novel CNVs to maximize the detection rate of carriers. Simulations demonstrate robust detection of CNVs across a range of length scales, and further analysis reveals that NGS-based CNV detection has expected accuracy comparable to MLPA.

CONCLUSIONS: CNV detection is required to maximize identification of cystic fibrosis carriers and can be applied to all patients undergoing NGS-based ECS validated to detect these complicated variants. Clinical guidelines recommending screening of only the 23 most frequent variants miss critical identification of carriers and should be revisited. Supported by: Counsyl, Inc.
hypothesized that the aneuploidy patterns in BRCA patients may be different than an infertile population. To study this, we analyzed an anonymized data base from a major commercial reproductive diagnostics laboratory of women undergoing PGT.

**DESIGN:** Retrospective analysis of an anonymized data base at a commercial reproductive genomic laboratory. Women with BRCA mutations who also underwent PGT-A (PGT for aneuploidy) were age-matched at a 1:3 ratio with infertile women, and their PGT-A results were comparatively analyzed.

**MATERIALS AND METHODS:** Sixty-five women carrying BRCA mutation (study group) who underwent COH for PGT-A were compared with 193 age-matched infertile patients. All embryos were biopsied at blastocyst stage and aneuploidy testing was done on the Illumina MiSeq NGS method. Main outcome measures were embryo aneuploidy types and rates within each group.

**RESULTS:** The mean age of patients were similar in two groups (32.8 vs. 33.7 years, p=0.85). There were 277 and 1364 embryos analyzed in the BRCA+ and infertile patient groups. Mean number of embryos per patient was similar between the groups (7.2 vs 7.3, p=0.71). We found that the overall embryo aneuploidy rate was lower in the BRCA+ group (42%) vs. infertile patients (55%; p<0.01). When aneuploidy types were compared, Monosomy (14% vs. 22%; p<0.01) and Trisomy (10.8% vs 20%; p<0.001) rates were significantly lower in the BRCA+ patients. However, there was no difference between the BRCA+ and infertile patients in complex aneuploidy rate (11% vs 14%; p=0.074).

**CONCLUSIONS:** Aneuploidy rate and types appear to be different between the embryos of BRCA mutation carriers and infertile patients. While there is evidence from animal studies that BRCA is involved in meiotic function, comparison to an infertile population did not indicate increased aneuploidy in BRCA carriers. This could however be due to an elevated rate of aneuploidy in infertile patients as well as elimination of most severely BRCA-deficient oocytes at the primordial follicle stage or during follicle development. Further studies with non-infertile controls may provide further information.

**References:**
stress exposure, were stronger predictors of menstrual cyclicity (overall model $p < 0.001$, pseudo-$R^2 = 0.38$).

CONCLUSIONS: This analysis uncovered novel associations between subjectively-reported stress and ovarian reserve, while being unable to definitively demonstrate a relationship between subjectively-reported stress and menstrual cyclicity. Ongoing research may help to refine the true nature of the complex relationship between stress, personality and ovarian function.

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OBJECTIVE: Increased awareness of age-related decline in fertility in conjunction with advances in cryopreservation technology have led to a dramatically increased utilization of elective oocyte cryopreservation for social indications (“EOC”). Despite removing the experimental designation in 2013, the ASRM cites inadequate evidence about emotional hazards as a rationale to withhold its recommendation1. Recognizing the need to enhance our understanding of the EOC experience from the patients’ perspective, we sought to illuminate the personal experience and emotional response in a cohort of women who underwent EOC.

DESIGN: Qualitative thematic analysis

MATERIALS AND METHODS: Women who underwent EOC at a university center from 2012–16 were invited to participate in an online survey focused on decision regret. Data from this quantitative analysis was published separately. The questionnaire ended with an unstructured, open-ended question which allowed respondents to write in their own perspective on the EOC experience. Thematic content analysis was undertaken using qualitative methodology to identify emergent themes from these written responses.

RESULTS: Of the 201 women who participated in the survey, 117 (58%) provided a written response. Average age was 36 yrs at time of EOC. 74% were white; 76% possessed a graduate degree. Thematic analysis revealed four recurrent themes: 1) Contrasts with IVF patients (“Egg freezing patients ARE NOT the same as your IVF patients”), 2) Confutation of number of eggs frozen with fertility status (“Doing egg freezing just made it clear how hard it will be to become pregnant”), 3) Re-evaluation of priorities (“The process helped me evaluate what I really want in life”), and 4) Unanticipated emotional hazards (“I’ve had mental health concerns ever since I went through this procedure,” and “I felt terribly empowered and sad all at once”).

CONCLUSIONS: Because EOC is an elective medical intervention undertaken for social indications, patient-reported outcomes should dominate the assessment of the EOC experience. Women undergoing EOC may have distinct preparation and expectations compared with IVF patients, and may perceive differential treatment in an intimidated clinical setting. They may also experience increased distress if they equate “low” egg yield with impaired fertility. Providers should be aware that EOC has symbolic meaning in the lives of many women and may represent an important value clarification process. While many women report relief of pressure and new empowerment, others experience more complex emotional reactions including increased anxiety, shame, loneliness, diminishment and ambivalence. Providers should be cognizant of these potential psychological hazards, incorporate them as a vital component of informed consent and relationship self-esteem.

REFERENCES:

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RELATIONSHIPS AMONG PSYCHOSOCIAL CHARACTERISTICS IN MEN PRESENTING FOR FERTILITY EVALUATION. S. Quallich, K. Lindstrom, D. Quallich, M. Hajj-Moussa, J. M. Dupree, D. A. Ohl. Michigan Medicine, Ann Arbor, MI; Wayne State University, Detroit, MI.

OBJECTIVE: Psychosocial and sexual characteristics of men presenting for a new fertility evaluation are poorly described, as is willingness to complete a collection of survey instruments. Previous research suggests that men undergoing fertility evaluation experience anxiety, depression and sexual function issues, but these dimensions have not been examined with men as the sole subject. This is a prospective survey of men presenting for male infertility evaluations with validated psychometric instruments, building on our previous pilot data.

DESIGN: Prospective design

MATERIALS AND METHODS: All male patients $> 18$ presenting for infertility evaluations were eligible to participate and were approached during their first clinic visits. After informed consent, participants completed paper copies of a demographic form and validated psychometric instruments that assess stress, positive/negative affect, depression/anxiety, sexual function and relationship self-esteem.

RESULTS: 141 men were approached to participate, and 136 men were consented (96.5%); all 136 survey packets were completed in full. The partner was present for 53 men (39%). Average age was 35.28 ± 8.08 years; sample was predominantly Caucasian (n = 102). Instrument scores are presented in the table. Independent $t$ tests demonstrated no difference in scores with partners absent or present; therefore, correlation testing was performed on the full sample. There were large positive correlations between anxiety and negative affect ($r = .534$, $p < .001$) and anxiety and depression ($r = .533$, $p < .001$). There was a large negative correlation between positive affect and depression ($r = -.529$, $p < .001$). Regression analysis did not reveal a clear impact from any of the measured traits to the low score seen for the SEAR self-esteem subscale, although 24.3% of the variance was explained by the total IEF score and PANAS negative subscale together, and a large positive correlation was seen between the self-esteem subscale and the IEF total scale ($r = .467$, $p < .001$).

CONCLUSIONS: Men presenting for fertility evaluations reported moderate levels of stress, little depression, anxiety or negative affect and overall high levels of sexual function. In contrast, there were moderate scores for sexual relationship satisfaction and lower scores for sexual self-esteem reported. Results suggest that for men presenting for fertility evaluation prior to diagnosis, stress, anxiety and negative affect are factors in their psychosocial presentation, but additional psychosocial factors may influence their overall sexual self-perceptions.

REFERENCES:

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PREMATURE OVARIAN AGING IS A RISK FACTOR FOR BRUXISM. T. Kayani, T. Bunn, L. Pal. Wesleyan University, Orange, CT; Yale New Haven Hospital, New Haven, CT; Obstetrics, Gynecology & Reproductive Sciences, Yale School of Medicine, New Haven, CT.

OBJECTIVE: To determine if the prevalence of bruxism (teeth grinding) relates to reproductive aging.

DESIGN: Prospective observational study

MATERIALS AND METHODS: Women attending a reproductive endocrinology & infertility subspecialty clinic in a tertiary care facility ($n = 641$) completed a survey that inquired about symptoms of teeth grinding (day or night time), depression, anxiety, insomnia, interrupted sleep, and tinnitus. A subset ($n = 431$) was screened for depressive symptoms (PHQ). Indications for consultation were infertility, including diminished ovarian reserve (DOR), PCOS, premature ovarian insufficiency (POI), menopause, and osteoporosis. DOR and POI were categorized as premature ovarian aging (POA). Relationships between clinical diagnoses, age, depression, age, anxiety, sleep, tinnitus, and PHQ score with teeth grinding were determined. Multivariable logistic analysis identified independent predictors of bruxism.
RESULTS: Prevalence of bruxism was 29%. Depression (OR 2.5, 95% 1.7-3.7), anxiety (OR 3.8, 2.7-5.5), insomnia (OR 1.8, 1.3-2.7), interrupted sleep (OR 2.9, 2-4), tinnitus (OR 4, 2-7), white race (OR 1.8, 1.2-2.6) & age ≥ 38 (OR 1.5, 1-2.2) were significantly associated with bruxism. POA (n = 21, OR 2.9, 1.03-8.3) was associated with a significantly higher likelihood for bruxism compared to other clinical diagnoses after adjusting for age, anxiety, depression, sleep & tinnitus. Bruxism did not demonstrate any association with age appropriate menopause (n = 52, p = 0.05). On adjusted analysis, anxiousness (OR 2.9, 1.7-4.9) and interrupted sleep (OR 1.8, 1.1-3.1) were also predictive of bruxism.

CONCLUSIONS: Anxiety, interrupted sleep, and POA are independent predictors for bruxism. This relationship between POA and bruxism has not been previously reported, and merits further examination.

THE FERTILITY QUALITY OF LIFE AND SEXUAL DYSFUNCTION IN MEN SEEKING FERTILITY TREATMENT. Z. Zhang. Peking University Third Hospital, Beijing, China.

OBJECTIVE: Infertility has been reported to have a negative effect on sexual function, especially in men. With the rapid increase in the number of men seeking fertility treatment, there is urgent to better understand the interrelatonship between the fertility quality of life and sexual function. The aim of this study was to investigate the fertility quality of life (FertiQoL) and the prevalence of erectile dysfunction (ED) and premature ejaculation (PE) in infertile men.

DESIGN: Observational study.

MATERIALS AND METHODS: In a cross-sectional study, a total of 351 men seeking fertility treatment completed a questionnaire about sexual experiences and quality of life. ED was evaluated through the International Index of Erectile Function-15 (IIEF-5), ejaculation status was determined by the PE diagnostic tool (PEDT), and the quality of life was measured using the FertiQoL tool.

RESULTS: Reliability analyses for the FertiQoL tool demonstrate sufficiently strong fit (Cronbach's alpha=0.891). Social and relational domains of FertiQoL were lower in infertile men compared that reported in other countries. ED was found in 125 (35.6%) and PE in 90 (25.6%) subjects. The emotional, mind/body, relational and social domain scores of FertiQoL were positively associated with IIEF-5 score whereas scores were negatively associated with PEDT score. In a logistic multivariate model, emotion, relational and positive experiences with donor-linked peer contact. Findings hold implications for open-identification donors, with one unexpected outcome being that donors may link adults and families, regardless of interest.

Positive experiences with donor-linked peers suggest that benefits include more than information access, including relationships and sources of support that DC adults may not initially consider. Donor-linked peer contact appears to serve as an important, potential resource for adults in the unique context of being raised in a DC family.

Supported by: Gay & Lesbian Medical Association: Lesbian Health Fund

CONTACT AMONG ADULTS WHO SHARE THE SAME OPEN-IDENTITY SPERM DONOR. J. E. Scheib, E. McCormick, K. R. Haupt, S. Meola, A. Ruby, J. M. Benward. 1Psychology, The Sperm Bank of California & University of California, Davis, CA; 2University of California, San Diego, CA; 3Psychology, University of California, Davis, CA; 4The Sperm Bank of California, Berkeley, CA; 5Psychology, San Ramon, CA.

OBJECTIVE: Increased openness in sperm donor-conceived (DC) families has led to information seeking about donors and others who share a donor. “Donor-linked” individuals often are similar ages and unknown to each other. The current study examined the experiences of adults who had obtained their donor’s identity at one program. Here we focus on adult interest in and experiences with donor-linked peers.

DESIGN: Retrospective interview, online questionnaire

MATERIALS AND METHODS: Participants were 47 DC adults (ages 19-29; 68.1% female; 53.2% raised with a sibling) whose parent(s) conceived through the same program. No participants shared the same donor. Participants were born to two mothers (46.9%), a single mother (29.8%) or a mother and father (23.4%).

Participants were interviewed by phone and completed online questions about growing up in a DC family, obtaining their donor’s identity, and contacting the donor. Questions here focus on interest in, motivations for and/or experiences with contacting donor-linked peers.

Interviews were transcribed, with identifying information removed. Two research assistants (RAs) and two authors read transcripts and created coding schemes. RAs coded questions. We conducted descriptive analyses.

RESULTS: Almost half (46.8%) of participants had contacted donor-linked peers, most often via a mutual-consent linking registry. Donors had connected 27.3%, something welcomed but unanticipated.

Over 80% of the remaining participants expressed interest in donor-linked peer contact. (Some had not known this was possible.) Motivations included curiosity (81.1%), interest in a relationship (54.1%), shared experiences (35.1%) and less pressure than contact with the donor (35.1%; those already in contact reported this more often). Most (81.8%) felt positively about donor-linked peer contact, described their shared experiences and origins (90.9%), and current (81.8%) or hoped for (32%) relationships with them. Contact was sometimes described more positively than contact with a donor. Many felt that this contact improved their overall experience of receiving their donor’s identity.

CONCLUSIONS: DC adults in this sample expressed strong interest in and positive experiences with donor-linked peer contact. Findings hold implications for open-identification donors, with one unexpected outcome being that donors may link adults and families, regardless of interest.

Support: Gay & Lesbian Medical Association: Lesbian Health Fund
contact with DCPs seemingly contradicts the donors’ choice to not discuss their donation with their children and creates a potential complication for their children in the future should contact be made by DCPs through DNA-based linking websites. Although most donors would choose to donate again feelings are nuanced as seen in donors being happy about donating yet not using the word “proud” to describe their feelings. Future research is needed to understand the layers and complexities of these feelings. Increasing counseling, as some current cryobanks are implementing which reflects the belief that donor transparency with their own children and DCPs is highly valued, and will effectuate better outcomes for all stakeholders.

References:

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IMPLEMENTATION OF PSYCHOLOGICAL SCREENING IN A LARGE SPERM BANK.

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OBJECTIVE: To identify the psychological reasons for disqualification of sperm donors through clinical interview and psychological testing.

DESIGN: A quantitative retrospective chart review study.

MATERIALS AND METHODS: Donor applicants who applied to a major sperm bank from February 2017 to February 2018 were evaluated by qualified mental health professionals with clinical interview and testing with the Personality Assessment Inventory across all branches of a major sperm bank.

RESULTS: Donors ranged from age 19-36 with an average age of 26. A total of 229 donors passed initial qualification steps and advanced to the psychological assessment stage of donor screening. The psychological screening was a new screening step was inserted prior to other screening steps, such as genetic family history interview, which may have screened out some of these donors. Of those eliminated after the psychological assessment step, 13% of those 229 donors were disqualified following recommendation by the mental health professional and subsequently 32 other candidates self-selected out of the program following the detailed discussion that occurs within the psychological clinical interview session. Of the 33 donors not recommended to proceed, 36% had psychological testing not within normal limits; and 15% had an abnormal clinical interview. Issues identified through the psychological assessment leading to disqualification included: Donor appeared to be unable to manage the long-term demands of being a sperm donor with regard to the possibility of contact with donor conceived offspring, family history of psychopathology, findings consistent with substance use or other high risk behavior, donor unwilling to donate to homosexual couple or single parent, personal history of major pathology, and inability to attend clinical interview in a timely/responsible manner.

CONCLUSIONS: Therefore sperm donors were medically but not psychologically evaluated or counseled as part of the donor application process in most major sperm banks. In this new process at one major sperm bank, as expected within a normal population of men, a small number of donors were disqualified because of abnormal psychological testing and clinical interviews. A smaller but significant number choose not to move forward as a result of having the opportunity to explore the complex decision to be a sperm donor with a mental health professional. As gamete donation becomes increasingly open, the need for candidates to understand the process and be able to manage contact with the donor-conceived is critical. Heritability concerns for the donor-conceived, in addition to promoting the donor’s own positive emotional health, makes psychological assessment and psychoeducation even more critical for the donor evaluation process for better outcomes for donors, donor conceived persons, and families.

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AN ANALYSIS OF SURROGATE RELATIONSHIPS WITH INTENDED PARENT(S) (IP) DURING GESTATION AND POST DELIVERY.

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OBJECTIVE: Propensity to surrogacy has suggested that relinquishing the baby at birth is potentially distressful and may cause psychological harm to surrogates. Parents may also be reluctant to maintain ongoing contacts due to concerns that the surrogates’ involvement in their child’s life may undermine their role as parents. We investigated Canadian gestational surrogates’ relationships with IPs during and post surrogacy.

DESIGN: A cross-sectional survey with Canadian surrogates recruited from the surrogacy community and via digital media.

MATERIALS AND METHODS: University of Toronto REB approval was obtained (#32847). An anonymous online survey was carried out from June 2016 to February 2017. A total of 184 Canadian gestational surrogates participated in the survey; 131 live birth cases involving 90 participants were selected for this sub-analysis.

RESULTS: Of the 131 live birth cases, most parents were heterosexual couples (n=81, 61.8%); the remainder were same-sex male couples and single men (n=49, 37.4%) and single woman (n=1, 0.8%). About three-quarters of IPs (n=96, 73.3%) were residents of Canada. 90% of participants reported not having emotional struggles when relinquishing the baby at birth, 76.5% had frequent contact with the IPs post-birth, and 75% found the amount of contact ‘just right’. Of the 9 cases where contact was discontinued post-birth, 6 participants reported that the relationship with the IPs after birth had deteriorated. Bivariate analyses showed that the amount of ongoing contact was positively correlated with participants’ emotional connection with the IPs during their gestational [r(128) = .32, p < .001], as well as with the quality of their relationships after birth [r(128) = .40, p < .001]. Whether the IPs reside in Canada or not, had no effect on the amount of ongoing contact (p > .05). Furthermore, the surrogate’s satisfaction with their experience was independent from the subtype of IP [heterosexual vs. others] (p > .05), the type of surrogacy arrangement [agency vs. others] (p > .05), and the IPs’ place of residence [Canada vs. international] (p > .05).

CONCLUSIONS: We found that most surrogates were able to establish an appropriate emotional boundary with the surrogacy child, and had a harmonious relationship with the IPs during gestation and post birth. Most surrogate-IP relationships do not discontinue post birth. We did not find evidence to claim that IPs were reluctant to maintain ongoing contact with their surrogates, or that surrogacy is psychologically harmful to surrogates.

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WHAT PREDICTS ANXIETY IN IVF PATIENTS?.

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OBJECTIVE: IVF treatment has been associated with increased anxiety and depression in women. This study was designed to prospectively compare anxiety at several time points during IVF. We wanted to evaluate factors that may predict increased anxiety in these patients.

DESIGN: A prospective case control study enrolling 208 women who underwent an IVF cycle at a single academic institution.

MATERIALS AND METHODS: 208 IVF patients between the ages of 20-44 undergoing IVF were included in this study. The State-Trait Anxiety Inventory (STAI) was used to assess anxiety at cycle day (CD) 2, stimulation, time of retrieval, time of transfer and time of pregnancy test (ToP). A score of ≥40 on the State Anxiety scale (S-Anxiety) was used to detect clinically significant anxiety symptoms. Nonparametric tests, student t-tests and Chi-squared tests were used where appropriate and a p < .05 was considered to be significant.

RESULTS: The mean age of the IVF patients was 37.5 (±0.34) and they had 1.26 (±0.115) prior attempts of IVF treatment. 112 patients (53.8%) underwent IVF for the first time and 96 patients (46.2%) had had ≥1 failed cycles in the past. 78.8% of enrolled patients completed a cycle of IVF, 14.9% had cancelled cycles and 1.3% did not start the cycle. Overall, there was significant increase in S-Anxiety from cycle CD2 to time of pregnancy test (mean 43.5 vs 50.1, p < .001). This rise persisted regardless of pregnancy test result (p < .001) or presence of a partner (p < .05). Furthermore, parous patients did not have a significant increase in S-Anxiety from CD2 to ToP, whereas nulliparous patients did (mean 43.5 vs 50.1, p < .001). Given that a failed IVF cycle has been associated with increased anxiety (Verhakk et al., 2005), we wanted to evaluate these parameters based on prior IVF attempts. Both groups had increased anxiety throughout the IVF
cycle (first time IVF; mean 45.2 vs 47.7, p<0.05); 2) 1 IVF treatment, mean 45.5 vs 53.0, p<0.05). When controlled for ultimate IVF outcome, again there was no difference between the groups of first time IVF or unsuccessful prior IVF cycles. Finally, the presence of a partner did not impact the anxiety level in either first time IVF patients or patients with multiple failed cycles.

CONCLUSIONS: Overall, there is a significant increase in patient S-Anxiety from CD2 to ToP and this difference was present regardless of the results of the pregnancy test or the presence of a partner. There was also no significant difference in S-Anxiety throughout the cycle between first time IVF patients and patients who had ≥1 failed cycles. Nulliparous patients had increased anxiety throughout the IVF cycle. However, parous patients did not have an increase in anxiety.

References:

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SERUM LEVELS OF IL-6 CORRELATE WITH ANXIETY AND DEPRESSION IN IVF PATIENTS AND DONORS.
*Weill Cornell Medicine, New York, NY; †Reproductive Medicine Associates of New Jersey, Englewood, NJ; ‡CRMl, Weill Cornell Medical College, New York, NY; †Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, New York City, NY.

OBJECTIVE: Infertility as well as IVF treatments can cause distress for women undergoing IVF. As a result, anxiety and depression are frequent conditions in this patient population. Increased levels of inflammatory cytokines such as interleukin 1 beta and 6 (IL-1β, IL-6) and heat-shock protein 70 (hsp70) have been shown to be associated with depression and anxiety. We hypothesized that levels of anxiety, depression and serum cytokines would differ between patients undergoing IVF and oocyte donors.

DESIGN: Prospective case-control study.

MATERIALS AND METHODS: 170 women that underwent IVF and 55 donors were included in this study. Sera were obtained at day 2 of the cycle, before stimulation, from both groups and on the day of embryo transfer (ET) from the IVF group. Levels of IL-6, IL-1β and hsp70 were measured by ELISA. Anxiety and depression were measured by the State-Trait Anxiety Inventory (STAI) scale (cut-off for clinically significant symptoms of anxiety, ≥40) and the Beck Depression Inventory-II (BDI-II) (cut-off for mild and moderate depression ≥14 and ≥20 respectively). Results were analyzed by SPSS version 23.0.

RESULTS: A total of 88 women and 63 men provided data at both time points; mean age 34 years. At baseline, mean (SD) anxiety scores were 50.6 (8) for women, 48.4 (8) for men; depression scores were 46.8 (6) for women and 44.9 (4) for men. Baseline FertiQoL scores were 68.9 (15) for women and 79.8 (12) for men. By 12 months, 54% of participants were pregnant or parenting a child (birth or adoption/foSTERING). Those who were pregnant/parenting by 12 months reported significantly better FertiQoL scores and higher depression at 12 months. Higher anxiety at 12 months was related to baseline anxiety and lower relationship satisfaction. Likewise, higher depression at 12 months was related to baseline depression and lower relationship satisfaction. Neither anxiety diagnoses (male-factor, female-factor, or unexplained) nor invasive medical treatments (IUI or IVF) were related to anxiety, depression, or FertiQoL scores at 12 months.

CONCLUSIONS: Baseline psychological status is predictive of subsequent anxiety and depression during ongoing infertility treatment, with scores worsening over time. It is imperative that early identification of needs and provision of treatment resources be provided to patients. Embedding behavioral health services within the clinic promotes ease of access to care and reduces stigma of seeking treatment. After this research was conducted, the addition of a clinical health psychologist in the clinic has afforded opportunities to implement screening measures and promote early intervention.

Supported by: Funding came from R21HD071332 from the National Institute of Child Health and Human Development.

P-112 Tuesday, October 9, 2018 6:30 AM

GENERAL FAMILY COMMUNICATION STYLES: DIFFERENTIAL EFFECTS ON ADJUSTMENT OF ADOLESCENTS DISCLOSED EARLIER OR LATER.
M. Chen. University of Minnesota Twin Cities, St.Paul, MN.

OBJECTIVE: To examine if general family communication styles indirectly influence adolescents’ psychosocial adjustment through parenting stress among adolescents who knew about the use of medical assistance earlier or later.

DESIGN: Longitudinal descriptive study of 81 adolescents (M age = 13.38 years, SD = 1.23) conceived using medically assisted reproduction (IVF, ICSI or IUI; 5% donor-conceived). Thirty-five adolescents knew about the use of medical assistance earlier in life (before age 7); 46 adolescents knew at a later age (between ages 7 and 13).

MATERIALS AND METHODS: Based on the Family Communication Patterns Theory (Koerner & Fitzpatrick, 2002a), general family communication styles were conceptualized as communication orientation and communication orientation. High conversation orientation emphasizes open and frequent communication between family members. High conformity orientation stresses family communication that parents make decisions for the family and that children conform to parents’ rules. At Wave 1, mothers reported conversation orientation (α = .83) and conformity orientation (α = .82) on the Revised Family Communication Patterns Questionnaire (Ritchie & Fitzpatrick, 1990). Parenting stress (α = .95) as the mediator was reported by

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mothers using the Stress Index for Parents of Adolescents (Sheras et al., 1998) at Wave 2. Mothers reported the dependent variables, adolescents’ emotional and behavioral problems, at Wave 2 on Child Behavior Checklist internalizing (α = .84) and externalizing (α = .89) subscales. Covariates included child’s gender status and biological sex. The proposed associations were tested by two path models (model 1: emotional problems; model 2: behavioral problems) using Mplus 8.

RESULTS: Among adolescents disclosed earlier, conversation orientation (M = 5.81, SD = .57) but not conformity orientation (M = 3.53, SD = .56) had a marginally significant indirect effect on adolescents’ emotional problems (β = -.30, p = .052) and a significant indirect effect on adolescents’ behavioral problems (β = -.27, p = .027) through parenting stress. Among adolescents disclosed later, conformity orientation (M = 3.72, SD = .51) but not conversation orientation (M = 5.66, SD = .62) was marginally significantly related to parenting stress (model 1: β = .29, p = .064; model 2: β = .30, p = .050), which in turn was positively related to adolescents’ adjustment problems (model 1: β = .65, p < .001; model 2: β = .65, p < .001). Despite this, conformity orientation did not have a significant indirect effect on adolescents’ emotional or behavioral problems via parenting stress.

CONCLUSIONS: It appears that families of adolescents disclosed earlier tend to use conversation orientation, whereas families of adolescents disclosed later tend to use conformity orientation. General family communication style may indirectly influence adolescents’ adjustment via parenting stress among adolescents disclosed earlier but not among adolescents disclosed later.

References:

Supported by: University of Minnesota (UMN) Agriculture Experiment Station, UMN Grant-in-Aid, UMN College of Education & Human Development Research Development Investment Grant, Development Investment Grant, UMN Women’s Philosophic Leadership Circle Award, and UMN Eva Miller Endowed Fellowship.

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THE PREVALENCE OF SLEEP DISORDERS IN AN INFERTILE FEMALE POPULATION. S. E. Slaven, S. Ibrahim, J. Tantbirodyangkul, M. Radeva, R. Flyckt. Case Western Reserve University School of Medicine, Cleveland, OH; Cleveland Clinic, Cleveland, OH.

OBJECTIVE: To evaluate the prevalence of sleep disorders and their impact in women presenting to an urban medical center with an infertility diagnosis compared to the general population of pre-menopausal women.

DESIGN: Cross-sectional study.

MATERIALS AND METHODS: A sample of 142 female patients between 21 and 45 years old with a diagnosis of infertility (ICD-9 628) were surveyed about their sleep habits using four standardized sleep measures: STOP-BANG Sleep Apnea Questionnaire, Sleep Apnea Scale of the Sleep Disorders Questionnaire (SA-SDQ), Insomnia Symptom Questionnaire, and Restless Leg Syndrome (RLS) Questionnaire. The impact of these sleep disturbances were measured using Epworth Sleepiness Scale (ESS) and Patient Health Questionnaire (PHQ-9). Of the 142 total patients enrolled, 131 were included in the final analysis and 11 were removed due to incomplete responses. Patients with a diagnosis of polycystic ovarian syndrome (PCOS) were compared to those without. Potential confounders, such as age and BMI were also included in the analysis. Categorical factors were summarized using frequencies and percentages, while continuous measure summaries used means and standard deviations. To evaluate risk factors for early outcomes, Pearson chi-square tests, Fisher’s exact test, and ANOVA tests were used. Analysis was performed using SAS software (version 9.4; Cary, NC). P < 0.05 was considered statistically significant.

RESULTS: The self-reported prevalence of disturbed sleep in this population was 26% with 21% endorsing past or current use of sleep aids. Among the surveyed, 9.2% had an intermediate-high risk of having moderate to severe obstructive sleep apnea according to the STOP-BANG questionnaire, but 67.7% had moderate-severe OSA symptoms according to their SA-SDQ score. The prevalence of insomnia was 13.1%, and 7.6% endorsed symptoms consistent with RLS. Patients with PCOS had increased risk of sleep apnea compared to patients with causes of infertility other than PCOS (28% and 4%, p = 0.001), but not insomnia, restless legs or daytime sleepiness. Additionally, 14.5% had excessive daytime sleepiness (ESS >10) and 16.2% had a high likelihood of depression according to their PHQ-9 scores (PHQ9 >10).

CONCLUSIONS: The overall prevalence of disturbed sleep in the infertile female population is similar to that of the general pre-menopausal female population as it pertains to RLS and insomnia. However, these women have increased prevalence of OSA as compared to the general population as well as an increased risk of depression. Women with PCOS had the highest risk of OSA compared to those with other causes of infertility.

References:
**P-115 Tuesday, October 9, 2018 6:30 AM**

**A COMBINATION PROTOCOL OF VITAMIN D, PREDNISONE, ASPRIN, AND VITAMIN B-FOLATE COMPLEX IMPROVES ONGOING PREGNANCY RATES IN PATIENTS WITH RECURRENT PREGNANCY LOSS OR MULTIPLE FAILED EUPLOID SINGLE EMBRYO TRANSFER CYCLES.** C. Pratt,¹ I. Levin,² K. Bergin,² L. Nargi,³ J. B. Davis.⁴ *Reproductive Medicine Associates of New York, New York, NY; Albany Medical Center, Albany, NY.*

OBJECTIVE: While preimplantation genetic testing (PGT) is increasingly being utilized to identify euploid embryos and to improve the likelihood of successful outcomes, many patients still experience recurrent pregnancy loss (RPL) and/or repeated implantation failure (RIF). Patients who experience RPL and/or RIF must cope with physical and emotional distress. Reproductive immunologists often utilize combination medication therapies to treat patients with RPL and RIF, however, these protocols often are not well supported by evidence-based research. This study evaluated the clinical outcomes for RIF and RPL, patients who were treated with a specific combination protocol.

DESIGN: Retrospective, cohort study.

MATERIALS AND METHODS: The study included patients who underwent single, euploid frozen embryo transfers (FET) with the combination medication therapy from 2014-2018. The combination medication protocol includes: Vitamin D, Prednisone, Aspirin and a Vitamin B12/Vitamin B6/Folate (CBE) complex. Patients with a history of ≥2 failed euploid, single embryo transfers (SET), ≥3 clinical spontaneous abortions (SAB), or a combination of 2 SABs and 1 failed SET were included in the analysis. Only patients who utilized autologous oocytes were included.

RESULTS: A total of 54 IVF-FET cycles meeting criteria were included. Patient average age was 35.74 years old (range: 24 - 44). Upon review of the cycle outcomes, a total of 79.62% (n=43/54) achieved positive clinical pregnancy loss and 7.41% (n=4/54) achieved positive clinical pregnancy (CBP). Of those who passed the 8-week gestation period, 74.19% (23/31) reached their estimated date of delivery and 91.30% of those (n=21/23) achieved live birth. A total of 14.81% (n=8/54) cycles resulted in clinical pregnancy loss and 7.41% (n=4/54) resulted in biochemical pregnancy loss. Finally, 20.38% (n=11/54) cycles resulted in negative pregnancy tests.

CONCLUSIONS: While the etiology of RPL and RIF are not well understood, our study sought to identify an affordable and minimally invasive alternative treatment regimen. Due to the high levels of anxiety and distress associated with failed euploid embryo transfers and spontaneous abortions, we sought to develop a new viable treatment strategy. Although the study was limited by sample size and design, the results were encouraging and future randomized control trials should be done to provide further support for this combination-medication treatment protocol.

**P-117 Tuesday, October 9, 2018 6:30 AM**

**IMPACT OF VITRIFIED EGG BANKING ON DONOR OOCYTE SOURCE: IS RECRUITMENT BY PRACTICES A DYING ART?** K. R. Hammond,¹ C. A. Long,¹ N. Cataldo,¹ *America Institute of Reproductive Medicine, Birmingham, AL; Epidemiology, UAB School of Public Heath, Birmingham, AL.*

OBJECTIVE: To survey the source(s) of donor oocytes currently used by US programs, and the impact of oocyte vitrification (VIT) and commercial egg banks (CEB) on in-house donor recruitment.

DESIGN: Voluntary, one-page questionnaire survey.

MATERIALS AND METHODS: At an April, 2018, US third-party reproduction conference, professional attendees were offered a 1-page questionnaire on the source(s) of donor oocytes their program uses, availability of onsite VIT, actual or planned discontinuation of onsite recruitment, and perceived benefits of using CEB oocytes. Data were analyzed using descriptive and comparative statistics.

RESULTS: US respondents were from 72 practices offering oocyte-donor (OD) IVF with broad geographic distribution (27 states). They were nurses (79%), physicians (11%), and other/not stated (10%). In 2017, they performed 4 to 900 OD-IVF cycles [median 55, interquartile range (IQR) 36-146]. Fresh oocytes were used in 60% of cycles (median; IQR 12-90%); 14% of programs never use fresh oocytes. VIT-warmed eggs were used in 30% of cycles (median; IQR 5-75%); 14% never used warmed oocytes. Embryos created by another facility were used by 24% of programs reporting, for a mean of only 1% of their cycles.

Use of in-house donor recruitment showed bimodal frequency; only 11% of programs recruited all, and only 17% none, of their donors. The proportion of in-house recruited donors was not related to practice volume. Agency-found donors (AD) were used by 51% of programs in under 5% of their cycles; only 13% used AD in 90% or more of their cycles. The proportion of OD recruited AD was also not related to practice volume. Oocyte VIT is performed by 40% of practices for their own later use. CEB were used never by 23% of practices and in 80% or more of cycles by 14%. The proportion of cycles using a CEB was not related to practice volume. No practice has stopped in-house recruiting in favor of CEB use, and only 3% plan to stop in the next year. Practices offering use of a CEB utilize one (44%), two (24%) or three or more banks (24%).

Respondents’ preferred egg sources were from their own recruitment (38%), a bank (19%), or no preference (36%). When asked who benefits most from using a CEB, 52% cited the CEB, 43% the recipient, 10% the donor, and 10% the coordinator (12% multiple responses). While no association was found between preferring EB-sourced eggs and belief that banks, not donors, recipients, or coordinators, benefit the most from CEB use, a trend was found suggesting an association between preferring recruited-donor-sourced eggs and the belief that banks benefit the most from CEB use (p=0.13).
**P-118** Tuesday, October 9, 2018 6:30 AM

**A LAY-LED SUPPORT GROUP IS MORE POPULAR THAN A PROFESSIONALLY-LED SUPPORT GROUP AT A LARGE REPRODUCTIVE MEDICINE OFFICE.** L. Schuman,† L. Rosenthal,‡ S. Richlin,‡ R. Mangieri,∥ M. Kelleher,∥ M. P. Leonildres,∥ †RMMA of CT, Norwalk, CT,∥ Reproductive Medical Associates of Connecticut, Norwalk, CT.

OBJECTIVE: The internet has created many opportunities for emotional support for women undergoing fertility treatment. Since the rise in popularity of the internet for home use, fertility counselors have reported a diminished interest in professionally-led support groups. We have noticed this as well and we also offer a lay-led support group. This group is an internet-based, lay-led support group with associated in-person group meetings. The in-person group has been well attended since its inception and has continued to receive positive feedback from patients. We set out to better understand the popularity of the in-person group.

DESIGN: Retrospective analysis.

MATERIALS AND METHODS: Since 2008, our lay-led group has been run by two women who are fertility clinic employees. They are not trained as mental health professionals. Both women engage with patients in group meetings three times monthly in the evenings and on the associated Facebook page. Current and former members were asked to complete an online anonymous survey. Of the 85 women who responded, 3 did not complete the survey. Between 6-14 people attend each in-person group. The survey included questions about participant demographics and different aspects of the in-person group meetings. The later used 4-point rating scales.

RESULTS: 82% of respondents said they are more comfortable attending the lay-led group than a traditional support group. 74% said they like having a place to go in the evenings and 82% said they like the free dinners provided at the group meetings. Although 44% of respondents said they believe, “there is a stigma associated with psychotherapy”, 42% disclosed they are currently engaging in psychotherapy and 68% of respondents have engaged in psychotherapy in the past. The free, professionally-led support groups at the center typically have 0-2 participants. It is noteworthy that 64% of patients who participate in the Facebook page have also attended the in-person group. It is also interesting that 28% of respondents stated that the lay-led group is one of the reasons they chose our center over other clinics and 96% of patients surveyed said they would recommend the clinic to their friends.

CONCLUSIONS: The benefits of group support have been widely accepted within the field of reproductive medicine. However, most reproductive counselors have difficulty recruiting participants. Our lay-led group has been consistently attended for ten years and is valued by the members. We hypothesize that the more casual aspects of the lay-led group, with the absence of a mental health professional and free dinner may be more appealing to patients. Accessing support in their fertility journey may improve patient retention and reduce feelings of isolation as they move through fertility therapy. Moreover, some attendees stated that our lay-led group is one of the reasons they chose our program. Additional studies are needed to better understand the popularity of this lay-led support group.

References: N/A.

**P-119** Tuesday, October 9, 2018 6:30 AM

**THE IMPACT OF ADMINISTRATION OF IN VITRO FERTILIZATION MEDICATIONS AT ASSISTED REPRODUCTION CENTER BY NURSES VERSUS SELF-ADMINISTRATION AT HOME ON PATIENT SATISFACTION: A COHORT STUDY.** T. Farghaly,∥ A. Abbas,∥ E. Badran,∥ M. K. Ali,∥ ✷Assiut University, Assiut, Egypt;∥ Faculty of Medicine, Assiut University, Assiut, Egypt;∥ Reproductive Endocrinology, Assiut, Egypt.

OBJECTIVE: Improving patient satisfaction with in-vitro fertilization (IVF) medications has a positive impact on the psychological and mental state of patients and in turn, affect the outcome of fertility treatments. Our objective is to evaluate the effect of administration of IVF medications at assisted reproduction center by nurses versus self-administration at home on patient satisfaction and IVF outcomes.

DESIGN: Cohort study.

MATERIALS AND METHODS: Infertile women scheduled for IVF cycles were enrolled. Patients were counseled to receive the IVF medications in the center by nurses at regular daily visits (study group) versus self-administration at home with scheduled visits for ovulation monitoring (control group). The ovulation induction protocol was tailored according to the patient's condition. Assessment of patient satisfaction was carried-out after embryo transfer. The primary outcome was the difference in satisfaction rate between both groups. Secondary outcomes included the clinical pregnancy rate, the rate of cycle cancellation and the miscarriage rate. Patients' satisfaction was assessed by 5 points Likert-scale. Student’s t-test and Chi-square test were utilized for analysis of the outcomes.

RESULTS: One hundred-twenty patient were enrolled and distributed as study group (n=60) and control group (n=60). Both groups were comparable in age, educational level, residence, BMI, type, duration and cause of infertility. The statistically significant difference was found in the satisfaction rate between both groups (70% in study group vs. 86.7% in control group, p=0.01). Moreover, the clinical pregnancy rate was significantly higher in the control group (46.7% vs. 30%) than the study group (p=0.01). No statistical significant difference regarding the rate of cycle cancellation (5% vs. 3.3%, p=0.735) and miscarriage rate (4/18 patients [22.2%] vs. 8/28 [28.6%, p=0.173] in the study versus control groups respectively.

CONCLUSIONS: Self-administration of IVF medications at home could improve the patient’s satisfaction and this can be associated with higher clinical pregnancy rates.

**SEXUALITY**

**P-120** Tuesday, October 9, 2018 6:30 AM

**EVALUATION OF FEMALE SEXUAL DYSFUNCTION IN ADULT ENTERTAINERS.** J. M. Dubin,* A. B. Greer,* C. Valentine,* L. O’Brien,* E. Leue,* L. Paz,* A. Winter,* R. Ramasamy,*∥∥*Urology, University of Miami Miller School of Medicine, Miami, FL;∥∥Free Speech Coalition, Canoga Park, CA;∥Urology, Kaiser Permanente, Clackamas, OR.

OBJECTIVE: Female Sexual dysfunction has not been evaluated among adult entertainers. We evaluated the prevalence of female sexual dysfunction (FSD) in women working in the adult entertainment industry.

DESIGN: A 41-question online survey was distributed to female adult entertainers via email through collaboration with the Free Speech Coalition (FSC), the North American Trade Association of the Adult Industry. Surveys were sent by the FSC to those within the Performer Availability Screening Services (PASS) database who met the criteria of having biological vaginas and having experience as adult entertainers.

MATERIALS AND METHODS: The survey acquired baseline characteristics, use of contraceptives, sexual activity, work versus home satisfaction and orgasm, in addition to evaluation of female sexual function using the Female Sexual Function Index (FSFI) survey. An FSFI total score <26.55 is indicative of FSD. The surveys were answered anonymously. Statistical analysis was performed in Microsoft Excel.

RESULTS: Of the 98 respondents, 61 met inclusion criteria of having a biological vagina and working in the adult entertainment industry. The mean age was 32.7 ± 9.8 years (range 20-59). Of the 61 women, 10% (6/61) have undergone menopause, 41% (25/61) use oral contraceptives, 43% (26/61) use contraceptive devices, and 16% (10/61) do not use any form of contraception. Based on the FSFI survey, the average FSFI score was 28.8 ± 5.34, 26% (16/61) of entertainers had scores indicative of FSD, and women from between ages 20-29 had a significantly lower average FSFI score of 27.44 ± 5.51 when compared to women older than 40 (31.36 ± 4.24, p = 0.020). Overall, women found their personal sex lives more satisfying when compared to their adult entertainment sex lives (4.02 vs 2.95, p = 0.0002).

When comparing women with FSD to those without FSD, women with FSD had less sexual satisfaction at home (2.8 vs 4.4, p = 0.004), had similar number of sexual events, but had fewer satisfying sexual events (3.5 vs 10.1, p = 0.0006).

CONCLUSIONS: This is the first study to evaluate female sexual dysfunction among female adult entertainers. Female sexual dysfunction appears to be prevalent amongst female adult entertainers, especially in those who have less satisfying personal sex lives.
SEXUAL FUNCTION IN OLDER PREMENOPAUSAL INFERTILE WOMEN DOES NOT CORRELATE WITH PATIENT DEMOGRAPHICS AND ENDOCRINE PARAMETERS. V. A. Kushnir,a,b S. K. Darmon,a D. H. Barad,a,b A. Weghofer,c,a N. Gleicher,a,c,d Center for Human Reproduction, New York, NY; Obstetrics & Gynecology, Wake Forest University, Winston-Salem, NC; 2Foundation for Reproductive Medicine, New York, NY; 3Department of Obstetrics and Gynecology, Medical University Vienna, Vienna, Austria; 4Stem Cell Biology and Molecular Embryology Laboratory, Rockefeller University, New York, NY; 5Medical University Vienna, Vienna, Austria.

OBJECTIVE: To assess whether sexual function, as assessed by the Female Sexual Function Index (FSFI) score,1 is related to demographics and endocrine parameters of female infertile patients.

METHODS: From 87 consecutively presenting new patients who agreed to participate in this IRB- approved study were asked to complete a self-reported FSFI questionnaire. Concomitantly, they underwent the same comprehensive endocrine evaluation all new patients undergo.

RESULTS: Patients had a mean age of 40.7 ± 4.1 years and BMI 24.6 ± 5.5 kg/m²; 82% were married, and 40.5% were parous. Caucasian women represented 53.7%, African American 18.3%, Hispanic 13.4% and Asian women 13.4%. Baseline endocrine evaluation were: FSH 11.6 ± 7.4 mIU/mL, AMH 0.9 ± 3.1 ng/mL, total testosterone 22.7 ± 13.9 ng/dL, free testosterone 1.2 ± 0.9 pg/mL, DHEAS 243.6 ± 137.3 μg/dL, cortisol 9.2 ± 5.6 μg/dL, SHBG 91.7 ± 46.6 nmol/L. The total FSFI score for all patients was 27.1 ± 7.0; domain scores were: 3.6 ± 1.1 for desire, 4.3 ± 1.3 for arousal, 4.8 ± 1.5 for lubrication, 4.6 ± 1.5 for orgasm, 4.8 ± 1.3 for satisfaction, and 5.2 ± 1.4 for pain. Pearson correlation showed no relationship between FSFI scores and patient demographics, BMI, ovarian reserve parameters (AMH and FSH levels), androgen levels (testosterone, DHEAS, DHEA), or cortisol or SHBG.

CONCLUSIONS: FSFI scores (27.1 ± 7.0) in a group of mostly older premenopausal infertile women were lower than those previously described among healthy controls of similar age (30.5 ± 5.3) but higher than among patients with female sexual arousal disorder (19.2 ± 6.6).1 There was, however, no correlation noted between FSFI scores and patient demographics, ovarian reserve parameters or androgen levels.


MALE REPRODUCTION AND UROLOGY - CLINICAL

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PREDIABETES IN PRIMARY INFERTILE MEN - RESULTS FROM A CROSS-SECTIONAL STUDY. L. Boeri,a,b P. Carpeggiosover,c F. Pederzoli,b,a E. Pozzi,b,c F. Deho,b M. Alfano,b F. Gaboardi,b F. Montorsi,b,c A. Salonia,b,c E. Montanardi,b,a Department of Urology, IRCCS Fondazione Ca’ Granda – Ospedale Maggiore Policlinico, Milan, Italy; Division of Experimental Oncology/Unit of Urology, IRCCS Ospedale San Raffaele, Milan, Italy; Vita-Salute San Raffaele University, Milan, Italy; IRCCS Fondazione Ca’ Granda - Ospedale Policlinico, Milan, Italy.

OBJECTIVE: Diabetes Mellitus (DM) can induce long-term damages, dysfunctions and failures of various organs, including male reproductive system. Previous studies showed the impact of DM on semen parameters, nuclear DNA fragmentation and chromatin quality. Conversely, the association between prediabetes (pDM), a precursor to diabetes characterised by impaired fasting glucose or tolerance, and reproductive function has been scarcely analyzed.

DESIGN: We investigated the risk of prediabetes among men presenting for couple’s infertility. Descriptive statistics and logistic regression analysis tested the association between pDM and hormonal and seminal characteristics in the whole cohort.

MATERIALS AND METHODS: Complete demographic, clinical and laboratory data from 536 primary infertile men were analyzed. Health-significant comorbidities were scored with the Charlson Comorbidity Index (CCI; categorized 0 vs ≥1). Body mass index (BMI) was calculated and serum hormones were measured in all cases. Semen analysis was based on 2010 WHO reference criteria. Azospermia was defined as the absence of sperm in 2 consecutive semen analyses. Men were defined as having pDM if they had impaired glucose fasting plasma concentration from 100 mg/dL to 125 mg/dL; (ii) 2-h plasma glucose concentration in the 75 g oral glucose tolerance test from 140 mg/dL to 199 mg/dL. (American Diabetes Association 2015).

RESULTS: Overall, pDM was found in 58 (10.8%) patients. Men with pDM were older (p = 0.03), had higher BMI (p < 0.001) and lower total testosterone (p = 0.04) and SHBG values (p = 0.02) than those without pDM. Higher DFI scores (p = 0.04) and a greater proportion of non obstructive azospermia (NOA) (28.1% vs. 16.6%; p = 0.033) were more frequent in patients with pDM than in those without pDM. Seminal parameters did not significantly differ between groups. At multivariable logistic regression analysis, FSH values (OR 1.12, p < 0.001) and having pDM (OR 2.45, p = 0.04) achieved independent predictor status for NOA, after accounting for age, BMI, genetic abnormalities, cryptorchidism and testicular volume.

CONCLUSIONS: Prediabetes was found in up to 10% of our cohort of primary infertile men. Men with pDM depicted a higher risk of NOA compared

MALE REPRODUCTION AND UROLOGY - CLINICAL

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THE PREVALENCE OF SEXUALLY TRANSMITTED INFECTIONS IN A LOW-RISK GAMETE DONOR POPULATION. S. Chang,a,b J. Lee,a S. Adler,a N. Bar-Chama,a J. M. Shamoni,a C. Antonelli,a A. B. Copperman,a,b 2Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY; 2Reproductive Medicine Associates of New York, New York, NY; 3Icahn School of Medicine at Mount Sinai, New York, NY; 4California Cryobank, Los Angeles, CA.

OBJECTIVE: The Federal Drug Administration (FDA) is tasked with preventing the transmission of sexually transmitted infections (STIs) from gamete donors to recipients. To ensure that we “first, do no harm,” donors undergo an intensive screening process, including a medical interview, physical examination, and clinical evaluation for relevant communicable diseases. When considering predictive values of diagnostic or screening tests, it is important to first identify the disease prevalence in the population being tested. This study aimed to evaluate the prevalence of STIs in the largest cohort of US sperm and egg donors to date.

DESIGN: Retrospective.

MATERIALS AND METHODS: The study included infectious screening data from potential sperm and egg donors presenting to a gamete bank from 2016-2018. Infectious disease testing (Human Immunodeficiency Virus (HIV), Hepatitis B (HBV), Hepatitis (HCV), Treponema pallidum (syphilis), Neisseria gonorrheae/chlamydia trachomatis (GC/CT), and Human FVymphotropic virus (HTLV)) was performed on all donors during initial screening, repeated for sperm donors at 3 month intervals (GC/CT repeated at 1 month intervals), and for egg donors within 30 days of oocyte retrieval. In addition to serologic testing, qualitative in vitro nucleic acid testing (NAT) for HIV, HBV, and HCV was performed using the Procleix Ultro Assay. The prevalence of each disease was calculated.

RESULTS: A total of 1041 unique sperm donors and 355 unique egg donors were included in the study. Among sperm donors, 1.73% (N=18) tested positive for GC/CT, 0.19% (N=2) tested positive for HBV, 0.10% (N=1) tested positive for HIV, 0.38% (N=4) tested positive for syphilis, and 0.29% (N=3) tested positive for HTLV. No sperm donors tested positive for HCV. Among egg donors, 2.54% (N=9) tested positive for Chlamydia/Gonorrhea. No egg donors were positive for HIV, HBV, HCV, syphilis, or HTLV. No sperm or egg donors tested positive for more than one disease.

CONCLUSIONS: In the largest US study of gamete donors to date, we found that the incidence of STIs is reassuringly low. Analysis of covariates demonstrated that the presence of any one infection did not increase the likelihood of a second infection. Recipients of donor sperm and eggs should be reassured that with appropriate medical interviews, examinations, and screening for relevant communicable diseases, the risk of STI transmission is minimal. By understanding disease prevalence, we can quantify risk of infectivity, counsel patients appropriately, and improve the safety and efficacy of third party reproduction.
Objective: Each year in the US, approximately 500,000 men choose to undergo a vasectomy for permanent sterilization (1). Despite being a very common procedure, studies reporting demographic data and characteristics that motivate men to choose a vasectomy are somewhat limited. With this analysis, the primary objective was to determine if a difference existed between the ages and number of children among men choosing to have a vasectomy at urology practices in urban (Austin, TX, population 947,890) and rural (Temple, TX, population 76,277) settings. A secondary objective was to establish if there was a trend in these variables over time.

Design: retrospective, multi-institutional cohort analysis.

Materials and Methods: After IRB approval was obtained from each institution, a retrospective chart review was undertaken to identify men who had undergone a vasectomy at each facility from 2011-2017. Demographic data was recorded. Statistical analysis was done using student's t-test and linear regression.

Results: A total of 1565 vasectomies were performed - 860 in City A and 705 in City B over a 7 year period. The mean age in City A was 37.41 years of age versus 36.18 in City B at time of vasectomy (<0.001). Men in City A underwent vasectomy after an average of 1.96 children, versus a mean of 2.6 children in City B (<0.001). There was no statistically significant trend in the mean age or number of children over time for either patient population.

Conclusions: Men in an urban setting opted to have a vasectomy at an older age and with fewer children than those in a rural practice setting. Mean paternal age is increasing overtime in the US, with a mean age for fathers of 30.9 in 2015, compared to a mean age of 27.4 in the early 1970s (2). Further analyses are needed to evaluate why there seems to be some insulation of this effect in the rural practice environment, although possible reasons include lower rate of men with college and professional degrees, or decreased numbers of selected groups of minorities who have been shown to have children at a later age (2).

References: 1. Eisenberg ML, Zhang CA, Ying L. The age of fathers in the USA is rising: 30.9 in 2015, compared to a mean age of 27.4 in the early 1970s (2). Further analyses are needed to evaluate why there seems to be some insulation of this effect in the rural practice environment, although possible reasons include lower rate of men with college and professional degrees, or decreased numbers of selected groups of minorities who have been shown to have children at a later age (2).

Summary of Data for City A vs City B

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<thead>
<tr>
<th>Year</th>
<th>City A</th>
<th>City B</th>
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<tr>
<td>Mean Age (SD)</td>
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<tr>
<td>2011</td>
<td>37.75 (6.87)</td>
<td>2.32 (1.04)</td>
</tr>
<tr>
<td>2012</td>
<td>35.77 (7.11)</td>
<td>1.90 (1.17)</td>
</tr>
<tr>
<td>2013</td>
<td>37.17 (7.38)</td>
<td>1.74 (1.2)</td>
</tr>
<tr>
<td>2014</td>
<td>37.34 (5.65)</td>
<td>2.01 (1.28)</td>
</tr>
<tr>
<td>2015</td>
<td>38.38 (7.42)</td>
<td>1.96 (1.43)</td>
</tr>
<tr>
<td>2016</td>
<td>38.53 (7.21)</td>
<td>1.94 (1.2)</td>
</tr>
<tr>
<td>2017</td>
<td>37.03 (6.32)</td>
<td>1.94 (1.24)</td>
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<tr>
<td>Total</td>
<td>37.41 (6.81)</td>
<td>1.96 (1.25)</td>
</tr>
</tbody>
</table>
EFFECTS OF NATESTO® ON REPRODUCTIVE HORMONES AND SEMEN PARAMETERS: A PROSPECTIVE CLINICAL TRIAL. T. Masterson, M. Molina, D. M. Lopategui, E. Ibrahim, R. Ramasamy, T. Masterson, E. Ibrahim, R. Ramasamy. University of Miami, Miami Beach, FL; University of Miami, Miami, FL; University of Miami and Translational Science Institute, Miami, FL; University of Miami / Department of Urology, Miami, FL; Urology, University of Miami, Pinecrest, FL.

OBJECTIVE: To evaluate the effect of Natesto (4.5% nasal testosterone Gel) on serum testosterone (T), follicle stimulating hormone (FSH), luteinizing hormone (LH) and semen parameters in men with low testosterone. We present preliminary results from our ongoing prospective clinical trial.

DESIGN: Prospective clinical trial.

MATERIALS AND METHODS: Men between the age of 18-55 with low testosterone (total testosterone<350 on two consecutive T samples collected greater than 2-4 weeks apart) and symptoms were offered therapy with Natesto (4.5% nasal testosterone Gel) TID. All patients were TRT naive or had an appropriate wash out period of at least 2 months. Baseline T, LH, FSH, Estradiol, SF-36, IIEF as well as two semen analyses (collected at least 1 week apart) were evaluated prior to therapy. Patients with azospermia and severe oligospermia (total motile sperm count < 5 million) were excluded. We repeated serum T at 1 month and FSHE, LH, T, E, SF-36, IIEF and 2 SA’s at 3 and 6 months after therapy. Monitoring for symptoms and adverse events was performed at each patient visit.

RESULTS: A total of 16 patients have been enrolled out of goal of 40. Median patient age 37.1±8.1 years, T 206±64 ng/dl, LH 4.0±2.3 mIU/ml, FSH 4.8±1.0 mIU/ml and SA parameters were concentration 23.2±8.7 million/cc, Motility 45.9±16.1%, TMSC 52.0±18.7 million, SF-36 of 107±4 and IIEF-Q15 of 25.6±4.3. At three months 5/6 men reached a normal T level (> 350 ng/dl). Interestingly, despite a decrease in FSH and LH levels by -50.9% and -55.8%, the TMSC at 3 months remained unchanged (48.8±17.0 vs 46.6±23.8 million). The average SF-36 and IIEF score remained unchanged at 3 months following Natesto treatment. CONCLUSIONS: Natesto, likely due to its short half-life, appears to increase testosterone while preserving both gonadotropins (FSH and LH) as well as semen parameters. If the trial results continue to be favorable for the remainder of the study, intranasal short-acting testosterone can be a revolutionary change in the treatment of men with low testosterone who wish to preserve fertility.

Supported by: Natesto was provided at no cost to the patient by Aytru BioScience and provided grant support. RR was supported by research scholar award from Urology Care Foundation.

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OXIDATION REDUCTION POTENTIAL IN MALE INFERTILITY MANAGEMENT: A REPORT OF 4080 CASES. H. Elbardisi, M. Arafa, A. Agarwal, S. AlSaid, K. AlRumaili, A. AlAnsari, A. Majzoub, Haam Medical Corporation, Doha, Qatar; Cleveland Clinic Foundation, Cleveland, OH.

OBJECTIVE: Oxidation reduction potential (ORP) has been recently used as a comprehensive indicator for oxidative stress in semen and as an independent diagnostic tool to differentiate normal and abnormal semen parameters. The main objective of the current study was to report our experience with ORP in the diagnosis of male infertility.

DESIGN: Retrospective chart review.

MATERIALS AND METHODS: Demographic, clinical and laboratory data of patients who attended the male infertility unit in a tertiary hospital over a period of 3 years were collected. Semen analysis was performed in compliance with WHO 5th edition guidelines. ORP was measured using a MOXYS analyzer and sperm DNA fragmentation (SDF) was done using Halosperm kits. Based on our previous studies, the cutoff value of 1.38 mv/10^6 sperm/ml was used to differentiate normal for abnormal semen parameters. X2 test and Mann Whitney test were used to analyze categorical and numerical values respectively. Spearman correlations between different numerical variables were assessed. A p value of < 0.05 was considered statistically significant.

RESULTS: A total of 4080 patients were included in the study. The patients’ mean age was 35.85±7.71, mean right and left testicular sizes 12.77±8.3 and 10.37±5.4 respectively. Semen and hormone data are presented in Table 1. ORP was significantly negatively correlated with sperm count (r = -0.844, p < 0.0001), total motility (r = -0.123, p < 0.0001) and progressive motility (r = -0.463, p < 0.0001) and positively correlated with abnormal sperm morphology (r = 0.529, p < 0.0001) and SDF (r = -0.255, p < 0.0001). Testicular size was negatively correlated (r = -0.087, p < 0.01) while FSH and LH were positively correlated with ORP (r = 0.279, p < 0.001 and r = 0.201, p < 0.001 respectively). The ORP cut-off value of 1.38 could differentiate between normal and abnormal semen parameters with a sensitivity of 80.2% and specificity of 61.5% (PPV 80.2%, NPV 70.9%).

CONCLUSIONS: The utility of ORP as an independent measure for semen quality in infertile men has proven to be consistent and accurate.


<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstinence (days)</td>
<td>3.86</td>
<td>1.61</td>
</tr>
<tr>
<td>Volume (ml)</td>
<td>3.08</td>
<td>2.13</td>
</tr>
<tr>
<td>Count (million /ml)</td>
<td>31.84</td>
<td>26.11</td>
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<tr>
<td>Total motility (%)</td>
<td>80.4</td>
<td>19.4</td>
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<tr>
<td>Progressive motility (%)</td>
<td>11.93</td>
<td>11.83</td>
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<tr>
<td>Abnormality (%)</td>
<td>95.26</td>
<td>5.88</td>
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<tr>
<td>SDF (%)</td>
<td>29.84</td>
<td>19.5</td>
</tr>
<tr>
<td>ORP (%)</td>
<td>5.24</td>
<td>4.9</td>
</tr>
<tr>
<td>LH (IU/L)</td>
<td>4.75</td>
<td>3.7</td>
</tr>
<tr>
<td>SDF (IU/L)</td>
<td>5.02</td>
<td>3.8</td>
</tr>
<tr>
<td>Testosterone (nmol/L)</td>
<td>18.49</td>
<td>9.48</td>
</tr>
</tbody>
</table>
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PREDICTIVE VALUE OF THE HOMOGENEOUS SEMINIFEROUS TUBULES DIAMETER ON SPERM RETRIEVAL RATE OF MICRO-TESE. J. Zhang, G. Liu, X. Liang. “Reproductive Center, The Sixth Affiliated Hospital of Sun Yat-sen University, GuangZhou, China; Center of Reproductive Medicine, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; Reproductive Medicine Center, Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.

OBJECTIVE: To investigate whether the diameter of seminiferous tubules can predict the sperm retrieval rate (SRR) in micro-TESE, when all the tubules are morphologically identical after opening the tunica albuginea.

DESIGN: This is a retrospective study. From Sept. 2014 to Dec. 2017, 287 NOA patients underwent micro-TESE. 169 of them were seen to have homogeneous seminiferous tubules after the tunica albuginea was opened. Patients with homogeneous seminiferous tubules were divided into three groups according to the tubal thickness under direct vision: homogeneously thick (group A, n=24), homogeneously thin (group B, n=57), severely thin and lost the tubal appearance (group B, n=88).

MATERIALS AND METHODS: Micro-TESE was performed at x10 to x20 magnification. An attempt was made to identify seminiferous tubules that were larger and more opaque than other tubules. The procedure was terminated when sperm were retrieved. If all tubules in testis were seen to have an identical appearance, at least three samples (upper, middle, and lower) were extracted. The three groups were compared in age, testicular volumes, FSH, LH, testosterone, SRR and diameter of 50 tubules per case.

RESULTS: Mean seminiferous tubule diameters of each group were significantly different (group A, 13.1±2.61 μm; group B, 17.8±1.63 μm; group C, 46.3±17.1 μm, p=0.05). No significant differences were observed in age and testosterone between the three groups (31.0±3.3, 31.6±4.2 and 32.1±6.1 years; 4.1±1.3, 3.8±2.0 and 3.1±2.0 mg/dL, respectively; p>0.05). Serum FSH, LH and testicular volumes between the three groups were significantly different (group A, 16.1±10.8 IU/L, 7.6±3.1 IU/L and 8.3±2.8 mL; group B, 22.5±9.0 IU/L, 10.5±4.4 IU/L and 6.6±2.9 mL; group C, 50.5±12.5 IU/L, 15.4±7.0 IU/L and 4.7±2.4 mL, respectively; p<0.05).

SRR of group C was higher than group A and group B (72.7% vs. 41.7% and 17.5%, p<0.05). 69 patients in group C (78.4%) were found heterogeneous seminiferous tubules finally, 64 of them (92.8%) obtain sperms. No patient in group A had heterogeneous seminiferous tubules.

CONCLUSIONS: Patients undergoing micro-TESE with homogeneously and severely thin tubules are easier to find focal spermatogenesis area and have higher SRR than those with thicker tubules.

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THE MINIMAL CYCLOPHOSPHAMIDE EQUIVALENT (MCED) DOSE AS AN APPROACH TO PREDICT OUTCOME OF MICRODISSECTION TESTICULAR SPERM EXTRATION IN PATIENTS WITH PERSISTENT AZOOSPERMIA AFTER CHEMOTHERAPY. I. Huang, W. J. Huang, J. Wen, N. E. Bennett, R. E. Brannigan. *Urology, Northwestern University Feinberg School of Medicine, Chicago, IL.

OBJECTIVE: To investigate whether minimal Cyclophosphamide Equivalent Dose (mcED), a novel approach for estimating minimal alkylating agent exposure, serves as a prognostic factor for sperm retrieval rate by microdissection testicular sperm extraction (mTESE) in azoospermic post-chemotherapy survivors of cancers.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: After IRB approval was obtained, we retrospectively reviewed the medical records of azoospermic patients from June 2002 to Oct 2017, and found 28 azoospermic postchemotherapy cancer survivors undergoing mTESE. Oncological data, age, pretreatment hormone levels, testicular size and outcomes of mTESE were reviewed. Chemotherapy regimens were available for 22 of the patients from their medical records. For the purposes of this study, the mcED value for each patient’s regimen received was estimated using the lowest recommended dosing regimen from the range of recommended doses at the time of administration.

RESULTS: Spermatozoa were successfully retrieved in 11 (39.3%) of the patients. The average age of receiving chemotherapy and mTESE were 17.5 years and 34.3 years, respectively. mcED and age of receiving chemotherapy are significant factors associated with sperm retrieval (p=0.01 and 0.01). mcED < 4000 mg/m² had a higher sperm retrieval rate (10/14=71.4%) than mcED > 4000 mg/m² (0/8=0%). Hormone (FSH, LH, Testosterone and prolactin) levels did not show a significant difference when comparing patients with and without successful sperm retrieval. Regarding cancer subtypes, testicular seminoma, testicular non-seminiferous germ cell tumor, and acute lymphoblastic leukemia are subgroups of cancer patients with favorable sperm retrieval rates [100% (2/2), 66.7% (2/3) and 66.7% (2/3), respectively], although the numbers of subjects in each group are small.

CONCLUSIONS: Minimal Cyclophosphamide Equivalent Dose (mcED) is a novel approach for estimating minimal alkylating agent exposure during chemotherapy. Among this cohort of cancer patients who required chemotherapy regimens, successful sperm retrieval by mTESE was only seen among patients receiving a lower mcED regime (<4000 mg/m²). These findings are consistent with the emerging published body of literature regarding Cyclophosphamide Equivalent Dose (mcED) and semen parameters.


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THE HIGH MACROLIDE RESISTANCE IN GENITAL TRACT INFECTION OF CHINESE INFERTILE POPULATION SHOULD RECEIVE MORE ATTENTION. W. Li, W. Zhu, G. Liu. Reproductive and Genetic Hospital of CITIC-Xiangya, Changsha, China; Institute of Reproduction and Stem Cell Engineering, Central South University, Changsha, China.

OBJECTIVE: It is estimated that approximately 15% of male infertility is related to infections in the genital tract. Mycoplasma genitalium is an important emerging causative agent of sexually transmitted infections (STIs). World-wide, azithromycin treatment of great children due to its very low macrolide resistance (AMR). The aim is to examine the prevalence of M. genitalium and to determine the prevalence of mutations leading to resistance to macrolides in infertile patients in China.

DESIGN: This study was performed as a retrospective survey of 33,434 urogenital swabs and 30,094 semen specimens collected between October 2016 and December 2017 in our hospital.

MATERIALS AND METHODS: M. genitalium was detected using a novel simultaneous amplification testing based on RNA detection. Positive specimens were further studied for mutations associated with macrolide resistance within the 23S rRNA gene using Polymerase Chain Reaction (PCR) and Sanger sequencing.

RESULTS: The M. genitalium incidence was 2.33% (1480 of 63,528), which was significantly higher than that in the control group of fertile men (0.5%). One hundred sixty-four patients with a positive test-of-cure result (164/918,17.9%; 95% CI, 15.4-20.3%) were categorized with treatment failure. There were 80 (34.48%; 95% CI, 28.32-40.64%) cases of treatment failure with macrolides. The overall incidence of treatment failure was 13.4% (123/918; 95% CI, 11.2-15.6) irrespective of the drug used. Macrolide resistance were detected in 54 samples (98.18%; 95% CI, 94.54-101.83%). The most common mutations in the 23S rRNA were A2059G (39/62, 62.9%), A2058T (15/62, 24.2%), A2059G (7/62, 11.3%) and T2086C (1/62, 1.6%) (Escherichia coli numbering). Seventeen of the 18 specimens that were collected prior to macrolide treatment initially carried a point mutation in the 23S rRNA gene.

CONCLUSIONS: Prevalence of macrolide resistance is high in China. This could impair the first line therapy of Mycoplasma genitalium infection. Moreover, the broad range of antibiotic regimes used, without microbiological guidance, was inappropriate and will have increased the risk of antibiotic resistance. There is a need of conducting surveillance of genital tract susceptibility pattern in China for macrolide resistance which can be used for the empirical treatment. A local evidence-based clinical practice guideline should be developed and implemented.
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**DAYS OF ABstinence DOES NOT AFFECT POST-VASECTOMY SEMEN ANALYSIS RESULTS.** D. I. Mazur, J. C. Gondokusumo, J. A. McBride, L. I. Lipshultz, Urology, Baylor College of Medicine, Houston, TX.

OBJECTIVE: The American Urologic Association (AUA) Vasectomy Guidelines recommend that a post-vasectomy semen analysis (PVSA) be done 8-16 weeks after vasectomy with either azoospermia or <100,000 non-motile sperm/mL serving as the criteria for vasectomy success.\(^1\) The impact of the period of abstinence (POA) on the results of a PVSA is unknown. A short POA prior to PVSA may serve as a marker of higher sexual activity (i.e. more ejaculations) in the post-vasectomy interval and thus lead to an increased chance of an acceptable PVSA. However, while studies have shown alterations in sperm concentration and motility with variable POAs for a routine semen analysis, it is unclear if POA has an impact on the chance of finding <100,000 non-motile sperm/mL on PVSA.

DESIGN: Retrospective review of patients who had a vasectomy by a single urologist.

MATERIALS AND METHODS: With institutional board approval, the PVSAs of men who had a vasectomy by a single urologist between January 2000 and July 2017 were retrospectively analyzed. Information was collected on the time since vasectomy, days of abstinence prior to collection, sperm count, and motility. Student t-tests were performed to examine the impact of POA on PVSA.

RESULTS: In total, 875 men who underwent a vasectomy returned for a PVSA. Of these, 794 men (90.7%) had a PVSA demonstrating azoospermia and 48 (5.3%) had >100,000 sperm/mL or motile sperm. In the azoospermic men, the mean time since vasectomy was 151 days (range 104-1989) compared to 100 days (range 24-189) in those with >100,000 sperm or motile sperm (p = 0.15), and no difference in the POA was observed (4.4 vs 5.3 days, respectively, p = 0.27). When examining men whose PVSA was done within the recommended 8-16 weeks after vasectomy, no difference in the POA between men with azoospermia and those with >100,000 sperm/mL or motile sperm was observed (3.4 vs 3.3 days, p = 0.84). Even when azoospermic men were compared to those with the presence of any sperm on PVSA, there was no difference in the POA (3.4 vs 3.5 days, p = 0.84). Of those men tested < 8 weeks after vasectomy, 23/25 were azoospermic with intervals since vasectomy as short as 10 days and 2/25 demonstrated >100,000 sperm/mL or motile sperm.

CONCLUSIONS: The POA does not appear to affect the results of a PVSA. As such, the length of the POA does not need to be considered with regards to when men should provide a PVSA.


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**TESTICULAR DOPPLER RESISTIVE INDEX (RI) IS NOT A MARKER OF SPERMAGENESIS OR ABNORMAL SEMEN ANALYSIS PARAMETERS.** B. Abititan,\(^a\) K. Chen,\(^b\) S. K. Girardi,\(^a\) H. Pek,\(^b\) J. S. Fishbein,\(^c\) S. L. Bristow,\(^d\) A. Hershlag,\(^b\) Department of Obstetrics and Gynecology, North Shore University Hospital, Manhasset, NY; \(^b\)Northwell Health Fertility, Manhasset, NY; \(^c\)Department of Urology, Baylor College of Medicine, Houston, TX.

OBJECTIVE: To ascertain differences in testicular volume and vascular flow between patients with varying degrees of oligoasthenoteratozoospermia.

DESIGN: Retrospective cohort of all males presenting for testicular sonogram for infertility evaluation between January 2014 to December 2016 at one radiology center.

MATERIALS AND METHODS: Patient demographics, semen analysis (SA) parameters, hormonal profiles, and scrotal sonographic measurements were reviewed. The resistive index (RI) was calculated for each testicular artery from the measured peak systolic velocity and end-diastolic velocity. Normal SA was defined based on 2010 World Health Organization (WHO) criteria.\(^1\) Mild to Moderate OAT was defined as concentration 5-15 million/cc, motility 6-39%, and Kruger normal forms 1-4%. Severe OAT was defined as concentration < 5 million/cc, motility 0-5%, and Kruger normal forms <1%. 286 patients fit the inclusion criteria and were subsequently divided into two groups: normal by WHO criteria (n=73), mild to moderate OAT (n=12), and severe OAT (n=65). The remaining 136 subjects had one or two SA abnormalities and were excluded from analysis. ANOVA was used to determine significant difference between the variables, and post-hoc Bonferroni tests were used to correct for individual significant variables.

RESULTS: There was no difference between the mean age, BMI and serum testosterone levels between the three groups (p = 0.7, 0.67, 0.67, respectively). Mean concentration, motility and normal morphology (by Kruger criteria) were significantly different between the groups (p=1.1E-16, 1.1E-16, 1.4E-09, respectively).

Patients with severe OAT had a significantly higher FSH (p=0.0002), lower mean testicular volume (p=2.64E-09), and resistive index (p=0.0082) than those with mild/moderate OAT, and those with normal sperm (Table 1).

CONCLUSIONS: Severe oligoasthenoteratozoospermia (with high FSH levels) is associated with lower testicular volume and increased vascular resistance flow in the testicles. Urological evaluation is warranted in all such cases of diminished testicular reserve.

Demographic, Hormonal, and Demen parameters between forms of OAT

<table>
<thead>
<tr>
<th></th>
<th>Normal WHO Criteria (n=73)</th>
<th>Mild-Moderate Oligoteratoasthenospermia (n=12)</th>
<th>Severe Oligoteratoasthenospermia (n=65)</th>
<th>F statistic</th>
<th>p value</th>
<th>Bonferroni p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>36.2 (±6.3)</td>
<td>36.8 (±6.5)</td>
<td>37.1 (±6.4)</td>
<td>0.36</td>
<td>0.7</td>
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</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.3 (±5.4)</td>
<td>30.0 (±6.8)</td>
<td>30.2 (±6.5)</td>
<td>0.41</td>
<td>0.67</td>
<td>N/A</td>
</tr>
<tr>
<td>FSH (IUL)</td>
<td>4.7 (±2.6)*</td>
<td>6.4 (±2.9)</td>
<td>13.6 (±13.3)*</td>
<td>0.00002</td>
<td>1.86E-05</td>
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<tr>
<td>Testosterone (ng/dL)</td>
<td>346.8 (±138.8)</td>
<td>342.9 (±141.1)</td>
<td>184.6 (±163.0)</td>
<td>0.4</td>
<td>0.67</td>
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<tr>
<td>Testicular Volume (cm³)</td>
<td>16.3 (±4.9)*</td>
<td>14.9 (±7.0)*</td>
<td>10.1 (±5.6)*</td>
<td>22.7</td>
<td>2.64E-09</td>
<td>1.46E-09</td>
</tr>
<tr>
<td>Resistive Index (RI)</td>
<td>0.55 (±0.07)*</td>
<td>0.49 (±0.06)**</td>
<td>0.57 (±0.09)*</td>
<td>0.0082</td>
<td>0.005</td>
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<tr>
<td>Concentration (million/mL)</td>
<td>70.5 (±4.5)*</td>
<td>11.2 (±2.5)*</td>
<td>0.15 (±0.6)</td>
<td>100.3</td>
<td>1.1E-16</td>
<td>4.38E-09</td>
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<tr>
<td>Motility (%)</td>
<td>59.3 (±12.1)*</td>
<td>31.4 (±7.1)*</td>
<td>0.8 (±2.96)*</td>
<td>738.2</td>
<td>1.1E-16</td>
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<tr>
<td>Morphology (normal %)</td>
<td>7.7 (±3.4)*</td>
<td>2.4 (±1.2)*</td>
<td>0.2 (±0.4)</td>
<td>26</td>
<td>1.4E-09</td>
<td>3.82E-06</td>
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</tbody>
</table>

FERTILITY & STERILITY®

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peak systolic velocity and end-diastolic velocity. 530 scrotal ultrasounds were reviewed; 174 were excluded and 356 met criteria for inclusion in the final analysis. Correlation between the RI and each semen parameter was performed using Spearman’s rank correlation coefficient. Summary statistics (e.g. min and max) were used to assess if there is a cutoff RI below which 100% of patients have normal semen parameters.

RESULTS: Mean age (± SD) was 36.6 (± 5.9), and mean BMI was 29.2 (± 5.8). Mean concentration, motility and morphology were 34.7 million/mL (± 41.7), 47.4% (± 18.9), and 3.9% (± 3.9), respectively. There was no significant relationship between the left or right RI and any of the measured semen parameters (Table 1). There was no RI value below which 100% of patients have normal semen parameters. However, mean RI was higher in patients with abnormalities in all three major semen parameters (oligoasthenoteratozoospermia) (F=4.97, p=0.0082).

CONCLUSIONS: RI is not correlated with any single measured semen analysis parameter, although a higher mean resistant index is observed in patients with multiple sperm abnormalities. This finding suggests against the use of testicular spectral Doppler sonography as a noninvasive tool for evaluation of testicular function.

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IMPARED SLEEP IS ASSOCIATED WITH LOW TESTOSTERONE IN US ADULT MALES: RESULTS FROM THE NATIONAL HEALTH AND NUTRITION SURVEY. P. Patel,1 T. P. Kohn,2 R. Ramasamy.1 1Department of Surgery, University of Manitoba, Winnipeg, MB, Canada; 2Johns Hopkins, Baltimore, MD; 3Department of Urology, University of Miami, Miami, FL.

OBJECTIVE: Testosterone deficiency has been linked to several adverse health outcomes - including cardiovascular disease, erectile dysfunction, and metabolic syndrome. Recent data has suggested that abnormal sleep quality may result in lower testosterone levels. Our study was to evaluate the association between serum testosterone levels and sleep.

DESIGN: Using the 2011-2012 National Health and Nutrition Surveys (NHANES) we assessed the effect of self-reported sleep patterns on serum testosterone while controlling for co-morbidities, and baseline demographics.

MATERIALS AND METHODS: NHANES is a national cross-sectional survey program designed to assess the health and nutritional status of adults and children in the United States. Using the 2011-2012 NHANES dataset, we extracted serum total testosterone level, sleep duration, physical activity, demographic and co-morbidities for men aged 16 years and older. Univariate and multivariate linear regression was used to estimate the association of number of hours slept, prior co-morbidities, and demographics with serum testosterone.

RESULTS: Among the 9,756 individuals in the NHANES dataset, 2,296 (23.5%) were males 16 years and older with a median patient age of 46.10 who had serum testosterone levels drawn. Mean serum testosterone level was 393.33 ng/dL (43.39 - 779.2 ng/dL). Median number of hours slept was 6.86 hours (2 -12 hours). On multivariate linear regression, we found serum testosterone decreased by 0.49 ng/dL per year of age (p = 0.04), 5.85 ng/dL per hour loss of sleep (p =< 0.01), 0.04 ng/dL per year of age (p = 0.01) and 2.99 ng/dL per each increase in alcoholic beverage (p =< 0.01).

CONCLUSIONS: Among men aged 16-80 in the United States, we found low testosterone is associated with increasing age, impaired sleep, increasing alcohol intake and elevated BMI. It is important, therefore, that evaluations of reduced testosterone levels should focus on diet, as well as sleep quality and habits.

Supported by: This work was supported in part by the Urology Care Foundation / Sexual Medicine Society of North America Research Scholar from the American Urological Association to RR.

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EFFECT OF VARICOCELE REPAIR ON SPERM DNA FRAGMENTATION: A SYSTEMATIC REVIEW AND META-ANALYSIS. M. Roque,1 G. Bedoschi,1 T. P. Kohn,2 R. Ramasamy.1 1Innovation Institute for Fertility Preservation and IVF, New York, NY; 2Androfert, Campinas, Brazil.

OBJECTIVE: To evaluate if the varicoceal repair is an effective strategy for reducing the sperm DNA fragmentation (SDF).

DESIGN: Systematic review and meta-analysis.

MATERIALS AND METHODS: We conducted a systematic search using PubMed/Medline, EMBASE, Scielo and Google Scholar to identify all relevant studies published from their inception until March 2018. The search combined terms and descriptors related to "sperm DNA fragmentation", "sperm DNA damage", "sperm chromatin integrity OR damage", and "varicocele", "varicocele repair", "varicocelectomy". For the advanced search, article type selected was: clinical study, comparative study, journal article, meta-analysis, observational study, randomized controlled trial, review, and systematic review. Patients included in the meta-analysis were those with clinical varicocele and SDF measurement that was submitted to varicocele repair. The primary outcome was the Mean Difference (MD) between the SDF fragmentation levels before and after the varicocelectomy. We also performed sub-analysis considering the different tests used to evaluate the SDF, namely: sperm chromatin structure assay (SCSA); Terminal deoxyribonucleotide transferase-mediated dUTP nick-labeling (TUNEL); Acridine Orange; and sperm chromatin dispersion (SCD). The data were pooled using the inverse variance model, and the effect measure was presented as mean difference (MD) with its 95% confidence interval (CI).

RESULTS: Nineteen studies were included in the meta-analysis, involving 1,153 men with clinical varicocele and SDF measurements. Overall, there was a statistically significant decrease in the SDF levels after the varicocele repair (MD -8.31%, 95% CI -10.27%, -6.36%; P<0.0001). This difference was statistically significant independently on the method used to evaluate the SDF: SCSA (MD -7.10%; 95% CI -9.32%, -4.88%; P=0.001), TUNEL (MD -15.02%; 95% CI -21.35%, -8.69%; P<0.0001), Acridine Orange (MD -9.30%; 95% CI -15.28%, -3.32%; P=0.002).

CONCLUSIONS: Current evidence supports oxidative stress and SDF as a primary factor in the pathophysiology of varicocele-induced infertility. The varicocele repair is associated with improvements in SDF and should be considered as part of treatment in infertile couples when a clinical varicocele and high levels of SDF are present.

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THE EFFECTS OF OBESITY ON MALE FERTILITY. M. Bazzi,1* M. Deebajah,6 S. Fakhouri,6 A. H. Arabi,1 M. F. Carter,5 S. Alaneé,6 A. Dabaja.6 1Wayne State University School of Medicine, Deaborn, MI; 2Urology, Henry Ford Hospital, Detroit, MI; 3Henry Ford Health System, Clinton Township, MI; 4Urology, Medical Student, Dearborn, MI; 5Urology, Administrator, Detroit, MI; 6Henry Ford System, Detroit, MI; 7Henry Ford Health System, Detroit, MI.

OBJECTIVE: Men with a higher body mass index (BMI) may experience testosterone (T) to estradiol (E2) conversion leading to possible infertility.
TABLE 1.

<table>
<thead>
<tr>
<th>BMI</th>
<th>Total sperm count (M)</th>
<th>Volume (mL)</th>
<th>Total motility (%)</th>
<th>Progressive motility (%)</th>
<th>Morphology (%)</th>
<th>pH</th>
<th>Viscosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 30</td>
<td>139.3</td>
<td>3.0</td>
<td>44.5</td>
<td>40.2</td>
<td>6.8</td>
<td>6.7</td>
<td>.096</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>160.5</td>
<td>3.1</td>
<td>46.1</td>
<td>40.9</td>
<td>6.3</td>
<td>7.7</td>
<td>.88</td>
</tr>
</tbody>
</table>

p-value (for differences): .149 < .05 was considered significant.

RESULTS: 102 men had a BMI ≥ 30 kg/m² and 119 men had a BMI < 30 kg/m². Men within the higher BMI group had an average T level of 283.97 ng/dL versus 362.70 ng/dL within the lower BMI group, a difference of 79.74 (p = 0.001). Men within the high BMI group had an average E₂ level of 40.7 pg/dL versus 35.3 pg/dL in the lower BMI group, a nonsignificant difference of 5.35 (p = 0.071). This gave us a T/E₂ ratios of 8.17 and 11.74, in high and low BMI groups respectively (p = 0.001). There were no significant differences in Luteinizing or Follicle-stimulating hormones levels between the two groups, differences of 0.121 mIU/mL (p = 0.852) and 1.32 mIU/mL (p = 0.411) respectively. There was also no significant difference in SA between the two groups which is demonstrated in table 1.

CONCLUSIONS: Although men with higher BMIs had a significantly lower T level, and an abnormal T/E₂ ratio, there was no difference in E₂ levels and semen parameters in between the two groups. This suggests that T to E₂ conversion may not play a role in male infertility and that most of the conversion does not occur in periadipose tissue and might be localized to the testicle.

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Although men with elevated BMI may have abnormal hormonal profiles (HP), it has been hypothesized that men with elevated BMI may present with infertility for reasons other than T to E₂ conversion.

DESIGN: Retrospective cohort study done by reviewing medical records of men presenting at our institution for infertility from July of 2012 to February of 2018.

MATERIALS AND METHODS: Retrospective analysis of electronic medical records of men presenting with infertility who received a HP and semen analysis (SA). The cohort was divided into two main groups above and below BMI of 30 kg/m². A multivariable analysis was performed. P-value < 0.05 was considered significant.

RESULTS: 102 men had a BMI ≥ 30 kg/m² and 119 men had a BMI < 30 kg/m². Men within the higher BMI group had an average T level of 283.97 ng/dL versus 362.70 ng/dL within the lower BMI group, a difference of 79.74 (p = 0.001). Men within the high BMI group had an average E₂ level of 40.7 pg/dL versus 35.3 pg/dL in the lower BMI group, a nonsignificant difference of 5.35 (p = 0.071). This gave us a T/E₂ ratios of 8.17 and 11.74, in high and low BMI groups respectively (p = 0.001). There were no significant differences in Luteinizing or Follicle-stimulating hormones levels between the two groups, differences of 0.121 mIU/mL (p = 0.852) and 1.32 mIU/mL (p = 0.411) respectively. There was also no significant difference in SA between the two groups which is demonstrated in table 1.

CONCLUSIONS: Although men with higher BMIs had a significantly lower T level, and an abnormal T/E₂ ratio, there was no difference in E₂ levels and semen parameters in between the two groups. This suggests that T to E₂ conversion may not play a role in male infertility and that most of the conversion does not occur in periadipose tissue and might be localized to the testicle.

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OBJECTIVE: To identify differences in the testicular transcriptome of men with non-obstructive azoospermia (NOA) and determine markers to predicit the best candidates for a successful surgical sperm retrieval.

DESIGN: Over 9 months, surgical samples were collected from NOA men (n=5) undergoing a testicular sperm extraction (TESE). Samples were assessed for differential gene expression by next-generation RNA-sequencing and expression patterns were classified based on a successful (NOA+)(n=2) or failed (NOA-)(n=3) sperm retrieval. Gene expression profiles of these men were compared to a control with acquired obstructive azoospermia (OA).

MATERIALS AND METHODS: Testicular samples from 5 NOA men were assessed; no Y microdeletions were detected. Samples that did not yield spermatozoa (NOA-) were searched extensively (71 ± 10 minutes) by several embryologists to confirm a failed TESE attempt. About 200µl of tissue from each sample was processed for RNA isolation using a commercially available kit and protocol. RNA isolates were sequenced by Illumina HiSeq at 2x150bp configuration per lane with ~50M reads per sample. A log fold change of >2 and an FDR of P<0.05 were considered significant.

RESULTS: TESE RNA samples yielded a concentration of 41.1 ± 29 ng/µL and an RNA integrity number of 4.6 ± 1. Analysis of differential gene expression grouped by ontology revealed a significant reduction in gene expression related to spermatogenesis in NOA men versus OA. Expression levels of germ cell markers in NOA samples were present yet significantly lower than the control, such as DAZL (P<0.001), indicating a reduced germ cell presence. NOA- patients had 30.8% of spermatogenesis-related genes significantly under-expressed while NOA+ men evidenced a reduction of only 16.7% compared to a control. Interestingly, a subset of genes were significantly under-expressed exclusively in NOA- patients, primarily related to meiosis, and evidenced a reduced expression in 77.8% of genes related to the synапtonemal complex assembly (HORMAD1, SYCE1, SYCE3, SYCP1, SYCP2, and TRIP13; P<0.0001) and regulations of the meiotic organization (MEIOB; P<0.00001) and segregation (STAG3; P<0.01). These genes were not significantly under-expressed in NOA+ men. These findings suggest that failure to retrieve spermatozoa was due to a maturation arrest of the germ cells in the extracted tubules.

CONCLUSIONS: While the etiology of NOA is still unclear, RNA-seq can help gauge the spermatogenetic state and potentially provide the urologist with a noninvasive marker to select the best candidates for a successful sperm retrieval, which could be tested on the seminal fluid, sparing the patient a surgical procedure. This information may also be useful for
OE: In 2017, the YO<sup>®</sup> Home Sperm Test (YO) entered the consumer market as the first FDA-cleared, video-based smartphone platform for home sperm testing. YO measures Motile Sperm Concentration (MSC), a composite of concentration and motility (% of sperm moving) by utilizing the Smartphone’s camera and light source to capture a moving sperm video. Using proprietary algorithms, the YO app analyzes light fluctuations caused by sperm movement in the video and translates these movements into MSC. The objective of the current study was to test the accuracy and precision of the YO to generate Motile Sperm Concentration (MSC) results vs the SQA-Vision (Medical Electronic Systems), an automated laboratory analyzer that directly measures MSC.

DESIGN: Measurement of motile sperm concentration in fresh semen sample and comparison of the YO score derived from WHO 2010 sperm criteria table in a blinded fashion.

MATERIALS AND METHODS: Human semen samples were collected according to WHO manual (5th edition) guidelines and MSC was analyzed in 144 duplicates (288 tests) by the SQA-Vision automated semen analyzer (comparator system) vs Smartphone (iPhone 7). The study included 7 different operators, participating in a blind manner. Precision and accuracy of YO device and SQA-Vision was established based on coefficient of variation (CV) of actual MSC values using MedCalc software.

RESULTS: The MSC results showed good correlation and agreement between the YO device and SQA-Vision with Pearson Correlation coefficient above 0.92. Normal MSC results (6 M/mL cut-off value) reported by the SQA-Vision favorably compared to the YO device results, as demonstrated by a high positive and negative predictive value above 94% with overall accuracy of 97.8%. The CV of both devices were comparable (9.35% to 11.17%) and lower than the manufacturer’s claim (≤ 20%).

CONCLUSIONS: When compared to the automated SQA-Vision laboratory device, the high level of accuracy and precision of the YO Home Sperm Test to detect abnormal (low) cases of MSC below the 6 M/mL cut-off supports it’s use as an effective home sperm test for screening low and moderate/normal MSC test results. In addition, YO Home Sperm Test effectively detects varying levels of NORMAL MSC in a precise manner over a wide range of normal Motile Sperm Concentrations ("YO Score").

MALE REPRODUCTION AND UROLOGY - RESEARCH

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OBJECTIVE: We have previously shown that mir-202-5p is significantly down regulated in Sertoli Cell Only (SCO) men compared to normal fertile men using QT-PCR. However, NextGen RNAseq results failed to reproduce these results in an extended cohort of 11 SCO men and 10 men with normal spermatogenesis. The objective of this study was to evaluate the contribution of isomiRs as a potential biological explanation underpinning this discrepancy.

DESIGN: Testicular biopsies obtained at the time of surgical sperm retrieval were submitted to next generation RNA sequencing, RT-PCR, northern blot analysis, and in situ hybridization.

MATERIALS AND METHODS: NextGen RNAseq was performed on testis biopsies from 11 men with SCO and 10 with normal spermatogenesis using the Illumina HiSeq 2000 platform. Reads were trimmed, and aligned to the Hg38 using TopHat (v2.0.8) and reads were quantified with cufflinks (v2.1.1) in the original analysis. In our secondary focused analysis, unmapped reads were evaluated for miRbase v22 canonical seed and mature mir-202-5p and mir-202-3p sequences. Adaptor sequences from Illumina were recognized using Trimmm_galore auto-detection. Custom script was then used to align exact seed sequences and canonical mir-202-202 lengths. 25bp reads were cut and processed for isomiRs. Northern blots and in situ hybridization were performed to validate RNA sequencing results.

RESULTS: No statistical differences were observed between mir-202-5p in normal or SCO using the traditional RNAseq analysis pipeline, despite significant loss demonstrated among SCO in RTPCR, northern blot and in situ hybridization among Sertoli cells in SCO compared to normal controls. Secondary analysis identified a significant number of isomiRs among 202-5p with only 11,604 reads with 100% canonical alignment; however, the majority, 36,335 reads demonstrated a G to A single nucleotide polymorphism in position 22, accounting for the majority of mir-202-5p reads in both normal and SCO samples. Only 10% of all 202-5p reads follow the canonical sequence as compared to 70% of 202-3p in both normal controls and SCO specimens. The majority of isomiRs occur in the final 4 nucleotide positions; we have determined these to significantly alter the functional binding energy for interactions with target mRNAs and the heterogeneity of 202-5p isomiRs may have significant biological implications in infertility, and specifically SCO.

CONCLUSIONS: Non-classical sequence variants of mir-202-5p are expressed in human testis in greater quantities than the accepted canonical form. These isomiRs effect the binding energy of the miRNA to the UTR of target messenger RNAs. IsoMir prevalence and heterogeneity appears to be gene specific, as mir-202-5p is not characterized by such deviation from the reference genome. Further study is required to elucidate the role of such isomiRs in the physiology of spermatogenesis.

Supported by: P50 HD076210, U1 U101HD074542-01; Frederick J. and Theresa Dow Wallace Fund of the New York Community Trust, the Mr. Robert S. Dow Foundation; Irena and Howard Laks Foundation.

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OBJECTIVE: Prior in situ hybridization studies have demonstrated nuclear localization of some microRNAs that are differentially expressed in normal men versus individuals with Sertoli-Cell Only Syndrome. We sought to clarify if this noncanonical staining was accurate or due to nonspecific binding of precursor microRNAs.

DESIGN: Nuclear and cytoplasmic fractions of normal human testis tissue were separated and evaluated by in situ hybridization in both fractions with determining RT-PCR. Custom probes for immature and mature microRNAs of interest were developed to confirm initial results.

MATERIALS AND METHODS: Testicular biopsies were obtained from men undergoing testicular sperm extraction for infertility. Samples were snap frozen in liquid nitrogen for storage prior to processing. Specimens were independently read by two pathologists. 4 samples with near normal amounts of spermatogenesis were chosen for the study. Nuclear and cytoplasmatic fractions were separated using SurePrep kits per manufacturer’s instructions (Fisher Scientific). RT-PCR was conducted on a LightCycler 480 (Roche) utilizing the miRCURY LNA Universal RT microRNA PCR System (Exiqon). Custom probes were designed for mir-34c-3p, mir-34c-5p, mir-202-5p, and mir-202-3p, and mir-202-5p and mir-202-3p for both mature and precursor targets (Exiqon). In similar fashion, RT-PCR was conducted to quantify expression in duplicate. Quantitative control was assumed using interplate calibrators, PCR efficiency controls, and positive/negative controls. The transcription factor for Sp6 was used to confirm nuclear enrichment. Expression of mir-503 was used for normalization based upon analysis by NormFinder (MOMA, Denmark).

RESULTS: A total of 677 microRNAs were included in the final analysis. Of the screened microRNAs, 37 had higher expression within the nuclear fraction when compared against the cytoplasmic portion. Regarding mir-34c-3p, mir-34c-5p, mir-202-3p, and mir-202-5p, less than 1% of the total small RNA in our samples were in a precursor form when comparing mature to precursor transcripts with the same seed sequence. As expected, precursors for these 4 microRNAs were enriched in the nucleus, whereas their mature forms favored, although nonexclusively, the cytoplasm.

CONCLUSIONS: Noncanonical localization of mature microRNAs to the cell nucleus occurs in the normal human testis. Although mir-34c-3p, mir-34c-5p, mir-202-3p, and mir-202-5p preferentially localized to the cytoplasm, mature forms were detected in the nucleus as well, thereby confirming...
earlier in situ hybridization findings. Further study is required to assess the role and implications of microRNAs that primarily localize to the cell nucleus.

Supported by: R50 HD076210, U1 U101HD074542-01; Frederick J. and Theresa Dow Wallace Fund of the New York Community Trust, the Mr. Robert S. Dow Foundation; Irena and Howard Laks Foundation.

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SEMINAL OXIDATIVE REDUCTION POTENTIAL AP- Pears TO BE HIGHER IN PATIENTS WITH NON- OBSTRUCTIVE AZOSPERMIA & KLINEFELTER SYNDROME. S. J. Parekattil,a M. Etafy,b R. A. Mendelson,c J. Brahmbhatt,d Urology, PUR Clinic, Clermont, FL; bPUR Clinic, Weston, FL; cGraduate Industrial and Organizational Psychology, Keiser University, Cooper City, FL; dCo-Director, PUR Clinic, Clermont, FL.

OBJECTIVE: Seminal Oxidative Reduction Potential (ORP) in a simple and cost-effective method of measuring oxidative stress in semen samples. This study assesses if seminal ORP values may be significantly elevated in patients with non-obstructive azoospermia (NOA) and Klinefelter syndrome compared to controls (post-vasectomy and vasectomy reversal patients).

DESIGN: Prospective review of seminal ORP in patients presenting for semen analysis with a variety of male factor infertility conditions and controls (post-vasectomy and vasectomy reversal patients) from Jan 2018 to May 2018.

MATERIALS AND METHODS: Normalized ORP was measured in semen analysis samples from 40 patients utilizing the Mioxsys (Ayto Inc.) system: 2 patients had Klinefelter syndrome, 5 had NOA, 11 were post vasectomy, 11 were post-vasectomy reversal, 8 had varicoceles and 3 had oligospermia.

RESULTS: Median normalized ORP values were as follows: Klinefelter’s-136, NOA-136, Post-vasectomy-34, Vasectomy reversal-6, Varicocele-1.1 and Oligospermia-8.46.

CONCLUSIONS: This preliminary study suggests that ORP values tend to me much higher in patients with NOA and Klinefelter syndrome compared to controls. Further evaluation and greater sample size are warranted.

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UBI-P63E IS REQUIRED FOR THE SELF-RENEWAL AND DIFFERENTIATION OF GERMILNE STEM CELLS. J. Yu,a X. Chen,a X. Luan,a Y. Yan,a J. Fang,b aDepartment of Obstetrics and Gynecology, Affiliated Hospital of Jiangsu University, Zhenjiang, China; bDepartment of Obstetrics and Gynecology, Affiliated Hospital of Jiangsu University, Zhenjiang, China.

OBJECTIVE: Our aim was to investigate the regulatory effect and possible mechanism of intrinsic signals and their niche on self-renewal and differentiation of germline stem cells (GSCs) in the Drosophila testis.

DESIGN: We conducted a large-scale RNA interference (RNAi) screen in Drosophila testis and analyzed the functions of the identified gene Ubisp63E in stem cell niche.

MATERIALS AND METHODS: For the genome-wide RNAi screen, we used Gal4 expressed in the testis to drive the expression of UAS-RNAi vectors in different cell types. Knockdown of Ubi-p63E gene, phenotypes of the fly and mouse testes were observed by immunocytochemistry and microscopy.

RESULTS: We screened 2881 RNAi lines corresponding to 2937 genes to identify potential candidate genes involved in intestinal stem cell regulation in Drosophila. Cell Rep 2011; 8: 580-593.

CONCLUSION: This work was supported by grants from the Natural Science Foundation of Jiangsu Province [BK2017040259], Key Research Foundation of Zhenjiang Social Development [SH2016028] and Science Foundation of Doctorate Research of Affiliated Hospital of Jiangsu University [jdfyRC2016005].

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THE ADULT HUMAN TESTIS CELL ATLAS VIA SINGLE CELL RNA SEQUENCING. J. Guo,a E. J. Grow,b D. T. Carrell,b J. M. Hotaling,c B. Cairns.a aHuntsman Cancer Institute, Salt Lake City, UT; bSurgery and Human Genetics, Andrology/IVF, Salt Lake City, UT; cDepartment of Surgery, Salt Lake City, UT.

OBJECTIVE: Human spermatogenesis involves the differentiation of adult spermatogonial stem cells (SSC) into mature sperm through a complex process regulated by the testis niche. Human SSCs must carefully balance their self-renewal and differentiation, and then undergo niche-guided transitions between multiple cell states and cellular processes - including a commitment to mitosis, meiosis, and the subsequent stages of sperm maturation, which are accompanied by chromatin repackaging and major morphological changes. Study this process is of particular significance to understand causes of male infertility and germ cell tumor formation. Here, we aim to offer new insights into the regulation of SSCs and male gametogenesis in humans using single cell RNA-seq (scRNA-seq).

DESIGN: We performed scRNA-seq of testicular cells from three healthy men of peak reproductive age.

MATERIALS AND METHODS: We isolated single testicular cells from cell suspensions from testes sampled from 3 individuals using a standard two-step enzymatic digestion and 40-μm physical filtering. For each individual, two separate technical replicates were performed.

RESULTS: We yielded ~ 6500 testicular cells from our scRNA-seq experiments (six experiments total). Further analysis of the dataset revealed distinctive transcriptional signatures/states of self-renewing and differentiating spermatogonia, spermatogenesis, and five niche/somatic cell populations (Leydig, myoid, Sertoli, endothelial, macrophage) and candidate germine-niche interactions. Spermatogenesis was reconstructed computationally, which identified sequential and specific coding, noncoding, and repeat-element transcriptional signatures. We computationally identify five discrete transcriptional/developmental states along spermatogonial development. Moreover, epithelial features and nascent transcription (velocity) analyses suggest developmental plasticity within SSC states.

CONCLUSIONS: Our datasets describe the key transcriptional and epigenetic signatures of the normal adult human testis and provide new insights into germ cell developmental transitions and plasticity.

References:
OBJECTIVE: The use of marijuana has been increasing among U.S. men of reproductive age and its recreational consumption was legalized in Washington State (WS) on November 12th, 2012. Marijuana and its active metabolite tetrahydrocannabinol (THC) can alter the signaling system within spermatozoa which may result in negative effects on spermatogenesis and male fertility. We aimed to characterized differences in semen quality among men with variable consumption of marijuana.

MATERIALS AND METHODS: We prospectively evaluated semen analyses (SA) from men who presented for infertility evaluation at a single male fertility laboratory. Semen analyses were performed from July 2017 to April 2018. All participants completed a reproductive health questionnaire which included specific queries on past and present marijuana consumption. Questionnaire data included age, ethnicity, marijuana use (≤1 or >1 time per week), duration (months), and tobacco smoking. SA was performed in accordance with World Health Organization (WHO) 2010 criteria. SA parameters included volume (mL), concentration (million/mL), motility (%), progressive motility (%), and strict normal morphology (%).

RESULTS: A total of 409 patients underwent SA and completed the questionnaire of which 174 (43%) men reported marijuana use (ever users). Among the ever users, current and past users comprised 71 (18%) and 103 (25%) respectively. Compared to non-user, semen quality was significantly decreased in volume, concentration, morphology, total motile count (TMC) and total progressive motile count (TPMC) compared to never users (Table 1). In multivariate logistic regression analyses, controlling for age, marijuana use was associated with increased odds of abnormal morphology (OR 2.28 (95% confidence interval (CI): 1.52-3.43)), volume (OR 2.02 (1.04-3.94)), and TPMC (OR 1.8 (1.05-3.06)). There was no significant association between marijuana use and sperm concentration, motility or progressive motility as solitary parameters.

CONCLUSIONS: Marijuana use is common among men presenting for fertility evaluation in our cohort and may have a detrimental effect on semen quality, particularly morphology, volume, and TPMC. Given these findings, large, prospective studies of both semen quality and fertility in this growing, at-risk population are warranted.

TABLE 1. Percentages of normal and abnormal semen analysis [WHO 2010] among three groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group</th>
<th>Normal Semen Analysis N (%)</th>
<th>Abnormal Semen Analysis N (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>Never</td>
<td>216 (92%)</td>
<td>19 (8%)</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td>Past</td>
<td>93 (90%)</td>
<td>10 (10%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>58 (82%)</td>
<td>13 (18%)</td>
<td></td>
</tr>
<tr>
<td>Concentration</td>
<td>Never</td>
<td>209 (89%)</td>
<td>26 (11%)</td>
<td>0.086</td>
</tr>
<tr>
<td></td>
<td>Past</td>
<td>87 (85%)</td>
<td>16 (15%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>56 (79%)</td>
<td>15 (21%)</td>
<td></td>
</tr>
<tr>
<td>% Motility</td>
<td>Never</td>
<td>145 (62%)</td>
<td>90 (38%)</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>Past</td>
<td>75 (73%)</td>
<td>28 (27%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>56 (79%)</td>
<td>15 (21%)</td>
<td></td>
</tr>
<tr>
<td>% Progressive motility</td>
<td>Never</td>
<td>162 (69%)</td>
<td>73 (31%)</td>
<td>0.513</td>
</tr>
<tr>
<td></td>
<td>Past</td>
<td>73 (71%)</td>
<td>30 (29%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>54 (77%)</td>
<td>17 (23%)</td>
<td></td>
</tr>
<tr>
<td>% Strict morphology</td>
<td>Never</td>
<td>156 (67%)</td>
<td>79 (33%)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Past</td>
<td>48 (47%)</td>
<td>55 (53%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>35 (49%)</td>
<td>36 (51%)</td>
<td></td>
</tr>
<tr>
<td>Total motile count</td>
<td>Never</td>
<td>199 (85%)</td>
<td>36 (15%)</td>
<td>0.608</td>
</tr>
<tr>
<td></td>
<td>Past</td>
<td>84 (82%)</td>
<td>19 (18%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>57 (80%)</td>
<td>14 (20%)</td>
<td></td>
</tr>
<tr>
<td>Total progressive motile count</td>
<td>Never</td>
<td>204 (87%)</td>
<td>31 (13%)</td>
<td>0.111</td>
</tr>
<tr>
<td></td>
<td>Past</td>
<td>83 (81%)</td>
<td>20 (19%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>55 (76%)</td>
<td>16 (25%)</td>
<td></td>
</tr>
</tbody>
</table>
VALIDATION OF KEY SEMINAL PLASMA PROTEINS

DESIGN: Semen samples used in this study were obtained from men diagnosed with TCS undergoing sperm banking before starting the cancer therapy (TCS group; N = 15), and from healthy donors with proven fertility (Control group; N = 15).

MATERIALS AND METHODS: A routine semen analysis was conducted before cryopreservation of the samples. The cryopreserved samples were thawed, cryoprotectant removed and spermatozoa proteins were extracted before cryopreservation of the samples. The cryopreserved specimens except low ROS levels (P < 0.001) as well as tyrosine/tyrosol (P < 0.014), as well as the overexpression of complement C3 (P < 0.003) relative to control group. However, this result did not match with the proteomic analysis that indicated an overexpression of complement C3.

RESULTS: Total motility and sperm concentration showed significant improvement (P < 0.05) as well as tyrosine/tyrosol (P < 0.014), as well as the overexpression of complement C3 (P < 0.003) relative to control group. However, this result did not match with the proteomic analysis that indicated an overexpression of complement C3.

CONCLUSIONS: Annexin A2, which is involved in sperm binding, may be a potential biomarker for the diagnosis of men with primary infertility. Further validation of additional proteins is necessary to identify other candidate proteins that may also be implicated in male infertility.

Supported by: Ana D, Martins was funded by the Fulbright Research Grant (ID: E0585654) and the Portuguese Science and Technology Foundation (SFRH/BD/108726/2015).

OXIDATIVE STRESS

META-ANALYSIS OF DOUBLE-BLIND PLACEBO CONTROL TRIALS EVALUATING THE ROLE OF COENZYME Q10 ON SEMEN PARAMETERS. A. Agarwal, a A. Sharma, b K. Master, b R. Sharma, b R. Henkel, f American Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH; Department of Medical Bioscience, University of the Western Cape, Bellville, South Africa.

OBJECTIVE: Coenzyme Q10 is an antioxidant molecule that plays an important role in energy metabolism. In spermatozoa, coenzyme Q10 is concentrated in the mitochondria and is responsible for all energy-dependent processes. Reduction in levels of coenzyme Q10 have been reported in seminal plasma of infertile patients characterized by low sperm motility and abnormal sperm morphology. The objective of this study was to evaluate the effect of coenzyme Q10 supplementation on semen parameters in fertile men with idiopathic oligo-astheno-teratozoospermia and idiopathic asthenozoospermia.

DESIGN: Meta-analysis of double-blind placebo controlled, randomized clinical trials.

MATERIALS AND METHODS: Literature review was conducted using Google Scholar, Med-Line, PubMed and Wiley Online Library. The key words used were: coenzyme Q10, semen parameters, double-blind placebo controlled, semen parameters, motility, male infertility, sperm quality. The inclusion criteria were human studies and clinical trial from the last 15 years. After reviewing the literature, 7 studies were found on the role of coenzyme Q10 on semen parameters, out of which 4 double-blind placebo-controlled randomized trials were selected. The study design included 395 patients with idiopathic infertility who received 100-200 mg of coenzyme Q10 or placebo for 3-9 months. Semen samples were compared at baseline and after the completion of the treatment period. Coenzyme Q10 levels were also measured in the seminal plasma. Improvement in sperm concentration and total sperm motility were the two parameters that were common in all four studies. Meta-analysis was carried out using the MedCalc 18.2.1 software.

RESULTS: Total motility and sperm concentration showed significant improvement (P < 0.0001) after coenzyme Q10 supplementation. Patients...
with a lower baseline value of motility had a statistically significant higher probability to respond to the treatment. Statistical analysis showed a confidence interval from 97.56 to 99.04% for sperm motility, while for sperm concentration, the confidence interval obtained was 98.22 to 99.24%. No side effects such as nausea and or drowsiness were reported in any of these studies.

CONCLUSIONS: This is the first meta-analysis of double-blind placebo-controlled trials examining the effect of coenzyme Q10 in improving sperm concentration and motility in infertile men with idiopathic infertility, and oligo-asthen-teratozoospermia or idiopathic asthenozoospermic men. Effect of coenzyme Q10 on semen quality is largely attributed to its antioxidant properties that helps in reducing oxidative stress and improving fertility potential. However, additional double-blind placebo-controlled studies are still needed to establish the efficacy of coenzyme Q10 in these patients.

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UNDERSTANDING THE MOLECULAR DYNAMICS OF FERTILITY PRESERVATION IN ROS POSITIVE MEN: A PROTEOMIC INSIGHT. A. Agarwal, T. R. Dias, L. Samanta, A. Sharma, B. Gopalan, D. Durairajanyagam, B. B. Willard, S. C. Vij. American Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH; University of Beira Interior, Covilhã, Portugal; University of Porto, Porto, Portugal; Redox Biology, Ravenshaw University, Cuttack, India; Yorg Corporation, Plano, TX; Faculty of Medicine, Université Teknologi MARA, Sungai Buloh, Malaysia; Research Core Services, Cleveland Clinic, Cleveland, OH; Department of Urology, Cleveland Clinic, Cleveland, OH.

OBJECTIVE: To identify proteomic markers in semen samples of fertile men with high reactive oxygen species (ROS) levels.

DESIGN: Normozoospermic men (WHO 2010) who fathered a child in the last two years were divided into two groups; control (N=10; ROS < 93 RLU/s/10^6 sperm) and ROS+ (N=10; ROS > 93 RLU/s/10^6 sperm). Spermatozoa and seminal plasma were analyzed separately for proteomics and Western blot (WB) analysis.

MATERIALS AND METHODS: Semen samples were collected after 2-5 days of abstinence from 20 proven fertile men after Institutional Review Board approval. ROS levels were evaluated by a lumino-based chemiluminescence assay. Liquid chromatography-tandem mass spectrometry (LC/MS-MS) was used for quantitative proteomic analysis to identify the differentially expressed proteins (DEPs). Using Ingenuity Pathways Analysis, DEPs involved in molecular pathways related to redox balance were selected and validated by WB (N=5/group). WB results were analyzed by Mann-Whitney test and considered significant when P < 0.05.

RESULTS: The DEPs identified in spermatozoa (571) and seminal plasma (44) are primarily involved in oxireductase, endopeptidase inhibitor, and antioxidant activities. Among the selected DEPs, the mitochondrial NADH:Ubiquinone Oxidoreductase Core Subunit S1 (NDUFS1) was overexpressed (P<0.01), while several antioxidant proteins including superoxide dismutase 1 (SOD1; P=0.03) and peroxiredoxin 4 (PRDX4; P=0.04) were overexpressed in spermatozoa of ROS+ group as revealed by both proteomics and WB. Similarly, seminal plasma proteomic data showed that haptoglobin, S100 calcium-binding protein A9, PRDX4, and Serpin B6 were overexpressed in ROS+ group. However, no significant difference was observed in their expression level when analyzed by WB.

CONCLUSIONS: Preservation of fertility in ROS+ men may be facilitated by the overexpression of antioxidant proteins. Proteins SOD1 and PRDX4 may serve as potential biomarkers for the management of infertile men with high ROS level from different etiologies.

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OBJECTIVE: Oxidation-reduction potential (ORP) is a measurement of oxidative stress that represents the redox imbalance between oxidants and antioxidants in biological samples. High ORP measurements are associated with decreased quality and sperm parameters during a semen analysis (SA). Men with obesity, however, are known to induce systemic oxidative stress through multiple biochemical mechanisms. The aim of this study is to evaluate the association between male body mass index (BMI) and semen oxidative stress levels.

DESIGN: Prospective.

MATERIALS AND METHODS: Male patients underwent diagnostic semen analysis between January 2018 and March 2018. Semen concentration, motility, and morphology were collected. Patients were separated into cohorts according to the BMI-World Health Organization (WHO) classification. Abnormal semen was categorized if had at least one of the following abnormal sperm parameters: semen volume <1.5 mL, sperm concentration <15 X10^6 sperm/mL, total motility <40%, or normal morphology <4%. Normal sperm parameters fell within the 2010 WHO normal reference ranges. ORP was measured in millivolts (mV) using galvanostat-based technology (MIOXSYS System; Aytu Bioscience, Englewood, CO, USA) using 30 µL of semen obtained after 30 minutes within the semen sample collection. Raw ORP values (mV) were normalized to sperm concentration. Data for normalized ORP are presented as mV/10^6 sperm/mL. A reported cut off value 1.36 mV/10^6 was used to categorize results as normal ORP values. A multivariate linear regression controlling for patients age and normal SA was used. Wilcoxon and Kruskal wallis ANOVA test was performed to compare differences between BMI cohorts.

RESULTS: A total of 36 patients (35 ±5.4 years) with BMI (27 ±5.3) and ORP (3.44 ±8.7 mV/10^6 sperm/mL) was reported. Over half (52%) of the SA samples were diagnosed as normal during sperm analysis (n=19/36). Patients were separated in 3 cohorts by WHO BMI classification (Group 1: category 2 (n=16), Group 2: category 3 (n=9) and Group 3: category 4 (n=11)). A significant difference was found on BMI among groups (p<0.001), while no other significant differences were found among BMI classification as normal ORP values 

References:

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IMPACT OF YOGA BASED LIFESTYLE INTERVENTION ON SPERM OXIDATIVE DNA DAMAGE: STUDY ON FATHERS OF NON-FAMILIAL SPORADIC HERITABLE RETINOBLASTOMA PATIENTS. S. Bish, P. Chaurasia, R. Dada. Department of Anatomy, All India Institute of Medical Sciences, New Delhi, India.

OBJECTIVE: Sperm chromatin integrity is essential for fertilization, proper embryonic development and birth of healthy offspring. Sperm is highly vulnerable to oxidative damage to both nuclear and mitochondrial DNA due to minimal cytosolic antioxidants. Retinoblastoma is the most common childhood malignancy where the de novo germline mutations are mainly inherited from paternal allele. The present study is planned as a case control study on the fathers of children affected with affected with non-familial sporadic heritable retinoblastoma to see the effect of yoga based lifestyle intervention on the decline in oxidative stress and oxidative DNA damage.

DESIGN: A case control study with 75 fathers of children affected with non-familial sporadic heritable retinoblastoma. 75 cases and 50 fathers of healthy children were enrolled as healthy controls. Study duration was 6 months.

MATERIALS AND METHODS: Fathers of children affected with non-familial sporadic heritable retinoblastoma were enrolled in a yoga-based lifestyle intervention programme. Semen samples were collected at base line (day 0), after 1 month, 3 months and 6 months of yoga intervention. ROS, DNA fragmentation index (DFI) and 8-hydroxy-2’-deoxyguanosine (8-
OHdG) levels were estimated at baseline (day 0), 1 month, 3 months and 6 months duration. ROS, DFI, 8-OHdG were also assessed in fathers of healthy children.

RESULTS: Semen parameters were assessed as per the WHO, 2010 guidelines. The seminal mean ROS levels (p<0.05), sperm DFI (p<0.001), 8-OHdG (p<0.01) levels were significantly higher in fathers of children with non-familial sporadic heritable retinoblastoma as compared to fathers of healthy children. There was a reduction in mean DFI levels post yoga-based lifestyle intervention at 1 month (p=0.63), 3 months (p=0.046) and 6 months (p=0.032). Similarly, there was a reduction in seminal mean ROS levels at 1 month (p=0.74), 3 months (p=0.030) and 6 months (p=0.026). The levels of DNA oxidative base adduct i.e., 8-OHdG were also significantly reduced at 1 month (p=0.68), 3 months (p=0.043) and 6 months (p=0.022) with respect to its baseline levels (day 0).

CONCLUSIONS: Yoga-based simple lifestyle intervention meditation may significantly lower oxidative stress and oxidative DNA damage, and levels of mutagenic base 8-OHdG in the sperm DNA. Thus, yoga-based intervention is alternative and complementary treatment for maintaining/restoring levels of mutagenic base 8-OHdG in the sperm DNA. Therefore, yoga-based intervention could be one of the reasons.

References:

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PYRROLOQUINOLINE QUINONE (PQQ) SUPPLEMENTATION DURING IN VITRO CULTURE OF MURINE EMBRYOS ALTERS MITOCHONDRIAL ACTIVITY BUT HAS MINIMAL EFFECTS ON EMBRYO DEVELOPMENT. D. M. Logsdon, J. N. Knoche, W. B. Schoolcraft, R. L. Krisher. Colorado Center for Reproductive Medicine, Lone Tree, CO.

OBJECTIVE: Pyrroloquinoline quinone (PQQ) has been proposed as a culture medium supplement to support embryo mitochondrial function and mitigate the negative effects of reactive oxygen species (ROS) in vitro, particularly in embryos of women of advanced maternal age. The aim of this study was to determine whether PQQ supplementation during mouse embryo culture is beneficial, and how PQQ may affect embryo mitochondrial function.

DESIGN: Research study.

MATERIALS AND METHODS: First, a high (2.5 uM) and low (0.25 uM) concentration of PQQ during the culture period (112 h) was investigated. Two-cell embryos were assessed for mitochondrial activity using JC-1. Remaining embryos were cultured to the blastocyst stage and analyzed for cell number and allocation, and PTP, this was common across experiments. Next, 0.25 uM PQQ was used in step 1, step 2, or throughout a sequential culture system. Two-cell embryos were removed for ROS staining. Finally, oocytes were collected from aged (15 mo) and young (1 mo) mice and cultured in 0 uM or 0.25 uM PQQ in step one of a sequential culture system. Two-cell embryos were cultured with JC-1. Significance was determined at p<0.05.

RESULTS: There were no differences in blastocyst development or cell allocation at either level of PQQ supplementation. There were also no differences in PTP, which was the case in all experiments. An increase was observed in mitochondrial activity (n=38) of 2-cell embryos following culture in 0.25 uM PQQ. There was no difference in blastocyst development depending on when or if PQQ was supplemented, or in abundance of ROS. Blastocyst total cell number was increased when embryos were cultured with PQQ in step one only compared to control (132.7 ± 5.2 and 114.4 ± 6.7 respectively, n=74). More embryos from aged females hatched when PQQ was included in culture step 1 (n=301). Embryos from aged mice cultured with PQQ had increased mitochondrial activity compared to those without PQQ (n=40).

CONCLUSIONS: Supplementation of embryo culture medium with PQQ did not result in production of more blastocysts, though blastocysts resulting from culture with PQQ in step 1 only had more total cells. In addition, more blastocysts from aged females hatched when PQQ was included in culture step 1. PQQ consistently increased mitochondrial activity in two-cell embryos. These results suggest that improvement in mitochondrial metabolism in early cleavage stages may provide some benefit to blastocyst quality.

ENVIRONMENT AND REPRODUCTION

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SEASONAL VARIATION OF SEMEN QUALITY FROM OVER 100,000 ANALYZED SAMPLES. T. G. Nazem,a,b L. Sekhon,a,b C. J. Lee,a C. Britton-Jones, a,b N. Bar-Chama,a,b A. B. Copperman,a,b,c aObstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY; bReproductive Medicine Associates of New York, New York, NY.

OBJECTIVE: Male factor accounts for 1/3 of infertility, but often the underlying etiology is not identified. Climate shifts have been suggested as potential rationale for hormonal alterations and infertility. Literature demonstrates that seasonal shifts affect testosterone and estradiol levels; but, studies evaluating variation in semen analysis (SA) parameters are conflicting. This study aimed to determine whether seasonality affects semen quality.

DESIGN: Retrospective.

MATERIALS AND METHODS: SAs performed from 2001-2018 were included. Patient age, body mass index (BMI), state of origin, and date of

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collection were recorded. SA parameters included volume, concentration, % motility, % normal morphology (strict Kruger criteria) and total motile count (TMC). Seasons were determined by date of collection: winter (December-February), spring (March-May), summer (June-August), fall (September-November). Data were analyzed using an ANOVA, Chi square, and multivariate linear regression.

RESULTS: A total of 112,301 SA samples from 28,865 patients were processed. Baseline characteristics are shown in table 1. Oligospermia was highest among fall samples (26.2%, p=0.007). TMC (117.7 ± 112.6 million (M) sperm/mL, p<0.0001), total concentration (69.9 ± 76.3 M sperm, p<0.0001), and percent motility (56.4 ± 16.7%, p<0.0001) were highest in the spring, and % normal morphology was greatest in the fall (51.3 ± 3.1%, p<0.0001). TMC (β=7.5, p=0.0009), total concentration (β=2.4, p=0.03) and morphology (β=0.27%, p=0.63) were lower in the summer compared with winter, after adjusting for confounders. TMC (β=5.4, p=0.001) and morphology (β=0.33%, p=0.0001) were higher in the fall compared with winter after accounting for covariates.

CONCLUSIONS: This study is the largest evaluating seasonal variability in semen parameters. Semen quality is decreased in summer and mildly improved in fall/spring compared to winter. Higher environmental temperatures in the summer may impair testicular thermoregulation, spermatogenesis, DNA synthesis and repair. Seasonal variation in physical activity, BMI, sleep patterns, light exposure and melatonin levels may also impact hormone levels and semen parameters. We suggest providers counsel patients about the potential variations in SA samples based on season of collection.

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LIFESTYLE AND FECUNDABILITY AMONG HEALTHY COUPLES ATTEMPTING PREGNANCY. S. L. Mumford,1 R. Sundaram,1 K. Kim,1 L. D. Levine,1 E. Schisterman,2 G. M. Buck Louis,2 1Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD; 2Eunice Kennedy Shriver National Institute of Child Health and Human Development, Division of Intramural Population Health Research, North Bethesda, MD; 3NICHD, Bethesda, MD; 4Dean’s Office, George Mason University, Fairfax, VA.

OBJECTIVE: Lifestyle factors, including caffeine and multivitamin intake, have been shown to influence several reproductive processes, including steroidogenesis, and pregnancy outcomes, though associations with these factors measured during sensitive windows of reproduction and fecundability are uncertain. Thus, we investigated the relationship between lifestyle factors and fecundability among couples attempting pregnancy.

DESIGN: This was a prospective population-based cohort study of 501 couples attempting pregnancy and discontinuing contraception.

MATERIALS AND METHODS: Couples recorded daily use of cigarettes, caffeinated and alcoholic beverages, and multivitamins for up to 12 cycles. Exposures during the weeks before and after expected ovulation based on the fertility monitor were evaluated for both the male and female partners. Marginal structural Cox proportional odds models were used to estimate associations with fecundability adjusting for age, body mass index, race, physical activity, education, income, and time-averaging confounding by other lifestyle factors. Fecundability odds ratios (FORS) < 1 denote reduced fecundability or a longer time to pregnancy.

RESULTS: Female alcohol exposure in the weeks before and after ovulation was associated with increased fecundability (FOR 2.19, 95% CI 0.97, 4.93). Multivitamin intake and cigarette smoking were not associated with fecundability in either the male or female partners during the week before or the week after ovulation.

CONCLUSIONS: These results highlight the importance of lifestyle factors in both male and female partners during sensitive windows of reproduction to influence fecundability, and the need for appropriate preconception guidance for couples seeking pregnancy.

Supported by: Intramural Research Program, DIPHR, NICHD, NIH.

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HIGHER FOLLICULAR FLUID (FF) LEVELS OF DI(2-ETHYLHEXYL) PHthalate (DEHP) METABOLITES IN INDIAN WOMEN WITH POOR OVARIAN RESERVE (POR). F. R. Parikh,4 S. Utamchandani,4 A. S. Velumani,4 A. Athalye,2 P. Sinker,2 N. Naik,2 P. Khandare,2 A. Velumani.1 FertilTree Jaslok International Fertility Centre, Jaslok Hospital and Research Centre, Mumbai, India; 2Thyrocare Technologies Limited, Mumbai, India.

OBJECTIVE: While higher urinary levels of DEHP metabolites have been previously associated with a significant decrease in the antral follicle count (AFC) in women undergoing IVF (1), this study aimed to revalidate this in follicular fluid (FF). India is now witness to a trend where young women present a diminished ovarian reserve, low AMH values and have an early menopause. The role of Endocrine Disrupting Chemicals (EDCs) in these needs to be investigated. Since the oxidative metabolites do not form as a result of contamination during collection or storage they are considered more sensitive biomarkers of exposure to DEHP. The FF of women diagnosed with POR was screened for two oxidative metabolites of DEHP to establish the association with the disease etiology.

DESIGN: A total of n = 58 Indian women (median age 33.5 years, range 26 - 42 years) seeking treatment for infertility and undergoing oocyte retrieval were included after consent. Of these, 30 with a serum AMH value < 2 ng/ml and an AFC < 6 were diagnosed with poor ovarian reserve [POR] and n = 28 women with a serum AMH value >2 ng/ml and an AFC > 6 were classified as having a good ovarian reserve. The study was approved by the Scientific Advisory Committee at Jaslok Hospital and Research Centre.

MATERIALS AND METHODS: The cryopreserved FF samples that were collected on the day of oocyte retrieval were processed using enzymatic deconjugation followed by the solid-phase extraction technique and analyzed by liquid chromatography tandem–mass spectrometry (LC-MS/MS) to detect the levels of two oxidative metabolites of DEHP - mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) and mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP).

RESULTS: The overall median [range] level of MEOH in the FF of 58 women was 3.6 [0.35-11.27] ng/ml. In women with POR, the median [range] of MEOH was 4.1 [0.35-11.27] ng/ml while in those with a good ovarian reserve it was 1.7 [0.35-6.8] ng/ml. The overall median [range] of MEHHP in the FF of 58 women was 1.8 [0.14-13.02] ng/ml. In women with POR the median [range] was 2.0 [0.14-3.02] ng/ml relative to 1.7 [0.17-7.13] ng/ml in women with a good ovarian reserve. Neither difference was statistically significant [p values of 0.85 and 0.69 respectively].

CONCLUSIONS: This is a preliminary result of an ongoing larger Indian study. The median values of the DEHP metabolites are higher in the FF of women with POR though they do not reach statistical significance. A larger sample size may help support or refute the theory that higher levels of these metabolites in FF contribute to a diminished ovarian reserve.
OBJECTIVE: The levels of certain Endocrine Disrupting Chemicals (EDCs) detected in serum have previously shown potential to predict the levels of the same EDCs in follicular fluid (FF) (1, 2). This study aimed to assess if the BPA levels seen in the serum of women undergoing intracytoplasmic sperm injection (ICSI) were associated with BPA values found in their FF.

DESIGN: A total of n = 117 Indian women (median age 34 years, range 26 - 47 years) seeking treatment for infertility and undergoing oocyte retrieval were included after written informed consent. The study was approved by the Scientific Advisory Committee at Jaslok Hospital and Research Centre.

MATERIALS AND METHODS: Paired serum and FF samples were collected from all 117 women at the time of oocyte retrieval. Samples were processed using enzymatic deconjugation followed by the solid-phase extraction technique and analyzed by liquid chromatography tandem-mass spectrometry (LC-MS/MS) to detect levels of BPA. Quantitative data are expressed as median and range and assessed for normality. A correlation analysis was done for the serum and FF total BPA values based on Spearman correlation test. A simple linear regression was done using total serum BPA as the predictor and FF as the dependent variable. All analyses were done at 5% significance using Microsoft Excel.

RESULTS: The median [range] levels of total serum BPA were 1.81 [0.2 - 66.32] ng/ml versus 0.53 [0.09 - 19.11] ng/ml in the FF with the difference being statistically significant [p < 0.0001]. A positive correlation was found between the two [rho = 0.7, p < 0.005]. A one-unit change in serum BPA resulted in a 0.24-unit change in FF BPA level [coef. 0.24, 95% CI 0.15-0.33, p < 0.001, R² 19.5%].

CONCLUSIONS: The study shows a potential causal relationship between serum and FF BPA levels in Indian women seeking treatment for infertility. This methodology could be further developed so as to offer a non-invasive and reliable method to predict FF levels for BPA estimation to women with unexplained infertility.

References:

OBJECTIVE: To examine the association between polychlorinated biphenyl (PCB) exposure and reproductive health outcomes. Specifically, we evaluated associations between PCB levels and gynecological outcomes, infertility, delivery outcomes, and pregnancy complications.

DESIGN: Cross-sectional study.

MATERIALS AND METHODS: Accidental contamination of livestock in Michigan in 1973, with polybrominated biphenyl (PBB) led to the establishment of a registry of exposed individuals that have been followed for > 40 years. Besides being exposed to PBBs, this cohort has also been exposed to PCBs, a structurally similar environmental pollutant, at levels similar to average US exposure. Recruitment for this study was conducted between 2012 and 2015 from members of the original PBB registry via mailed invitations. Eligibility criteria to participate in this study were that individuals had to have lived in the state of Michigan during the time of contamination (1973-1974), or had to be offspring of those who lived in the state during that time. Participation in this study required a blood draw and completion of an in-depth health questionnaire. This analysis included only female participants (N=262). Multivariable linear regressions were used to identify associations between log-transformed serum PCB levels and each reproductive health outcome. We controlled for age, body mass index, lipid standardization, and serum PBB levels in all analyses. A p-value of <0.05 was used to determine statistical significance.

RESULTS: There were no associations between serum PCB exposure and the measured gynecological outcomes (pelvic inflammatory disease, endometriosis, polycystic ovarian syndrome, uterine fibroids, menstrual cycle abnormalities, ovarian cysts, or sexually transmitted infections). No associations were identified between serum PCB exposure and the prevalence of pelvic inflammatory disease in women reporting ever having sexual intercourse with a male partner. Among the 190 women who reported ever being pregnant, there was a significant negative association, with higher total PCB exposure associating with fewer lifetime pregnancies (P=0.018) and fewer singleton live births (P=0.015). There were no associations identified between serum PCB exposure and other delivery outcomes (multiple gestation, miscarriages, stillbirths, ectopic pregnancies, preterm births, low or high birth weight, or birth defects). Additionally, there were no associations with pregnancies complicated by hypertensive disorders of pregnancy or gestational diabetes.

CONCLUSIONS: Higher total serum PCB exposure was associated with fewer numbers of lifetime pregnancies and singleton live births, but not with other reproductive outcomes. Further research is needed to determine if and how PCB reduces fecundity.

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HIGHER RISK OF DELAYED MENARCHE IN GIRLS AT SCHOOL LOCATED IN MORE DEPRIVED AREAS. E. Yu,a S. Choe,a J. Kim,a J. Hwang,a Y. Hur,a R. Kim,a Y. Lee,a M. Kim,a Y. Kim,a J. Kim,a Y. Kim,a I. Kang,a M. Koong,a T. Yoon.a aCHA Gangnam Medical Center, CHA University, Seoul, Korea, Republic of; bCHA University, Cranston, RI; cCHA Fertility Center, Seoul Station, CHA University, Seoul, Korea, Republic of.

OBJECTIVE: Menarche is a major biologic event associated with women’s health throughout the lifespan. Social and economic deprivation is known to be related with delayed menarche. We explored the association between delayed menarche and deprivation index of the school area.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: A total of 187,024 female middle- and high-school students in the Korea Youth Risk Behavior Web-based Survey (KYRBS) from 2006 to 2015 were analyzed. Delayed menarche was defined as absent of menarche by 14 years of age. Area-level deprivation index was divided into 4 groups by deprivation index quartiles, late menarche was defined as absence of menarche by 14 years of age. Area-level deprivation index was calculated using 2010 Korean Census data. We conducted regression analyses including body mass index, father’s and mother’s education, presence of one of the parents, year of survey and birth cohort (1988-1992, 1992-1997, 1998-2003) to calculate the odds ratio (OR) for delayed menarche.

RESULTS: Delayed menarche occurred in 6.5% in the study population. The birth year-specific prevalence decreased from 8.3% (236/2,950) in girls born in 1988 to 3.8% (210/1,076) in those born in 1999. When the population was divided into 4 groups by deprivation index quartiles, late menarche occurred in 6.0% (least deprived), 6.1%, 6.5%, and 8.7% (most deprived) of each group. In the multivariable regression model, girls going to school in area with upper 3rd (1.11, 95% CI: 1.02, 1.21) and 4th quartiles (1.16, 95% CI: 1.07, 1.25) of deprivation index had higher risk for late menarche.

CONCLUSIONS: This study suggests going to school located in more deprived area is associated with higher odds for delayed menarche. Future
BISPHENOL A EXPOSURE NEGATIVELY IMPACTS EMBRYO DEVELOPMENT THROUGH A MECHANISM THAT INVOLVES ZINC DEPLETION, REACTIVE OXYGEN SPECIES OVERPRODUCTION AND INDUCTION OF APOPTOSIS

OBJECTIVE: Background: Bisphenol A (BPA) is a ubiquitous xenobiotic utilized during the manufacturing of plastic products, including food containers, paper products, water pipes, toys, medical equipment, and electronics. Females exposed to BPA may be susceptible to its detrimental effects including infertility. Recent studies have shown that BPA exposure at levels as low as 100 μg/kg/day can impair embryo implantation in the mouse model. BPA can also interfere with the endocrine function of hypothalamic-pituitary axis and affect fertility. It can accumulate in reproductive organs and act as an endocrine disruptor due to its structural similarity to estrogen. No known study investigated the mechanism on how BPA affects embryo development. Potential mechanisms may involve induction of apoptosis, reactive oxygen species (ROS) overproduction and zinc depletion. Zinc supports embryo development and is important in egg activation.

OBJECTIVE: This study we hypothesize that BPA exposure affects embryo development and survival through a mechanism that involves induction of apoptosis, intracellular zinc depletion and ROS overproduction.

DESIGN: A case-control study of mouse pronuclear embryos pre-exposed in vitro to increasing BPA concentrations for 18 hours and then followed through day 5 of development. They were photographed, graded and treated to examine ROS generation, zinc depletion and induction of apoptosis.

MATERIALS AND METHODS: Mice oocytes were retrieved from 8-10 weeks female mice and were fertilized using IVF. The embryos were subsequently divided in 4 groups that were exposed to increasing concentrations of BPA (10 - 100 μM) for 18 hours and one group that were untreated controls (n = 20 / group). The embryos were photographed and graded daily based on their appearance and development. A subgroup of the treated embryos (n = 10 / group) were further evaluated for induction of apoptosis, overproduction of ROS and zinc depletion using commercially available assays.

Confocal microscopy was used to assess the embryos. Statistical analysis was performed using ANOVA repeated measures, chi-square and survival curves. P < 0.05 was considered statistically significant.

RESULTS: Day 5 embryos that were exposed to BPA concentrations > 50 μM had fewer progressions to blasts, lower blast grades and more were arrested compared to controls (p < 0.05). Enhancement of ROS production as well as increased apoptosis was observed in the treated groups compared to controls (p < 0.05). Zinc depletion was evident in embryos treated with BPA at concentrations > 50 μM (p < 0.05).

CONCLUSIONS: Exposure to BPA, may negatively affect embryo development through mechanisms that involve alteration of the redox potential and increased oxidative stress, induction of apoptosis and intracellular zinc depletion.

Supported by: None.

NICKEL EXPOSURE IN VITRO PREVENTS HATCHING IN MOUSE EMBRYOS BY DOWN-REGULATING PLURIPOTENT GENES AND REPRESSING TROPHODERM MODERNISM CDX2

OBJECTIVE: S. M. Maxwell,1 A. K. Masbou,1 F. M. Bourroul,1 D. L. Keefe,2,3Department of Obstetrics and Gynecology, NYU Langone Health, New York, NY; 1New York University Langone Fertility Center, New York, NY.

OBJECTIVE: To evaluate the effect of exposure to the environmental toxicant Nickel on preimplantation embryo development in vitro using a mouse model.

DESIGN: Prospective Laboratory Study.

MATERIALS AND METHODS: Mouse zygotes (Embryotech) were thawed in M2 medium and randomly treated with 0 μM (control group), 50μM or 100μM (exposure groups) of Nickel(II) chloride (Sigma) in Global medium (Lifeglobal) supplemented with 0.4% BSA until blastocyst stage. The rate of blastocyst embryo development to 2-Cell, 4-Cell, and blastocyst stages were recorded by imaging. Relative gene expression of 4-Cell embryos and Blastocysts were analyzed by RT-qPCR in SYBR green system. Statistical analysis used GraphPad Prism software.

RESULTS: Nickel at 100μM completed eliminated hatching, which was significantly different from controls (P = 0.0032, Fisher’s exact test). The rate of hatching under 50μM of Nickel exposure (22%) was lower than that of controls (78%), a difference which almost reached significance (P = 0.0567, Fisher’s exact test). Development (%) to 2-Cell, 4-Cell and blastocyst stages (see table) under exposure to Nickel did not differ from controls (P > 0.05, Fisher’s exact test). Pluripotent gene expression (Nanog, Oct4, Sox2 and Klf4) expression levels in blastocysts exposed to Nickel were down-regulated in a dose-depend manner compared to controls (P < 0.05, One-way ANOVA). Relative mRNA levels of the trophectoderm gene Cdx2 in blastocysts exposed to 50μM and 100μM Nickel were significantly down-regulated compared to controls (139.59 ± 7.974 and 1.003 ± 0.118 respectively vs.

WORK RELATED EXPOSURES: IMPACTS ON HORMONE LEVELS, ANOVULATION AND THE MENSTRUAL CYCLE

OBJECTIVE: Work related exposures may influence health, but few data are available about routine day-to-day work activities and reproduction. The goal of this study was to examine impacts of environmental work exposures on hormone levels, risk of anovulation and menstrual cycle changes.

DESIGN: Prospective cohort study of 1,184 women enrolled in the EAGRe (Effects of Aspirin in Gestation and Reproduction) Trial, a randomized clinical trial of conception-initiated low dose aspirin on live birth, with information on work exposures.

MATERIALS AND METHODS: Women aged 18-40 years and attempting pregnancy completed an occupational exposure questionnaire focused on employment status and job-related exposures (night work, rotating shift, whole body vibration, loud noise, extreme heat, heavy exertion, and prolonged standing). Urinary reproductive hormones including pregnanediol glucuronide (PdG), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estrone-3-glucuronide (E1G) were measured up to 5 times per cycle during the first 2 cycles of study participation. Anovulation was assessed using fertility monitors and luteal phase urinary PdG levels for up to 6 cycles.

Mixed models estimated associations between work exposures and urinary hormones and cycle length; general linear mixed models were used for outcomes of anovulation. Models were weighted for the number of contributed cycles per woman and adjusted for age, BMI, race, physical activity, income, education, and treatment assignment.

RESULTS: Overall, 76.5% of participants were working while attempting pregnancy. There were no associations between employment status and urinary hormone concentrations. However, lower levels of urinary PdG were found among night workers compared to non-employed women (β = -0.18 ng/mL, 95% confidence interval [-0.31, -0.05]), though no associations were observed with cycle length or risk of anovulation. Though exposure to loud noise was associated with longer follicular phase length (β = 1.11 days, 95% CI 0.03, 2.19), no associations were found with hormones or anovulation. Exposures to other work exposures were not associated with reproductive hormones, cycle length, or anovulation.

CONCLUSIONS: Though night shift work was linked to lower urinary PdG and loud noise exposure was associated with longer follicular phase length, no work-related exposures were associated with anovulation. These data suggest that the exposures studied here are likely not harmful to menstrual cycle function.

Supported: By the Intramural Research Program of the Eunice Kennedy Shriver, National Institute of Child Health and Human Development (NICHD).
232.561 ± 28.389, P = 0.0002 and P < 0.0001, One-way ANOVA). Expression levels of the pluripotent genes (Oct4, Sox2 and Klf4) were not affected by Nickel in 4-Cell embryos (P > 0.05, One-way ANOVA).

CONCLUSIONS: Nickel disrupted blastocyst hatching in a dose-dependent manner. Cleavage stage embryo development was not impacted by exposure to Nickel at concentrations below 100µM. Down-regulation of pluripotent genes and repression of trophectoderm differentiation may mediate the detrimental effects of Nickel on embryo development.

Supported by: By March of Dime Foundation (MOD 82713) and the Stanley H. Kaplan Fund of NYU School of Medicine.

P-165 Tuesday, October 9, 2018 6:30 AM
THE EFFECT OF FOLLICULAR FLUID TRACE ELEMENTS CONCENTRATIONS ON INTRACYTOPLASMIC SPERM INJECTION OUTCOMES. I. Elnashar,a T. Farghaly,a A. M. Abdelmagied,a A. Youssf,b E. Badran,c S. A. Alkhwanky,d M. A. Elhamshary,a A. Abdelmagied,a O. A. Khamiss,a T. K. Al-Hussaini,a Assiut University, Assiut, Egypt; Obstetrics and Gynecology, Assiut University, Assiut, Egypt; Reproductive Endocrinology, Assiut, Egypt; Alsalama IVF Center, Assiut, Egypt; Sheba Elkom University, Assiut, Egypt; Assiut University Hospital, Assiut, Egypt; Animal Biotechnology, Genetic Engineering and Biotechnology Institute, Sadat City, Egypt; Obstetric Gynecology, Faculty of Medicine, Assiut, Egypt.

OBJECTIVE: Evaluation of micro-environment is a surrogate mean for oocyte quality assessment. This study tested the hypothesis that an association exists between follicular fluid trace elements and IVF outcomes.

DESIGN: Prospective Cohort study.

MATERIALS AND METHODS: Through one year, women attending a university-affiliated IVF center were counseled to participate in our study. FF from large follicles; 17 mm or more, containing only one follicle was eligible for sampling. Samples were centrifuged at 1500 rpm for 5 minutes and the supernatants were stored at -80°C till IVF results were disclosed. Samples were categorized into 2 groups; group 1 included pregnant women, while group 2 samples from non-pregnant women. Twenty-five (n=25) women samples were randomly selected from the consecutively frozen samples in each group for trace element analysis. Cadmium, lead, and zinc was measured. The research randomizer (www.randomizer.org) used. Correlation and regression analysis were done to assess the relation between the studied trace elements and IVF outcomes.

RESULTS: 25 pregnant and 24 non-pregnant women samples were analyzed. Both groups were comparable in age, BMI, AMH, antral follicle count, infertility duration and IVF indications. Non-pregnant women showed less number of retrieved and fertilized oocytes than pregnant women (median[IQR]:7(11.8) vs 11(15.5); P<0.05 and 0.03, respectively). Women with poor ovarian response were more in non-pregnants compared to the other group (37.5% vs 12%, P<0.04). FF of pregnant subjects showed higher concentrations of Zinc compared to non-pregnant (Mean±SD; 641±364 vs 424±226 ng/ml, P<0.03). Comparable trend for Lead and Cadmium concentrations was demonstrated in FF between pregnant and non-pregnant women (Median[IQR]:1.24(4.9) vs 1.21(1.1) ng/ml, P>0.05 and 1.2(3.4) vs 1.5(1.7) ng/ml, P>0.05). A significant Positive correlation was found between zinc concentrations and occurrence of pregnancy(r=0.34, P<0.02) as well as between the quality of embryos and pregnancy (r=0.5, P<0.01). In stepwise multivariable logistic regression model, good quality embryos (OR:0.125, CI:0.037-0.427, P<0.001) and zinc(OR:0.043, CI:0.003-0.615, P<0.02) were predictors for successful IVF. Adjusted for good quality embryos and other covariates, Zinc was still a predictor for pregnancy(OR:0.005, CI:0.001-0.275, P<0.01).

CONCLUSIONS: In addition to the quality of embryos, maintenance of higher zinc in FF seems to be essential for favorable IVF outcome.

P-166 Tuesday, October 9, 2018 6:30 AM
SPERM MOTILITY CHARACTERISTICS AND OXIDATIVE STRESS IN CRUDE OIL EXPOSED RATS. S. A. Bamiro,a S. O. Elias,b L. C. Ajonuma. aPhysiology, Lagos State University College of Medicine, Ikeja, Lagos, Nigeria; Reproductive Medicine, Lagos State University College of Medicine, Ikeja, Lagos, Nigeria; Department of Physiology, Lagos State University College of Medicine (LASUCOM), Lagos, Nigeria.

OBJECTIVE: Environmental toxicants are increasingly implicated in the decline of male reproductive functions and crude oil has been reported as a toxicant with endocrine disrupting effects. In the Niger Delta region, the entire ecosystem and humans are exposed to crude oil regularly due to crude oil spillage. This study is designed to evaluate the effects of crude oil on sperm motility, concentrations, velocities and oxidative stress.

DESIGN: Basic animal research in a university teaching hospital setting

MATERIALS AND METHODS: 25 male Sprague Dawley rats were divided into groups(A,B,C,D,E) of 5 rats each. Group A is the control while group B, C, D and E are the test groups. The control received orally, 0.5mls of normal saline daily while groups B,C,D and E were given 50mg/kg,100mg/kg, 200mg/kg and 400mg/kg of Bonny light crude oil daily respectively for 6 weeks as oral gavage. The rats were sacrificed after 6 weeks and epididymal sperm were analysed. sperm motility, kinetics (VAP(average path velocity),VCL(curvilinear velocity),VSL(straight line velocity),ALH(amplitude of lateral head),BCF(Beat Cross Frequency),Percent of line moving, LIN(linearity), STR(Straightness),WOB(wobble), MAD(mean angle velocity)) and concentration were assessed using Computer Assisted Sperm Analysis (CASA) machine. Oxidative stress was assessed using Nitroblue tetrazo- nium (NBT) test.

RESULTS: VAP(average path velocity),VCL(curvilinear velocity),VSL(straight line velocity),ALH(amplitude of lateral head),BCF(Percent of line moving, LIN(linearity), STR(Straightness),WOB(wobble), MAD(mean angle velocity) were reduced in the test groups. Sperm concentrations were reduced in the test groups. There was deposition of formazan (indicating oxidative stress) in the sperm of test groups treated with NBT.

CONCLUSIONS: This study demonstrates that crude oil induces oxidative stress in sperm and also suppresses sperm motility, concentration and velocities. This may lead to subfertility in exposed individuals.

P-167 Tuesday, October 9, 2018 6:30 AM
HIGH THROUGHPUT SCREENS USING STRESS-FORCED ESC IDENTIFY AND CLASSIFY DRUGS BY EMBRYOTOXICITY AND DOSE-DEPENDENT STRESS EFFECTS. E. Puscheck,a G. Perez,b S. Dutta,a M. Abdulhasan,a E. Louden,a D. A. Rappolee,a Wayne State University School of Medicine, Detroit, MI; Reproductive Stress 3M, Grosse Pointe Farms, MI; Augusta University, Augusta, GA.

OBJECTIVE: To validate fluorescent reporter Embryonic Stem Cells (ESC); R Rex1-RFP/red fluorescent protein reports stemness, Pdgfra-GFP/green fluorescent protein as toxic stress causes doses dependent changes in stemness and differentiation reports 1st lineage differentiation using a High Throughput Screen (HTS) for +control hyperosmotic stress and stress for Pharma to validate the Pdgfra-GFP ESCs HTS2 using differentiation co-markers Dab2, laminin and GFP in dose- and time-dependent responses.

DESIGN: Experimental study design

MATERIALS AND METHODS: GFP knocked into the Pdgfra gene are regulated by Pdgfra promoters in ESC. A key test was stress-forced differentiation in the presence of LIF, which maintains proliferation and potency.

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Microarray, Immunofluorescence, Immunoblot and Flow Cytometry assays tested Pdgfra-GFP ESC responses. Dose and kinetic responses were tested using hyperosmotically sorbitol as a +stress control. Retinoic acid (RA) is a 1st lineage inducer used as a +control. A set of Strong-, weak- and non-embryotoxic drugs were also tested for dose dependent increased stemness in Rex1-RFP/ESC HTS1 and increased differentiation using Pdgfra-GFP/ESC HTS2.

RESULTS: Hyperosmotic stress +/-LIF decreased ESC stemness and increased differentiation as shown by Hoechst staining and microplate reader, and co-localization of Pdgfra-GFP, Dab2 and laminin co-markers for 1st differentiated lineage. Microplate reader assays for stress-induced Pdgfra-GFP differentiation were corroborated by Immunoblot for Dab2 and GFP and showed similar dose responses. Preliminary flow cytometric results suggest that 1-7% of Pdgfra-GFP cells are bright after 3day retinoic acid or high dose sorbitol induction despite LIF and another 10-17% of intermediate bright GFP cells are induced.

CONCLUSIONS: Stress decreases ESC cell growth and increases early differentiation of fewer cells despite optimized culture conditions (termed “forced differentiation”). Hypothetically, early differentiation to 1st lineage cells provides sufficient nutrient-acquiring 1st lineage function despite from fewer cells. Rex1-RFP stemness decrease ~22% and Pdgfra-GFP differentiation increase ~25% with high stress exposures. Drugs were tested by exposure to these cells and were characterized into three categories: non-embryotoxic, weak embryo toxic and strong embryo toxic. Non-embryotoxic drugs like penicillin did not decrease Rex1-RFP nor decrease Pdgfra-GFP, whereas strong embryotoxic drugs (i.e. methotrexate) and weak embryotoxic drugs (i.e. methoxyacetic acid) decreased Rex1-RFP and increased Pdgfra-GFP. These assays will provide complementary HTS for measuring toxicity early in drug development.

P-168 Tuesday, October 9, 2018 6:30 AM

FOLATE INTAKE MODIFIES THE RELATION BETWEEN TRAFFIC-RELATED AIR POLLUTION AND LIVE BIRTH AMONG WOMEN UNDERGOING ASSISTED REPRODUCTION. A. J. Gaskins,a,b L. Minguez-Alarcon,a,b Q. Di,a J. E. Chavarro,a,b J. B. Ford,a B. A. Coull,a J. Schwartz,a J. A. Attaman,a R. Hauser,b F. Laden,a,b Chan Division of Network Medicine, Harvard Medical School and Brigham and Women’s Hospital, Boston, MA; bHarvard T.H. Chan School of Public Health, Boston, MA; cOB/GYN, MGH, Boston, MA; dEnvironmental Health, Harvard TH Chan School of Public Health, Boston, MA.

OBJECTIVE: Traffic-related air pollution has been linked to higher risk of pregnancy loss. Our goal was to evaluate whether folate intake could modify the relation between exposure to traffic related air pollution and live birth among women undergoing assisted reproduction.

DESIGN: Prospective cohort study.

MATERIALS AND METHODS: Our study included 327 women who underwent 550 ART cycles at a fertility center in Boston between 2005 and 2016. Dietary intake was assessed at study entry via a validated food frequency questionnaire. Validated spatiotemporal models were used to estimate daily average exposure to nitrogen dioxide (NO2), ozone (O3), and fine particulates (PM2.5) (based on residential address) in the three months prior to the start of the ART cycle. Residential distance to nearest major roadway was calculated using information from the Massachusetts Department of Transportation. ART outcomes were abstracted from electronic medical records. We used generalized linear mixed models with interaction terms to evaluate whether the associations between traffic-related air pollution and ART outcomes were modified by folate intake adjusting for age, BMI, race, smoking status, education, and census tract level income.

RESULTS: Supplemenat folate intake significantly modified the association of distance to major roadway and NO2 exposure prior to ART with live birth rates (p-for-interaction=0.02 and 0.06, respectively). Among women with supplemental folate intake <800 µg/day (57% of women), the odds of live birth were 17% (95% CI -4%, 42%) higher for every 250m further away a woman lived from a major roadway and the odds of live birth were 20% (95% CI 0, 36%) lower for every 20 pp/n increase in average NO2 exposure during the 3 months prior to ART. There was no association between residential distance to major roadways or average NO2 exposure prior to ART and probability of live birth among women with supplemental folate intakes ≥800 µg/day. Folate intake did not modify the association between PM2.5 or O3 and live birth following ART.

CONCLUSIONS: High supplemental folate intake may protect against the adverse reproductive effects of exposure to traffic-related air pollution. Taken together with findings from previous studies, our results suggest epigenetics could be a plausible mechanism driving the modification of the associations by folate intake. Further evaluation in other human populations is needed.

Supported by: Grants P30ES000002, R01ES009718, R01ES022955, and K99ES026648 from the National Institute of Environmental Health Sciences.

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ALCOHOL USE AND TOBACCO SMOKING IN RELATION TO OVARIAN RESPONSE AMONG EGG DONORS. A. Canha,a M. Molina,b L. Fernandez,b M. Nicolas,a M. Trabalon,b J. Landeras,b P. Coya,b J. E. Chavarro,b cPhysiology, University of Murcia, Murcia, Spain; bIVI Murcia, Murcia, Spain; cHarvard T.H. Chan School of Public Health, Boston, MA.

OBJECTIVE: To evaluate the associations of alcohol intake and tobacco smoking and markers of ovarian response to hyperstimulation among young, healthy egg donors.

DESIGN: Prospective cohort study.

MATERIALS AND METHODS: Women participating in the oocyte donation program at the IVI-Murcia clinic, between January 2017 and January 2018, were invited to participate in the study. Donors who enrolled, were asked to report their habitual use of alcohol and tobacco over the previous year. We fitted linear regression models to evaluate the association between these behaviors and peak E2 levels and Poisson regression models to evaluate their relation with oocyte yield and yield of MII oocytes while adjusting for age, body mass index (BMI) and co-adjusting for these two behaviors. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM Corporation, Armonk, NY, USA).

RESULTS: A total of 88 donors, with a mean age of 24 years and BMI of 22 kg/m2, were recruited into the study. Most women (55%) reported smoking in the past year and nearly half (42%) reported moderate (1-2 times/week) alcohol use in the past year. Women who reported moderate alcohol consumption over the previous year had a 14% lower (95% CI -5%, -22%) oocyte yield than women who reported no alcohol consumption. Peak E2 and yield of MII oocytes, however, did not differ according to alcohol consumption. Tobacco smoking was unrelated to the three markers of ovarian response to stimulation.

CONCLUSIONS: Low to moderate alcohol consumption in the year prior to the stimulation cycle was related to a lower number of oocytes retrieved among donors.

References:

FERTILITY PRESERVATION

P-170 Tuesday, October 9, 2018 6:30 AM

OBJECTIVE: To evaluate the effects of cancer stage and grade on fertility preservation outcome and ovarian stimulation response.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: We evaluated 402 fertility preservation treatment cycles. The inclusion criteria were age 18-38 years, first stimulation cycle, GnRH-antagonist protocol only, and early follicular phase stimulation start only. Patients with ovarian pathology, previous ovarian surgery and previous chemo- or radiotherapy were excluded. Women with low-stage cancer (stage I, II and no lymph node involvement) were compared with those with high-stage disease (stage III, IV or lymph node involvement). Similarly those with low-grade (grade I, II) and high-grade (grade III, IV) disease were compared. Primary outcome was the number of mature oocytes retrieved. Secondary outcomes included total number of oocytes retrieved, total number of vitrified oocytes, and number of frozen embryos. A power calculation was performed. A sample size of 60 in each group has 80% power of showing a 20% difference in primary outcome with an alpha of 5%. To determine factors associated with good fertility preservation outcome (over 10 mature oocytes retrieved), we used multivariate logistic regression.

RESULTS: A total of 147 patients were included in the analysis. The demographic and ovarian reserve parameters of study groups in stage- and grade-based analyses were similar. Compared to women with low-stage cancer (n = 83), those with high-stage cancer (n = 64) required a higher dose of gonadotropin (p = 0.02). The number of mature oocytes retrieved and frozen oocytes as well as the number of immature oocytes (GV and MI) and maturation rate were similar between the two groups. However, in cycles where fertilization of retrieved oocytes was performed (n = 53), the fertilization rate (p = 0.03) and the number of vitrified embryos (p = 0.01) were higher in the low-stage group. Compared to patients with low-grade cancer (n = 62), those with high-grade disease (n = 85) had significantly lower number of mature retrieved (10.5 (7-15) vs. 8 (5-10.5); p = 0.002) and totally vitrified (11.5 (8-15) vs. 10 (6.5-11); p = 0.005) oocytes. Similarly the number of vitrified embryos was lower in high-grade group (p = 0.03) in cycles where the fertilization was performed. In multivariate logistic analysis, the grade of cancer was found to be one of the factors significantly associated with good fertility preservation outcome (p = 0.004; OR = 3.93; 95% CI 1.50 - 10.33), along with AFC and number of follicles >14 mm on the trigger day.

CONCLUSIONS: In women with malignancy, the grade of cancer has a significant negative impact on the number of mature oocytes retrieved and cryopreserved embryos.

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P-172 Tuesday, October 9, 2018 6:30 AM

OBJECTIVE: Women with early stage cervical cancer who are of reproductive age and wish to preserve fertility may be candidates for fertility-sparing surgery (FSS). The goal of this study was to examine the presence of disparities in the use of fertility-preserving surgery (FSS) and to investigate factors that influence the use of FSS.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: The National Cancer Database was used to identify patients aged <35 years diagnosed with cervical cancer between 2004-2015. Those with stage IA2 or IB1 squamous cell carcinoma (SCC) or adenocarcinoma (AC) who underwent definitive treatment by hysterectomy (HYST) versus cone resection or trachelectomy (FSS) were identified. Univariate analysis was performed with chi-square and Mann-Whitney tests. Overall survival (OS) was evaluated for cases diagnosed between 2004-2014 after generation of Kaplan-Meier curves and compared with the log-rank test. A Cox model was constructed to control for founders.

RESULTS: A total of 2623 patients met the inclusion criteria. Median patient age at diagnosis was 31 years (IQR:5). The majority had squamous cell carcinoma (62.4%) and stage IB1 disease (84.1%). The rate of FSS was 13.6%. Compared to patients who underwent HYST, those who received FSS were younger (median 30 vs 32 yrs, p<0.001), had fewer co-morbidities (3.6% vs 7.6%, p=0.007), were more likely to reside in large metropolitan areas (61.1% vs 49.5%, p<0.001), have private insurance (75.8% vs 62.9%, p<0.001), higher median income (p<0.001), present with stage IA2 disease (25.2% vs 14.4%, p<0.001) and adenocarcinoma (45.4% vs 36.3%, p=0.001). No differences were noted based on patient race (p=0.14). After controlling for clinical stage, histology, age, presence of co-morbidities, and area of residence, private insurance and higher income were associated with the receipt of FSS. There was no difference in OS between patients who received HYST (n=2036) and FSS (n=595), p=0.37; 5-yr OS rates were 93.5% and 94.5%, respectively. After controlling for age, clinical stage, histology, presence of medical comorbidities and performance...
of lymph node dissection, receipt of FSS was not associated with a worse survival (HR: 0.75, 95% CI: 0.42, 1.37).

CONCLUSIONS: Socio-economic disparities exist in the utilization of FSS for early stage cervical cancer. For this selected population no difference in OS was found. This is critical information for patients referred for onco-fertility consultation.

References: n/a

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OBJECTIVE: Since 2011, we have been initiating ovarian stimulation (random-start), at the time of the initial fertility preservation (FP) consultation, to minimize delays in cancer treatment. In this study, we aim to determine if random-start controlled ovarian stimulation (COS) is an effective method for FP, and if starting stimulation during a particular phase in the menstrual cycle yields different results.

DESIGN: Retrospective cohort.

MATERIALS AND METHODS: From 6/2011 to 3/2018, 1120 cancer patients were referred to our clinic for FP. All referred patients with no prior chemotherapy treatment, who underwent emergent FP treatment with an antagonist protocol, were included. Three hundred and eight patients met the inclusion criteria, with a total of 110 cycles initiated in the early follicular phase and 150 and 106 cycles initiated during the late follicular and luteal phases, respectively. ANOVA, T test and descriptive statistics were used to analyze the data as appropriate.

RESULTS: There was no difference in age, BMI and AFC across the groups. Number of dominant follicles (≥13mm) on the day of trigger, mature oocytes retrieved, maturity rate (MII/total oocyte ratio) and mature oocyte yield (MII/AFC ratio) were similar across the groups (Table). There were significantly higher fertilization rates in random-start COS cycles compared to early follicular start. Additionally, number of high quality embryos frozen on Day 3 per MII oocyte retrieved was significantly higher in random-start cycles compared to early follicular start. The peak estradiol levels per mature follicle measured was significantly lower in random-start COS cycles.

CONCLUSIONS: Ovarian Stimulation throughout the menstrual cycle yields similar oocyte maturity/developmental competence and high quality embryos. To minimize delays in cancer treatment, random-start COS should be considered the standard of care for patients undergoing emergent FP.

Comparison between early, late follicular and luteal phase COS; means (SEM). NS: not significant.

<table>
<thead>
<tr>
<th>Oocyte &amp; Embryo Cryopreservation</th>
<th>Early Follicular Start (n=110)</th>
<th>Late Follicular Start (n=150)</th>
<th>Luteal Start (n=106)</th>
<th>p value</th>
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<tr>
<td>Total Stim Dose</td>
<td>3594 (112)</td>
<td>3817 (97)</td>
<td>4191 (128)</td>
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<td>Days of Stimulation</td>
<td>9.8 (0.2)</td>
<td>10.2 (0.1)</td>
<td>10.8 (0.2)</td>
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<td>Follicles ≥ 13 mm</td>
<td>12.9 (0.7)</td>
<td>14.0 (0.7)</td>
<td>14.6 (0.8)</td>
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<td>Mature Oocytes (MII) Retrieved</td>
<td>12.3 (0.7)</td>
<td>12.3 (0.8)</td>
<td>12.8 (0.9)</td>
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<td>MII Oocyte / Total Oocyte Ratio</td>
<td>0.75 (0.03)</td>
<td>0.73 (0.02)</td>
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<td>MII Oocyte / AFC Ratio</td>
<td>0.98 (0.06)</td>
<td>1.00 (0.07)</td>
<td>0.99 (0.06)</td>
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<th>Oocyte &amp; Embryo Cryopreservation w/out Letrozole</th>
<th>Early Follicular Start (n=40)</th>
<th>Late Follicular Start (n=63)</th>
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<tr>
<td>Estradiol / Follicles ≥ 13 mm</td>
<td>216 (18)</td>
<td>212 (10)</td>
<td>168 (10)</td>
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<th>Embryo Cryopreservation</th>
<th>Early Follicular Start (n=62)</th>
<th>Late Follicular Start (n=54)</th>
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<td>Fertilization Rate (2PN/MII)</td>
<td>0.72 (0.03)</td>
<td>0.84 (0.04)</td>
<td>0.87 (0.03)</td>
<td>0.0034</td>
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<td>Frozen Embryos / MII Oocyte</td>
<td>0.60 (0.03)</td>
<td>0.75 (0.05)</td>
<td>0.81 (0.03)</td>
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SPERM QUALITY AND PROTEOMIC PROFILE IN MEN WITH HODGKIN’S LYMPHOMA. A. Agarwal,a A. D. Martins, P. N. Pushparaj,b B. Willard,c R. Sharma,a A. Agarwal,a A. D. Martins, P. N. Pushparaj,b B. Willard,c R. Sharma,a American Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH; bInst de Ciencias Biomédicas Abel Salazar, Porto, Portugal; cCenter of Excellence in Genomic Medicine Research, Jeddah, Saudi Arabia; aResearch Core Services-Proteomics, Cleveland Clinic, Cleveland, OH.

OBJECTIVE: The Hodgkin’s lymphoma (HD) is one of the most common cancers affecting men in reproductive age. This study aims to analyze sperm parameters and alterations in proteomic profiles of spermatozoa from men with HD undergoing sperm banking before cancer therapy.

DESIGN: Evaluation of sperm parameters and proteomic profiles of men with HD.

MATERIALS AND METHODS: We analyzed the sperm parameters in fertile men (donor) (n=42) and men with HD before cancer therapy (patients) (n=38). We used Mann-Whitney test to deduce statistical differences in sperm parameters (p<0.05). We compared the proteomic profiles of spermatozoa from donors (n=3) and patients (n=3) using LTQ-Orbitrap Elite hybrid MS system. Samples were analyzed using Mascot and SEQUEST software to search the Human Reference Sequence database. The identified differently expressed proteins (DEPs) were evaluated using Ingenuity Pathway Analysis (IPA).

RESULTS: We observed a lower concentration, total count, and total motile spermatozoa in patients compared to donors. Global proteomic analysis identify a total of 1169 proteins. Among the 134 identified DEPs: 35 were overexpressed: 80 were underexpressed: 16 were unique to donors; and 3 were unique to patients. The IPA analysis revealed that proteins involved in capacitation, acrosome reaction, binding of sperm to the zona pellucida, sperm motility, regulation of sperm DNA damage, and apoptosis were significantly downregulated in HD. Cancer and reproductive system disease were the top significantly regulated diseases and disorders in the spermatozoa of patients. The molecular and cellular functions such as cell-to-cell signaling and interaction, cellular assembly and organization, and protein modifications were significantly impaired in the spermatozoa of patients. Heat shock factor proteins 1 and 2; and 1,2-dithiol-3-thione were predicted to the top inhibited upstream regulators.

CONCLUSIONS: Semen quality was significantly decreased in men with HD relative to fertile men. However, proteomic data showed an altered proteome in spermatozoa of men with HD, which may explain how these alterations can potentially compromise the fertility in these men and help identify therapeutic strategies to increase the quality of sperm and successful pregnancies.

Supported by: Ana D Martins was funded by the Fulbright Research Grant (ID: E0585654) and the Portuguese Science and Technology Foundation (SFRH/BD/108726/2015).
NOVEL PROTEOMIC SIGNATURES IN SPERMATOZOA OF MEN WITH SEMINOMATOUS AND NON-SEMINOMATOUS GERM CELL TUMORS. A. Agarwal, a T. R. Dias, a,b,c P. N. Pushparaj, d G. Ahmadian, d R. Sharma. a American Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH; b University of Beira Interior, Covilhã, Portugal; c University of Porto, Porto, Portugal; d Center of Excellence in Genomic Medicine Research, Jeddah, Saudi Arabia; e Prince Sultan Bin Abdulaziz University, Riyadh, Saudi Arabia; f University of Health Sciences, Lahore, Pakistan.

OBJECTIVE: To identify novel proteomic signatures in spermatozoa of patients with seminomatous germ cell tumors (SGCT) and non-seminomatous germ cells tumors (NSGCT) undergoing sperm banking before starting cancer treatment.

DESIGN: Thirty semen samples were collected from men with SGCT and NSGCT undergoing sperm banking before starting cancer treatment (N=15 per group). Sperm protein samples were used for quantitative proteomic analysis for the identification of differentially expressed proteins (DEPs).

MATERIALS AND METHODS: Before cryopreservation of semen samples, a routine semen analysis was conducted. Spermatozoa were isolated from cryopreserved samples by centrifugation and total protein was extracted. One pool of three samples from each experimental group was analyzed in triplicate by liquid chromatography tandem mass-spectrometry (LC-MS/MS). Ingenuity Pathway Analysis software was used to select key reproductive proteins for validation by WB. Statistical analysis was assessed by Mann-Whitney test using MedCalc and differences with P<0.05 were considered significant.

RESULTS: Ejaculate volume, sperm motility and concentration were similar between patients with SGCT and NSGCT. However, proteomic data revealed the differential expression of 292 proteins. Through IPA analysis, we selected ubiquinol-cytochrome C reductase core protein 2 (UQRC2) involved in oxidative phosphorylation, ATP Synthase F1 Subunit Alpha (ATPSA1) involved in ATP production, matrix metallopeptidase 9 (MMP9) involved in extracellular matrix remodeling, and heat shock-related 70 kDa protein 2 (HSPA2) and sperm surface protein 17 (SPA17) involved in sperm-zona pellucida binding. WB results showed underexpression of DEPs.

CONCLUSIONS: Overexpression of MMP9 was correlated with the higher invasiveness of NSGCT relative to SGCT. Decreased expression levels of UQRC2, HSPA2, and SPA17 may explain why the fertility problems are usually more severe in patients with NSGCT. These proteins may serve as a new diagnostic tool to distinguish between both types of testicular cancer.

Supported by: Tania R Dias was funded by the Fulbright Research Grant (E0585639) and the Portuguese Science and Technology Foundation (SFRH/BD/109284/2015).

HOW DO OVARIAN RESERVE AND ANEUPLOIDY IN BRCA CARRIERS COMPARE TO THAT OF THE GENERAL POPULATION UNDERGOING ART? N. Herlity, a L. Sekhon, b M. Oliva, b D. Gounko, b J. Lee, a J. Lekovich, c M. Lederman, b A. B. Copperman. a, b Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY; c Reproductive Medicine Associates of New York, New York, NY.

OBJECTIVE: BRCA1 and BRCA2 play an integral role in DNA mismatch repair. Patients who express a BRCA mutation have been shown to accumulate damaged DNA, which may stimulate oocyte aging and depletion. Limited studies have assessed the relationship between BRCA carrier status with ovarian reserve, response to controlled ovarian hyperstimulation (COH) and rate of embryo aneuploidy and have presented conflicting results. The objective of this study was to evaluate cycle outcomes of BRCA1/2 patients who undergo assisted reproductive technologies (ART) treatment.

DESIGN: Retrospective.

MATERIALS AND METHODS: The study included patients who underwent COH for IVF or oocyte cryopreservation between 2002 and 2018. Patients who were carriers of BRCA1 or BRCA2 mutation were compared to controls. Outcomes included patient age, AMH, BAFC, number of mature oocytes retrieved, fertilization, blastulation and aneuploidy rates. Student’s t-test, chi square and multivariate linear regression were used for statistical analysis. A mixed model was utilized for patients undergoing multiple cycles.

RESULTS: A total of 80 BRCA1 and 44 BRCA2 patients were compared to 15749 controls. BRCA1 carriers were significantly younger than the control population (35.2 vs. 37.0, p<0.03). Controlling for age, AMH was not reduced in BRCA1 (β=-1.6, p=0.82) and BRCA2 carriers (β=-3.9, p=0.67). BAFC was significantly reduced in BRCA1 carriers (β=-2.5, p=0.02) and trended towards a significant reduction in BRCA2 carriers (β=-2.4, p=0.07). Controlling for age and AMH, the number of oocytes retrieved was significantly reduced in BRCA1 carriers (β=-4.5, p=0.02), but not in BRCA2 carriers (β=-1.7, p=0.49). Controlling for age, fertilization rate was not modified in BRCA1 carriers, however, there was a trend towards decreased blastulation rate in BRCA1 (β=-0.15, p=0.07) and BRCA2 carriers (β=-0.17, p=0.06). Controlling for age, aneuploidy rate was not modified in BRCA1 (β=0.1, p=0.26) and BRCA2 carriers (β=0.5, p=0.64).

CONCLUSIONS: BRCA patients commonly undergo IVF and egg freezing, most likely due to the recommendation for prophylactic salpingo-oophorectomy by age 35 to 40. Despite the subtle decrease in ovarian reserve and trend towards reduced blastulation rate seen in BRCA carriers, embryo quality was not affected. BRCA carriers undergoing COH for IVF or oocyte cryopreservation can be reassured that they will have outcomes comparable to the general population and of the achievability of their goals to grow their family.


P-177 Tuesday, October 9, 2018 6:30 AM

PATTERNS OF REFERRAL FOR FERTILITY PRESERVATION AMONG FEMALE ADOLESCENTS AND YOUNG ADULTS (AYA) WITH BREAST CANCER: A POPULATION-BASED COHORT STUDY.
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OBJECTIVE: To assess the fertility preservation (FP) referral rates and patterns of newly-diagnosed female Adolescent and Young Adult (AYA) breast cancer patients in Ontario, Canada.

DESIGN: Population-based cohort study employing provincial-level, universal healthcare databases.

MATERIALS AND METHODS: Women aged 15-39 years with newly-diagnosed breast cancer in Ontario from 2000-2016 were identified using the Ontario Cancer Registry. Exclusion criteria included history of a sterilizing procedure, ineligibility for provincial health insurance coverage at the time of diagnosis, prior infertility diagnosis, and prior cancer diagnosis other than breast or a cancer diagnosis before 2000. Women with a Gynecology consultation between diagnosis of their cancer and commencement of chemotherapy were used as a surrogate for FP referral. The effect of age, parity, year of cancer diagnosis and initiation of chemotherapy. Older patients (RR 0.20; 95% CI 0.15-0.26) and marginalization (RR 0.53 95% CI: 0.36-0.79) were inversely correlated with referrals. Parity and marginalization remained statistically significant after multivariate analysis (p<0.0001) and 15 days after the last chemotherapy cycle in breast cancer patients (3.1±0.2 ng/ml; p=0.0003), respectively. 18 months post-chemotherapy treatment, AMH concentration remained stable in breast cancer patients (2.3±0.9 ng/ml) while a tendency toward an increase of AMH concentration was observed (9.1±3.7 ng/ml) in Hodgkin lymphoma patients. Meanwhile, cf-DNA concentration dramatically decreased 15 days after chemotherapy treatment in Hodgkin lymphoma patients compared to baseline measure (2282±2.753 vs 907.4±837 fg/al), and thus, until 18 months post-treatment (144±1.58 ng/ml). In breast cancer patients, there is no significant or tendency before, during and after chemotherapy treatment. As cf-DNA concentration has been reported to be negatively correlated to follicular size and embryo quality, our cf-DNA results suggest a relationship between cf-DNA and follicular status, which could serve as a biomarker of ovarian function.

RESULTS: At baseline, serum AMH concentrations were 29.2±6.2 and 24±13.9 ng/ml (mean ± SEM) in Hodgkin lymphoma and breast cancer patients, respectively. AMH concentration decreased significantly 15 days after the first chemotherapy cycle in Hodgkin lymphoma (7.9±1.4 ng/ml; p<0.0001) and 15 days after the last chemotherapy cycle in breast cancer patients (3.1±0.2 ng/ml; p=0.0003), respectively. 18 months post-chemotherapy treatment, AMH concentration remained stable in breast cancer patients (2.3±0.9 ng/ml) while a tendency toward an increase of AMH concentration was observed (9.1±3.7 ng/ml) in Hodgkin lymphoma patients. Meanwhile, cf-DNA concentration dramatically decreased 15 days after chemotherapy treatment in Hodgkin lymphoma patients compared to baseline measure (2282±2.753 vs 907.4±837 fg/al), and thus, until 18 months post-treatment (144±1.58 ng/ml). In breast cancer patients, there is no significant or tendency before, during and after chemotherapy treatment. As cf-DNA concentration has been reported to be negatively correlated to follicular size and embryo quality, our cf-DNA results suggest a relationship between cf-DNA and follicular status, which could serve as a biomarker of ovarian function.

CONCLUSIONS: Fertility preservation referral rates remain low and non-invasive prospective biomarkers are needed to help evaluate and predict ovarian reserve status as well as oocyte quality in Hodgkin lymphoma and breast cancer patients in fertility preservation programs. This finding opens new perspectives in cancer care patient especially for fertility preservation program and counseling. cf-DNA may serve as a non-invasive objective biomarker of cryopreserved oocytes quality in breast cancer and Hodgkin lymphoma patients.

Supported by: Our project is supported by a grant from INCA (Institut National du Cancer; N° PRT-K15-084).

P-179 Tuesday, October 9, 2018 6:30 AM

HOW LONG WILL IT TAKE? TIME TO PREGNANCY IN FEMALE YOUNG ADULT CANCER SURVIVORS.
K. Pinson,8 E. Myers,8 S. S. Stark,9 K. Shihahtitsavas,8 C. Lam,8 A. C. Medica,9 B. Whitcomb,9 H. Su,9 “University of California San Diego, La Jolla, CA; 8Biostatistics and Epidemiology, University of Massachusetts, Amherst, MA.

OBJECTIVE: Although many treatments for cancer are gonadotoxic, little is known about their association with time to pregnancy in adolescent and young adult (AYA) cancer survivors. We tested the hypothesis that AYA cancer survivors who received gonadotoxic cancer treatment have higher risk of clinical infertility, compared to survivors who did not receive gonadotoxic cancer treatment.

DESIGN: Retrospective Cohort.

MATERIALS AND METHODS: Female AYA survivors recruited to the Reproductive Window study on ovarian function completed an enrollment questionnaire with self-reported data regarding demographic, cancer and cancer treatment, and reproductive characteristics including time to pregnancy. Participants were age 18-40 at enrollment, age 15-35 at cancer diagnosis, completed primary cancer treatment, and had at least one unassisted pregnancy after cancer (N=249). The primary exposures were gonadotoxic cancer treatments, i.e. alkylating chemotherapy, abdomino-pelvic radiation, bone marrow transplant (BMT), The primary outcome was clinical infertility, or no pregnancy by 12 months. Chi-square, Fisher’s Exact, and log binomial regression estimated associations between exposures and clinical infertility.

RESULTS: Mean participant age was 35 ± 3.5 years, 71% identified as Caucasian, 27% as Hispanic, and the most common cancers were hematologic (37%) and breast (17%). The proportions of pregnancies occurring by 3, 6, 9 and 12 months of attempt were 60%, 81%, 87% and 89%, respectively. While survivors exposed to gonadotoxic therapies appeared to have lower rates of pregnancy by 12 months compared to unexposed survivors, only prior BMT was statistically significantly associated with clinical infertility
participant characteristics associated with clinical infertility

<table>
<thead>
<tr>
<th>Gonadotoxic cancer treatments</th>
<th>Total cohort N=249 N (%)</th>
<th>Pregnancy &lt; 12 months in N=222 N (%)</th>
<th>Pregnancy ≥ 12 months in N=27 N (%)</th>
<th>RR Clinical Infertility (95% CI) p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMT</td>
<td>7 (3%)</td>
<td>4 (57%)</td>
<td>3 (43%)</td>
<td>4.9 (2.2-17.6)</td>
</tr>
<tr>
<td>Alkylating chemotherapy</td>
<td>60 (24%)</td>
<td>53 (88%)</td>
<td>7 (12%)</td>
<td>1.3 (0.6-3.2)</td>
</tr>
<tr>
<td>Abdomino-pelvic radiation</td>
<td>31 (13%)</td>
<td>27 (87%)</td>
<td>4 (13%)</td>
<td>1.5 (0.5-4.3)</td>
</tr>
<tr>
<td>None of the above</td>
<td>150 (60%)</td>
<td>137 (91%)</td>
<td>13 (9%)</td>
<td>Reference</td>
</tr>
</tbody>
</table>

Infertility prior to Cancer

<table>
<thead>
<tr>
<th></th>
<th>Infertility prior to Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>14 (6%)</td>
</tr>
<tr>
<td></td>
<td>8 (57%)</td>
</tr>
<tr>
<td></td>
<td>6 (43%)</td>
</tr>
</tbody>
</table>

(4.9, 95% CI 2.2-17.6, p=0.002) (Table). History of infertility prior to cancer was associated with lower rates of pregnancy by 12 months (RR 4.8, 95% CI 2.3-9.9, p<0.001). Prior smoking, race, medical comorbidity, history of miscarriage, and number of prior pregnancies were not associated with clinical infertility.

CONCLUSIONS: The majority of cancer survivors who conceived became pregnant within 12 months, with a similar distribution of time to pregnancy to the general population. History of infertility prior to cancer and BMT exposure were associated with clinical infertility in female AYA cancer survivors. The lack of significant association with alkylators and radiation is likely due to a smaller effect that could not be detected by this sample size.

Supported by: HD 080952-04

P-180 Tuesday, October 9, 2018 6:30 AM

RANDOM START VERSUS CONVENTIONAL START CONTROLLED OVARIAN STIMULATION IN WOMEN WITH CANCER: COMPARING OOCYTE YIELD AMONG FERTILITY PRESERVATION CYCLES.

V. M. Alexander, J. F. Kawwass, H. Hipp, J. B. Spencer, L. J. Mckenzie. Division of Reproductive Endocrinology, Gynecology and Obstetrics, Emory University, Atlanta, GA.

OBJECTIVE: To determine if random start controlled ovarian stimulation provides similar oocyte yields compared to conventional ovarian stimulation in women with cancer.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: All stimulation cycles for patients undergoing oocyte cryopreservation for fertility preservation due to recent cancer diagnoses and upcoming chemotherapy or radiation were reviewed from 2012-2018. Of the 180 oocyte cryopreservation cycles, 42 cycles (40 unique patients) met inclusion criteria. Patients were grouped into either random start or non-random cycle start. Conventional start was defined as scheduled early follicular phase (prior to cycle day six) initiation of gonadotropins. A two-sample t test was used to compare the primary outcome (number of mature oocytes cryopreserved) between the random and conventional starts.

RESULTS: The mean number of mature oocytes cryopreserved were similar in random (n=22) and conventional start controlled ovarian stimulation cycles (n=20) (12.3 versus 10.8, p=0.58). There were no differences in cancellation rate, patient age, patient body mass index (BMI), days of stimulation, peak estradiol, or total cycle gonadotropin use. Mean BMI was 27.4. The addition of letrozole to the stimulation cycles in women with breast cancer (18 cycles) did not change the mean number of oocytes retrieved (17.5 versus 15.2, p=0.52) or the mean number of mature oocytes cryopreserved (12.8 versus 9.7, p=0.25) compared to non-letrozole stimulation cycles.

CONCLUSIONS: Fertility preservation is of great interest for women with cancer preparing to undergo potentially gonadotoxic cancer treatments. Random cycle start controlled ovarian stimulation reduces the time delay for initiation of cancer treatment and provides similar oocyte yields in comparison to conventional cycle start. Minimizing cancer treatment delays will expand fertility preservation options for women with cancer.

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OOCYTE VITRIFICATION USING A NEW VITRIFICATION MEDIUM AND A NEW CLOSED VITRIFICATION DEVICE. A SIBLING OOCYTE STUDY. O. Perez, J. Tilley, G. Navarrete, L. Lay, L. M. Little, R. Gadd, S. Chantilis. Dallas Fertility Center, Dallas, TX; Dallas Fort Worth Fertility Associates, Dallas, TX.

OBJECTIVE: Vitrification has been successfully applied in the cryopreservation of human oocytes. The currently applied vitrification techniques differ from each other in technique, vitrification solution, device, and it is a more complex skill compared to blastocyst freeze techniques. The objective of this study is to analyze the vitrification, warming survival rates and birth outcome of a new vitrification protocol in conjunction with a new closed system device.

DESIGN: Prospective sibling oocyte vitrification study.

MATERIALS AND METHODS: Oocytes were collected from twenty four non-donors, aged 26-35 years old. 387 sibling MII oocytes were randomly assigned in two treatment groups. Half of the mature oocytes were vitrified and warmed (vitrification group). The remaining mature oocytes were not vitrified and served as the control group. Oocytes were vitrified between 2-3 hours post oocyte retrieval using a newly developed vitrification medium specifically for oocytes (RapidVit and Rapid Warm Oocyte: Vitrolife Inc.), and a newly closed vitrification device (Rapid-I Vitriflhe, Inc). The set up temperature was 33.6°C. Thaw procedures were performed at 37°C. Vitrified and control oocytes underwent ICSI at the same time and kept in separate dishes throughout culture. Best quality blastocysts were selected for embryo cryopreservation in both groups. Frozen/thaw blastocysts from the vitrification group were consequently selected for a frozen embryo transfer.

RESULTS: As expected, the number of blastocysts and its cryopreservation rate was significantly lower in the vitrification group versus the control group. The vitrification group showed an acceptable survival rate. Even...
though the embryo development of this treatment group was lower when compared with the control group, the delivery rate compensates for this difference. Eight successful deliveries of healthy babies occurred out of 14 frozen embryo transfers in the vitrification group. CONCLUSIONS: The vitrification and warming media of this new system could be considered in oocyte vitrification protocols. This new closed vitrification device will represent another viable option for oocyte vitrification.

Summary of Results of the New Oocyte Vitrification System

<table>
<thead>
<tr>
<th>Control Group</th>
<th>Vitrification Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td># Mature Oocytes</td>
<td>197</td>
<td>190</td>
</tr>
<tr>
<td># Survived Oocytes (%)</td>
<td>N/A</td>
<td>179 (94%)</td>
</tr>
<tr>
<td># Fertilized Oocytes (%)</td>
<td>158 (80%)</td>
<td>144 (80%) NS</td>
</tr>
<tr>
<td># Cleaved Embryos (%)</td>
<td>157 (99%)</td>
<td>137 (95%) NS</td>
</tr>
<tr>
<td># Day-5 Blastocysts (%)</td>
<td>84 (53%)</td>
<td>52 (36%) 0.003</td>
</tr>
<tr>
<td># Cryopreserved Blastocysts (%)</td>
<td>60 (38%)</td>
<td>38 (26%) 0.03</td>
</tr>
<tr>
<td># Patients with FET</td>
<td>N/A</td>
<td>14</td>
</tr>
<tr>
<td># Patients with Negative Pregnancy (%)</td>
<td>N/A</td>
<td>6 (42%)</td>
</tr>
<tr>
<td># Patients with no Embryos for FET (%)</td>
<td>N/A</td>
<td>5 (35%)</td>
</tr>
<tr>
<td># Patients with Delivered Babies (%)</td>
<td>N/A</td>
<td>8 (57%)</td>
</tr>
</tbody>
</table>

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THE ALTERATION OF METHYLATION ON TUMOR ASSOCIATED IMPRINTING GENES IGF2R/H19, SNRPN AND PLAGL1 IN THE OFFSPRING MICE GENERATED FROM OVARIAN TISSUE CRYOPRESERVATION AND TRANSPLANTATION. Y. Wang, OB&GYN, Reproductive Medicine Center, Chengdu, China.

OBJECTIVE: To establish the animal models and to evaluate the health condition and cancer predisposition based on the status of cancer susceptibility gene on the offspring mouse generated from the ovarian cryopreservation and transplantation.

DESIGN: The mouse model of ovarian tissue cryopreservation and transplantation and the evaluation of the offspring mouse.

MATERIALS AND METHODS: 1) The mice models of ovarian cryopreservation transplantation, including slow freezing group (Group S) and vitrification group (Group V), fresh ovarian transplantation/group F) and control group/group C) were established. 2) The ovarian deep cryopreservation transplantation filial generation’s growth and development was evaluated and compared with the control group; 3) The methylation status and gene expression level of filial generation mice’s imprinted genes IGF2R, H19, SNRPN and PLAGL1 was assayed.

RESULTS: Both cryopreservation methods showed no significant difference in terms of ovarian preservation and fertility restoration. The birth, growth, development, weight gaining, movement condition and anti-fatigue ability of frozen transplanting group’s filial generation had no significant difference in comparison with Group C and Group F, and there were no malformation in the vital organs (brain, heart, liver and kidney) of which, observed by both gross specimens and sections for microscope. The IGF2R gene’s methylation of the cryopreservation and transplantation group significantly declined in comparison with Group C (P<0.001), with the mRNA expression markedly increased (P<0.001), the H19 gene methylation of liver tissue in Group V significantly increased compared with Group C (P=0.040), with the mRNA expression decreased remarkably (P<0.001); however, there was no significant difference of methylation rate of brain tissue among groups (P=0.346), with the mRNA suggested the opposite (P<0.001). The SNRPN gene methylation (P=0.953, 0.983) and mRNA expression (P=0.202, 0.809) maintained stable in different organs and groups. The PLAGL1 gene methylation in both brain and liver tissue of Group V &S significantly decreased compared with Group C and Group F (P<0.001), with the mRNA increased significantly.

CONCLUSIONS: The health condition of the offspring mice generated from ovarian tissue cryopreservation and transplantation was normal, whether the birth defects have increased needs further study. However the methylation status of imprinting genes IGF2R,H19,PLAGL1 were changed in different organs, which suggested the potential health risks (including cancer susceptibility) for the offspring mice, and the technology of female fertility cryopreservation needs to further optimization and to be improved.

References:

Supported by: National Natural Science Foundation of China (Grant No; 3101117)

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PATIENT AND OVARIAN RESERVE PARAMETERS THAT PREDICT ADEQUATE OOCYTE YIELD IN WOMEN UNDERGOING ELECTIVE CRYOPRESERVATION OF OOCYTES. C. Mostisser, N. Pereira, N. J. Shah, I. Kligman, R. Elias, Z. Rosenwaks, Obstetrics and Gynecology, New York Presbyterian Weill Cornell, New York, NY; Reproductive Medicine, Weill Cornell Medicine, New York, NY.

OBJECTIVE: Oocyte cryopreservation is being utilized by an increasing number of women who wish to delay motherhood due to personal or professional reasons. However, whether one or more ovarian stimulation cycles are required to cryopreserve an adequate number of oocytes is currently unknown. The current study investigates the patient and ovarian reserve parameters that predict adequate oocyte yield in women undergoing elective cryopreservation of oocytes.

DESIGN: Case-control study.

MATERIALS AND METHODS: All women <42 years undergoing elective cryopreservation of oocytes between 2012-2016 were assessed for potential inclusion. Women undergoing ovarian stimulation for cancer-related indications or those recently treated with chemotherapy or radiation were excluded. In addition to baseline demographics, ovarian reserve and ovarian stimulation parameters were also recorded. Total oocytes retrieved was considered the primary outcome. Women with at least 12 oocytes (our center’s mean oocyte yield) were considered to have an adequate oocyte yield. Women with <12 oocytes (cases) were compared to those with ≥12 oocytes (controls). Receiver operating characteristic (ROC) curves and Corresponding area-under-the-curve (AUCs) were generated for any patient or ovarian reserve parameters that were statistically significant.

RESULTS: A total of 1481 women were included - 991 (66.9%) and 490 (33.1%) had <12 and ≥12 oocytes retrieved, respectively. There was no difference in the age, ethnicity and blood type of cases and controls. However, when compared to women with ≥12 oocytes, women with <12 oocytes had a higher body mass index (25.7±5.9 vs. 22.5±5.2; P<0.001), lower AFC

References:

Supported by: National Natural Science Foundation of China (Grant No; 3101117)
Among the infertility treatment cohort, mean age and BMI were 37 and 24.6, respectively. The majority were also nulliparous (74%) and non-smoking (93%). Reasons for treatment were male factor (62%), diminished ovarian reserve (32%), other (18%), unexplained (10%), tubal factor (8%), endometriosis (7%), polycystic ovaries (6%), and uterine factor (4%) - 42% of patients had multifactorial causes. Mean AMH was 2.30 overall and 0.67 for those with POR. Mean number of oocytes retrieved per cycle was 11; 22% of cycles had POR.

The AMH cut-off at 90% specificity for predicting POR established using ROC curve analyses was 0.660 with an associated sensitivity of 53.8% for the fertility preservation cohort versus 0.595 with an associated sensitivity of 61.7% for the infertility treatment cohort. The difference in area under the ROC curves for the two groups was not statistically significant (0.872 versus 0.880, p=0.41).

CONCLUSIONS: This is the first study to our knowledge to characterize AMH as a predictor of oocyte yield in the reproducibly healthy fertility preservation population. The ability of AMH to predict POR appears to be similar between fertility preservation and infertility patients.

**References:**

**P-188 Tuesday, October 9, 2018 6:30 AM**


OBJECTIVE: GnRH-a is a well-established method for oocyte maturation in high-responders at risk for ovarian hyperstimulation syndrome (OHSS). While normal and low responders are at lower risk for OHSS, even a small risk may be unacceptable in EOC. The primary objective of this study is to evaluate MR in normal, low, and very-low responders undergoing EOC using GnRH-a trigger.

DESIGN: Retrospective Cohort.

MATERIALS AND METHODS: All EOC cycles performed from April 2016-April 2018 at Extend Fertility Medical Practice, a large single-center oocyte cryopreservation program, were included in the study. Demographic, clinical, and embryologic data were collected and categorized from the electronic medical record. MR was calculated using the quotient of mature (MII) and retrieved oocytes. Peak estradiol (E2) levels on day of trigger were used as a surrogate for ovarian response. Associations were made using X², student’s-t test, Mann-Whitney U, and Kruskall Wallace, where appropriate.

RESULTS: 1125 total cycles, 491 (43.6%) GnRH-a, 609 (54.1%) hCG, and 24 (2.1%) dual-trigger (DT) cycles were included. Mean retrieved and MII oocytes were 15.9±10.9 and 10.8±8.4. Both were significantly higher in GnRH-a (19.5±12.8, 13.7±9.8) compared to hCG (13.0±8.0, 8.5±6.2) and DT (14.9±7.7, 10.7±6.2) (p<0.01). Median MR (IQR) was 0.70 (0.26) overall. MR for hCG (0.670,0.251) was significantly lower than the GnRH-a [0.740,0.251] and DT [0.780,0.211] (p<0.01). Mean E2 level was 2352.9±1485.5 pg/mL overall and was significantly lower for hCG compared to GnRH-a (1872.1±912.0 vs. 2974.0±1810.0, p<0.01). Table 1 demonstrates oocytes retrieved, MII, and MR for GnRH-a categorized by E2 level on day of trigger. While mean oocytes retrieved and MII were significantly higher in the higher E2 groups, the MR was not significantly different. 45/487 (9.0%) of GnRH-a triggers were categorized as very-low responders (peak E2<1000). Median MR was significantly lower for E2<1000 compared to E2>1000 [0.640,0.26] vs. 0.750(0.23), p=0.002. Overall, there were a total of 174 very-low responders, 126 (71.2%) hCG, 45 (25.4%) GnRH-a, and 3 (1.7%) DT. The median MR for very-low responders was 0.660(0.34) and did not significantly differ between hCG and GnRH-a [0.680(0.45) vs 0.655(0.26), p=0.10].

**TABLE 1.**

<table>
<thead>
<tr>
<th></th>
<th>&quot;Low&quot; (E2&lt;2000) n=160</th>
<th>&quot;Normal&quot; (E2 2001-3000) n=116</th>
<th>&quot;High&quot; (E2 3001-4000) n=91</th>
<th>&quot;Very-High&quot; (E2&gt;4000) n=111</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oocytes retrieved Mean±SD</td>
<td>9.56±6.86</td>
<td>20.21±10.09</td>
<td>23.63±10.68</td>
<td>30.08±12.81</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MII oocytes Mean±SD</td>
<td>6.69±4.90</td>
<td>13.88±8.43</td>
<td>16.13±8.80</td>
<td>21.61±10.30</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MR Median (IQR)</td>
<td>0.72 (0.26)</td>
<td>0.75 (0.22)</td>
<td>0.75 (0.22)</td>
<td>0.76 (0.22)</td>
<td>0.78</td>
</tr>
</tbody>
</table>
CONCLUSIONS: GnRH-a trigger is a suitable option for women undergoing EOC, where even a small risk of OHSS may be unacceptable. No significant decline was seen in MR when used in normal and low responders undergoing EOC. Very-low responders had lower MR overall, regardless of trigger type. Based on these data, GnRH-a can be used reliably for the induction of maturation in EOC cycles regardless of response.

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OBJECTIVE: Data for evidence-based counseling of women considering EOC is scarce. Realistic expectations for oocyte yield and LBR is critical in allowing women to appropriately estimate the physical and financial investment necessary to achieve their reproductive goals. The primary objective of this study is to examine the probability of cryopreserving a cohort of oocytes sufficient for a 60% age-based LBR with the 1st EOC cycle.

DESIGN: Retrospective Cohort.

MATERIALS AND METHODS: All patients undergoing EOC at Extend Fertility Medical Practice, a large single-center oocyte cryopreservation program, from March 2016-April 2018, were included in the study. We collected demographic, clinical and embryologic data from the electronic medical record. Oocyte thresholds per age group were calculated for 50, 60, and 70% LBR using published data. Analyses for 60% LBR are presented here. Associations were calculated using X2, student’s t-test, ANOVA, Mann-Whitney-U, and Kruskall Wallace, where appropriate. ROC curves were used to determine appropriate cut-off values for bivariate analyses.

RESULTS: 764 women undergoing a total of 1088 EOC cycles were included in the study. Each subject had a mean of 1.4±0.4 cycles and 15.3±9.1 frozen MII oocytes per cycle. Mean age and median AMH was 35.6±3.4 and 2.3(IQR 2.4), respectively. Mean gonadotropin (GND) dose was 3686.7±1496.2IU per cycle. Using published data, we determined that a threshold of 11 frozen MII oocytes for ages ≥35, 13 for 35-37, 21 for 38-40, and 30 for ≥41 represented a 60% LBR for each group. 39.0% (298/764) met their age-based threshold for 60% LBR in their 1st cycle. An additional 116 (15.2%) met the threshold with a 2nd cycle (Table I) and 21 (2.8%) with a 3rd or 4th cycle. Mean age was significantly lower (34.2±2.9 vs. 36.4±3.3; p<0.001) and median AMH was significantly higher [3.4(3.6) vs. 1.5(1.5); p<0.001] for those who met the threshold in 1 cycle compared to those who did not. Subjects were more than twice as likely to achieve a 60% LBR threshold in their 1st cycle if they were age <35 (RR 2.2 95%CI 1.9-2.7) or had an AMH >2.6 (RR 2.4 95% CI 2.0-2.8). Despite higher response, mean total GND dose was significantly lower in subjects who met their threshold with the 1st cycle compared to those who did not (204(96±12005) vs. 3827±0±1542.1; p<0.001).

CONCLUSIONS: Even with a conservative LBR of 60%, less than half the subjects met the threshold with their 1st cycle. Women seeking EOC, especially at high-cost programs, may be financially limited to a single cycle. Counseling should include individualized estimates for 1st cycle oocyte yield, associated LBR, and the probability of needing more than one cycle to achieve their reproductive goals.

TABLE I.

<table>
<thead>
<tr>
<th>Cycles</th>
<th>Age ≤34</th>
<th>Age 35-37</th>
<th>Age 38-40</th>
<th>Age ≥41</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBR</td>
<td>(MII=11)</td>
<td>(MII=13)</td>
<td>(MII=21)</td>
<td>(MII=30)</td>
<td>n=674</td>
</tr>
<tr>
<td>n=253</td>
<td>n=333</td>
<td>n=135</td>
<td>n=43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>153 (60.5%)</td>
<td>132 (29.6%)</td>
<td>12 (8.9%)</td>
<td>1 (2.3%)</td>
<td>298 (39.0%)</td>
</tr>
<tr>
<td>2</td>
<td>42 (16.6%)</td>
<td>64 (19.2%)</td>
<td>9 (6.7%)</td>
<td>1 (2.3%)</td>
<td>116 (15.2%)</td>
</tr>
</tbody>
</table>

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FERTILITY PRESERVATION IN PATIENTS WITH BREAST CANCER DOES NOT APPEAR TO AFFECT LONG-TERM CANCER OUTCOMES EVEN IF PERFORMED PRIOR TO BREAST SURGERY. J. Letourneau, K. A. Wald, E. Harris, F. Juarez-Hernandez, N. Sinha, M. Cedars, M. Rosen. Obstetrics, Gynecology & Reproductive Sciences, UCSF, San Francisco, CA; University of California San Francisco, San Francisco, CA; University of California San Francisco Center for Reproductive Health, San Francisco, CA; UCSF School of Medicine, San Francisco, CA.

OBJECTIVE: Determine whether fertility preservation prior to breast cancer treatment is associated with differences in breast cancer recurrence and long-term survival.

DESIGN: Prospective Study, Single University Fertility Center.

MATERIALS AND METHODS: 354 women were included in this study. Each woman was seen for fertility preservation consultation prior to breast cancer treatment from the years 2007 to 2017. These women were followed prospectively to evaluate for disease recurrence or cancer-related death. For follow-up, the following were utilized: clinic visits, pathology reports, cancer treatment reports, surveys, and electronic medical record review. Demographic characteristics, reproductive health history, cancer treatment and tumor characteristics were compared among those who did (FP) and did not undergo fertility preservation (No FP) using Fisher Exact tests, Chi-Square, T-Tests, or Wilcoxon Rank Sum Tests, where appropriate. Time to cancer recurrence or death was calculated in months from the fertility preservation consultation visit. Survival analysis was carried out using Kaplan-Meier survival estimates and Cox proportional hazard regression analysis. To assess the impact of different factors on overall-survival and disease-free survival, univariable and multivariable Cox regression analyses were carried out.

RESULTS: Of the 354 women, 222 (63%) underwent egg or embryo cryopreservation prior to cancer treatment (FP) and 132 (37%) did not (No FP). 349 (99%) women had cancer follow-up information available. FP patients were younger (mean = 35 vs. 36.6 years, p = 0.009), were more likely to have estrogen-receptor negative disease (23% vs. 20%, p = 0.001), and were more likely to have stage 2 or greater disease (66.8% vs. 54.8%, p = 0.027). Of the women who received chemotherapy, 47% did so in the neoadjuvant setting. With median follow-up of 45 months (range 2-131 months), 26 patients have recurred and 9 have died from breast cancer. Overall, the risks of recurrence (7.3% vs. 7.6%, HR 1.2, 95% CI 0.5-2.6) and death (2.3% vs. 3.1%, HR 0.9, 95% CI 0.2-3.3) were similar among those undergoing FP vs. No FP. Patients with Estrogen-Receptor (ER) positive tumors (recurrence: HR 2.0, 95% CI 0.7-5.8; death: HR 1.2, 95% CI 0.1-11) and those who underwent neoadjuvant chemotherapy (recurrence: HR 1.4, 95% CI 0.1-16; death: HR 1.2, 95% CI 0.1-9.6) also had a similar risk of recurrence and death in the FP vs. No FP groups, after controlling for tumor stage, cancer treatment type, and HER2 receptor status.

CONCLUSIONS: Fertility preservation with egg or embryo cryopreservation is unlikely to increase recurrence or death in women with breast cancer, even among women who undergo FP in the neoadjuvant treatment setting, where the tumor remains in situ during FP.

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FERTILITY PRESERVATION DECISION-MAKING PRIOR TO GONADOTOXIC TREATMENT: AN ANALYSIS OF 451 PATIENTS. J. Y. Maher, C. N. Cordeiro Mitchell, K. Hunkler, M. E. Gornet, R. A. Garbose, L. J. Collins, M. S. Christianson. Obstetrics, Gynecology and Stereistics, Division of Reproductive Endocrinology and Infertility, Johns Hopkins University School of Medicine, Lutherville, MD; Johns Hopkins University School of Medicine, Baltimore, MD; Johns Hopkins University School of Medicine, Lutherville, MD; Johns Hopkins University School of Medicine, Baltimore, MD; Johns Hopkins University School of Medicine, Lutherville, MD.
University School of Medicine, Baltimore, MD; ∗Gynecology and Obstetrics, Johns Hopkins School of Medicine, Baltimore, MD; ∗∗Population, Family, and Reproductive Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

OBJECTIVE: A growing number of patients are referred for fertility preservation treatment (FPT) prior to gonadotoxic therapy. FPT options include embryo, oocyte and ovarian tissue cryopreservation (OTC). Our objective was to identify factors associated with FPT and fertility outcomes in women facing gonadotoxic therapies.

DESIGN: Retrospective analysis.

MATERIALS AND METHODS: We performed an analysis of 451 female ages 6-42 years old seen for FPT consultation at an academic fertility center from 2001-2017. Patients were categorized by diagnosis: breast cancer, gynecologic (Gyn) cancer, benign Gyn, leukemia/lymphoma, non-malignant anemia, other cancer and other non-cancer. We calculated proportions for patient diagnosis, demographics, type of FPT, planned treatment and assisted reproductive technology (ART) outcomes. Pearson chi-squared and Fisher’s exact tests were performed to test for associations.

RESULTS: Our cohort of 451 patients had a mean age of 29.1 ± 7.6 years, of which 54.8% (n=247) underwent FPT. Regarding type of FPT, 21.7% (n=98) chose embryo cryopreservation, 19.5% (n=88) oocyte cryopreservation, 2.8% (n=13) half oocyte/half embryo cryopreservation, 15.7% (n=39) ovarian tissue cryopreservation (OTC) and 5.3% (n=13) underwent oophorectomy or trachelectomy. Factors associated with choosing FPT included parity (p<0.005), prior chemotherapy (p=0.001), planned chemotherapy (p<0.001) and planned radiation (p=0.001). No significant differences were seen when comparing age, race or education status. There was a significant difference among diagnosis category and type of fertility preservation chosen (p<0.001). The prevalence of various diagnoses included breast cancer 27.9% (126/451), Gyn cancer 22.4% (101/451), leukemia/lymphoma 20.4% (92/451), other cancer 18.2% (82/451) and 9.1% (41/451) benign Gyn/other non-cancer. During the study period, 62 women had a total of 79 conceptions; 39 women had a total of 55 live born babies. After ART, 38 women underwent embryo transfer, with a clinical pregnancy rate of 30.3% (27/89) and a live birth rate of 23.6% (21/89) per transfer. ART outcomes were significantly different by age group, age difference between FPT visit and age of diagnosis (p<0.001), number of oocytes retrieved and number of embryos frozen (p<0.05).

CONCLUSIONS: Among patients referred for FPT prior to gonadotoxic treatment, more than half decided to move forward with FPT. Significant factors for choosing FPT included diagnosis, parity, prior and planned chemotherapy and radiation. Further work is needed to use these factors to help improve access for FPT.

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UTILIZATION AND PREDICTORS OF OVARIAN TRANSPOSITION AMONG YOUNG WOMEN WITH PELVIC MALIGNANCIES WHO UNDERGO RADIOThERAPY, J. Selter, ∗ L. Grossman Becht, ∗ K. Palmerola, ∗ E. J. Forman, ∗ Z. Williams, ∗ C. Ananth, ∗ A. Neugut, ∗ D. Hershman, ∗ J. Wright, ∗ Department of Obstetrics and Gynecology, Columbia University Medical Center, New York, NY; ∗ Department of Hematology/Oncology, Columbia University Medical Center, New York, NY.

OBJECTIVE: To determine the use and predictors of ovarian transposition in young women with pelvic malignancies treated with radiation.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: The Truven Health MarketScan database was used for analysis, which includes inpatient and outpatient medical claims from approximately 350 payers. The database captures over 50 million privately insured patients and 6 million Medicaid enrollees. Women less than 35 years of age with cervical, anorectal, or uterine cancer who underwent pelvic radiotherapy were identified from the years 2009-2016. Performance of ovarian transposition was identified using available CPT, ICD9, and ICD10 billing codes. Insurance status, sequence of radiation with cancer-directed surgery of the tumor site, year of treatment, race, and region of residence were recorded. Associations between ovarian transposition and demographic factors were analyzed using chi-squared tests and multivariable logistic regression models.

RESULTS: A total of 828 women including 587 (70.9%) with cervical cancer, 141 (17.0%) with anorectal cancer, and 100 (12.1%) with uterine cancer who underwent pelvic radiation were identified. The overall rate of ovarian transposition was 6.9% and varied from 8.2% for cervical cancer versus 5.0% for anorectal cancer versus 2.0% for uterine cancer (P=0.048). Transposition was performed in 9.6% of women with commercial insurance versus 3.5% of those with Medicaid (P <0.001). Women who underwent cancer-directed surgery prior to radiation were more likely to undergo transposition than women who underwent radiation prior to cancer-directed surgery or those who did not undergo primary tumor resection (12.7% vs. 3.6% vs. 4.5%, P <0.001). In multivariable analysis, patients with cervical cancer (OR=7.6; 95% CI 1.8-32.3), those with commercial insurance (OR=2.8; 95% CI 1.4-5.7), and those who underwent cancer-directed surgery prior to radiation (OR=2.8; 95% CI 1.6-6.5) were more likely to undergo ovarian transposition. There was no association between race, region, or year of treatment and performance of transposition.

CONCLUSIONS: Ovarian transposition was performed in a minority of women with pelvic malignancies who received radiotherapy. Not only are there clear medical benefits for preservation of ovarian function, but studies have shown that reproductive function remains a major concern among young cancer patients and that reproductive services are consistently underutilized (1). These data highlight the importance of need to raise awareness of the sequelae of ovarian failure and the benefits of ovarian transposition.

References:
ASSESSMENT OF KNOWLEDGE REGARDING ELECTIVE OOCYTE CRYOPRESERVATION AMONGST HEALTHCARE PROFESSIONALS IN TRAINING. P. Aaalami-Harandi,a N. Amirilatifia, D. Akionda, E. Holden,b P. McGovern,b A. Fechner. aOB/GYN, St Joseph’s University Medical Center, Paterson, NJ; bOB/GYN, New Jersey Medical School, Newark, NJ.

OBJECTIVE: To assess physician trainee knowledge of and attitude towards elective oocyte cryopreservation.

DESIGN: Survey study.

MATERIALS AND METHODS: A survey was created to assess knowledge of and attitudes towards elective oocyte cryopreservation among female and male medical students, residents and fellows. This 19-question survey was distributed to trainees in various specialties in an inner-city hospital. Our aim was to assess their basic knowledge of egg freezing, assess their family planning goals, and determine whether they had concerns about delaying childbearing and ovarian aging.

RESULTS: One-hundred fifty three respondents completed the survey, of which 43% were female and 57% were male. The average age was 29 years old, and the level of medical education was: 36% medical students, 61% residents, and 2% fellows. Thirty-one percent were married, 30% in a relationship, 37% were single, and 1.3% were divorced. The majority of respondents (87%) had no children. Most plan to have children (80%), but nearly half plan to wait until after training (43%). Despite the impact of advancing age on fertility, 34% stated they weren’t concerned about delaying childbearing while 21% ‘haven’t thought about it.” Although 84% of respondents have heard of egg freezing, most have not considered it (71%), and the majority of those surveyed overestimated the cost (68%). Fewer than half of respondents knew that eggs can be stored indefinitely (46%), while 67% overestimated the chance of success per frozen egg. Half of respondents recognized that the recommendation is to store at least 15 eggs. Fifty-four percent of respondents properly estimated the chance of natural conception per cycle, however 81% underestimated the risk of embryo aneuploidy. Thirty-one percent of females plan to delay childbearing until after training (60%), whereas men plan to have children during medical training or when ready, regardless of training status (60%). When asked whether they had concerns over delaying childbearing, fifty-five percent of women responded affirmatively, while only 34% of men had similar concerns.

CONCLUSIONS: Medical trainees have some understanding that delaying childbearing could adversely impact their ability to conceive. Despite this realization, however, most have not considered egg freezing. This may be due in part to their overestimation of the cost and their underestimation of the length of time eggs can be stored. The fact that respondents overestimated the chance of success per oocyte and underestimated the risk of aneuploidy with advancing age may explain why they have not considered this option, as they may not appreciate the full impact of age on fertility. As reproductive endocrinologists, we must do a better job educating trainees about the potential impact of delayed childbearing as well as the option for egg freezing.

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THE EFFECTS OF MOUSE AGING ON IN VITRO OVARIAN FOLLICLE DEVELOPMENT AND OOCYTE COMPETENCE. E. Kim,a H. Youn,a S. Kim,a J. Lee,a C. Suh,a S. Kim,a Department of Obstetrics and Gynecology, Seoul National University Bundang Hospital, Gyeonggi-do, Korea, Republic of; bDepartment of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, Korea, Republic of; cDepartment of Obstetrics and Gynecology, Seoul National University Hospital, Seoul, Korea, Republic of.

OBJECTIVE: The objective of this study is to evaluate the effects of mouse aging on in vitro follicle growth and oocyte competency.

DESIGN: Experimental animal study.

MATERIALS AND METHODS: Ovaries were collected from BDF-1 mice of age 11-days (young-age group), 7-weeks (reproductive group) and 22-weeks (old-age group) and mechanically dissected to isolate secondary follicles. Collected follicles were in vitro cultured for 10 days and ovulation was induced on day 10. To assess the growth of individual follicles, follicular survival rate and mean follicle diameter were measured. Following ovulation induction, oocytes were collected and analyzed for mature oocyte rate, normal spindle and chromosome rate, mitochondrial membrane potential (MMP) level and reactive oxygen species (ROS) level. For control, mature oocytes were obtained from 6 weeks-old mice by superovulation.

RESULTS: On day 10, the survival rate was statistically higher in prepuberual and reproductive groups than old-age group (94.3%, 94.5% and 86.0% respectively). Mean follicle diameter on day 10 was significantly higher in the prepuberual group than others. The prepuberual group showed significantly improved mature oocyte rate than others (50.9%, 34.6% and 15.4% in prepuberual, reproductive and old-age groups, respectively). In normal oocyte spindle rate, prepuberual and reproductive groups showed no statistical difference with in vivo control group. MMP in oocyte was significantly higher in prepuberual and reproductive groups (925.18 ± 47.41 and 903.94 ± 74.49, respectively) than old-age group (595.88 ± 36.30). Prepuberual group results significantly reduced ROS level in oocyte than old-age group (1338.42 ± 51.28 and 1871.21 ± 210.34 respectively). The reproductive group showed significantly improved results in mature oocyte rate and MMP in oocyte than the old-age group, however, there is no significant difference in other results.

CONCLUSIONS: The ovarian follicles from prepuberual mice showed superior results in in vitro growth and oocyte competency than follicles from reproductive and old-age mice. Base on the results, aging of mouse results in not only inadequate follicle development but also improper cellular activity and maturation in the oocyte.

Supported by: This study was supported by a grant of the Korea Healthcare Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI12C0055) and National Research Foundation of Korea (NRF-2017R1C1B203897).

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VARIABLE ASPECTS OF OOCYTE FREEZE PRESERVATION OUTCOMES WARRANT CONTINUED INVESTIGATION. R. vanTol,a J. B. Whitney,a S. Zorozla,b R. E. Anderson,c M. C. Schiewe,c ART Lab, Ovation Fertility, Newport Beach, CA; dOvation Fertility, Newport Beach, CA; eSCCRM, Ovation Fertility, Newport Beach, CA.

OBJECTIVE: A RCT of 15 donor egg freeze cycles previously showed that microSecure vitrification (μSVTF) without DMSO effectively produced good survival, fertilization and live birth outcomes (87%, 81% and 47%, respectively), but inconsistently yielded blastocysts (BLs) with 4 of 15 oocyte batches failing to generate a BL(1). The aim of this study was to contrast the developmental incompetence of vitrified-warmed oocytes to fresh controls, and to further show that problems in BL development do not correlate to the type of VTF device method (open or closed) or solution (VS) used.

DESIGN: Retrospective cohort analysis.

MATERIALS AND METHODS: Our 2014-2018 autologous oocyte warming-ET cycles were contrast to fresh cycles (2015-2017). Fertilization, BL production, euploidy, and pregnancy rates of 30 freeze preservation patients (n=439 vitrified oocytes) were statistically compared to 649 fresh cycles (n=9398 oocytes). Furthermore, we assessed our control μSVTF/DMSO-free VS method (n=21 cycles,330 eggs) to conventional open VTF/EG-DMSO system (n=9 cycles,109 eggs) outcomes, focusing on different BL development. All human oocytes were vitrified/warmed using standardized protocols. All oocytes were ICSI’ed 2-3h post-warming or 2-6h post-retrieval, and cultured in Life Global medium+7.5% LGPS under tri-gas, humidified incubation (37°C) up to Day 7. Blastocysts underwent ET, biopsy/PGS and/or VTF/ET. Statistical differences were determined by Chi-squared analysis (p<0.05).

RESULTS: Control μSVTF eggs survived (88%) better than open VTF devices (67%; p<0.05), while fertilization and cleavage rates were similar. Although, BL formation tended to be higher in DMSO/EG (40%) than EG only (31%), both were lower (p<0.05) than fresh egg-derived. Vitrified eggs had slower growing BL on Day 5 (4%vs.23%) and Day 6 (18% vs.34%), and more failed BL cycles than fresh eggs. Once BL formed, euploidy and live birth rates were comparable.

<table>
<thead>
<tr>
<th>Oocyte / Cycle Type</th>
<th>Vitrified-warmed</th>
<th>Fresh</th>
</tr>
</thead>
<tbody>
<tr>
<td>#Pts / # with PGS</td>
<td>30 / 19</td>
<td>649 / 649</td>
</tr>
<tr>
<td>Mean Age (+/-SD; yr)</td>
<td>35 (4.6)</td>
<td>37.3 (4.3)</td>
</tr>
<tr>
<td>#Mat. Oocytes</td>
<td>439</td>
<td>7733</td>
</tr>
<tr>
<td>Fert. Rate #2PN%</td>
<td>253 (70%)</td>
<td>5916 (77%)*</td>
</tr>
<tr>
<td>BL Rate:Day 5-7 # (%)</td>
<td>83 (33%)</td>
<td>5170 (54%)*</td>
</tr>
<tr>
<td>Oocyte:BL:LRB # (%)</td>
<td>9 of 14 (65%)</td>
<td>259 of 365 (71%)*</td>
</tr>
<tr>
<td>Pts. w/ &gt;2BL # (%)</td>
<td>21 (70%)</td>
<td>501 (77%)*</td>
</tr>
<tr>
<td>Pts. w/o BL: # (%)</td>
<td>6 (20%)</td>
<td>62 (10%)*</td>
</tr>
<tr>
<td>Avg. #MII to yield 2BL</td>
<td>17.1</td>
<td>13.3</td>
</tr>
</tbody>
</table>
CONCLUSIONS: Vitrified oocyte-derived BLs can produce genetically normal, healthy live birth outcomes. However, our clinical analysis of autologous oocyte freeze preservation cycles revealed a continued pattern of developmental incompetence problems with a 2-fold increase in egg batches failing to produce a BL. Additionally, overall BL growth was delayed and reduced, supporting our hypothesis that frozen eggs are not the same as fresh likely due to poorly understood cytosolic factors, independent of VTF method or US used. Clearly, elective egg VTF should still be approached as “experimental.”

References:

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IS OVARian RESERVE AND REPRODUCTIVE OUTCOME COMPROMISED IN BREAST CANCER PATIENTS? EXPERIENCE IN 1000 WOMEN UNDERGOING FERTILITY PRESERVATION (FP). A. Cobo,1,2 A. Coello,6 A. Pellicer,7 J. Remohi,1 A. J. Garcia-Velasco,8 J. Domingo.1,9 (1)VI-Valencia, Valencia, Spain; (2)IVIRMA Valencia, Valencia, Spain; (3)Profesor of Obstetrics and Gynecology, University Medical School, Valencia, Valencia, Spain; (4)Valencia:Professor of Obstetrics and Gynecology, University Medical School, Valencia, Valencia, Spain; (5)Reproductive Endocrinology & Fertility, Madrid, Spain; (6)IVI-Las Palmas, Las Palmas, Spain.

OBJECTIVE: To evaluate the results of controlled ovarian stimulation (COS) in women diagnosed with breast cancer versus women diagnosed with other types of cancer, and the reproductive outcomes in those who have returned to use their oocytes.

DESIGN: Retrospective analysis.

MATERIALS AND METHODS: 1003 cancer patients (N=1070 cycles) undergoing FP treatment were included. Among them, 642 patients (N=688 cycles) were affected by breast cancer (group 1) and 361 (N=382 cycles) suffered from other types of cancer (group 2). Reproductive outcomes were evaluated in 47 and 24 women who returned to use their oocytes in groups 1 and 2 respectively. Outcomes were compared by T test or chi-square as appropriate. Significance was set as P<0.05.

RESULTS: Age at vitrification was 34.1±4.1 and 28.8±6.2 years in group 1 vs group 2 (P<0.05). Letrozole protocol was used for COS in 94.5% of breast CA patients and in 9.6% of patients in group 2 (P<0.05). Antagonist protocol was used in 5.5% and 85.7% of groups 1 and 2 respectively (P<0.05). Clomiphene and agonist protocols were used in 3.1% and 1.6% of the remaining patients in group 2. Length of COS was comparable (10.6±2.9 vs 10.6±2.5 days; NS). Mean dose of FSH was (1835.5±614.1 vs 1560.8±633.8 IU) (P<0.05). Mean dose of hCG and LH were comparable. Mean E2 level (pg/ml) was significantly lower (P<0.05) in group 1 (390.2±194.5) vs group 2 (1299.7±425.7). Measured (11.1±8.2 vs 12.7±9.4) and vitrified (8.5±6.6 vs 9.7±7.5) oocytes were significantly lower in group 1 vs group 2 (P<0.05). Oocytes survival rate was comparable (82.3% vs. 83.3% respectively; NS). Mean inanuminiated sex (5.5±3 vs 7.7±3.4) and fertilized (4.2±2.5 vs 5.5±3.2) oocytes were lower in group 1 vs 2 (P<0.05). Implantation (31.8% vs 41.6%), clinical (42.5% vs 56.3%) and ongoing pregnancy (32.5% vs 43.8%) rates were lower in group 1, although no statistical differences were observed (NS). A total of 17 and 8 babies are born to date.

CONCLUSIONS: Low ovarian reserve and the compromise of reproductive outcome may be suggested for breast cancer patients, although the limited sample size makes the results inconclusive. Analysis of the data, as the number of returning patients continues to grow, is necessary for further confirmation of these observations.

Oocyte cryopreservation outcomes in children

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Diagnosis</th>
<th>AMH (ng/mL)</th>
<th>FSH</th>
<th>AFC</th>
<th>Oocytes cryopreserved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>45XO/ 47XXX</td>
<td>1.59</td>
<td>5.7</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>45XO/ 46XX</td>
<td>0.9/1.7</td>
<td>5.3</td>
<td>12</td>
<td>117*</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>45XO/ 46 XX</td>
<td>0.76</td>
<td>5.6</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>45XO/46XX</td>
<td>5.6</td>
<td>5.8</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>Germ Cell Tum</td>
<td>1.6</td>
<td>5.6</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>ALL</td>
<td>1.3</td>
<td>7.8</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>45XO/ 46XX</td>
<td>2.06</td>
<td>5.4</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>Non-Hodgkin</td>
<td>0.98</td>
<td>4.1</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>9</td>
<td>16</td>
<td>Autoimmune</td>
<td>0.05</td>
<td>77.6</td>
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<td>1</td>
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<tr>
<td>10</td>
<td>14</td>
<td>45XO/46XX</td>
<td>1.5</td>
<td>6.8</td>
<td>10</td>
<td>9/8*</td>
</tr>
</tbody>
</table>

Ovarian tissue cryopreservation was performed in 22 girls (age range: 2-18 years). Of those, 2 subsequently underwent ovarian transplantation as adults and their ovarian function was restored.

CONCLUSIONS: Fertility preservation is feasible in most children at risk for ovarian insufficiency. To maximize success, early referral to a reproductive specialist should be encouraged.

FERTILITY & STERILITY®

References:

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RESCUE OF AGE-RELATED DECLINE IN FERTILITY OF FEMALE MICE AGED 18 MONTHS BY VISFATIN. K. Lee,1,2 S. Han,2 K. Yun,b B. Park,1 M. Park,1 B. Joo, b J. Joo.1 (1)Obstetrics and Gynecology, Pusan National University School of Medicine, Busan, Korea, Republic of; (2)Obstetrics and Gynecology, Pusan National University Hospital, Busan, Korea, Republic of. Supported by: National Research Foundation of Korea (2016R1A2B4007599).

OBJECTIVE: To examine whether visfatin rescues age-related decline in fertility of 18-months-old female mice, and further investigate whether the
effect of visfatin is related to the mTOR/P3K and Hippo signaling pathway for the activation of primordial follicles and ovarian germline stem cells, and ovarian angiogenesis.

DESIGN: Conducted experimental study.

MATERIALS AND METHODS: Female mice were intraperitoneally injected with 0.1 ml of 500ng/ml or 1,000ng/ml of recombinant mouse visfatin three times at intervals of 2 days. The control group was not treated with visfatin. In the first experiment, the day after the last injection of visfatin, the mice were superovulated with 5 IU pregnant mare’s serum gonadotropin and 5 IU human chorionic gonadotropin injection 48 hours later. Then the mice were immediately mated with an individual male. After 18 hours zygotes were collected and cultured for 4 days. Immediately after zygote retrieval, ovarian tissues were removed and the expression of mTOR/P3K and Hippo signaling pathway-associated components, ovarian stem cell marker, and angiogenic factors were examined by real-time PCR. In the second experiment, visfatin-administered mice were superovulated and were mated with male for 2 weeks and then the pregnancy outcome was monitored up to 20 days. Number of zygotes retrieved, embryo developmental competency, fertility potential, ovarian expression of stem cell marker (oct4), Hippo signaling pathway component (MST1) and mTOR/P3K signaling pathway components (4EBP1, S6K1, and RPS6), and angiogenic factors (VEGF, visfatin, and SDF-1α).

RESULTS: Visfatin treatment of 500ng/ml significantly increased the number of zygotes retrieved (mean 2.33 and 1.66), embryo developmental rate to the blastocyst (42.8% and 33.8%), pregnancy rate (100% s) and the number of fetuses per pregnant mice (2.33) compared to 100ng/ml visfatin treatment group (1.66 zygotes, 33.8% blastocyst development rate, no pregnancy). In the control group, there were no zygotes retrieved and pregnancy. Visfatin treatment of 500ng/ml significantly increased the expressions of MST, S6K1, and RPS6 as well as the expression of VEGF, visfatin, and SDF-1α in ovarian tissues.

CONCLUSIONS: These results suggest that visfatin treatment of an optimal dose induces the stimulation of ovarian angiogenesis and signaling pathways for the activation of primordial follicles and ovarian stem cells, and can recover age-related decline in fertility in old female mice aged 18 months.

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PATHWAYS: A FERTILITY PRESERVATION PATIENT DECISION AID WEBSITE FOR WOMEN WITH CANCER - EFFICACY AND FEASIBILITY OF DISSEMINATION PRIOR TO ONCOFERTILITY CONSULTATIONS. S. Campbell, A. Hoffman, J. Weston, L. Crocker, D. Holman, A. Housten, G. Chisholm, J. Ma, R. Bassett, R. Volk, T. Woodard. 1Reproductive Endocrinology and Infertility, Baylor College of Medicine, Houston, TX; 2Health Services Research, University of Texas MD Anderson Medical Center, Houston, TX; 3Gynecologic Oncology and Reproductive Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX; 4Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, TX; 5Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX.

OBJECTIVE: Although the American Society of Clinical Oncology guidelines recommend that all women of reproductive age with cancer be offered fertility counseling, only 12.2% of eligible women receive it and long-term regret remains high.[1] Challenges persist in providing women with valid information about fertility preservation and decision support during the brief, complex time between diagnosis and treatment. We previously developed Pathways: a fertility preservation patient decision aid website for women with cancer. This study tested its efficacy at improving knowledge and MATTERing decision conflict as well as feasibility of delivery prior to a fertility consultation.

DESIGN: Pre/post-interventional study at a comprehensive cancer center.

MATERIALS AND METHODS: The research team and stakeholder panel previously co-designed and pilot-tested the Pathways website. Women who were 18 to 45 years-old, comfortable with English, and scheduled for a fertility preservation consultation following a new diagnosis of various malignancies were recruited. Women were offered Pathways pre-consultation, and asked to complete baseline, post-decision aid and post-consultation questionnaires assessing their fertility preservation knowledge, decisional conflict, and perceptions of the website. Analyses summarized the rates of successful delivery/viewing, and mean scores at each time point.

RESULTS: As of the time of submission, the study coordinator has reached 26 of 31 eligible women (including 15 with same/next day appointments), and 18 women were able to complete Pathways prior to their consultation. Women’s knowledge improved from baseline to post-decision aid to post-consultation (mean 55%, 63%, and 71% correct responses to 13 items, as did decisional conflict (mean 49, 26.1, and 27.2 out of 100). After viewing Pathways, women felt prepared (mean 88 out of 100) and reported positive self-efficacy (mean 78 out of 100). All women were Mostly/Very Satisfied with their decision-making process and would recommend Pathways to other women with cancer.

CONCLUSIONS: Pathways decision aid improves women’s fertility preservation knowledge and decision-making process. Dissemination remains a challenge; upstream delivery routes (e.g. post-diagnostic consultation) may be needed for large-scale implementation to meet guidelines. Pathways may be an important tool in improving the quality of decisions, patient-centered care planning, and long-term survivorship of women with cancer.


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INFLUENCE OF BREAST CANCER PROGNOSTIC FACTORS ON IN-VITRO MATURATION OUTCOMES IN PATIENTS SEEKING URGENT FERTILITY PRESERVATION. L. Raad, C. Sonigo, N. Sermonda, F. Zeghari, C. Sifér, M. Gryneguy. 1Department of Reproductive Medicine and Fertility Preservation, Hôpital Antoine-Béclère, Clamart, France; 2Department of Reproductive Medicine, Hôpital Kremlin-Bicêtre, Le Kremlin-Bicêtre, France; 3Inserm U1185, Le Kremlin Bicêtre, France; 4Department of Cytogentic and Reproductive Biology, Hôpital Tenon, Paris, France; 5Department of Reproductive Medicine and Fertility Preservation, Hôpital Jean-Verdier, Bondy, France; 6Department of Cytogenetic and Reproductive Biology, Hôpital Jean-Verdier, Bondy, France; 7Hôpital Antoine Beclere, Clamart, France.

OBJECTIVE: To study the influence of prognostic and predictive factors for breast cancer (BC) on in-vitro maturation of immature oocytes (IVM) outcomes, in patients seeking urgent fertility preservation.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: From November 2013 to December 2016, data of 321 BC patients were prospectively studied. Patients were aged 18-41 years, and underwent oocyte cryopreservation following IVM. Number of oocytes recovered, maturation rate and total number of cryopreserved oocytes were assessed. Ovarian reserve markers (Antral-Follicle Count (AFC) and serum Anti-Müllerian Hormone (AMH) levels) and IVF outcomes were compared between women with BC prognostic factors (Ki67>20%, progesterone and/or estrogen receptors status, HER2 status and SBR grade). Then, logistic regression analysis was performed to determine the variables that could be independently associated with poor IVM outcomes determined as maturation rate <60% or number of oocytes cryopreserved <5.

RESULTS: Overall, the mean age of the population was 32.3±4.1 years. Mean AFC and serum AMH levels were 22.8±13.9 follicles and 3.8±3.1 ng/ml respectively. AMH levels were significantly lower in case of triple-negative BC when compared to ER/PR/HER2 positive cancers (3.1±2.6 ng/ml vs. 4.0±3.3 ng/ml, p = 0.02). The mean number of oocytes recovered was 10.2±9.1. After a mean maturation rate of 58±26.1%, 5.8±5.3 mature oocytes were vitrified per cycle. The number of retrieved and cryopreserved oocytes were significantly decreased in patients presenting SBRIII tumor when compared with SBRI or II (9.6±8.7 vs. 11.7±9.8, p = 0.02 and 5.4±5.4 vs. 6.5±6.5, p = 0.02 respectively, vs. SBRII). Multivariate statistical analysis showed that HER2 positive status was positively correlated with a mean maturation rate <60% (OR: 0.54; 95% CI (0.30-0.97)). However, Ki67, SBR classification or hormonal status were failed to be related with poor IVM outcomes.

CONCLUSIONS: BC prognostic factors may impact IVM outcome. Our findings revealed that HER2 status was correlated with IVM rate, providing additional biological value to the already hypothesized role of this peptide in the oocyte maturation process. Further investigations are needed to better understand the precise mechanisms at play and further the possible impact after thawing.
EFFICIENCY OF ELECTIVE OOCYTE VITRIFICATION FOR REPRODUCTIVE AGING WOMEN SEEKING FERTILITY PRESERVATION TO DELAY MOTHERHOOD. T. W. Schlenker, S. McCormick, R. Smith, C. Pospisil, W. B. Schoolcraft, M. Katz-Jaffe. Colorado Center for Reproductive Medicine, Lone Tree, CO.

OBJECTIVE: There is an increasing demand for fertility preservation for women who wish to delay motherhood for a variety of non-medical reasons. The efficiency and safety of oocyte vitrification allows women the opportunity to conceive in the future with their own genetic offspring. The aim of this study was to analyze the efficacy of oocyte vitrification techniques in preserving female fertility for reproductive aging women.

DESIGN: Retrospective matched cohort study.

MATERIALS AND METHODS: Female patients (n=98) that underwent an elective autologous oocyte vitrification cycle for fertility preservation (mean maternal age = 37±4.39 years) and returned to undergo in vitro fertilization (IVF) at a later date, were directly compared to maternally aged-matched female patients that underwent IVF using fresh autologous oocytes. Mature oocytes were vitrified using the Cryotop method following standard controlled ovarian stimulation. All normally fertilized embryos were cultured to the blastocyst stage prior to embryo vitrification. Statistical analysis included Students t-test and Fishers exact test where appropriate, significance at P<0.05.

RESULTS: Fertility preservation patients (n=98) returned for an oocyte warming cycle at a mean maternal age of 40.7±4.6 years, representing on average, three years and three months after oocyte vitrification; IVF outcomes with vitrified oocytes were significantly reduced compared to maternally age-matched infertility patients utilizing fresh autologous oocytes (Table 1). Nevertheless, 84% of oocytes survived vitrification resulting in 3.8 usable blastocysts per elective fertility preservation patient (Table 1). To date, there have been 72 frozen embryo transfers from these vitrified oocytes that have resulted in a respectable 51.4% live birth rate. Even though this clinical outcome is reduced compared to FETs with fresh oocytes, 76.4% of the fertility preservation cycles underwent preimplantation genetic testing for aneuploidy (PGT-A) (Table 1).

CONCLUSIONS: In conclusion, women in their mid-late thirties seeking elective oocyte vitrification for fertility preservation can expect good IVF outcomes when they return in their early forties. Although these outcomes are lower than if they had utilized their own fresh oocytes at the time of oocyte vitrification, they can be presumed to be higher than if they had initiated treatment in their early forties without fertility preservation.

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<tr>
<td>Mean # oocytes survived post warm (%)</td>
<td>N/A</td>
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</tr>
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<td>Mean # oocytes fertilized</td>
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<td>8.9±5.8*</td>
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<td>Mean # usable blastocysts (%)</td>
<td>6.2 (57%)</td>
<td>3.8 (39%)*</td>
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<tr>
<td>Live birth rate (%)</td>
<td>67.7%</td>
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<td>100%</td>
<td>76.4%</td>
</tr>
</tbody>
</table>

*P<0.05

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DOES THE PRESENCE OF AN INTRATERINE DEVICE DURING OVARIAN STIMULATION IMPACT OOCYTE YIELD? P. Ghosh, a N. Pereira, a I. Kligman, a Z. Rosenwaks, a Obstetrics and Gynecology, Weill Cornell Medicine, New York, NY; aThe Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medical College, New York, NY.

OBJECTIVE: Intra-uterine devices (IUDs) have become an increasingly popular method of contraception in young women. The latest available data indicate that of the 11.6% of U.S. women who rely on long-acting reversible contraception, 10.3% use IUDs. Young women with IUDs often serve as oocyte donors or choose to undergo elective cryopreservation of oocytes. Thus, this study investigates whether the presence of an IUD during ovarian stimulation impacts oocyte yield in oocyte donors or in women undergoing elective cryopreservation of oocytes.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: Women <35 years old undergoing ovarian stimulation between 2012 and 2016 for oocyte donation or elective cryopreservation of oocytes with normal ovarian reserve parameters were assessed for potential inclusion. Women with a known history of poor ovarian reserve (AMH<1, FSH >12, or AFC<5), PCOS, endometriosis, or oophorectomy were excluded. The type of IUD (Copper (Cu) or Levonorgestrel (LNG)) was also noted. Twenty age-matched cycles in women without IUDs undergoing oocyte donation or elective cryopreservation of oocytes were selected randomly for each cycle with an IUD. Randomization was carried out using the random number generator function in Microsoft Excel. Ovarian response parameters recorded were duration of ovarian stimulation, total gonadotropins administered, peak estradiol (E2) levels, and total oocytes retrieved (primary outcome). A multivariate regression model was constructed for the primary outcome, while controlling for confounders of interest.

RESULTS: A total of 33 ovarian stimulation cycles with IUDs were identified: 25 for oocyte donation and 8 for elective cryopreservation of oocytes. Of these cycles, 21 and 12 were with Cu and LNG IUDs, respectively. A total of 660 control cycles were identified. There were no differences in the mean (26.4 vs. 26.7 years) or body mass index (22.1 vs. 21.9 kg/m²) of women with and without IUDs. Although the duration of ovarian stimulation (10±1.6 vs. 10±1.1 days) and peak E2 level (3342±950 vs. 3106±845 pg/mL) was comparable, the total amount of gonadotropins administered was higher in the IUD group compared to controls (2269±1141 vs. 2210±1055 units; P=0.01). The number of total oocytes (19.5±7.0 vs. 19.7±7.2), mature oocytes (16.1±5.8 vs. 16.6±5.9) and fertilization rates (81.4% vs. 79.9%) were similar between women with and without IUDs, respectively. Multivariate regression confirmed the similar yield of mature oocytes when controlling for age, body mass index, duration of ovarian stimulation and gonadotropins administered (co-efficient -0.25; 95 CI -0.61,0.32; P=0.49).

CONCLUSIONS: The results of this study suggest that the presence of an IUD during ovarian stimulation does not adversely impact oocyte yield in oocyte donors or in women undergoing elective cryopreservation of oocytes.

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ASSOCATION BETWEEN CYTOLAPMATIC GRANULARITY OF OOCYTES AND AGE IN PATIENTS UNDERGOING ELECTIVE OOCYTE CRYOPRESERVATION. M. Toledo, a B. Heifetz Ament, a A. Adler, a B. L. Maslow, a J. U. Klein, a U. L. Franca, a L. B. Ramirez. aEx- tend Fertility, New York, NY; aBoston Children’s Hospital / Harvard Medical School, Boston, MA.

OBJECTIVE: Centrally localized cytoplasmic granularity (CLCG) is an intracytoplasmic abnormality characterized by a dark, spongy-like granular appearance in the center of the oocyte. While several studies have investigated the association of CLCG with the quality of oocytes retrieved from patients during infertility treatments, elective oocyte cryopreservation (EOC) cycles provide a unique opportunity to understand the frequency and impact of CLCG in a different population. The purpose of this study was to assess the CLCG rates in a cohort of patients undergoing EOC treatments and the association between CLCG and patient age.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: CLCG of 5.318 metaphase II (MII) oocytes obtained from 422 oocyte cryopreservation cycles from 05/2017 to 04/01/2018 with a minimum of 5 MII oocytes were analyzed. Cycles were classified according to the percentage of MII oocytes with CLCG in the cohort of each retrieval: no CLCG (Grade 0), low CLCG (Grade 1; 1 to 25% MII oocytes with CLCG), intermediate CLCG (Grade 2; 26 to 50% MII oocytes with CLCG), high CLCG (Grade 3; 51 to 75% MII oocytes with CLCG), and severe CLCG (Grade 4; 76 to 100% MII oocytes with CLCG). Patients were grouped into four age categories: <35, 35-36, 37-38, and >38 years. Frequencies of CLCG grades in each age group were compared using Monte Carlo resampling and CLCG percentage comparisons were assessed using Kruskal-Wallis H test. P<0.05 was considered statistically significant.

RESULTS: Approximately three-fourths (n = 322, 75.8%) of the cycles presented no to low CLCG. The median percentage of MII oocytes with CLCG was higher in cycles of patients >38 years (22.2 [IQR: 9.2 - 42.9])

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REVERSIBLE CONTRACEPTION: IUD VERSUS CLOREXARDYN. R. Smith, C. Pospisil, W. B. Schoolcraft, M. Katz-Jaffe. Colorado Center for Reproductive Medicine, Lone Tree, CO.

OBJECTIVE: There is an increasing demand for reversible contraception for women with IUDs undergoing oocyte donation or elective cryopreservation of oocytes. They can be presumed to be higher than if they had utilized their own fresh oocytes at the time of ovarian stimulation. However, age-matched infertility patients utilizing fresh autologous oocytes (Table 1). Nevertheless, 84% of oocytes survived vitrification resulting in 3.8 usable blastocysts per elective fertility preservation patient (Table 1). To date, there have been 72 frozen embryo transfers from these vitrified oocytes that have resulted in a respectable 51.4% live birth rate. Even though this clinical outcome is reduced compared to FETs with fresh oocytes, only 76.4% of the fertility preservation cycles underwent preimplantation genetic testing for aneuploidy (PGT-A) (Table 1).

CONCLUSIONS: In conclusion, women in their mid-late thirties seeking elective oocyte vitrification for fertility preservation can expect good IVF outcomes when they return in their early forties. Although these outcomes are lower than if they had utilized their own fresh oocytes at the time of oocyte vitrification, they can be presumed to be higher than if they had initiated treatment in their early forties without fertility preservation.

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</tr>
</tbody>
</table>

*P<0.05
Cycles in each CLCG grade for each age group (%).

<table>
<thead>
<tr>
<th>CLCG Grade</th>
<th>No CLCG (Group 0)</th>
<th>Low CLCG (Group 1)</th>
<th>Intermediate CLCG (Group 2)</th>
<th>High CLCG (Group 3)</th>
<th>Severe CLCG (Group 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35 years</td>
<td>26.2</td>
<td>53.2</td>
<td>12.7</td>
<td>4.8</td>
<td>3.2</td>
</tr>
<tr>
<td>35-36 years</td>
<td>27.7</td>
<td>53.6</td>
<td>13.4</td>
<td>4.5</td>
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<td>37-38 years</td>
<td>30.6</td>
<td>46.8</td>
<td>14.5</td>
<td>4.8</td>
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<td>&gt;38 years</td>
<td>22.2</td>
<td>33.3</td>
<td>23.8</td>
<td>15.9</td>
<td>4.8</td>
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OVARIAN RESERVE TESTS ARE ASSOCIATED WITH THE NUMBER OF OOCYTES MATURED IN VITRO AND WITH THE PRIMORDIAL FOLLICLE DENSITY IN A POPULATION OF CANDIDATES FOR FERTILITY PRESERVATION. N. Sermondade, C. Sonigo, C. Sifer, J. Raad, M. Gryenberg, Reproductive Biology; Jean Verdier University Hospital, Bondy, France; Inserm U1185, Le Kremlin Bicêtre, France; IVF Unit Jean Verdier, Bondy, France; Gynecologist Obstetrician - Reproductive Medicine, Clamart, France; Hospital Antoine Beclere, Clamart, France.

OBJECTIVE: Oocyte vitrification after in vitro maturation (IVM) and ovarian tissue cryopreservation may constitute alternative options for fertility preservation (FP). Since both techniques are considered experimental, their combination might increase the overall success rate. Antral follicle count (AFC) and serum anti-Müllerian hormone (AMH) levels are commonly used for oncofertility counselling because providing information regarding the number of expected oocytes. Our study aimed to evaluate the relationship between ovarian reserve markers, number of oocytes cryopreserved after IVM and primordial follicle density within ovarian tissue in a population of young adult women undergoing urgent FP.

DESIGN: Prospective study.

MATERIALS AND METHODS: From July 2013 to December 2016, we prospectively studied 67 patients, 18 to 39 years of age, presenting breast cancer (n=61), lymphoma (n=4) or other indication (n=2). Median AFC and AMH levels were 12 follicles and 1.7 ng/mL, respectively. Cumulus-oocyte complexes were recovered under ultrasound guidance, matured oocytes were vitrified. Ovarian tissue was lapa- roscopically harvested and cryopreserved. For each patient, at least one fresh sample of cortex was processed for pathological analysis, including primordial follicle density assessment.

RESULTS: AFC and AMH levels were strongly correlated with the number of COC (r=0.65 and 0.63 for AFC and AMH, respectively, p<0.0001), and with the number of in vitro matured oocytes (r=0.56 and 0.51 for AFC and AMH, respectively, p<0.0001). A significant correlation was also found between primordial follicle density and the number of COC and in vitro matured oocytes (r=0.37 and 0.32 for COC and mature oocytes, p<0.003 and 0.008, respectively).

CONCLUSIONS: Although presenting limits, our findings suggest that, if AFC and AMH predict a poor to “normal-low” ovarian reserve, only the number of retrieved oocytes for IVM will be low, but the primordial follicle density within the frozen samples of ovarian cortex will also be poor, possibly leading to suboptimal efficiency of the further transplantation.

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OBJECTIVE: Patients with cancer may overestimate FP success rates. PGT-A aids in embryo selection and may provide a more accurate picture of future reproductive potential among banked embryos. We investigated the use of PGT-A among patients undergoing EB cycles for FP prior to cancer treatment.


MATERIALS AND METHODS: Analysis of medical EB cycles performed in patients with cancer. PGT-A performed using trophectoderm biopsy with aCGH or NGS. Exclusive oocyte cryopreservation cycles were excluded. Data analyzed using student’s T-test, chi square, and Fishers Exact test (mean ± SD, p<0.05).

RESULTS: 58 medical EB cycles were identified and compared: 34 cycles (59%) utilized PGT-A, 67% of patients banking embryos for breast cancer (18/27) utilized PGT-A; patients with lymphoma, endometrial ca, ovarian ca, and other cancers were evenly divided between PGT-A and no-PGT. PGT-A utilization increased over the study period. PGT-A and no-PGT groups were similar when comparing age (y) at FP cycle start (34.2±4 vs 35.5±6), days of stimulation (11.8±2 vs 11.1±2), days from initial FP consultation to initiation of cancer treatment (36.9±26 vs 36.4±28), and timing of EB cycle start including day-2 or random-start protocol (p>0.05). Equal patients in each group cryopreserved both oocytes and embryos (n=5 PGT-A vs n=3 no-PGT). Groups were similar in no. oocytes retrieved (19 ±15 vs 17.5 ±14), 2PN zygotes (10.7 ±9 vs 10 ±9), and blastocysts (7.2 ±7 vs 6.7 ±5) excluding 6 patients in the no-PGT group who cryopreserved 2PN zygotes and 4 who froze an average of an additional 10.8 un-biopsied embryos (p>0.05). 5 PGT-A patients underwent a 2nd EB cycle (vs 2 among no-PGT); 2 for poor response, 3 for low or no euploidy. 6 in the no-PGT group cryopreserved 2PN zygotes; 3 were BRCA-positive and intended future PGT-M. Among PGT-A patients, 6.7 ±5 blastocysts underwent PGT-A with 3.5 ±3 (48.2%) euploid embryos available for future frozen embryo transfer (FET). Overall, PGT-A patients understood their final “usable” embryo number to be 3.5 ±3 euploid embryos vs 7.2 ±7 untested embryos in the no-PGT group. 2 breast cancer survivors in the PGT-A group have since undergone FET with 1 livebirth and 1 ongoing pregnancy; 2 others intend an upcoming FET.

CONCLUSIONS: PGT-A in medical EB cycles provides critical information about future embryo potential and may be a helpful counseling tool. In some cases, poor PGT-A results informed patients to pursue a 2nd EB cycle without delaying cancer treatment. FP patients without PGT-A have a greater number of vitrified embryos but with unknown reproductive potential; patients may thus overestimate future success rates with devastating consequences. PGT-A results may require patients to prematurely address a terminal fertility diagnosis. The knowledge gained from PGT-A must thus be weighed against the financial cost and possible emotional toll; additional psychosocial support should be offered given the potential magnitude of information gained.

breast cancer are frequently referred for fertility preservation treatment (FPT) consultation. Our objective was to identify predictive factors for FPT and fertility outcomes in breast cancer patients.

**DESIGN:** Retrospective analysis.

**MATERIALS AND METHODS:** We analyzed 126 breast cancer patients, ages 18–42 years old, seen for FPT consultation at an academic fertility center from 2001-2017. We calculated proportions for patient diagnosis, demographics, type of FPT chosen, planned treatment, and in vitro fertilization (IVF) outcomes. Pearson chi-squared and Fisher’s exact tests were performed to test for associations.

**RESULTS:** Our cohort included 126 patients with a mean age of 33.6 ± 4.9 years. Breast cancer stage, known in 106 patients, included 34.9% (n=37) Stage 1, 50.0% (n=53) Stage 2, 8.5% (n=9) Stage 3, 6.6% (n=7) Stage 4. At the time of consult, 15.1% (19/126) had prior chemotherapy and 12.7% (16/126) had prior radiation, while 79.4% (100/126) and 64.3% (81/126) had planned to receive chemotherapy and radiation, respectively. After counseling, 61.1% (77/126) underwent FPT. Treatment modalities included embryo cryopreservation 61.0% (47/77), oocyte cryopreservation 29.9% (23/77), and did not utilize their frozen eggs or embryos. No patients returned to utilize their frozen oocytes thus far. The data.

**CONCLUSIONS:** In our analysis of breast cancer patients seen for FPT consultation, over half underwent either embryo or oocyte cryopreservation. However, over the 16-year period, less than 20% returned to attempt pregnancy with frozen eggs or embryos and of those there was a less than 20% live birth rate. Further research is needed regarding utilization of FPT services in this group.

**References:**
5. Supported by: Ministero della Salute “Fertility Preservation in gonadotoxic treatments” project code RF-2011-02348826.
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MITOCHONDRIAL TRANSFER FROM AUTOLOGOUS BONE MARROW MESENCHYMAL STEM CELLS IMPROVES OOCYTE QUALITY. R. Huang, C. Fang, L. Jia, G. Cao, Z. Zhang, X. Liang. Reproductive Medicine Center, Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.

OBJECTIVE: Embryo quality ranks one of the most important predictors in determining the success of implantation, and, clinically, some patients experience repeated IVF failure because of refractory poor embryo quality due to poor oocyte quality. Researches over the past decades leave no doubt that mitochondria are a hallmark of quality and developmental potential of human oocytes, therefore, mitochondrial transfer (MIT), i.e. injecting mitochondria into oocyte, was proposed to improve oocyte quality. Recent studies showed that mitochondrial transfer of mesenchymal stem cells (MSC) effectively protects epithelial cells from mitochondrial damage, suggesting mitochondria in MSC is healthy enough to be good sources for MIT treatment. Therefore, the aim of this study is to investigate the effect of MIT from autologous MSC in improving oocyte quality and clinical outcome in an IVF/ICSI program.

DESIGN: Patients with repeated IVF/ICSI failure due to refractory poor embryo quality (no good-quality embryos obtained in at least two previous IVF cycles) were recruited in this retrospective study.

MATERIALS AND METHODS: 52 patients were recruited in this study. Prior to ovarian stimulation, 20 ml of bone marrow were aspirated from each patient’s iliac crest under local anesthesia and BMSCs were isolated, cultured and frozen in vitro, and then thawed two days before oocyte retrieval for mitochondria preparation through differential centrifuge. Fluorescent real-time PCR was applied to quantify the absolute copy number of mtDNA. All mitochondria were suspended in fertilization medium for injection and 2 pl of solution (approximately 4000-5000 copy number of mtDNA) were injected into each mature oocyte together with one sperm during ICSI procedure.

RESULTS: The average age and number of previous failed IVF cycles of this group of patients were 37.69±5.96 y and 4.75±1.20 respectively. The mean number of oocytes obtained, mature oocytes, 2PNs, transferrable embryos and good-quality embryos were 8.04±5.41, 6.06±4.23, 4.54±3.46, 2.21±1.29 and 1.48±1.84, respectively. One in three D3 embryos was graded as good-quality after MIT, the rate of good-quality embryo was significantly higher than that in previous cycles (33.17% vs. 0%, P<0.05). Fresh embryo transfer was performed in 19 patients, and the pregnancy rate was 31.58% (6/19). In 18 patients, fresh embryo transfer was cancelled and the mean number of embryos frozen was 1.61±1.20.

CONCLUSIONS: In summary, transferring mitochondria from autologous BMSCs into oocytes offer a new potential treatment to rescue compromised oocytes and normalizes embryo development without disturbing patients’ mtDNA fingerprint.

References:

Supported by: No.

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A COMPARISON OF PRE-TREATMENT WITH AND WITHOUT GNRH-AGONIST OR LETROZOLE IN WOMEN WITH 2 FAILED EMBRYO TRANSFERS UNDERGOING A FROZEN CYCLE AND NO EVIDENCE OF ENDOMETRIOSIS. M. H. Dahan, S. Tannus, S. Tan. McGill University, Montreal, QC, Canada.

OBJECTIVE: Endometriosis is common in infertility populations, affecting 30-50%. Endometriosis goes undiagnosed with laparoscopy in infertility patients mostly abandoned. Treatment of endometriosis with depo-gonadotropin releasing hormone agonists (GnRH-ag), prior to embryos transfer improves outcomes. In non-fertility patients GnRh-ag and letrozole is more effective at treating endometriosis than either alone. Our previous pilot study demonstrated improvement in outcomes in 38 subjects pre-treated with GnRh-ag-letrozole. This study was performed to confirm the finding in a large cohort.

DESIGN: A prospective cohort study was performed on subjects who failed two embryo transfers of blastocysts between June 2013 and September 2017. The study excluded women with known endometriosis or endometriomas. Each subject was included only once.

MATERIALS AND METHODS: 204 subjects were not pretreated, 143 received 2-months of luprolide-acetate only, 176 received luteolride acetate 3.7� mg monthly IM and letrozole 5 mg daily orally for 60 days. Subsequently, the subjects underwent an estradiol valerate (2mg TID orally) and progesterone endometrin 100 mg bid vaginally, supported frozen blastocyst transfer. Data were compared by ANOVA (α& Tukey HSD) or Chi-squared tests. Data are presented as % or mean±SD. Power analysis suggested ≥84 subjects were required in each arm. beta=0.8, alpha error 0.05 and 35% difference. All subjects had a normal uterine cavity, & non-severe male factor infertility and were ≤40 years female age. Ongoing pregnancies are at least 24 weeks gestation.

RESULTS: Data is presented as no pre-treatment, GnRh-ag, GnRh-ag-letrozole groups respectively. Female age, AFC, basal serum FSH levels duration of infertility, previous pregnancies and full-term deliveries were similar (P>0.05). Number of frozen blastocysts were similar as were Gardner’s grade of embryo transferred. All subjects had failed 2 previous blastocyst transfers. Clinical Pregnancy rates and third-trimester pregnancies were highest among the GnRh-ag-letrozole. No difference was noted in the no pre-treatment and GnRh-ag groups.

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### Table: Differences in Pregnancy Rate and Ongoing Pregnancy Rate (%) among Study Groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Results</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Age (Years)</td>
<td>35.3±3.2</td>
<td>34.8±3.6</td>
</tr>
<tr>
<td>AFC</td>
<td>14.6±2.4</td>
<td>14.0±3.4</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>8.3±1.4</td>
<td>8.2±1.3</td>
</tr>
<tr>
<td>Preg prog</td>
<td>0.8±0.5</td>
<td>0.7±0.4</td>
</tr>
<tr>
<td>Preg deliveries</td>
<td>0.6±0.5</td>
<td>0.6±0.5</td>
</tr>
<tr>
<td>Days of stimulation</td>
<td>10.3±3.3</td>
<td>9.8±3.2</td>
</tr>
<tr>
<td>Gonadotropin dose</td>
<td>2204±1246</td>
<td>1979±1478</td>
</tr>
<tr>
<td>#Frozen Blasts</td>
<td>2.9±1.2</td>
<td>2.7±1.4</td>
</tr>
<tr>
<td>Number of embryos transferred</td>
<td>1.2±0.4</td>
<td>1.2±0.3</td>
</tr>
<tr>
<td>Gardner’s grade of transferred embryo AA</td>
<td>12% (29)</td>
<td>14% (24)</td>
</tr>
<tr>
<td>AB</td>
<td>28% (68)</td>
<td>31% (53)</td>
</tr>
<tr>
<td>BA</td>
<td>42% (103)</td>
<td>33% (57)</td>
</tr>
<tr>
<td>BB</td>
<td>18% (45)</td>
<td>22% (38)</td>
</tr>
<tr>
<td>Clin Preg</td>
<td>40% (82/204)</td>
<td>42% (60/143)</td>
</tr>
<tr>
<td>Ongoing Preg</td>
<td>34% (70/204)</td>
<td>36% (51/143)</td>
</tr>
</tbody>
</table>
CONCLUSIONS: Patient with 2 failed embryo transfers perform better if pretreated with GnRH-ag-luterolo. Luterolo+ GnRH-ag improves outcomes as compared to GnRH-ag alone, which is not better than no pretreatment. We hypothesize that this improvement is due to treatment of undiagnosed endometriosis. Other mechanisms are possible. Why GnRH-ag alone failed to improve outcomes may be due to duration or a mechanism of action unrelated to endometriosis.

EFFECTS OF BUSHEN HUATAN RECIPE ON THE AKT-Glut4 INSULIN SIGNAL PATHWAY OF OVARIAN GRANULAR CELLS IN POLYCYSTIC OVARIAN SYNDROME AND IVF OUTCOMES IN THESE INFERTILE PATIENTS.

OBJECTIVE: To investigate the effect of Kidney-Tonifying and Phlegm-Resolving Method on the key molecules (AKT, p-AKT and GLUT4) of the AKT-Glut4 insulin signal pathway in ovarian granular cells (OGC) and its effect on oocyte quality, embryo development and pregnancy outcomes of these infertile patients with polycystic ovary syndrome.

DESIGN: Investigate the effect of Kidney-Tonifying and Phlegm-Resolving Method on the key molecules (AKT, p-AKT and GLUT4) insulin signal pathway in ovarian granular cells (OGC) by measuring HOMA-IR, high-quality oocytes rate, high-quality embryos rate, clinical pregnancy rate, and the expression of AKT, p-AKT and GLUT4 in ovarian granulosa cells on the day of retrieval.

MATERIALS AND METHODS: Sixty-six PCOS patients with Kidney-deficiency and phlegm-dampness treated by in vitro fertilization-embryo transfer (IVF-ET) were randomly and equally (33 patients per group) divided into two groups: the Erzhi Tiangui combined with Qi Gong Keli group (treatment group) and placebo (control group). Two groups of patients were treated with double-drop program (GnRH-a+Diane 35) and placebo. The treatment group of patients taking the Diane 35 at the same time to giving the above traditional Chinese medicine, until HCG injection day. Patients in the placebo group were given placebo granules as described above. Score changes of Kidney-deficiency and phlegm-dampness symptom before and after treatment were measured, other outcomes including HOMA-IR, high-quality oocytes rate, high-quality embryos rate, clinical pregnancy rate, and the expression of AKT, p-AKT and GLUT4 in ovarian granulosa cells on the day of retrieval.

RESULTS: Compared to the placebo group, the Kidney-deficiency and phlegm-dampness symptom scores significantly improved in the Chinese treatment group. In addition, the treatment group take a turn for the better in the HOMA-IR, high-quality oocytes rate, high-quality embryos rate, and clinical pregnancy rate (P < 0.05 respectively). Compared with the other treatment group, the placebo group showed significantly high-regulated p-AKT levels and GLUT4 protein contents (P < 0.05 respectively).

CONCLUSIONS: The Erzhi Tiangui combined with Qi Gong Keli could significantly improve Kidney-deficiency and phlegm-dampness status in infertile patients, reduce HOMA-IR and increase their high-quality oocytes ratio, high-quality embryos ratio, and clinical pregnancy rate. Bushen Huanan Recipe might improve the insulin resistance status of ovary in PCOS patients, high-quality embryos ratio, and clinical pregnancy rate. BUSHEN HUATAN significantly improve Kidney-deficiency and phlegm-dampness status in Chinese treatment group.

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OBJECTIVE: This study characterizes the uptake of fertility intervention and the outcomes after in vitro fertilization (IVF) and surrogacy for all patients with Mullerian agenesis at a university-based fertility clinic over the past 10 years.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: Patients age 18 years or older with a diagnosis of uterine and/or cervical agenesis were identified based on ICD-9 and ICD-10 codes recorded from January 2008 to December 2017. Patient electronic medical records were queried for demographic and clinical data, including IVF cycle information.

RESULTS: Forty-three patients with Mullerian agenesis were identified who had presented for at least one reproductive endocrinology clinic visit. Of these patients, 40 had MRKH and 3 had cervical agenesis. The median age at initial presentation to reproductive endocrinology care was 19 years. The vast majority of patients initially presented for the purpose of diagnostic clarification (55.8%) and/or therapeutic vaginal dilation (30.2%). Thirty-one patients (72.1%) had at least one visit with a documented discussion of future fertility, though only 10 had a specific appointment dedicated to discussing initiation of IVF with surrogacy or embryo banking (25.3% of the study cohort, 32.3% of those for whom fertility was addressed). Those who presented for such an appointment tended to be older and married, with a median age of 30.5. Of the 10 patients who presented for a dedicated IVF informational appointment, only half proceeded to undergo IVF. Four patients (80%) went through IVF for immediate use in gestational carrier and 1 (20%) banked embryos for future use. As of this study, no patients had pursued oocyte banking. All four patients who used gestational carriers ultimately conceived, three of whom had one or more subsequent live births. The remaining patient has a current third trimester gestational carrier pregnancy.

CONCLUSIONS: Of the patients presenting to a tertiary care clinic with Mullerian agenesis, the majority had visits in which fertility options were considered.
DECREASED OVARIAN RESERVE BIOMARKERS ARE ASSOCIATED WITH REDUCED FECUNDABILITY IN WOMEN WITH NO HISTORY OF INFERTILITY. K. Hunter Cohn,1 A. Z. Zhang,2 B. Miller,3 F. Arredondo,4 M. Hinckley,5 J. N. Gutmann,6 C. A. Benadiva,5 J. Nelsen,7 M. P. Leondres,8 G. Letterie,9 J. E. Hirshfeld-Cytron,10 A. B. Copperman,11 P. Yurttas Beim,12 Celmatix Inc., New York, NY; RMA of Michigan, Troy, MI; RMA of Texas, San Antonio, TX; Reproductive Science Center of the San Francisco Bay Area, San Ramon, CA; RMA of Philadelphia, Philadelphia, PA; CARIS, Farmington, CT; RMA of Connecticut, Norwalk, CT; Seattle Reproductive Medicine, Seattle, WA; Fertility Centers of Illinois, Chicago, IL; RMA of New York, New York, NY.

OBJECTIVE: Biomarkers for ovarian reserve such as anti-Mullerian hormone (AMH), basal antral follicle count (BAFC), and day 3 follicle-stimulating hormone (FSH) represent a woman’s remaining follicular pool and are prognostic for infertility treatment. However, there has been some recent controversy about how well these biomarkers predict reproductive potential in women of unknown fertility status. Here we examine the relationship between ovarian reserve biomarkers and reproductive potential in women without male partners seeking intratubal insemination with donor sperm (DIUI) as a proxy to the general population.

RESULTS: We found that, after controlling for patient age, biomarkers for decreased ovarian reserve were associated with lower probabilities of OP (Table 1). We quantified the relative fecundability using the hazard ratio (HR) and found that patients with AMH ≤ 1 ng/mL had a significantly lower probability of OP compared to those with AMH 1-6 ng/mL, HR 0.67 (0.47-0.96). We also found significantly lower probability of OP in patients with low BAFC (HR 0.67 (0.50-0.88)) and in those with high FSH (HR 0.74 (0.57-0.97)). Patients with high AMH and BAFC did not differ significantly from those with normal ranges.

CONCLUSIONS: Biomarkers suggestive of decreased ovarian reserve are associated with reduced fecundability in women seeking DIUI. These women are representative of women in the general population, indicating that these biomarkers can provide insight into fecundability, independent of age. Ovarian reserve biomarkers are not only informative for infertile patients, but can also provide valuable information for women who proactively seek to understand their reproductive potential.

TABLE 1. Association of biomarkers for ovarian reserve and probabilities of ongoing pregnancy

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
<th>Cumulative probability of ongoing pregnancy by 6 cycles using mean age 36.7, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMH, ng/mL</td>
<td>≤1 261 0.67 (0.47-0.96) 0.03</td>
<td>31.6 (21.4-40.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-6 743 [Reference] -</td>
<td>43.3 (35.7-49.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;6 111 1.15 (0.80-1.66) NS</td>
<td>47.9 (32.9-59.6)</td>
<td></td>
</tr>
<tr>
<td>BAFC</td>
<td>≤5 440 0.67 (0.50-0.88) 0.004</td>
<td>38.1 (28.6-46.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9-25 1067 [Reference] -</td>
<td>51.3 (43.3-58.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;25 150 0.98 (0.71-1.40) NS</td>
<td>50.7 (36.7-61.67)</td>
<td></td>
</tr>
<tr>
<td>FSH, mIU/mL</td>
<td>≤9 1496 [Reference] -</td>
<td>48.5 (41.1-54.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;9 373 0.74 (0.57-0.97) 0.03</td>
<td>39.0 (29.6-47.1)</td>
<td></td>
</tr>
</tbody>
</table>

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ELECTIVE SINGLE EMBRYO TRANSFER (eSET) VERSUS DOUBLE EMBRYO TRANSFER (DET) FOLLOWING FAILED MANDATORY SINGLE EMBRYO TRANSFER (mSET). A. C. Mancuso, A. E. Sparks, H. E. Duran, B. J. Van Voorhis, J. Kaphamer. Obstetrics and Gynecology, University of Iowa, Iowa City, IA.

OBJECTIVE: To compare live birth and multiple birth rates among women who underwent eSET versus DET in the first frozen embryo transfer (FET) cycle following a failed mSET.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: All patients at our institution from 1/1/ 2012-9/14/2017 who met criteria for mSET (age <38, good quality blastocyst, and no previous failed fresh cycle), did not have a live birth following their first frozen embryo transfer, had at least 2 remaining cryopreserved blastocysts, and subsequently underwent FET were included. Primary outcomes were live birth per transfer and multiple birth per delivery. Secondary outcomes were clinical pregnancy rate, miscarriage rate, ectopic pregnancy rate, term vs. preterm delivery, vaginal delivery vs. cesarean section, and infant birth weight. Exclusion criteria were preimplantation genetic testing (PGT) cycles, FET cycles in which only 1 embryo survived the thaw process, mSET due to maternal condition (e.g. unicornuate uterus), cycles in which birth data were not available, and donor oocyte cycles.

Chi-squared tests and t-tests were used to compare demographic, cycle characteristics, and outcome data between groups. Medians with interquartile ranges, means with standard deviation, or percentages are presented.

RESULTS: Of the 731 patients who underwent an initial mSET and had outcome data available, 450 had a live birth (61.5%). Of the 281 that failed their fresh mSET, 218 of these went on to have a FET within our time frame (77.6%). Of those, 54 patients were excluded due to no outcome data available (n = 9), <2 blastocysts frozen (n = 15), only 1 surviving embryo available to transfer after warming (n = 27), or mSET due to maternal condition (n = 3). This left 164 patients, of which 88 (53.7%) chose to transfer 1 embryo and 76 (46.3%) chose to transfer 2 embryos in their FET. Demographic and cycle characteristics were similar between eSET and DET patients (Table 1).

DEET patients had a significantly higher live birth rate and clinical pregnancy rate than eSET patients. However, DET patients also had a significantly higher multiple birth rate, C-section rate, and lower birth weight (Table 1). There was no other differences in outcomes seen between groups.

CONCLUSIONS: In a group of good prognosis patients with an unsuccessful mandatory single embryo transfer, DET in the subsequent cycle resulted in a higher live birth rate than SET, but also was associated with a much higher multiple birth rate. When deciding on the number of embryos to transfer in this group, patients and providers should consider both the higher pregnancy rate and the significant risk of multiples with DET vs. SET.

<table>
<thead>
<tr>
<th>Demographic and Cycle Characteristics</th>
<th>eSET (n=88)</th>
<th>DET (n=76)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (n=88)</td>
<td>31 (29-34)</td>
<td>32 (29-34)</td>
<td>0.248</td>
</tr>
<tr>
<td>BMI (n=88)</td>
<td>26.7 (21.9-31.5)</td>
<td>25.4 (22.6-32.7)</td>
<td>0.618</td>
</tr>
<tr>
<td>Number of oocytes retrieved (n=88)</td>
<td>18 (13-25)</td>
<td>18 (13-30)</td>
<td>0.377</td>
</tr>
<tr>
<td>Number of blastocysts cryopreserved (n=88)</td>
<td>3 (2-6)</td>
<td>4 (2-7)</td>
<td>0.345</td>
</tr>
<tr>
<td>Parity (n=88)</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>0.586</td>
</tr>
<tr>
<td>Live birth (n=88)</td>
<td>53 (63.3%)</td>
<td>52 (68.4%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Multiple birth (n=88)</td>
<td>1 (2.6%)</td>
<td>19 (35.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical pregnancy (n=88)</td>
<td>53 (63.3%)</td>
<td>57 (75.0%)</td>
<td>0.045</td>
</tr>
<tr>
<td>Preterm delivery (n=88)</td>
<td>5 (12.8%)</td>
<td>13 (25.0%)</td>
<td>0.149</td>
</tr>
<tr>
<td>C-section (n=88)</td>
<td>13 (33.3%)</td>
<td>29 (55.8%)</td>
<td>0.034</td>
</tr>
<tr>
<td>Birth weight (grams) (n=88)</td>
<td>3540 (3090-3720)</td>
<td>3090 (2584-3443)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

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LONG DISTANCE/CROSS BORDER EGG DONATION: A MODEL TO HAVE THE BEST OF BOTH WORLDS. C. C. Chang,1,2 G. Wright,1,2 T. A. Elliott,1,2 D. B. Shapiro,1,2 A. A. Toledo,1,2 Z. P. Nagy,1,2 Reproductive Biology Associates, Atlanta, GA; Prelude Fertility, Atlanta, GA.

OBJECTIVE: Long distance/cross border egg donation is driven largely by restrictive law, cost, and accessibility of egg donors. Current egg donation
methods require that either intended parents travel to clinics where donor eggs are located, or the vitrified donor eggs must be shipped to clinics where intended parents will do IVF and ET. Using a cryo-donor egg bank, donor eggs can be shipped to receiving clinics for long distance/cross border egg donation cases. However, it is not uncommon for there to be no high quality embryos available after a donor egg warming cycle. In order to avoid this frustrating and disappointing situation, we developed a novel model for long distance/cross border egg donation, with the objective being to test whether this model can provide the benefit of remaining at home for intended parents while simultaneously guaranteeing high quality embryo creation.

DESIGN: Retrospective study.

MATERIALS AND METHODS: All donors were submitted to COHS using GnRH antagonist with rFSH and GnRH agonist trigger. Cryopreservation of donor oocytes was performed using minimum volume vitrification. A total of 484 donor oocytes (54 individual donors) from the donor oocyte cryo-bank were matched to 70 recipients (22 recipient clinics) and were included in this study. The frozen sperm specimen of intended parents was delivered from remote clinics for the donor egg warming and insemination. ICSI using thawed sperm was performed after 3 hours in vitro culture and osmotic equilibration. The fertilized eggs were subsequently cultured to day-5/day-6 and embryos were vitrified at blastocyst stage. Cryopreserved embryos were then shipped to the recipient location for warming and transfer.

RESULTS:

<table>
<thead>
<tr>
<th>No. of recipient cycle</th>
<th>70</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of egg warmed (mean±sd)</td>
<td>484 (6.91±2.10)</td>
</tr>
<tr>
<td>No. of egg survived / fertilized (% per egg warmed)</td>
<td>453 (93.5) / 395 (81.6)</td>
</tr>
<tr>
<td>No. of day 5 / day 6 blastocyst (% per egg warmed)</td>
<td>144 (29.7) / 79 (16.3)</td>
</tr>
<tr>
<td>No. of blastocyst vitrified (mean±sd)</td>
<td>223 (3.18±1.48)</td>
</tr>
<tr>
<td>No. of Frozen ET cycle (cumulative)</td>
<td>88</td>
</tr>
<tr>
<td>No. of Embryo Transferred (mean±sd)</td>
<td>122 (1.38±0.49)</td>
</tr>
<tr>
<td>No. of Clinical Pregnancy (cumulative) (%)</td>
<td>44 (62.8)</td>
</tr>
<tr>
<td>No. of implantation (%)</td>
<td>53 (43.4)</td>
</tr>
<tr>
<td>No. of recipient delivered</td>
<td>25</td>
</tr>
<tr>
<td>No. of live birth</td>
<td>29</td>
</tr>
<tr>
<td>No. of ongoing pregnancy</td>
<td>18</td>
</tr>
</tbody>
</table>

CONCLUSIONS: The study demonstrates that long distance/cross border egg donation cycles can be operated efficiently by using the combination of the transport of frozen husband/partner sperm to the donor egg bank for fertilization followed by return shipment of resulting embryos to the recipient clinic. Since the embryos are created on-site at the donor egg bank, the quality and quantity of the resulting embryos can be assured before returning them to recipient clinic for subsequent embryo warming and transfer. Long distance/cross border egg donation can be operated by this model without increase in tangible and intangible costs relative to care received in one’s own community. By eliminating the need to travel, this model of embryo creation allows intended parents to get a minimum number of high quality embryos guaranteed while concurrently preventing dislocation from local support networks.

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IN VITRO EMBRYO MATURATION ALTERS RENAL RENIN-ANGIOTENSIN SYSTEM EXPRESSION AND EPIGENETIC MODIFICATION IN MICE. P. Pan,* F. Le,* F. Jin,* The Second Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; †Women’s Hospital, School of Medicine, Zhejiang University, Hangzhou, China.

OBJECTIVE: Increasing evidence has demonstrated that the abnormal embryo environment, such as in-vitro culture conditions and manipulation, can increase the risk of the cardiovascular and renal dysfunction of offspring later in life. However, the risk associated with the oocyte in vitro maturation (IVM) and its underlying mechanism are still uncertain. It has been reported that renal renin-angiotensin system (RAS) and its relative miRNAs are well-characterized factors that regulate genes involved in renal dysregulation, which might take part responsibility for cardiovascular disease. Thus, our study was designed to evaluate the effect of IVM on the genes expression of RAS and their epigenetic regulation.

DESIGN: The mouse models were established containing IVM (n = 20) and an in vivo control group (n = 22).

MATERIALS AND METHODS: RT-PCR, pyrosequencing and western blotting were used to detect the mRNA or microRNA (miRNA) levels, methylation status and protein levels of RAS in the renal tissue of adult and offspring mice.

RESULTS: At adult age, only mRNA expressions of angiotensin II type 1a receptor (Agtr-1A) and angiotensin-converting enzyme 2 (Ace2) were decreased, while other genes of RAS were increased in IVM group as compared with those in vivo control group. Moreover, expressions of mRNA-698, mRNA-27a and mRNA-155 were disturbed in the kidneys of adult IVM mice. Meanwhile, changes in the protein level of angiotensinogen (AGT) and methylation levels of Agtr angiotensin-converting enzyme (Ace) were also found in the renal tissue of the adult IVM mice. In the old-aged mice, only mRNA expressions of AngII and Ace were up-regulated in the kidneys of IVM mice, while other genes of RAS were down-regulated. The alterations in expression of mRNA-698, mRNA-27a, mRNA-155 and mRNA-143 were also observed in aged IVM mice. In addition, the lower methylation of Ace was detected in aged IVM mice than that in vivo mice. Furthermore, aged IVM-conceived mice showed the higher expression level of the of AGT protein.

CONCLUSIONS: IVM affects the gene expression of RAS system, which may be associated with the epigenetic regulations of RAS.

Supported by: This work was supported by the National Natural Science Foundation of China (81200475, 81510321, 81571300, 81370760) and Zhejiang Provincial Natural Science Foundation of China (LY17H040006, LZ15H040001, Z13H040002, and LY15H040008).

FERTILITY & STERILITY®
TABLE 1. Results

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=21)</th>
<th>Group 2 (n=345)</th>
<th>Group 3 (n=4)</th>
<th>Group 4 (n=7)</th>
<th>Genus and species</th>
<th>Folicular fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPIs-Score</td>
<td>0</td>
<td>20.2±3.8</td>
<td>16.3±5.0</td>
<td>15.2±2.9</td>
<td>11.6±6.0</td>
<td>19</td>
</tr>
<tr>
<td>AUC</td>
<td>0.72</td>
<td>1.21</td>
<td>1.08</td>
<td>1.09</td>
<td>0.74</td>
<td>10</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>74%</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
<td>74%</td>
<td>57%</td>
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<tr>
<td>Specificity</td>
<td>60%</td>
<td>46%</td>
<td>46%</td>
<td>46%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>48%</td>
<td>43%</td>
<td>43%</td>
<td>43%</td>
<td>48%</td>
<td></td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>82%</td>
<td>81%</td>
<td>81%</td>
<td>81%</td>
<td>82%</td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSIONS: The KPIs-Score is stronger than AFC for predicting clinical pregnancy. The total KPIs-Score seems to be useful for predicting clinical pregnancy and had satisfactory accuracy.
number of fair to good quality blastocysts and utilization rates of blastocysts. This study is unique from prior studies in that 96.4% of study patients under- went antagonist stimulation cycles with GnRH agonist trigger.

DESIGN: Prospective cohort study.

MATERIALS AND METHODS: All patients underwent IVF / ICSI bet- ween August 2016 and February 2017 at a tertiary academic fertility centre. All patients included were normal responders with > 8 mature follicles (> 17 mm) at retrieval. All patients were assigned to alternate ovarian (left or right) flushing on an alternating day allocation. Each patient was used as their own control comparing the ovary with the aspirated and flushed follicles to the contralateral ovary with follicles which were retrieved using standard aspiration without flushing. Because of this study design, statistical analysis was carried out using paired T-tests for comparison of flushed and non-flushed ovaries.

RESULTS: 111 patients were included with no statistical difference in any outcome if either the left or right ovary was allocated to be flushed. The mean number of oocytes retrieved from the flushed ovary was 9.5 compared to 8.8 in the unflushed ovary (P = 0.13). Mean mature (M2) oocytes retrieved was 7.5 from the flushed ovary, compared to 6.9 from the unflushed ovary (P = 0.12). Blastocysts of good quality obtained from the flushed and nonflushed ovaries were 2.5 and 2.1 (P = 0.17). Blastocyst utilization rates from the flushed and unflushed ovaries were 56% and 51% (P = 0.17).

CONCLUSIONS: All outcomes studied showed no statistically significant difference between the flushed and unflushed ovary. This is concordant with published studies showing no difference with follicular flushing. This study adds to the literature as uniquely 96.4% of IVF / ICSI cycles included had used GnRH antagonist stimulation and GnRH agonist trigger. This study sug- suggests that follicular flushing does not provide any clinical benefits in patients who are good responders when using an antagonist stimulation cycle with GnRH agonist trigger.

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PREDICTORS OF SUCCESSFUL OUTCOME IN VITRI- FIED-THAWED ICSI CYCLES PROVED BY LOGISTIC REGRESSION MODEL. M. E. Ghanem, L. Al Boghdad- dy, Y. M. Mesbah, M. H. Bedairy, Mansoura Integrated Fertility Center, Mansoura, Egypt; MIFC, Mansoura, Egypt; Obstetrics and Gynecology, Mansoura Faculty of Medicine, Mansoura, Egypt; Obstetrics and Gynecology, Gynecological Oncology, Mansoura, Egypt.

OBJECTIVE: Previous studies showed that top quality embryo transfer (ET) and endometrial preparation with natural cycle or mild stimulation , female BMI and number of transferred embryos independently affected the outcome in frozen thawed ET. The effect of cultivating thawed cleavage embryos (Cl-E) to blastocyst stage (Bi-E) on outcome was insufficiently elucidated. We aimed to evaluate the role of culture of thawed Cl-E to Bi-E among other independent variables as predictor of cycle outcome in vitrified thawed ICSI cycles using binomial logistic regression (BNLR).

MATERIALS AND METHODS: The material consists of 1042 consecu- tive cycles of vitrified -thawed ET done in a single IVF unit between 2014- 2017. Endometrial preparation methods were: natural , stimulation by anti- estrogens and / or gonadotropins, or replacement using sexual estradiol (E2) & progesterone (P4). The timing of ET was scheduled by hCG- trig- ering of ovulation or by monitoring spontaneous ovulation. Some thawed Cl-E were cultured for 24- hours to reach Bi-E. Thawed embryos were transferred and luteal support using vaginal P4 (200 mg/day) given. The end point was clinical pregnancy or spontaneous period. The primary aim was finding independent predictors of clinical pregnancy employing BNLR.

RESULTS: Overall clinical pregnancy rate (CPR) is 298/1042 is 28.5%. Comparing pregnant (n=298) and non-pregnant (n=744) showed respec- tively: age 28.76±5.0, 28.85±5.18 (p=0.8); BMI 31.06±5.9, 32.45 ±5.9 (p=0.02); Infertility duration 4.17±3.2, 4.6 ±3.5 (p=0.038); Endometrial thickness* 10.82±1.6, 10.13±2.06 (p=0.007); No. of ET* 3.35 ±1.5, 3.12±1.60 (p=0.035). The ratios of pregnancy were Frozen embryo stage Cl-E (198/502)(39.4%), Bi-E (100/ 336)(18.7%)(P<0.0001); Top quality ET (216/684) (3.1%), non-top quality ET (608/008) (p=0.000); endometrial preparation: natural 72/ 240.30.8%); stimulated (212/684) (30.9%); replacement (199/194) (18.8%) (p=0.01); Cultured Cl-E to Bi-E (116/704) (16.5%), non cultured 182/ 848 (21.4%) (P<0.001); Ovulation triggering by hCG YES: 212/ 610(34.7%), NO(66/370) (17.8%) (P<0.001) (t test; * Chi Square test); Fisher exact test; 4 Chi Square test) BNLR model was statistically sig- nificant Chi-square (9 df) = 160.2, p<0.000.The model explained 47.9% (Na- gelkerke R2) of the variance and correctly predicted 80.9% of the cases. The Wald criterion demonstrated that ( embryo grade, endometrial thickness , embryo culture cycle, Ovulation triggering Cl-E, freezing number of ET) inde- pendently predict positive clinical outcome (P<0.05) but ( infertility duration , BMI or endometrial preparation protocol did not P>0.05).

CONCLUSIONS: Top quality ET , embryo number, endometrial thick- ness, cultured Cl-E to Bi-E, Cl-E freezing timing ET by hCG independently predict successful outcome in frozen cycle ET.

OBJECTIVE: The aim of this study was to evaluate the efficacy of melatonin and/or resveratrol administration on embryo development and clinical outcomes in poor-prognosis IVF patients.

DESIGN: This study was a retrospective observational study conducted at Kyono ART clinic in Japan from October 2010 to November 2017.

MATERIALS AND METHODS: A total of 372 patients who failed to conceive in a previous ART cycle due to poor embryo development were included and divided into three groups: a melatonin administration group (MLT group), a resveratrol group (RSV group), and a melatonin and resveratrol administration group (MLT/RSV group). The numbers of cycles were 296, 35, and 116 in the MLT group, RSV group, and MLT/RSV group, respectively. We designated the previous ART cycle of each patient in the three groups as control. Primary endpoints were fertilization rate and miscarriage rate. Characteristics of each group and their control are shown in Table. Fisher’s exact test and Mann-Whitney U tests were used for statistical analysis.

RESULTS: In the MLT group, fertilization rate (72.5% vs. 63.5%; p < 0.01), blastocyst formation rate (45.7% vs. 31.0%; p < 0.01), and good-blastocyst rate (8.7% vs. 20.4%; p < 0.01) were significantly higher than control. In the RSV group, although fertilization rate (66.7% vs. 52.8%; p = 0.07) and good-blastocyst rate (25.6% vs. 8.0%; p = 0.08) were higher than control, the results did not reach statistical significance. In the MLT/RSV group, blastocyst formation rate (49.5% vs. 31.6%; p < 0.01) and good-blastocyst rate (23.6% vs. 13.6%; p < 0.01) were significantly higher than control. The MLT group showed significantly higher pregnancy rate (22.0% vs. 9.6%; p < 0.01) and lower miscarriage rate (30.6% vs. 60.6%; p < 0.01) than control. The RSV group showed no significant difference in pregnancy rate and miscarriage rate. The MLT/RSV group showed significantly higher pregnancy rate (20.8% vs. 6.6%; p < 0.05) and lower miscarriage rate (27.3% vs. 75%; p < 0.01) than control. There was no side effect of melatonin and resveratrol administration.

CONCLUSIONS: Our findings have shown that melatonin administration to poor-prognosis IVF patients during controlled ovarian stimulation in their ART cycle could improve embryo development and clinical outcomes. In consideration of the beneficial effect of resveratrol on SIRT1 activation, co-administration of resveratrol with melatonin might be more favorable.

Characteristics of patients in each group and their control.

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient age</th>
<th>AMH (ng/ml)</th>
<th>No. of oocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTL</td>
<td>39.5</td>
<td>1.7</td>
<td>5.2</td>
</tr>
<tr>
<td>MLT</td>
<td>40</td>
<td>1.7</td>
<td>5.5</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>CTL</td>
<td>40.3</td>
<td>0.7</td>
<td>2.6</td>
</tr>
<tr>
<td>RSV</td>
<td>40.9</td>
<td>0.7</td>
<td>3.4</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>CTL</td>
<td>39.9</td>
<td>1.3</td>
<td>4.8</td>
</tr>
<tr>
<td>MLT/RSV</td>
<td>40.5</td>
<td>1.4</td>
<td>5</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

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RISK OF BLASTOGENESIS BIRTH DEFECTS IN IVF, NON-IVF ART, AND FERTILE BIRTHS

B. Luke, M. B. Brown, E. Wantman, R. E. Meyer, N. E. Forestieri, S. Watkins, M. Yazdy, M. Browne, C. Fisher, M. A. Canfield, H. Nichols, S. Oehninger, K. J. Doody, Obstetrics, Gynecology, and Reproductive Biology, Michigan State University, East Lansing, MI; Biostatistics, University of Michigan, Ann Arbor, MI; Redshift Technologies, Inc., New York, NY; Birth Defects Monitoring Branch, North Carolina Department of Health and Human Services, Raleigh, NC; Women’s and Children’s Health Section, North Carolina Department of Health and Human Services, Raleigh, NC; Massachusetts Center for Birth Defects Research and Prevention, Massachusetts Department of Public Health, Boston, MA; Congenital Malformations Registry, New York State Department of Health, Albany, NY; Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, TX; Epidemiology, University of North Carolina, Chapel Hill, NC; Jones Institute for Reproductive Medicine, Norfolk, VA; Center for Assisted Reproduction, Bedford, TX.

OBJECTIVE: To evaluate the risk of blastogenesis birth defects (those occurring within the first four weeks after conception) in children conceived with IVF and non-IVF ART (subfertile), IVF siblings, and fertile controls.

DESIGN: Cohort study, with exposure groups defined as IVF-exposed, siblings of IVF-exposed, subfertile, and fertile.

MATERIALS AND METHODS: IVF cycles in SART CORS resulting in live births in 2004-13 were linked to birth certificates and birth defects registries in four States (NY, TX, MA, and NC). All other births to each IVF-treated woman were also identified (IVF siblings). A 10:1 sample of non-IVF births in the same month as the IVF births were selected as controls; those with infertility treatment indicated on the birth certificate (but not in SART CORS) were categorized as subfertile, all others were categorized as fertile. Risks were modeled separately by plurality using logistic regression (AOR, 95% CI), adjusted for maternal age, race and ethnicity, education, parity, pre-gestational and gestational diabetes and hypertension, State and year of birth; children of fertile women were the reference group.

RESULTS: The study population included 942,920 children (see table). Analyses limiting the IVF group to cycles with autologous oocytes, partner sperm, and fresh embryos are shown by (*).

CONCLUSIONS: There was an increased risk of blastogenesis birth defects for singleton IVF births, but not for multiples born with IVF. There also appeared to be an increased risk in subfertile children, especially in multiple births.

Supported by: NIH Grant R01 HD84377.

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RISK OF CANCER IN CHILDREN WITH BIRTH DEFECTS AND EFFECT OF IVF CONCEPTION

B. Luke, M. B. Brown, E. Wantman, R. E. Meyer, N. E. Forestieri, S. Watkins, M. Yazdy, M. Browne, C. Fisher, M. J. Schymura, M. A. Canfield, H. Nichols, S. Oehninger, K. J. Doody, Obstetrics, Gynecology, and Reproductive Biology, Michigan State University, East Lansing, MI; Biostatistics, University of Michigan, Ann Arbor, MI; Redshift Technologies, Inc., New York, NY; Birth Defects Monitoring Branch, North Carolina Department of Health and Human Services, Raleigh, NC; Women’s and Children’s Health Section, North Carolina Department of Health and Human Services, Raleigh, NC; Massachusetts Center for Birth Defects Research and Prevention, Massachusetts Department of Public Health, Boston, MA; Congenital Malformations Registry, New York State Department of Health, Albany, NY; Bureau of Cancer Epidemiology, New York State Department of Health, Albany, NY; Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, TX; Epidemiology, University of North Carolina, Chapel Hill.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Children</th>
<th>Number of IVF Birth Defects</th>
<th>Number of Nondrug Birth Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>811,989</td>
<td>106,721</td>
<td>72,515</td>
</tr>
<tr>
<td>Singleton</td>
<td>789,306</td>
<td>57,571</td>
<td>38,591</td>
</tr>
<tr>
<td>Multiples</td>
<td>22,683</td>
<td>49,150</td>
<td>33,924</td>
</tr>
<tr>
<td>Rate/10,000 All</td>
<td>377.7</td>
<td>485.7</td>
<td>482.5</td>
</tr>
<tr>
<td>Rate/10,000 All</td>
<td>21.9</td>
<td>27.3</td>
<td>26.9</td>
</tr>
<tr>
<td>AOR, 95% CI</td>
<td>1.00 (Reference)</td>
<td>1.43 (1.18, 1.74)</td>
<td>1.53 (1.22, 1.90)</td>
</tr>
<tr>
<td>Rate/10,000 All</td>
<td>37.0</td>
<td>708.0</td>
<td>708.9</td>
</tr>
<tr>
<td>AOR, 95% CI</td>
<td>1.00 (Reference)</td>
<td>1.00 (0.72, 1.39)</td>
<td>0.93 (0.65, 1.32)</td>
</tr>
</tbody>
</table>
OBJECTIVE: To evaluate the risk of cancer in children with birth defects among a study population of children conceived with IVF and children born to fertile women.

DESIGN: Cohort study.

MATERIALS AND METHODS: IVF cycles in SART CORS resulting in live births in 2004-2013 were linked to birth certificates, birth defects registries through age one, and cancer registries through ages one to nine in four States (NY, TX, MA, and NC). A 10:1 sample of non-IVF births delivered in the same month as the IVF births were selected as comparison; those without any indication of infertility treatment on the birth certificate were categorized as fertile. For this analysis, IVF cycles were limited to those using autologous oocytes and sperm, and fresh embryos (72,434 cycles out of 106,721 cycles). Risks were modeled separately by plurality using logistic regression (AOR, 95% CI), adjusted for maternal age, race, Hispanic ethnicity, education, parity, pre-gestational and gestational diabetes and hypertension, and State and year of birth; children without birth defects were the reference group.

RESULTS: The study population and results are presented in the table below: Cancer rates were increased in children with birth defects, and the increase was greater for children of IVF-treated women compared to children of fertile women. The pattern was similar for singletons and multiples.

CONCLUSIONS: The risk of cancer was increased in children with birth defects. There was a non-significant increase in children born to IVF-treated women compared to children born to fertile women; further study is needed to refine this association.

Supported by: NIH Grant R01 HD84377.

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OBJECTIVE: To determine if different gonadotrophins and long agonist versus short antagonist stimulation protocols have an influence on embryo development, morphokinetic changes or outcome in older women.

DESIGN: A single-centre observational study of women aged 38-45 years who underwent stimulation cycles with either long or short protocol over a period of 6 months.

MATERIALS AND METHODS: A total of 464 cycles were analyzed. Embryos were classified as cleavage (D3) and blastocyst (D5) stage. Morphokinetic parameters and outcome in cycles using either long or short protocol were compared using t-test and chi-squared test.

RESULTS: There were no significant differences in morphokinetic parameters or outcome between long and short stimulation protocols in this study.

CONCLUSIONS: Different gonadotrophin regimens and protocols do not influence embryo morphology or outcome in women aged 38-45 years.
one or more top quality pre-embryos was similar for all age groups. The negative influence of age on implantation, clinical pregnancy and live births was evident in the oldest age group (43-45 years) but results in the 40-42 year age group were similar to those obtained in the 38-39 year age group.

CONCLUSIONS: Gonadotrophin treatment, COH protocol or age had no effect on the morphokinetics of the retrieved oocytes. Using the HP-hMG/uFSH combination did not significantly improve outcome measures compared to using HP-hMG alone.

<table>
<thead>
<tr>
<th>Implantated embryos</th>
<th>Agonist protocol</th>
<th>Antagonist protocol</th>
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</thead>
<tbody>
<tr>
<td>HP-hMG</td>
<td>HP-hMG/uFSH</td>
<td>HP-hMG</td>
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<td>0</td>
<td>116.78</td>
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</tr>
<tr>
<td>1</td>
<td>31.20.5</td>
<td>24.26.4</td>
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<table>
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<th>Antagonist protocol</th>
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</thead>
<tbody>
<tr>
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<td>HP-hMG/uFSH</td>
<td>HP-hMG</td>
</tr>
<tr>
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<td>122.80.89</td>
<td>75.89.42</td>
</tr>
<tr>
<td>1</td>
<td>25.16.222</td>
<td>24.42.32</td>
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<td>2</td>
<td>2.4.28</td>
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<table>
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<th>Antagonist protocol</th>
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<tbody>
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<td>HP-hMG/uFSH</td>
<td>HP-hMG</td>
</tr>
<tr>
<td>0</td>
<td>134.88.71</td>
<td>89.45.37</td>
</tr>
<tr>
<td>1</td>
<td>16.10.10.11</td>
<td>24.14.16.26.2</td>
</tr>
<tr>
<td>2</td>
<td>1.0.7</td>
<td>1.0.6</td>
</tr>
</tbody>
</table>

Supported by: The study was financed by Ferring Lagemidler A/S.

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EFFECTS OF DYSLIPIDEMIA ON IN-VITRO FERTILIZATION/INTRACYTOPLASMIC SPERM INJECTION (IVF/ICSI) PREGNANCY OUTCOME IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME (PCOS). X. Li X. Ma. Department of Reproductive Medicine, First Affiliated Hospital of Nanjing Medical University, Nanjing, China.

OBJECTIVE: To investigate the impact of dyslipidemia on IVF/ICSI pregnancy outcome in patients with PCOS.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: From July 2013 to March 2016, 468 cases of PCOS patients with antagonist protocol in in-vitro fertilization and embryo transfer were included using CCRM database of our center, cycles were divided into dyslipidemia group(DG,n=108) and normal blood lipids group(NG,n=360) according to the serum cholesterol(TC), triglyceride(TG), high-density lipoprotein(HDL), low density lipoprotein(LDL) levels. The general condition and clinical outcomes of the two groups were analyzed retrospectively, including the implantation rate(IR), clinical pregnancy rate(CPR), and live birth rate(LBR), etc. Besides, stratified analysis and multivariate logistic regression analysis were used to correct the impact of body mass index(BMI).

RESULTS: 1.Age,years of infertility, basic hormone levels and other basic data of two groups were similar (P>0.05), BMI of DG was significantly higher than NG(25.01±2.96 vs. 23.11±3.05, P<0.001).2.The high quality embryo rate, endometrial thickness, progesterone and LH levels on the day of HCG injection, severe hyperstimulation rate and miscarriage rate in two groups failed to exhibit remarkable difference (P>0.05). However, the number of oocytes retrieved, estradiol(E2) level on the day of HCG injection, IR, biochemical pregnancy rate(BPR), CPR and LBR in DG were significantly lower than NG(10.24±5.06 vs. 11.48±6.52, 15824.53±18292.22 vs. 18985.61±10751.99, 31.03% vs. 52.97%, 57.14% vs. 77.68%, 40.00% vs. 70.54%, 25.71% vs. 59.82%,P<0.05), the dose of Gn and days of stimulation were significantly higher compared to NG(1778.94±797.20 vs. 1358.84±510.01, 10.83±2.43 vs. 9.76±1.90, P<0.05).3.Stratified analysis showed that no matter in BMI < 24 or BMI ≥24 group, the dose of Gn and days of stimulation were significantly higher in DG than NG (P<0.05).However, the number of oocytes retrieved, E2 level on the day of HCG injection had obvious downturn, and the difference was statistically significant (P<0.05) in BMI ≥24 group.Even after adjustment of BMI, dyslipidemia still had a negative impact on IR,BPR,CPR and LBR (OR 0.377, 0.84 vs. 1.24±0.65,P=0.045). Logistic regression analysis also showed that the increase of TG levels was negatively correlated with the CPR in PCOS patients(OR 0.274,P=0.041).

CONCLUSIONS: In patients with PCOS, patients combined with dyslipidemia have a higher BMI, and dyslipidemia increases the dosage of Gn, reduces the IR,CPR and LBR, especially the increase of TG level, which has adverse effects on IVF/ICSI outcome.A reasonable control of blood lipid level and weight may help to improve the pregnancy outcome in patients with PCOS.

Supported by: The National Key Research and Development Program of China(2017YFC1001004), National Natural Science Foundation of China(81571403), Project supported by Health Department of Jiasu Province(FXK201221, F201313).

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A PROSPECTIVE FOLLOW-UP ON NEONATAL HEALTH FOLLOWING CONTROLLED OVARIAN STIMULATION WITH FOLLITROPIN DELTA OR FOLLITROPIN ALFA. J. C. Havelock,a P. Claman,b F. Sanchez Martin,b M. Gothberg,c E. Andersen,c B. Mannaerts,d A. Pacific Centre for Reproductive Medicine, Burnaby, BC, Canada; bDivision of Reproductive Medicine, Dept. Obstetrics and Gynecology, University of Ottawa, Ottawa Fertility Centre, Ottawa, ON, Canada; cGinemed, Seville, Spain; dFerring Pharmaceuticals, Global R&D, Copenhagen, Denmark.

OBJECTIVE: To evaluate the neonatal outcome and incidence of congenital malformations following treatment with an individualised dosing regimen of follitropin delta, a new recombinant FSH.

DESIGN: A prospective follow-up study of pregnant patients participating in comparative Phase 3 trials of follitropin delta (ESTHER-1 and -2).

MATERIALS AND METHODS: Subjects with a confirmed ongoing pregnancy 10-11 weeks after blastocyst transfer were followed with respect to pregnancy outcome and neonatal health at birth and 4 weeks after birth. The phase 3 trials were assessor-blind and all congenital malformations were adjudicated and graded as either major or minor in a blinded review. This is the first pooled analysis of all ongoing pregnancies following fresh and frozen cycles including 824 ongoing pregnancies and 898 fetuses.

RESULTS: In total, this follow-up included 444 fetuses (34 twins) in the follitropin delta group and 454 fetuses (40 twins) in the follitropin alfa group. At term, 401 women gave birth to 433 live-born neonates in the follitropin delta group and 404 gave birth to 440 live-born neonates in the follitropin alfa group, thus 2.5% (n=11) and 3.1% (n=14) of the fetuses, respectively, did not result in a live birth. In total 6 fetuses (3 in each group) were electively terminated due to major congenital malformations. The mean gestational age was 38.7 weeks in both groups. In the live-born neonates, 61 minor and major congenital malformations were reported in 47 neonates (45 pregnancies), 6.2% (34 in 27 neonates) occurred in the follitropin delta group and 4.5% (27 in 20) neonates in the follitropin alfa group. Major malformations included patent ductus arteriosus, ventricular septal defect, coarctation of the aorta, bicuspid aortic valve, double outlet right ventricle, pterylocnectasis, urethral valves, pelvic kidney, cleft palate, Beckwith-Wiedemann syndrome, adactyly, polydactyly and cryptorchism. The incidence of major malformations was 1.6% in both groups, 9 in 7 live-born neonates in the follitropin delta group and 10 in 7 live-born neonates in the follitropin alfa group.

CONCLUSIONS: This first comparative analysis of neonatal health following treatment with follitropin delta indicates no safety concern related to perinatal complications or birth defects.

Supported by: This study was sponsored by Ferring Pharmaceuticals.

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EFFECTS OF ADVANCED PATERNAL AGE AND MATERNAL AGE ON THE OUTCOME OF ICSI USING TESTICULAR SPERM. Y. Park,a S. Yoon,a J. Lee,a C. Lim,a I. Song,a C. Park,b H. Lee,c J. Lee,c J. Seo,c S. Lee. aLaboratory of Reproductive Medicine, Cheil General Hospital & Women’s Healthcare Center, Dankook University College of Medicine, Seoul, Korea, Republic of; bDepartment of Obstetrics & Gynecology, Cheil
than 40 years of age?.

Which is the cost for having a live born considering the impact in our national health system. The statistical analysis was performed using the Fischer’s exact test and ANOVA test with a significant p value <0.05.

RESULTS: During this period we performed 3496 IVF cycles, from which 93.2% (3258) corresponded to cycles financed by the health system coverage and 33.8% of which were IVF cycles in women over 40 years of age. In the same period we compared THBR in women <35 years and 35-40 years with health coverage (48.9% and 42.3 % respectively), which were significantly higher than those in women >40 (p<0.05). In our country for every completed IVF treatment, social and private health system destine about USD 5000 (including assisted reproduction techniques and medication). Therefore, the cost for a healthy live born in women over 40 years is approximately USD 70.641 (1102 cycles x USD 5000/N) of live born: 78), 35-40: USD 11820 and <35: USD 10231.

CONCLUSIONS: Maternal age directly influences THBR, with significant higher rates in women <35 or 35-40 when compared to >40. There is no statistical difference (p=0.18) in THBR within patients <40. The monetary cost estimated for having a healthy live born in women over 40 year of age is nearly 6 times higher when compared with women under 40. In women older than 40, our cost per healthy live born is higher than reported in the literature for the same age group. This might be a useful information in order to reevaluate the public health politics particularly in countries, like Argentina, that provides free assisted reproductive treatments in women over 40 year.

References: Yildiz MS, Khan MM. Opportunities for reproductive tourism: cost and quality advantages of Turkey in the provision of in-vitro fertilization (IVF) services. BMC Health Serv Res. 2016 Aug 12;16(a):378.

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Usable Blastocyst Rate in Donor Oocyte Cycles: Performance of Frozen Sperm with ICSI in an Extended Culture System. H. Shakarzi,1 L. Gilroy,2 S. Amaral,1 M. P. Leonires,1 E. Paganietti,3 S. Richlin.4 Obsetrics and Gynecology, The Stamford Hospital, Stamford, CT;4 Reproductive Medicine Associates of Connecticut, Newington, CT;4 Reproductive Medical Associates of Connecticut, Newington, CT.

OBJECTIVE: We sought to assess the fertilization and usable blastocyst rates in donor oocyte (DO) cycles using cryopreserved and fresh sperm with ICSI in an extended culture system.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: Data was collected from our EMR for patients using fresh DO from January 2017-April 2018 at a single private IVF center. Inclusion criteria: fresh DO cycles, use of fresh or cryopreserved sperm and use of ICSI for fertilization. Exclusion criteria: Surgically retrieved sperm, concentration <5 million/mL, samples with 0% motility.
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CLINICAL PREGNANCY FOLLOWING GnRH AGONIST ADMINISTRATION IN LUTEAL PHASE OF FRESH OR FROZEN ASSISTED REPRODUCTIVE TECHNOLOGY (ART) CYCLES: SYSTEMATIC REVIEW AND META-ANALYSIS. C. Le,a P. Lehert,b D. V. Do,c T. Q. Le,d T. M. Vo,c aDepartment of Infertility, Tu Du Hospital, Ho Chi Minh, Viet Nam; bUniversity of Melbourne, Melbourne, Australia; cUniversity of Medicine and Pharmacy of Ho Chi Minh City Vietnam, Ho Chi Minh, Viet Nam; dTu Du Hospital, Ho Chi Minh, Viet Nam.

OBJECTIVE: To study if the GnRH agonist administration in luteal phase improves clinical pregnancy rate of fresh and frozen embryo transfer. Also, this meta-analysis compares the treatment effect of luteal GnRH agonist administration between two ovarian stimulation protocols of fresh cycles (long agonist and antagonist), and between two types of treatment: fresh and frozen embryo transfers.

DESIGN: Systematic review and meta-analysis (according to PRISMA statement). PROSPERO registration number was CRD42017059152.

MATERIALS AND METHODS: For fresh cycles, we include randomised control trials to assess the effects of the GnRH agonist in luteal phase. For frozen embryo transfer cycles, we include randomised control trials and prospective cohort studies (in assessing a possible difference through meta-regression). Studies examining women undergoing assisted reproductive technology (ART) treatment with fresh or frozen embryo transfer cycles (including oocyte recipient cycles) were eligible for the review. Unpublished studies were also included. The intervention was addition of GnRH agonist during the luteal phase. Clinical pregnancy among participating women is the primary outcome. A computerized literature search in PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and RCT registries (clinicaltrials.gov) covering the period up to May 2017 was performed.

RESULTS: For the overall 20 studies (4824 patients), clinical pregnancy rate significantly increased in GnRH agonist administration group (RR 1.25, 95% CI 1.15-1.36; p<0.001). Among fresh cycles, no significant difference was observed between long agonist and antagonist protocol (RR = 1.13, 95% CI 0.94-1.39, p=0.194). The effect in frozen embryo cycles is homogenous (I²=0%, Q-test, p=0.845) and significantly more benefit than in fresh cycles (RR = 1.22, 95% CI 1.03-1.43, p=0.016).

CONCLUSIONS: GnRH agonist administration in luteal phase may improve clinical pregnancy rate in patients undergoing ART treatment, regardless fresh or frozen embryo transfers. This effect in frozen cycles is homogenous and higher than in fresh cycles. No significant difference of benefit is found between two protocols of fresh cycles.

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ATTACHMENT IN DONOR CONCEPTION: CURIOSITY, SEARCH, AND CONTACT. E. Lozano,a C. Fraley,a W. Kramer,a bUniversity of Illinois at Urbana-Champaign, Urbana-Champaign, IL; cDonor Sibling Registry, Nederlands, CO.

Primary outcomes: Fertilization rate and usable blastocyst rate (UBR) were calculated as 2 pm/MII and 2 pm/usable blast respectively. Cycles utilizing different sperm sources with one egg source were considered individually. All mature oocytes were fertilized using ICSI. Use of fresh or cryopreserved sperm. Embryos were grown in a 2 step extended culture system, evaluated on day 1 for fertilization and days 5-7 for blastocyst development. Embryos deemed as usable blastocysts were those acceptable for embryo transfer and/or cryopreservation using Gardner’s criteria. Statistical analysis was performed by the Stanford Hospital statistician using IBM SPSS software.

RESULTS: A total of n=105 fresh donor oocyte cycles met inclusion criteria. A total of n=1470 mature oocytes (MI) were injected. The mean oocyte age was 27.0. Of these cycles, n=16 (15.2%) utilized fresh sperm. ICSI was performed on n=295 MII in the fresh sperm group. Fresh sperm displayed a mean fertilization rate of 79.7% (SD=0.163) and an average UBR of 57.1% (SD=0.260). The remaining cycles, n=89 (84.8%) used cryopreserved sperm, in which a total of n=1175 MII were injected. For the cryopreserved sperm group, the mean fertilization rate was 77.9% (SD=0.189) and the average UBR was 56.4% (0.228).

CONCLUSIONS: Frozen sperm in donor egg cycles demonstrated equivalent fertilization and usable blastocyst rates as compared to fresh sperm. Patients utilizing DO may not be able to use a fresh sperm sample. This is especially important in cycles using a gestational carrier. These data are reassuring for patients who need to use frozen sperm with DO in a modern extended culture system. Prospective trials will need to be completed to truly answer the question: Is frozen sperm as good as fresh using ICSI in the modern IVF laboratory.

References:

Donor Oocyte Data Jan 2017- April 2018

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<th>Sperm Type</th>
<th>Cycles</th>
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</tbody>
</table>

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OBJECTIVE: Through examining the level of serum vitamin D in couples undergoing IVF/ICSI, the study was aimed to investigate whether serum vitamin D correlated with fertilization, embryo development and endometrial receptivity in IVF/ICSI laboratory.

RESULTS: Women were grouped by serum 25OHD quartiles: (r<0.05, P=0.1889) and the average UBR was 56.4% (0.228).

65.53%, respectively (r<0.016). The effect was observed between long agonist and antagonist protocol (RR= 1.13, 95% CI 0.94-1.39, p=0.194). The effect in frozen embryo cycles is homogenous (I²=0%, Q-test, p=0.845) and significantly more benefit than in fresh cycles (RR= 1.22, 95% CI 1.03-1.43, p=0.016).

CONCLUSIONS: Maternal vitamin D mainly may have an effect on fertilization process in IVF, but not on embryo development and endometrial receptivity. Besides, fertilization, embryo development and endometrial receptivity were not correlated with serum 25 OHD levels in men. Further randomized controlled trials about vitamin D supplementation and fertilization process were merited.

Supported by: Supported in part by grants from the National Natural Science Foundation of China 81571464; Chinese Medical Association Clinical Medicine Research Special Fund 16020430659.

REFERENCE:
OBJECTIVE: The present study examined whether individual differences in attachment predict adults’ self-reported curiosity about their donor conception identity, as well as attempts to find the donor and establish contact.

DESIGN: Self-report data was collected from 488 donor conceived adults from the Donor Sibling Registry (DSR). More specifically, the Experiences in Close Relationships-Relationship Structures (ECR-RS) was administered to evaluate individual differences in attachment, with respect to their general attachment (avoidance: α = .86; anxiety: α = .85), and attachment to several interpersonal targets: (1) biological parent (avoidance: α = .95; anxiety: α = .86); (2) non-biological, social parent (avoidance: α = .95; anxiety: α = .91); (3) donor - if known to the participant (avoidance: α = .89; anxiety: α = .90). To measure donor exploration, we used a forced choice question: “Have you tried to locate or find your donor” (yes/no). Additionally, we asked, “Have you made any attempt to contact your donor” (yes/no), although this question was only presented to participants who possessed knowledge of their donor’s identity. The Donor Conception Identity Questionnaire (DCIQ) assesses individuals’ willingness to integrate knowledge of donor conception into their subjective sense of identity (α = .62) and Avoidance (α = .76) of donor contact.

MATERIALS AND METHODS: Our basic analytic plan was pre-registered on the Open Science Foundation (OSF) project page before data analysis began (https://osf.io/as9bm/). All multivariate analyses were conducted in R. The dataset used in this manuscript is available at the Open Science Foundation (OSF) project page.

RESULTS: Contrary to our prediction, there was no association between donation status and attachment. As reported above, the DCIQ has two subscales: Curiosity (α = .62) and Avoidance (α = .76) of donor contact.

CONCLUSIONS: The current investigation is the first of its kind to investigate individual differences in adult attachment with respect to donor conception. Overall, the current study demonstrates that people who are anxious in their attachments with the parents who raised them tend to be more curious about their donor conception than those who are not, but they are not necessarily more likely to have searched for the donor or established contact with him/her.

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DELIVERIES IN VERY ADVANCED MATERNAL AGE: SHOULD WE TRANSFER A SINGLE EMBRYO OR MORE?: R. Meyer, R. Orvieto, Y. Tinterman, T. Gorodesky, S. Toussia-Cohen, A. Israel, I. Hendler, M. Simchen, R. Machtlinger, Obstetrics and Gynecology, Sheba Medical Center, Ramat-Gan, Israel; δSackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel; &Faculty of Medicine, St. Gorge’s University of London Medical School, London, United Kingdom; δFamily Medicine, Clalit Health Services, Jerusalem, Israel.

OBJECTIVE: Given the high probability of achieving a viable pregnancy with the use of oocyte donation in the fifths and sixths decades of life, the number of transferred embryos is an important factor to consider. The aims of this study were to compare the outcomes of twin vs. singleton gestations and to assess the effect of age on adverse maternal and neonatal outcomes among women who were ≥45 years old at delivery.

DESIGN: A retrospective cohort study.

MATERIALS AND METHODS: We reviewed the medical records of all women aged ≥45 at delivery that gave birth ≥24 weeks gestation at a single tertiary medical center, between March 2011 and January 2018. Only women that conceived by in vitro fertilization (IVF) were included. Analysis included baseline maternal characteristics, pregnancy, delivery, neonatal and postpartum outcomes. Multivariate logistic regression was used to evaluate the associations between twin pregnancies and adverse outcomes. Additional analyses were performed to evaluate the association between age and complications in both groups and to compare the outcomes between first and second delivery among a group of women that delivered singletons twice during the study period.

RESULTS: Out of 68,466 deliveries during this period, 612 (0.9%) were of women ≥45 years old, of whom 492 women conceived by IVF (395 singletons and 97 twin pregnancies) and were included in the analysis. Baseline characteristics did not differ between groups. Patients with twins had higher mean maternal age (47.5% vs. 46.6%, p = 0.001), gestational diabetes mellitus (35.4% vs. 23.8%, p = 0.02), cholestasis of pregnancy (5.2% vs. 0.5%, p = 0.004), deliveries <32 weeks of gestation (8.2% vs. 1.3%, p = 0.001), and small for gestational age neonates (18.6% vs. 7.6%, p = 0.001). Cesarean section was performed in 91.8% of twin and 83.3% of singleton pregnancies (p = 0.015). Post-partum, those who delivered twins needed more blood transfusions (10.3% vs. 4.8%, p = 0.039). There were no cases of maternal or neonatal mortality in either group. The risk of any pregnancy or neonatal complications did not increase with advancing maternal age for either group. Among women who delivered twice at the age of 45 years and more there was no significant difference in outcomes between first and second pregnancies.

CONCLUSIONS: In women ≥45 years old, twin gestations conceived by IVF are associated with significantly higher rates of adverse pregnancy outcomes compared with singleton gestations, whereas the effect of further advanced maternal age is limited. Effort should be directed towards reducing the number of iatrogenic twin pregnancies in the older population.

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**K. Kitaya**, T. Ishikawa. Reproduction Clinic Osaka, Osaka, Japan; Reproduction Clinic Tokyo, Tokyo, Japan.

**OBJECTIVE:** Undescribed tests (UT) is associated with impairment of germ cell maturation and subsequent infertility in adulthood because the UT is exposed to a higher temperature compared with the scrotal temperature and there is progressive Leydig and Sertoli cell atrophy. There has been very few studies of ICSI with a focus on, or large enough numbers to examine, the specific outcomes associated with male factor infertility including NOA with the history of cryptorchidism.

**DESIGN:** A retrospective study in a reproductive center.

**MATERIALS AND METHODS:** This study was conducted in 50 NOA patients post cryptorchidism, 526 unexplained NOA patients without past history (unexplained NOA; not including after orchidopexy, Klinefelter syndrome, cryptozoospermia, mumps orchitis, etc), and 141 OA patients and the ICSI outcomes of their wives were assessed between September 2013 to December 2017. We evaluated sperm retrieval rate (SRR) of micro dissection TESE (micro TESE), two pronuclei (2PN) oocyte rates, blastocyst development rates, good-quality blastocyst (Grade 3BB and above on day 5 by the Gardner scoring) rates, and clinical pregnancy rates per embryo transfer (ET) in 33 cases the history of UT, 96 cases of unexplained NOA, and 123 cases of OA. The wives age at ICSI post cryptorchidism, unexplained NOA, and OA were 34.1±3.6 years, 34.9±3.8 years, and 34.6±4.8 years, respectively.

**RESULTS:** SRR of micro TESE in NOA with the history of cryptorchidism (32/50=64.0%) was higher than unexplained NOA (107/526=20.3%) (p<0.001). No correlation was found between serum FSH, LH, and T level with the success of sperm retrieval. Testicular volume and patient age at orchidopexy also did not affect the SRR for micro TESE. 2PN oocyte, blastocyst development, and good-quality blastocyst rates were 52.5%, 34.7%, and 22.4% in NOA post cryptorchidism, 54.5%, 47.2%, and 19.3% in unexplained NOA, and 62.3%, 52.2%, and 21.9% in OA, respectively. 2PN oocyte rate of NOA post cryptorchidism and unexplained NOA were lower than OA (P<0.001). Blastocyst development rate of unexplained NOA was lower than OA (P<0.05). Clinical pregnancy rates per ET were 33.8% in NOA post cryptorchidism, 29.0% in unexplained NOA, and 39.3% in OA, respectively (no significant difference). Seventeen healthy children have been born and 3 patients are on going pregnancy in NOA post cryptorchidism couples.

**CONCLUSIONS:** Micro TESE is particularly helpful for sperm retrieval for NOA post cryptorchidism and ICSI outcomes in NOA post cryptorchidism are unexplained NOA and OA.

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**MATERNAL ENDOMETRIAL SECRETIONS AT THE TIME OF TRANSFER IS PREDICTIVE OF IVF OUTCOME.** N. McCubbin, J. Parks, B. McCallie, W. B. Schoolcraft, M. Katz-Jaffe, Colorado Center for Reproductive Medicine, Lone Tree, CO.

**OBJECTIVE:** Successful implantation is dependent on the elaborate molecular dialogue between a viable embryo and a receptive endometrium. Tight regulation of embryonic signaling pathways, as well as specific molecular dialogue between a viable embryo and a receptive endometrium.

**DESIGN:** Research study.

**MATERIALS AND METHODS:** In fertile women were recruited with IRB consent prior to an estradiol/progesterone replacement frozen embryo transfer (FET) with a euploid blastocyst. Uterine secretions were collected by gentle aspiration (≤2-5ul) immediately before the FET. The aspiration techniques had no impact on clinical pregnancy rate nor were any maternal complications reported. Individual endometrial aspirates (n = 22) were blindly analyzed for mirRNA expression using qPCR (TaqMan™, Thermo Fisher) before un-blinding to determine significance in association with outcome (negative [intra-cytoplasmic or implantation with fetal heart tone] using REST™ statistical software (Qiagen), with significance at P<0.05.

**RESULTS:** A significant uterine mirRNA profile was observed for each of the three implantation outcomes at the time of FET (P<0.05; ≥2-fold change). Negative implantation was associated with increased expression of 9 miRNAs, including miR-17 (P<0.05; 4.5-fold change). A known target gene of miR-17 is VEGFA, a signal protein essential for implantation that is secreted by the implanting embryo, miR-17 negatively regulates VEGFA and validation in individual blastocysts co-cultured with endometrial cells confirmed decreased VEGFA expression with poorer outcomes (P<0.05).

A biochemical pregnancy was associated with increased expression of 4 miRNAs, including miR-232 (P<0.05; 3.7-fold change), a known repressor of transcription factors that play critical roles in reproductive processes. There were no miRNAs that displayed increased expression with positive implantation (with fetal heart tone).

**CONCLUSIONS:** This study utilized a minimally invasive technique of sampling the uterine environment immediately prior to a euploid embryo transfer, to reveal a unique miRNA expression that distinguishes the different implantation outcomes. This altered miRNA expression impacts the embryo-endometrial molecular dialogue, including transcription levels of key signaling molecules, compromising implantation. Predicting the endometrial molecular microenvironment may allow for fine tuning of procedures for infertility patients thereby improving implantation outcomes.

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**ANEUPLOIDY RATES AMONG YOUNG OOCYTE DONORS: IS THERE AN OPTIMAL AGE FOR DONATION?** L. R. Hoyos,a C. Y. Cheng,a K. Brennan,a G. Hubert,a B. Wang,a R. P. Buyalos,b M. Shamoni,a bOB/GYN, University of California, Los Angeles, Los Angeles, CA; cFertility and Surgical Associates of California, Thousand Oaks, CA; dREI, FSAC UCLA, Thousand Oaks, CA.

**OBJECTIVE:** Women age ≤25 have been reported to have less favorable IVF treatment outcomes compared to women age 25-35 (1). A bimodal distribution of aneuploidy rates has also been described in the general IVF population, with most women ≤25 in that study having higher aneuploidy rates than women age 35-37 (2). A difference in euploidy rates among young oocyte donors could change the way donors are selected, provide evidence of benefit for preimplantation genetic testing for aneuploidy (PGT-A) in some of these cycles, as well as increase our overall understanding of euploidy according to age. Therefore, our objective was to examine euploidy rates among age sub-groups of young oocyte donors.

**DESIGN:** Retrospective cohort.

**MATERIALS AND METHODS:** All donor oocyte IVF cycles with trophectoderm biopsy for PGT-A using either aCGH or NGS between January 2015 and December 2016 at a single fertility clinic were screened for inclusion. Only cycles from donors age 21-30 were included for analysis. Cycles were then divided by donor age in two groups: Group 1: 21-25, Group 2: 26-30. The main outcome measure was blastocyst euploidy rate. Statistical analysis were performed with a t-test; percentage data were transformed using arcsine transformation and then compared with the t-test. Differences with p<0.05 were considered significant in all comparisons.

**RESULTS:** A total of 132 donor cycles with 1123 biopsied blastocysts were included. There were 64 cycles done with donors age 21-25 and 68 cycles with donors age 26-30; mean donor age was 23.2 and 27.8 years respectively. The total number of blastocysts formed were 865 and 760, whereas the total number of blastocysts biopsied were 546 and 577 for group 1 and 2 respectively. There were no statistical differences in the average amount of gonadotropins administered, average peak estradiol, or blastocyst formation rate. The average number of oocytes retrieved (33.4 ± 13.3 (SD) vs. 28.1 ± 11.2 (SD), p=0.015) and the euploidy rate (81.40% ± 18.20% (SD), p=0.037) in group 1 were significantly higher than in group 2.

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<th>Age group 1</th>
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**CONCLUSIONS:** In contrast to prior studies, these data demonstrate that oocyte donors age 21-25 have higher euploidy rates compared to donors age...
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INCREASED MEAN ARTERIAL PRESSURE IN CHILDREN CONCEIVED FROM IVF COMPARED TO OTHER METHODS OF ASSISTED REPRODUCTION. A. Adeleye,1 M. Laron,2 L. Zablotska,2 P. Rinaudo,3 R. Lustig,1 M. Cedars,1 University of California San Francisco, San Francisco, CA; UC San Francisco, San Francisco, CA; Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA; University of California San Francisco, San Francisco, CA; University of California San Francisco Center for Reproductive Health, San Francisco, CA.

OBJECTIVE: The Developmental Epidemiological Study of Children born from Reproductive Technologies (DESCRT) is the first prospective investigation of children conceived with assisted reproductive technologies (ART) in the U.S. The objective of this pilot study was to determine if the infertility diagnosis or treatments used are associated with signs of early metabolic dysfunction.

DESIGN: Prospective single center cohort study.

MATERIALS AND METHODS: Children conceived at an academic infertility practice with ART (intrauterine insemination (IUI), in vitro fertilization (IVF/ICSI), frozen embryo transfer (FET)), or spontaneously after greater than one year of trying during 2000-2014, were invited for an assessment, which included anthropomorphic measurements, blood pressure, fasting insulin, glucose, and lipid panels. The primary outcomes were mean arterial pressure (MAP), BMI Z-score, HOMA-IR, and triglyceride/HDL ratio (Tg/HDL). Participants were compared by parental infertility diagnosis or conception method using Kruskal-Wallis test.

RESULTS: The median age of the 29 children enrolled was 7.1 years (3.6 – 12.6 years). The majority of children were conceived with couples with unexplained infertility (n=18, 65.7%), with others conceived in the presence of PCOS, male factor, or tubal disease (n=11). Children were conceived with ART methods as follows: 48% (n=14) from IVF/ICSI, 27% (n=8) from FET and 24.1% (n=7) from IUI or spontaneously (non-ART). There were no differences in MAP, BMI z-score, HOMA-IR, or Tg/HDL ratio (Tg/HDL). Participants were compared by parental infertility diagnosis or conception method using Kruskal-Wallis test.

MAP 74 [69.75-7.5] 77.5 [75.5-83.0] 72.0 [64.5-75.5] 0.03* Mean Systolic Blood Pressure (mmHg) 105 [103-108.5] 110.8 [102-115.5] 100.8 [89.5-107.3] 0.06 Mean Diastolic Blood Pressure (mmHg) 56.5 [49.5-6.1] 62.5 [59.8-66.8] 55.8 [51.3-62.0] 0.03* BMI z-score -0.4 [-1.0-0.11] 0.12 [-0.1-0.76] 0.35 [-0.79-0.79] 0.42 HOMA-IR 0.54 [0.41-0.64] 0.41 [0.31-0.84] 0.25 [0.09-0.63] 0.56 Tg/HDL 1.2 [1.16-1.24] 0.84 [0.63-1.05] 0.64 [0.58-1.02] 0.06

OBJECTIVE: To determine if instructional videos about ovarian stimulation medications through the Learning from Online Video Education (LOVE) study could improve confidence in medication administration and infertility self-efficacy scale scores during a first ovarian stimulation cycle.

DESIGN: Single center double-blinded randomized clinical trial.

MATERIALS AND METHODS: Patients undergoing their first cycle of ovarian stimulation were eligible to participate. Enrolled participants received a unique login to an internet based video platform developed at our infertility practice. Each account was randomized to show control videos about the ovarian stimulation process or experimental videos about preparing and administering stimulation medications. Participants were blinded to the video content categories, but informed that two types of videos existed. Investigators were blinded to treatment assignments. Subjects completed an internet-based questionnaire prior to oocyte retrieval which included questions about confidence taking medications, medication errors and the Infertility Self Efficacy questionnaire (ISES). The primary outcome of the LOVE study was the ISES score. Significance was determined at the 0.05 level. Outcomes were evaluated using a univariate ANOVA or logistic regression were appropriate. This study was enrolled with clinicaltrials.gov NCT02979990.

RESULTS: 314 patients participated in the LOVE study after accounting for dropouts (n=54). There were no differences in age, income, education, or employment between the two groups. Participants were randomized to medication videos (n=161) or control videos (n=153). There was no difference in ISES scores between control and experimental groups (p = 0.92). Participants randomized to medication administration videos were more likely to report feeling confident taking their medications, OR3.52 (CI [1.18 to 6.83] p <0.01). Fifty-five percent of participants watched study videos (n=137). In a per protocol analysis, participants randomized to medication administration videos were more likely to find videos helpful OR 2.43 (CI 0.96-6.13) and this neared significance p=0.06. Medication errors were reported by 32.8% of control participants compared to just 15% (n=11) of subjects who watched medication videos. Those who watched medication videos had a 37% lower risk of errors (OR 0.63 (CI [0.33-1.19]) p=0.159 though this difference was not significant.

CONCLUSIONS: Watching instructional videos about ovarian stimulation medication was associated with increased confidence in medication administration and decreased medication errors during the first cycle of ovarian stimulation. Though instructional videos may make patients feel more confident, this was not associated with a change in infertility self-efficacy scale scores.

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A RANDOMIZED DOUBLE BLIND CLINICAL TRIAL: BUILDING CONFIDENCE DURING OVARIAN STIMULATION THROUGH THE LOVE STUDY. A. Adeleye,4 S. Takimoto,3 K. Cruz,3 L. A. Pasch,2 H. G. Heddleston,4 University of California, San Francisco, San Francisco, CA; UCGBYN, UCSF, San Francisco, CA.

OBJECTIVE: To determine if instructional videos about ovarian stimulation medications through the Learning from Online Video Education (LOVE) study could improve confidence in medication administration and infertility self-efficacy scale scores during a first ovarian stimulation cycle.

DESIGN: Single center double-blinded randomized clinical trial.

MATERIALS AND METHODS: Patients undergoing their first cycle of ovarian stimulation were eligible to participate. Enrolled participants received a unique login to an internet based video platform developed at our infertility practice. Each account was randomized to show control videos about the ovarian stimulation process or experimental videos about preparing and administering stimulation medications. Participants were blinded to the video content categories, but informed that two types of videos existed. Investigators were blinded to treatment assignments. Subjects completed an internet-based questionnaire prior to oocyte retrieval which included questions about confidence taking medications, medication errors and the Infertility Self Efficacy questionnaire (ISES). The primary outcome of the LOVE study was the ISES score. Significance was determined at the 0.05 level. Outcomes were evaluated using a univariate ANOVA or logistic regression were appropriate. This study was enrolled with clinicaltrials.gov NCT02979990.

RESULTS: 314 patients participated in the LOVE study after accounting for dropouts (n=54). There were no differences in age, income, education, or employment between the two groups. Participants were randomized to medication videos (n=161) or control videos (n=153). There was no difference in ISES scores between control and experimental groups (p = 0.92). Participants randomized to medication administration videos were more likely to report feeling confident taking their medications, OR3.52 (CI [1.18 to 6.83] p <0.01). Fifty-five percent of participants watched study videos (n=137). In a per protocol analysis, participants randomized to medication administration videos were more likely to find videos helpful OR 2.43 (CI 0.96-6.13) and this neared significance p=0.06. Medication errors were reported by 32.8% of control participants compared to just 15% (n=11) of subjects who watched medication videos. Those who watched medication videos had a 37% lower risk of errors (OR 0.63 (CI [0.33-1.19]) p=0.159 though this difference was not significant.

CONCLUSIONS: Watching instructional videos about ovarian stimulation medication was associated with increased confidence in medication administration and decreased medication errors during the first cycle of ovarian stimulation. Though instructional videos may make patients feel more confident, this was not associated with a change in infertility self-efficacy scale scores.
comparing to IVF. Disadvantages include lower pregnancy rates and thus longer time to conception. PGT-A provides the advantage of lower miscarriage rates (SAB). We sought to compare the pregnancy outcomes and cost per cycle of IUI and IVF/PGT-A.


**MATERIALS AND METHODS**: An analysis of 2 years of IUI cycles (n=2447) and outcomes was performed. All protocols were included; natural, oral medication (letrozole or clomid) and gonadotropin (GND) cycles. Primary outcomes were clinical pregnancy rates (CPR) defined by presence of gestational sac/cycle and SAB rates. Comparisons were then made to IVF/PGT-A with Next Generation Sequencing (NGS) outcomes at the same center. Students T-test and chi-squared tests were used (p < 0.05).

**RESULTS**: 312 patients from IUIs had a clinical pregnancy (CP) for a CPR of 12.8%. CPRs were then compared by IUI protocol. 9.0% of CPs resulted from Natural IUI cycles with an SAB rate of 14.6%. Use of letrozole resulted in 12.8% of CPs with an SAB rate of 25.2%. Clomid IUI cycles resulted in 30.2% of CPs with an SAB rate of 25.2%. Clomid IUI cycles resulted in 46.5% of CPs with an SAB rate of 31.7%. GND IUI cycles were 14.2% of CPs with an SAB rate of 23.3%. The SAB rate was not statistically different across protocols. All IUI outcomes were then compared to IVF/PGT-A outcomes as well as a comparison of cost (Table 1). The average cost of 1 IUI cycle was approximately $1/10th the cost of IVF with PGT-A but with approximately 1/8th the rate of ongoing pregnancy/live birth (OP/LB).

**CONCLUSIONS**: IUI is an inexpensive treatment method when compared to IVF/PGT-A; ~10 IUIs achieve a similar OP/LB rate at a lower total cost. However, the price does not reflect the emotional and financial cost of SAB and the extended period to OP/LB. Understanding that IUI can be characterized by half the price but twice the time and twice the SAB rate may be a helpful tool for patient counseling.

### Pregnancy Outcomes and Cost comparison of IUI compared with IVT/PGT-A tested with NGS

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<tbody>
<tr>
<td>Age</td>
<td>34.8±3.9</td>
<td>35.6±4.6</td>
<td>&lt;0.59</td>
</tr>
<tr>
<td>CPR</td>
<td>12.8% (312/2447)</td>
<td>71.6% (379/529)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BFR</td>
<td>5.8% (20/344)</td>
<td>8.7% (36/416)</td>
<td>&lt;0.14</td>
</tr>
<tr>
<td>SAB rate</td>
<td>26.6% (83/312)</td>
<td>12.4% (47/379)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>OP/LB rate</td>
<td>7.32% (179/2447)</td>
<td>60.2% (328/529)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Avg Cost/cycle</td>
<td>$1,750.00</td>
<td>$30,000.00</td>
<td></td>
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<tr>
<td>(includes 1 transfer)</td>
<td></td>
<td></td>
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<tr>
<td>Natural IUI Cycle</td>
<td>$500.00 (14.6%)</td>
<td></td>
<td></td>
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<tr>
<td>Cost (SAB rate)</td>
<td></td>
<td></td>
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<tr>
<td>Letrozole IUI Cycle</td>
<td>$1750.00 (25.2%)</td>
<td></td>
<td></td>
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<tr>
<td>Cost (SAB rate)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Clomid IUI Cycle</td>
<td>$1750.00 (31.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost (SAB rate)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>GND IUI Cycle</td>
<td>$3750.00 (23.3%)</td>
<td></td>
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<tr>
<td>Cost (SAB rate)</td>
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</table>

**FRESH vs. Commercially-Banked FROZEN DO. Mean no. of blastocysts (BL) transferred/cycle=1 for both.**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>FRESH DO (n=174; mean no. oocytes used/cycle=21)</th>
<th>FROZEN DO (n=67; mean no. oocytes used/cycle=7)</th>
<th>P Value (mean no. oocytes used/cycle: &lt;0.0001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2PN Fertilization Rate</td>
<td>2295/2939 (78%)</td>
<td>327/420 (78%)</td>
<td>0.90</td>
</tr>
<tr>
<td>CUR/2PN</td>
<td>1485/2317 (64%)</td>
<td>180/327 (55%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Non-PGT-A Cycles n (with ET)</td>
<td>33 (33)</td>
<td>60 (59)</td>
<td></td>
</tr>
<tr>
<td>*In these cycles, 0/33 (0%) FRESH vs.</td>
<td></td>
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<tr>
<td>5/60 (8%) FROZEN were cancelled</td>
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<tr>
<td>for poor embryo development</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPR for FIRST ET</td>
<td>22/33 (67%)</td>
<td>36/59 (61%)</td>
<td>0.66</td>
</tr>
<tr>
<td>LBR for FIRST ET</td>
<td>20/33 (61%)</td>
<td>31/59 (53%)</td>
<td>0.52</td>
</tr>
<tr>
<td>No. cycles with supernumerary BL - Mean</td>
<td>32/33 (97%) - 7</td>
<td>41/59 (70%)</td>
<td>0.001</td>
</tr>
<tr>
<td>BL frozen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGT-A Cycles n (with ET)</td>
<td>119 (93)</td>
<td>7 (5)</td>
<td></td>
</tr>
<tr>
<td>No. Cycles with at Least 1 Euploid BL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Euploid BL / Biopsied BL</td>
<td>534/1050 (51%)</td>
<td>12/22 (55%)</td>
<td>0.83</td>
</tr>
<tr>
<td>CPR for FIRST ET</td>
<td>62/93 (67%)</td>
<td>1/5 (20%)</td>
<td>0.033</td>
</tr>
<tr>
<td>LBR for FIRST ET</td>
<td>56/93 (60%)</td>
<td>0/5 (0%)</td>
<td>0.01</td>
</tr>
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</table>

**References:**

Supported by: None.

**P-242 Tuesday, October 9, 2018 6:30 AM**

**FRESH VS. FROZEN DONOR OOCYTES (DO) - LOOKING AT THE BIG PICTURE, IS ONE SUPERIOR?**

NYU Fertility Center, New York, NY.

**OBJECTIVE:** Since the first reported birth in 1983, many children have been born using DO. Donated sperm is mostly frozen, quarantined and purchased from banks; however, using FRESH female gametes has long been viewed as the gold standard in DO. As FROZEN DO banks have emerged in recent years, using FROZEN DO has become common, changing the treatment-process model. The use of FROZEN DO may simplify logistics and allow recipients more choices as well as lower infection risk, time pressures and/or cost. Thus, we aimed to compare outcomes and processes using FRESH vs commercially-banked FROZEN DOs at our program.

**DESIGN**: Retrospective cohort at a single large university program.

**MATERIALS AND METHODS**: We reviewed all FRESH and FROZEN DO cycles from 1/1/2015 - 12/31/2017. Cycles with and without preimplantation genetic testing for aneuploidy (PGT-A) were included. Primary outcomes were clinical pregnancy rate (CPR) and ongoing pregnancy (>12 weeks gestation) / live birth rate (LBR).

**RESULTS**: See Table. 164 FRESH (126 w ET) + 67 FROZEN (64 w ET) DO cycles were evaluated. Notably, significantly more oocytes were available for use in FRESH vs. FROZEN cycles (21 vs. 7, p < .0001). 2PN fertilization was similar (p = .9), whereas Blastocyst Utility (BUR; transferred + frozen) was greater in FRESH (p = .002). PGT-A was performed in 119/164 (73% ; 93 w ET) FRESH, but only 6/67 (9% ; 5 w ET) FROZEN. In non-PGT-A cycles, CPR and LBR for FIRST embryo transfer (ET) were similar. In PGT-A cycles, CPR was not different, but LBR was higher for FRESH than FROZEN (p = .01). When comparing non-PGT-A to PGT-A FRESH, CPR and LBR were not different (p = 1). Total annual program costs for recruiting, screening, stimulating and retrieving 65 FRESH DO cycles was $644,645, (thus, single usable donor cost was $9900; Meds $4200, Staffing $2371, Cycle Treatment $1594, Labs $1415). In contrast, one batch of eight FROZEN DOs costs ~$8500.

**CONCLUSIONS**: FRESH DO cycles have the advantage of more oocytes, fresh fertilization and higher BUR. Disadvantages include recipient coordination, lower donor availability and production of more supernumerary blastocysts that may never be used. FROZEN DOs are more readily available albeit at lower oocyte numbers and have an 8% no-ET rate due to poor embryo development. PGT-A does not offer improvement in LB outcomes in DO while adding cost (as well as a second freeze and potentially lower quality embryos). Perhaps FRESH donor “splitting” between recipients with fresh fertilization, then blastocyst freeze with subsequent frozen ET makes the most sense from a logistical, cost and efficiency standpoint. DO banks remain a viable option.
THE POP! TOOL: PREDICTION MODEL OF OUTCOME OF PREGNANCY IN IVF. M. Rowen, G. Dehghan, A. Guedon, R. Antaki, M. Mayrand, N. Dean, S. Phillips, L. Lapensée, Obstetrics-Gynecology, University of Montreal, Montreal, QC, Canada; Applied Clinical Research Unit, CHU St-Justine, Montreal, QC, Canada; CHU St-Justine, Montreal, QC, Canada; University of Montreal and CRCHUM, Montreal, QC, Canada; CRCHUM, CHUM, Montreal, QC, Canada; Fertility, OVO Clinic, Montreal, QC, Canada.

OBJECTIVE: We aimed to create a tool to predict the probability of live birth following a single embryo transfer (SET) in vitro fertilisation (IVF) cycle with a positive b-HCG.

DESIGN: Retrospective study.

MATERIALS AND METHODS: We studied 2,908 IVF cycles undertaken between 2012 and 2016 at an academic fertility center in Montreal, Canada. Following ethics approval, we restricted our analysis to SET cycles and to the first pregnancy of each patient during the study period. We first analysed twelve variables related to patient characteristics and treatment modalities that could influence the chance of live birth. We then conducted a multivariate analysis to select variables most predictive of live birth. With the positive predictive factors, we created a prediction tool of live birth after a positive b-HCG following a SET IVF cycle. We then did an external validation of our tool with a cohort of 1,426 patients from another fertility center in Montreal.

RESULTS: We identified 576 patients who met our inclusion criteria of which 84 pregnancies came from modified natural IVF, 313 from stimulated IVF and 179 from frozen embryo transfer (FET). Of these, 379 (66%) women had a live birth. The following factors were independently associated with live birth in SET: first and second b-HCG (day 15 and 17 post-oocyte retrieval), age at oocyte retrieval and treatment protocol: stimulated IVF vs. modified natural IVF vs. FET. The prediction tool incorporates these four variables with a discrimination C-index of 0.83. The externally validated tool has a C-index of 0.71 which shows good fit of our model to our external cohort.

CONCLUSIONS: In this retrospective cohort study, we describe a novel predictor of live birth following a positive b-HCG after a SET IVF cycle: treatment protocol. Using the four positive predictive factors, we created a prediction tool that was externally validated. This unique tool can be used by patients and physicians to better counsel patients on their chance of live birth after a positive b-HCG in SET IVF cycle.

References:
1. https://depotsbgyn.umontreal.ca/pop!}

P-245 Tuesday, October 9, 2018 6:30 AM

WAIST CIRCUMFERENCE IN RELATION TO OUTCOMES OF INFERTILITY TREATMENT WITH ASSISTED REPRODUCTIVE TECHNOLOGIES. M. Li, L. Mínguez-Alarcón, M. Arivizu, Y. Chiu, J. B. Ford, P. L. Williams, J. C. Petrozza, R. Hauser, J. E. Chavarro, Harvard T.H. Chan School of Public Health, Boston, MA; Massachusetts General Hospital Fertility Center, Boston, MA.

OBJECTIVE: To examine the relation between waist circumference (WC) and the probability of live birth among women undergoing infertility treatment with assisted reproductive technologies (ART).

DESIGN: Prospective cohort study.

MATERIALS AND METHODS: We followed 258 women who underwent 371 fresh ART (in vitro fertilization or intracytoplasmic sperm injection) cycles for infertility treatment at the Massachusetts General Hospital between 2010 and 2017. WC was assessed at enrollment. We used generalized linear mixed models with random intercepts to model the probability of live birth by tertiles of WC (7.75, 7.75-87.87, >87 cm), accounting for multiple treatment cycles while also adjusting for age, race (white vs. non-white), smoking (ever vs. never), infertility diagnosis (male factor, female factor, unexplained), day 3 FSH, BMI, and height.

RESULTS: Mean WC and BMI were 84 cm and 24.2 kg/m². WC and BMI were positively related to each other (r=0.68, p<0.0001). WC was inversely related to the probability of live birth after adjusting for BMI and other potential confounders. The multivariable adjusted probability of live birth (95% CI) for women in increasing tertiles of WC were 45% (35-56%), 32% (23-41%) and 30% (21-40%) (p trend=0.03). When BMI and WC were simultaneously considered, women with BMI ≥ 25 and WC ≥ 77.5, had the lowest live birth rate (29% (20-40%), while women with 18.5 ≤ BMI < 25 and WC < 77.5 had the highest (44% (33-56%). The results were similar using different WC cut-off values.

CONCLUSIONS: WC is inversely related to the probability of live birth among women undergoing ART independently of BMI. Jointly considering BMI and WC could identify women most likely to benefit from lifestyle interventions aimed at improving treatment outcomes.

Supported by: Grants P30ES000002, R01ES009718, R01ES022955 and P30DK046200 from the National Institutes of Health. Grant MOST-106-2917-I-564-066 from the Ministry of Science and Technology, Taiwan.

P-246 Tuesday, October 9, 2018 6:30 AM

PREDICTING LIVE BIRTH IN THE FIRST IVF CYCLE: COMPARISON OF THE LUKE AND SART PREDICTION MODELS IN EXTERNAL VALIDATION. J. P. Dubaut, A. L. Regens, J. D. Peck, H. Burks, K. R. Hansen, L. B. Craig, OB/GYN, OU Health Sciences Center, Oklahoma City, OK; Biostatistics & Epidemiology, University of Oklahoma College of Public Health, Oklahoma City, OK.

OBJECTIVE: The SART ‘Patient Predictor’ (SARTPP) is the only IVF prediction model/online calculator developed using national United States data. In this external validation, we compare model performance of the
TABLE 1. Comparison of models’ Hosmer-Lemeshow partition and calibration

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<td>1st</td>
<td>11</td>
<td>10.8</td>
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<tr>
<td>2nd</td>
<td>14</td>
<td>17.4</td>
<td>-7%</td>
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<td>3rd</td>
<td>21</td>
<td>20.9</td>
<td>0%</td>
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<tr>
<td>4th</td>
<td>27</td>
<td>25.1</td>
<td>+3%</td>
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<td>5th</td>
<td>27</td>
<td>24.9</td>
<td>+4%</td>
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<td>6th</td>
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<td>27.3</td>
<td>-4%</td>
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<td>7th</td>
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<td>-2%</td>
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<td>21.6</td>
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<td>10th</td>
<td>28</td>
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Updated SARTPP with the original published Luke model predicting live birth in the first cycle of IVF.

DESIGN: External validation by retrospective analysis of IVF cycles in our university-based infertility clinic.

MATERIALS AND METHODS: With IRB approval, patient age, BMI, parity, infertility diagnoses and live birth (>22 weeks, ≥300 grams) outcome were extracted from clinic SARTCORS data. All first, fresh, autologous IVF cycles 2012-2016 were included. This sample size exceeds the minimum 100 events and 100 nonevents for validation (1). The Luke logistic regression model derivation was previously described (2). To generate SARTPP individual probabilities, two authors entered each patient’s variables into the calculator available at https://www.sartconline.com/Predictor/Patient. Model performance was analyzed with SAS 9.4 and GraphPad Prism 7.03.

RESULTS: Live birth resulted in 229 of 498 cycles (46.0%). Predicted individual probabilities were higher for the Luke model (2.5-59.5%, median 49.6%) than the SARTPP (3.52%, median 43%). Discrimination, as measured by the area under the ROC curve (AUC), was greater for the SARTPP, 0.628 (95% CI 0.580-0.677), than the Luke model, 0.618 (95% CI 0.569-0.667). The Luke model showed excellent calibration with a Hosmer-Lemeshow p-value of 0.99, while the SARTPP p-value of 0.11 was closer to rejecting the null hypothesis: that a straight line fits well. Table 1 shows the models’ differences in expected and observed live births, the SARTPP underestimated outcomes in 6/10 deciles by more than 5%. The net reclassification index was -2.1% for the SARTPP compared to the Luke model.

CONCLUSIONS: Use of the SARTPP is better informed by an understanding of its discrimination (proportion of outcome pairs where live birth was assigned higher prediction) and calibration (agreement between expected and observed outcomes of deciles). Similar to other validated IVF prediction models, both studied models have modest discrimination, but the SARTPP has a slightly higher AUC. This improved discrimination comes at the expense of inferior calibration, and calibration is clinically more relevant (3). In our external validation, the SARTPP underestimated IVF success and provided no gain in predictive performance according to net reclassification. We therefore favor the Luke model.

References:
1. Vergouwe Y, Steyerberg EW, Eijkemans MJ, Habbema JD. Substantial and provided no gain in predictive performance according to net reclassification models, both studied models have modest discrimination, but the SARTPP compared to the Luke model.

P-247 Tuesday, October 9, 2018 6:30 AM
IS THE NUMBER OF OOCYTES ASPIRATED AFTER OVARIAN STIMULATION FOR IVF/ICSI ASSOCIATED WITH THE NUMBER OF TOP/GOOD QUALITY EMBRYOS? A SYSTEMATIC REVIEW AND META-ANALYSIS. T. M. D’Hooghe,a,b,c,b B. G. Vermeys,b,b,d S. Chua,b H. Zafarmand,b R. Wang,b S. Longobardi,c E. Cotelli,c F. Beckers,b B. W. Mol,c C. A. Venetis,d Mercik KGAA, Darmstadt, Germany, bKU Leuven, Leuven, Belgium; cYale University, New Haven, CT; dUniversity of New South Wales, Sydney, Australia; bMonash University, Clayton, Australia; cAMC, University of Amsterdam, Amsterdam, Netherlands; cUniversity of Adelaide, North Adelaide, Australia.

OBJECTIVE: To evaluate the association between the number of oocytes collected and the number of top or good quality embryos (T/GQE) at cleavage (Day 2/3) and/or blastocyst (Day 5/6) stages.

DESIGN: Systematic review and meta-analysis.

MATERIALS AND METHODS: A literature search was performed in MEDLINE, EMBASE, Scopus, CINAHL, and Web of Science for published randomized controlled trials and cohort studies until November 18th 2017. Included studies provided data on the association between the number of oocytes aspirated following ovarian stimulation for IVF/ICSI and the number of T/GQE either at the cleavage and/or blastocyst stage (primary outcome), or the number of 2PN, MII and euploid embryos (secondary outcomes). Pairwise comparisons were performed using a random effects model and by calculating standardized mean differences (SMD) between Group 1 (<4 oocytes retrieved), Group 2 (4-15 oocytes) and Group 3 (>15 oocytes). Graphical synthesis of correlations was performed and a weighted r correlation coefficient (r_w) was calculated when meta-analysis was constrained by a high level of clinical and methodological heterogeneity among the studies.

RESULTS: 28 eligible studies evaluated 291,752 ART cycles. Graphical synthesis of correlations (17 studies) confirmed a strong positive association between the number of oocytes retrieved and the number of T/GQE at Day 2/3 (r_w = 0.791), T/GQE at Day 5/6 (r_w = 0.901), euploid embryos (r_w = 0.851), 2PN oocytes (r_w = 0.987), and MII oocytes (r_w = 0.988) (p<0.001 for all comparisons). Meta-analysis was conducted on 12 studies. In Group 2 compared with Group 1 a mean 1.4 more T/GQE at Day 2/3 (SMD [95% CI] 1.41 [0.79, 2.03]), 1.75 more 2PN (SMD [95% CI] 1.74 [1.46, 2.01]) and 2.0 more MII oocytes (SMD [95% CI] 1.99 [1.87, 2.05]) were obtained. The findings were similar comparing Group 3 to Group 1; 1.9 more T/GQE at Day 2/3 (SMD [95% CI] 1.91 [1.05, 2.77]), 3.2 more 2PN (SMD [95% CI] 3.19 [1.97, 4.40]) and 3.6 more MII (SMD [95% CI] 3.63 [2.64, 4.61]). This effect persisted when Group 3 was compared with Group 2; 1.2 more T/GQE (at day 2/3; SMD [95% CI] 1.15 [0.74, 1.55]), 1.9 more 2PN (SMD [95% CI] 1.89 [1.70, 2.08]), 1.9 more MII (SMD [95% CI] 1.89 [1.35, 2.43]) and 0.70 more euploid embryos (SMD [95% CI] 0.70 [0.55, 0.85]).

CONCLUSIONS: We found a strong positive association between the number of oocytes aspirated following ovarian stimulation for IVF/ICSI and the number of T/GQE. Furthermore, as the number of aspirated oocytes increases, the number of MII oocytes, 2PN oocytes, and euploid embryos also increase. Even though the associations observed were always positive, a high level of heterogeneity between studies warrants caution when interpreting these results.

Supported by: Merck KGaA, Darmstadt, Germany.

P-248 Tuesday, October 9, 2018 6:30 AM
ASSESSING VITRIFICATION CYCLE OUTCOMES: COMPARISON BETWEEN PATIENTS TRANSFERRING BLASTOCYSTS AFTER PGS SCREENING VERSUS UNTESTED BLASTOCYSTS. N. Desal,¹ J. M. Goldberg,² C. Austin,³ T. Falcone,³ OB-GYN, Cleveland Clinic, Beachwood, OH; ²Cleveland Clinic, Cleveland, OH.

ASRM Abstracts
OBJECTIVE: The use of preimplantation genetic screening (PGS) varies amongst clinics. Clinics with an on-site genetics lab tend to be more committed to PGS for all patients. Other considerations for integration of PGS into the routine IVF treatment regimen include lab staffing, technical skills of embryologists, physician views and patient acceptance of PGS. It is not however clear if PGS for all patients offers a clear advantage. This study examines cryopreservation outcomes after transfer of PGS tested unscreened blastocysts in an IVF program where less than 30% of patients undergo PGS.

DESIGN: Retrospective analysis of blastocyst vitrification cycle outcomes.

MATERIALS AND METHODS: Frozen cycle outcomes from 1042 transfers of vitrified-warmed blastocysts (n=1612) were evaluated. No exclusion criteria were applied. All blastocysts were derived from culture of normally fertilized oocytes in the Embryoscope time-lapse incubation chamber with 6% CO2. Blastocysts of good quality with ICMs were cryopreserved. For PGS screening laser trophectoderm biopsy was performed. Biopsied cells were frozen and sent out for chromosome analysis using the Next Generation Sequencing technique. Blastocysts were cryopreserved using a two step ethylene glycol/DMSO vitrification procedure: 7.5% for 5 min, then 15% for 1 min before loading on the Rapid i carrier and immersion in liquid nitrogen. Patients were prepared for frozen embryo transfer using endometrial priming with estrogen and progesterone. Outcome data was stratified by age at freeze and whether blastocysts underwent PGS screening. Statistical differences between groups were analyzed using the Chi square and students t-test as appropriate. P values <0.05 were considered significant.

RESULTS: The Rapid i vitrification carrier gave excellent outcomes. The overall blastocyst survival rate was 97%. The odds of achieving a pregnancy were 2.6 fold higher (95% CI 1.09-6.48) with transfer of a PGS screened blastocyst (P=0.03).

CONCLUSIONS: Significant increase in IR with PGS was only seen in women 39 and older. With culture to blastocyst programs not as aggressive in using PGS can still expect to achieve high implantation rates in their younger patient population.

References:
2. The new Rapid i carrier is an effective system for human embryo vitrification at both the blastocyst and cleavage stage. Repro Biol & Endocrin 2013;11:41.

P-250 Tuesday, October 9, 2018 6:30 AM
AGONIST OR ANTAGONIST? THE IDEAL IVF PROTOCOL BY BODY MASS INDEX CATEGORY. C. Gordon,a O. J. Carpinello,b S. Boulet,c A. H. DeCherney.b aUC Irvine, Orange, CA; bNIH, Bethesda, MD; cCDC, Atlanta, GA.

OBJECTIVE: To compare in vitro fertilization (IVF) cycle outcomes for agonist and antagonist cycles stratified by body mass index (BMI) categories and to assess whether these associations varied by age, race/ethnicity, and parity.

DESIGN: Retrospective cohort analysis.

MATERIALS AND METHODS: National Assisted Reproductive Technology Surveillance System (NASS) data from 2010-2015 were used; all IVF first-cycles were included. Race/ethnicity and BMI were imputed for cycles with missing data. Clinical pregnancy rates (CPR) and live birth rates (LBR) per transfer and cycle cancellation rates were compared for agonist and antagonist cycles overall and stratified by BMI (18.5-24.9, 25.0-29.9, 30.0-34.9, 35.0-39.9, 40+ kilograms/meter^2 [kg/m^2]). Data were further stratified by age group, race/ethnicity, and parity. Chi-square tests were used for comparisons.

RESULTS: Of 294,703 first IVF cycles, 114,788 resulted in clinical pregnancy and 95,816 resulted in live birth. Among all embryo transfers, total CPRs and LBRs were higher in the agonist group compared with the antagonist group (54.4% and 46.4% vs 47.6% and 39.4%, respectively) (p<0.05). Likewise, CPRs and LBRs were significantly higher in the agonist group for each BMI stratum. When stratified by age, LBRs were significantly higher in
agonist versus antagonist cycles for patients <35 years who were overweight (BMI 25.0-29.9 kg/m²) or had class II (BMI 30.0-39.9 kg/m²) or class III (BMI ≥40 kg/m²) obesity; comparisons for older ages were not significant. Among non-Hispanic white and non-Hispanic black women with class II or class III obesity, antagonist cycles were also higher for agonist versus antagonist cycles. Among women with a prior spontaneous abortion, LBRs were significantly higher for those using agonist vs antagonist protocol for all BMI categories. Cycle cancellation rates were higher for antagonist versus agonist cycles for each BMI category; however, cancellation due to ovarian hyperstimulation occurred less frequently in the antagonist cycles for each BMI category.

CONCLUSIONS: Overall, pregnancy and live birth rates were higher in agonist versus antagonist cycles in all BMI categories. Among women who had class II or III obesity, use of agonist protocol resulted in higher LBRs in those who were <35 or were non-Hispanic white or non-Hispanic black. Cancellation due to hyperstimulation was less frequent in the antagonist versus agonist cycles, as expected, but this must be weighed with improved IVF outcomes with the agonist protocol.

Supported by: Supported in part by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health.

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EFFECT OF ENDOMETRIAL THICKNESS ON LIVE BIRTH RATE IN BOTH FRESH AND FROZEN BLASTOCYST TRANSFERS. T. Plate,1 R. Mejia,2 A. E. Sparks,3 H. E. Duran,4 K. M. Summers,5 P. Ten Eyck,6 B. J. Van Voorhis,7 1ObGyn, University of Iowa, Iowa City, IA; 2University of Iowa, Iowa City, IA; 3Obstetrics and Gynecology, University of Iowa, Iowa City, IA; 4Ob/Gyn, University of Iowa, Iowa City, IA; 5Research Assistant, Iowa City, IA; 6College of Public Health, University of Iowa, Iowa City, IA; 7Ob-Gyn, University of Iowa College of Medicine, Iowa City, IA.

OBJECTIVE: Prior studies investigating the relationship between a thin endometrium and IVF outcomes have overwhelming been performed in fresh, cleavage stage embryo transfers. Given the recent trend toward frozen blastocyst transfers, we aimed to determine whether endometrial thickness predicts live birth rate in both fresh and frozen blastocyst stage embryo transfers.

MATERIALS AND METHODS: First fresh or frozen IVF blastocyst transfers at the University of Iowa between 9/2011 and 9/2017 were included in this study. Donor cycles, PGS cycles, and cycles with incomplete information were excluded. Endometrial thickness was measured on the day of HCG trigger +/− 1 day (for fresh cycles) or at the end of estrogen priming (just prior to progesterone administration) in a frozen transfer cycle. Statistical analysis was performed using a generalized linear mixed model. We controlled for potential confounding factors including age, weight/BMI, embryo quality, days of stimulation, number of embryos transferred, and parity.

RESULTS: In fresh blast transfers (n=1042), endometrial thickness (median =10.9 mm; range 2.6-22 mm) was significantly correlated with live birth rate when controlling for other confounding factors. For every 1 mm increase in endometrial thickness, the odds of live birth increased by 7.9% (p<0.001). The effect of endometrial thickness was negatively affected by female age and increasing days of stimulation, and positively affected by higher blastocyst stage and trophoderm grade (A better than B/C). In frozen blast transfers (n=566), endometrial thickness (median 8.7 mm; range 4.9-18.9 mm) was not significantly correlated with live birth rate when controlling for the same factors. Increasing female age negatively affected, and increasing number of embryos transferred positively affected the live birth rate in frozen transfers. Frozen blast transfers did not affect either the live birth rate or endometrial thickness in either dataset.

CONCLUSIONS: We have shown that a thicker endometrium on the day of trigger is associated with improved live birth rates after fresh blastocyst transfer. In frozen transfers, there was a trend toward improved live birth rate with increasing endometrial thickness, but this was non-significant. These data suggest that endometrial thickness is more important in fresh than in frozen embryo transfers. However, these results could be explained by the fact that frozen transfers are generally not performed at our institution until an endometrial thickness of >6.0 mm is achieved. Further studies will be required to clarify these differences.

References:
10. Supported in part by: Financial report was supplied by the Davis Foundation, University of Iowa Department of ObGyn.

WITHDRAWN

IN FREEZE ALL EMBRYOS (FAE) BIRTH RATES IN SUBSEQUENT FROZEN EMBRYO TRANSFER (FET) ARE COMPARABLE TO THOSE OF CONTROLS, DESPITE HIGH RATES OF EF RECURRENTNESS AND CYCLE CANCELLATION. L. Preaubert,1 T. Antaki,2,3 R. Stutz,4 C. Grysole,5 S. Phillips,2,6 L. Lapensee,6 1OVO Clinic, Montreal, QC, Canada; 2University of Montreal, Montreal, QC, Canada; 4“Scientific Affairs, JSS Medical Research, St-Laurent, QC, Canada.

OBJECTIVE: We aimed to compare the clinical outcomes of subsequent FETs between patients having had FAE for endometrial fluid (EF) and controls having had a FAE for other indications, including the recurrence rate of EF and live birth rates (LBR) during subsequent frozen cycles.

DESIGN: A retrospective cohort study including all patients with FAE for EF at a university-affiliated private IVF center between 2010 and 2016.

MATERIALS AND METHODS: Controls were randomly generated cycles having had FAE for other indications during the same period. Gestational carriers, PGD/PGS cycles, egg donation cycles, patients having no embryo to transfer or hydrosalpinx were excluded. The primary outcome was cumulative LBR (CLBR) per started FET cycle and per patient. Secondary outcomes included rates of EF recurrence, cancellation, pregnancy rate (PR), and pregnancy loss rate. Between-group differences were ascertained with Chi-Square or Student’s t-test, as appropriate.

RESULTS: A total of 83 patients with FAE for EF and 219 controls were included. Population characteristics were comparable between the two groups. In controls, the indications for FAE included OHSS (46%), elevated progesterone (37%), uterine causes (9.1%) and other (7.3%). The endometrial fluid rate in three subsequent FET cycles was significantly higher in the study group compared to the control group: (15.7% vs. 0.5%, p<0.001; 22.9% vs. 0%, p<0.001; 17.3% vs. 1.8%, p=0.02). Cancellation rates in subsequent FET cycles were significantly higher in the study group compared to the control group: (18.1% vs. 4.1%, p<0.001; 22.9% vs. 8.5%, p=0.02). Main cumulative outcomes are shown in the Table. The PR, pregnancy loss rate and LBR were comparable between the two groups. However, in patients with FAE for EF presenting with at least one EF recurrence during subsequent FETs, cumulated PR per FET cycle was 16.4% and CLBR per FET cycle was 5.4%.
CONCLUSIONS: Despite higher rates of EF recurrence and cycle cancel- lation, patients with FAE for EF ultimately have comparable pregnancy and LBR to those having had a FAE for other indications. Nonetheless, patients presenting with at least one EF recurrence during subsequent FETs seem to have lower PR and LBR.

References: N/A.

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INITIAL SERUM HUMAN CHORIONIC GONADOTROPIN LEVELS PREDICT LIVE BIRTH OUTCOMES FOLLOWING FROZEN EMBRYO TRANSFER WITH AND WITHOUT PREIMPLANTATION GENETIC TESTING FOR ANEUPLOIDY (PGT-A). S. N. Dolitsky,a S. A. Neal,b M. Olcha,c K. Hong,d M. D. Werner,e S. Morin,f A. W. Tiegsc L. Sun,f R. Scott, 5 Obstetrics and Gynecology, Robert Wood Johnson School of Medicine, New Brunswick, NJ; bIVIRMA, Basking Ridge, NJ; cAlbert Einstein College of Medicine, Bronx, NY; dIVIRMA of New Jersey, Morristown, NJ; eREI, IVI-RMA NJ, Basking Ridge, NJ; fReproductive Medicine Associates of New Jersey, Basking Ridge, NJ.

OBJECTIVE: Initial serum human chorionic gonadotropin (hCG) levels have an established association with IVF pregnancy outcomes.1,2 However, many studies that have examined this association involved fresh transfers, transfer of multiple embryos, and embryos at varying stages of development. As contemporary practice patterns have shifted towards frozen transfer of a single blastocyst, evaluating the predictive value of initial hCG levels in this population is of interest. Additionally, it is not known if the predictive value of the initial hCG level is different for embryos that have undergone PGT-A.

The objective of this study is to evaluate early serum human chorionic gonadotropin levels as a predictor of live birth following frozen embryo transfer (FET) of a single blastocyst with and without PGT-A.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: All FETs of a single blastocyst at a large IVF center between 2010 and 2016 were reviewed for inclusion. Only those FET cycles resulting in a positive hCG nine days post-transfer were included in this analysis. Initial hCG levels were stratified and live birth rates were analyzed. Chi square analysis was used to compare live birth rates for each hCG category following transfer of embryos with and without PGT-A.

RESULTS: A total of 5280 FET cycles were included and 3417 (64.7%) of those cycles resulted in live birth. The mean hCG for a pregnancy resulting in live birth was 185 (±101.4) versus 60.7 (±76.1) mIU/mL for a non-viable gestation (P<0.01). Table 1 displays the live birth rate following FET of embryos with and without PGT-A, stratified by hCG level 9 days post-transfer. Initial serum hCG levels < 50 mIU/mL were associated with reduced live birth rates. For initial hCG levels between 50 and 150 mIU/mL, the live birth rate was approximately 10% higher following transfer of a genetically screened embryo.

CONCLUSIONS: Even when initial serum hCG levels nine days after FET are low, there is still a chance of live birth. When the initial hCG level is between 50 and 150 mIU/mL, live birth rates are significantly higher with genetically screened embryos.

References:
FIRST TRIMESTER SUBCHORIONIC HEMORRHAGE IS NOT ASSOCIATED WITH ADVERSE PREGNANCY OUTCOMES AFTER IN VITRO FERTILIZATION. K. L. Anderson, P. T. Jimenez, K. R. Omurtag, E. S. Jungherr. Washington University in St. Louis, Saint Louis, MO.

OBJECTIVE: Prior work demonstrates adverse associations between incidental subchorionic hemorrhage (SCH) detected on ultrasound and outcomes in naturally occurring pregnancies. However, ultrasound is often performed earlier in gestation with in vitro fertilization (IVF) pregnancies than in natural conceptions. Our objective was to determine the association between incidental SCH on ultrasound and outcomes in IVF pregnancies.

DESIGN: retrospective cohort study.

MATERIALS AND METHODS: Women were identified from a first-trimester ultrasound database kept for IVF pregnancies from 2009 to 2017. Inclusion criteria were fresh or frozen autologous transfer after IVF with a viable pregnancy on first trimester ultrasound. Exclusion criteria were absence of heartbeat on ultrasound and multiple gestation pregnancy. Exposure and covariates included SCH, age, BMI, race, history of prior live birth, fresh vs frozen cycle, day 3 or day 5 transfer, number of embryos transferred, and interpregnancy interval. The primary outcome was live birth and secondary outcomes included preterm delivery and infant weight at delivery. Appropriate statistics were used for univariate analyses. A logistic regression model was built to further investigate associations between significant covariates and outcomes. All analyses were performed in SPSS.

RESULTS: 659 women met criteria and 17.8% had a SCH. In univariate analysis, SCH was not associated with live birth whereas increasing maternal age (34.9 vs. 32.9, p<0.001) was negatively associated with live birth. In regression analysis, increasing maternal age remained significant, (OR 0.90, CI 0.83-0.96). No associations were found between SCH or the covariates and preterm birth or fetal weight.

CONCLUSIONS: Incidentally detected subchorionic hemorrhage on first trimester ultrasound is not associated with fetal birth weight or probability of live birth or preterm birth after IVF. This information may be reassuring to patients undergoing IVF.

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RESULTS: A clinical pregnancy was confirmed for 196 (67%) of the 291 patients who underwent the dual trigger protocol and had a fresh embryo transfer 5 days after oocyte retrieval were included. Maternal age, BMI, gravidity, parity, antral follicle count (AFC), oocytes retrieved, endometrial thickness, number of embryos transferred and frozen were compared for subjects who achieved clinical pregnancy, defined as an intrauterine gestational sac confirmed by ultrasound, and those who did not. Mann Whitney-U test was used to compare demographic, cycle characteristics, and outcome data between groups. Medians with interquartile ranges are presented with p-values. Additional analysis between subjects who had <30 and ≥30 oocytes retrieved was conducted. Logistic regression was used to identify predictors of clinical pregnancy.

RESULTS: A clinical pregnancy was confirmed for 196 (67%) of the 291 patients who underwent the dual trigger protocol with fresh embryo transfer. The cohort achieving clinical pregnancy had significantly lower age and a higher number of embryos cryopreserved (Table 1). After stratifying for number of oocytes retrieved, 216 (74%) patients had <30 oocytes and 75 (26%) had ≥30 oocytes, there was no difference in clinical pregnancy rates of 66.8% and 69.2% respectively. Logistic regression analysis identified number of embryos cryopreserved as the only parameter to predict clinical pregnancy, with an odds ratio of 1.079. There were no cases of OHSS in patients that underwent a fresh embryo transfer.

CONCLUSIONS: This data supports the use of dual trigger to both minimize ovarian hyperstimulation risk as well as obtain appreciable pregnancy rates in the fresh cycle. The high number of oocytes obtained was not associated with lower pregnancy rates in the fresh cycle supporting fresh embryo transfers in this good prognosis group of patients.

<table>
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<th>TABLE 1. Cohort characteristics</th>
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<tr>
<td>Age (years)</td>
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<td>BMI</td>
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<td>Gravida</td>
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<td>Para</td>
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<tr>
<td>Antral follicle count</td>
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<td>Oocytes retrieved</td>
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<td>Endometrial thickness (mm)</td>
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<td>Fresh embryos transferred</td>
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<td>Embryos frozen</td>
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THE VAGINAL MICROBIOME AS PREDICTOR FOR IN VITRO FERTILIZATION WITH OR WITHOUT INTRACYTOPLASMIC SPERM INJECTION OUTCOME: A PROSPECTIVE STUDY. R. Koedsoeder, M. Singer, D. E. Budding, S. Schoenmakers, P. H. Savelkoul, S. A. Morre, J. S. Laven, Obstetrics & Gynecology, PhD Student, Rotterdam, Netherlands; Medical Biotechnology and Infection Control, VU University Medical Center, Amsterdam, Netherlands; Obstetrics & Gynecology, Erasmus University Medical Center, Rotterdam, Netherlands; Medical Microbiology, Maastricht University Medical Center, Maastricht, Netherlands; Reproductive Endocrinology and Infertility, Dept OB/GYN, Erasmus Medical Centre, Rotterdam, Netherlands.

OBJECTIVE: Success rates for in vitro fertilization (IVF) and IVF with intracytoplasmic sperm injection (IVF-ICSI) vary between 25% and 35% and it is hard to predict in advance who will or will not get pregnant after embryo transfer (ET). Recently, it was discovered that - prior to treatment - the composition of the vaginal microbiome might predict pregnancy outcome. Analysis of the vaginal microbiome prior to IVF/IVF-ICSI treatment might offer a new opportunity to improve the success rate of IVF or IVF-ICSI. We therefore wanted to answer the following questions: Is the presence or absence of certain bacteria associated with failure to become pregnant after embryo transfer (ET)? Secondly, can the composition of the vaginal microbiome be used as an independent predictor for IVF or IVF-ICSI outcome?

METHODS: We therefore wanted to answer the following questions: Is the presence or absence of certain bacteria associated with failure to become pregnant after embryo transfer (ET)? Secondly, can the composition of the vaginal microbiome be used as an independent predictor for IVF or IVF-ICSI outcome?

DESIGN: In a prospective study 303 women undergoing IVF or IVF-ICSI treatment were included between June 2015 and March 2016.

MATERIALS AND METHODS: Women provided a vaginal sample before the start of the IVF or IVF-ICSI procedure. The vaginal microbiota composition was determined using the IS-pro technique. IS-pro is a eubacterial technique based on the detection and categorization of the length of the IS6-235 rRNA gene interspace region. Microbiome profiles were assigned to a community state type based on the dominant bacterial species. The predictive accuracy of the microbiome profiles for IVF and IVF-ICSI outcome of fresh ET was evaluated by a combined prediction model based on a small number of bacterial parameters.
RESULTS: In total 192 women underwent a fresh ET and the vaginal microbiota profile could be analyzed of these women. Women with a low percentage of Lactobacillus in their vaginal sample were less likely to have a successful embryo implantation. The prediction model named ReceptIVFity identified a subgroup of women (n = 34) who had a low chance of pregnancy following ET. This failure to become pregnant was correctly predicted in 32 out of 34 women based on ReceptIVFity applied to the vaginal microbiota composition, resulting in a predictive accuracy of 94% (sensitivity 26%, specificity 97%).

CONCLUSIONS: Our results indicate that microbiome profiling using the IS-pro technique enables accurate prediction of failure to become pregnant prior to the start of an IVF or IVF-ICSI treatment. Knowledge of their microbiome profile may enable couples to make a more balanced decision regarding continuation and timing of their IVF or IVF-ICSI treatment cycles.

Supported by: This study was financed by NGI Pre-Seed 2014-2016, RedMedTech Discovery Fund 2014-2017, STW Valorisation grant 1 2014-2015, STW Take-off early phase trajectory 2015-2016.

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MALE PARTNER AGE IMPACTS DONOR OOCYTE OUTCOMES. E. L. Dodge, A. S. Penzias, D. Sakkas.

OBJECTIVE: How does male partner age impact the outcomes of in vitro fertilization (IVF) among couples using donor oocytes?

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: All patients at least 18 years of age and who underwent their first non-canceled donor IVF cycle from January 1995 through February 2014 were included. Gestational carrier cycles were excluded. The outcome of only the first donor transfer, whether fresh or frozen, was analyzed. We used log-binomial regression to calculate risk ratios (RR) and 95% confidence intervals (CI) of clinical pregnancy (presence of fetal heart beat), spontaneous abortion, and live birth among categories of male partner age, which was defined as follows: <40, 40-<45, 45-<50, and ≥50 years of age.

RESULTS: A total of 543 couples were included in the analysis. Among the male partners, 197 (36.3%) were <40 years of age, 172 (31.7%) were 40-<45, 101 (18.6%) were 45-<50, and 73 (13.4%) were ≥50. The median (interquartile range) recipient and donor ages were 41.7 (38.1-44.8) and 26.0 (24.0-28.0) years, respectively. The proportion of fresh cycles in the four age groups was 73.9%, 83.8%, 77.4%, and 75.8%, respectively. After controlling for recipient age and fresh vs. frozen cycle, compared to couples whose male partner was <40 years old, couples whose male partner was 40-<45 and ≥50 were significantly more likely to experience a spontaneous abortion (RR: 5.78, 95% CI: 1.48-22.66 and RR: 5.65, 95% CI: 1.01-31.72, respectively; Table 1). Spontaneous abortion was also more common among couples whose male partner was 45-<50 (RR: 4.67, 95% CI: 0.92-22.64), though this difference was not significant. Compared to couples whose male partner was <40, those whose male partner was 40-<45 and ≥50 were less likely to have a live birth (RR: 0.58, 95% CI: 0.36-0.93 and RR: 0.51, 95% CI: 0.26-1.01, respectively), though the ≥50 group did not reach statistical significance. Adjusting for donor age had no effect on the estimates.

CONCLUSIONS: Among couples undergoing IVF using donor oocytes, younger male age is associated with higher incidence of live birth and lower incidence of spontaneous abortion.

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OBJECTIVE: In the literature, an increased birthweight of singletons born following frozen-thawed embryo transfers (FET) was associated with the procedures of cryopreservation. This study aimed to investigate the impact of endometrial preparation with artificial cycle (AC) or mild gonadotropin ovarian stimulation (OS) on neonatal birthweight in singletons born after FET.

DESIGN: This retrospective study was carried out in a single academic fertility centre from January 2013 to December 2016.

MATERIALS AND METHODS: In OS group, gonadotropins (37.5 to 75 IU/d) were initiated between Day 2 and 10 followed by hCG triggering. Vaginal micronized progesterone (200 mg/day) was given systematically (max 6 weeks if pregnancy). In AC group, estradiol (E2) orally (2mg x 2 or 3d) or transdermally (200 µg/3d) started on Day 1. Vaginal micronized progesterone (600 mg/day) was added to E2 according to embryo stage (cleaved embryo or blastocyst) and for 12 weeks if pregnancy. The main outcome was the birth weight in 139 live-born singletons among all FET cycles performed during the study period (N=1021), achieved through OS FET (N=68) or AC FET (N=71). Multiple logistic regression analyses were performed with maternal and paternal age at freezing, woman smoking status, woman body mass index and IVF technique as potential confounding factors.

RESULTS: The two groups were comparable for maternal age, primiparous rate, neonate sex, gestational age and embryo’s characteristics (slow-freezing or vitrification of cleavage embryos or blastocysts). If we consider births at 37-41 weeks of gestation (WG), the mean birthweight was significantly higher (+299g) in the 65 AC than in the 58 OS group singletons (3234g ± 496g vs. 3035g ± 413g, p=0.036). The rate of babies whose birthweight exceeded 4000g appeared significantly higher in AC group (11.3% (8/65) vs. 1.5% (1/58), p=0.01), and close to significance due to lack of power after adjustment (p=0.69). No difference was found in low birth weight, small and large for gestational age rates.

CONCLUSIONS: The endometrial preparation seems to affect the birthweight of singletons. Overweight and neonatal weight exceeding 4000g described by many authors after FET could be avoided by careful patient selection and appropriate hormonal preparation. Artificial cycle might have advantages over gonadotropin preparation. This study aims to reinforce by broader studies.

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HETEROZYGOUS BIOTINIDASE DEFICIENCY DOES NOT IMPACT OVARIAN RESERVE, RESPONSE, OR REPRODUCTIVE POTENTIAL. L. Sekhon, D. Ahmad, T. A. Cacihome, J. Lee, A. B. Copperman.

OBJECTIVE: Biotinidase deficiency (BTD) impairs fatty acid and glucose metabolism by reducing utilization of biotin. Animal studies show biotin-deficient fruit flies have 28% fewer larvae hatched per egg compared to biotin-sufficient controls. Heterozygous BTD carriers have reduced serum biotinidase levels as compared to non-carriers but the impact on human fertility has yet to be explored. The study evaluated ovarian reserve, response, and cycle outcome in heterozygous BTD patients.

DESIGN: Retrospective.

MATERIALS AND METHODS: Patients who did expanded carrier screening (ECS) with IVF from 2012-2018 were evaluated. BTD carriers and negative controls were compared by demographics, ovarian reserve, IVF outcomes, embryonic aneuploidy and embryo transfer outcomes. A sub-analysis of euploid frozen embryo transfers (FET), was done. Student’s t-test, chi-square test, and multivariate linear and binary logistic regression models were used.

RESULTS: BTD carriers (n=227) were compared to non-carriers (n=12144) (Table 1). Controlling for age, BTD heterozygosity did not impact AMH (β = -0.02, p=0.9362) or AFC (β = -0.15, p=0.7993). Controlling for age and AMH, BTD heterozygosity did not modify oocyte yield (β = -1.15, p=0.1051), fertilization (β = 0.04, p=0.22), blastulation (β = 0.02, p=0.45) or aneuploidy (β = 0.03, p=0.43). A sub-analysis, restricted to euploid FETs, compared outcomes in BTD carriers (n=74) vs. controls (n=307). Controlling for age, BMI, endometrial thickness, and day of biopsy, BTD heterozygosity did not impact implantation (OR 1.25 [95% CI 0.73-2.16], p=0.421), ongoing pregnancy (OR 0.85 [95% CI 0.51-1.43], p=0.53), early pregnancy loss (OR 1.61 [95% CI 0.80-3.24], p=0.18) or live birth (OR 1.43 [95% CI 0.74-2.78], p=0.29).

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CONCLUSIONS: Our study is the first to assess the effects of BTD heterozygosity on human reproduction. Our findings suggest that despite having a genotype associated with reduced biotinidase enzyme activity, BTD carriers have ART outcomes comparable to non-carriers. BTD carriers can be reassured that a single mutation does not adversely impact treatment outcome. Further research is needed to assess whether BTD heterozygosity can affect fertility in a non-ART population and the minimal threshold of biotinidase activity below which human reproductive function may be impacted.

<table>
<thead>
<tr>
<th>TABLE 1. Hydroxyurea (n=227) Controls (n=1214)</th>
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<tr>
<td>BMI (m²)</td>
<td>23.3±4.0</td>
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<tr>
<td>AMH (ng/ml)</td>
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<tr>
<td>Patients</td>
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<td>undergoing</td>
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<tr>
<td>IVF/ # IVF cycles</td>
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<td>Mature oocytes retrieved</td>
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<tr>
<td>Fertilization rate</td>
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<td>Day 3 embryos</td>
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<td>Embryos biopsied for PGT</td>
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<td>Ongoing pregnancy rate</td>
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<td>Clinical pregnancy loss rate</td>
<td>10.6% (5/47)</td>
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<tr>
<td>Live birth rate</td>
<td>50.0% (22/44)</td>
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PREDICTING THE NUMBER OF BIOSPY QUALITY BLASTOCYSTS BASED ON OOCYTES RETRIEVED. K. W. Keefe, a L. V. Farland, a R. Goldman, a A. M. Thomas, a C. Racowsky, a Obsterics and Gynecology, Brigham and Women’s Hospital, Boston, MA; Obsterics & Gynecology, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA; Brigham and Women’s Hospital, Boston, MA.

OBJECTIVE: Preimplantation genetic testing (PGT) involves trichotoderm biopsy to test blastocysts with the goal of optimizing the chance of a healthy singleton live birth. Attrition occurs from the number of oocytes retrieved to the number of blastocysts biopsied, yet the extent of this attrition is often difficult for patients to conceptualize. The purpose of this study was to develop a reference chart showing the age-related reduction in numbers of oocytes retrieved to blastocysts biopsied, to assist in future counseling for patients as they consider whether to choose PGT as an adjunct technology for their ART cycle.

RESULTS: The total number of oocytes retrieved decreased with increasing age, even after controlling for AMH (Table). Neither the incidence of mature (MI) oocytes (range: 70-74% of oocytes retrieved) nor the incidence of 2PN zygotes (range: 77-85% of MI oocytes) statistically significantly differed among age groups. Though there were trends toward decreased numbers of blastocysts and biopsied blastocysts across age groups, only women aged ≥41y had a statistically significantly decreased risk of treating fewer biopsy quality blastocysts than women <35y (Table).

CONCLUSIONS: With increasing age, the rate of attrition increases from oocytes retrieved to mature oocytes to 2PN zygotes to blastocysts to biopsy quality blastocysts. The results of this analysis can be used for counseling in PGT cycles to help guide a patient’s expectations regarding the number of blastocysts available for trichotoderm biopsy based on her age at retrieval.
TIME-LAPSE CINEMATOGRAPHY FOR PREDICTING EMBRYOS OBTAINED FROM HIGH-RESOLUTION DEEP LEARNING BASED ON IMAGES OF HUMAN EMBRYOS

I. Matsumoto, T. Shimura, K. Yumoto, A. Negami, Y. Mio. Reproductive Sciences, University of Vermont Medical Center, Burlington, VT; aBiostatistics Unit, Humanitas Research Hospital, Rozzano (Milan), Italy; bYale University Fertility Center, New Haven, CT; cBiostatistics Unit, Humanitas Research Hospital, Rozzano (Milan), Italy.

OBJECTIVE: The aim of the present study was to report our experience on homologous intrauterine insemination (IUI) with controlled ovarian stimulation (COS) and to examine different variables for predicting IUI success.

DESIGN: Retrospective analysis including all the IUI with COS cycles in an academic tertiary ART center between January 1997 and December 2017.

MATERIALS AND METHODS: We included in the analysis 7,457 procedures, performed in 2,970 couples. We analyzed the association between pregnancy outcomes (clinical pregnancy rate and live birth rate) and clinical features, including age, body mass index (BMI), smoking habit, duration of infertility, sperm characteristics before and after treatment (total motile count, morphology and vitality), day 3 FSH, types of ovarian stimulation, total gonadotropin dose and number of mature follicles. Multivariate logistic regression analysis was used to obtain odds ratio (OR).

RESULTS: The median female age was 35.1±3.9 years and the median BMI was 21.7±3.2 kg/m². The most common single infertility diagnoses were unexplained infertility (53.03%), mild male factor (19.55%) and anovulation (10.88%). The male partners had total progressive motile sperm count [OR 0.888 (CI 95% 0.850 - 0.928) e 0.871 (CI 95% 0.850 - 0.928) respectively] and day3 FSH [OR 0.888 (CI 95% 0.850 - 0.928) e 0.871 (CI 95% 0.850 - 0.928) respectively] and day3 FSH [OR 0.888 (CI 95% 0.850 - 0.928) e 0.871 (CI 95% 0.850 - 0.928) respectively] and day3 FSH [OR 0.888 (CI 95% 0.850 - 0.928) e 0.871 (CI 95% 0.850 - 0.928) respectively].

CONCLUSIONS: Clinical pregnancy rate and live birth rate following homologous IUI are significantly influenced by female age and FSH level. Semen parameters seem not impact on clinical outcomes, if they were considered suitable for IUI (>1 million TMC).

References:

FERTILITY & STERILITY®
COMES IN IVF/ICSI.

PROTOCOL CAN PREDICT PREGNANCY OUT-
SERUM ESTRADIOL LEVEL ON THE FIFTH DAY OF
Tuesday, October 9, 2018 6:30 AM
health care center.

REI nurses and fellows. Further subgroup analysis may yield additional in-
tricis and Gynaecology, Western University, London, ON, Canada;cThe

slightly lower pregnancy rate as compared to cycles without (12.3% vs. 16.15
(17%). Three quarters of IUIs used ovulation induction, which resulted in a
creation (24%), unexplained infertility (21%) and diminished ovarian reserve
most common diagnosis with pregnancies from IUI included same sex pro-

Sixty percent of pregnancies resulted from fresh specimens (p < 0.08). The mean post-wash total motile sperm count resulting in pregnan-
cy was 22 million (±19.6).

CONCLUSIONS: Pregnancy rates are similar when IUIs are performed by
REI nurses and fellows. Further subgroup analysis may yield additional in-
formation regarding prognosis for success in an IUI program in an academic
health care center.

P-267 Tuesday, October 9, 2018 6:30 AM

SERUM ESTRADIOL LEVEL ON THE FIFTH DAY OF
OVARIAN STIMULATION IN A GnRH ANTAGONIST
PROTOCOL CAN PREDICT PREGNANCY OUT-
COMES IN IVF/ICSI. J. N. Blom,a L. Tan,b,c L. Hughes,b F. Tekpetey,B, A. B. Abu Rafea,B,2
Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON, Canada;3 Obstet-
rics and Gynaecology, Western University, London, ON, Canada; The Fertility Clinic, London Health Sciences Centre - Victoria Hospital, London, ON, Canada.

OBJECTIVE: Serum estradiol (E2) levels are routinely measured in controlled ovarian hyperstimulation for in vitro fertilization (IVF) to assess ovarian response. Evidence suggests a relation between E2 levels on the day of ovulation trigger and reproductive outcomes. However, little is known about the predictive value of early cycle E2 levels. The aim of this study was to assess the value of serum E2 on day five of ovarian stimulation in a GnRH antagonist protocol in predicting IVF reproductive outcomes.

DESIGN: Retrospective observational study.

MATERIALS AND METHODS: Data was collected retrospectively following GnRh antagonist cycles for ART at the Fertility Clinic in London, Ontario, Canada between 2006 and 2017. This included 734 patients receiving conventional IVF and 1586 receiving IVF/intracytoplasmic sperm injection (ICSI). Exclusion criteria included unconfirmed diagnoses, donor gametes, surrogates and cycles with incomplete records (E2 on day 5 of ovarian stimulation not measured). Primary outcomes were live birth rate, clinical pregnancy rate, and biochemical pregnancy rate. Secondary outcomes included E2 on the day of trigger, number of oocytes retrieved, percent of retrieved oocytes that were fertilized, and number of embryos transferred. Clinical outcomes were compared by linear regression for continuous vari-
ables and logistic regression for binary outcomes, controlling for day 3 FSH, age, BMI and number of embryos transferred.

RESULTS: In the entire data set, E2 on day 5 of ovarian stimulation was significantly associated with an increase in both E2 on the day of trigger (p < 0.001) and number of oocytes retrieved (p < 0.001). In the combined data-
set and in the conventional IVF only group, association between serum E2 on
day 5 of ovarian stimulation and live birth rate was not statistically significant (p = 0.261 and p = 0.179 respectively). Using ICSI however, an increase in E2 on day 5 of ovarian stimulation was associated with an increased likelihood of live birth (OR = 1.00021, p = 0.012). There were no statistically significant associations found between E2 on day 5 of ovarian stimulation and biochemical pregnancy rate, clinical pregnancy rate, percent of retrieved oocytes that were fertilized or number of embryos transferred.

CONCLUSIONS: These data indicate that higher E2 levels on day 5 of ovarian stimulation predict increased live birth rates using a GnRh antago-
nist protocol for IVF/ICSI. Thus, early serum E2 measurements should be considered when counselling patients undergoing IVF/CSI about their possible reproductive outcome during the cycle.

References:

P-268 Tuesday, October 9, 2018 6:30 AM

IS A THIN ENDOMETRIAL LINING ASSOCIATED
WITH INCREASED RISK OF ECTOPIC PREGNANCY
IN SINGLE EUPLOID FROZEN EMBRYO
TRANSFERS?. S. Chang,1,3 T. T., G. Nazem,1,3 C. Hernandez-Nieto,1,3 D. Gounko,b J. Lee,a B. McAvey.a Obstetrics, Gy-
necology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY; Reproductive Medicine Associates of New York, New York, NY; Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai West, New York, NY.

OBJECTIVE: Ectopic pregnancy (EP) rates are higher in women who conceive using assisted reproductive technology (ART). Clinicians continue to investigate risk factors for EP, exploring number of embryos transferred, developmental stage, and ploidy. It is unclear whether endometrial factors, particularly endometrial thickness (EnT) and pattern (EnP), play a role in EP risk. A study reported a 4-fold increased risk of EP with EnT <9 mm dur-
ing fresh IVF transfers compared to >12mm. Single, euploid frozen embryo transfers (FET) are associated with the lowest risk of EP, yet no study has evaluated the influence of EnT in this setting. We sought to determine the relationship between EnT/EnP and EP in single euploid FETs.

DESIGN: Retrospective.

MATERIALS AND METHODS: Patients who underwent single euploid FET cycles (2011-2018) were included. EP was identified using natural lan-
guage processing and manual review. IVF cycles were grouped by outcome (EP vs. no EP) and EnT was treated as a continuous variable. A subgroup analysis was performed with EnT as a dichotomous variable, thin (<7mm) or not thin (≥7mm). Age, body mass index (BMI), gravidity, parity, anti-
mullerian hormone (AMH) level, embryo age, and EnT/EnP on day of trans-
fer were collected. T-tests, Chi-square analysis, and a general estimate equa-
tion model (GEE) were used.

RESULTS: A total of 3733 single euploid FET cycles were included. Baseline characteristics were similar between groups, with the exception of parity. The overall rate of EP was 3.9% (n=146). There was no increase

<table>
<thead>
<tr>
<th>Patient Demographics and Cycle Characteristics</th>
<th>Ectopic pregnancy (N= 146)</th>
<th>Not ectopic pregnancy (N= 3587)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ectopic pregnancy (N= 146)</td>
<td>Not ectopic pregnancy (N= 3587)</td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>36.13 ± 3.56</td>
<td>36.47 ± 3.97</td>
<td>0.31</td>
</tr>
<tr>
<td>Gravidity</td>
<td>1.29 ± 1.26</td>
<td>1.27 ± 1.43</td>
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</tr>
<tr>
<td>Parity</td>
<td>0.37 ± 0.65</td>
<td>0.48 ± 0.76</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>AMH (ng/mL)</td>
<td>4.25 ± 4.67</td>
<td>3.75 ± 4.50</td>
<td>0.28</td>
</tr>
<tr>
<td>Embryo Age</td>
<td>Day 5: 90 (61.64%) / Day 6: 51 (34.93%) / Day 7: 5 (3.42%)</td>
<td>Day 5: 2228 (62.11%) / Day 6: 1272 (35.46%) / Day 7: 87 (2.43%)</td>
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</tr>
<tr>
<td>EnT (mm)</td>
<td>9.19 ± 2.17</td>
<td>9.38 ± 2.06</td>
<td>0.27</td>
</tr>
<tr>
<td>EnP: 2 - 3</td>
<td>14 (9.59%) - 132 (90.41%)</td>
<td>534 (14.94%) - 3041 (85.06%)</td>
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</tr>
</tbody>
</table>

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in EP incidence when looking at EnT as a continuous function (OR 0.97, [95% CI 0.87-1.06]). When performing a sub-analysis grouping cycles by EnT ≥7mm and <7mm, there was a significant increase in EP in the EnT <7mm cohort (OR 1.81, [95% CI 1.05-3.12]). EnP was not a risk factor for EP (OR = 0.62, [95% CI 0.36-1.08]).

CONCLUSIONS: In a single, euploid FET model, an EnT of <7mm appeared to be an independent risk factor for EP. These findings are consistent with a previous study reporting increased EP in fresh transfers with thin EnT. The ability to predict endometrial non-receptivity and increased likelihood of EP non-invasively will minimize the morbidity and mortality from EP. Given that EnT is likely a surrogate for endometrial receptivity, future studies would benefit from correlating EnT with activation of molecular pathways affecting the implantation window.

References:

P-271 Tuesday, October 9, 2018 6:30 AM
RELATIONSHIP BETWEEN PROGESTERONE LEVEL FOLLOWING FRESH EMBRYO TRANSFER AND THE RISK OF ECTOPIC PREGNANCY
OBJECTIVE: To assess whether increased progesterone level during controlled ovarian stimulation increases the risk of ectopic pregnancy (EP) following fresh embryo transfer.

DESIGN: Retrospective case-control study.

MATERIALS AND METHODS: All cases (n=29) of EP (study group) were compared to 79 cases of documented viable intra-uterine pregnancies (control group) between August 2009 and December 2016 at a private fertility clinic (OVO clinic, Montreal, Canada). The control group cases were selected based on a random number generator model on a year-to-year basis. Bivariate analysis was conducted to assess the effect of all collected variables on EP.

RESULTS: The two groups did not differ significantly in factors traditionally associated with EP (previous EP, endometriosis, tubal disease, history of pelvic infection, and abdominal surgery). Patients with EP were more likely to have had day 3 rather than a day 5 transfer (p = 0.001), had double rather than a single embryo transfer (p = 0.001), and finally were more likely to have had a difficult transfer (p = 0.004), independently of the use of a rigid catheter. Progesterone level measured on the day before or on the day of ovulation trigger was not statistically different between the two groups (2.55 ng/ml for the study group vs. 2.52 ng/ml for the control group, p = 0.169).

CONCLUSIONS: Progesterone has multiple known physiologic effects on the fallopian tube, such as causing relaxation of the isthmic and interstitial portion, degeneration of the ciliated cells, and increased ciliary beat frequency. These combined could lead to reverse embryo migration into the tube after intrauterine transfer. However, our results do not support this hypothesis as no relationship between progesterone level and EP could be demonstrated.


P-272 Tuesday, October 9, 2018 6:30 AM
WHICH FACTORS CAN AFFECT ONGOING PREGNANCY IN SINGLE EUPLOID FROZEN EMBRYO TRANSFERS? ANALYSIS OF A LARGE COHORT FROM A SINGLE CENTRE.

OBJECTIVE: To analyze factors associated with pregnancy outcome in single euploid frozen embryo transfer.

DESIGN: Observational retrospective single-centre analysis.

MATERIALS AND METHODS: This retrospective study compiled 607 euploid single blastocyst frozen embryo transfer undergoing ICSI/PGT-A between October 2015 to August 2017. Trophoderm (TE) biopsy was performed and next generation sequencing (NGS) was used aneuploidy screening. Clinical indications for PGT-A included recurrent implantation failure (RIF), recurrent miscarriage (RM) and advanced maternal age (AMA). We checked the possible influence of patient characteristics, treatment history, ovarian stimulation variables, embryo scores and day, mitochondrial DNA on ongoing pregnancy. To identify characteristics that may be associated with the ongoing pregnancy univariate regression analyses were performed. Variables found to have tendency of association with the primary outcome (p<0.25) in the univariate analysis were included in the multivariate analysis.

RESULTS: The mean age of patients was 35.8 ± 4.7 years, and the mean number of blastocysts per patient was 3.3 ± 2.2. The total number of blastocysts available to the analysis was 2003, and 54% of them where euploid after PGT-A. Following transfer of 607 single euploid embryos, 414 (68.5%) had positive hCG levels leading to 390 (64.3%) had clinically confirmed and 333 (54.9%) ongoing pregnancies. 57 patients (14.6%) had miscarriage. Although BMI, advanced maternal age, diagnosis of PCOS, endometriosis, number of mature oocytes, maturation rate, day of blastocyst cryopreservation and biopsy, inner cell mass and trophectoderm score were significant factors in univariate analysis (p<0.25), multiple regression analysis showed that BMI, day of blastocyst cryopreservation and biopsy, inner cell mass and trophectoderm score were the only independent predictors of ongoing pregnancy. Results confirm that BMI >25, biopsy and cryopreservation on day 6, having inner cell and trophectoderm score of C have a negative impact on ongoing pregnancy. Female age, although is shown to be linked with diminishing clinical outcome in regular ART cycles, is no more a negative factor for ongoing pregnancy rate in euploid embryo transfers.

CONCLUSIONS: In summary, female age has no prominent effect on ongoing pregnancy rate with euploid single frozen embryo transfers. Embryo-associated variables such as day of blastocyst formation, biopsy and cryopreservation, TE and inner cell quality and patient characteristics such BMI appeared to affect the implantation and ongoing pregnancy.

OBJECTIVE: To compare clinical outcomes after fresh embryo transfer on laser-assisted zona pellucida opening (LAO) versus thinning (LAT) according to maternal age in patients with repeated implantation failure (RIF).

DESIGN: A retrospective study of 509 (n = 458 patients) in vitro fertilization/intracytoplasmic sperm injection cycles was investigated from January 2013 to July 2017.

MATERIALS AND METHODS: We compared whether LAT and LAO affect the clinical outcomes in young maternal age (YMA, <38 years) and old maternal age (OMA, ≥38 years) patient groups with ≥2 of RIF. The cycles with an oocyte donation, oocyte activation, genetic diagnosis, and that used surrogate mothers were excluded. Participants were divided into 4 groups according to maternal age and the two types of laser-assisted hatching (YMA: LAT: n = 119 vs. LAO, n = 179 and OMA: LAT: n = 72 vs. LAO, n = 139). LAO was opened using 3-4 laser shot in the zona pellucida. The laser thinning was performed by making 3-4 holes without reaching the inner membrane at a depth of 60%-80% of the zona pellucida thickness. Laser-assisted hatching was performed 2 hours before the embryo transfer.

RESULTS: The characteristics of patients did not differ significantly among the groups (p > 0.05), with the exception of mixed factor infertility, which was more common in the LAT group than in the LAO group among patients <38 years of age (10.1% vs. 2.8%, p = 0.008). We also observed similar rates of clinical pregnancy (27.7% vs. 24.6%, p = 0.543; 16.7% vs. 18.7, p = 0.715), ongoing pregnancy (22.7% vs. 21.8%, p = 0.854; 8.3% vs. 15.1, p = 0.163), abortion (18.2% vs. 11.4%, p = 0.397; 50.0% vs. 19.2, p = 0.052), implantation (17.2% vs. 16.5%, p = 0.811; 11.1% vs. 11.2, p = 0.990), and twin pregnancy (5.0% vs. 5.6%, p = 0.498; 0.0% vs. 2.2, p = 0.553) between LAT and LAO in the YMA or the OMA group, respectively.

CONCLUSIONS: Clinical outcomes were similar between LAT and LAO in the YMA or the OMA group. However, the OMA group who underwent LAO tended to have a lower abortion rate. Further study is necessary to confirm these results in a larger population.

PIEZO-ICSI AS ALTERNATIVE TOOL TO IMPROVE OOCYTE ACTIVATION IN IN VITRO MATURED BOVINE OOCYTES MODEL. G. M. Alvarez, S. Villanueva, M. Geller, P. Cetica, G. Dalvit. CONICET, Buenos Aires, Argentina; In Vitro BA, Buenos Aires, Argentina; University of Buenos Aires, Buenos Aires, Argentina.

OBJECTIVE: Evaluate the fertilization rates in a bovine oocyte activation failure model of Piezo-ICSI compared to conventional ICSI.

DESIGN: We aimed to evaluate the participation of Piezo-pulse and sperm species in oocyte activation. In vitro matured bovine oocytes were randomly allocated to one of four groups: 1-conventional ICSI with bull sperm, 2-Piezo-ICSI with bull sperm, 3-conventional ICSI with human sperm, 4-Piezo-ICSI with human sperm.

MATERIALS AND METHODS: Cumulus-oocyte complexes were obtained from bovine ovaries from slaughterhouse and matured in vitro. Cryopreserved sperm from bulls and humans with proven fertility were used. Conventional ICSI was performed with beveled spiked micropipettes. Piezo-ICSI was performed with flat-tipped micropipettes. Fertilization rates were evaluated 18 h after ICSI by fixing and staining the presumptive zygotes with Hoechst 33342. Cleavage rates were evaluated 48 h after ICSI.

RESULTS: Fertilization rate (2 pm) was higher with Piezo-ICSI (22.3%) than conventional ICSI (5.9%) with bull sperm (P < 0.05). The same was observed using human sperm (Piezo-ICSI 81.1%, conventional ICSI 10.7%, P < 0.05), but the magnitude of the increase in fertilization rate was higher using human (70.4%) than bull sperm (16.4, P < 0.05). In an analogous way, cleavage rates were higher with Piezo-ICSI than conventional ICSI using bull (18.4% vs. 4.2%) and human sperm (83.1% vs 9.6%; P < 0.05). The magnitude of the increase in cleavage rate was higher using human (73.5%) than bull sperm (14.2%, P < 0.05).

CONCLUSIONS: Interaction of Piezo pulse with sperm and oocyte membranes improves oocyte activation in this animal model of activation failure. Calcium oscillation studies after Piezo ICSI, and trials with human oocytes are necessary to confirm this finding and evaluate Piezo-ICSI as an alternative protocol to chemical activation.


OBJECTIVE: The zona pellucida (ZP) surrounding human embryo breaks out at the blastocyst stage to start the deployment process. It is known the ZP hardens during vitrification and embryos can become trapped or hatching may be difficult after thawing. The artificial rupture of the ZP named as assisted hatching (AH) has been used in attempts to improve the chances of implantation in frozen-thawed embryo transfer cycles. We hypothesized that taking off higher amount of ZP, about 25% (quarter-laser-AH), in frozen-thawed blastocysts allow faster and complete hatching compared to regular-laser-AH, in which just a small piece of ZP is taken off. This strategy could improve clinical outcomes. The aim of this study was to evaluate clinical outcomes of frozen-thawed blastocysts submitted to quarter-laser AH compared to regular-laser AH to opening ZP before transfer.

DESIGN: Retrospective cohort of frozen-thawed embryo transfers cycles performed during 2017 in a private reproductive medicine center.

MATERIALS AND METHODS: This study reviewed 316 frozen-thawed embryos transfers. Cycles with cleavage embryos transfers and preimplantation genetic screening were excluded and 193 cycles with frozen-thawed blastocyst transfers were analyzed. Cycles were split into two groups according to AH: 78 cycles had regular-laser-AH and 115 had quarter-laser-AH. AH was performed on day 5 by using laser (Octax Eyeware, Germany), 1.8 ms, directed to the proper region of ZP where inner cell mass was not adjacent to the inner membrane. In regular-AH the ZP was punctured by 2-3 shoots and produced a small opening. In quarter-laser-AH a quarter of ZP was taken off by 5-6 shoots.

RESULTS: Patients age (37.4 ± 4.9 versus 37.5 ± 4.8, p = 0.993) were similar in regular-laser-AH and quarter-laser-AH groups, respectively. A mean of two frozen-thawed blastocysts were transferred per patient (1.8 ± 0.5 versus 1.9 ± 0.6, p = 0.299, respectively) and a top quality blastocysts was transferred when available in 56.0% of cycles in regular-laser-AH and 66.1% of quarter-laser-AH groups (p = 0.162). The biochemical pregnancy (56.4% versus 57.4%, p = 0.505), clinical pregnancy (43.6% versus 42.6%, p = 0.505) and live birth rates (37.2% versus 37.5%, p = 0.993) were equivalent between regular-laser-AH and quarter-laser-AH groups, respectively.

CONCLUSIONS: Despite of hypothesis that quarter-laser-AH could improve clinical outcomes due to ZP hardening in frozen-thawed blastocysts transfers, we demonstrated similar results compared to regular-laser-AH. The outcomes should be interpreted with caution as the number of cycles included in this study is relatively small and the retrospective design are limitations of this study. Nonetheless, we may suggest that once AH is performed, the size of opening is not determinant of clinical outcomes in frozen-thawed blastocysts transfers.


EMBRYOLOGISTS TEAM VS. AUTOMATED ANNOTATION SOFTWARE OUTCOMES. L. Alegre, T. Peura, B. Aparicio Ruiz, A. Adam, A. Coello, D. Castello, M. Meseguer. IVIRMA Valencia, Valencia, Spain; *Genex Biomedx, Sydney, Australia; *INCLIVA, Valencia, Spain.
ANOTATIONS PERFORMED IN A ROUTINE CLINICAL PRACTICE TO THOSE PERFORMED BY AN AUTOMATED EMBRYO ASSESSMENT SOFTWARE.

DESIGN: Key development events of embryos cultured in Geri time-lapse incubator were annotated manually by embryologists at IVIRMA clinics. Embryo videos were separately analysed with an automated annotations software, and event detection and annotation timing accuracies between the two compared.

MATERIALS AND METHODS: A busy embryologist team annotated nine developmental events of 311 embryos as per normal clinical practice using Geri Assess (GA) 1.3 software. MP4 videos were uploaded to a server and analysed with a Beta version of GA 2.0 automated annotations software (βGA 2.0), and the outcome data analysed.

RESULTS: Detection: From 2,799 putative developmental events, IVI detected 89%, βGA 2.0 94%, and both concurrently 86%. Mismatch rate of βGA 2.0 annotation without IVI (IVI-no annotation), was 8%, and of IVI annotation without βGA 2.0 (βGA 2.0-no annotation) was 2%. Accuracy: Annotation timings varied between the methods, with largest differences in late M and EB events. Mean difference of PNd to 6-cell events varied between 12-46 (median 5-13), and of M and EB between 89-110 (median 39-63) frames (1 frame = 5 min). Non-annotated events accumulated largely on same embryos, with only 152 embryos (49%) having all events annotated by both methods. Lack of annotations reflects interpretation difficulties associated with poor embryo quality. Such embryos also had the highest differences in annotation timings. The expected accuracy may vary between clinics, but e.g. an arbitrarily assigned limit of outcomes with the utilization of PGT evaluation for aneuploidy testing.

When multiple cells herniating from the zona pellucida on day 5 and day 6, embryos were biopsied for aneuploidy testing. Embryo biopsy consisted of laser removal of 5 to 7 cells from the trophoectoderm juxtaposed to the inner cell mass. The biopsied cells were treated according to the reference laboratory protocol for off site Next-generation sequencing for aneuploidy screening. Embryos available for testing were vitrified and stored under liquid nitrogen until results were obtained from the reference laboratory.

RESULTS: A total of 147 frozen donor oocytes were thawed in 24 patients and 807 oocytes in the 38 fresh donor cycles. There was a significantly more oocytes per patient in the fresh subgroup as compared to the frozen thawed. Where the fresh subgroup had and average of 21 oocytes per patient compared to 6.12 oocytes per patient in the frozen-thawed subgroup. In the frozen-thawed subgroup, a total of 107 (72%) oocytes fertilized normally resulting in 15/20 (75%) euploid day 5 and 24/36 (67%) euploid day 6 embryos. In the fresh donor oocyte subgroup there were 532 (66%) normally fertilized oocytes. Yielding 95/137 (69%) day 5 euploid and 76/104 (73%) day 6 euploid embryos (Not Significant). There were 15 frozen embryo transfers in the Frozen-Thawed subgroup, where 10 (67%) patients resulted in ongoing pregnancy with an average of 1.0 embryos transferred per patient. There was no significant difference for the 33 frozen embryo transfers from fresh oocyte cycles where 19 (57%) resulted in ongoing pregnancies with an average of 1.12 embryos transferred per patient (Not Significant).

CONCLUSIONS: This study shows that cryopreserved oocytes do not result in higher rates of aneuploidy as compared to fresh oocytes. Anonymous donors are an excellent control for comparing the efficacy of frozen-thawed oocytes. Fresh and frozen oocytes resulted in excellent pregnancy outcomes with the utilization of PGD assessment for aneuploidy testing.

PGD with Fresh vs Frozen-Thawed Donor Oocytes

<table>
<thead>
<tr>
<th></th>
<th>Frozen-Thawed</th>
<th>Fresh</th>
<th>P-Value</th>
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<tbody>
<tr>
<td># Patients</td>
<td>24</td>
<td>38</td>
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</tr>
<tr>
<td>Oocytes</td>
<td>147</td>
<td>807</td>
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<tr>
<td># Fertilized (%)</td>
<td>107 (72)</td>
<td>531 (66)</td>
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<tr>
<td>Day 5 Euploidy (%)</td>
<td>15/20 (75)</td>
<td>95/137 (69)</td>
<td>N.S.</td>
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<tr>
<td>Day 6 Euploidy (%)</td>
<td>24/36 (67)</td>
<td>76/104 (73)</td>
<td>N.S.</td>
</tr>
<tr>
<td># FET’s</td>
<td>15</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td># Ongoing (%)</td>
<td>10 (67)</td>
<td>19 (57)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Avg ET</td>
<td>1.0</td>
<td>1.12</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

OBJECTIVE: To compare pre-implantation genetic testing (PGT) for anonymous fresh and frozen donor oocytes.

DESIGN: Retrospective cohort study of PGT for fresh and frozen anonymous donor oocytes.

MATERIALS AND METHODS: Frozen thawed oocytes were treated with intracytoplasmic sperm injection (ICSI) two hours post thaw. Fresh donor oocytes were treated with ICSI 40 to 42 hours post ovulation trigger for retrieval. Fertilization confirmation occurred 18 to 20 hours post ICSI and placed in a single step culture media through day 6 of embryo development. Embryos were evaluated on day 3 and assisted hatched for via laser ablation.

When multiple cells herniating from the zona pellucida on day 5 and day 6, embryos were biopsied for aneuploidy testing. Embryo biopsy consisted of laser removal of 5 to 7 cells from the trophoectoderm juxtaposed to the inner cell mass. The biopsied cells were treated according to the reference laboratory protocol for off site Next-generation sequencing for aneuploidy screening. Embryos available for testing were vitrified and stored under liquid nitrogen until results were obtained from the reference laboratory.

RESULTS: A total of 147 frozen donor oocytes were thawed in 24 patients and 807 oocytes in the 38 fresh donor cycles. There was a significantly more oocytes per patient in the fresh subgroup as compared to the frozen thawed. Where the fresh subgroup had and average of 21 oocytes per patient compared to 6.12 oocytes per patient in the frozen-thawed subgroup. In the frozen-thawed subgroup, a total of 107 (72%) oocytes fertilized normally resulting in 15/20 (75%) euploid day 5 and 24/36 (67%) euploid day 6 embryos. In the fresh donor oocyte subgroup there were 532 (66%) normally fertilized oocytes. Yielding 95/137 (69%) day 5 euploid and 76/104 (73%) day 6 euploid embryos (Not Significant). There were 15 frozen embryo transfers in the Frozen-Thawed subgroup, where 10 (67%) patients resulted in ongoing pregnancy with an average of 1.0 embryos transferred per patient. There was no significant difference for the 33 frozen embryo transfers from fresh oocyte cycles where 19 (57%) resulted in ongoing pregnancies with an average of 1.12 embryos transferred per patient (Not Significant).

CONCLUSIONS: This study shows that cryopreserved oocytes do not result in higher rates of aneuploidy as compared to fresh oocytes. Anonymous donors are an excellent control for comparing the efficacy of frozen-thawed oocytes. Fresh and frozen oocytes resulted in excellent pregnancy outcomes with the utilization of PGD assessment for aneuploidy testing.
OBJECTIVE: To find out whether there is any relationship between blastulation on day 5 or day 6 and the embryo categorization provided by Eeva.

DESIGN: Retrospective cohort study in our oocyte donation program. The study includes embryos that were incubated in a conventional incubator with Eeva system in the past two years.

MATERIALS AND METHODS: Embryos were cultured in a standard incubator with temperature control. Using automatic cell-tracking software, we analyzed the exact timing of first cleavages, which provides an embryo classification on day 3 and blastulation rates in day 5 and day 6 in each Eeva category, separating between viable embryos (transferred or vitrified) and good morphology blastocysts (A/B ASEBIR categories) as well as the relationship between blastocyst day and P2 and P3 values obtained by Eeva.

RESULTS: From the total number of embryos that reached blastocyst stage (N=1248), the majority did it on day 5 (89.85%; n=1121). Only a small percentage reached blastocyst stage on day 6 (10.2%; n=127). These blastocysts where categorized according to Eeva classification showing how many of them had reached blastocyst stage on day 5 (HIGH 96.5%; MEDIUM 72.3%; LOW 65.2% p<0.0001). When we focus on viable blastocysts (transferred or vitrified), we still observed a direct correlation between Eeva categories and viable blastocysts on day 5 (HIGH 85.4%; MEDIUM 76.2%; LOW 65.2% p<0.0001). Similar observations with those with good morphology (A/B ASEBIR) (HIGH 90.4%; MEDIUM 84.9%; LOW 72.3% p<0.0001).

CONCLUSIONS: There is a direct correlation according to Eeva categories, morphokinetic variables and embryo blastulation pattern. The important differences at the early stages of embryo development occurred between embryos that blastulated in D5 or D6 may help to understand the reduced implantation potential of those embryos with delayed blastulation and may allow us to improve embryo selection by using continuous embryo monitoring.

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REVALIDATION OF DIAGNOSTIC EQUIPMENT IN FERTILITY CLINICS IS CRITICAL UPON SOFTWARE OR TECHNICAL UPGRADE. A. Agarwal,1,* R. Henkel,1,2 S. Gupta,1 R. Sharma.1,2 American Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH; Department of Medical Bioscience, University of the Western Cape, Bellville, South Africa.

OBJECTIVE: The past decade has seen rapid developments of analytical and diagnostic equipment used in andrology laboratories and in vitro fertilization (IVF) clinics. One such example is flow cytometers used to evaluate sperm DNA fragmentation by TUNEL-assay. Often, new developments of equipment necessitate software and technical updates to existing equipment. This is more common than the introduction of a completely new equipment, which is also expensive. Since the turnover of equipment, particularly in smaller centers, is less frequent, laboratories continue using settings and clinical cut-off values that were validated on older machines with old settings. The use of older settings and cut off values on upgraded models may impact the clinical results of a patient. In this study, we compared the TUNEL results of sperm DNA fragmentation obtained using an older flow cytometer with a newer version of the same instrument.

DESIGN: Determination of the sperm DNA fragmentation and comparing the results against the newer version of the same instrument.

MATERIALS AND METHODS: A total of 23 semen samples were read in parallel using the BD-Accuri C6 flow cytometer and its updated C6-Plus version. The validated C6 and the C6-Plus were used with the same parameters as well as adjusted new settings. Spearman rank correlation, Chi-square test, concordance correlation coefficient and receiver operating characteristic (ROC) areas were used to compare the clinical value of the newer C6-Plus version with the results from the older version.

RESULTS: A significant (P<0.0001) difference was observed between the adjusted and unadjusted C6-Plus with the standardized C6. The unadjusted C6-Plus failed to correctly detect 5 out of 23 samples. Lower concordance correlation coefficient (0.6155 vs. 0.9775), precision (p=0.7479 vs. p=0.9954) and accuracy (Cmax=0.8230 vs. Cmax=0.9840) were seen with unadjusted C6-Plus. Unadjusted C6-Plus had lower sensitivity (94.4%) and specificity (80%) compared with 100% sensitivity and specificity for the adjusted C6-Plus. With adjusted settings, C6-Plus could predict infertility in the same way as the C6.

CONCLUSIONS: We recommend that all new and/or updated diagnostic flow cytometers should have settings and adjustments validated in order to obtain comparable diagnostic results. To prevent misreporting clinical results, this adjustment and revalidation is also essential for all other diagnostic equipment used in andrology and/or IVF labs.

CONCLUSIONS: Non-invasive methods of assessing nutrient uptake and utilization of the presence of factors in the media have been developed and are being tested. The results are heavily reliant on the time the embryo is present in culture media and use of clean supplements that will not mask signals. This preliminary data indicates that a novel ultrasensitive digital immunooassay could be one new method that may allow for a clinically accessible platform and could act as an important adjunct to other embryo selection criteria. Our clinical study is ongoing.
TABLE 1. HCG concentration in culture media and in samples of Embryoglue media containing embryos

<table>
<thead>
<tr>
<th>Sample</th>
<th>Mean HCG concentration, pg/mL</th>
</tr>
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<tbody>
<tr>
<td>Assay Buffer</td>
<td>&lt; Limit of Detection</td>
</tr>
<tr>
<td>Embryoglue (EG)</td>
<td>&lt; Limit of Detection</td>
</tr>
<tr>
<td>CSC + 10% SPS</td>
<td>23.9</td>
</tr>
<tr>
<td>SPS alone</td>
<td>362.2</td>
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<tr>
<td>Negative FHB Pooled EG</td>
<td>0.07</td>
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<td>Positive FHB Pooled EG</td>
<td>0.29</td>
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PERFORMANCE OF COMMON DISPOSABLE PLASTICWARE IN A LARGE-SCALE MOUSE EMBRYO ASSAY TESTING PROGRAM: PERENNIAL TROUBLEMAKERS AND SAFE BETS. C. Grimm, C. Graham, R. Kile, R. Smith, W. B. Schoolcraft, J. E. Swain, R. L. Krisher. Colorado Center for Reproductive Medicine, Lone Tree, CO.

OBJECTIVE: To investigate the long term performance of common disposable plastics used in the ART laboratory in a mouse embryo assay (MEA), and identify specific items that more frequently fail testing.

DESIGN: Retrospective Study.

MATERIALS AND METHODS: Mouse embryos were produced by in vitro maturation (IVM) and fertilization (IVF) of oocytes collected from an outbred mouse strain (Swiss-Webster; Envigo), resulting in a sensitive MEA assay (Herrick et al., 2015; JARG 33:237). Culture medium was exposed to plasticware overnight at 37°C for all tested items except serological pipets, and then used to make culture drops. For serological pipets, several pipets were rinsed multiple times with medium. The same medium without test material exposure was used for control. Post IVF, zygotes were randomly assigned to control or test treatment. Preset minimum developmental standards (≥75% cleaved embryos, ≥65% blastocyst day 4 (96 hrs of culture), and ≥60% hatching blastocysts day 5 (112 hrs)) must be met by both the control and test item for the MEA to be considered passing. At least 25 zygotes in control and each test were required. Items used are routinely tested via IVM MEA in our laboratory before implementation in clinical ART. For inclusion, a minimum of three lots of any particular product were tested.

RESULTS: In total, 14 disposable plasticware items in our QC program were included in the study. Ten of these items (71%) have never failed a MEA test (100x15mm petri dish, 35x10mm tissue culture dish, 60x15mm tissue culture dish, 1 mL serological pipet, 5 mL serological pipet, 10 mL serological pipet, 15 mL centrifuge tube, 14 mL snap cap tube, stripper tips (all sizes), and 1250 µL pipet tips. Four items (29%) failed MEA testing for a single lot; 150 µL receiver units (1/3, 20% failure), center well dishes (1/3, 33% failure), 25 mL pipets (1/3, 33% failure), and 200 µL pipet tip (1/3, 33% failure). We have tested additional sizes of receiver units but only one lot of each (250 µL and 500 µL passed, whereas the 1000 µL unit failed. In our experience, pipet tips that pass MEA testing can be brand dependent. We have done limited testing of pre-tested MEA items, including the Culture Coin, Life Global Universal and Mini GPS dishes (1 lot each), Oosafe 6 well dishes (2 lots), and Origo stripper tips (6 lots); all passed. Items that have never passed our MEA test include specimen cups and gloves; they consistently fail even with very short exposure times.

CONCLUSIONS: Almost a third of untested disposable plasticware products in our QC program present lots that are detrimental to mouse embryos. Two items that have failed our MEA test would have directly contacted eggs or embryos in the laboratory. These results emphasize the importance of vigilant MEA testing of all items before utilization in the ART laboratory to optimize IVF outcomes.

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IVF INSEMINATION PROVIDES HIGHER BLASTULATION RATES COMPARED TO ICSI-A SIBLING OOCYTE STUDY. M. Sauerbrun-Cutler, W. Huber, III, R. Hackett, C. Shen, P. Has, R. Alvero, S. Wang. Brown University/Women & Infants Hospital, Providence, RI; Obstetrics and Gynecology, Warren Alpert Medical School of Brown University/Women and Infants Hospital, Providence, RI; Division of Research, Brown University/Women & Infants Hospital, Providence, RI; OB GYN, Brown University, Providence, RI.

OBJECTIVE: To identify morphokinetic annotations of developing human embryos with neural networks trained on time-lapse videos.

DESIGN: We performed a retrospective cohort study with IRB approval on 1309 embryos from 113 patients undergoing in vitro fertilization from 2014-2016 at the Cleveland Clinic Fertility Center.

MATERIALS AND METHODS: Embryos were imaged from approximately 18-140 hours post-fertilization every 15 minutes using an EmbryoScope® incubator. An embryologist recorded the earliest time an embryo met each developmental milestone, including beginning of observation (tStart), breakdown of the pronuclei (tPN), appearance of 2 cells (t2), 3 cells (t3), 4 cells (t4), 5 cells (t5), 6 cells (t6), partially compacting embryo (t+6), morula (tM), start of blastulation (tBL), blastulation (tB), expanded blastocyst (tEB) and hatching blastocyst (tHB). Annotations for frames between transition times were interpolated. Models were divided as training/validation/test sets with 93/10/10 patients, respectively. A convolutional neural network was trained on the first 70 hours of each embryo to predict the first 6 morphokinetic stages (remaining stages condensed to t++) using a ResNet architecture (1). Monotonicity of progression through developmental stages was enforced through a dynamic programming (DP) postprocessing step. Additional models incorporating surrounding video frames (early fusion) or more distant frames (late fusion) as well as time post-fertilization were constructed. Per frame accuracy of predictions, mean absolute error (MAE) and root mean squared error (RMSE) were computed for each model variation.

RESULTS: Video frames were distributed across classes as 10.3%, 5.3%, 19.4%, 4.5%, 19.4%, and 40.7% for tStart through t++, respectively. A pre-trained ResNet model successfully classified frames into the appropriate developmental stage with 82% accuracy. After incorporating a late fusion model including the 14 surrounding frames, we achieved 84% accuracy, which improved to 87% following DP postprocessing (MAE 8.594, RMSE 24.334). Still, this model consistently misclassified developmental stage in embryos with cellular fragments or undergoing chaotic division.

CONCLUSIONS: Convolutional neural networks can predict morphokinetic annotations of early development directly from time-lapse videos for many embryos with high frame-level accuracy. Future work will refine these models to better distinguish cells from debris and predict later developmental annotations as well as implantation potential.

CONCLUSIONS: This unique IVF/ICSI split design confirmed a higher quality blastulation rate in the IVF group compared to the ICSI group, while limiting multiple confounding variables, including infertility diagnosis, age and semen analysis parameters. This suggests that the inferior high quality blastulation rate in the ICSI group is unlikely due to poorer semen quality.

OBJECTIVE: Preimplantation genetic screening (PGS) for aneuploidy has become a commonplace practice in many ART centers. Although PGS is an excellent tool to increase IVF efficiency in appropriately selected couples, PGS is not perfect in its diagnostic accuracy. There is a chance of misdiagnosis from both biological and technical limitations. One of the technical limitations is varying TB cell numbers among blastocyst: group A were (low cell numbers; ≤6 cells) and group B (high cell number; > 6 cells). Euploidy and aneuploidy rates, structural segmental abnormal, complex abnormal and no-results rates were calculated between two groups.

RESULTS: Euploidy rate was significantly higher in group B compared to group A (54.2% vs 40.0% respectively; P<0.08), and the no-results rate was significantly lower (2.1% vs 8.8%, respectively; P=0.001). There were, however, no differences in the rate of aneuploidy, segmental abnormality, or complex abnormality. Cell number biopsied did not vary between testing platforms.

CONCLUSIONS: A larger number of TB cells at biopsy correlates with a higher euploidy rate and lower no-result rate. While taking a smaller number of cells is morphologically beneficial to the embryo, smaller TB cell numbers yield a higher chance of no-result. Our findings illustrate the need for a larger study to standardize the technical variability associated with PGS in order to improve the diagnostic efficiency while maintaining embryo integrity.

References: Non
Supported by: Non

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OBJECTIVE: To demonstrate the effect of assisted oocyte activation (AOA) on reproductive outcomes after previous fertilization failure (FP) cycle associated to a male factor.

DESIGN: Retrospective Cohort Study.

MATERIALS AND METHODS: We described the outcome from 273 oocytes from 66 patients who underwent first attempt of ICSI without AOA, for Reproductive Medicine, Reston, VA; 4George Washington University, Dc, DC.

for Reproductive Medicine, Reston, VA; 4George Washington University, Dc, DC.

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getting either fertilization failure or low percentage of fertilization (<30%) and were compared with 620 oocytes from the same cohort of patients (84 cycles) in which a new attempt (48 with one cycle and 18 patients with two cycles) were performed with AOA. Study period included between April 2013 and September 2016. The injection of the oocytes by AOA was carried out by injecting the spermatozoa together with a previous phase of buffered media with Ica (1/3 of pipette in 40x magnification microscope). Later, they were kept for ten minutes in the incubator with fertilization media and ICA in a 37°C, 6%CO2 atmosphere. Embryo culture was carried out in standard incubator under culture conditions of 37°C, 6% CO2, 5% O2 atmosphere. Fertilization, pregnancy, implantation and abortion rates were analysed and compared in both groups by X^2, t-Student and ANOVA tests when were needed.

RESULTS: Statistically significant differences were found in favor to AOA group vs. control according to normal fertilization rate (51.3% vs 15%), ongoing pregnancy rate (47.2% vs 15.4%), implantation rate (30.5% vs 7.7%) as well as cancellation rate per cycle (20.9% vs 57.6%).

CONCLUSIONS: Our findings described in a remarkable population of patients that the use of AOA, in those cases with either total failure or very low fertilization rate, is significantly enhanced the reproductive success. The improvement is a consequence of an increase in the fertilization rate and the number of viable embryos available for the cycle. Our results are demonstrating the utility of this technique after previous fertilization failure as an alternative to be offered to our patients.

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OBJECTIVE: Factors that guide the decision to transfer or freeze a borderline blastocyst are not well defined, despite having the ability to affect patient outcomes. Due to limited objective guidelines, the decision to transfer or freeze is likely influenced by individual patient factors and embryologist decisional factors, especially when the level of uncertainty is high. This research explored whether patient and embryologist factors impacted the decision to freeze blastocysts of borderline quality.

DESIGN: An online cross-sectional decisional process survey consisting of 8 clinical vignettes and accompanying borderline blastocyst images was completed by 162 embryologists. The survey asked the embryologist to make ratings of the likelihood they would freeze a given embryo.

MATERIALS AND METHODS: The survey was disseminated via embryologist message boards and was open to currently practicing embryologists. Vignettes included patient information that systematically varied in terms of maternal age in years (35 or 40), number of previous IVF cycles (first cycle or 4 prior cycles), and number of additional blastocysts frozen in the cohort (5 blastocysts frozen or none frozen). Self-report measures assessing dispositional Intolerance of Uncertainty (IU) and Decision Making Style were included. A mixed model ANOVA assessed the influence of the 3 patient variables and embryologist intolerance of uncertainty on the likelihood of freezing.

RESULTS: Consistent with previous work, analyses showed disagreement between embryologists regarding blastocyst viability. In all 8 scenarios, likelihood ratings between 1 (very unlikely) and 7 (very likely) were obtained. Likelihood of freezing was greater with lower maternal age, fewer blastocysts frozen in the cohort and a greater number of previous cycles (p<0.001). Interaction terms indicated that maternal age was more influential in decision-making when there were no other blastocysts frozen in the cohort (p<0.001) or where there were greater previous cycles (p=0.002). No effects were observed for embryologist IU and Decision Making Style.

CONCLUSIONS: This study is the first to investigate patient and embryologist factors that may contribute to variation in evaluations of blastocyst viability under conditions of uncertainty. While high levels of disagreement highlights that objective measures of borderline blastocyst morphology are lacking, the finding that embryologist decisional factors may be influenced by specific factors indexing patient characteristics and treatment history is important and may provide insight into the decisional processes underlying grading. According to these analyses, when the decision to freeze is uncertain, embryologists may use contextual factors such as maternal age and number of previous cycles to guide the decision making.

Supported by: Funded by Fertility Associates New Zealand.

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THE USE OF CAPILLARY-CUMULUS OOPHORUS SELECTION MODEL BY INTRACYTOPLASMIC MORPHOLOGICALLY SELECTED SPERM INJECTION (IMSI). M. M. Piccolomini, L. Cremonesi, A. R. Lorenzon, T. C. Bonetti, C. Serafini, J. Allegretti, E. L. Motta. Embriology, Huntington Medicina Reprodutiva, Sao Paulo, Brazil; Scientific Coordinator, Huntington Medicina Reprodutiva, Sao Paulo, Brazil; Department of Gynecology, Federal University of Sao Paulo, Sao Paulo, Brazil; Clinical Director, Huntington Medicina Reprodutiva, Sao Paulo, Brazil; Department of Gynecology and Obstetrics, University of Sao Paulo, Sao Paulo, Brazil.

OBJECTIVE: The use of the capillary-cumulus oophorus model for evaluating spermatozoa selection by intracytoplasmic morphologically selected sperm injection (IMSI).

DESIGN: This is a cross-sectional study. Sperm and cumulus oophorus cells were obtained from patients attending Huntington Reproductive Medicine Clinic for in vitro fertilization (IVF) procedures between October and December 2015, after informed consent was obtained.

MATERIALS AND METHODS: After routine semen analysis, the semen was incubated with the swim up method. Only samples with normal parameters in our IVF program (WHO, 2010) were used in this study. A pre-warmed (37°C) sperm suspension was adjusted to a final concentration of 10 million motile sperm/mL. Oocytes were recovered by follicular aspiration. The excess of cumulus cells were removed mechanically by using two insulin needles. Expanded mature cumulus cells were separated on a plate prewarmed to 37°C with a glass pipette. The capillary-cumulus model consisted of 1.1 cm column filled with a 5 cm long loaded with a 3 cm column of culture media. A 1 cm column of cumulus cells dipped into 500 uL droplet of sperm suspension containing 10x10^4/mL (SU-CC) at a 45° angle. The system was covered with mineral oil and warmed at 37°C for 1 h. A capillary-cumulus model in the same conditions, except by the cumulus layer (SU-C) and swim-up conventional (SU) were used as controls. All samples were analysed by concentration, motility and intracytoplasmic morphologically selected sperm injection (IMSI). Data analyses were performed using SPSS 22 (IBM SPSS Software, USA), and we considered p-values <0.05 to be statistically significant.

RESULTS: Thirty-three semen samples with normal parameters and thirty-three expanded oocytes cumulus samples were obtained. The sperm characteristics after SU were: motile sperm concentration average of 33.4 million/mL and class I morphology at high magnification microscopy of 39.94%. After application in the capillary-cumulus model, the motile sperm concentration was lower as expected in both groups (SU-C: 3.7 million/mL, p<0.001 and SU-CC: 0.74 million/mL, p<0.001). However, the morphology evaluated by IMSI was higher after SU-C (51.52%, p<0.001) and even higher in SU-CC (65.30%, p<0.001) when compared with sample after SU only.

CONCLUSIONS: Based on the results obtained in this study, we suggest that the capillary-cumulus oophorus model may be used as a tool to select sperm with top morphology parameters, evaluated by a high magnification microscope, which could be beneficial for sperm selection with greater potential for fertilization and embryo development.

References:

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PRIMING SPERMATOZOA WITH AUTOLOGOUS CUMULUS ENHANCES FERTILIZATION AND BLASTOCYST FORMATION RATES, SPERM MOTILITY, AND EMBRYO PERFORMANCE. W. Wun, V. Pham, I. Wun, G. Grunert, S. Chauhan, R. Mangal, L. Schenk, E. Kovanci, Y. Anaya, R. Dunn. IVF Lab, Aspire Fertility, Houston, TX; University of Queensland, Brisbane, Australia; Aspire Fertility, Houston, TX; Houston Fertility Specialists, Houston, TX.

OBJECTIVE: In human, non-male factor ICSI cases show significantly lower implantation and live birth rates (Boulet et al, 2015). This phenomenon may be due to introduce of un-needed acrosomal enzymes (hyaluronidase and acrosin) into the egg (Morozumi and Yanagimichi, 2005; Morozumi et al, 2006). Part I of this study has found physiological selection of spermatozoa by cumulus can significantly enhance sperm hyperactivation/engaging acrosome reaction. This study is to examine the effect of primed sperm with cumulus upon fertilization, embryo development and quality.

Supported by: Funded by Fertility Associates New Zealand.
TABLE 1.

<table>
<thead>
<tr>
<th>parameters</th>
<th>Group A</th>
<th>Group B</th>
<th>p-value</th>
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<tr>
<td>Total number of embryos</td>
<td>568</td>
<td>606</td>
<td>0.0001</td>
</tr>
<tr>
<td>Day 3 Embryos</td>
<td>201</td>
<td>301</td>
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</tr>
<tr>
<td>Day 5 Embryos</td>
<td>230</td>
<td>238</td>
<td>NS</td>
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<tr>
<td>Mean Number of embryos</td>
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<td>2.7 ± 0.4</td>
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<tr>
<td>Implantation Rate</td>
<td>53.1%</td>
<td>51.5%</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical Pregnancy Rate</td>
<td>47.8%</td>
<td>44.6%</td>
<td>NS</td>
</tr>
<tr>
<td>Missed Abortion</td>
<td>10.5%</td>
<td>9.2%</td>
<td>NS</td>
</tr>
</tbody>
</table>


OBJECTIVE: Heated IVF work surfaces, which attempt to emulate physiological temperatures, have greatly improved oocyte and embryo safety. Many manufacturers produce factory calibrated heated surfaces, however, these devices are highly variable and need to be operationally validated and continuously monitored for optimal use. Factory issued digital set points often do not correlate with desired micro-drop temperatures. We analyzed temperature variations of both laminar flow hood and inverted microscope heated surfaces in culture (CUL) and micromanipulation (MM) dishes.

DESIGN: Prospective temperature analysis of heated surfaces overtime. MATERIALS AND METHODS: CUL dishes with 40 mL drops and a 10 mL oil overlay were incubated overnight at 37°C. MM dishes with 20 mL drops and 4 mL of 37°C oil overlay were placed on a laminar flow hood heated surface. Using a certified calibrated thermocouple, temperatures of the drops were measured at various set times ranging from 0 to 70 minutes for the CUL dishes and from 1 to 30 minutes for the MM dishes. Repeated measurements (CUL n=92, MM n=42) with multiple dishes (CUL n=12, MM n=6) were taken over the course of the testing times. To monitor the temperature of a dissecting microscope heated stage in a laminar flow hood, CUL dishes from a 37°C overnight incubator were placed on the heated surface with a digital set point of 41.3°C at a marked spot. To monitor the temperature of a micromanipulation heated stage, MM dishes from a 37°C heated surface, were placed on the micromanipulation stage with a digital set point of 39.9°C at a marked spot.

RESULTS: In order to achieve 37°C in the dishes, the laminar flow hood digital set point was required to be 39.9°C. Multiple cycles of heating and cooling occurred on both surfaces. CUL dishes measured a mean temperature of 36.7°C with a standard deviation of 0.22°C (range 35.5-37.5°C), MM dishes measured a mean temperature of 37.2°C with a standard deviation of 0.50°C (range 36.6-38.6°C). CONCLUSIONS: The heated surfaces of laminar flow hoods and micromanipulation stages were found to greatly vary in micro-drop temperature compared to their digital set point. The time periods measured can be used to represent common IVF procedures. We believe there can be a reduction in stress on oocytes and embryos through designing clinical protocols and procedures that minimize the exposure times to these varying temperatures that do not correlate with manufacturer digital set points. These changes could include regulating the number of oocytes/embryos undergoing a procedure simultaneously in one dish or having a second embryologist assist during procedures with a large number of oocytes/embryos. Every laboratory should perform their own independent temperature validation prior to using any manufacturer issued set point.

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IS TIME LAPSE A BETTER OPTION TO IMPROVE CLINICAL OUTCOME OVER STANDARD INCUBATOR- A CASE CONTROLLED STUDY. K. D. Nayar, R. Gahlot, G. Kant, M. Singh, N. Sharma, K. Nayar, Akanksha IVF Centre, New Delhi, India.

OBJECTIVE: To study the Clinical outcome of In Vitro Fertilization cycles using Time Lapse incubator versus standard incubator for selection of embryos.

DESIGN: Case control study was conducted from 1st January 2017 to 31st December 2017. A total of 200 women undergoing IVF for tubal factor were included in the study and divided in to 2 Groups(Gr). Gr A: 100 women whose embryos were cultured in Time lapse incubator(TL) (Primovision) Gr B: 100 women whose embryos were cultured in standard incubator(SI). Antagonist protocol and freeze all technique was used. Demography of the patients was similar in both the groups.

MATERIALS AND METHODS: 586 Embryos were incubated in Time lapse incubator and selected on the basis of morphokinetic parameters while 606 embryos were incubated in Standard incubator and selected on the basis of morphology (Istanbul consensus). Embryos with best morphokinetic and morphology were selected for freezing and transferred in subsequent cycle on day 18 or 19.

RESULTS: Total number embryos incubated in TL and SI were 586 and 606 respectively. Day 3 culture Grade A embryos in TL vs SI (51.4% vs 49.8%, p<0.05) and Day 5 Grade A (40.5% vs 39.4%, p<0.05). Mean number of Frozen embryos transferred which were incubated earlier in TL and SI were (2.7 ± 0.5 vs 2.7 ± 0.4, p<0.05). Implantation rate (53.1% vs 51.5%) and clinical pregnancy rate were found to be similar in both groups (47.8% vs 44.6%) with p>0.05. Missed abortion rate were also non significant (10.5% vs 9.2%) in both the groups.

Time lapse Vs. standard incubator

<table>
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<th>Parameters</th>
<th>Group A (Time Lapse)</th>
<th>Group B (Standard Incubator)</th>
<th>p-value</th>
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<td>Total number of embryos</td>
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<td>10.5%</td>
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</tr>
</tbody>
</table>
CONCLUSIONS: There is no statistical difference in the reproductive outcomes from the embryos cultured either in Time lapse or Standard incubator. Cost effectiveness and further research work are required to use Time Lapse routinely.

References:

Supported by: NII

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COMPARISON OF EMBRYO QUALITY AND EUPOIDY RATE USING TWO DIFFERENT TIME-LAPSE SYSTEMS AND A BENCHTOP INCUBATOR IN THE SAME IVF LABORATORY.

B. Aparicio Ruiz,1 N. Basille,1 L. Alegre,1 T. Viloria,1 J. Remohi,1 M. Meseguer.1 IVIRMA, Valencia, Spain;2 IVIRMA Madrid, Madrid, Spain;3 Embryologist IVIRMA, Valencia, Spain.

OBJECTIVE: Our aim was to analyze embryo quality and euploidy rate using different incubation conditions: two time-lapse systems (TS) with different features and a conventional benchtop incubator (CI), all systems co-existing in the same IVF laboratory.

MATERIALS AND METHODS: We examined 4010 cycles with deferred embryo transfer. Patient’s embryos were cultured either in the Embryoscope (ESD) (n=1448), GERI (n= 119) or in an ASTEC benchtop incubator (CI) (n= 2443). For CI cycles, embryos were removed from the incubator only on day 1 for fertilization check, on day 3 for media change and on day 5 for blastocyst formation/quality check. Embryos on ESD and GERI were never removed, although culture conditions were different: for ESD all patients shared the same incubator whereas in GERI each patient was cultured in an individual chamber. Good quality blastocysts were defined as those presenting A or B inner cell mass (ICM) and/or trophoectoderm (TE) according to Gardner’s classification. In addition, the percentage of euploid embryos was analyzed using next generation sequencing (NGS).

RESULTS: No significant differences were observed for patient’s demographics between the three groups (including age, BMI and sperm concentration). Table 1 shows the proportion of viable, good quality and euploid blastocysts according to the type of incubator.

CONCLUSIONS: The distribution of good quality and euploid blastocysts differs significantly according to the incubation conditions. There are more good quality embryos in both time-lapse systems, ESD and GERI, than in CI. There are more euploid embryos in GERI than in ESD and CI. Although clinical outcome was not analyzed due to the limited sample size we could observe a trend in favor of less frequent scoring would could be confirmed statistically.

Supported by: None.

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BLASTOCYST MORPHOMETRY IS PREDICTED BY THE DIAMETER OF THE ORIGINATING OVARIAN FOLLICLE.

B. S. Shapiro,a A. Raman,b F. C. Garner,a M. C. Aguirre,c C. Morrison,c A. Bill,c S. J. Thomas,c C. E. Bedient,d Fertility Center of Las Vegas, Las Vegas, NV; dOvation Fertility, Las Vegas, NV; cUniversity of Nevada Las Vegas, Las Vegas, NV; dOvation Fertility, Las Vegas, NV.

OBJECTIVE: Fewer trophoderm (TE) cells and smaller inner cell masses (ICMs) have been associated with increased risks of implantation failure and early pregnancy loss. This study will assess relationships, if any, between blastocyst morphology and the diameter of the follicle from which the oocyte originated.

DESIGN: IRB-approved prospective observational cohort study.

MATERIALS AND METHODS: Patients underwent routine ovarian stimulation with exogenous gonadotropins. During oocyte collection, follicle diameters were sonographically measured on two perpendicular axes, and the mean of these two measurements was calculated for each follicle. Embryos were group-cultured to the blastocyst stage according to mean follicle diameter (6, 9.5, 10-12.5, 13-15.5, 16-18.5, 19-21.5, 22-24.5, 25-27.5, 28mm). Analysis of variance was used to compare inner cell mass (ICM) size (expressed as cross-sectional area) and trophoderm (TE) perimeter cell counts across follicle diameter groups. Significant overall tests were followed by means comparisons. P < 0.05 was considered significant.

RESULTS: There were 566 blastocysts of good quality and 540 of these were derived from measured follicles, while 26 blastocysts derived from oocytes of uncertain or unmeasured follicular origin were excluded. Analysis of variance found a significant overall difference in ICM areas among follicle size groups (P < 0.05). Subsequent comparison of means found that follicle groups ≥ 16mm in mean follicle diameter were associated with significantly larger ICM sizes when compared to other follicle size groups. Analysis of variance found a significant overall difference in TE perimeter cell counts among follicle size groups (P < 0.05). Subsequent comparison of means found that follicles 10-12.5mm in mean follicle diameter were associated with significantly fewer TE perimeter cells when compared to other groups.

CONCLUSIONS: Among formed blastocysts, those derived from small ovarian follicles (<16mm) tend to have inferior morphology (smaller ICM or fewer TE cells) when compared to those derived from larger ovarian follicles. This suggests that transfers of blastocysts derived from small follicles might have increased risk of inferior outcomes due to inferior morphometry and morphology. These observations may help to clarify relationships between folliculogenesis and embryogenesis.
OBJECTIVE: To identify the relationship between the traditional blastocyst morphological evaluation and karyotyping.

DESIGN: This is a single center retrospective observational study performed from July to September 2017. A total of 682 embryos derived from 86 patients were included and analyzed by SNP in this study.

MATERIALS AND METHODS: Patients with known translocation are recruited in this study. Trophoderm biopsy and embryo assessment were carried out simultaneously. Biopsy was performed only when the blastocysts were expanded or hatching after the use of laser. Six to eight cells were taken routinely for SNP analysis. The blastocysts were classified into four groups (excellent, good, medium and poor) based on the morphological grading and they were also divided into euploid group and aneuploid group based on the SNP results.

RESULTS: The euploidy rate was 38.4%, 21.0%, 19.5% and 10.3% in the excellent, good, average and poor blastocyst morphology groups, respectively. There was significantly higher euploid rate in excellent group, when compared with other groups (P<0.01). There was a significant increase in incidence of non-visible 1st PB and that had effect on embryo euploidy compared with a large-angle of spindle and 2nd PB. This non-invasive system for ploidy classification may contribute to improve pregnancy rate by selecting embryos more likely to be euploid.

CONCLUSIONS: Oocytes having small-angle of spindle and 2nd PB showed a higher probability of being embryo euploidy compared with a large-angle of spindle and 2nd PB. This non-invasive system for ploidy classification may contribute to improve pregnancy rate by selecting embryos more likely to be euploid.

<table>
<thead>
<tr>
<th>TABLE 1. Values are mean ± SE.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean follicle diameter</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>≤9.5mm</td>
</tr>
<tr>
<td>10-12.5mm</td>
</tr>
<tr>
<td>13-15.5mm</td>
</tr>
<tr>
<td>16-18.5mm</td>
</tr>
<tr>
<td>19-21.5mm</td>
</tr>
<tr>
<td>22-24.5mm</td>
</tr>
<tr>
<td>25-27.5mm</td>
</tr>
<tr>
<td>≥28mm</td>
</tr>
</tbody>
</table>

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THE RELATIONSHIP BETWEEN THE CONVENTIONAL BLASTOCYST MORPHOLOGICAL ASSESSMENT AND KARYOTYPING. B. Lu, J. Wang. Reproductive Medical Center, Sun Yat-sen University, GuangZhou, China.

MATERIALS AND METHODS: Patients with known translocation are recruited in this study. Trophoderm biopsy and embryo assessment were carried out simultaneously. Biopsy was performed only when the blastocysts were expanded or hatching after the use of laser. Six to eight cells were taken routinely for SNP analysis. The blastocysts were classified into four groups (excellent, good, medium and poor) based on the morphological grading and they were also divided into euploid group and aneuploid group based on the SNP results.

RESULTS: The euploidy rate was 38.4%, 21.0%, 19.5% and 10.3% in the excellent, good, average and poor blastocyst morphology groups, respectively. There was significantly higher euploid rate in excellent group, when compared with other groups (P<0.01). There was a significant increase in incidence of non-visible 1st PB and that had effect on embryo euploidy compared with a large-angle of spindle and 2nd PB. This non-invasive system for ploidy classification may contribute to improve pregnancy rate by selecting embryos more likely to be euploid.

CONCLUSIONS: Oocytes having small-angle of spindle and 2nd PB showed a higher probability of being embryo euploidy compared with a large-angle of spindle and 2nd PB. This non-invasive system for ploidy classification may contribute to improve pregnancy rate by selecting embryos more likely to be euploid.

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OBJECTIVE: Meiotic spindle plays a crucial role in the successful segregation of chromosomes and it was associated with clinical outcomes. Our previous study reported that the angle of spindle was correlated with the angle between the pronuclear axis and the 2nd PB and that had effect on embryo quality. However, the relationship between these angles and embryo euploidy was unknown. This study aims to investigate whether the angle of spindle and 2nd PB are related with embryo euploidy.

DESIGN: This study was performed from Jan 2016 to Mar 2017 in the Fertility center of CHA Gangnam medical center. The meiotic spindles were assessed by Polyscope before intracytoplasmic sperm injection. And, exact timing of the developmental events were investigated by Embryoscope.

RESULTS: Clinical pregnancy and implantation rates showed statistical difference among the four age groups when transferring day-five blastocysts (p-value=0.0207 and p-value=0.008), but not when transferring day-six blastocysts (p-value=0.3664 and p-value=0.1692). The odds ratio among the different age groups for clinical pregnancy rates obtained when transferring day-five blastocysts (0.1113,0.6357) for G3; and OR=0.3793,0.9616) for G2; OR=0.6065 (0.3793,0.9616) for G2; OR=0.8243 (0.1113,0.6357) for G3; and OR=0.5161 (0.9599,2.4007) for G4. However, when comparing the outcomes between the two vitrification day groups within the same age group there were no statistical difference. For
implantation rate: G1, 39.6 vs 31.6 (p-value=0.515); G2, 24.7 vs 28.0 (p-value=0.740); G3: 15.0 vs 25.0 (p-value=0.373); G4: 47.4 vs 60.0 (p-value=0.384). For clinical pregnancy rate: G1, 39.7 vs 35.3 (p-value=0.733); G2, 28.6 vs 31.8 (p-value=0.774); G3: 15.8 vs 25.0 (p-value=0.574); G4: 50.0 vs 57.1 (p-value=0.634).

CONCLUSIONS: Blastocysts vitrified in day 5 and 6 of culture have the same implantation rate when transferred in freeze-thaw cycles of women of the same age group. As expected day-five blastocysts implantation potential and clinical pregnancy rates decrease as maternal age increases. Surprisingly, the same behaviour is not observed with day-six blastocysts, however, this can be due to the low number of cases present in some of the age groups.

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OBJECTIVE: To evaluate if the interval between a failed fresh embryo transfer and a subsequent natural frozen-thawed embryo transfer (FET) cycle has an impact on live birth rates.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: All women who underwent at least one natural FET (spontaneous LH surge without hCG trigger) with transfer of a blastocyst(s) following ovarian stimulation for in vitro fertilization (IVF) and a failed fresh embryo transfer attempt from January 2011 to December 2016 were analyzed. Cycles were excluded if the natural FET and the original IVF cycle were interrupted by another treatment cycle (IVF cycle or other type of FET). Cycles in which PGS testing was performed were also excluded. The cohort was then divided according to the interval between the oocyte retrieval and the FET cycle start date; ≤ 22 days was classified as immediate transfer, > 22 days as delayed transfer. The following data were analyzed: age at cycle start, BMI, protocol (GnRH antagonist vs GnRH agonist-suppressed), trigger type (hCG vs luteinizing hormone), number of embryos transferred, highest embryo grade transferred, cycle outcome. Student’s t-test and multivariable logistic regression were calculated with p-value <0.05 considered significant.

RESULTS: A total of 852 cycles met inclusion criteria with 164 cycles classified as immediate transfer and 688 cycles classified as delayed transfer. There was a significantly higher live birth rate in the delayed transfer group as compared to the immediate transfer group (47.1% after delayed transfer vs. 26.8% after immediate transfer, OR 2.43, 95% CI 1.67-3.54, P<0.0001). This difference in live birth rate persisted even after adjusting for age, BMI, protocol, trigger type, number of embryos transferred and highest embryo grade (adjusted OR 2.49, 95% CI 1.68-3.68, p<0.0001). The median number of embryos transferred in the immediate transfer group was lower than the median for delayed transfer group (1.51 ±1.04 (SEM) vs 1.72 ±0.02 (SEM), P<0.0001), however, there was no difference in highest embryo grade transferred between the two groups. There was also a significantly higher live birth rate in the age group less than 35 years as compared to other age groups, as well as in the normal weight group as compared to the overweight and obese groups.

CONCLUSIONS: There was a significantly higher live birth rate in the delayed transfer group as compared to the immediate transfer group (47.1% after delayed transfer vs. 26.8% after immediate transfer), which persisted even after adjusting for age, BMI, protocol, trigger type, number of embryos transferred and highest embryo grade transferred. This data suggests that ovarian stimulation has carryover effects on the hormonal milieu of the natural cycle following an IVF cycle, which may impact the optimal timing of a subsequent FET. This is a new finding which has a significant impact on counseling patients regarding the timing of natural FET cycles.

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DAY OF EMBRYO BIOPSY SIGNIFICANTLY AFFECTS THE CLINICAL OUTCOME IN OBLIGATORY BUT NOT ELECTIVE FROZEN SINGLE EUPLOID BLASTOCYST TRANSFERS. N. Findikli, M. Gultomruk, K. Boyunaklin, T. Aksoy, M. Bahceci. IVF Laboratory, Bahceci Fulya IVF Centre, Istanbul, Turkey; R&D Department, Bahceci Fulya IVF Centre, Istanbul, Turkey; infertility Clinic, Bahceci Fulya IVF Centre, Istanbul, Turkey.

OBJECTIVE: Recent studies have indicated that nearly a quarter of human embryos reach blastocyst stage on day 6 of embryo development and the use of a cryopreserved day 5 or a day 6 blastocyst produces similar clinical outcome in frozen embryo transfers (ET). It is also generally well-accepted that human embryo implantation is still considerably limited by the age-induced increase in aneuploidy. The application of PGT-A is proposed to diminish this negative effect by selecting euploid embryos for transfer. The aim of the current study is to analyze and compare whether a euploid day 5 and a day 6 blastocyst can result in similar clinical outcome in frozen single blastocyst transfers.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: Current study includes 584 frozen euploid single blastocyst transfer (ESBT) cycles performed between January 2016 and December 2017. Cycles were initially grouped and compared with respect to number of euploid embryos available for ET (Obligatory or elective ESBT) for their clinical outcome. An additional subgroup analysis was then performed according to maternal age (<40 years and ≥40 years) and the day of embryo biopsy (day 5 and day 6) within and between groups respectively.

RESULTS: Basic patient/cycle characteristics, laboratory parameters including mean number of oocytes/m2 oocytes collected and fertilized as well as sperm parameters were comparable among matched groups.
A total of 353 obligatory and 231 elective ESBT cycles were performed. There were no statistically significant differences for clinical pregnancy rates (p > 0.05). In a group of patients undergoing pregnancy/Live birth rates (OP/LBR: 58.1% vs. 64.5%) and implantation rates (IR: 68.8% vs. 69.6%) between groups (p > 0.05). However, subgroup analysis showed significantly higher OP/LBR and IR in obligatory ESBT cases with <40 years of age utilizing day 5 biopsied embryos (81.4%, 71.4% and 82.1%) than cases utilizing day 6 embryos (50.6%, 42.3% and 50.6%; p < 0.025). Although there is a tendency towards higher clinical outcome, differences observed in cases with <40 years diminished in obligatory ESBT cases with ≥40 years of age as well as elective ESBT groups respectively (p > 0.05).

CONCLUSIONS: Our results show that, once a euploid embryo is found, similar clinical outcome is obtained both in obligatory and elective ESBT cases utilizing bisected and vitrified blastocysts irrespective of the day of day 6 biopsied embryos. On the other hand, Patients with <40 years of age undergoing obligatory euploid ESBT with day 5 biopsied embryos can have higher clinical outcome than the great majority of cases utilizing day 6 biopsied embryos. Well-designed prospective studies with larger sample sizes are awaited to draw a firm conclusion on the real impact of biopsy day in such cases.
DOES AMH CORRELATE WITH OOCYTE QUALITY OBTAINED FROM DONORS? C. C. Chang, D. Shapiro, A. A. Toledo, S. Sadruddin, G. Wright, Z. P. Nagy, Reproductive Biology Associates, Atlanta, GA.

OBJECTIVE: AMH levels have been used as reliable indicators for ovarian response to gonadotropins, and it has been shown to be closely associated with oocyte yield and to some extent with clinical outcomes in human IVF treatment cycles. However, it remains controversial whether AMH is associated not only with oocyte quantity but possibly also with oocyte quality. To compare cycle outcomes from cycles with variable oocyte numbers, we looked at recipient cycles using cryo-banked warmed oocytes from two groups of oocyte donors; those with AMH levels below 2.0 ng/ml and those with an AMH greater than 5 where 5 represented the median AMH value for the data set. Once segregated around the median AMH value, we compared outcomes for multiple parameters as a function of AMH.

DESIGN: Retrospective study.

MATERIALS AND METHODS: Oocyte donors recruited for our donor egg bank were required to have an AMH of at least 2.0 ng/ml and a basal antral follicle count of at least 20 (donors with PCOS and with other conditions not fulfilling the established requirements were excluded). All donors were treated with rFSH/GnRH antagonist and using GnRH agonist as trigger, with transvaginal egg collection occurring 36 hours after the trigger injection. Cryopreservation of donor oocytes derived from 274 oocyte retrievals was performed using minimum volume vitrification. Oocytes were warmed for each matched recipient independently (402 recipient cycles, total of 2707 oocytes warmed). Outcome data was grouped by serum AMH level: 1) <5 ng/ml, 2) ≥5 ng/ml. Outcome parameters were analyzed by Chi-square. There were no cases of OHSS among the donors. All other variables, including semen parameters were similar in both groups.

RESULTS: 

<table>
<thead>
<tr>
<th>AMH&lt;5</th>
<th>AMH=5</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total # of retrieval cycle for donation</td>
<td>138</td>
<td>136</td>
</tr>
<tr>
<td>AMH (mean±SD)(ng/ml)</td>
<td>3.37±2.94</td>
<td>7.86±3.27</td>
</tr>
<tr>
<td># of retrieval</td>
<td>31.74±4.95</td>
<td>40.89±15.67</td>
</tr>
<tr>
<td>follicle (mean±SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total # of recipient cycle</td>
<td>200</td>
<td>202</td>
</tr>
<tr>
<td>Total # of oocyte warmed (mean±SD)</td>
<td>1327(6.64±1.70)</td>
<td>1380(6.83±1.75)</td>
</tr>
<tr>
<td>Total # of oocyte survived (%)</td>
<td>1247(93.97)</td>
<td>1295(93.84)</td>
</tr>
<tr>
<td>Total # of oocyte fertilized (%)</td>
<td>1029(77.50)</td>
<td>1032(74.78)</td>
</tr>
<tr>
<td>Total # of blastocyst (d5/d6) (%)</td>
<td>744(56.06)</td>
<td>697(50.50)</td>
</tr>
<tr>
<td>Total # of ET (mean±SD)</td>
<td>222(1.11±0.31)</td>
<td>229(1.13±0.34)</td>
</tr>
<tr>
<td>Total # of implantation (%)</td>
<td>134(60.36)</td>
<td>122(53.27)</td>
</tr>
<tr>
<td>Total # of clinical pregnancy (%)</td>
<td>122(61.00)</td>
<td>108(53.46)</td>
</tr>
</tbody>
</table>

CONCLUSIONS: Our results demonstrate that oocyte yield is strongly correlating with AMH levels in oocyte donors. Survival and fertilization rates after warming were not significantly different between low and high AMH groups. Similarly, pregnancy and implantation rates were not significantly different between groups. It is noteworthy that the blastocyst conversion rate was slightly (but statistically significant) lower when the donors’ AMH level was equal to and/or above 5 ng/ml. Our findings imply that AMH can be a good indicator for oocyte yield in oocyte donors. All laboratory and clinical outcomes were similar between low and high AMH groups except for the blastulation rate, which warrants further study.

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FROZEN-TAUGHT EMBRYO TRANSFERS: A COMPARISON BETWEEN NATURAL VS HCG-PRIMED CYCLES. F. Cirillo, a P. Patrizio, a C. Leggieri, a V. Canevisio, a R. De Cesare, a G. Bruno, a A. Baggiani, a P. E. Levi-Setti. b,c aGynecology, Division of Gynecology and Reproductive Medicine, Fertility Center, Humanitas Research Hospital, Rozzano (Milan), Italy; bYale University Fertility Center, New Haven, CT.

OBJECTIVE: Frozen-thawed embryo transfers (FET) are widely used to increase the cumulative pregnancy rate in IVF. However, the optimal strategy for endometrial preparation remains debatable. This study compared clinical pregnancy rates (CPR) between natural frozen-thawed embryo transfer cycles (NC-FET) versus modified natural cycle HCG-triggered ovulation (mNC-FET).


MATERIALS AND METHODS: From a total of 2,866 FET cycles analyzed, 2,262 FET were included. Patients were divided into two groups: group I (NC-FET: n = 529) and group II (mNC, n = 1,733). An ultrasound was performed to determine the day of ovulation using the number of days after the LH surge was obtained from day 8 with daily ovulation tests for detecting urinary LH. When the endometrial thickness reached 7.5 mm and dominant follicle was greater than 16 mm in diameter, HCG was administered for cases with no urinary LH surge. Embryo thawing and transfer was planned 7 days after LH surge or HCG administration, whether G5 or G6 blastocyst. To avoid potential confounders, only single transfers of vitrified blastocysts were included; PGT-a cycles were excluded. Exogenous progesterone supplementation was started 2 days after HCG administration in mNC group and on same day of embryo transfer procedure in NC-FET.

RESULTS: The cancellation rate was 18.98%. In 16 cases (2.85%) FET was not carried out because the embryos did not survive the thawing. The average age at freezing was 35.48 ± 4.2 years for NC and 35.44 ± 4.0 years for the mNC (P = 0.822), the age at transfer was 36.07 ± 4.2 years for NC and 36.03 ± 4.01 years for the mNC (P = 0.822). The FSH value was 7.09 ± 2.49 mIU/mL in patients with NC and 6.84 ± 2.42 mIU/mL in those triggered with HCG (P = 0.044). The average value of AMH was 2.86 ± 2.33 ng/ml in NC.
group versus 3.31 ± 2.65 ng/mL in mNC group (p < 0.001) and the mean value of BMI was 21.78 ± 3.0 kg/m² and 21.79 ± 3.03 kg/m² (p = 0.913), respectively. CPR in NCs was 29.79% (157/527), while in mNC was 39.2% (678/1732) with an Odds ratio (OR) of 1.52 (95% CI 1.23-1.88). After multivariate analysis, adjusting for confounders, the OR resulted 1.51 (95% CI 1.21-1.89).

CONCLUSIONS: These results demonstrated higher CPR following FET in a HCG-triggered ovulation cycle compared to a NC. Adopting mNC-FET allow less variability in detecting ovulation and a more controlled endometrial exposure to progesterone. A randomized prospective study is required to assess the true clinical significance of these data.

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OBJECTIVE: Although there are studies comparing the effect of true natural and modified natural cycle on clinical outcome, with the exception of a study of donation cycles with fresh embryo transfer (Madero et al., 2016), there is only one randomized clinical trial (RCT) study in the literature comparing the effect of two different routes of the artificial cycle, oral and transdermal estrogen. However, the number of patients included in this study is very limited, only 45 patients in each arm (R. Davar et al., 2016). In our RCT, a total of 267 patients were included, the largest one comparing the efficiency of transdermal and oral estrogen.

DESIGN: Randomized Controlled Trial.

MATERIALS AND METHODS: This randomized controlled trial was undertaken in Assisted Reproductive Technologies and Genetics Center at Istanbul Memorial Hospital between May 2017 and October 2017 (ClinicalTrials.gov identifier NCT03155048). The primary outcome measure was endometrial thickness on the day of progesterone administration and secondary outcome measure was clinical outcome. A total of 267 patients undergoing FET cycles with oral (n = 137) and transdermal patch (n = 130) were evaluated. Oral estrogen or transdermal patch started from the second day of menstruation after basal ultrasonography to rule out the presence of ovarian cysts. USG scan was repeated on 11th day of cycle to measure endometrial thickness. Second, separate GLMMs with logit link were conducted to analyze the factors. When patient specific variables were analysed, we found no difference in the ongoing pregnancy rate between the oral and transdermal routes.

CONCLUSIONS: No significant difference in clinical outcomes between transdermal estrogen and oral estrogen in PCOS patients undergoing FET cycle was found. Transdermal estrogen can be used as it has the advantages of being more patient-friendly, less stressful, cost effective and avoids the first-pass hepatic metabolism.

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OBJECTIVE: To investigate the differences in self-reported quality of life scales in women undergoing egg freezing and in vitro fertilization (IVF).

DESIGN: Prospective descriptive survey.

MATERIALS AND METHODS: Patients undergoing oocyte collection at a single institution were offered a voluntary, anonymous and written questionnaire. The survey was adapted from a validated questionnaire, FertiQol, which assesses self-reported quality of life scales for patients with infertility. The main outcome measures were demographic information and quality of life scales.

RESULTS: A total of 461 patients (331 IVF, 130 egg freeze) were included in the analysis. We found differences in perceptions of and responses to fertility treatment when comparing IVF versus egg freeze patients. For patients undergoing their first retrieval, egg freeze patients reported feeling more drained and worn from the cycle (IVF: 3.63 ± 0.99, egg freeze: 3.33 ± 0.11, p = 0.03) and experienced more negative mood (IVF: 4.21 ± 0.08, egg freeze: 3.89 ± 0.12, p = 0.02) than IVF patients. IVF patients reported increased emotional side effects of fertility treatment with repeat cycles, whereas repeat egg freeze patients viewed the process as less complicated compared to patients undergoing first cycles. Older patients also had fewer complaints with first-time fertility treatment for both IVF and egg freeze patients.

CONCLUSIONS: Patients undergoing egg freezing have similar responses to questions pertaining to quality of life measurements as patients undergoing IVF. Repeat cycles and age at first cycle contribute to perceptions of stress. This new information can help practitioners appropriately counsel egg freeze patients, both at the initial consultation and during treatment.

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SERUM PROGESTERONE AND CYCLE OUTCOME FOLLOWING BLASTOCYST TRANSFER IN PROGRAMMED CYCLES. P. C. Brady, L. V. Farland, A. M. Thomas, C. Racowsky. Obstetrics & Gynecology, Brigham & Women’s Hospital and Harvard Medical School, Boston, MA.

OBJECTIVE: The corpus luteum secretes 25-50 mg/day of progesterone (P), but the optimal serum P level in programmed frozen or donor embryo transfer (ET) cycles remains unknown. The purpose of this study was to evaluate the association between serum P levels and pregnancy rates in cycles using a prepared uterus, and whether body mass index (BMI) impacts this association.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: Frozen autologous and fresh/frozen donor day 5 embryo transfers from 2013-2016 in our program using intramuscular (IM) P for luteal support (50-100 mg/day) were included (n = 801, 20.4% donor cycles). Only the first cycle for each patient was included. P was measured at a single laboratory using the Roche Elecsys electrochemiluminescence immunoassay, with coefficients of variation <3%. P levels were measured on day 3 or day 5 after exogenous P initiation, and P dose was increased by 50-100% if <20 ng/mL per our clinic practice. The main outcome measure was live birth rate (LBR) (>20 weeks gestation). Secondary outcomes included clinical pregnancy rate (CPR) and implantation rate (fetal cardiac activity per embryo transferred). Following testing

Clinical outcomes by serum progesterone (P) in programmed cycles with intramuscular P luteal support

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>P&lt;20 ng/mL (n=195)</th>
<th>P≥20 ng/mL (n=606) (Referent)</th>
<th>Odds ratio or risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implantation failure, n (%)</td>
<td>60 (30.8%)</td>
<td>135 (22.3%)</td>
<td>1.54 (1.07, 2.22)</td>
</tr>
<tr>
<td>Implantation rate, % (SD)</td>
<td>49.6% (50.0%)</td>
<td>57.8% (48.0%)</td>
<td>0.82 (0.65, 1.03)</td>
</tr>
<tr>
<td>Spontaneous abortion, n (%)</td>
<td>25 (12.8%)</td>
<td>59 (9.7%)</td>
<td>1.34 (0.82, 2.22)</td>
</tr>
<tr>
<td>Clinical pregnancy, n (%)</td>
<td>113 (57.9%)</td>
<td>411 (67.8%)</td>
<td>0.66 (0.47, 0.91)</td>
</tr>
<tr>
<td>Live birth, n (%)</td>
<td>88 (45.1%)</td>
<td>352 (58.1%)</td>
<td>0.60 (0.43, 0.83)</td>
</tr>
</tbody>
</table>

1 On day 3 or 5 of IM P supplementation; 2 At embryo transfer on day 5; 3 Negative serum hCG; 4 Fetal cardiac activity per embryo transferred.
for confounders, logistic and Poisson regression models, adjusted a priori for oocyte age, donor egg, and serum P measurement on day 3, were used to estimate the odds ratio (OR) or relative risk (RR) and 95% confidence interval (CI) of these births.

RESULTS: Mean serum P at transfer on day 5 was 28.4 ± 10.5 ng/mL. Compared to patients with P > 20 ng/mL, patients with P < 20 ng/mL on day 3 or 5 had a significantly higher implantation failure rate (negative hCG, 30.8% vs. 22.3%, OR 1.54, 95% CI 1.07-2.22), lower CPR (57.9% vs. 67.8%, OR 0.66, 95% CI 0.47-0.91) and lower LBR (45.1 vs 58.1%, OR 0.60, 95% CI 0.43-0.83), even after increasing P dose (Table). LBRs were stable from serum P 20 to 60 ng/mL (assay upper limit); there was no upper limit of P above which the LBR declined. Among obese patients (BMI > 30 kg/m2, n = 129), P < 20 ng/mL was more common than in non-obese patients (n = 672) (52.7% vs. 18.4%, OR 4.76, 95% CI 3.2-7.1). Among patients with P > 20 ng/mL, the LBR was significantly lower in obese vs. non-obese patients (44.6 vs. 57.7%, OR 0.60, 95% CI 0.38-0.96).

CONCLUSIONS: Serum P > 20 ng/mL was associated with increased CPR and LBR following blastocyst transfer into a prepared uterus. LBRS were not rescued by increasing P doses for serum levels < 20 ng/mL. Obese recipients may require higher initial doses of IM P for luteal support. Future research is needed to define the optimal serum P at transfer, and to determine whether this varies according to patient characteristics, such as BMI.

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OBJECTIVE: To analyze the relationship between serum progesterone (P) the day of embryo transfer and Ongoing pregnancy rates (OPR) in artificial endometrial preparation cycles.

DESIGN: Single center prospective cohort study including infertile patients undergoing embryo transfer after an artificial endometrial preparation cycle with estradiol valerate and vaginal micronized progesterone (400 mg/12 hours). Sample size (n = 1197) was calculated to detect a 10% difference in OPR (40-50%) between 2 groups (P > 255 or P ≤ 255) according to serum P levels, in a two-sided test with a statistical power of 80% and a confidence level of 95%. This is an interim analysis of the 50% of the sample (n = 599) which includes all patients recruited from September 12th, 2017 to March 15th, 2018. ClinicalTrials.gov Identifier: NCT03127412.

MATERIALS AND METHODS: Patients undergoing embryo transfer in the context of an artificial endometrial preparation cycle, either with own or donor eggs, aged < 50, BMI < 30 Kg/m2, with a normal uterine cavity in 2D ultrasound, a triple layer endometrium > 6.5 mm; in a private infertility center. Serum P determination was performed the day of embryo transfer. Primary endpoint was ongoing pregnancy rate at the time of abstract submission (> 9 weeks for the last cases included).

RESULTS: Of 599 patients recruited, 542 fulfilled all the inclusion/exclusion criteria. Reasons for exclusion were: changes of doses or ways of administration of progesterone. The mean age of the included women was 37.4 ± 4.3 years; Endometrial thickness: 8.7 ± 1.6 mm. Mean serum P the day of embryo transfer was 12.0 ± 6.2 ng/mL (p25: 8.0; p50: 11.2; p75: 14.8). The ongoing pregnancy rates according to serum P levels were: < p25: 35.8%; p25 - p50: 46.2%; p50 - p75: 57.0%; > p75: 55.1%. Women with serum P < 8.0 ng/mL (p25) had a significantly lower ongoing pregnancy rate compared to the rest of patients: 91.1% vs 52.8%: p < 0.001. Clinical pregnancy rate was 47.0% vs. 60.1% (p = 0.008) and pregnancy loss rate (including biochemical and clinical miscarriages) was 36.0% vs. 19.4% (p = 0.008). The ROC curve showed a significant predictive value of serum P levels on the day of embryo transfer for OPR, with an AUC of (95% CI) 0.59 (0.55-0.64), p = 0.000.

CONCLUSIONS: The results of the present study suggest that there is a minimal threshold of serum P values the day of embryo transfer that needs to be reached in artificial endometrial preparation cycles to optimize the pregnancy rate. It cannot extrapolate these findings when using other ways of progesterone administration.

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UNIVERSAL WARMING PROTOCOL* FOR VITRIFIED HUMAN EMBRYOS: A RETROSPECTIVE STUDY ON COMBINATION OF 3 DIFFERENT VITRIFICATION/ WARMING KITS. L. Parmegiani, A. Arnone, S. Bernardi, G. Cognigni, M. Filicori, GynecPro Medical Centers, Bologna, Italy.

OBJECTIVE: In previous pilot studies, we paved the way for the clinical use of a single “universal warming protocol” based on subsequent steps with 1 and 0.5 M of extracellular cryoprotectant (ECCP), irrespective of the cryopreservation method used for freezing. Nowadays, embryos are routinely frozen using different commercial brands of ready-to-use vitrification solutions which differ only slightly in their composition. This is the first large-scale clinical study to demonstrate that vitrification and warming solutions of different brands can be successfully combined on vitrified embryos.

DESIGN: Retrospective longitudinal cohort study. 847 embryos frozen at cleavage stage obtained from patients’ own oocytes. Duration: 01/01/2013 - 31/12/2015.

MATERIALS AND METHODS: Each patient’s embryos were vitrified and warmed in various combinations by using three different kits: i) Vitrification Kit (Kitazato, Japan), ii) Sage Vitrification Kit (Origio, Denmark), iii) “home-made” in house in our laboratory. Vitrification/warming kits from different brands are routinely used in our center and warming procedures are randomly performed with any available kit on a “first-in-first-out” basis, irrespective of the brand used for vitrification. Group names: KK, KS, SK, SS, SH, HK, HS, HH. • KK - vitrification Kitazato / warming Kitazato • KS - vitrification Kitazato / warming Sage, • SK - vitrification Sage / warming Kitazato, • SS - vitrification Sage / warming Sage, • SH - vitrification Sage “in house kit”, • HK - vitrification “in house kit” / warming Kitazato, • group HS - vitrification “in house kit” / warming “Sage”, • group HH - vitrification “in house kit” / warming “in house kit”. No embryos were vitrified with Kitazato and warmed with “in house kit” Primary endpoint: survival rate (number of embryos surviving per number of embryo warmed). Secondary endpoint: implantation rate (number of embryos implanted per number of embryos transferred).

RESULTS: Female mean age and survival rate were statistically comparable between the study groups. Cryo-survival rate was: group KK 96.4% (54/ 56), group KS 100.0% (13/13), group SK 98.8% (80/81), group SS 97.2% (174/179), group SH 97.6% (40/41), group HK 95.2% (2021), group HS 99.5% (187/188), group HH 97.4% (261/268). Implantation was generally comparable in all study groups - exceptions were KS 46.2% (6/13) vs. SK 17.5% (14/80 - P = 0.049), SS 14.7% (24/163 - P = 0.012), HS 14.5% (26/ 179 - P = 0.010), HH 17.3% (45/260 - P = 0.025); and SH 30.0% (12/40) vs. SS (P = 0.042), HS (P = 0.035).

CONCLUSIONS: This study confirms that it is possible to combine different kits for vitrification/warming. Other large-scale multi-center studies are needed to confirm the implantation potential of these warmed embryos. The “universal warming protocol” (ECCP 1 - 0.5 M) permits warming of vitrified embryos, irrespective of brand, cryoprotectants and basic medium in the vitrification kit. The possibility to combine different vitrification/warming kits may favour embryo exchange between IVF centres.


Supported by: Sage Vitrification/Warming Kits were supplied by Origio.

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“UNIVERSAL WARMING PROTOCOL” FOR A TRANS-NATIONAL EGG DONATION PROGRAM WITH VITRIFIED OOCYTES. L. Parmegiani, A. Arnone, G. Cognigni, L. Quintero, R. Viioles, M. Filicori. GynecPro Medical Centers, Bologna, Italy; Embrilegia, Bologna, Italy; GynePro Medical Centers, Bologna, Italy; Instituto de Medicina Reproductiva (IMER), Valencia, Spain.

OBJECTIVE: Transnational shipment of cryopreserved oocytes between centers is nowadays a common procedure as the use of frozen oocytes facilitates donor/recipient matching and can solve donor recruitment problems. Oocytes are frozen using ready-to-use vitrification solutions of different scales.
commercial brands. In previous basic research studies, we demonstrated that it is possible to warm cryopreserved human oocytes, regardless of the vitrification kit used, with a single “universal warming protocol” based on subsequent steps with 1M and 0.5 M concentration of extracellular cryoprotectant (ECCP). The aim of the present study is to verify for the first time the clinical efficacy of the “universal warming protocol” on shipped oocytes by testing two different brands of ready-to-use warming kits.

DESIGN: Retrospective observational study on a cohort of 101 patients enrolled in egg donation programs from 27/04/2017 to 26/03/2018. Primary endpoint was the survival rate (number of oocytes surviving per number of oocytes warmed). Secondary endpoints were fertilization rate (number of fertilized oocytes per number of injected oocytes), blastulation rate (number of blastocysts obtained per number of fertilized oocytes) and implantation rate (number of implanted embryos per number of transferred embryos).

MATERIALS AND METHODS: Donated oocytes were obtained and vitrified in a Spanish gamete cryobank, then shipped to the ART center in Italy where warming, ICSI procedures, and embryo transfer (ET) were performed. Number of oocytes thawed 820, ET performed 105. All the oocytes were vitrified with VitriFry Kit (Kitazato, Japan) and warmed using two different kits: Kitazato Warming Kit and Vit Kit®-Thaw (Irvine, US). Both these kits involve subsequent steps with 1M and 0.5 M concentration of ECCP. At warming the oocytes were assigned to 2 groups: group (K) - 233 oocytes, and group (K) - 587 oocytes. Vitrification was performed with the carrier Cryotop (Kitazato); embryo culture was performed with Embryoscope+ (Vitrolife, Sweden). ET was performed at blastocyst stage.

RESULTS: Donors and recipients mean age, survival, fertilization, blastulation and implantation rates were statistically comparable between the study groups. Survival rate was 82.8% (193/233) in group K vs 82.6% (485/587) in group K. Fertilization rate was 81.9% (158/193) vs 80.4% (390/485), and blastulation rate 58.9% (93/158) vs 62.3% (243/390). Implantation rate was 37.7% (75/193) in group K vs 48.2% (55/114) in group K.

CONCLUSIONS: The findings of this study indicate that it is possible to combine Vit Kit®-Thaw with Kitazato Vitrification kit and to obtain good clinical results with shipped oocytes. The use of a “universal warming protocol” with ready-to-use warming kits containing 1 and 0.5 M of ECCP simplifies oocyte exchange between IVF centers.

References:

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OBJECTIVE: Blastocyst re-expansion within a few hours of warming is considered a strong indicator of blastocyst potential. This study analyzed objectively and quantitatively the predictive value of blastocyst re-expansion on implantation. Additionally, the effect of trophoectoderm grade was also estimated.

DESIGN: Prospective study.

MATERIALS AND METHODS: The study included 427 warmed blastocysts which were evaluated using time lapse imaging (Embryoscope®, Vitrolife). Embryos were vitrified and warmed with Cryotop method (KitazatoBiopharma). Variables studied included pre-vitrification trophoecoderm grade (A, B and C), initial area (IA; blastocyst area immediately after warming) and final area (FA; blastocyst area before transfer). Warmasted blastocysts were divided into four groups according to blastocoele re-expansion, calculated from the above variables (FA-IA): group 1, 13463.0 μm²; group 2, 2463.0-6867.5 μm²; group 3, 6867.5-11112.5 μm²; and group 4, <11112.5 μm². Ongoing implantation rate (OIR) was compared between groups. The odd ratio (OR) of the effect of all variables on implantation was expressed in terms of 95% confidence interval (CI) and significance.

RESULTS: Significant differences were observed in the OIR between groups 1, 2, 3 and 4 (31.8%, 34.6%, 44.9% and 48.6%, respectively, P < 0.05). Evaluation of implantation prediction in relation to the blastocyst re-expansion and trophoecoderm grade is presented in Table 1.

CONCLUSIONS: Blastocyst re-expansion and pre-vitrification trophoecoderm grade are strong predictors of implantation in vitrified-warmed cycles. Using time lapse imaging for the analysis of warmed blastocysts offers the possibility of establishing an objective value of re-expansion associated with implantation.

Logistic regression analysis for OIR according to blastocyst re-expansion and trophoecoderm grade

<table>
<thead>
<tr>
<th>Category</th>
<th>OR</th>
<th>95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2 vs. 1</td>
<td>1.03</td>
<td>0.55-1.94</td>
<td>NS</td>
</tr>
<tr>
<td>Group 3 vs. 1</td>
<td>1.72</td>
<td>0.94-3.15</td>
<td>NS</td>
</tr>
<tr>
<td>Group 4 vs. 1</td>
<td>1.94</td>
<td>1.06-3.56</td>
<td>0.03</td>
</tr>
<tr>
<td>B vs. C</td>
<td>1.56</td>
<td>0.77-3.16</td>
<td>NS</td>
</tr>
<tr>
<td>A vs. C</td>
<td>1.82</td>
<td>1.12-2.95</td>
<td>0.01</td>
</tr>
</tbody>
</table>

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DIFFERENCES IN VITRIFIED OOCYTE OUTCOME BASED ON SOURCE OF THE OOCYTES. E. Schenckman, a N. Siracusa, a S. Ozenosy, a F. Khan, a M. Simpkins, a J. Swain. a IVF, CCRM NY, NY, a IVF, CCRM CO, Lone Tree, CO.

OBJECTIVE: Oocyte vitrification is a complex process with various factors impacting success. Exposure timing to cryoprotectants, type of device used, number of oocytes vitrified per device and other variables are all critical to optimize vitrification. Furthermore, proper handling and a high warming rate can dramatically impact outcomes. Additionally, technical expertise within the laboratory during these processes is paramount; during both vitrification and warming. This study examines the impact of oocyte vitrification by comparing outcomes from oocytes vitrified using the same method at different locations, but warmed using the same method at the same laboratory.

DESIGN: A retrospective cohort study.

MATERIALS AND METHODS: All patients utilizing vitrified oocytes and undergoing ICSI with subsequent blastocyst biopsy and PGT-A between January 2017 and April 2018 without significant male factor were included in the study. Patients were divided into 3 groups based on source of the vitrified oocytes 1) Internally vitrified patient oocytes 2) Patient oocytes vitrified at an external lab and 3) Donor oocytes vitrified at a single commercial egg bank. All oocytes were vitrified using the same method on an open device. All oocyte warming were performed in an identical fashion using 5ml of thaw solution at 37°C following by dilution and washing steps. ICSI were performed in an identical fashion between groups. Culture for all cases was performed

<table>
<thead>
<tr>
<th>Category</th>
<th># CYCLES</th>
<th># PATIENTS</th>
<th>Avg Pt Age ± SD (range)</th>
<th># EGGS THAWED</th>
<th>% EGGS SURVIVED</th>
<th>% FERT</th>
<th>% GOOD BLASTS</th>
<th>% BIOPSED</th>
<th>% EUPLOID</th>
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</thead>
<tbody>
<tr>
<td>INTERNAL LAB</td>
<td>9</td>
<td>9</td>
<td>35.22±7.99 (22-45)</td>
<td>91</td>
<td>84% (76/91)</td>
<td>83% (63/76)</td>
<td>30%* (19/63)</td>
<td>33%* (21/63)</td>
<td>43%* (9/21)</td>
</tr>
<tr>
<td>EXTERNAL LAB</td>
<td>14</td>
<td>13</td>
<td>37.38±2.16 (33-41)</td>
<td>159</td>
<td>65%* (104/159)</td>
<td>66%* (69/104)</td>
<td>17%* (12/69)</td>
<td>26%* (18/69)</td>
<td>44%* (8/18)</td>
</tr>
<tr>
<td>COMERCIAL</td>
<td>17</td>
<td>15</td>
<td>26.88±2.91 (22-32)</td>
<td>116</td>
<td>91% (106/116)</td>
<td>82% (87/106)</td>
<td>52% (45/87)</td>
<td>53% (41/77)*</td>
<td>73% (30/41)</td>
</tr>
</tbody>
</table>

a p<0.05 considered to be statistically significant. b one pt did not have PGT-A testing.
using Sage sequential media +10% SPS over 7 days under low oxygen conditions.

RESULTS: A total of three hundred sixty six oocytes were warmed. There was a significant difference in survival rates between the internal lab and commercial Egg Bank compared to the external lab group (84%, 91% vs 65%, p<0.05). There also was a significant difference in fertilization rate between the internal lab and commercial egg bank compared to the those oocytes warmed from external labs (83%, 82% vs 66%, p<0.05). The result of the Morris water maze test

The frequency of crossing the former platform (times)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time to reach the platform (s)</th>
<th>Latency (s)</th>
<th>Distance (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>frozen group</td>
<td>13.04±1.87</td>
<td>23.45±1.56</td>
<td>212.74±19.38</td>
</tr>
<tr>
<td>IVF group</td>
<td>15.34±1.48</td>
<td>20.67±1.79</td>
<td>200.34±14.74</td>
</tr>
<tr>
<td>control group</td>
<td>13.46±1.75</td>
<td>21.86±1.21</td>
<td>218.53±12.47</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

References: Does embryo vitrification affect the mice offspring's growth, development and the nervous system? Abstract Objective This study focused on the effect of embryo vitrification on the growth, development and the nervous system of the offspring. Methods Mice were used as model animals, we designed three groups including natural pregnancy-born mice (control group), conventional IVF-ET pregnancy-born mice (IVF group), and embryonic vitrification-born mice (frozen group). The growth and development indicators and neurodevelopment indexes of offsprings were compared among the above groups; two-dimensional protein electrophoresis, mass spectrometry, and Western Blotting were used to determine the changes in brain tissues of the mice. Brain tissues of the offsprings were observed by immunohistochemical and electron microscopy. Physiological indicators such as physical strength were compared; the neural development indicators such as the intelligence, learning ability and memory were also compared through the Morris water maze test.

RESULTS: 1. There was no significant difference in the pregnancy rate between the fresh transplantation group and the vitrification group (48.89% Vs 51.22%, P<0.05). 2. The weights of the offsprings in the vitrification group were higher than that in the conventional IVF group and the natural conception group (1.95±0.22 Vs 1.96±1.89, P>0.05). 3. Two-dimensional differentially expressed proteins in brain tissue were searched by two-dimensional protein electrophoresis, protein profiling, and Western blotting. Bioinformatics analysis revealed that most protein expression differences did not cause functional changes.4. Through immunohistochemistry and electron microscopy, it was found that vitrified frozen embryos had no obvious damage to the brain tissue ultrastructures. 5. Vitrification has not affected the structure of brain tissue in the study of mouse embryos through immunohistochemical and electron microscopy.6. Time to reach the platform, latency, the total distance and the frequency of crossing the former platform were similar among the above groups (see the Table).

CONCLUSIONS: The weights of the offsprings born through embryo vitrification were increased, while fertility, learning and memory ability were not changed. The technique of embryo vitrification has no significant effect on brain protein expression and tissue ultrastructures. The vitrification technique commonly used in clinic has little effect on the offsprings.
has not affected the structure of brain tissue in the study of mouse embryos through immunohistochemical and electron microscopy. 6. Time to reach the platform, latency, the total distance and the frequency of crossing the former platform were similar among the three groups. (see the Table) Conclusion The weights of the offsprings born through embryo vitrification were increased, while fertility, learning and memory ability were not changed. The technique of embryo vitrification has no significant effect on brain protein expression and tissue ultrastructures. The vitrification technique commonly used in clinic has little effect on the offsprings. The result of the Morris water maze test classed as “MsoNormal” style="line-height: 21px;"=

FERTILITY & STERILITY

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RE-EXPANSION OF WARNED VITRIFIED BLASTOCYSTS BEFORE EMBRYO TRANSFER IS PREDICTIVE OF CYCLE OUTCOME. E. Schenkman, a

N. Siracusa, a A. Hanson, a M. Simpkins, b B. Levine, a N. Choi, c S. Talebian, d N. Knopman, e J. E. Swain. f IVF, CCRM NY, NY; cCMR, Lone Tree, CO.

OBJECTIVE: To assess if the expansion rate of vitrified warned CCS tested embryos at two hours post warming is associated with cycle outcome. DESIGN: A retrospective cohort study. MATERIALS AND METHODS: Two hundred and forty frozen blastocyst transfer cycles between January 2017 and February 2018 were reviewed for this study. Inclusion criteria were patients with SET and CCS testing performed on their embryos. Blastocysts were warmed approximately two hours prior to embryo transfer. Re-expansion status was evaluated at the time of transfer. The dataset was divided into three groups (Group I = ≤ 50% re-expansion, Group II = 60-90% re-expansion and Group III = 91-100% re-expansion rate). Comparison of cycle outcome data was compared between the three groups, including biochemical pregnancy rate (BPR), implantation rate (IR) and clinical pregnancy rate (CPR).

RESULTS: Comparison of Group I vs Group III embryos demonstrated that Group I had significantly lower rates of BPR, CPR, IR compared to Group III (29%, 21% vs 67%, 57%, 57%, p < 0.05). Group II vs Group III patients, with moderate re-expansion had a reduced CPR when compared to embryos that fully expanded ( 38% vs 57%, p = 0.0554), although the value was not quite yet significant. Group I vs Group II, embryos with low level expansion trended to have poorer outcomes when compared to patients with moderate expansion, but did not yet reach significance.

B. Svendsen, a C. Anania, H. DeMelo. Fertility Solutions, P.C., Dedham, MA.

CONCLUSIONS: Retrospective analysis of blastocyst re-expansion rate at 2 hours post-warming may lend insight into embryo quality and outcome success following frozen transfer. If extranumery blastocysts are available, this approach may give the option of thawing an additional blastocyst if re-expansion is absent.

TABLE 1: Re-Expansion of warned blastocysts before embryo transfer

<table>
<thead>
<tr>
<th>Group I %</th>
<th>Group II %</th>
<th>Group III %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 50%</td>
<td>60-90%</td>
<td>91-100%</td>
</tr>
</tbody>
</table>

a (Group I vs Group III), b (Group I vs Group II) = P-value < 0.05 was considered to be statistically significant.

DOES SIZE MATTER? COMPARISON OF OPENING SIZE WITH LASER ASSISTED HATCHING FOR DE-VITRIFIED BLASTOCYSTS. M. A. Lee, A. Kowalik, P. Huang, C. Anania, H. DeMelo. Fertility Solutions, P.C., Dedham, MA.

OBJECTIVE: To show any difference in outcome of laser assisted hatching using 2 different opening sizes on de-vitrified blastocysts. Endpoints

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DOES SIZE MATTER? COMPARISON OF OPENING SIZE WITH LASER ASSISTED HATCHING FOR DE-VITRIFIED BLASTOCYSTS. M. A. Lee, A. Kowalik, P. Huang, C. Anania, H. DeMelo. Fertility Solutions, P.C., Dedham, MA.
Comparison of Small (SLO) and Large (LLO) Laser openings in 1187 Frozen Embryo Transfers

<table>
<thead>
<tr>
<th>Opening Size</th>
<th># of Embryos Hatched</th>
<th># of FET’s</th>
<th>Implantation Rate/Embryo (IR)</th>
<th>Clinical Pregnancy Rate (CPR)</th>
<th>On Going or Delivered</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLO</td>
<td>793</td>
<td>535</td>
<td>36.9%</td>
<td>42.6</td>
<td>33.5%</td>
</tr>
<tr>
<td>LLO</td>
<td>902</td>
<td>652</td>
<td>35.7%</td>
<td>43.4%</td>
<td>35.7%</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.05 NS</td>
<td>&lt; 0.05 NS</td>
<td>&lt; 0.05 NS</td>
<td>&lt; 0.05 NS</td>
<td>&lt; 0.05 NS</td>
</tr>
</tbody>
</table>

were: implantation rate per embryo (IR), clinical pregnancy rate (CPR) and live birth rate (LBR) or on going pregnancy or live birth rate per transfer (LB/OG).

DESIGN: Retrospective Study.

MATERIALS AND METHODS: Embryos were cultured in 30 ul drops of Cook culture media in nunc 60 mm dishes in MINC incubators with 7.0% CO2/5.0% O2 gas. Blastocysts were vitrified on day 5 and/or 6 using I.C.E. vitrification solutions and HSV straws. I.C.E is non DMSO based Ethylene Glycol / Glycerol system. Statistical analysis was performed using Chi-square. Significance was set at $P < 0.05$. In natural cycle FET, progesterone was initiated the day after LH surge (vaginal endometrin BID or IM p4). Medicated cycles consisting of Estrace + 1M or vaginal p4. Embryos were replaced on day 7 of p4. Post thaw embryos were cultured in 30ul drops of BM with 15% HSA < 2 hrs prior to FET. Embryos were hatched with a Hamilton Thorne Zilos F460 nm IR laser. From 6/12 to 9/30/15 a small laser opening (SLO) 10um size, was made with 2-3 pulses of 400 usec duration of 270 uW. From 10/1/15 - 4/6/18 a large laser opening (LLO) 50um size with 15 pulses of 400 usec duration of 270 uW. Embryos were washed 2X in media post hatching. 30 minutes prior to transfer, embryos were put into Embryo Glue. All FET’s were ultra sound guided with the Cook Guardia Access embryo transfer cathether.

RESULTS: The overall survival rate post de-vitrification was 96.5%. The survival rate for SLO embryos was 96%. SLO was performed on 793 embroyos for 535 embryo transfers (FET). The implantation rate per embryo (IR) was 36.9% resulting in a clinical pregnancy rate (CPR) of 42.6% and a live birth rate (LBR) of 33.5%. The survival rate for LLO embryos was 97%. LLO was performed on 902 embryos for 652 FET. The IR was 35.7% per embryo resulting in a clinical pregnancy rate (CPR) of 43.4% and a live birth or on going pregnancy rate (LB/OG) of 34%. Implantation rate (IR) = the number of gestational saes via ultrasound / the number of embryos transferred. CPR = number of pregnancies documented by ultrasound / the number of FET’s. LBR = number of live births / the number of FET’s. LB/OG = number of live births + number of ongoing (> 2 us with gestational sac and fetal heart activity + interval growth) / by the number of FET’s.

CONCLUSIONS: From our data, laser hatching over 1,600 de-vitrified blastocysts using I.C.E, there is no statistical difference $(p = 0.05)$ in implantation rate per embryo, clinical pregnancy rate per FET, or ongoing and live birth rates per FET with differing sized (10um vs 50 um) zona pelludica opening size.

References:

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POST-WARMING DEGREE OF BLASTOCOELE RE-EXPANSION IS THE BEST PROGNOSTICATOR FOR LIVE BIRTH RATES IN VITRIFIED-WARMED SINGLE BLASTOCYST TRANSFER CYCLES. N. M. Chimote, B. N. Chimote, *Embryology, Vaunshidhara Fertility Center, Nagpur, India; bEmbryology, Endocrinology, Vaunshidhara Fertility Centre, Nagpur, India.

OBJECTIVE: Recent studies have presented contradictory results regarding significance of Inner-cell-mass (ICM)/Trophoectoderm (TE) gradation and degree of blastocoele expansion/re-expansion for increased live-birth rates. Also, few studies have reported combined results from fresh/frozen and single/double transfer cycles. This study aimed at individually assessing the relevance of grades of ICM, TE and degree of post-warm blastocoele re-expansion on live-birth rates exclusively in vitrified-warmed single-blastocyst transfer cycles.

DESIGN: Retrospective study $(n=216)$ vitrified-warmed elective single blastocyst transfer cycles. Oocyte donation, Embryo-donation, assisted hatching and preimplantation genetic diagnosis cycles were excluded. All blastocysts were graded as per Gardner and Scoulart method of classification as 1-6 for degree of expansion and grades A/B/C for ICM and TE.

MATERIALS AND METHODS: Natural-cycle endometrial preparation with hormone supplementation followed by luteal-phase support with micronized progesterone. Endometrial response was noted by ultrasound. Single blastocyst-transfer was done 3 hours after warming of vitrified blastocyst. Warmed blastocyst was compared with pre-vitrified blastocyst for degree of expansion, gradation of ICM/TE, beta-hCG level measured on day 8 of transfer indicated pregnancy. Live-birth was the primary outcome measure.

RESULTS: Women were classified into Live-birth (LB; n=74) and non-pregnant (NP; n=142) groups. Age, BMI, infertility period, number of oocytes retrieved, rate of formation of good quality cleavage-stage and blastocyst-stage embryos and survival rates post-warming did not differ significantly between the two groups. Same brand of embryo-transfer catheter and same brand and volume of media was used for transfer. However, degree of re-expansion was significantly higher in LB group than in NP group $(Mean ± SD: 3.6 ± 1.0 v 3.2 ± 0.94, P=0.0068)$. The Fisher-Exact test odds ratio (OR) for achieving a live-birth with 3-4 degree of re-expansion was 2.78 $(p=0.0016)$ whereas the odds ratio was much lower $(0.36)$ with any other degree of re-expansion. Although ICM grade was higher/better in Live-birth group than in non-pregnant group, the difference remained statistically non-significant (Odds ratio 1.25, $p=0.82$). No significant difference was observed in TE grades between the two study groups $(p=0.17)$. A notable difference was also observed in endometrial echopattern $(p=0.03)$ although the endometrial thickness remained comparable between the groups. Thus, post-warming degree of re-expansion is the single most promising predictive factor for live birth rates in such cycles.

CONCLUSIONS: Re-expansion of blastocoele to an expanded grade 3/4 is superior to ICM and TE cell gradation for better live-birth rates in vitrified-warmed single blastocyst transfer cycles. However, larger multicentric trials may be required to establish it as robust predictor of live-birth.
OBJECTIVE: Murine data have demonstrated altered placental growth and reduced expression of genes involved in transport of nutrients to the placenta (in particular Glut 3) in offspring generated by IVF. Altered placental transporters may affect nutrient supply to the fetus and result in abnormal fetal growth as predicted by the developmental origin of health and disease hypothesis. This pilot study aimed to assess if expression of selected transporter genes were altered in placenta of pregnancies conceived by IVF or spontaneously.

RESULTS: The median and interquartile gestational age of spontaneously and IVF conceived placentas was 39.1 weeks [39.0–40.0] and 37.6 weeks [34.0–40.3] respectively. There was no difference in gestational age between the two groups (p = 0.158). There were three late preterm (34 weeks) pregnancies and 3 preeclampsia pregnancies in the IVF group. Overall, expression of metabolic transporter 3 was similar between IVF and spontaneous placenta and only Glut 3 shown lower levels (p = 0.057) in IVF placentae, similar to what is found in mice. Interestingly, when comparing transporter expression levels between preeclampsia affected and all unaffected placentas, Glut 3 levels were lower in preeclampsia placentas (p = 0.03). There were no differences in placental expression when comparing term to preterm placentas.

CONCLUSIONS: Reassuringly, in this pilot study we found only minimal changes in transporter expression in IVF placentae. Similar to murine placenta, the expression of glucose transporter Glut 3 is lower in IVF placentae. If confirmed with larger sample size in our ongoing study, this finding would have important implication for nutrient supply to the fetus. If confirmed with larger sample size in our ongoing study, this finding would have important implication for nutrient supply to the fetus.
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POTENTIAL SIGNIFICANCE OF METHYLATION DIFFERENTIAL GENES IN CLINICAL DIAGNOSIS OF DOWN’S SYNDROME. R. Zhang, L. Xiao. The Second Affiliated Hospital of Soochow University, Suzhou, China.

OBJECTIVE: Prenatal preventions of Down’s syndrome include genetic counseling and prenatal diagnosis. The high cost of massive parallel sequencing prevents its routine use in clinics. Recent studies have found that certain genetic loci have opposite maternal-fetal methylation status, which suggests a new strategy to identify fetal DNA. The aim of this study is to investigate the feasibility of combining methylation markers together with MSRE-qPCR to achieve precise diagnostics of trisomy 21 with advantages of less time consuming and less costly, making it especially ideal for initial screening of 21-Trisomy syndrome.

DESIGN: Theoretically after methylation sensitive restriction endonuclease digestion, only the fetal DNA would be undigested in peripheral cell-free DNA. We detected cfDNA in maternal peripheral blood. On the other hand we mixed the placental DNA with normal blood genomic DNA in order to mimic clinical samples in enriching cfDNA in total cell-free DNA. Normal human blood genomic DNA was diluted in serial proportion as a control group (Table 1).

MATERIALS AND METHODS: CfDNA, placenta tissue DNA and peripheral blood genomic DNA were extracted in accordance with the instruction respectively. First steps, placental DNA (considered as fetal DNA) and genomic DNA (considered as the maternal DNA) were digested with methylation sensitive restriction endonuclease BstUI. Second, real-time fluorescence quantitative PCR amplification of HLCS, C21orf25 and RASSF1A gene were performed for 0.1-1% placental DNA in the 9 sample groups with BstUI digestion. Third, cfDNA samples were subjected to BstUI digestion, and followed by qPCR quantification targeting the three genes. The quantification of each gene target is calculated according to 2^{-ΔΔCt}. RESULTS: For cfDNA samples, the ratio of HLCS to RASSF1A in trisomy 21 to euploid was 1.442, which was close to theoretical chromosome dosage ratio 1.5:1. The trisomy 21 mixture samples could be differentiated from euploid mixture samples even when the fraction of placental DNA was as low as 0.1%, indicating the high sensitivity of the method using employed in the experiment. The approach correctly identified 3 cases of trisomy 21 from total 8 cases of clinical samples, which was 100% consistent with karyotyping result.

CONCLUSIONS: This study showed that HLCS gene and RASSF1A gene together with MSRE-qPCR, the approach was highly sensitive and highly specific for non-invasive prenatal diagnosis of 21-Trisomy syndrome. It is fast and cost efficient, making it especially ideal for initial screening of 21-Trisomy syndrome.

References:

Supported by: The National natural science foundation of China (NO.81741029). The Jiangsu Province’s clinical medical science and technology program (BL2013016, QN-568).The Jiangsu Province’s maternal and child health research project (F201757).The Suzhou’s Program (SZSZ201618, SYS201727)

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MENSTRUAL ENDOMETRIAL BIOPSY CYCLIN A2 EXPRESSION CORRELATES WITH ART OUTCOME. C. A. Marsh, J. Seymour, A. Graham, M. Lydic, K. Holoch, W. Nothnick. OB/GYN, University of Kansas, Overland Park, KS; *Physiology, University of Kansas, Kansas City, KS.

OBJECTIVE: Few biologic markers predict success with assisted reproductive technology (ART). Cyclin A2 (CCNA2) is a multi-functional protein capable of regulation tissue regeneration and RNA-binding. Absence of CCNA2 in the germ line is associated with embryonic lethality. Although considerable tissue regeneration occurs during the early stages of the menstrual cycle, the role of CCNA2 in the endometrium is poorly understood. In this study, we examine the function of CCNA2 in the endometrium and its association with pregnancy.

DESIGN: Prospective cohort in women, aged 18-45, seen in a university setting reproductive endocrine clinic undergoing ART.

MATERIALS AND METHODS: Women undergoing oocyte retrieval underwent endometrial biopsy, which was performed in normal sterile fashion with an endometrial pipelle on menstrual cycle day 3. Endometrium was prepared and subjected to immunohistochemical (IHC) localization for cyclin A2 (CCNA2) and qRT-PCR assessment of mRNA. Primary outcome of interest was clinical pregnancy, which was defined as fetal cardiac activity seen on ultrasound from pregnancy resulting in same cycle as endometrial biopsy. Fisher’s exact test was performed with p<0.05 used for determining statistical significance between the groups. CCNA2 IHC outcome values were expressed as H-SCOREs (intensity of staining X percent of cells staining at that intensity X 100%) for each cell type and data were separately analyzed using unpaired t-tests.

RESULTS: CCNA2 protein localized to stromal and glandular epithelium with stromal expression being more predominant. CCNA2 localization in both cell types was exclusively nuclear. Stromal and glandular epithelia positive nuclei were significantly greater in those women who achieved pregnancy compared to those that did not (P<0.0001: H-SCORE Stromata = 57 + 10 vs. 3 + 0.6; H-SCORE EPITHELIUM = 6 + 3 vs. 3 + 0.6). Despite significant differences in protein expression, CCNA2 mRNA expression levels were similar between groups. Based upon these data, we defined a positive Stromal H-SCORE of 25 or higher as positive outcome for CCNA2 staining. We constructed a 2 x 2 contingency table in which pregnancy outcome was

Placental DNA mixed groups and normal blood genomic DNA diluted groups

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<tr>
<th>Experimental groups</th>
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<td>Normal blood genomic DNA (diluted to 0.1%)</td>
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Supported by: The Jiangsu Province’s maternal and child health research project (F201757).The Suzhou’s Program (SZSZ201618, SYS201727)
defined as either positive or negative, and CCNA2 H-SCORE was defined as either positive (>25 stroma) or negative (<25 stroma). Fisher’s exact test revealed statistical significance between groups (P = 0.0045; sensitivity 95% CI = 0.664 - 1.00; specificity 95% CI = 0.292 - 1.00). There was no association between pregnancy outcome or CCNA2 H-SCOREs when controlling for patient age, cause of infertility, endometrial thickness or type of hormonal stimulation.

CONCLUSIONS: Endometrial CCNA2 expression is altered during menses. These alterations may impair proper endometrial development and/or responsiveness to hormonal signaling needed for successful pregnancy. A larger study population is needed to assess the validity of these findings and increase specificity and sensitivity.

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EXPRESSION PATTERN OF MIR-200 AND LET-7 TARGET GENE IN HUMAN ENDOMETRIAL STROMAL CELLS AND ENDOEMTRIAL TISSUES COLLECTED DURING MENSTRUAL CYCLE. Y. Choi, M. Kim, K. Jung, S. Choo, J. Kim, H. Jeong, M. Chung. 1Seoul Rachel Fertility Center, Seoul, Korea, Republic of; 2Hanyang University, Ansan, Korea, Republic of; 3OB&GYN, Seoul Rachel Fertility Center, Seoul, Korea, Republic of.

OBJECTIVE: The miRNA plays an important regulator in physiological processes such as homeostasis and cell differentiation. miR-200 and Let-7 were chosen because these miRNAs were known to be associated with the development and cell migration of endometrial cell. In this study, we investigated the target gene expression pattern of miR-200 and Let-7 in human endometrial stromal cells (T-hEnSCs) and endometrium in patients undergoing IVF.

DESIGN: Experimental study. Gene expression pattern analysis of human endometrial stromal cells (T-hEnSCs) and endometrial tissues.

MATERIALS AND METHODS: The human telomerase reverse transcriptase (htERT)-immortalized human endometrial stromal cells (T-hEnSCs) were decidualized with dibutyryl-c-AMP (abC-AMP) and medroxyprogesterone acetate (mpA). It was confirmed by the levels of prolactin (PRL) and insulin-like growth factor-binding protein-1 (IGFBP-1) gene expression. To analyze the continuously changing cellular transcriptome, we were performed RNA-sequencing analysis between control and decidualized group. Human endometrial tissues (n=17) were collected during the menstrual cycle (LH+5, LH+7, LH+9 and proliferative phase) in patients with good prognosis (n=5) and repeated implantation failure (n=12). All collected tissues were labeled and analyzed using Agilent SurePrint G3 Human GE 8X60K array.

RESULTS: In decidualized group, five target genes (PTEN, KLF4, e237, e238, e239) to T-hEnSC samples. The level of gene expression between the paired samples was compared using the paired t-test. The expression of PTEN, KLF4, e237, e238, and e239 was significantly upregulated (P < 0.05) in decidualized group compared to control group. The expression of PTEN, KLF4, e237, e238, and e239 was significantly downregulated (P < 0.05) in control group compared to decidualized group.

CONCLUSIONS: We found that the target gene expression of miR-200 and Let-7 were significantly up and down-regulated in control and decidualized group. Our data showed that miR-200 and Let-7 associated gene affected decidualization status in cell level. In addition, human endometrial tissues presented similar pattern in some genes. But we need to large-scale study providing greater reliability.

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DIFFERENTIAL EFFECTS OF CLOMIPHENE CITRATE ON ENDOMETRIAL EPITHELIAL AND STROMAL CELLS. J. Wu, B. Carr, O. Bukulmez, R. Word. 1UT Southwestern Medical Center, Dallas, TX, 2Obstetrics and Gynecology, Research, Dallas, TX.

OBJECTIVE: Selective estrogen receptor modulators such as clomiphene citrate (CC) exhibit cell- and gene-specific activities on estrogen responsive genes. Although it is well-appreciated that CC has negative effects on the endometrium, the precise cellular mechanisms are not known. Here, we used estrogen-responsive Ishikawa cells and human endometrial stromal cells as model systems to determine the effects of CC on gene expression and growth of endometrial epithelium (epi) and stroma, respectively.

DESIGN: Cell-based laboratory investigation.

MATERIALS AND METHODS: Human endometrial stromal cells (hESC) were obtained from premenopausal women undergoing hysterectomy for benign indications. Ishikawa cells and hESCs were pretreated for 48 h in serum free media prior to treatment with estradiol (E2, 3-3000 pM) ± (20nM). Gene expression of PR-B, total PR, TGF-α, and FGF-9 was quantified by qPCR. An MTS cell proliferation assay (Promega CellTiter 96) was used for determination of cell viability/growth. ANOVA and Student’s T test were used for statistical analyses as appropriate.

RESULTS: Progestrone receptor (PR) is an E2-responsive gene in the endometrium. Epi cells were extraordinarily sensitive to E2 with 73 ± 8- and 93 ± 6-fold increases in total PR and PR-B mRNA, EC50 = 43 and 39.3 pM, respectively. CC (20 nM) antagonized E2-induced total PR and PR-B modestly (EC50 = 69 pM and 46 pM) with no effect on maximal E2-induced responses. Likewise, E2 induced TGF-α (an important growth factor for epithelial cells) 11.8-fold (EC50 = 16.6 pM) which was minimally affected by CC (EC50 = 23.2 pM). Interestingly, E2 had no effect on epi cell growth in vitro. In contrast, CC inhibited epi cell growth dramatically (from 1.0 ± 0.13 to 0.21 ± 0.02 RU, p < 0.01). Further, E2 did not reverse the negative effects of CC on epithelial cell growth (0.17 ± 0.01 RU). Stromal cell responses to CC differed significantly from epi. Specifically, CC acted as an ER agonist in stromal cells with increased baseline and E2-induced PR-B and total PR mRNA. Further, expression of FGF-9 (growth factor for stromal cells) was increased significantly by CC alone. In contrast to epi, the effects of CC on cell viability/growth of primary stromal cells were negligible either alone or in combination with E2 (1.2- and 1.3-fold respectively).

CONCLUSIONS: These data indicate that CC has selective antagonist/agonist effects on different cell types within the endometrium. CC inhibits epi cell growth and antagonizes epi PR expression. In contrast, CC acts as an agonist in stromal cells. Together, the results provide mechanistic insights regarding the dysfunctional out-of-phase endometrium induced by CC during controlled ovarian stimulation.

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GRANULOCYTE COLONY STIMULATING FACTOR (GCSF) TREATMENT AUGMENTS HUMAN ENDOMETRIAL DECIDUALIZATION: MECHANISM OF A THERAPEUTIC EFFECT. L. Hawkins Bressler, L. Yuan, V. Fitz, H. Hoff, M. Fritz, S. L. Young. Obstetrics & Gynecology, University of North Carolina School of Medicine, Chapel Hill, NC.

OBJECTIVE: GCSF is widely used to treat recurrent implantation failure and use is supported by a randomized trial. We previously found endometrial GCSF receptor (GCSFR) to be primarily expressed by the stromal cells and expression was reduced in women with endometriosis-associated infertility, a disorder characterized by impaired stromal decidualization and decreased endometrial receptivity to implantation. The objective of this work is to evaluate the impact of GCSF treatment on endometrial stromal decidualization.

DESIGN: Endometrial stromal cells (EdS) were cultured by either static or dynamic culture. In contrast, EdS cultures were stimulated by GCSF receptor (GCSFR) to be primarily expressed by the stromal cells and expression was reduced in women with endometriosis-associated infertility, a disorder characterized by impaired stromal decidualization and decreased endometrial receptivity to implantation. The objective of this work is to evaluate the impact of GCSF treatment on endometrial stromal decidualization.

MATERIALS AND METHODS: Stromal cells were treated in vitro with 10 nM estradiol and 3.8 μM medroxyprogesterone acetate (E2) +/- varying concentrations of GCSF (Sigma) for varying durations in media supplemented with 1% charcoal-stripped fetal bovine serum. Concurrent solvent controls were included in all experiments. RNA was extracted using Trizol and reverse transcribed using iScript® (BioRad). Specific mRNA transcripts were quantitated using TaqMan® PCR with pre-designed primer-probe sets (ThermoFisher). Intra- and inter-experimental variability was addressed by multiple wells per condition in each experiment and repetition of each experiment at least 2 times.

RESULTS: As expected, stromal expression of decidualization markers, IGFBP1 and prolactin, was markedly increased (6-1000 fold) by EP treatment. Addition of 10 ng/mL GCSF augmented expression of both markers in a duration-dependent fashion: GCSF treatment increased IGFBP1 expression 1.1, 3.1, and 4.4 fold over EP alone at 8, 12, and 14 days, respectively. Prolactin expression increased 1.1, 1.3, and 6.0 fold at the same time points. GCSF expression was increased by EP and further augmented by GCSF. GCSF response was correlated with GCSFR expression and with response to EP. The highest GCSFR expression at baseline (30 fold variance seen between cells from different subjects) predicted the highest fold increases in markers of decidualization with GCSF treatment. Similar results were seen at 1ng/mL GCSF and no reproducible effect was seen at 0.1ng/mL GCSF.

CONCLUSIONS: GCSF augmented EP stimulation of decidual marker expression in a time and dose-dependent fashion. GCSF response was correlated with expression of its primary receptor, GCSFR. These data strongly...
suggest a mechanism for the observed benefit of GCSF treatment in patients with recurrent implantation failure. Previously described, reduced GCSFR expression in endometriosis patients represents a possible mechanism for altered clinical response to GCSF treatment. Ongoing work evaluating the mechanisms of GCSF action is aimed at better understanding the therapeutic role of GCSF in assisted reproduction.

References:

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ROLES OF EXOSOME-ASSOCIATED GLYCOSPHINGOLIPIDS IN IMMUNE TOLERANCE OF EMBRYO IMPLANTATION AND PREGNANCY. H. Wu. Obstetrics and Gynecology, Chang Gung Memorial Hospital, Taoyuan, Taiwan.

OBJECTIVE: Establishment of pregnancy requires synchronized growth between the endometrium and the blastocyst. Functional interaction between these occurs both during the pre-implantation phase of embryo implantation and during placentation. Pregnancy is a unique event in which a fetus, despite being genetically and immunologically different from the mother, develops in the uterus. Successful pregnancy implies avoidance of rejection by the maternal immune system. Exosomes released from the endometrium and the embryo are present in uterine fluid. These can transfer mRNA, miRNA, proteins and lipids between cells, thus affecting endometrial-embryo communication in the peri-implantation period. Exosomes have been considered of critical importance for embryo implantation and programming of human pregnancy. In the present study, we examined that the action of glycosphingolipids (GSLs) in exosomes, and their role as preventing the embryo from being attacked by the maternal immune system.

DESIGN: In this in vitro study, we examined whether GSLs could be purified from exosomes derived from abortus villi. To demonstrate the immunomodulatory capacity of exosomes, we tested macrophage M1/M2 polarization, indicating the role of exosomes in embryo implantation and pregnancy.

MATERIALS AND METHODS: Human villus trophoblast cells were isolated from the abortus tissue from healthy women undergoing pregnancy termination of a pregnancy at 6-12-week gestation, after informed consent. GSLs transferred from exosomes to monocytes. Macrophage M1/M2 polarization was tested by flow cytometry with CD68/CD80/CD163 markers. Transmission electron microscopy (TEM) images of isolated exosomes were performed.

RESULTS: GSLs were successfully transferred from exosomes to monocytes. Pretreatment with exosomes significantly induced macrophage M2 polarization. Moreover, isolated exosomes from villus trophoblast cells were confirmed by transmission electron microscopy images. Pretreatment with exosomes derived from villus trophoblast cells of a normal pregnancy significantly induced macrophage M2 polarization compared with an embryonic pregnancy. Macrophage M1/M2 polarization was tested by flow cytometry with CD68/CD80/CD163 markers. Transmission electron microscopy (TEM) images of isolated exosomes were performed.

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20.7 vs.10.8% +/- 17.8%) or than single women (9.6% +/- 18.6) (p=0.04). Most clinics (79.7%) have a sperm quarantine policy, which range from 7 days to 12 months, though most (85.1%) are 6 months. While 60 (42.0%) respondents permit no quarantine protocol deviation, 41 (28.7%) allow a complete waiver, and 11 (11.2%) allow shortening the duration in a given view of quarantine varied widely: 47 (34.8%) see it as “absolutely unnecessary protection”, while 41 (30.4%) view it as a “risk reduction option patients should be able to waive.” Nearly half (47.4%) considered mandatory quarantine an undue burden, with doctors younger than 60yo (p =0.03) and LGBT physicians (p=0.04) more likely to think so. LGBT physicians were also more likely (p<0.03) to treat donors participating in home inseminations as a SIP of the biological mother, though this was overall an uncommon (30.4%) view.

CONCLUSIONS: The management of directed sperm donors varies greatly, as do physician views regarding length, flexibility and duration of quarantine. In particular, younger and self-identified LGBT physicians expressed concern that mandated quarantine would restrict patient autonomy, while older REIs focused on the benefits of risk reduction. Given these findings, further detailed study may allow for an updated consensus that balances patient safety with expansion of treatment options for patients using directed sperm donors.

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AN INTERDISCIPLINARY APPROACH TO IMPROVING THE UNDERSTANDING OF DIAGNOSTIC AND MANAGEMENT DILEMNAS SURROUNDING CHRONIC ENDOMETRITIS.

S. L. Margules, a V. Flores, a V. Parkash, b L. Pali. a Department of Obstetrics, Gynecology & Reproductive Sciences, Yale School of Medicine, New Haven, CT, b Department of Pathology, Yale School of Medicine, New Haven, CT.

OBJECTIVE: To: 1) evaluate consistencies and discrepancies in histological criteria utilized by pathologists for diagnosing chronic endometritis (CE), and 2) assess ambiguities in the understanding of pathophysiology and management of CE by obstetrician/gynecologists (OB/GYNs).

DESIGN: Observational study

MATERIALS AND METHODS: Members of national and international professional OB/GYN and Pathology societies were surveyed utilizing two anonymous electronic surveys designed to respectively examine diagnostic criteria utilized by pathologists, as well as clinicians’ understanding of the pathophysiology and clinical implications of CE and if the prevalent treatments varied between national and international practitioners.

RESULTS: The surveys are still open. Findings demonstrate inconsistencies in the histological criteria utilized by pathologists for diagnosing CE. OB/GYN responses underscore the following: lack of clarity on provider understanding of mechanisms underlying CE—infectious (bacterial, viral, chlamydial, fungal), immune, foreign body; need for consensus on the understanding of the clinical presentation and implications— asymptomatic pelvic pain, infertility, pregnancy loss; prevalent heterogeneity in management approaches to CE—choice of antimicrobial, duration of treatment, follow-up thereafter.

CONCLUSIONS: The results of these surveys reflect the disparity of beliefs regarding the etiology, diagnosis and treatment of chronic endometritis. Our results underscore a need for directed efforts aimed at achieving consensus among the pathologists on histological criteria for diagnosing CE and improving the understanding of CE with OB/GYNs. The observed deficiencies in practitioners’ understanding of a prevalent condition is likely responsible for substantial cost (monetary and psychological) to both patients and the healthcare system. We propose consideration for establishment of a task force to systematically examine existing literature on the topic. Knowledge deficiets should be identified with the goal of establishing evidence-based management guidelines for this prevalent, yet misunderstood, entity.

Supported by: Department of Obstetrics, Gynecology & Reproductive Sciences and Department of Pathology at Yale School of Medicine

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A DIDACTIC INTERVENTION TO IMPROVE FERTILITY KNOWLEDGE AMONG RESIDENT PHYSICIANS. L. M. Roberts, a S. Ackroyd, a R. Kudesa, b M. Rose, a Department of Obstetrics, Gynecology and Reproductive Sciences, Temple University Hospital, Philadelphia, PA; bDivision of Reproductive Endocrinology & Infertility, CCRM Houston, Houston, TX.

OBJECTIVE: Knowledge of family planning and reproductive health is recommended as part of the Core Competencies for Internal Medicine (IM) trainees, yet is rarely assessed. The goal of this study was to evaluate fertility knowledge among IM residents and the impact of a formal didactic session on this knowledge.

DESIGN: Quasi-experimental study

MATERIALS AND METHODS: IM residents at a single institution were recruited via a program-wide email to voluntarily attend a didactic session on fertility. The intervention consisted of an interactive slideshow with case presentations based on guidelines of the American Society for Reproductive Medicine and the American College of Obstetricians & Gynecologists. Attendees of the session were invited to complete an online test to assess demographics and fertility knowledge, measured by the validated Fertility & Infertility Treatment Knowledge Score (FIT-KS) tool. The FIT-KS was administered both before ("pre-test") and after ("post-test") the intervention.

RESULTS: 20 residents (18.5%) attended the session, 19 completed the pre-test survey, and 10 completed the post-test survey. Pre-test responders were 52.6% female, primarily (83.0%) aged 26-30, and represented an even distribution of years in training. There was no significant association between fertility knowledge and demographics. The mean pre-test FIT-KS score was 65.1% (+/- 9.1%) correct. The post-test mean FIT-KS score was 70.3% (+/-8.8%) correct. When matching only those who completed both tests (7 participants), the average score improved from 64% (+/- 8.2) to 72.4% (+/- 4.9) (p=0.047). Participants demonstrated significant improvement in the areas: awareness of a partner’s age affecting fertility (<p=0.03), awareness that the sperm survives for 3-5 days increased from 11.1% to 47.4% (p<0.01). On the pre-test, 59% of respondents stated that they were concerned about their own future fertility, and only 12% felt comfortable answering patient questions about fertility. While 12% have children, only half of these residents felt comfortable providing counseling. If faced with their own infertility, 18% stated they would consider fertility medications, 35% would undergo IVF, 35% would adopt, and 12% would choose not to have children. In a paired analysis, the rates of feeling comfortable answering patient questions about fertility increased from 14.3% to 62.5% (p<0.03).

CONCLUSIONS: Substantial gaps exist in fertility knowledge among IM residents, with understanding of male fertility being particularly limited. Despite a small sample size, intervention significantly improved IM resident fertility knowledge and their comfort in discussing fertility with patients. A larger study group and expanded application of such interventions may improve fertility knowledge among IM trainees, and should be encouraged.

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KEY PERFORMANCE INDICATORS (KPIs) SCORE TO EVALUATE EMBRYOLOGIST PERFORMANCE IN ART LABORATORY.

M. C. Mattila, a V. A. Comar, a L. D. Vagnini, b A. Renzi, b B. Petersen, a, b A. Nicoletti, a F. Dieamant, a, b J. B. Oliveira, a, b R. Baruffi, a, b J. G. Franco, Jr., a, b aCenter for Human Reproduction Prof. Franco Jr, Ribeirao Preto, Brazil; bPaulista Center for Diagnosis, Research and Training, Ribeirao Preto, Brazil.

OBJECTIVE: To evaluate if the Key performance indicators (KPIs) score is a useful strategy to evaluate an embryologist performance in an ART laboratory.

Recently a KPIs score, built with clinical KPIs (C-KPIs) and laboratory KPIs (L-KPIs), was proposed to predict clinical pregnancy and for detecting problems in the clinical-laboratorial interface. It has been proposed that patients with good clinical performance (C-KPIs score ≥ 9) and with good laboratory performance (L-KPIs score ≥ 6) could be favorable for achieving ongoing pregnancy.

DESIGN: Prospective cohort

MATERIALS AND METHODS: A total fo 373 women (35.0±3.8years) undergoing ICSI cycles were included

C-KPIs score was obtained just before ICSI as follows:

-Number of metaphase-II oocytes: ≥ 2; 5 points; ≥ 1; 1 point
-AMH(ng/ml): ≥ 2: 5 points; ≥ 1; 2 points; < 1; 1 point

L-KPIs score was obtained as follows just before the fresh embryo transfer (cleavage stage):

-Fertilization rate (%): ≥65%; 5 points; ≥50%-<65%; 3 points; <50%; 1 point

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**TABLE 1. Results**

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients with favorable C-KPIs(9-15 points)</th>
<th>Embryologist-A</th>
<th>Embryologist-B</th>
<th>Embryologist-C</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years)</td>
<td>34.8±3.8</td>
<td>35.1±3.8</td>
<td>35.3±4.1</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>C-KPIs</td>
<td>12.1±2.2</td>
<td>12.2±2.1</td>
<td>12.6±1.7</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Achieved appropriate L-KPIs(&gt;6 points)</td>
<td>9.1±0.9</td>
<td>8.9±1.0</td>
<td>9.1±0.9</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>-L-KPIs</td>
<td>70%(82/117)</td>
<td>75%(71/95)</td>
<td>73%(33/45)</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>-Implantation rate</td>
<td>30%</td>
<td>26%</td>
<td>24%</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>-Ongoing pregnancy rate</td>
<td>41%</td>
<td>42%</td>
<td>33%</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Not achieved appropriate L-KPIs(≤6 points)</td>
<td>4.7±1.6</td>
<td>4.1±1.3</td>
<td>4.4±1.3</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>-L-KPIs</td>
<td>30%(35/117)</td>
<td>25%(24/95)</td>
<td>27%(12/45)</td>
<td>&gt;0.99</td>
<td></td>
</tr>
<tr>
<td>-Implantation rate</td>
<td>19%</td>
<td>17%</td>
<td>18%</td>
<td>&gt;0.99</td>
<td></td>
</tr>
<tr>
<td>-Ongoing pregnancy rate</td>
<td>20%</td>
<td>29%</td>
<td>25%</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Group II: Patients with unfavorable C-KPIs(&lt;9 points)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embryologist-A</td>
<td>Embryologist-B</td>
<td>Embryologist-C</td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age(years)</td>
<td>40.3±2.7</td>
<td>39.0±3.0</td>
<td>40.0±3.3</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>C-KPIs</td>
<td>5.2±1.8</td>
<td>5.3±1.7</td>
<td>5.5±1.6</td>
<td>&gt;0.99</td>
<td></td>
</tr>
<tr>
<td>Achieved appropriate L-KPIs(&gt;6 points)</td>
<td>8.4±1.0</td>
<td>8.4±1.0</td>
<td>8.1±1.0</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>-L-KPIs</td>
<td>40%(20/50)</td>
<td>46%(20/43)</td>
<td>47%(11/23)</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>-Implantation rate</td>
<td>15%</td>
<td>3%</td>
<td>18%</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>-Ongoing pregnancy rate</td>
<td>20%</td>
<td>5%</td>
<td>18%</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Not achieved appropriate L-KPIs(≤6 points)</td>
<td>4.6±1.7</td>
<td>4.7±1.5</td>
<td>4.4±1.6</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>-L-KPIs</td>
<td>60%(30/50)</td>
<td>54%(23/43)</td>
<td>53%(12/23)</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>-Implantation rate</td>
<td>6%</td>
<td>6%</td>
<td>0</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>-Ongoing pregnancy rate</td>
<td>7%</td>
<td>4%</td>
<td>0</td>
<td>&gt;0.99</td>
<td></td>
</tr>
</tbody>
</table>

-Morphological quality of embryonic lot: ≥2 embryos/top-quality: 5 points; 1 top-quality embryo ≥2 intermediate embryos: 3 points; only low-quality embryos: 1 point

Patients were stratified into two groups by C-LPIs:
- Group I: with favorable C-LPIs scores (≥9 points)
- Group II: with unfavorable C-LPIs scores (<9 points)

The performance of 3 embryologist was compared through laboratorial performance evaluation (Achieved appropriate L-KPIs >6 points; not Achieved appropriate L-KPIs ≤6 points) and their respectively outcomes (implantation and ongoing pregnancy).

RESULTS: No significant differences between the three population groups analysed by the embryologists were observed.

Group I: The results were similar between the 3 embryologist (P>0.05).

The percentage of negative inversion (from appropriate C-KPIs≥9 points to not-appropriate L-KPIs ≤6 points) was similar (Table 1).

Group II: The results were similar between the 3 embryologist (P>0.05).

The percentage of positive inversion (from not-appropriate C-KPIs <9 points to appropriate L-KPIs >6 points) was similar (Table 1).

CONCLUSIONS: The C-KPIs and L-KPIs score strategy was useful to evaluate embryologist performance. A comparative analysis between values of the C-KPIs score and L-KPIs score can detect problems in individual performance of embryologists.

**CLINICAL PROCEDURES AND TECHNIQUES**

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**NEW THERAPEUTIC PROTOCOL FOR IMPROVEMENT OF ENDOMETRIAL RECEPTIVITY (PRIMER) FOR PATIENTS WITH RECURRENT IMPLANTATION FAILURE (RIF) - A PILOT STUDY.** F. Dimeant, a,b L. D. Vagnini, a,b J. B. Oliveira, a,b R. Baruffi, a,b C. G. Petersen, a,b A. L. Mauri, a,b M. C. Mattila, a V. A. Comar, a A. Renzi, b B. Petersen, b A. Nicoletti, a J. G. Franco, Jr, a,b "Center for Human Reproduction Prof. Franco Jr, Ribeirao Preto, Brazil; "Paulista Center for Diagnosis Research and Training, Ribeirao Preto, Brazil.

OBJECTIVE: To evaluate if a therapeutic protocol for improvement of endometrial receptivity (PRIMER) based on platelet-rich plasma (PRP) and granulocyte colony-stimulating factor (G-CSF) can improve the ART-outcomes in patients with recurrent implantation failure (RIF).

Patients with a thin-endometrium seem to benefit from the use of these therapies, which indicates a beneficial effects of promoting cell differentiation/proliferation/growth, and neoangiogenesis. Most likely, these effects arise because both PRP/G-CSF contain/stimulate several growth factors/cytokines.

- Morphological quality of embryonic lot: ≥2 embryos/top-quality: 5 points; 1 top-quality embryo ≥2 intermediate embryos: 3 points; only low-quality embryos: 1 point.

Patients were stratified into two groups by C-LPIs:
- Group I: with favorable C-LPIs scores (≥9 points)
- Group II: with unfavorable C-LPIs scores (<9 points)

The performance of 3 embryologist was compared through laboratorial performance evaluation (Achieved appropriate L-KPIs >6 points; not Achieved appropriate L-KPIs ≤6 points) and their respective outcomes (implantation and ongoing pregnancy).

RESULTS: No significant differences between the three population groups analysed by the embryologists were observed.

Group I: The results were similar between the 3 embryologist (P>0.05).

The percentage of negative inversion (from appropriate C-KPIs≥9 points to not-appropriate L-KPIs ≤6 points) was similar (Table 1).

Group II: The results were similar between the 3 embryologist (P>0.05).

The percentage of positive inversion (from not-appropriate C-KPIs <9 points to appropriate L-KPIs >6 points) was similar (Table 1).

CONCLUSIONS: The C-KPIs and L-KPIs score strategy was useful to evaluate embryologist performance. A comparative analysis between values of the C-KPIs score and L-KPIs score can detect problems in individual performance of embryologists.

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- Morphological quality of embryonic lot: ≥2 embryos/top-quality: 5 points; 1 top-quality embryo ≥2 intermediate embryos: 3 points; only low-quality embryos: 1 point.

Patients were stratified into two groups by C-LPIs:
- Group I: with favorable C-LPIs scores (≥9 points)
- Group II: with unfavorable C-LPIs scores (<9 points)

The performance of 3 embryologist was compared through laboratorial performance evaluation (Achieved appropriate L-KPIs >6 points; not Achieved appropriate L-KPIs ≤6 points) and their respective outcomes (implantation and ongoing pregnancy).

RESULTS: No significant differences between the three population groups analysed by the embryologists were observed.

Group I: The results were similar between the 3 embryologist (P>0.05).

The percentage of negative inversion (from appropriate C-KPIs≥9 points to not-appropriate L-KPIs ≤6 points) was similar (Table 1).

Group II: The results were similar between the 3 embryologist (P>0.05).

The percentage of positive inversion (from not-appropriate C-KPIs <9 points to appropriate L-KPIs >6 points) was similar (Table 1).

CONCLUSIONS: The C-KPIs and L-KPIs score strategy was useful to evaluate embryologist performance. A comparative analysis between values of the C-KPIs score and L-KPIs score can detect problems in individual performance of embryologists.
OBJECTIVE: To identify the impact of using single-lumen vs double-lumen needles with follicular flushing during oocyte retrieval in poor responders undergoing in vitro fertilization (IVF). Our hypothesis was that the use of double-lumen needles with follicular flushing would improve oocyte yield and IVF outcomes.

DESIGN: Retrospective cohort study of IVF cycles with 7 or fewer follicles measuring >10mm at time of hCG administration.

MATERIALS AND METHODS: A total of 132 IVF cycles had ≤7 follicles measuring >10mm at time of hCG administration. Of these, 93 underwent retrieval with a single-lumen needle and 39 with a double-lumen needle with utilization of follicular flushing. Cycle characteristics of the two groups were collected and compared. All cycles underwent fresh embryo transfers three or five days post oocyte retrieval without preimplantation genetic testing. Oocyte number, mature oocyte number, procedure time, fertilization rate, pregnancy rate, implantation rate, clinical pregnancy rate, and live birth rate were assessed for each group. A subgroup analysis was also conducted on cycles with ≤5 follicles at time of hCG administration. Statistical analysis was performed using Student’s t-test, Chi-square, or Fisher’s exact test.

RESULTS: When compared to the single-lumen cohort, the double-lumen cohort had a statistically significant fewer number of oocytes retrieved (5.26 vs 7.11, p < 0.001), fewer mature oocytes (4.59 vs 6.0, p 0.001), increased procedural time (24.15 vs 9.41, p < 0.001), and fewer 2pn embryos observed (3.15 vs 3.94, p 0.03). There was no difference in the number of embryos transferred. Cycles with single-lumen retrieval had statistically significant higher positive pregnancy rate (55.91% vs 28.21%, p 0.004), implantation rate (27.67% vs 16.25%, p 0.044), and clinical pregnancy rate (45.16% vs 25.64%, p 0.036). The live birth rate was also higher in the single-lumen group but did not reach statistical significance (40.86% vs 25.64%; p 0.097). Subgroup analysis of cycles with ≤5 follicles at time of hCG administration showed similar results in respect to number of oocytes retrieved, number of mature oocytes, procedural time, and number of 2pn embryos observed. There was no difference in any of the pregnancy outcomes in those cycles with ≤5 follicles at time of hCG administration.

CONCLUSIONS: Our results suggest that there is no improvement in IVF outcomes with the use of a double-lumen needle with follicular flushing compared to the use of a single-lumen needle in poor responders. We found that the use of a double-lumen needle with follicular flushing not only increased the procedural time but had a negative impact on the number and quality of oocytes retrieved, implantation and clinical pregnancy rates when compared to retrieval with a single-lumen needle.

Supported by: KL2 TR001118 (JK) for abstract

TABLE 1. General characteristics and main results.

<table>
<thead>
<tr>
<th></th>
<th>PRIMER/RIF Group (n=33)</th>
<th>Control Group (n=33)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous Embryo transfers (n)</td>
<td>4.0±1.5</td>
<td>3.7±3.9</td>
<td>0.94</td>
</tr>
<tr>
<td>Female age (y)</td>
<td>37.8±3.8</td>
<td>37.8±3.9</td>
<td>0.10</td>
</tr>
<tr>
<td>Male age (y)</td>
<td>41.8±4.8</td>
<td>39.1±6.2</td>
<td>0.43</td>
</tr>
<tr>
<td>AMH (ng/dl)</td>
<td>2.4±2.7</td>
<td>2.7±4.7</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>24.4±3.3</td>
<td>24.8±3.9</td>
<td>0.23</td>
</tr>
<tr>
<td>-Male factor (%)</td>
<td>42.4%</td>
<td>36.4%</td>
<td>0.62</td>
</tr>
<tr>
<td>-Tuboperitoneal (%)</td>
<td>12.2%</td>
<td>9.1%</td>
<td></td>
</tr>
<tr>
<td>-Idiopathic (%)</td>
<td>24.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Endometriosis (%)</td>
<td>21.2%</td>
<td>21.2%</td>
<td></td>
</tr>
<tr>
<td>FSH total dose (IU)</td>
<td>3245.9±1357.7</td>
<td>2864.±1125.8</td>
<td>0.23</td>
</tr>
<tr>
<td>Total oocytes (n)</td>
<td>7.8±4.4</td>
<td>6.4±3.6</td>
<td>0.14</td>
</tr>
<tr>
<td>MII oocytes (n)</td>
<td>6.1±3.5</td>
<td>5.3±3.1</td>
<td>0.35</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>60.6±23.2%</td>
<td>68.2±25.4%</td>
<td>0.28</td>
</tr>
<tr>
<td>Embryos transferred (n)</td>
<td>2.3±0.9</td>
<td>2.2±0.9</td>
<td>0.53</td>
</tr>
<tr>
<td>Only good quality embryo transferred (%)</td>
<td>54.5%</td>
<td>60.6%</td>
<td>0.62</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>14.2%</td>
<td>17.1%</td>
<td>0.38</td>
</tr>
<tr>
<td>Clinical pregnancy rate (%)</td>
<td>36.4%</td>
<td>30.3%</td>
<td>0.61</td>
</tr>
<tr>
<td>Miscarriage rate (%)</td>
<td>25.0%</td>
<td>9.0%</td>
<td>0.43</td>
</tr>
<tr>
<td>Ongoing pregnancy rate (%)</td>
<td>27.3%</td>
<td>27.3%</td>
<td>0.99</td>
</tr>
</tbody>
</table>

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IN VITRO FERTILIZATION OUTCOMES WITH DIRECT ASPIRATION WITH SINGLE-LUMEN NEEDLES COMPARED TO FOLLICULAR FLUSHING WITH DOUBLE-LUMEN NEEDLES FOR OOCYTE RETRIEVAL IN POOR RESPONDERS. S. Rippentrop, J. Knutson, J. McLaughlin, T. Chang, A. Cardenas, R. D. Robinson, OB-GYN; University of Texas Health Science Center, San Antonio, San Antonio, TX.

OBJECTIVE: To evaluate the impact of aspiration pressure during oocyte retrieval on oocyte yield, embryo quality and pregnancy rate.

DESIGN: Retrospective analysis

MATERIALS AND METHODS: Institutional Review Board approval was obtained. All in vitro fertilization retrievals performed by reproductive endocrinology attending physicians between 9/1/16 to 8/31/17 were reviewed. Low-pressure oocyte aspiration was defined as less than 150 mmHg while high-pressure oocyte aspiration was defined as greater than 300 mmHg. Baseline characteristics and outcomes were compared between groups.

RESULTS: 171 retrievals using low-pressure and 366 retrievals using high-pressure were included. The mean patient age was similar between groups, 36.3 (SD 4.7) vs 36.3 (SD 4.7) years. In the low-pressure group, there were significantly more oocytes retrieved (16 vs 13 oocytes, p = <0.001), more oocytes/follicle measured (1.1 vs 0.9, p < 0.001), greater oocyte maturity (77% vs 75%, p < 0.02) and fewer oocytes with an empty zona pelludica (2.0% vs 3.4%, p < 0.001) compared to the high-pressure group. There was no difference in the fertilization rate between groups. 232 cycles were cultured to the blastocyst stage, 80 in the low-pressure group and 152 in the high-pressure group. Of these, the blastocyst rate per fertilized oocyte was not significantly different, 45% vs 48%, p=0.2. The low-pressure group had significantly more usable embryos, defined as the number of embryos either transferred or frozen, 4.5 vs 3.8, p=0.01. There were 80 fresh transfers in the low-pressure group and 175 fresh transfers in the high-pressure group. Of these, the pregnancy rate per transfer was 53.8% in the low-pressure group and 54.9% in the high pressure group, p=1.0. There was no difference in the percent of transfers occurring at the cleavage or blastocyst stage between groups.

CONCLUSIONS: The use of low aspiration pressure resulted in a significantly greater oocyte yield, maturity and fewer oocytes with an empty zona

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IMPACT OF ASPIRATION PRESSURE DURING OOCYTE RETRIEVAL. D. McQueen,* C. E. Boots,* T. Jain,* J. X. Zhang,* J. Robins,* Northwestern University, Chicago, IL; *Obstetrics and Gynecology, Northwestern Feinberg School of Medicine, Chicago, IL.

OBJECTIVE: To evaluate the impact of aspiration pressure during oocyte retrieval on oocyte yield, embryo quality and pregnancy rate.

DESIGN: Retrospective analysis

MATERIALS AND METHODS: Institutional Review Board approval was obtained. All in vitro fertilization retrievals performed by reproductive endocrinology attending physicians between 9/1/16 to 8/31/17 were reviewed. Low-pressure oocyte aspiration was defined as less than 150 mmHg while high-pressure oocyte aspiration was defined as greater than 300 mmHg. Baseline characteristics and outcomes were compared between groups.

RESULTS: 171 retrievals using low-pressure and 366 retrievals using high-pressure were included. The mean patient age was similar between groups, 36.3 (SD 4.7) vs 36.3 (SD 4.7) years. In the low-pressure group, there were significantly more oocytes retrieved (16 vs 13 oocytes, p = <0.001), more oocytes/follicle measured (1.1 vs 0.9, p < 0.001), greater oocyte maturity (77% vs 75%, p < 0.02) and fewer oocytes with an empty zona pelludica (2.0% vs 3.4%, p < 0.001) compared to the high-pressure group. There was no difference in the fertilization rate between groups. 232 cycles were cultured to the blastocyst stage, 80 in the low-pressure group and 152 in the high-pressure group. Of these, the blastocyst rate per fertilized oocyte was not significantly different, 45% vs 48%, p=0.2. The low-pressure group had significantly more usable embryos, defined as the number of embryos either transferred or frozen, 4.5 vs 3.8, p=0.01. There were 80 fresh transfers in the low-pressure group and 175 fresh transfers in the high-pressure group. Of these, the pregnancy rate per transfer was 53.8% in the low-pressure group and 54.9% in the high pressure group, p=1.0. There was no difference in the percent of transfers occurring at the cleavage or blastocyst stage between groups.

CONCLUSIONS: The use of low aspiration pressure resulted in a significantly greater oocyte yield, maturity and fewer oocytes with an empty zona

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Study of Women 43 Years of Age and Older.

OBJECTIVE: Intrauterine insemination (IUI) is a widely used treatment in reproductive medicine. The aim of this study was to determine how female age at the end of the reproductive spectrum affects success of IUI alone or in combination with ovarian stimulation.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: We performed a retrospective cohort study of women 43 years of age and older at the time of intrauterine insemination in a single academic fertility center between January 2011 and March 2018. Primary outcomes were both pregnancies (defined by a Beta HCG > 10 mIU/ml) and live births per cycle of IUI. Data are presented as percentage of IUIs or mean±SD. Fisher exact or Chi-squared analysis were performed.

RESULTS: There were 9,334 IUI cycles conducted during the study period. Of these cycles, 325 (3.5%) were for women 43 years and over at the time of insemination, (43.6±0.8, range 43 to 47 years). This included 36 (11%) cycles with IUI alone, 78 (24%) cycles in combination with Clomiphene or Letrozole and 211 (64%) Gonadotropin-stimulated IUI cycles. Analysis of these 325 IUI cycles revealed 5 biochemical pregnancies (1.5%) and only 1 live birth (0.3%). The pregnancy rate did not differ between IUIs using donor sperm (N=1, 0.3%) compared to IUIs with partner sperm (N=4, 1.5%); Fisher exact = 0.55. The pregnancy rate did not differ between IUIs with gonadotropins (N=2, 0.9%), Clomiphene/Letrozole N=2, 2.6%), Clomiphene/Letrozole N=2, 2.6%) or natural cycles (N=11, 1.2%; p=0.11).

CONCLUSIONS: The use of intrauterine inseminations in women 43 years of age and older is an ineffective treatment strategy. This is irrespective of the use of ovarian stimulation or donor sperm. Costly gonadotropin injections did not increase the chance of pregnancy in women 43 years of age and older, nor did oral medication when compared to natural cycle IUIs.

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A TRIAL OF THREE INTRAUTERINE INSEMINATIONS: AN ANALYSIS BY PATIENT AGE AND SPERM SOURCE. J. Ruiter-Ligeti, a N. Al Mamari, b A. Volodosky-Perele, b M. H. Dahan, b W. Buckett, b McGill University, Montreal, QC, Canada; bGynecologic Reproductive Endocrinology and Infertility, McGill University, Montreal, QC, Canada; bMcGill University, Montreal, QC, Canada.

OBJECTIVE: A trial of at least three IUIs before proceeding to IVF is a widely used treatment plan in couples with normal sperm parameters and women using donor sperm. The aim of this study is to determine how female age and sperm source affect the success of this plan.

DESIGN: Retrospective Cohort Study.

MATERIALS AND METHODS: We performed a retrospective cohort study of women undergoing their first three intrauterine inseminations at a
single academic fertility centre in Montreal, Quebec between January 2011 and March 2018. Our primary outcomes are pregnancy rates per IUI and cumulative pregnancy rates after three IUIs, stratified by age group and sperm source. Pregnancies are defined by a serum Beta HCG of greater than 5 mIU/ml. IUIs were excluded if the post-wash total motile sperm count was less than ten million. A sample size of 130 in each group has a 90% power of showing a 20% difference in primary outcome with an alpha of 5%. Chi-squared analyses were performed.

RESULTS: There were 9,334 IUIs conducted during the study period. Of these, 4,865 IUIs met inclusion criteria. We found that the first insemination had a significantly higher chance of pregnancy compared to subsequent IUIs across all age groups, with \( P < 0.001 \) for each age group. After a trial of three IUIs, women less than 40 years old had a significantly higher cumulative pregnancy rate compared to older women, \( P < 0.001 \). For women 35 years and under, the cumulative pregnancy rate was also significantly higher when donor sperm was used (68.1%) compared to those using partner sperm (37.1%), \( P < 0.001 \) (Table 1).

CONCLUSIONS: The pregnancy rate per IUI and the cumulative rate over three IUIs are greatly affected by both female age and sperm source. The first IUI has a significantly higher chance of success compared to subsequent IUIs. A major limitation of our study is that variables such as the indication for IUI were unavailable, thus our study represents all comers in an unselected sample. Our data shows that a treatment plan of three IUIs prior to IVF is a viable option for most patients using normal sperm.

Patient characteristics and procedure details of patients undergoing OH and EMB

<table>
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<tr>
<th>Variables</th>
<th>Vaginal Misoprostol (n=97)</th>
<th>No Vaginal Misoprostol (n=87)</th>
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<tr>
<td>Age (years)</td>
<td>44.5±8.9</td>
<td>42.7±7.4</td>
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<td>Gravidity</td>
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<td>1 (0-8)</td>
<td>0.26</td>
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<td>Parous status</td>
<td>1 (0-1)</td>
<td>0 (0-1)</td>
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<td>Indication</td>
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<tr>
<td>Fibroid</td>
<td>71 (73.2%)</td>
<td>63 (72.4%)</td>
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<tr>
<td>Poly</td>
<td>3 (3.1%)</td>
<td>3 (3.4%)</td>
<td></td>
</tr>
<tr>
<td>Fertility testing</td>
<td>4 (4.1%)</td>
<td>4 (4.6%)</td>
<td></td>
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<tr>
<td>RPL</td>
<td>2 (2.1%)</td>
<td>3 (3.4%)</td>
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<tr>
<td>Others</td>
<td>17 (17.5%)</td>
<td>16 (13.1%)</td>
<td></td>
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<tr>
<td>Procedure completed</td>
<td>93 (95.9%)</td>
<td>77 (88.5%)</td>
<td>0.09</td>
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</table>

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OPIOID USE AND POSTOPERATIVE PAIN AFTER OOCYTE RETRIEVAL. J. Tuocry, R. Goldman, E. Y. Farland, R. Agarwal, A. M. Thomas, J. H. Fox, Obstetrics & Gynecology, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA.

OBJECTIVE: To quantify opioid use after oocyte retrieval and determine the patient- and procedure-specific characteristics that predict post-retrieval pain and opioid use.

DESIGN: Cross-sectional survey with medical chart review

MATERIALS AND METHODS: Patients who underwent an oocyte retrieval and returned for a fresh embryo transfer at a university-based infertility center from 4/2017 - 8/2017 were recruited. Patients with an allergy to opioids or history of chronic opioid use were excluded. On the day of embryo transfer, patients completed a survey to ascertain daily opioid use and pain following retrieval (0 - 10 numeric rating scale). The primary outcome was total number of opioid tablets consumed in the days following oocyte retrieval. Secondary outcomes included pain severity and the use of non-opioid pain relievers following oocyte retrieval. Multivariable logistic and linear regressions were used to determine the patient- and procedure-specific factors associated with opioid use and pain severity, respectively. Resultant odds ratios and beta coefficients with 95% confidence intervals were adjusted for BMI, parity, prior abdominal surgery, number of follicles, and amount of intra-operative anesthetic used.

RESULTS: A total of 197 patients were recruited. The median amount of opioids prescribed was 5 oxycodone tablets (Range 2 - 15). Seventy-one patients (36.6%) filled their opioid prescriptions. The majority of patients did not use any opioids (n=141, 71.2%) following retrieval. Of those who filled their prescriptions, patients reported using a median of 2 oxycodone tablets, leaving an excess of 3 tablets per patient. A total of 142 (72.1%) patients used non-opioid pain relievers such as acetaminophen and 60 (30.5%) used non-pharmacologic methods including warm compresses for pain control. Patients reported the worst pain on the day of retrieval. Prior abdominal surgery, number of follicles, amount of intra-operative anesthetic required, and need for opiate analgesia in the recovery room were identified as statistically significant predictors of opioid consumption post-oocyte retrieval. Patients with a history of endometriosis, prior abdominal surgery, and more oocytes retrieved reported increased pain post-oocyte retrieval.

CONCLUSIONS: The majority of patients undergoing oocyte retrieval do not require opioids post-procedure. Opioid prescriptions following oocyte retrieval should be minimized, and a personalized approach for prescribing opioids for postoperative pain should be implemented.
OBJECTIVE: The primary objective of this study is to assess pregnancy and live birth rates after performing an embryo transfer (ET) in the cycle subsequent to endometrial receptivity assay (ERA).

DESIGN: This is a retrospective single institution study. Demographics of patients undergoing ET over a one-year period were recorded.

MATERIALS AND METHODS: 21 patients met criteria for inclusion; each had an ERA biopsy performed because of failed implantation following multiple ET cycles (average of 4 prior ET). These included fresh and/or frozen ET with either genetically tested euploid blastocysts or untested high grade embryos. Number and type of previous ET cycles were documented; this included fresh versus frozen ET, number of embryos transferred, stage of ET, and use of PGT-A testing. ERA was performed on the day that we would typically perform ET in a programmed cycle. Modifications to the subsequent ET cycle were performed if ERA results were “non-receptive” (pre or post receptive), or “early or late” receptive.

RESULTS: 19/21 patients had failed both fresh and frozen ET. One patient each had undergone only fresh or frozen ET due to poor embryo development, and exclusive PGT only respectively. Seven patients had pre- or post- receptive results, 4 of whom had repeat biopsies during frozen ET cycles to assess receptivity at a different date after initiation of intra-muscular progesterone. All 7 patients’ subsequent ET cycles were adjusted accordingly. Two patients had early/late receptive results, and subsequent adjustment by 12 hours of ET schedules as recommended. 12 patients had normal (receptive) results. 14 patients proceeded with a subsequent frozen ET cycle, and one with a fresh ET cycle; each performed in cycle subsequent to ERA. Of these 15 patients, 14 achieved pregnancy in the cycle after ET, and 1 achieved pregnancy in the next ET after ERA (93%). All 8 patients whose previous ET cycles were adjusted due to ERA results achieved pregnancy in their next cycle, as did 6/7 with receptive ERA and unadjusted cycles. 10/14 pregnancies resulted in live birth or are currently ongoing (71% of pregnancies, and 67% of transfers). These pregnancies occurred in equal measure with ET of euploid, and untested embryos.

CONCLUSIONS: Our data demonstrates a high rate of both pregnancy and live birth after ET in the cycle subsequent to ERA, using both genetically tested and untested high grade embryos. Although many biopsies were receptive when performed after using our standard replacement protocol and nothing hormonally was changed, both these patients and those with non-receptive biopsies (who had modifications made in timing of ET in relation to progesterone exposure) had excellent outcomes. Whether the reasons for subsequent success is related to changes in hormonal stimulation, or proximity of the endometrial biopsy to subsequent ET remains to be elucidated. Further investigation is warranted to determine if an ERA is beneficial for women of all reproductive ages who have failed multiple previous high grade ET

FEMALE REPRODUCTIVE ENDOCRINOLOGY

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FSH COTRIGGER ALONG WITH HCG TRIGGER TO IMPROVE IVF OUTCOME. M. Dwarakanath,a D. P. S.,a G. T. Pranesh,a K. A. Rao,a A. Vohra.a Reproductive Medicine, Milann the Fertility Centre, Bangalore, India; Gynaecology, Milann, Bangalore, India; Laboratory Medicine, Milann, Bangalore, India; Reproductive Medicine, Milann -Fertility Center, Bangalore, India.

OBJECTIVE: Spontaneous ovulation is preceded by a surge of both follicle stimulating hormone (FSH) and luteinizing hormone. Studies on serum and follicular fluid FSH suggest a potential role for FSH at the time of final oocyte maturation. Dual trigger have shown good outcomes in ART supporting role of FSH in oocyte maturation. We hypothesized that giving FSH Co-trigger along with the standard HCG trigger in poor responders and suboptimal responders could improve developmental competence of the oocyte.

DESIGN: Prospective observational study done in tertiary care fertility centre between April 2017 to March 2018.

MATERIALS AND METHODS: The study was conducted over a period of 1 year at Milann the fertility centre Bangalore. 63 patients in the age group of 25-45 years, with previous poor response or sub-optimal response to stimulation with one or more cycles of IVF/ICSI cycles were included in the study. Antagonist protocol for IVF/ICSI was started after day2/3 scan and blood test. When 2 or more follicle of more than 17.5 mm, trigger was given with 300IU of Recombinant FSH along with 250mcg of Recombinant HCG. Oocyte aspiration was done 35 hrs after trigger. The primary outcomes -oocyte maturity rate, fertilization proportion, number of Grade 1 embryos

obtained Secondary outcomes- oocyte recovery rate, cleavage rate and implantation rate. Statistical significance was evaluated through Wilcoxon Signed Ranks Test

RESULTS: Of the 63 patients, 2 were excluded and 5 dropped out. Number of oocytes retrieved (7.17 in co-trigger v/s 5.3 in HCG group, p value-0.006), number of mature oocytes (5.3 in co-trigger v/s 3.57 in HCG trigger, p value-0.003), fertilization rate (5.03 in co-trigger v/s 3.13 in HCG trigger group, p value-0.002), cleavage rate(4.9 in co-trigger v/s 2.87 in HCG trigger group, p value-0.001) and total number of Grade 1 embryos on Day 3 (3.87 in co-trigger v/s 2.03 in HCG trigger group, p value-0.0001) were higher in the Co-trigger group in comparison to HCG trigger group.

CONCLUSIONS: In this study we noticed a significant improvement in outcome in FSH cotrigger group. Evidence from macaques has shown that midcycle recombinant FSH alone is able to promote resumption of oocyte meiosis, fertilization, and granulosa cell luteinization, though cannot sustain luteal function. Though GnRHs is an alternative, there is a startlingly lower levels of FSH when compared to FSH co-trigger in follicular fluid and GnRHa trigger is followed by massive uterolysis favouring FSH co-trigger in poor and suboptimal responders.

References:
5. Julie D Lamb, Shehua Shen,Charles McCulloch; Fert and Stert; vol 95, no 5, April 2011FSH administration during hCG trigger may improve oocyte development competence in IVF cycles; Fert and ster; vol 95, no 5, April 2011

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ELECTIVE SINGLE EMBRYO TRANSFER IN THE SETTING OF FUNDED IVF: TWO YEARS’ EXPERIENCE IN A HOSPITAL BASED FERTILITY CLINIC. S. Ilnitsky,a,b L. Hughes, b F. Tekpetey,c B. Abu Rafea,a,b G. Vilos,a,b Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Schulich School of Medicine, Western University, London, ON, Canada; The Fertility Clinic, London, ON, Canada; Western University, London, ON, Canada.

OBJECTIVE: Our objective was to compare patient and cycle characteristics, clinical pregnancy rates, and multiple gestation rates at a hospital based fertility clinic before and after the institution of government funded IVF/ICSI and mandated elective single embryo.

DESIGN: This is a retrospective database review of unlinked patient data.

MATERIALS AND METHODS: Clinic and embryology lab data for all patients undergoing IVF and ICSI cycles over a four year period was mined for patient and cycle characteristics, clinical pregnancy rates, and multiple gestation rates. Extracted data was not linked to patient identifiers, therefore ethics approval was not required. We compared IVF and ICSI cycles from two years before funding (January 1, 2014 to December 31, 2015) to two years after funding (January 1, 2016 to December 31, 2017).

RESULTS: The number of cycles performed over a two year period increased from 554 before funding to 853 after funding; 76.2% were funded cycles. Patient age, BMI, and parity were similar before and after funding. The majority of patients undergoing IVF or ICSI after funding had not had a previous cycle. Cycle cancellation rates were similar before and after funding, however there were fewer embryo transfers per cycle after funding (80.5% vs. 72.2%, P=0.001). The clinical pregnancy rate was similar before and after funding (37.8% vs. 32.5%, P=0.09), while the multiple gestation rate was significantly lower (13.1% vs. 3.5%, P<0.001).

CONCLUSIONS: Since the government of Ontario began funding IVF and ICSI cycles more patients are accessing treatment, many for the first time. At our clinic, the clinical pregnancy rate was maintained while multiple gestations were significantly reduced to well below the national average of...
10.7%. These findings support the benefit of eSET in the context of funded IVF/ICSI.

References:

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BURDEN OF DIABETES ON PREGNANCY IN THE INFERTILE POPULATION IN THE INDIAN SUBCONTINENT: AN OBSERVATIONAL STUDY. M. R. Palep-Singh1,2 S. B. Patil.1 1Dept of Reproductive Medicine & Surgery, Head of Infertility and Minimal Access Surgery, Fortis Hospital, Bangalore, India, 2Dept of Reproductive Medicine & Surgery, Creation, Fortis Hospital, Bangalore, India. 2Reproductive Medicine & Surgery, Associate Consultant Fortis Hospital, Bangalore, India.

OBJECTIVE: To evaluate the prevalence of Gestational diabetes in the infertile population in India and its impact on pregnancy

DESIGN: An ongoing observational study of 400 pregnant women treated for subfertility in a tertiary referral centre

MATERIALS AND METHODS: Baseline parameters of 400 pregnant women treated for infertility were noted including fasting sugars, glycosylated Hb and their progress through pregnancy was charted with assessment of 75 gms OGTT at 28 weeks of gestation and doppler blood flow at different stages and eventually fetal birth weight. Microsoft excel 2011 was used for analysis.

RESULTS: Mean age of the pregnant women was 30.1±4.2 years with a mean BMI of 24.3±4.2 kg/m². Mean Plasma glucose at 12 weeks was 102.7±15.3 mg/dl and HbA1c was 5.6±0.4%. Only 15.3% women had a HbA1c >5.7% at booking. 38% had a h/o PCOS, 31.5% had h/o Unexplained infertility and 16.5% h/o Male factor infertility. 54.3% women explained infertility and 16.5% had h/o Male factor infertility. 36.5% women with PCOS had an abnormal GTT as compared with 30.3% (p=ns); 23% women with abnormal GTT developed PIH as compared with 10.4% cases with normal GTT (p = 0.013 significant) The mean gestational age at delivery was 37±3.6 weeks and there was no significant difference in the birth weight of babies born to mothers with abnormal GTT (2.8±0.55 kg) when compared with those with normal GTT (2.8±0.64kg).

CONCLUSIONS: Nearly 1/6th women have an impaired glucose tolerance at antenatal booking and by 28 weeks a third (1/3) of women develop GDM. The onset of PIH in cases with GDM significantly higher (x2) and when compared with those with normal GTT (2.8±0.55 kg) was 37±3.6 weeks and there was no significant difference in the birth weight of babies born to mothers with abnormal GTT (2.8±0.55 kg) when compared with those with normal GTT (2.8±0.64kg).

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PREVALENCE AND PREDICTORS OF OLIGOMENORRHEA AND AMENORRHEA IN DIVISION 1 FEMALE ATHLETES. L. Verrilli, H. Blanchard, M. Landry, A. Stancic, Obstetrics and Gynecology, University of Wisconsin, Madison, WI.

OBJECTIVE: Long-term health is impacted by disorders of hypothalamic-pituitary-ovarian (HPO) axis that frequently manifest as oligomenorrhea and amenorrhea. Elite female athletes represent a group who may be at higher risk of HPO disorders. Despite long-standing observations that strenuous exercise, stress and weight impact the HPO axis, little is known the prevalence and predictors of oligo/amenorrhea in this population. Consequently, there exists a need for a comprehensive dataset to explore menstrual patterns and systemic hormone use in elite athletes. We conducted a cross sectional survey study in order to answer these questions.

FERTILITY & STERILITY®
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LOGISTICS REGRESSION ANALYSIS OF RISK FACTORS ASSOCIATED WITH INCREASED SPONTANEOUS ABORTION IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME. X. Li,a R. Huang,a C. Fang,b X. Liang,b,6 Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; aReproductive Medicine Center, Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.

OBJECTIVE: To analyze spontaneous abortion rate and explore associated risk factors in patients with polycystic ovarian syndrome (PCOS) after in vitro fertilization/ intracytoplasmic sperm injection intracytoplasmic sperm injection- embryo transfers (IVF/ICSI-ET).

DESIGN: A retrospective cohort study.

MATERIALS AND METHODS: We enrolled patients undergoing IVF/ICSI treatment in reproductive medicine center of the sixth affiliated hospital of sun yat-sen university between January 2013 and August 2017. A total of 2231 patients with PCOS were included. For comparison, we enrolled 2231 patients with tubular factors as control group. We compared spontaneous abortion rate and chromosomal abnormality rate between two groups in order to investigate the status of embryo-aneuploidy abnormality in etiologies of spontaneous abortion after IVF/ICSI-ET in PCOS patients. Furthermore, we compared clinical data between patients of spontaneous abortion and those of ongoing-pregnancy using univariate and multivariate analysis for risk factors of spontaneous abortion in PCOS patients after IVF/ICSI-ET.

RESULTS: Patients in PCOS group had higher spontaneous abortion rate (24.15% vs. 12.75%, P<0.0001) and difference reached statistical significance. Chromosomal abnormality rate was significantly lower in PCOS group (36.05% vs. 55.56%, P=0.009). In patients with PCOS, those of spontaneous abortion had older age, higher body mass index (BMI) and HOMA-IR than those of ongoing pregnancy. All difference reached statistical significance. The further logistics regress analysis confirmed that the age, BMI and HOMA-IR were risk factors of spontaneous abortion in PCOS patients. There was no significant difference in the type of cycles, the quality of embryo transferred, the number of embryo transferred, fasting blood glucose, fasting insulin etc.

CONCLUSIONS: Compared with non-PCOS patients, PCOS patients had higher rate of miscarriage, but chromosomal abnormalities were not a major factor for the high rate of miscarriage in PCOS patients. Age, BMI, and HOMA-IR were risk factors for spontaneous abortions after IVF/ICSI-ET in PCOS patients.

References:

Supported by: This work is supported by National Key Research and Development Project of China (2017YFC1001600).

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SIX-WEEKS PRETREATMENT WITH GROWTH HORMONE IMPROVES CLINICAL OUTCOMES OF POOR OVARIAN RESPONDERS (PORs) UNDERGOING IVF TREATMENT: A SELF-CONTROLLED CLINICAL STUDY. M. Cai, X. Liang, Y. Wu, R. Huang, X. Yang. Reproductive Medicine Center, The Sixth Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China.

OBJECTIVE: The purpose was to explore whether the six-weeks of growth hormone adjuvant can promote the live birth rate of poor ovarian responders (PORs).

DESIGN: A self-control retrospective study.

MATERIALS AND METHODS: This self-control retrospective study was performed among PORs diagnosed by Bologna criteria(1) who had a growth hormone adjuvant cycle (GH+ cycle) and a non-adjuvant cycle (GH- cycle) from October 2010 to April 2016. Both paired cycles were conducted with conventional control ovarian hyperstimulation protocol for IVF treatment. Growth hormone was injected daily initiated from the previous menstruation conventional control ovarian hyperstimulation protocol for IVF treatment. Though patients in GH+ cycles are at elder age, there was a significantly increase in the number of 2PN (2.06±1.95 vs 1.83±1.63), transferable embryo (1.68±1.74 vs 1.35±1.34) and good quality embryo (1.14±1.50 vs 0.11±0.48), (P<0.05). Fixed effects in mixed linear model revealed that after adjustment for potential confounders (cycle number, age, FSH, AMH, oocyte number), the application of GH was significantly associated with the promotion in the number of good quality embryos (P<0.001). Among which, 51 pairs of both fresh embryo transferred cycles were included to analyses effect of live birth rate. Growth hormone pretreatment significantly promoted live birth rate (23.53% vs 3.92%, P<0.05), accompanied with significantly decreased miscarriage rate (18.75% vs 80%, P<0.05).

CONCLUSIONS: The six-weeks pretreatment with low dose GH could be beneficial for the utilization of oocytes and finally promoted live birth rate in PORs.

References:

Supported by: No
response to induced stress indicating aberrant HPA function, which may influence fertility and/or response to treatment. Additionally, ELS is associated with chronic inflammation which has been implicated in altered reproductive function. These novel findings suggest that the impact ELS on fertility and IVF outcomes requires further investigation.

Supported by: Penn Presbyterian George L. and Emily McMichael Harrison Fund for Research in Obstetrics and Gynecology; NIH T32HD007440-21

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CONCOMITANT HYPOTHYROIDISM DOES NOT IMPACT OVARIAN RESERVE PARAMETERS IN POLYCYSTIC OVARY SYNDROME. I. Peregrin-Alvarez, a R. Roman, a N. Van De Velde, b M. Christiansen, c J. C. Gordon, d L. Detti, e Obstetrics and Gynecology, University of Tennessee Health Science Center, Memphis, TN; cUniversity of Tennessee Health Science Center, Memphis, TN; eUniversity of Tennessee Health and Science Center, University of Tennessee Health and Science Center, Memphis, TN; dUniversity of Tennessee Health Sciences Center, Memphis, TN.

OBJECTIVE: Hypothyroidism is among the differential diagnoses for polycystic ovary syndrome. We sought to evaluate the impact of hypothyroidism on ovarian reserve when isolated, and in the presence of PCOS, by evaluating reproductive hormonal profiles.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: Retrospective cohort study among women diagnosed with PCOS, hypothyroidism, or both, from 2015 to 2018. PCOS was diagnosed using the Rotterdam criteria. Subclinical or overt hypothyroidism was diagnosed with a TSH ≥ 2.5 ng/mL. Primary outcome was ovarian reserve evaluated as average ovarian volume, average antral follicular count (AFC), anti-mullerian hormone (AMH) and follicle-stimulating hormone (FSH). One-way ANOVA analysis with Tukey post-hoc test was performed with p<0.05 significance.

RESULTS: 283 women met the diagnosis: 189 patients had PCOS, 24 had hypothyroidism, and 70 had both conditions. Table 1 reports the study variables. Patients with hypothyroidism were significantly older and their TSH was higher than in patients with PCOS, or with both conditions. While the ovarian volume was not different among the groups, AFC AMH and testosterone were significantly lower, and FSH higher. Hypothyroidism was less severe when associated to PCOS.

CONCLUSIONS: Although hypothyroidism may cause menstrual irregularities and may mimic PCOS, when isolated it is associated with a decreased ovarian reserve. However in patients with concomitant PCOS hypothyroidism was not associated with decreased ovarian reserve. These results could help in counseling patients undergoing fertility treatments.

References:

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THE RELATIONSHIP BETWEEN BODY MASS INDEX AND ANTI-MULLERIAN HORMONE LEVELS IN REPRODUCTIVE OUTCOMES FOR WOMEN UNDERGOING INFERTILITY TREATMENT: IS THERE A NEGATIVE CORRELATION?. M. Pasternak, a P. Christos, a Z. Rosenwaks, b S. Spandorfer, c M. V. Thompson, c Well Cornell Medical College, New York, NY; bReproductive Medicine, Physician, New York, NY; cCornell University Medical College, NYC, NY; Center for Reproductive Medicine, Weill Cornell Medical College, New York, NY.

OBJECTIVE: The primary objective of this study is to identify whether a correlation exists between body mass index (BMI) and IVF outcomes in reproductive-age women without polycystic ovarian syndrome (PCOS), when stratified by anti-Mullerian hormone (AMH) levels.

DESIGN: This is a retrospective single institution study. Demographics of patients undergoing IVF from 2012-2015 for a total of 12,526 IVF cycles were recorded.

MATERIALS AND METHODS: A total of 12,020 women were included in this study; those with a diagnosis of PCOS were excluded. BMI was subdivided into 3 categories, <24.99, 25-29.99, and ≥ 30. AMH values were classified as low if <1.0, and normal if ≥1.0. Patients were separated into two age groups, <35yo and ≥35yo. Specific parameters explored include number of oocytes and percent mature oocytes at retrieval, estradiol levels at time of trigger, and clinical pregnancy rates.

RESULTS: Highly significant differences were noted in IVF outcomes when stratified by BMI and AMH. We first established that there was a significant association between lower AMH levels and increasing BMI across age demographics (P<0.03). In patients <35yo, those with low AMH were noted to have a significantly lower median percent and number of mature oocytes retrieved as their BMI increased (P<0.002). Women <35yo with normal AMH levels were also found to have a significant decrease in clinical pregnancy rates with increasing BMI (38.6% in BMI<24.99, 36.6% in women BMI 25-29.99, and 23.7% in women with BMI ≥30; P<0.002). Across all BMI categories, women ≥35yo with low AMH had significantly lower median number of mature oocytes and total oocytes retrieved, estradiol levels at the time of IVF trigger, and clinical pregnancy rates compared to those with normal AMH (P<0.0001).

CONCLUSIONS: Despite the speculated negative impact of obesity on AMH and reproductive function, little is known about the effect of this relationship in non-PCOS patients on IVF cycles and pregnancy outcomes. Previous data presented by our institution noted a negative correlation between BMI and AMH in both age groups, with overweight and obese patients having significantly lower AMH levels compared to their normal BMI counterparts. This was especially pronounced in women ≥35yo. However when exploring IVF outcomes, the effects of BMI stratified by AMH levels were consistent in both age groups, but only significant in women <35yo. These findings suggest that while increasing adiposity in the older age group may impact an already diminishing ovarian reserve, the clinical effects of obesity on IVF outcomes, especially clinical pregnancy rate, are more pronounced in our younger patients.

TABLE 1. Study variables

<table>
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<tr>
<th>Variable</th>
<th>PCOS (n=189)</th>
<th>HYPOHYTHYROIDISM (n=24)</th>
<th>PCOS-HYPOHYTHYROIDISM (n=70)</th>
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<td>Ovarian Volume (cm3)</td>
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<td>2.84</td>
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<td>AMH (ng/ml)</td>
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<td>1.27</td>
<td>5.11</td>
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<td>8.87</td>
<td>6.18</td>
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<td>Total TESTOSTERONE (ng/dl)</td>
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<td>20.83</td>
<td>34.73</td>
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</table>
ELEVATED ANTI-MULLERIAN HORMONE AS A PREDICTOR OF SPONTANEOUS PRETERM DELIVERY FOR WOMEN WITH POLYCYSTIC OVARY SYNDROME.

J. Y. Hsu, K. E. James, C. L. Bornmann, P. K. Donahoe, D. Pepin, M. Sabatini. Reproductive Endocrinology and Infertility, Washington University, St. Louis, MO; Pediatric Surgical Research Laboratories, Massachusetts General Hospital, Boston, MA.

OBJECTIVE: To investigate the association of elevated AMH levels with risk of spontaneous preterm delivery (PTD) in pregnancies conceived with in vitro fertilization (IVF).

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: A retrospective chart review was conducted of all consecutive cases of patients undergoing IVF at the Massachusetts General Hospital Fertility Center between January 2012 and October 2016. Demographic and clinical information pertaining to infertility evaluation, treatment, and pregnancy outcome was extracted from the electronic medical record. Cycles were included if they resulted in pregnancy, documented an AMH level within 1 year prior to IVF, and had complete information about pregnancy outcome (e.g. gestational age at birth, mode of delivery, and obstetric complications). Cycles were excluded if they utilized oocyte donation or gestational carrier, resulted in multiple gestation, suffered pregnancy loss prior to 20 weeks gestation, or were missing information. Medically indicated PTDS were also excluded from the analysis. Preterm was defined as delivery prior to 37 weeks. The study was approved by the Partners Healthcare Institutional Review Board.

Recognizing that the exposure variable of AMH level is highly skewed for patients with polycystic ovary syndrome (PCOS), the statistical analysis was stratified by diagnosis of PCOS. Chi-squared, Mann-Whitney, and t-test were used as appropriate. A p-value of < 0.05 was considered significant.

RESULTS: 432 IVF cycles met criteria for analysis. Within the group of women with PCOS (n=44), those who delivered preterm had substantially higher AMH (18 vs. 6.8 ng/mL, p = 0.004), were younger (31.9 vs. 33.9 years old, p = 0.049) and more overweight (BMI 29.3 vs. 25.7, p = 0.029) than those who delivered at term.

At the highest AMH values, preterm deliveries predominated. Two-thirds of women with AMH above the 75th percentile, or AMH of 13 ng/mL, delivered preterm. Of the 4 women with AMH above the 90th percentile, or AMH of 2.25 ng/mL for term and 2.55 ng/mL for preterm (p = 0.392), those who delivered at term.

CONCLUSIONS: In women with PCOS undergoing IVF, substantially elevated AMH levels are highly associated with PTD. Further studies are needed to confirm this association and to elucidate the underlying mechanisms contributing to PTD.

P-352 Tuesday, October 9, 2018 6:30 AM

LETROZOLE VERSUS CLOMIPHENE CITRATE FOR UNEXPLAINED INFERTILITY: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED, CONTROLLED TRIALS.

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OBJECTIVE: To investigate the clinical effectiveness of letrozole (LTZ) versus clomiphene citrate (CC) for ovulation induction in couples with unexplained infertility.

DESIGN: Systematic review and meta-analysis.

MATERIALS AND METHODS: We systematically searched multiple electronic databases of published literature (Ovid-Medline, Embase, Scopus, Cochrane Database of Systematic Reviews, Cochrane Register of Controlled Trials, Database of Abstracts of Reviews of Effects, and clinicaltrials.gov) for concepts of unexplained infertility, LTZ, CC and clinical outcomes including pregnancy and live birth. All searches were limited to English and completed in February 2018. Study inclusion criteria were randomized controlled trials comparing CC to LTZ in couples with unexplained infertility, documented infertility for at least one year, with at least one patent tube on hysterosalpingogram, confirmed ovulation and normal semen analysis or at least 5 million sperm per milliliter after wash prior to intrauterine insemination. Heterogeneity was assessed qualitatively using the Cochrane Q test and quantified using the Higgin’s I2. Random effects models were used to obtained pooled relative risks with 95% confidence intervals.

RESULTS: Of the initial 804 results obtained from the search, 17 full text articles were retrieved after exclusions with 8 randomized controlled trials including 2,647 couples with unexplained infertility met inclusion criteria. All studies had low risk of bias. There was significant heterogeneity between studies (I2 > 60.8%), with medication dose and duration varying among studies. Overall, there were no statistically significant differences in clinical outcomes between patients treated with LTZ compared to CC including clinical pregnancy (pooled RR 1.08 95% CI 0.85-1.36), spontaneous miscarriage (pooled RR 0.92 95% CI 0.61-1.38), twin gestation (pooled RR 0.81 95% CI 0.39-1.68) or live birth (pooled RR 0.94 95% CI 0.83-1.08). When stratified by LTZ dose, the lowest dose of LTZ (2.5mg) appeared to result in a higher clinical pregnancy rate per cycle compared to CC (RR 1.89 95% CI 1.41-2.55). Adverse events were inconsistently reported, but incidence of ectopic pregnancy and congenital anomalies were similar between groups.

CONCLUSIONS: Our findings suggest LTZ is as effective as CC for ovulation induction in couples with unexplained infertility. However, LTZ appears to result in a higher rate of clinical pregnancy per cycle at the lowest starting dose of 2.5 mg.

References:

Supported by: 5T32HD055172-09
which is at increased risk for preeclampsia. The aim of this study is to deter-
mine whether differences exist in these factors in IVF pregnancies with and
without ED, compared to spontaneous pregnancies.

**DESIGN:** Case control study

**MATERIALS AND METHODS:** Residual early second trimester maternal serum samples were available from women having prenatal screening at a single center, from 1/2015 to 12/2016. 57 third-party ED preg-
nancies were identified. Each ED case was matched to two control samples from spontaneously conceived pregnancies (n=114), and one control sample from a non-ED IVF pregnancy ("IVF", n=57). All controls were matched for gestational age and duration of frozen storage. All samples were from singleton pregnancies and had been tested for maternal serum alpha-feto-
protein (AFP), unconjugated estriol (uE3), human chorionic gonadotropin
(hCG) and inhibit A (inhA) prior to storage. Samples were retrieved from
storage for measurement of PI GF and sVEGFR-1 levels via ELISA. Samples
were tested in duplicate without operator knowledge of group assignment.
Maternal serum levels of all markers were corrected for gestational age ef-
fects by conversion to multiples of the median (MoM). Levels of each marker
were then analyzed for differences among the study groups using an analysis
of variance (ANOVA) with pair wise p-values adjusted for multiple com-
parisons.

**RESULTS:** SVEGFR-1 levels in ED subjects were 18.4% higher than
spontaneous controls, and 16.5% higher than non-ED IVF subjects. However,
these differences did not reach statistical significance (p=0.10). No signifi-
cant differences were noted in PIGF or uE3 levels when comparing the three
groups. ED pregnancies were remarkable in that AFP levels were signifi-
cantly elevated compared to non-IVF (p < 0.01) and IVF (p<0.05) levels. Both
IVF and ED subjects had greater levels of inhA than non-IVF controls
(p<0.01); and ED subjects had significantly higher levels of inhA than IVF
controls (p<0.01). HCG levels were significantly elevated in ED pregnancies
compared to non-IVF controls (p<0.05) however no significant difference
was noted in ED vs IVF pregnancies.

**CONCLUSIONS:** Second-trimester sVEGFR-1 and PIGF levels were not
significantly altered in ED pregnancies, when compared to IVF or sponta-
neous pregnancies. Our data supports previous findings that ED pregnancies
have significantly greater levels of AFP, inhA, and hCG–markers which have
been associated with placental disease. Further study is recommended to
correlate these markers with elevated rates of placental ischemia in the ED
population.

**P-355 Tuesday, October 9, 2018 6:30 AM**

**TRANSCRIPTOME ANALYSIS OF ENDOMETRIAL STROMA DERIVED FROM HUMAN INDUCED PLURIPOTENT STEM CELLS REVEALS NOVEL TRANSCRIPTION FACTORS ESSENTIAL FOR ENDOMETRIAL DEVELOPMENT.** A. Kohlmeier, K. Miyazaki,
B. D. Yilmaz, S. Bulun. Obstetrics and Gynecology, Northwestern Univer-
sity Feinberg School of Medicine, Chicago, IL.

**OBJECTIVE:** Transcription factors (TFs) play a crucial role in embryonic development and tissue homeostasis of the endometrium. Abrupt TF expression has been associated with the pathogenesis of various endometrial diseases including endometriosis. Our lab recently established a 14-day pro-
tocol during which human induced pluripotent stem cells (hiPSCs) are differ-
entiated into the coelomic epithelium, Mullerian duct (MD), and endometrial stromal cells (ESC). Our objective was to identify novel TFs which play crucial roles in endometrial development by comparing transcriptomic changes during differentiation of hiPSC into ESCs.

**DESIGN:** Prospective Experimental Design

**MATERIALS AND METHODS:** In our hiPSC differentiation model, Day 8 (D8) corresponds to MD with increased expression of ISL1 and PAX2; day 14 (D14) corresponds to progesterone receptor (PGR) positive ESCs which unmatured in vitro decidualization. We analyzed RNA-Seq data comparing D14 and normal endometrial stromal cells (NESCs) relative to D8 to deter-
mine commonly upregulated or downregulated TFs. We validated upregula-
tion or downregulation of selected TFs via RT-qPCR. We further compared
mRNA expression of these genes in NESCs and endometriotic stromal cells
from ectopic lesions (OESCs) to evaluate any aberrant expression.

**RESULTS:** Nineteen TFs were commonly upregulated, and 70 TFs were
commonly downregulated in D14 and NESCs relative to D8. We validated the
expression of 15 TFs by RT-qPCR. Commonly upregulated TFs included
PGR, Cyclic AMP Response Element Binding Proteins (CREBs) and
FOSL1, all of which are necessary for decidualization in response to ovarian
hormones. Upregulated TFs also included TFAP2A, a gene that plays a
crucial role in TGF-beta signaling, COUP-TF1, a protein essential for sup-
pression of steroidogenesis in healthy endometrium and VDR, Vitamin D3
receptor, which has shown to be downregulated in recurrent pregnancy
loss. Additionally, mRNA expression of many upregulated TFs, including
FOSL1 and GLI1, were higher in NESCs as compared to OESCs. Downregu-
lated TFs included TAL1 and KLF1, which have a roll in hematopoietic
differentiation, as well as HNF4A and HMGB3, which are known to be
important for the development of endodermal structures and maintaining
stem cell properties, respectively. Interestingly, TAL1 and HNF4A mRNA
levels were significantly higher in endometriotic cells as compared to NESCs
(p-value <0.01).

**CONCLUSIONS:** Differentially expressed TFs in D14 and NESCs rela-
tive to D8 included many genes which play essential roles in stem cell differ-
entiation and hormone responsiveness. Furthermore, expression of some of
those TFs was altered in OESCs compared with NESCs. These results sug-
ggest that the pathogenesis of endometriosis may be associated with an altered
pathway during the development of the endometrium. The possible role of
those TFs remains to be clarified to identify novel therapeutic targets in
the future.

Support: National Institutes of Health grant R37-HD36891

**P-356 Tuesday, October 9, 2018 6:30 AM**

**TRANSCRIPTOME ANALYSIS REVEALS EXPRESSION PROFILE OF SECRETION PROTEINS IN HUMAN ENDOMETRIAL STROMAL CELLS (HENSCS) DURING DECIDUALIZATION.** S. Choo, K. Jung, Y. Choi, J. Kim, H. Lee, Y. Chai, M. Chung. ‘Fertility Research Institute, Seoul Rachel Fertility Center, Seoul, Korea, Republic Of;’Hanyang University, An-
san, Korea, Republic Of.

**OBJECTIVE:** Decidualization of human endometrial stromal cells (hEnSCs) is essential for successful uterine implantation. Decidual hEnSCs
are a prerequisite to trophoblast invasion and placenta formation. To evaluate the effects of secreted proteins from decidual hEnSCs, we investigate the transcriptome of immortalized hEnSCs.

**DESIGN:** Experimental study.

**MATERIALS AND METHODS:** Immortalized hEnSCs (T-hEnSCs) were
cultured in DMEM/F12 supplemented with 1% ITS + Premix, 500 ng/ml pu-
romycin, 100 U/ml penicillin/100 μg/ml streptomycin and 10% charcoal-
stripped fetal bovine serum (FBS). Decidualization was induced by incu-
bating T-hEnSCs in DMEM/F12 supplemented with 2% charcoal-stripped
FBS, progesterone (MPA) and dibutyryl-cAMP (dbcAMP) for 6 day. To determine the assessment of the decidualization status, we performed expres-
sion analysis of major decidual marker genes, PRL and IGFBP1. In this study, we evaluated the gene expression profile using RNA-seq and their function using migratory potential of decidual T-hEnSCs.

**RESULTS:** Using RNA-seq, we identified some target genes related to the induc-
tion pattern of extracellular matrix organization and cell adhesion in decidual T-hEnSCs. Also, transcription levels of secretion proteins including
CCL8, END1, IL33, SHH, and TG were up-regulated in T-hEnSCs in response to MAP and dbcAMP. Furthermore, using pharmacological inhibi-
tors, we showed that decrease of those secreted proteins reduced the migra-
tory response in decidual T-hEnSCs and trophoblast cells.

**CONCLUSIONS:** These data suggest that those secreted proteins may be
important for the differentiative and migratory response in decidual hEnSC and trophoblast cells.

Support by: This work was supported by the Technology development Program (C0531351) funded by the Ministry of SMEs and Startups (MSS, Korea)
OBJECTIVE: The Society for Reproductive Endocrinology and Infertility (SREI) consists of board-certified REIs, who are American Society for Reproductive Medicine (ASRM) members. During REI fellowship, conducting research and writing a thesis play a significant role in training. A manuscript must be submitted prior to graduation, and the thesis comprises a substantial component of the certifying (oral) exam. We hypothesize because of exposure to research that REI physicians will continue to conduct research and contribute significantly to the field of reproductive medicine.

DESIGN: A short questionnaire regarding research was sent to SREI members and a retrospective review of publications of REI physicians was performed.

MATERIALS AND METHODS: A 12 question questionnaire was resent to SREI members by Survey Monkey to improve the previous response rate (18%). Topics included: current research, current and past funding, and topics of research interest. The list of SREI members was ordered by a table of random numbers, and the first 400 were selected to determine the number of PubMed publications: 1) in the last 3 years (2015-2017); 2) in the last 10 years (2008-2017); and 3) the total number of publications by each author.

RESULTS: The total response rate from the questionnaire was 24%, and the results were similar to the previous mailing showing most surveyed members are currently performing research. Analysis of publications was performed in 400/811 current members of SREI. The number of total publications ranged from 0 to more than 400. Findings for publications were as follows: 1) last 3 years—mean ± SD (4.5 ± 9.4) and median (1); 2) last 10 years—mean ± SD (12.9 ± 22.6) and median (4); total publications—mean ± SD (33.0 ± 52.9) and median (13).

CONCLUSIONS: Our survey indicates that a high percentage of board-certified REIs conduct (predominantly clinical) research, often related to their fellow thesis topic. There was a wide range in the numbers of peer-reviewed publications as evidenced by the wide standard deviations, likely reflecting that some physicians predominantly see patients, while others are more actively involved in research. Regardless of their practice, contributions to research continue post fellowship which ultimately translate into quality patient care. We believe that this type of undertaking is unique in that a large sample of physicians within a specialty has been evaluated for research productivity. In conclusion, REI physicians continue to publish significant research important to reproductive medicine, which reaffirms the value of research and contribute significantly to the field of reproductive medicine.

When mean values of metabolite concentrations according follicle size were analyzed, no significant variations were observed (p=0.2057 for 24,25(OH)2D3 and p=0.2626 for 25(OH)D3).

CONCLUSIONS: In this population of healthy and fertile women we confirmed a seasonal stability of 24,25(OH)2D3 and 25(OH)D3 concentrations in the follicular fluid as well as stability during follicular maturation. Both results could be the expression of ovarian auto regulatory and protective mechanisms to cope against environmental metabolic variations. The fact that serum vitamin D fluctuations due to season were not mirrored in the follicles suggests that vitamin D metabolism at specific levels may be required for optimal function and is thus conserved.

Supported by: IVI RMA Fundación IVI

P-358 Tuesday, October 9, 2018 6:30 AM

A COMPREHENSIVE COMPARATIVE TRANSCRIPTOMICAL AND TRANSLATIONAL ANALYSES OF THE IMPACT OF OVARIAN RESPONSE TYPE, STIMULATION PROTOCOL AND MODE OF TRIGGER ON THE LUTEAL FUNCTION. G. Bildik, A. Seyhan, K. Yakín, B. Ataş, B. Urman, O. Oktem, Koc University Graduate School of Health Sciences, Istanbul, Turkey; Women’s Health Center Assisted Reproduction Unit, American Hospital, Istanbul, Turkey; Obstetrics and Gynecology, The Division Reproductive Endocrinology and Infertility, Koc University School of Medicine, Istanbul, Turkey.

OBJECTIVE: We aimed to compare molecular characteristics of the luteal granulosa cells between natural vs. stimulated IVF cycles in good and poor responders.

DESIGN: Translational research study

MATERIALS AND METHODS: Luteinized granulosa cells were obtained from good (n=154) and poor responder (n=64) IVF patients comparable for age, type and dose of gonadotropin and IVF etiology. Good responders (14-15 oocytes) underwent natural (n=22), GnRH agonist (long protocol n=44) and antagonist IVF cycles triggered with rec-hCG (n=46) or GnRH agonist leuprolide acetate (n=42). Poor-responders fulfilling the Bologna criteria consisted of 64 patients undergoing GnRH antagonist protocol triggered with hCG (n=36) or hCG+GnRH agonist (n=28).

RESULTS: In the good-responders, natural cycle (NC) granulosa cells were significantly more viable (88%) compared to the stimulated IVF cycles (66%, 64% and 37% for gonadotropin and antagonist cycles triggered with hCG and agonist respectively, p<0.05). The mRNA expression of steroidogenic enzymes (SCC, stAR, 3B-HSD, 17B-HSD and aromatase), LH receptor and VEGF and in vitro E2 and P productions were comparable between hCG-triggered agonist and antagonist cycles, but significantly higher than NC in the first days of culture. However, on the following days their hormone productions and viability began to decline very rapidly with the most drastic decrease being observed in the agonist triggered cycles. By contrast, NC granulosa cells maintained their viability and produced E2 and P in increasing amounts in culture up to six days. The expression of anti-apoptotic genes (AKT-1, BCL2-L2) were significantly lower, and pro-apoptotic genes (BAD, BID, BAX, Cas3) were significantly higher in the stimulated cycles particularly in the agonist triggered ones compared to NC granulosa cells. Pulse exposure to isoplatin induced apoptosis only in a small fraction of the cells from the NCs whereas the same exposure caused massive apoptosis in the cells of the stimulated cycles (27% vs. 78% respectively, p<0.01). In the poor-responders both viability and steroidogenic activity of the cells were more severely reduced compared to the antagonist cycles of the good-responders. There were no significant differences between hCG and hCG+GnRH agonist triggered cycles in terms of viability, hormone production, VEGF and LH receptor expressions in the luteal granulosa cells.
CONCLUSIONS: Reduced survival and increased apoptosis of luteal granulosa cells leading to defective steroid production in stimulated cycles in comparison to natural ones may at least in part explain why luteal phase is defective and requires exogenous P supplementation for support in these cycles. Also dual trigger does not appear to improve luteal function in the poor-responders.

Supported by: Koc University Research Center for Translational Medicine (KUTTAM), equally funded by the Republic of Turkey Ministry of Development Research Infrastructure Support Program

P-360 Tuesday, October 9, 2018 6:30 AM

STIMULATION WITH RECOMBINANT FSH ACUTELY AND SIGNIFICANTLY INCREASES INHIBIN B AND ESTRADIOL IN WOMEN AFTER GnRH ANTAGONIST TREATMENT: A MODEL TO STUDY FSH REGULATION OF OVARIAN FUNCTION. K. Kuhn, A. Bradford, A. J. Polotsky, OB/Gyn, University of Colorado School of Medicine, Aurora, CO.

OBJECTIVE: Obesity is associated with decreased pituitary output of LH and FSH, inadequate folliculogenesis, and reduced ovarian steroid and peptide hormone production. It remains unclear whether the underlying pathophysiology is related to abnormal hypothalamic-pituitary dynamics, abnormal ovarian environment, or both. The persistent deficit in FSH secretion, despite the lack of restraint and normal pituitary FSH reserve, remains unexplained. FSH pulsatility is challenging to evaluate, given its long half-life and low signal-to-noise ratio, and current analytic methods fail to adequately characterize the hormone secretion dynamics of FSH and its feedback. We hypothesized that both Inhibin B and Estradiol (E2) levels will be acutely increased following exogenous, pulsatile recombinant (r) FSH administration, after a GnRH antagonist blockade. This will establish a model to study ovarian, FSH-stimulated E2 and inhibin secretion, independent of the pituitary, to determine mechanisms underlying the FSH/ovarian dysregulation in obesity.

DESIGN: A pilot, cohort study of 9 normal-weight, cycling women at the University of Colorado School of Medicine.

MATERIALS AND METHODS: Participants (mean age 26.3 ± 4.9 years; BMI 22.2 ± 1.3 kg/m²) underwent frequent blood sampling (q10 min) during a 26-hour overnight study visit. Following an initial baseline 10-hour collection to assess unstimulated LH and FSH secretion, Cetroside (EMD Serono) was administered subcutaneously twice: 3 mg at hour 10 and 0.25mg at hour 16. Frequent blood sampling resumed (hours 16-26) and rFSH (Gonal-F; 30 IU) was given intravenously every hour. LH, FSH and E2 were measured by immunoassays (Centaur XP, Siemens). Functional sensitivity is 0.1 mIU/mL and the intra- and inter-assay coefficients of variation were 3.8 and 4.1%, respectively. Inhibin B was analyzed by ELISA (Beckman Coulter). Functional sensitivity is 10 pg/mL and the intra- and inter-assay coefficients of variation were 1.8 and 4.9%, respectively. Statistical significance was determined by paired t-test.

RESULTS: Normal LH & FSH pulsatility was confirmed for the 10-hour baseline frequent sampling period for all subjects. Administration of Cetroside reliably suppressed endogenous LH and FSH secretion. Repeated boluses of rFSH mimicked endogenous FSH pulses and significantly increased FSH levels over the course of the infusion (p<0.001). Starting from 6 hours post rFSH administration (after 180 IU) we observed a significant increase in both Inhibin B (60%) and E2 (80%) production (p=0.01 and p<0.01 respectively).

CONCLUSIONS: We herein report that exogenous FSH, administered in a pulsatile fashion after GnRH blockade, induced significant, acute increases in both E2 and Inhibin B, in normal weight women. This experimental paradigm can be used to investigate FSH feedback mechanisms in obesity or other environmental insults impacting ovarian function. Supported by: NIH RO1 HD08116201A1

P-361 Tuesday, October 9, 2018 6:30 AM

ANTI-MULLERIAN HORMONE (AMH) AS A PREDICTOR OF MULTIPLE PRONUCLEI (PN) PRESENCE AND OOCYTE MATURITY IN ICSI TREATMENTS. N. Sayme, a M. Kljaic, b D. H. Maas, a

aTeam Kinderwunsch Hannover, Hannover, Germany; bIVF Laboratory, Saarland University Medical Center, Homburg, Germany.

OBJECTIVE: Anti-mullerian hormone is a widely used as a highly sensitive marker of ovarian reserve. Furthermore, AMH shows less intra-individual fluctuation than basal FSH levels and might be a better, cycle-independent parameter. Several hypotheses exist to explain the presence of multiple pronuclei but the underlying causes in human ART-derived zygotes remain unknown. In previous researches, a correlation between AMH level and presence of multiple pronuclei in zygotes was not investigated. Hence, the main question of our research was, does AMH affect the presence of multiple pronuclei in zygotes as well as a number of mature and immature oocytes and pregnancy rate?

DESIGN: This study analyzed the correlation between serum levels of AMH and (i) maternal age, (ii) number of aspirated follicles, (iii) number of retrieved oocytes, (iv) number of retrieved MII oocytes, (v) fertilization rate, (vi) presence of multiple pronuclei (PN) and (vii) pregnancy rate. A total of 113 patients undergoing ICSI cycles at Team Kinderwunsch Clinic Hannover, between August 2017 and November 2017 were included in this study. The assessment included 916 MII oocytes.

MATERIALS AND METHODS: The mean age of the cohort was 34.23 years. Oocyte stimulation was done in antagonist flexible protocol. Serum AMH level was measured by a commercial ELISA kit (AMH Gen II ELISA; manufactured by Beckman Coulter Inc, Brea, CA). Correlations between the data were calculated using logistic regression analysis and Spearman’s correlation test. Statistical significance was defined as p<0.05. All statistical analyses were performed using SAS software.

RESULTS: Obtained results showed an inverse statistically significant correlation between AMH levels and maternal age (R=-0.40 p<0.0001) and a positive correlation between the number of follicles (R=0.55 p<0.0001) as well as the number of cumulus-oocyte complexes (R=0.70 p<0.0001) and mature oocytes (R=0.68 p<0.0001). On the other hand, parameters such as the number of immature oocytes, fertilization or pregnancy rate did not show any significant correlation with AMH levels. Linear regression analysis shows that AMH significantly correlates with the presence of multiple pronuclei in the zygote (p=0.02). The further analysis indicated that the number of zygotes with the presence of multiple pronuclei increased when AMH levels were higher. Out of the 14 patients, which had AMH higher than 6.0 ng/mL, 11 (78.5%) of them had at least two zygotes with the presence of multiple pronuclei increased in AMH less than 1.0 ng/mL only 9 (27.2%) had at least two zygotes with the presence of multiple pronuclei.

CONCLUSIONS: The study results demonstrated that AMH might be a strong marker for quantitative aspects of assisted reproduction in an antagonist protocol. In addition, our results confirmed that increased AMH level is associated with the presence of multiple pronuclei. Obtained results, might serve as a strong base for future studies.

References:
ENDOMETRIUM AND IMPLANTATION

P-362 Tuesday, October 9, 2018 6:30 AM

ENDOMETRIAL MICROPOLYPSIS: PREVALENCE, NUMBER, AND LOCALIZATION IN INFERTILE PATIENTS WITH A HISTORY OF REPEATED IMPLANTATION FAILURE. K. Kitaya, a Y. Takaya, b K. Yamaguchi, c N. Kim, a T. Takeuchi, a H. Matsubayashi, a T. Ishikawa, a bReproduction Clinic Osaka, Osaka City, Japan. cReproduction Clinic Tokyo, Tokyo, Japan.

OBJECTIVE: Endometrial micropolypsis (EMP) is hysteroscopically recognized as subtle multiple protrusive lesions in the uterine cavity with typically 1-2 mm in major axis. EMP was reported to coexist at a high rate with chronic endometritis (CE). While CE is frequently identified in infertile women with unknown etiology, repeated implantation failure (RIF) following in vitro fertilization-embryo transfer (IVF-ET) treatment, and recurrent pregnancy loss, the clinical entity of EMP is largely unknown. The aim of this study was to investigate the prevalence, number, and localization of EMP as well as its association with CE in infertile patients with a history of RIF.

DESIGN: A retrospective case-control study.

MATERIALS AND METHODS: On day 6-12 of the menstrual cycle, fluid hysteroscopy was performed for 314 infertile women who were referred to the clinic because of a history of RIF following transfer of three or more morphologically good cleavage-stage embryos and/or blastocysts (the RIF group) and 1263 infertile women undergoing the first IVF cycle (the control group). The presence of the recorded intrauterine lesions was reviewed and evaluated by at least two experienced gynecologists. Endometrial biopsy and histopathologic examination using immunostaining for an endometrial stromal plasmacyte marker CD138 were simultaneously performed for the RIF group to assess the presence of CE. The data were statistically compared between the RIF group and the control group.

RESULTS: The patients with intrauterine adhesion, uterine cavity deformities, and suspicious endometrial hyperplasia/malignancy were excluded from the study. The detection rate of EMP was higher (relative risk 3.80, 95% confidence interval 2.24 - 6.40, p < 0.0001) in the RIF group (8.5%, 26/307) than in the control group (2.2%, 27/1210). The number of the EMP identified were similar between the two groups (median and range, 8 and 2-26 in the RIF group and 9 and 3-41 in the control group) as well as the localization (diffuse type/fundal type/corpus type, 57.7% (15/26)/11.5% (3/26)/30.8% (8/26) in the RIF group and 66.7% (18/27)/7.4% (2/27)/25.9% (7/27) in the control group). In the RIF group, the detection rate of histopathologic CE was higher (relative risk 1.82, 95% confidence interval 1.32 - 2.51, p = 0.0003) in the EMP cases 65.3% (17/26) than in the non-EMP cases 35.9% (101/281).

CONCLUSIONS: The prevalence of EMP was higher in the infertile women with a history of RIF than in the infertile women undergoing the first IVF cycle. The presence of the recorded intrauterine lesions was reviewed and evaluated by at least two experienced gynecologists. Endometrial biopsy and histopathologic examination using immunostaining for an endometrial stromal plasmacyte marker CD138 were simultaneously performed for the RIF group to assess the presence of CE. The data were statistically compared between the RIF group and the control group.

P-363 Tuesday, October 9, 2018 6:30 AM

FEMALE REPRODUCTIVE TRACT MICROBIOTA IN INFERTILE WOMEN WITH A HISTORY OF REPEATED IMPLANTATION FAILURE. K. Kitaya, a Y. Nagal, b Y. Sakuraba, a T. Ishikawa, a bReproduction Clinic Osaka, Osaka City, Japan. cVarinos Inc., Shinagawa-ku, Tokyo, Japan.

OBJECTIVE: Accumulating studies suggest that intrauterine infection such as chronic endometritis potentially impairs embryo implantation process. The microbial environment in the female reproductive tract (FRT) remains largely unknown in infertile patients. Using next-generation sequencing, we aimed to characterize the microbial composition in the endometrial fluid (EF) and vaginal secretions (VS) in women with a history of repeated implantation failure (RIF).

DESIGN: Preliminary analysis of an ongoing prospective case-control study.

MATERIALS AND METHODS: Twenty-eight infertile women with a history of RIF (defined as serial negative serum pregnancy tests following transfer of five or more morphologically good blastocysts) were enrolled in the study under a given informed consent. On day 6-8 after LH surge in natural cycle and hCG trigger in oocyte pick up cycle, or day 5 following initiation of luteal support in hormone replacement cycle, the paired EF and VS samples were obtained. Carefully avoiding contamination, extracted genomic DNA was pyrosequenced for V4 region of 16S ribosomal RNA using next-generation sequencer. The sequences were clustered to operational taxonomic units (OTU) and assigned to bacterial taxonomy using QIIME. Further alpha- and beta-analyses were performed at a rarefied depth of 3,800 sequences per sample to correct for differences across the samples. The results were statistically compared between VS and EF samples.

RESULTS: Mean OTU clustered sequences were 31,550 in EF and 38,403 in VS. The number of the microbial species observed was higher in EF (mean ± SE, 17.632 ± 8.263) than in VS (mean ± SE, 7.539 ± 2.139). Lactobacillus-dominant (90% or more) microbiota was detected at a similar level between EF (n = 17, 65.3%) and VS (n = 20, 76.9%).

CONCLUSIONS: To our best knowledge, this is the first study investigating microbiota in paired EF and VS samples in women with a history of RIF. EF samples contained more diverse microbial species compared with VS. While the proportion of each species were at a similar level between EF and VS within the same individual, there was a marked variance between the individuals.

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ENDOMETRIAL LEUKEMIA INHIBITING FACTOR (LIF) AND INTEGRIN αV/3 (ITG αVβ3) EXPRESSION AFTER KISSPEPTIN TRIGGER OF OVULATION IN MICE. A. O. Abdelkareem, a,b A. S. Ait-Allah, a S. M. Rasheed, a Y. A. Helmy, a M. S. Iews, b,b B. Peng, b M. A. Bedaiwy, c Obstetrics and Gynecology, Sohag University, Sohag, Egypt. cObstetrics and Gynecology, University of British Columbia, Vancouver, BC, Canada. cObstetrics and Gynecology, South Valley University, Qena, Egypt.

OBJECTIVE: Kisspeptin (KISS-1) is a hypothalamic neuropeptide that regulates hypothalamic pituitary ovarian axis function. Pre-ovulatory rise in serum KISS-1 leads to luteinizing hormone (LH) surge that triggers final oocyte maturation and ovulation. Exogenous trigger of ovulation is used in ovarian hyper-stimulation for some infertility cases. KISS-1 and its receptor (KISS-1R) are also expressed in the endometrium. Previous studies in mice showed increased endometrial KISS-1/KISS-1R expression around time of implantation with suggested implication in successful implantation (1,2).

In this study, we evaluated the expression of two important endometrial implantation marker genes, LIF and ITG αVβ3 after using KISS-1 as a trigger for ovulation compared to human chorionic gonadotrophin (hCG) or placebo in super-ovulated mice.

DESIGN: Experimental animal study.

MATERIALS AND METHODS: A total of 15 female (C57BL/6j) mice were super-ovulated via intraperitoneal injection of 5 IU pregnant mare serum gonadotrophin (Day 1). 48 hours later, mice were injected with either 1 x phosphate buffer saline (Group A), 5 IU hCG (Group B), or 3 nmol KISS-1 (Group C) (5 mice/group). On Day 7, mice were euthanized and uteri were excised. Paraformaldehyde-fixed paraffin-embedded sections of mouse uteri were cut and stained by Immunohistchemistry using 2 specific antibodies against LIF and ITG αVβ3. Slides were then scored for abundance and intensity of staining in both glandular epithelium (GE) and stromal cells (SCs) of endometrium using histoscore (H-score) method. Data were analyzed using Kruskal-Wallis test followed by Mann-Whitney U test for pairwise comparisons.

RESULTS: All ranks of the mean H-scores of group C were higher compared to both group B and group A in a descending manner (Table 1).

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TABLE 1. Results of Kruskal-Wallis test comparing ranks of mean H-scores of different groups.

<table>
<thead>
<tr>
<th></th>
<th>LIF (GE)</th>
<th>LIF (SCs)</th>
<th>ITG αV/Î³3 (GE)</th>
<th>ITG αV/Î³3 (SCs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean rank</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>4.8</td>
<td>4.4</td>
<td>6.0</td>
<td>3.4</td>
</tr>
<tr>
<td>Group B</td>
<td>7.2</td>
<td>6.6</td>
<td>7.4</td>
<td>10.0</td>
</tr>
<tr>
<td>Group C</td>
<td>12.0</td>
<td>13.0</td>
<td>10.6</td>
<td>10.6</td>
</tr>
<tr>
<td>P value</td>
<td>0.034</td>
<td>0.007</td>
<td>0.248</td>
<td>0.018</td>
</tr>
</tbody>
</table>

LIF expression was significantly higher in both GE and SCs of group C compared to group A, but only higher in SCs when compared to group B (p = 0.009). On the other hand, ITG αV/Î³3 expression was significantly higher in SCs of group C compared to group A only, with no difference in GE among the 3 groups. Additionally, we noticed increased vascularity and size of uteri excised from mice in group C compared to groups A and B.

CONCLUSIONS: Our study shows a tendency of higher expression of some implantation markers in mice endometrium after kisspeptin trigger of ovulation compared to hCG or placebo. Further studies are needed to correlate these results with pregnancy outcomes.

References:

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INTRAUTERINE ADMINISTRATION OF PERIPHERAL MONONUCLEAR CELLS IN RECURRENT IMPLANTATION FAILURE: A SYSTEMATIC REVIEW AND META-ANALYSIS. K. Yakin,1 O. Oktem,1 B. C. Urum.1
1Obstetrics and Gynecology, Koç University School of Medicine, Istanbul, Turkey; 2Koc University, Istanbul, Turkey; 3American Hospital, Istanbul, Turkey.

OBJECTIVE: Is intrauterine administration of peripheral blood mononuclear cells (PBMC) associated with improved live birth rates (LBR) in women with recurrent implantation failures (RIF)?

DESIGN: A systematic review and meta-analysis of published clinical trials that studied women undergoing any form of ART (IVF, ICSI) who had intrauterine administration of PBMC with or without hCG culture before fresh or frozen embryo transfer. No adjuvant medical therapy should be given in any trial. The primary outcome was live birth rate and the secondary outcome parameters were clinical pregnancy and miscarriage rates.

MATERIALS AND METHODS: Databases searched included MEDLINE, EMBASE, Scopus and Cochrane Central Register of Controlled Trials. Two randomized controlled trials and three cohort studies matched the inclusion criteria. Eligible studies were published between 2006 and 2017 and the sample sizes ranged from 35 to 663 patients. Odds ratio (OR) from individual studies were analysed using random effects models.

RESULTS: Live births were reported in four of the included studies (including 1119 patients). There was no difference in LBR between the PBMC treated and control groups (OR: 1.65, 95% CI: 0.84 - 3.25; p = 0.14; heterogeneity: I²:66%). All five of the included studies (including 1173 patients) reported clinical pregnancy rates which were found to be improved in women who had been given intrauterine PBMC before embryo transfer compared to those who had not (OR: 1.65, 95% CI: 1.30 - 2.10; p = 0.001). Two studies (including 295 patients) reported miscarriages following treatment, showing comparable rates in women treated with PBMC and controls (OR: 0.21, 95% CI: 0.02 - 2.43; p = 0.21). Cochrane’s and ROBINS-I tools were used to assess the quality of the included studies, suggesting low to moderate risk of bias.

CONCLUSIONS: Circulating mononuclear cells might be playing a critical role in the immune modulation of intrauterine environment favouring pregnancy. However, the current data shows that administration of PBMC with or without hCG culture into the uterine cavity before fresh or frozen-thawed embryo transfer does not improve LBR in women with RIF. A well designed randomized controlled trial with an optimal sample size should be considered to investigate the benefits of intrauterine PBMC administration.

References:

IMPACT OF VITAMIN D DEFICIENCY ON IVF OUTCOME IN ASIAN POPULATIONS. A. Mitra, S. Kundu, J. Bhattacharya, M. Bhattacharjee. Obstetrics and Gynecology, A.H IVF & Infertility Research Centre, Kolkata, India.

OBJECTIVE: Vitamin D is well-known for its function in promoting bone mineralization and maintaining calcium and phosphorus homeostasis. Recent studies show that in addition to sex steroid hormones, vitamin D also modulates reproductive processes in women and men. It has been also reported that the active form of Vitamin D (calcitriol) plays a huge role in implantation. Our aim of the study is to investigate the effect of vitamin D deficiency on IVF outcome in terms of ovarian reserve, embryo quality and clinical pregnancy rate.

DESIGN: This prospective cross-sectional study was conducted at A. H IVF & Infertility Research Centre, India from Jan-2016 to Dec-2017.

MATERIALS AND METHODS: 220 women with Asian origin, who all underwent IVF-ET/PET treatment, were enrolled in the study after signing written consent forms. All of them provided a serum sample for 25-hydroxy-vitamin D [25(OH) D] measurement and endocrine profiling at the time of cycle preparation. Vitamin D deficiency was defined as serum 25(OH)-D level <20 ng/mL, insufficiency as 20 < [25(OH) D] <29 ng/mL and replete status as serum 25(OH)-D >30 ng/mL. The impact of vitamin D deficiency was investigated on reproductive outcomes (ovarian reserve, embryo quality and clinical pregnancy rate).

RESULTS: Study population was divided into 3 groups according to vitamin D status: 40.92% had vitamin D deficiency (group 1), 22.72% had vitamin D insufficiency (group 2) and 36.36% had replete status of vitamin D (group 3). The 3 groups were comparable in terms of age, type of infertility, basal hormonal status and ovarian stimulation parameters. Ovarian response across the groups was found to be statistically different among the groups (1,2 & 3), but number of retrieved mature oocytes tended to be higher in group 3 than group 1, though it was statistically insignificant. Subgroup analyses showed that the group of women with the highest serum levels (>30 ng/mL) had the highest chances of pregnancy, as a significant difference has been found in clinical pregnancy rates among both the groups (1 & 3). The rates of clinical pregnancies were 40% (n=32) and 27.7% (n=25), respectively (P = 0.02). No significant difference had been found in pregnancy outcome between group 2 and 3 (p=0.05).

CONCLUSIONS: Vitamin D has an impact in implantation, embryo quality and clinical pregnancy rate in patients undergoing in-vitro fertilization, as our study showed that patients with vitamin D deficiency had significantly lower clinical pregnancy rates, compared to patients who were replete in vitamin D levels as the lining of the uterus produces calcitriol when the embryo has entered the uterine cavity just before implantation is due to take place. So, it is highly recommended to measure the vitamin D levels before starting any treatment.
undergoing any ART procedure and if required vitamin D supplementation should be considered prior to the treatment to increase the success rate.

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OBJECTIVE: Homozygous GJB2 mutations are a common cause of hereditary hearing loss. The GJB2 gene encodes connexin 26 (CX-26), a component of gap junctions in uterine luminal and glandular epithelium, required for endometrial receptivity. In the mouse model, targeted inhibition of uterine gap junctions has been shown to disrupt embryo implantation. Gap junctions have been shown to mediate the adaptive response to pregnancy, Syncytiotrophoblast cells are connected by CX-26 containing gap junctions. Whether a partial loss of GJB2-encoded CX-26 activity impacts human embryo implantation and placentation is currently unknown. The objective of our study was to examine the effect of GJB2 mutation heterozygosity on endometrial thickness and frozen embryo transfer (FET) cycle outcome.

DESIGN: Retrospective, cohort.

MATERIALS AND METHODS: Patients underwent expanded carrier screening and single, euploid FET from 2012-2018. Demographics and cycle outcomes were compared between GJB2 carriers and controls. Student's t-test, chi-square test, and multivariate linear and binary logistic regression models were used.

RESULTS: GJB2 carriers (n = 53, 88 FET cycles) were compared with non-carriers (n = 289, 437 FETs) (Table). Controlling for age and BMI, endometrial thickness was not modified in GJB2 carriers (β = 0.06, p = 0.8). Controlling for age, BMI, endometrial thickness, and day of trophectoderm biopsy implantation (OR 1.1 [0.64-1.72], p = 0.85) was not affected in carriers. Odds of ongoing pregnancy were increased in carriers (OR 1.9 [1.03-3.4], p = 0.04). In the same multivariate model, clinical pregnancy loss (OR 2.0 [0.81-4.72], p = 0.1) and live birth (OR 0.8 [0.41-1.6], p = 0.5) were similar among groups. Gestational age (β = 0.06, p = 0.9) and infant birthweight at delivery (β = 19.8, p = 0.87) were not modified in carriers.

CONCLUSIONS: GJB2 carriers can be reassured that they are not at increased risk for implantation failure, preterm delivery, or reduced infant birthweight. Partial activity of the GJB2 gene appears to generate enough CX26 to meet a critical threshold for normal gap junction activity and/or functional redundancy among connexin isoforms. Interestingly, GJB2 carriers were found to have increased odds of ongoing pregnancy, which may reflect a possible heterozygote advantage. As more patients undergo expanded carrier screening, larger studies will assess whether a possible compensatory mechanism that benefit implantation and pregnancy maintenance in GJB2 carriers is reproducible.

References:

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THE IMPACT OF NUMBER OF EMBRYOS TRANSFERRED ON PLACENTAL MORPHOLOGY. A. L. Harris, K. M. Basnet, C. R. Sacha, I. Souter, K. James, D. J. Roberts, T. L. Toth, Obstetrics & Gynecology, Wright Patterson Air Force Base, Wright-Patterson AFB, OH; "Massachusetts General Hospital, Boston, MA; "OBGYN, University of Massachusetts General Hospital, Boston, MA; "Massachusetts General Hospital Fertility Center and Harvard Medical School, Saint Barthelemy; "Pathology, Massachusetts General Hospital, Boston, MA; "Obstetrics and Gynecology Beth Israel Deaconess Medical Center and Harvard Medical School, Boston IVF, Boston, MA.

OBJECTIVE: To evaluate differences in placental morphology from infants conceived based on the number of embryos transferred, given that higher number of embryos transferred has been associated with negative neonatal outcomes.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: A retrospective cohort study from 2004 through 2015 of live births resulting from IVF with autologous oocytes. Gross and histologic placental specimens were examined. The placentas were divided by number of embryos transferred: single (SET), double (DET) and multiple („›3, MET) embryo transfer. Morphologic pathology was categorized into anatomic (e.g. cord malinsertion or circumvallate), infectious (e.g. chorioamnionitis), inflammatory (e.g. villitis of unknown etiology, deciduitis), and vascular/thrombotic (placental abruption, intervillos thrombus, maternal and fetal vascular malperfusion). T-tests and Chi square were used for analysis with 95% confidence intervals (CIs).

RESULTS: A total of 848 placentas were reviewed: 66% from two embryo transfer and 17% from both single and multiple embryo transfers. The majority of patients in all groups were Caucasian (75%) and the mean age increased with the number of embryos transferred. SET resulted in 98% singleton gestations as compared to 58% in the DET group and 68% of MET (p < 0.001). While gestational age was similar in SET and MET (38.5 and 38.2 weeks respectively), the gestational age was 37.2 weeks in DET (p < 0.001). SET was associated lower placental weights and higher rates of infectious etiologies. While MET was associated more inflammatory pathologies in than in the SET or DET (p=0.2).

CONCLUSIONS: There are significant associated with inflammatory and infectious etiologies based on number of embryos transferred. This may lead to differences in number of infants born and gestational age.

References:

Supported by: Funding was provided by a Vickery Grant from the Department of Pathology at the Massachusetts General Hospital and institutional funds from the Department of Obstetrics and Gynecology at Massachusetts General Hospital.

Placental Morphologies by Number of Embryos Transferred

<table>
<thead>
<tr>
<th></th>
<th>SET (n=116)</th>
<th>DET (n=486)</th>
<th>MET (n=135)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placental Weight (grams)</td>
<td>452.9</td>
<td>565.2</td>
<td>533.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Anatomic</td>
<td>71 (61%)</td>
<td>239 (49%)</td>
<td>73 (54%)</td>
<td>0.057</td>
</tr>
<tr>
<td>Infectious</td>
<td>12 (10%)</td>
<td>64 (13%)</td>
<td>29 (21%)</td>
<td>0.021</td>
</tr>
<tr>
<td>Vascular/Thrombotic</td>
<td>38 (33%)</td>
<td>105 (22%)</td>
<td>27 (20%)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

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PLACENTAL GENE EXPRESSION IN MISCARRIAGE: A CASE-CONTROL STUDY. C. A. Marsh, C. Mason, S. Paul, OBGYN, University of Kansas, Overland Park, KS; OBGYN, University of Kansas, Kansas City, KS; Pathology, University of Kansas, Kansas City, KS.
OBJECTIVE: Although miscarriage is the most common pregnancy complication, the etiology is often unexplained. In this study, transcriptomes and miRNomes of first trimester placental villi were examined for differential expression by gestational age in miscarriage and terminated pregnancies.

DESIGN: We performed a prospective case-control study on women, aged 18-45. Cases were defined as women who experienced first trimester miscarriage and controls were women who underwent elective termination of pregnancy in the first trimester. Cases were further categorized as recurrent miscarriage loss (RPL) defined as >2 total miscarriages and miscarriage (first miscarriage). Controls were categorized as: Group 1 (termination <7 weeks, Group 2 (termination >7 weeks) and cases were categorized as: Group 3 (miscarriage <8 weeks), Group 4 (miscarriage >8 weeks). Specimens from aneuploid products of conception were excluded from analysis.

MATERIALS AND METHODS: Placental villi were collected at time of dilation and curettage with specimen placed on ice for immediate transport to lab for processing. The placental villi were isolated under a stereomicroscope for differential reproduction technology cycles. Hum Reprod 2015; 30(12):2846-2852. LINKED TO ENDOMETRIAL THICKNESS IN A RETROSPECTIVE COHORT STUDY OF 8120 ASSISTED REPRODUCTION TECHNOLOGY CYCLES. HUM REPROD 2015; 30(12):2846-2852.

RESULTS: Control specimens had clustered gene expression which globally differed from case specimens. Cluster patterns also differed by gestational age. Quantitative difference in expression of genes was seen among cases vs control samples. Several genes including INHBB, MMP10, IGFBP1, OBPA2, PRL, and TMEM252 were dramatically upregulated (>10-fold) in miscarriage samples compared to controls.

CONCLUSIONS: Global placental gene expression is different between women with normal placentaion and those who had miscarriage. Although placental gene expression between women with RPL and first miscarriage were not statistically different, this may be due to sample size. For future directions, we use human trophoblastic stem cells to establish patient specific cell lines and test molecular regulation.

References:

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ENDOMETRIAL, BUT NOT OVARIAN RESPONSE AF- FECTS CLINICAL OUTCOMES AND CAN BE IMPROVED BY PROLONGED PITUITARY DOWN- REGULATION IN PATIENTS WITH THIN AND ME- DIUM ENDOMETRIUM. J. Song1, K. Qian2,3, Reproductive Medicine Center, Tongji Hospital, Huazhong University of Science and Technology, Wuhan, China; 2Reproductive Medicine Center Tongji Hospital Tongji Medical College Huazhong University of Science, Wuhan, China.

OBJECTIVE: To study the effect of ovarian and endometrial response on live birth rates in young normal and high responders and prolonged pituitary down-regulation on endometrial receptivity and clinical outcomes in patients with different endometrial thickness.

DESIGN: Retrospective analysis of cycles performed between January 2013 and December 2017.
MATERIALS AND METHODS: Women with age ≤35 years, basal serum FSH on day 2-5 < 10 IU/l and with ≥4 retrieved oocytes were included. Serum estradiol (E₂) levels on the HCG day in patients underwent first short GnRH-a long protocol were classified into four groups: group1 (<3000pg/ml); group2 (3000-5000pg/ml); group3 (5000-7000pg/ml) and group4 (≥7000pg/ml). The clinical outcomes of different groups was examined multivariate logistical analysis was performed. Endometrial thickness (EMT) on the HCG day was divided into four groups: thin endometrium (≤7mm); medium endometrium (7<EMT≤10mm, 10<EMT<14mm) and thick endometrium (≥14mm). The clinical outcomes were compared between short GnRH-a long protocol and GnRH-a prolonged protocol with different EMT.

RESULTS: 7665 patients underwent first short GnRH-a long protocol and 1846 underwent GnRH-a prolonged protocol were included. There were no significant differences among the four E₂ groups in implantation rates, clinical pregnancy rates and live birth rates. Logistic regression analysis suggested that endometrial thickness, but not estradiol levels was one of independent predictive factors of live birth rates. For thin and medium endometrium, there were significantly higher clinical pregnancy rates (36.00% vs. 30.00%, P=0.000; 53.69% vs. 43.70%, P=0.000) and implantation rates (28.57% vs. 22.00%, P=0.000; 50.24% vs. 32.56%, P=0.000) in prolonged protocol compared with short GnRH-a long protocol. What interesting is that the thinner the endometrium, the greater the difference of clinical outcomes between the two protocols.

CONCLUSIONS: In conclusion, our large sample size study proved that endometrial response, but not ovarian response had effect on the clinical pregnancy rate and live birth rate in young women ≤35 years old with normal and hyper ovarian response. Prolonged pituitary down-regulation with long acting GnRH-a was an effective treatment to improve endometrial receptivity and clinical outcomes in patients with medium, especially thin endometrium, although the precise mechanism needs to be further investigated.

TABLE I.

<table>
<thead>
<tr>
<th>Endometrial thickness</th>
<th>Low Weight &lt;150 lbs</th>
<th>Moderate Weight 150-199 lbs</th>
<th>High Weight ≥200 lbs</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Median (Q1, Q3)</td>
<td>n</td>
<td>Median (Q1, Q3)</td>
</tr>
<tr>
<td>Fresh Progesterone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live Births</td>
<td>304</td>
<td>63 (39.05, 154.15)</td>
<td>267</td>
<td>49.1 (30.98, 154.15)</td>
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<tr>
<td>Abnormal Pregnancies</td>
<td>124</td>
<td>63.44 (30.15, 91.15)</td>
<td>94</td>
<td>26.75 (22.6, 35.3)</td>
</tr>
<tr>
<td>Fresh Estradiol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live Births</td>
<td>304</td>
<td>913.5 (443.5, 1466.5)</td>
<td>267</td>
<td>700 (335.1196)</td>
</tr>
<tr>
<td>Abnormal Pregnancies</td>
<td>124</td>
<td>478 (102, 993)</td>
<td>94</td>
<td>226.5 (105, 498)</td>
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<tr>
<td>Frozen Progesterone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live Births</td>
<td>167</td>
<td>29.2 (24.31, 37.79)</td>
<td>171</td>
<td>23.7 (19.3, 30.7)</td>
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<tr>
<td>Abnormal Pregnancies</td>
<td>153</td>
<td>30.05 (22.95, 36.8)</td>
<td>118</td>
<td>24.6 (20, 30.9)</td>
</tr>
</tbody>
</table>

Supported by: This work was supported by grants from National Natural Science Foundation of China (81170583 and 81571464).
when evaluating these hormone levels for prognostic and diagnostic purposes.

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EARLY β-hCG VALUE AS PREDICTOR OF LIVE BIRTH (LB) FOR SINGLE THAWED EUPLOID EMBRYO TRANSFER (STEET) PREGNANCIES. A. H. Buyea, S. DeVore,b S. M. Maxwell, D. H. McCulloch,c J. A. Grifod. Obstetrics & Gynecology, NYU School of Medicine, New York, NY; *New York University, New York, NY; †New York University Langone Fertility Center, New York, NY; ‡NYU Langone Fertility Center, New York, NY; †Ob/Gyn, NYU Langone Medical Center, NY, NY.

OBJECTIVE: Current data suggests that LB following transfer of an euploid embryo is independent of age or type of ART treatment. Because of their relatively uniform efficiency, STEET are well-suited to evaluate the prognostic value of cycle day (CD) 28 and CD 35 serum β-hCG levels for LB.

DESIGN: Retrospective analysis.

MATERIALS AND METHODS: All STEET between 2/2014 and 12/2016 with β-hCG >5 collected on CD 28 or 35 were included in the analysis. Preimplantation genetic testing for aneuploidy was performed with array comparative genomic hybridization and next generation sequencing. Transfers were excluded if β-hCG was drawn on an alternative CD, birth outcome was unknown, or if an elective termination was performed. The primary outcome was LB. ROC curves were constructed for β-hCG levels on CD 28 and 35 as predictors of LB. A rolling average of β-hCG level was also calculated to graphically represent the likelihood of LB for a given β-hCG value.

RESULTS: Data from 459 transfers (431 patients, ages 24-45 at time of retrieval) met inclusion criteria on CD 28, and 316 transfers (311 patients, same age range) also had values for CD 35. There were 299 LB, four of which were twins. There were five ectopic pregnancies, 73 biochemical pregnancies, 78 spontaneous abortions, two second-trimester losses at 20 weeks, and one full-term demise. The lowest β-hCG value on CD 28 that resulted in a LB was 23 (range 23-615, mean 169.6 ± 84.6). The area under the ROC curve for CD 28 was 0.83 as a predictor of LB. The ROC curve predicted that a β-hCG value of 100 on CD 28 is associated with a LB with 80% sensitivity and 70% specificity. CD 35 β-hCG values that resulted in a LB ranged from 160 to 8401 (mean 3072.8 ± 1560.5). The area under the ROC curve for CD 35 was 0.83 as a predictor of LB. The ROC curve predicted that a β-hCG value of 1621 on CD 35 is associated with a LB with 85% sensitivity and 68% specificity. The rolling average demonstrated an 80% incidence of LB with β-hCG of 100 on CD 28 or 1619 on CD 35. A 90% incidence of LB on the rolling average graph was associated with β-hCG of 210 on CD 28 or 1759 on CD 35.

CONCLUSIONS: Serum β-hCG levels on CD 28 and 35 have good prognostic value for predicting LB outcomes in STEET pregnancies. While there is no single threshold β-hCG that can predict a LB 100%, these models can be useful in counseling patients who are interested in knowing what the likelihood of LB is relative to their β-hCG level.

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SUBCLINICAL CHRONIC ENDOMETRITIS AND TEST OF CURE RATES IN A RECURRENT PREGNANCY LOSS COHORT. L. Verrilli,a S. Vaughnb, E. Ryan,c R. B. Lathid. aObstetrics and Gynecology, University of Wisconsin, Madison, WI; bObstetrics and Gynecology, Reproductive Endocrinology and Infertility, Stanford University, Sunnyvale, CA; cStanford University School of Medicine, Stanford, CA; dStanford University Medical Center, Sunnyvale, CA.

OBJECTIVE: There is a paucity of data regarding antibiotic efficacy in the treatment of subclinical chronic endometritis (SCE) in recurrent pregnancy loss (RPL). The objectives of this study were to assess the prevalence of SCE in RPL, to determine the efficacy of doxycycline as first line treatment and to compare RPL patients who required first line treatment only (treatment sensitive) to those who required multiple courses of antibiotics (treatment resistant).

DESIGN: A retrospective, single-center, cohort study.

MATERIALS AND METHODS: Patients with RPL (defined as a history of 2 or more first trimester miscarriages) who had at least one endometrial biopsy were included. SCE was defined as the presence of plasma cells by CD-138 or H&E staining. Patients with RPL and SCE underwent treatment with doxycycline for 2 weeks. Repeat endometrial biopsy was recommended as a test of cure. Patients with persistent plasma cells underwent second line treatment with 10-14 days of ciprofloxacin and metronidazole. Plasma cell numbers were compared between treatment sensitive and treatment resistant groups.

RESULTS: 107 women with a RPL were included, of which 59 (55%) were diagnosed with SCE. 41 patients with SCE completed first line treatment with doxycycline and repeat endometrial biopsy. Resolution of plasma cells after first line treatment was 46%. Treatment sensitive (n=19) and treatment resistant (n=22) SCE subjects were similar in baseline characteristics such as age, BMI, ethnicity and number of prior miscarriages. Treatment resistant patients had more late loss miscarriages (>12 weeks gestational age) (25% vs. 0%, p<0.05) as well as more subsequent fetal demises than treatment sensitive patients (20% vs. 0%, p<0.05). The density of plasma cells on the first biopsy did not differ significantly between those who were treatment sensitive and those who were resistant. Pregnancy outcomes including subsequent miscarriages, ongoing pregnancies and live births were similar between groups.

CONCLUSIONS: We found a similar prevalence rate of SCE defined by CD-138 staining in RPL patients. Our data suggests that doxycycline was curative in at least 46% of subjects undergoing test of cure. In our preliminary observations, treatment resistant subjects were more likely to have had late loss miscarriages suggesting that this may be a higher risk subset of RPL patients. Density of plasma cells on biopsy did not seem to be a good predictor of treatment sensitivity. Subsequent pregnancy outcomes were largely similar among those who were treatment sensitive and treatment resistant. Further studies with a greater number of subjects as well as more longitudinal data on birth outcomes would be performed to determine the effects on pregnancy outcomes of treatment of SCE.

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STUDY ON THE PROTECTIVE EFFECT OF G-CSF ON RIF AND RA PATIENTS WITH LOW HCG LEVEL IN EARLY PREGNANCY. W. Wu. Department of Reproductive Endocrinology, Women’s Hospital, School of Medicine, Zhe Jiang University, Hangzhou, China.

OBJECTIVE: To investigate the protective effect of G-CSF on RIF/RA patients with low HCG level in early pregnancy.

DESIGN: Prospective randomized controlled study.

MATERIALS AND METHODS: A total of 112 RIF/RA patients were randomly allotted into two study groups including G-CSF (n=52) and control group (n=50). All RIF/RA patients were excluded from autoimmune diseases, but at least combined with one of the following immune abnormalities: 1. Increased NK cells in peripheral blood; 2. Antinuclear antibody (+); 3. Increased TNFα/IL10 ratio; 4. Anticardiolipin antibody (+); 5. Increased ratio of anticoagulant in lupus; 6. Complement C3/C4 reduction. The HCG value was detected 9 days after transplantation or 12 days after ovulation. According to literature reported, 9 days after transplantation / 12 days after ovulation, the cutoff value of HCG was the reference standard. Drug intervention was given below this value. In control group, low molecular weight heparin 8000IU was injected daily, and in the experimental group additional G-CSF (150μg, QOD) was injected subcutaneously up to 30-35 days after transplantation / ovulation. B-ultrasound examination showed fetal heart beat as clinical pregnancy. Furthermore, the experimental group was divided into two subgroups, one was combined with 0.4 mg/day NK cells or TNFα/IL10 ratio, another one was combined with residual immune abnormalities. The difference of clinical pregnancy rate between two groups was analyzed.

RESULTS: G-CSF can significantly increase the clinical pregnancy rate in the experimental group (48.1% vs 33.3%, p<0.01), and has a significant protective effect on patients with RIF/RA, especially who are associated with elevated NK cells or TNFα/IL10 ratio (56.7% vs 36.7%, p<0.01). This result is consistent with the literature reporting that G-CSF can inhibit peripheral blood NK cells activity and increase the Th2 response, thus having a protective effect on pregnancy.2,3,4

CONCLUSIONS: G-CSF may increase clinical pregnancy rate in RIF/RA patients with low HCG level in early pregnancy who are possibly combined with immune abnormalities.

References: 1. Nayoung Sung, Joanne Kwak-Kim, H. S. Koo, K. M. Yang. Serum hCG-β levels of postovulatory day 12 and 14 with the sequential application of hCG.
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FIRST TRIMESTER LOW FETAL HEART RATE AND SMALL CROWN-RUMP LENGTH, BUT NOT SUBCHORIONIC HEMORRHAGE OR YOLK SAC DIAMETER, PREDICT PREGNANCY LOSS AMONG WOMEN WITH HISTORY OF PREGNANCY LOSS. E. A. DeVilbiss,a S. Mumford,b L. Sjaarda,c M. T. Connell,a S. Rafique,b T. C. Plowden,b R. Silver,a E. Schisterman,b, aEpidemiology Branch, NICHD, Bethesda, MD; bThe Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD; cEpi- nomics, Cordoba, Argentina.

OBJECTIVE: Jointly examine prospective associations between early ultrasound characteristics and risks of clinical pregnancy loss. DESIGN: Cohort nested within the EAGeR trial, a block-randomized, double-blind, placebo-controlled trial, conducted at 4 clinical sites in the United States in 2007-2011; women had 1-2 previous pregnancy losses and no documented abortions. Journal of Reproductive Immunology, 2015; 108:123-135. MATERIALS AND METHODS: Serum samples were obtained from 14 women with ultrasound confirmed EP (n = 5), miscarriage (SAB; n = 5), and viable intrauterine pregnancy (IUP; n = 4). Mean gestational age (days) was similar (EP 52.0, SAB 59.6, IUP 53.8; p = 0.97). sRNA libraries were prepared and sequenced in collaboration with BGI (Cambridge, MA) using the next-generation sequencing (NGS) platform, BGISEQ-500. RNA was extracted using TRIzol, separated with PAGE, and RNAs 18-30 nt in length were selected. cDNA was synthesized, amplified by PCR, and products sequenced. sRNA expression was calculated as Transcripts per Kilobase Million (TPM). NOIseq was used to screen for differentially expressed sRNA. Levels of expression were compared among groups and candidates were screened using a 2-fold differential of expression and probability of >0.8. RESULTS: Using the pre-specified cutoff of expression and probability, we identified 867 miRNAs: 339 were upregulated in SAB, 113 in IUP, and 119 in EP. Many of these miRNAs were novel. Of the known miRNAs, 2, hsa-miR-378d and hsa-miR-5585-3p, were upregulated in SAB vs. IUP; hsa-miR-378-d was upregulated in EP vs. IUP; hsa-miR-464 was upregulated in SAB vs. EP; four, hsa-miR-122-3p, hsa-miR-194-3p, hsa-miR-1299, and hsa-miR-4755-5p were upregulated in EP vs. SAB. Ten known miRNAs were upregulated in IUP vs. EP and of these, hsa-miR-378 was most highly expressed, followed by hsa-miR-6736-5p and hsa-miR-1299-3p. We detected 8825 piRNAs: 4271 were associated with SAB, 903 with IUP, and 1128 with EP. Most piRNAs were novel and overall expression of known piRNAs was relatively low. However, hsa_piR_000657 was upregulated in SAB vs. EP. hsa_piR_0011349 was upregulated in SAB vs. EP. One piRNA, hsa_piR_000586, was upregulated in IUP vs. EP. Few siRNAs were detected with 0 associated with SAB, 5 with IUP, and 2 with EP. One novel srRNA was upregulated in SAB and EP vs. IUP.

CONCLUSIONS: We were successful in the proof of concept that sRNA could be obtained from serum samples in the early first trimester to serve as a potential biomarker for women at risk for EP. With NGS, we detected several differentially expressed sRNAs in SAB, EP, and IUPs that may be potential biomarkers to distinguish viable and non-viable pregnancy. Future work will aim to validate whether sRNA expression may be a predictor of pregnancy location or viability.

Supported by: R01HD076279, T32-HD040135-15, ITMAT Scholarship University of Pennsylvania.

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OBJECTIVE: Small non-coding RNAs (sRNAs) regulate gene expression in various disease processes and have emerged as potential biomarkers of disease. Among the most well-studied of small non-coding RNAs are micro-RNAs (miRNAs), small interfering RNAs (siRNAs), and PIWI-interacting RNAs (piRNAs). In this study, we aimed to assess if the family of sRNA, detected in serum, can be used as a potential biomarker for women at risk for ectopic pregnancy (EP).

DESIGN: Retrospective Cohort.

MATERIALS AND METHODS: Serum samples were obtained from 14 women with ultrasound confirmed EP (n = 5), miscarriage (SAB; n = 5), and viable intrauterine pregnancy (IUP; n = 4). Mean gestational age (days) was similar (EP 52.0, SAB 59.6, IUP 53.8; p = 0.97). sRNA libraries were prepared and sequenced in collaboration with BGI (Cambridge, MA) using the next-generation sequencing (NGS) platform, BGISEQ-500. RNA was extracted using TRIzol, separated with PAGE, and RNAs 18-30 nt in length were selected. cDNA was synthesized, amplified by PCR, and products sequenced. sRNA expression was calculated as Transcripts per Kilobase Million (TPM). NOIseq was used to screen for differentially expressed sRNA. Levels of expression were compared among groups and candidates were screened using a 2-fold differential of expression and probability of >0.8.

RESULTS: Using the pre-specified cutoff of expression and probability, we identified 867 miRNAs: 339 were upregulated in SAB, 113 in IUP, and 119 in EP. Many of these miRNAs were novel. Of the known miRNAs, 2, hsa-miR-378d and hsa-miR-5585-3p, were upregulated in SAB vs. IUP; hsa-miR-378-d was upregulated in EP vs. IUP; hsa-miR-464 was upregulated in SAB vs. EP; four, hsa-miR-122-3p, hsa-miR-194-3p, hsa-miR-1299, and hsa-miR-4755-5p were upregulated in EP vs. SAB. Ten known miRNAs were upregulated in IUP vs. EP and of these, hsa-miR-378 was most highly expressed, followed by hsa-miR-6736-5p and hsa-miR-1299-3p. We detected 8825 piRNAs: 4271 were associated with SAB, 903 with IUP, and 1128 with EP. Most piRNAs were novel and overall expression of known piRNAs was relatively low. However, hsa_piR_000657 was upregulated in SAB vs. EP. hsa_piR_0011349 was upregulated in SAB vs. EP. One piRNA, hsa_piR_000586, was upregulated in IUP vs. EP. Few siRNAs were detected with 0 associated with SAB, 5 with IUP, and 2 with EP. One novel srRNA was upregulated in SAB and EP vs. IUP.

CONCLUSIONS: We were successful in the proof of concept that sRNA could be obtained from serum samples in the early first trimester to serve as a potential biomarker for women at risk for EP. With NGS, we detected several differentially expressed sRNAs in SAB, EP, and IUPs that may be potential biomarkers to distinguish viable and non-viable pregnancy. Future work will aim to validate whether sRNA expression may be a predictor of pregnancy location or viability.
OBJECTIVE: Human chorionic gonadotropin is secreted by syncytiotrophoblast and appears in maternal circulation approximately 6-8 days after fertilization. The maternal plasma levels of hCG continue to double about every 2 days and peaks at 6-8 weeks after conception. Thus, the β-hCG levels can be used to assist and guide the clinician in better management and monitoring of post-IVF pregnancies in conjunction with a transvaginal sonography. (1,2) Low values after transfer require to repeat the 48 hours later to confirm pregnancy. Clinical pregnancy (defined by sonography when a gestational sac with a heartbeat is observed) is a good predictor for evolutionary pregnancy. Determining threshold values of β-hCG that are predictive of clinical pregnancy (CP) is important for the future management of the patient. Also, to identify values below which pregnancy is not achieved (staying as biochemical pregnancy (BP), could also help to manage levels of anxiety caused by the assisted reproduction treatment (3,4,5,6,7). The aim of this study was to determine β-hCG thresholds predictive of a clinical pregnancy (CP) after the transfer of embryos in cleavage (D2/D3) or blastocyst (D5) stage. Also, to determine if there is any minimum value below which it is not possible to observe CP.

DESIGN: single center retrospective cohort study.

MATERIALS AND METHODS: 387 women that underwent fresh ICSI cycles were included. The determination of β-hCG was performed by ECLIA (ELECSYS-ROCHE) fourteen days after an embryo transfer (ET). The sensitivity of the assay was 2 IU/L. All patients underwent transvaginal ultrasound at 6 weeks after ET. Considering the day in which the embryos was transferred to the uterus of the mother, the groups were classified in D+2, in D+3 and in D+5. The initial β-hCG and β-hCG1 for both fresh and frozen cycle were measured. In addition, sensitivity and specificity levels (S/S) for each of these values was determined.

RESULTS: Similar ROC curve analyses were performed to determine β-hCG threshold predictive of CP. The proposed optimal thresholds predictive for CP were: D+2: 0.89 IU/L [ROC: D+2: 0.89 (J = 0.68), S/S 80.6%, 87.5%]; D+3: 256 IU/L [ROC D+3: 0.89 (J = 0.68) S/S 83.2%, 85.2%] and D+5: 379 IU/L [ROC: 0.93 (J = 0.85) S/S 92%, 92.9%]. Under 60 IU/L none of the pregnancies evolved to CP.

CONCLUSIONS: The data from this study provide a set of values for initial β-hCG levels that are dependent on the day of ET and are a reliable and highly predictive tool for CP outcomes. Above those values, repeating the β-hCG at subsequent visits may be considered. We propose each institution must find a cutoff value below which BP is defined, helping in better patient counseling. Further studies are needed to confirm our findings, in order to establish valid and clinically informative β-hCG thresholds.

References:
4. Physiological range of human chorionic gonadotropin for support of early pregnancy hormone levels in early pregnancies following IVF cycles.
5. PROGNOSTICATE THE EARLY PREGNANCY OUTCOME IN AN IN-VITRO FERTILIZATION CYCLE?
6. Beta subunit levels in pregnancies achieved by invitro fertilization with single embryo transfer in both fresh and frozen cycles. A 100 lb difference in weight was associated with a 34.8% reduction in βhCG for both fresh and frozen cycle pregnancies. The rate of increase in βhCG was unaffected by body weight. A 100 lb difference in weight was associated with a 53.3% and a 32.8% reduction in βhCG, respectively.
7. CONCLUSIONS: Increasing body weight is associated with significantly lower βhCG and P concentrations in early pregnancy following blastocyst single embryo transfer in both fresh and frozen cycles. However the rise in βhCG is not affected by weight. Clinicians should consider this when evaluating these hormone levels for prognostic and diagnostic purposes.
8. Supported by: Supported in part by the Henrietta Rose and Mary Ellen Molinario-Blonigan Research Fund, University of Iowa College of Medicine.

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PRENATAL DIAGNOSTIC TESTING IN PATIENTS WITH FERTILITY TREATMENTS, DIFFERENCES IN INDICATIONS. N. Joshi, a J. L. Chan, a E. Wang, a E. Sauro, a R. Buttle, a J. Williams, b M. D. Pisarska. a aObstetrics and Gynecology, Cedars-Sinai Medical Center, Los Angeles, CA; bObstetrics and Gynecology, Cedars-Sinai Medical Center, Los Angeles, CA.

OBJECTIVE: Indications for prenatal diagnostic testing via chorionic villus sampling (CVS) include advanced maternal age (AMA), personal or family history of genetic abnormalities, abnormal genetic screening results, and fetal anomalies. With the advent of emerging prenatal screening tests, definitive testing is decreasing. Preimplantation genetic testing (PGT) for in-vitro-fertilization (IVF) is also considered screening and not diagnostic, despite a low false negative rate. However, it may give patients greater confidence that the pregnancy is genetically normal. We hypothesized that indications for CVS differ for patients receiving fertility treatments, including those that had IVF with and without PGT, compared to those with spontaneous conceptions. In addition, we wanted to determine if genetically abnormal test results varied among the groups.

DESIGN: Retrospective cohort analysis.

MATERIALS AND METHODS: From 2008 until the present time, data were collected prospectively on patients undergoing chorionic villus sampling at 10.5-13.5 weeks under institutional IRB approval. Subject demographics were collected. Primary outcome was indication for CVS, and the exposure of interest is use of fertility treatments including PGT. Maternal age is also reported. A one-way analysis of variance (ANOVA) with Bonferroni correction was used to compare maternal age between groups. Chi-square tests were used to compare differences between groups. A p-value of <0.05 was considered significant.

RESULTS: No significant difference was found in the proportions of abnormal results among groups (7.1% for spontaneous pregnancy, 5.0% for non-IVF fertility treatment, 9.0% for IVF without PGT, and 7.3% for IVF with PGT). However, false negatives in the IVF with PGT were present. Abnormalities included two balanced translocations, Trisomy 21 and a duplication, 7q11.23.

CONCLUSIONS: Patients who undergo IVF are more likely to pursue CVS for a personal or family history of genetic abnormalities or fetal anomalies compared to spontaneous pregnancies. Among IVF patients, those who have PGT are more likely to have fetal anomaly as an indication for CVS.
Maternal age and indications for testing.

<table>
<thead>
<tr>
<th>Spontaneous (S)</th>
<th>Non-IVF Fertility treatment (NIFT), n=164</th>
<th>IVF with PGT, n=41</th>
<th>IVF without PGT, n=203</th>
<th>Significant differences among groups (p-value)</th>
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<tbody>
<tr>
<td>Maternal age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced maternal age, n (%)</td>
<td>37.9 (77.5%)</td>
<td>38.9 (78.2%)</td>
<td>38.9 (85.4%)</td>
<td>39.5 (83.3%)</td>
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<tr>
<td>Abnormal first trimester screen, n (%)</td>
<td>122 (6.5%)</td>
<td>135 (82.3%)</td>
<td>14 (8.5%)</td>
<td>19 (9.4%)</td>
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<tr>
<td>Personal or family history of genetic abnormality, n (%)</td>
<td>273 (14.5%)</td>
<td>21 (12.8%)</td>
<td>12 (29.3%)</td>
<td>33 (16.3%)</td>
</tr>
<tr>
<td>Fetal anomaly, n (%)</td>
<td>22 (1.17%)</td>
<td>4 (2.44%)</td>
<td>2 (4.9%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*Denotes significance (p<0.05).

suggesting utilization of diagnostic testing only in the presence of an anomaly. In addition, although differences in the rate of chromosomal abnormalities did not exist among the groups, genetic abnormalities were identified in the PGT group. Therefore, PGT should not be considered diagnostic.

Supported by: NICHD (R01 HD074368).

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ARE CYCLE DAY 28 ESTRADIOL LEVELS ASSOCIATED WITH ADVERSE PERINATAL OUTCOMES IN IVF SINGLETONS? A. Petriu,1,2 C. Mosteller,3 N. Pereira,1 S. Spandorfer,1 Z. Rosenwaks,4 *Ob/Gyn, Weill Cornell Medical College, New York, NY; New York Presbyterian Weill Cornell, New York, NY; Weill Cornell Medicine, New York, NY; Cornell University Medical College, NYC, NY; Reproductive Medicine, Physician, New York, NY.

OBJECTIVE: Early luteal estradiol levels have been shown to predict conception versus nonconception cycles in IVF pregnancies1,2. Those with cycle day (CD) 28 estradiol (E2) levels that are lower have also been shown to have poorer early pregnancy outcomes such as ectopic and biochemical pregnancies3. Our aim was to determine, once a pregnancy progresses, whether lower luteal E2 levels, specifically CD 28 levels, have a bearing on perinatal outcomes such as low birth weight (LBW) or preterm delivery (PTD).

DESIGN: Case-control study.

MATERIALS AND METHODS: Patients undergoing fresh IVF embryo transfer (ET) at our center between 2010 and 2016 with live singleton births were included. Those with vanishing twins, multiple gestations, or donor oocyte were excluded. Patients underwent human chorionic gonadotropin (hCG) and E2 measurements on CD 28 and 30. Cycle day of blood draw was verified for each patient. Adverse perinatal outcomes of interest were PTD (<37 weeks) and LBW (<2500 grams). Cycles were stratified by CD 28 estradiol levels into three groups: group A with E2 ≤ 50 pg/mL, group B with E2 > 50-100 pg/mL, and group C with E2 > 100 pg/mL. Patients were also stratified by hCG level ≤ 50 mIU/mL or > 50 mIU/mL. CD 28 E2 levels and hCG were compared in patients with and without PTD and LBW. The rise of hCG levels through CD 28 and 30 was also compared between those with and without PTD and LBW. All hormone measurements were performed with IMMULITE 2000 Immunoassay System. Student’s and nonparametric t-tests, Mann Whitney U tests, and Chi-square tests were used as indicated, with p < 0.05.

RESULTS: A total of 2674 patients met the inclusion criteria. There were no differences in the baseline demographics between patients with PTD and term birth or LBW and normal birth weight (NBW). Between groups A, B, and C, stratified by E2 level on CD 28, there were no differences in the incidence of LBW or PTD. Those with CD 28 hCG levels ≤ 50 mIU/mL and > 50 mIU/mL also had a similar risk of LBW or PTD. When the groups stratified by E2 levels were categorized by CD 28 hCG ≤ 50 mIU/mL or > 50 mIU/mL, there remained no differentiation in perinatal outcomes. Finally, the slope of CD 28 to 30 rise was similar for those with and without LBW and with and without PTD.

CONCLUSIONS: CD 28 E2 levels do not predict perinatal outcomes of LBW or PTD, even when further stratified by CD 28 hCG. The rise of hCG on CD 28 to 30 similarly cannot predict LBW or PTD. While luteal E2 can predict early pregnancy outcomes, it has no bearing on LBW or PTD once a pregnancy is achieved.

References:

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BEHIND THE BLEED: ANALYSIS OF THE FORMATION OF SUBCHORIONIC HEMATOMAS (SCH) IN SINGLE EUPLOID EMBRYO TRANSFER CYCLES BY PROTOCOL. N. Edison,1 J. K. Blakemore, K. N. Goldman, B. Hodes-Wertz, J. A. Grifo. NYU Langone Medical Center, New York, NY.

OBJECTIVE: Subchorionic hematomas (SCH) are a known risk factor for poor obstetric outcomes such as spontaneous abortion and preterm delivery. We sought to determine if there is a difference in the prevalence of SCH formation in pregnancies after frozen embryo transfer (FET) between natural and programmed preparation.

DESIGN: Retrospective cohort study of single euploid FET cycles resulting in clinical pregnancy performed between 1/2016 and 12/2017 at our center.

MATERIALS AND METHODS: All single euploid FET cycles utilizing Next Generation Sequencing were reviewed. Exclusion criteria included FET cycles with ploidy determined by aCGH, or cycles in which untested, mosaic, or multiple embryos were transferred. All transfer cycles that resulted in clinical pregnancy (defined as presence of gestational sac) were included. These cycles were analyzed by protocol: natural versus programmed. Patients undergoing programmed cycles took oral estradiol daily followed by either 50-75 mg intramuscular progesterone (P4) in oil or vaginal P4 suppository. Patients undergoing natural cycles (or supplemented with letrozole for 5 days) were monitored until a dominant follicle reached >18mm and ovulation was confirmed followed by the initiation of vaginal P4 suppository. SCH were documented at the time of luteal ultrasound as a measurable clot behind the gestational sac. Primary outcome was the rate of SCH noted on luteal ultrasound. Statistical analyses included students t-test, chi-squared and Fischer’s Exact test where appropriate (mean ± SD, p < 0.05).

RESULTS: A total of 719 cycles were included; 86 natural and 633 programmed (Table 1). SCH formation was diagnosed in 12.9% (n = 93) of clinical pregnancies. The formation of SCH was significantly lower in natural cycles compared to programmed cycles (RR 0.4, 95% CI 0.17 - 0.98, p < 0.04). Relevant cycle parameters were similar between groups (Table 1); cycle day 28 estradiol was higher in programmed cycles reflecting exogenous estrogen exposure. When programmed cycles utilizing vaginal P4 only were excluded (n=36), the formation of SCH is still statistically lower in natural compared to programmed cycles (5.8% v 14.2%, RR 0.4 (0.17-0.97, p < 0.03).
CONCLUSIONS: SCH occurred less frequently in single euploid embryo transfers using a “natural” endometrial preparation. Further analyses of long term outcomes could help provide insight into estimates of obstetric risk.

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FERTILITY OUTCOMES ARE NOT COMPROMISED AFTER SPONTANEOUS PREGNANCY LOSS FOLLOWING THE FIRST EUPLOID BLASTOCYST TRANSFER. L. Henry, S. McReynolds, K. De Klerk, J. B. Schipper, T. Jarvis, W. B. Schoolcraft, M. Katz-Jaffe, Colorado Center for Reproductive Medicine, Lone Tree, CO.

OBJECTIVE: Spontaneous pregnancy loss occurs in up to 20% of known clinical pregnancies; with a significant contribution (>60%) resulting from an aneuploid fetus. Preimplantation genetic testing for aneuploidy (PGT-A) allows for the transfer of euploid embryos in an in vitro fertilization (IVF) cycle, potentially reducing miscarriage (MAB) rates, especially for women of advanced maternal age that are at increased risk of oocyte aneuploidy. The aim of this study was to evaluate the fertility potential of IVF patients following their first euploid frozen embryo transfer (FET) that resulted in a pregnancy loss.

DESIGN: Retrospective study.

MATERIALS AND METHODS: Subjects included in this study experienced a MAB following the first euploid blastocyst FET (n=104; mean maternal age 35.9±4.1 years). Infertility patients with a history of recurrent MAB were excluded. Overall incidence of MAB (ultrasound confirmation of a fetal heart tone) following IVF with PGT-A, and the transfer of a euploid blastocyst was 5.1% (156 MABs from 3077 clinical pregnancies). Blastocysts were biopsied on either day 5 or 6 of embryonic development, with removal of 3-6 trophectoderm (TE) cells prior to vitrification. Chromosome enumeration of TE biopsies was performed and only euploid blastocysts were selected for transfer. Standard protocols for hormone replacement FET were utilized. Fertility assessment was measured by clinical outcomes of subsequent euploid FETs. Statistical analysis included, where appropriate, Student’s t-test and Fishers exact test with significance at P<0.05.

RESULTS: Only 58.7% of MAB patients (n=61) returned for subsequent FETs. Close to a quarter of the MAB patients (22.1%), did not have any remaining euploid blastocysts, while the remaining 19.2% withdrew from further treatment. MAB patients with no remaining euploid blastocysts were significantly older than MAB patients that had subsequent FETs (mean maternal age 37.7±4.2 years vs. 35.2±3.9 years; P<0.05). Excellent clinical outcomes from a subsequent euploid FET was observed for these prior MAB patients: implantation (FHT) = 67.1%, biochemical (bhCG) = 85.3%, clinical pregnancy = 77.1%, MAB = 17.0% and live birth 63.9%. A small subset of prior MAB patients (n=17) who had not achieved a live birth in their second FET, pursued a third or fourth euploid FET revealing comparable clinical outcomes: implantation (FHT) = 55.2%, biochemical (bhCG) = 88.2%, clinical pregnancy = 76.5%, MAB = 23.1% and live birth 58.8% (P≥0.05; ns).

CONCLUSIONS: Spontaneous pregnancy loss following IVF with PGT-A does not reflect compromised fertility potential. This study has shown that MAB patients have a very good chance to conceive and achieve a live birth in a subsequent euploid FET/s, if they have additional euploid blastocysts available and if the couple continues to pursue IVF treatment.


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HOME COLLECTION OF PRODUCTS OF CONCEPTION: CAN KARYOTYPES BE OBTAINED?

M. Siegel, P. Amato, D. Lee, D. Wu, S. Krieg. Reproductive Endocrinology and Infertility, Oregon Health & Science University, Portland, OR.

OBJECTIVE: To investigate the ability to perform chromosomal analysis on products of conception following use of misoprostol, expectant management, or dilation and curettage (D&C) after miscarriage.

MATERIALS AND METHODS: This is a case series of patients who had first-trimester pregnancy losses and desired chromosomal analysis of the products of conception (POC) in 2015-2017 at the Oregon Health & Science University fertility center. This study investigated patient preference in management of losses, whether karyotype was successfully completed on POC, if prolonged time between diagnosis and receipt of tissue still resulted in successful analysis, and frequency of aneuploidy among these patients.

RESULTS: A total of 24 patients with ultrasound diagnosis of miscarriage desired chromosomal analysis of POC. Of these patients, 6 chose D&C, 16 chose misoprostol, and 2 chose expectant management. Chromosomal analysis was successfully obtained for 6/6, 8/16, and 1/2 of patients choosing D&C, misoprostol, or expectant management, respectively. Patients who chose misoprostol or expectant management to manage their miscarriages. Patients who chose misoprostol or expectant management self-collected samples; samples were examined by an RN prior to analysis. The method of obtaining POC tissue, time between diagnosis of pregnancy loss and receipt of tissue by the lab, and karyotype outcomes were included. Chi-squared testing between proportions was performed using Graphpad Prism 7.04.

RESULTS: All 24 patients with ultrasound diagnosis of miscarriage participated in POC analysis. Of these patients, 6 chose D&C, 16 chose misoprostol, and 2 chose expectant management. Chromosomal analysis was successfully obtained for 6/6, 8/16, and 1/2 of patients choosing D&C, misoprostol, or expectant management, respectively. Patients who chose misoprostol or expectant management to manage their miscarriages. Patients who chose misoprostol or expectant management self-collected samples; samples were examined by an RN prior to analysis. The method of obtaining POC tissue, time between diagnosis of pregnancy loss and receipt of tissue by the lab, and karyotype outcomes were included. Chi-squared testing between proportions was performed using Graphpad Prism 7.04.

RESULTS: All 24 patients with ultrasound diagnosis of miscarriage participated in POC analysis. Of these patients, 6 chose D&C, 16 chose misoprostol, and 2 chose expectant management. Chromosomal analysis was successfully obtained for 6/6, 8/16, and 1/2 of patients choosing D&C, misoprostol, or expectant management, respectively. Patients who chose misoprostol or expectant management to manage their miscarriages. Patients who chose misoprostol or expectant management self-collected samples; samples were examined by an RN prior to analysis. The method of obtaining POC tissue, time between diagnosis of pregnancy loss and receipt of tissue by the lab, and karyotype outcomes were included. Chi-squared testing between proportions was performed using Graphpad Prism 7.04.

CONCLUSIONS: Traditionally, physicians have advised patients interested in POC analysis that D&C is a superior option to obtain tissue for testing. While our results confirm this finding, this preliminary study shows that home POC collection can result in satisfactory tissue for SNP analysis, with the caveat that a higher incidence of MCC may be found versus D&C.

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IMPACT OF ABO BLOOD TYPE ON LIVE BIRTH OUTCOMES IN FROZEN EMBRYO TRANSFER CYCLES.

N. J. Shah, N. Pereira, C. Mostisser, R. Elias, I. Kligrman, Z. Rosenwaks. New York Presbyte-

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DOES DECREASING AMH CORRELATE WITH INCREASING FREQUENCY OF ANEUPLOID MISCARRIAGE IN PATIENTS WITH RECURRENT EARLY PREGNANCY LOSS? A. M. Zamah, C. Burks, E. Hobeika, T. Jackson-Bey, M. D. Stephenson. Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Illinois at Chicago, Chicago, IL.

OBJECTIVE: Anti-Mullerian hormone (AMH) is an established serum marker of ovarian reserve and predictor of fertility treatment success. Its association with other reproductive disorders, such as recurrent pregnancy loss, is controversial. It is well documented that advancing maternal age is associated with an increased frequency of trisomic pregnancies, suggestive of an increased miscarriage rate. The purpose of this study is to determine the whether AMH is associated with the frequency of aneuploidy miscarriage in a cohort of women with recurrent early pregnancy loss (RPL).

MATERIALS AND METHODS: Inclusion criteria for this RPL cohort included having 2 or more pregnancy losses at less than 10 weeks and having frozen embryo results for one or more pregnancy losses. The RPL biopsy repository contains prospectively collected biospecimens and clinical data is stored within a RPL Database. Cryopreserved serum samples were analyzed for serum AMH and analysis performed to assess the correlation of serum AMH to probability of live birth, miscarriage, and miscarriage due to chromosome errors in each patient’s subsequent pregnancy. Data were analyzed by two-way ANOVA and chi-square where appropriate, with p<0.05 considered as significant.

RESULTS: A total of 130 patients were included for analysis. For the cohort, the mean age was 35.5 (SD 4.3), BMI 25.8 (SD 5.6) and mean AMH 4.59 ng/ml (SD 3.94, range 0.76 - 18.9). The cohort was stratified by AMH into 3 groups (AMH ≥ 2; AMH 1-2; AMH < 1) for analysis. The mean AMH (SD) for the 3 groups are 6.44 (3.61) ; 1.56 (0.33) ; and 0.52 (0.30). The mean ages (SD) for the 3 groups are 34.4 (3.2) ; 37.0 (4.7) ; and 38.1 (4.6) p < 0.0001. The number of cycles to conceive was not significantly different between the 3 groups (2.5, 2.6, 2.5 cycles respectively). The probability of live birth in the subsequent pregnancy was not significantly different between the different AMH groups (p = 0.63). Out of 72 miscarriages analyzed, 63 (88%) had confirmed chromosomal analysis results. When stratified by AMH, there was no significant difference in the
rate of euploid and non euploid pregnancy losses among miscarriages with confirmed chromosomal analysis results (p=0.665) [Table 1]

CONCLUSIONS: Our results show that serum AMH does not correlate with aneuploidy miscarriage in a cohort of women with RPL.

Supported by: None.

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ASSOCIATION BETWEEN SPERM DNA FRAGMENTATION AND UNEXPLAINED RECURRENT PREGNANCY LOSS: SYSTEMATIC REVIEW & META-ANALYSIS. J. Tan,1 O. Taskin,2 A. Y. Albert,2 M. A. Bedaiwy,4 Obstetrics & Gynecology, University of British Columbia, Vancouver, BC, Canada; 1UBC, Vancouver, BC, Canada; 2Women’s Health Research Institute, Vancouver, BC, Canada; 4Obstetrics and Gynecology, University of British Columbia, Vancouver, BC, Canada.

OBJECTIVE: Previous meta-analyses have demonstrated an association between high levels of sperm DNA fragmentation (SDF) and adverse IVF outcomes. Similarly, elevated SDF has been associated with an increase in early miscarriage, but a relationship with unexplained recurrent pregnancy loss (RPL) has yet to be established. To improve our understanding of the male factor contribution to RPL, this meta-analysis investigates the relationship between elevated SDF in patients with a history of RPL.

DESIGN: Meta-analysis.

MATERIALS AND METHODS: A literature search was performed from inception to March 2017 using PubMed, Embase, Medline, Cochrane, and Google Scholar. Random effects meta-analysis was employed to calculate the estimated average mean difference (MD) in SDF between RPL and fertile control groups. Heterogeneity of exposure effects was evaluated using Forest plots and I² statistic. Publication bias was assessed using Egger’s test. Subgroup analyses were performed using different sperm fragmentation assays and meta-regression employed to evaluate the possible confounding effects of paternal age and mean sperm motility.

RESULTS: 12 prospective and 2 retrospective studies were included involving males with a history of RPL who had SDF testing (by Comet, TUNEL, sperm ELISA) in both RPL and fertile controls. SDF was significantly increased among RPL patients compared to fertile controls (MD =11.98, p<0.001). Subgroup analysis demonstrated a similarly significant average mean difference between RPL and control using SDF compared to TUNEL assay (MD in SCD =10.14, 95% CI = 8.93 to 11.35, p = 0.0002; MD in TUNEL = 14.62, 95% CI = 7.04 to 22.21, p = 0.0002). Mean paternal age and mean sperm motility in the RPL groups tested by meta-regression demonstrated no significant effect on this relationship (p > 0.10). There was no evidence of systematic bias in the funnel plots and Egger’s test was non-significant.

CONCLUSIONS: Although the inherent heterogeneity and complex etiology of RPL made study comparisons challenging, our results demonstrate a clear association between high levels of SDF and RPL using both TUNEL and SCD assays. This association appears independent of differences in mean paternal age and mean sperm motility. However, differences between studies such as variations in the duration of abstinence prior to semen collection and differences in assays used likely account for the heterogeneity observed. Furthermore, the observed association supports the diagnostic capabilities of SDF, but its predictive capacity cannot be inferred. As genetic abnormalities are thought to contribute to early miscarriage, further prospective studies are required to further elucidate a possible paternally derived genetic origin of unexplained recurrent pregnancy loss.

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INDUCTION OF SECOND TRIMESTER MISSED MISCARRIAGE USING FOLEY’S CATHETER BALLOON WITH OR WITHOUT TRACTION APPLIED: A RANDOMIZED CONTROLLED TRIAL. A. Abbas,a M. K. Ali,b T. Farghaly,c A. M. Abdelmagied.e aFaculty of Medicine, Assiut University, Assiut, Egypt; bWomen’s Health Hospital, Assiut, Egypt; cAssiut University, Assiut, Egypt; dObstetrics and Gynecology, Assiut University, Assiut, Egypt.

OBJECTIVE: Our objective is to determine whether the traction placed to a trans-cervical Foley catheter balloon inserted for induction of second-trimester missed miscarriage results in faster times to delivery.

DESIGN: Randomized controlled trial (clinicaltrial.giv-NCT02842164).

MATERIALS AND METHODS: We included in our study only nulliparous women or those delivered before by transverse lower segment elective cesarean section who were pregnant in singleton second-trimester missed miscarriage (12-24 weeks). Eligible women who gave their informed consent were randomized to trans-cervical Foley catheter balloon insertion either (with traction; group I) or (no traction; group II). The primary outcome was to determine the insertion to delivery time with or without traction applied on the Foley’s catheter. The secondary outcomes included insertion to catheter expulsion time, the associated pain (measured by visual analogue scale) and vaginal bleeding. Mann-Whitney U and chi-square test were used for analysis of the outcomes. A logistic regression model was utilized to examine the association between patient’s characteristics and the failure of Foley’s catheter balloon expulsion within 24 hours.

RESULTS: Two hundred women were recruited (100 women in each group). The insertion to delivery time was significantly shorter in group I (traction group) than group II (no traction group) (16.49 ± 2.59 vs 18.24 ± 3.30 hours; p=0.000). Insertion to balloon expulsion time in group I was also significantly shorter (7.92 ± 0.86 vs 9.12 ± 1.19 hours; p=0.000). However, a significant higher rate of vaginal bleeding and a higher degree of pain was perceived by the women in group I (p=0.008, p=0.000; respectively). The nulliparity, longer inter-pregnancy interval (>22 month), smaller gestational age (<14 weeks) and lower Bishop Score before insertion (<2) were significantly associated with a higher likelihood of Foley catheter balloon expulsion failure within 24 hours.

CONCLUSIONS: Application of traction on Foley’s catheter balloon results in faster delivery and catheter expulsion time with more pain and bleeding in patients with second-trimester missed miscarriage.

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IS EARLY HCG PREDICTIVE OF PREGNANCY AFTER EMBRYO TRANSFER IN BLASTOCYST CYCLES? F. Shararaa M. R. Goodwin,b aVirginia Center for Reproductive Medicine, Reston, VA; bEmbryology, Virginia Center for Reproductive Medicine, Reston, VA.

OBJECTIVE: Most ART programs perform β-hCG measurement 9-12 days after ET to detect a pregnancy. A prior study using hyperglycosylated hCG in a small sample size showed that a single measurement 6 days after ET had 100% sensitivity and specificity in identifying biochemical and ongoing pregnancies (Strom 2012). We sought to determine whether routine β-hCG measurement at 5-6 days after ET is predictive of ongoing pregnancies. This is important in patient counseling.

DESIGN: Retrospective.

MATERIALS AND METHODS: A total of 369 patients undergoing ART with blastocyst transfers had their early serum β-hCG measured 4-6 days after ET. There were 233 fresh IVF cycles and 136 FET cycles. Of these, 244 β-
lower hCG were performed on days 5–6 after ET (146 IVF and 98 FETs), and then on days 9–11. A test was positive if the b-hCG measurement was \( \geq 3 \text{ mIU/mL} \).

RESULTS: There were 160 positive and 84 negative b-hCG tests measured 5-6 days after ET. Of the 84 negative tests, 17/84 were positive on day 9 or 10, and 67/84 were biochemical losses, 3 (3.6%) were clinical pregnancies yielded a live birth. Of the 154 positive b-hCG tests measured 5-6 days after ET, 25 (16.2%) did not produce a clinical pregnancy, and 113 yielded live births (73.9%). In the IVF group, 119/146 (81.5%) were early positive, 22/146 (15.6%) were biochemical pregnancies, 97 had clinical pregnancies, and 83 (56.9%) were live births. In the IVF fresh ET group, if the early b-hCG was negative no cases were positive on days 9-11. In the FET group, 98 had testing on day 5-6. Of these, 41 were early positive (41.8%) and 54 were positive on days 9-11 (52.1%). Of the 57 that were negative, 13 were positive on days 9-11 and 10/13 (76.9%) ended up being biochemical losses, and 3 were live births. The low birth rate in the FET group when the early beta was negative was 3/57 (5.3%). The mean early b-hCG levels in the pregnant IVF group was 40.06 mIU/mL which was significantly higher than in the FET 28.9 IUI (P=0.01), however, if first b-hCG level on days 9-11 there were no differences in the mean b-hCG between the 2 groups (23.4 vs 274.6, P=0.40).

CONCLUSIONS: Early b-hCG measured 5-6 days after ET is very predictive of successful pregnancies in blastocyst cycles in both fresh and FET cycles. A positive test is associated with about a 75% chance of a live birth. In the fresh group, an early negative b-hCG was 100% predictive of no pregnancy, but in the FET group an early negative in the FET group which was positive on days 9-11 led to a live birth in only 5% of cases. Women undergoing fresh cycles using blastocyst ET who have a negative b-hCG test on days 5-6 can safely stop their progesterone supplementation and assume this is a failed cycle. In FET cycles however, the early b-hCG test is only 95% predictive. In addition, FET cycles were associated with lower early b-hCG levels than fresh transfers 5-6 days after ET, but the b-hCG levels became similar to fresh cycles on the first day of the actual pregnancy test. The new information is of potential benefit in counseling women undergoing ART.

References:

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LOWER CONCEPTION PROBABILITY OBSERVED IN MENSTRUAL CYCLES WITH HIGHER PHYSIOLOGICAL STRESS AS MEASURED BY WRIST-WORN WEARABLES. M. Shilha, a F. Kuebler, a C. Argyle, a B. Leeners. a b aAva AG, Zurich, Switzerland; bUniversity Hospital Zurich, Zurich, Switzerland.

OBJECTIVE: Recent literature has demonstrated negative effects of stress on the probability of conception as well as pregnancy outcomes. Heart rate variability parameters are known to correlate with both perceived and physiological stress. Until recently, measuring said parameters was only possible in clinics. We demonstrate here the utility of wearables capable of measuring heart rate variability parameters in reflecting the negative effects of stress on conception rates.

METHODS: Healthy women aged 18-42, with self-reported regular cycles (23 days < cycle length < 36 days), were recruited for a prospective observational study at the university hospital Zurich.

MATERIALS AND METHODS: A total of 360 participants wore the Ava bracelet daily during sleep for up to one year, and if they became pregnant until term. Ovulation day was estimated using a home LH-urine test. Users were instructed to use an HCG home urine test to test for pregnancy every cycle. Pregnancy test results and other potential chemical losses were recorded through a daily questionnaire, and heart rate variability parameters were calculated from R-R intervals recorded by the bracelets optical sensor. Mixed effects and Cox proportional hazard models with random intercept and slopes for the respective users and cycles were used to assess the effect of perceived and physiological stress on time to a positive pregnancy test.

RESULTS: We regressed the time-to-a positive pregnancy test on participants’ per cycle mean daily stress level, mean daily mood, mean heart rate variability (HRV) ratio, mean daily alcohol consumption, and total sexual encounters. The total number of sexual intercourse acts were positively correlated with the rate of positive pregnancy tests, hazard ratio = 1.3, P<0.05. The resulting shared frailty revealed a significant effect of HRV ratio on conception likelihood, such that women with higher average HRV ratio, or physiological stress levels in the luteal phase of their cycle, were less likely to become pregnant, hazard ratio=0.76, P<0.05. When included both in the final model, only physiological stress was significantly associated with lower chances of a positive pregnancy test.

CONCLUSIONS: Physiological stress has negative effects on the probability of a positive pregnancy test, while perceived stress did not show a correlation with positive abortion. Wrist worn wearables are a useful tool to study peri-implantation and early pregnancy factors that are otherwise challenging to collect. Heart rate variability parameters could provide an objective stress measure.

References: NA.
Supported by: This study is supported by the Swiss Commission for Technology and Innovation and Ava AG.

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OSTEOSTERO-ANDROGENIC EFFECT OF DEHYDROEPIANDROSTERONE SULPHATE (DHEAS) CRITICALLY FOMENTS THE INTRACRINE REGULATION OF IMPLANTATION AND EARLY PREGNANCY IN WOMEN UNDERGOING IVF. B. N. Chnimote a N. M. Chnimote a b Embryology, Endocrinology, Vaunshdhara Fertility Centre, Nagpur, India; a Embryology, Vaunshdhara Fertility Centre, Nagpur, India.

OBJECTIVE: Higher incidences of early pregnancy loss in PCOS women could be due to very high levels of DHEA, which inhibit endometrial-stromal cell differentiation via prevention of glucose-flux through pentose-phosphate-pathway. Contrarily, low DHEA women with diminished ovarian-reserve, when supplemented with DHEA show significant reduction in early miscarriage rates. Sulphonated-DHEA (DHEAS) is the most abundant circulating oestro-androgenic steroid precursor for estrogen production in humans. Objectives of this study was to evaluate significance of innate, endogenously circulating DHEAS during implantation in predicting implantation failure/early miscarriage in eumenorrheic non-PCOS women undergoing IVF.

DESIGN: Prospective pilot study. n=85 non-PCOS eumenorrheic, normo-responder women undergoing conventional antagonist stimulation protocol IVF. All women were provided day 5 fresh, elective single-blastocyst transfer (eSBT) and Luteal phase support.

MATERIALS AND METHODS: Serum DHEAS levels in baseline, day 7, day 14 post-eSBT were measured by radio-immuno-assay using diagnostic kits. Serum estradiol, b-hCG, progesterone levels were also measured on d7, d14 post-eSBT, b-hCG measurement on d7 of eSBT was considered early indicator of pregnancy. Implantation rate and live birth rate were main outcome measures. Cycles were classified into live birth (LB, n=33), biochemical pregnancy (BCP, n=3), early miscarriage (EM, n=2) and no implantation (NI, n=47). Statistical analysis: Student’s t-test, One-Way ANOVA, ROC analysis using Graph-pad Prism VI software. Sample size was devised to give 80% power to the study.

RESULTS: Overall rates of LB, BCP, EM and NI were 38.82%, 3.53%, 2.35% and 55.29% respectively. DHEAS levels depicted a steady rise from baseline to d7 to d14 post-eSBT in women with LB (165±11.01 ng/ml vs 257±10.34 ng/ml; P=0.0001). Although a rising trend was also observed in women with EM, the rise from baseline to d7 post-eSBT was rather steep (68.5±3.5 vs. 247.5±7.5 vs. 255±10). However, the rising pattern was disrupted in BCP cycles where the levels dropped from baseline to d7 and then increased on d14 post-eSBT (211.7±31.67 vs. 120±5.8 vs. 258±30.10; 14), and in NI cycles where a sharp rise on d7 was followed by a decrease in levels on d14 post-eSBT (201.1±13.95 vs. 1221.134 vs. 791.7±103.34). A significant difference in the ratio of d7:baseline DHEAS levels was observed in LB vs. BCP vs. EM vs. NI cycles (2.59 vs. 0.61 vs. 3.61 vs. 9.65; P<0.0001). Thus, a twofold rise in DHEAS levels from baseline to d7 post-eSBT was rather steep (68.5±3.5 vs. 247.5±7.5 vs. 255±10). However, the rising pattern was disrupted in BCP cycles where the levels dropped from baseline to d7 and then increased on d14 post-eSBT (211.7±31.67 vs. 120±5.8 vs. 258±30.10; 14), and in NI cycles where a sharp rise on d7 was followed by a decrease in levels on d14 post-eSBT (201.1±13.95 vs. 1221.134 vs. 791.7±103.34). A significant difference in the ratio of d7:baseline DHEAS levels was observed in LB vs. BCP vs. EM vs. NI cycles (2.59 vs. 0.61 vs. 3.61 vs. 9.65; P<0.0001). Thus, a twofold rise in DHEAS levels from baseline to d7 and d7 to d14 is critical for successful implantation and live-birth.

CONCLUSIONS: Maintenance of a steady/balanced rise in serum DHEAS levels is an early indicator of successful implantation and predicts implantation failure/early miscarriage in eumenorrheic non-PCOS women undergoing IVF.

References:
3. Makieva S, Saunders PTK, Norman JE. Androgens in pregnancy: roles in...
OBJECTIVE: Studies show that b-HCG levels are similarly predictive of pregnancy outcomes in both fresh and frozen ET cycles(1). The objective of this study is to identify the b-HCG level at which the chance of biochemical pregnancy is the lowest.

DESIGN: A retrospective cohort study.

MATERIALS AND METHODS: A retrospective cohort study at a single academic center between 2013 and 2017. 1076 pregnancies obtained with fresh single embryo transfer (SET) were included after the result of day 16 embryo dated serum b-HCG levels. Exclusion criteria included: ≥15 transferred, multiples gestational sacs, ectopic pregnancies and those without a day 16 b-HCG. Statistics were compared using one-way ANOVA and chi-squared testing. Data is presented as Mean±SD. Blood samples were assayed on the Immulite 2500, with a solid-phase two-site chemiluminescent immunoassay, sensitive to 1 mIU/ml and calibrated to 5000 mIU/ml. Intra and inter-assay coefficients of variation <7%.

RESULTS: The 1076 pregnancies were divided into decile (10%) groupings of 107 or 108 patients each. Serum b-HCG levels increased across groups (18±7, 50±13, 103±19, 167±19, 223±15, 287±21, 350±20, 432±26, 547±49, 1274±1556, P=0.0001). The 10 groups did not differ for female age (P=0.07), male age (P=0.46), #folicles <14mm, #folicles ≥14mm (P=0.10), #oocytes collected (P=0.10), number of 2pn (P=0.43), % fertilized (P=0.54), number of cleavage (P=0.43), day of ET (P=0.14), #blastocysts (P=0.47) or embryo quality (P=0.21). The likelihood of a biochemical pregnancy loss decreased as b-HCG levels increased (97%, 84%, 50%, 21%, 12%, 7%, 5%, 4%, 2%, 1%, P<0.0001). Interestingly, at a b-HCG level of 103±13 (range 74-135), 50% had a biochemical loss. Biochemical pregnancy losses remained 21% at b-HCG range (136-197). It was only once serum b-HCG level reached 199-252 that the probability of a biochemical pregnancy loss was 12%. Once b-HCG level reaches the range 391-10764, the probability of a biochemical pregnancy loss was lower than 1%.

CONCLUSIONS: Half of subjects with a serum b-HCG level of 100 will have a biochemical pregnancy loss. The risk of biochemical pregnancy loss normalizes once serum b-HCG is 200IU/L, a level higher than expected. The rate reaches its lowest level once serum b-HCG levels are 400IU/L on day 16 of embryo life.


REPRODUCTIVE HORMONES

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LARGER SIZE OF THE OOCYTE COHORT DOES NOT AFFECT RISK OF EMBRYO ANEUPLOIDY WHEN USING NEXT GENERATION SEQUENCING (NGS).


OBJECTIVE: Recent advances in comprehensive chromosomal screening technology with NGS, have enhanced our ability to identify euploid embryos with high implantation potential (1,2). Embryos with lower potential for live birth containing aneuploidy or mosaicism, are discarded or reserved. Given this improved ability of NGS to detect the number of normal embryos developing from a single cohort of oocytes, we sought to evaluate whether oocyte retrieval yield, number of mature oocytes, or number of blastocysts biopsied, correlates with euploidy rate.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: 477 in vitro fertilization (IVF) cycles performed at a large university-based center during a three-year period were evaluated. IVF cycles with planned preimplantation genetic testing (PGT) performed using NGS were included for analysis. PGT results were reported as euploid, aneuploid or mosaic. Patients were divided into approximately equal groups based on number of oocytes retrieved, number of mature oocytes, and number of blastocysts biopsied. Patients were further stratified by age according to SART criteria. The primary outcome was rate of euploid embryos per cohort. Continuous variables were evaluated using Student’s t-test and ANOVA with Tukey’s multiple comparison test. Chi-square was used to assess categorical variables. Multivariate logistical regression was performed to control for potential confounding variables.

RESULTS: Euploidy rates differed based on number of oocytes retrieved (1-5: 23.9%, 6-10: 26.2%, 11-15: 29.5%, >16: 35.4%; P<0.03), number of mature oocytes (1-5: 19.1%, 6-10: 30.4%, 11-15: 32.6%, >16: 36.1%; P<0.01), and number of embryos biopsied (1-2: 24.3%, 3-4: 29.7%, 5-8: 35.8%, >9: 35.0%; P<0.01). After performing multivariate linear regression to control for potential confounders, no association between increasing oocyte yield and euploidy was appreciated (P=0.59). Similar findings were noted when analyzing euploidy rates by the number of mature oocytes (P=0.07) and embryos biopsied (P=0.43). After stratifying by age, only patients in the 38-41yo cohort were found to have higher rates of euploidy when more than 10 oocytes were retrieved, with a trend towards higher rates in the younger groups (Table).
CONCLUSIONS: Euploidy rate is not adversely affected when more oocytes are retrieved when measured within age strata. With the advent of Leuprolide trigger, reliable cryopreservation, and FET, this finding will likely lead us to more aggressive ovarian stimulation protocols, increase the odds of a euploid blastocyst, and maximize the chance of live birth with a single ovarian stimulation.

References:

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OBJECTIVE: To compare the ELISA (Enzyme Linked Immunosorbent Assay) and the ECLIA (Electro-chemiluminescence Immunoassay) for the estimation of AMH and its correlation with AFC and oocytes retrieved.

DESIGN: Prospective and retrospective observational study.

MATERIALS AND METHODS: AMH and FSH estimation is done using ECLIA method by analyzing the serum sample on the Roche-Cobas e411 autoanalyser on a real time basis with a coefficient of variance as 5.5% for level 1 and 5.7% for level 2 for AMH and 2.1% for level 1 and 2.4% for level 2 for FSH. For the ELISA method, all the data collected retrospectively.

INCLUDE EXCLUSION CRITERIA: All patients undergoing IVF treatment.

OUTCOMES MEASURED: Primary: Method of AMH estimation. ECLIA vs ELISA and its better correlation with AFC. Secondary: Method of AMH estimation, ECLIA vs ELISA and its better correlation with number of oocytes retrieved.

STATISTICAL ANALYSIS: Done on MS Excel 2010 and SPSS version 16. Correlation compared with ROC curves. A correlation analysis was performed to determine the degree of agreement between the ELISA and ECLIA kits for AMH estimation using the Kruskall Wallis test.

RESULTS: Post Hoc Tests were carried out for the two groups and shows that when the AFC was compared within the group (AFC: 1-6; 7-19; >/=20) where AMH was measured using ELISA there was no significant difference amongst them showing that AMH was not significantly different between those who had a low AFC and those who had a higher AFC; result substantiated with Kruskall Wallis test. (p=0.135) However when done with ECLIA - AMH was significantly different, also corroborated by the Kruskall-Wallis test. (p=0.0001).

When group was divided into three sub groups based on the number of oocytes retrieved (1-3; 4-14; >/=15) and with AMH being measured using ELISA as a constant the three groups were compared with each other. The AMH again was not significantly different among the three groups and further evaluation by Kruskall- Wallis test also showed no significance. (p=0.885) ; with ECLIA AMH was significantly different amongst them (p=0.0001).

CONCLUSIONS: ECLIA method of AMH estimation has better correlation with AFC as well as oocytes retrieved than the ELISA method. Cut off value for AMH for poor response in the ECLIA method using the ROC curve analysis is 0.81 with 95% sensitivity and 51% specificity. Cut off value for AMH for hyper response in the ECLIA method using the ROC curve analysis is 6.63 with 63% sensitivity and 95% specificity. ECLIA is an automated method and results can be generated faster with more predictive value. AFC and AMH can be used as a screening tool for poor response, but the index IVF cycle remains the best diagnostic tool for poor response. AFC and AMH can be used as a diagnostic test for hyper response.

References:

19.2 28.9

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<tr>
<td>Oocytes Retrieved</td>
<td>≤10 ≥11</td>
<td>36.1 47.8</td>
<td>41.2 46.2</td>
<td>19.2 28.9</td>
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Bold: p<0.05

| TABLE. Age & Euploidy Rates by Number of Oocytes Retrieved |
|------------------|--------|-------|--------|-------|
| Oocytes Retrieved | ≤10 ≥11 | 36.1 47.8 | 41.2 46.2 | 19.2 28.9 | 15.9 10.9 |

Supported by: None.
ESTRADIOL AND PROGESTERONE IN IN VITRO FERTILIZATION AND PROGESTERONE ELECSYS® ASSAYS. N. Polyzos, P. Drakopoulos, H. Tournaye, J. Schiettecatte, E. Anckaert, H. Donner, G. Bobba, G. Miles, W. Verhagen-Kamerbeek, E. Bosch. Deutsches Krebsforschungszentrum, Heidelberg, Germany; Roche Diagnostics, Indianapolis, IN; Roche Diagnostics, Penzberg, Germany; Roche Diagnostics International Ltd, Rotkreuz, Switzerland; Roche Diagnostics, Indianapolis, IN; Roche Diagnostics, Valencia, Spain.

OBJECTIVE: To assess estradiol (E2) and progesterone (P) results taken during ovarian stimulation for IVF when determined by third (III) and second (II) generation (Gen) Elecsys® assays. DESIGN: ESTRAT was a retrospective, non-interventional study, in which blood samples were collected from patients on a GnRH-agonist/antagonist protocol who had a normal, high or low (antagonist only) response to controlled ovarian stimulation, at two sites (UZB, n = 152, agonist and antagonist; IVI, n = 78, antagonist only). Samples were collected at 3-4 visits during the stimulation cycle, at time points reflecting the site’s routine clinical practice.

MATERIALS AND METHODS: Women (18-45 years, BMI 18-35kg/m²) with regular menstrual cycles (25-35 days) and both ovaries present were included in the study. The inclusion criteria were a positive serum hCG on day 14, at least 1 retrieved oocyte and a pre-implantation genetic testing. The assessed outcome was pregnancy. RESULTS: Patient baseline characteristics were balanced; 62 patients received a GnRH agonist protocol and 168 an antagonist protocol. Elecsys® Gen III and Gen II assay results were highly correlated for E2 (Pearson’s r = 0.99) and P (Pearson’s r = 0.89). For sites combined, the mean relative difference between E2 results (n = 801) determined with Gen III was -15.13% (SD = 13.32) compared with Gen II, whereas P results (n = 816) determined with Gen III were -43.31% (SD = 25.61) compared with Gen II. At day of triggering, Gen III E2 and P levels showed a difference of -14.98% and -27.89%, respectively. For 20 out of 36 patients with Gen II P levels > 1.5 ng/mL, results for Gen III were concordant. However, 16 patients had a P level < 1.5ng/mL with Gen III. Differences observed for E2 had minimal clinical relevance. E2 and P were shown to increase during controlled ovarian stimulation; the increases were greater in high responders versus normal clinical relevance. E2 and P were shown to increase during controlled ovarian stimulation, at two sites (UZB, n = 152, agonist and antagonist; IVI, n = 78, antagonist only). Samples were collected at 3-4 visits during the stimulation cycle, at time points reflecting the site’s routine clinical practice.

MATERIALS AND METHODS: Women (18-45 years, BMI 18-35kg/m²) with regular menstrual cycles (25-35 days) and both ovaries present were included in the study. The inclusion criteria were a positive serum hCG on day 14, at least 1 retrieved oocyte and a pre-implantation genetic testing. The assessed outcome was pregnancy. RESULTS: Patient baseline characteristics were balanced; 62 patients received a GnRH agonist protocol and 168 an antagonist protocol. Elecsys® Gen III and Gen II assay results were highly correlated for E2 (Pearson’s r = 0.99) and P (Pearson’s r = 0.89). For sites combined, the mean relative difference between E2 results (n = 801) determined with Gen III was -15.13% (SD = 13.32) compared with Gen II, whereas P results (n = 816) determined with Gen III were -43.31% (SD = 25.61) compared with Gen II. At day of triggering, Gen III E2 and P levels showed a difference of -14.98% and -27.89%, respectively. For 20 out of 36 patients with Gen II P levels > 1.5 ng/mL, results for Gen III were concordant. However, 16 patients had a P level < 1.5ng/mL with Gen III. Differences observed for E2 had minimal clinical relevance. E2 and P were shown to increase during controlled ovarian stimulation; the increases were greater in high responders versus normal responders.

CONCLUSIONS: E2 and P levels determined with Elecsys® Gen II and III assays were highly correlated. Results for both E2 and P were lower for Gen III versus Gen II. The differences observed for P at the day of triggering may be clinically relevant. Thus, clinicians changing to the Elecsys® Progesterone III assay should be aware of the differences during clinical decision-making.

Supported by: Funding: Roche Diagnostics.

P-399 Tuesday, October 9, 2018 6:30 AM


OBJECTIVE: To measure reproductive hormones, as well as inflammatory and angiogenic markers during pregnancy in 3 cohorts: pregnant women with 0, 1, or greater than 1 corpus luteum (CL).

DESIGN: Women were studied before, during and after pregnancy with up to 6 visits during pregnancy in each woman with 0 (n = 24), 1 (n = 22), or > 1 (n = 19) CL. Women with 0 and > 1 CL conceived using in vitro fertilization (IVF). Those with 1 CL were singleton pregnancies conceived without IVF.

MATERIALS AND METHODS: Participants were first studied before pregnancy in the follicular phase or in some cases of IVF during hypoalaminemic-pituitary suppression, in both cases without a CL. Pregnant women with 0 CL conceived by either donor embryo or autologous frozen embryo transfer (FET) or in ICSI. In the 0 CL group, subjects with 1 and > 1 CL conceived without IVF and standard IVF protocols, respectively. After the pre-pregnancy study, they were evaluated during gestation at 5-6 weeks, 7-9 weeks, 10-12 weeks, 14-16 weeks, 23-25 weeks, 32-35 weeks, and, on average, 11.5 months postpartum. Plasma samples were obtained at each visit and stored at -80°C until assay, which consisted of validated immunoassays, or in the case of low sensitivity CRP by Piccolo methodology. The pattern of change over time for each factor among the 3 cohorts was analyzed by linear mixed model applying nonparametric cubic spline.

RESULTS: There was no difference among the 3 cohorts for either hCG or E2. P4 showed a transient, but significant small peak at 5-6 weeks for the > 1 CL group. Otherwise, P4 was comparable among the groups throughout gestation. As expected, relaxin was undetectable in the 0 CL cohort and significantly elevated in the > 1 CL cohort compared to the 1 CL. The > 1 CL subjects showed a dichotomous response with approximately 50% having greatly elevated and 50% normal relaxin concentrations. sFLT1 demonstrated a peak at 32-35 weeks for all cohorts, but the concentrations were significantly higher in both the 0 and > 1 CL groups. This corresponded with decreasing PLGF from 23-25 to 32-35 weeks, whereas PLGF continued to increase in the 1 CL group between these two gestational age ranges. Interestingly, low sensitivity CRP was significantly elevated throughout gestation at < 15 mg/L in all 1 CL groups, and doubling from the assay threshold of 5 mg/L at pre-pregnancy to 10 mg/L, but was markedly suppressed throughout gestation for the > 1 CL cohort (< 5 mg/L).

CONCLUSIONS: Our findings suggest that, in addition to relaxin, IVF impacts both angiogenic and inflammatory marker profiles during pregnancy. Alteration of these hormone profiles may reflect compromised placental and predispose to adverse obstetrical outcomes, such as pre-eclampsia and intrauterine growth restriction.

Supported by: PO1 HD065647-01A1 — NIH NCATS UL1TR001427.
HCG-H and HCG among pregnancy outcome groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean (SD)</th>
<th>Linear regression β (95% CI)</th>
<th>Mean (SD)</th>
<th>Linear regression β (95% CI)</th>
<th>Mean (SD)</th>
<th>Linear regression β (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCG-H (mg/L)</td>
<td>19.0 (10.3)</td>
<td>-11.5</td>
<td>12.2 (8.4)</td>
<td>-6.8</td>
<td>4.1 (5.7)</td>
<td>-14.9 (-18.3,-11.5)</td>
</tr>
<tr>
<td>HCG (IU/L)</td>
<td>3.3-47.5</td>
<td>(-15.0,-8.0)</td>
<td>1.0-31.6</td>
<td>(-12.0,-1.6)</td>
<td>0.0-20.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>422.1 (222.5)</td>
<td>-234.6</td>
<td>338.1 (216.3)</td>
<td>-84.0</td>
<td>84.7 (118.0)</td>
<td>-337.4</td>
</tr>
<tr>
<td></td>
<td>56.0-1193.0</td>
<td>(-319.8,-149.4)</td>
<td>16.0-805.0</td>
<td>(-214.6,46.6)</td>
<td>4.0-442.0</td>
<td>(-408.3,-266.6)</td>
</tr>
</tbody>
</table>

**P-401 Wednesday, October 10, 2018 6:30 AM**

**MILITARY ACCESS TO FERTILITY TREATMENT: AN ASSESSMENT OF SOCIETY FOR REPRODUCTIVE TECHNOLOGY (SART) FERTILITY PRACTICE WEBSITES.** T. Zore, N. Joshi, S. B. Schon, P. Masson, E. Wang, M. D. Pisarska, J. L. Chan, Obstetrics and Gynecology, UCLA, Los Angeles, CA; 2Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI; 3University of Pennsylvania, Philadelphia, PA; 4Obstetrics and Gynecology, Cedars-Sinai Medical Center, Los Angeles, CA.

**OBJECTIVE:** Despite a recent law enabling wounded veterans to receive discounted fertility care, access to fertility evaluation and treatment for active duty and retired military personnel remains limited. Our objective was to evaluate the availability and quality of information that is inclusive of the military population on fertility practice websites.

**DESIGN:** Cross-sectional evaluation.

**MATERIALS AND METHODS:** Between 3/2017-4/2017, SART-member fertility practice websites were systematically examined by two separate reviewers. Websites were categorized by size (< 500 cycles/year vs. ≥ 500 cycles/year) and type of practice (academic vs. private). Websites were surveyed for contextual keywords including veteran or military that categorized them as being "veteran friendly". Additional information assessed included: availability/amount of IVF discounts, partnership with Compassionate Corps-a program that offers discounted fertility medications and acceptance of Tricare insurance. Chi-square tests were used to evaluate differences between groups. P < 0.05 was considered statistically significant.

**RESULTS:** 96% (372/388) of practices had a unique, active website of which 79% were private practice and 21% were academic. 235 practices performed < 500 cycles a year. Overall, only 79 (21%) practices were considered "veteran friendly." Of those 79 practices, 71 of them advertised a specific military discount and one practice offered free IVF to military personnel. The most common discount offered was between 21-30% and the highest discount advertised was 52%. Private practice websites were more likely to be "veteran friendly" (23.5% vs. 12.8%, p=0.04) as well as were more likely to offer a discount on IVF services or medications compared to academic centers (21.2% vs. 11.5%, p=0.05). Large volume practices (≥ 500 cycles) were more likely to be "veteran friendly" (34% vs. 14.9%, p< 0.01) while not statistically significant, more likely to offer a discount compared to small volume practices (32% vs. 13.3%, p=0.05). There was no difference between advertised discount amounts between different practice sizes or types. 25 practices advertised that they partnered with Compassionate Corps and large volume practices were more likely to advertise this than small volume practices (10.7% vs. 4.7%, p=0.04). Tricare insurance was advertised to be accepted by 37 practices with no difference in practice types or sizes.

**CONCLUSIONS:** This study suggests that only a minority of fertility practices are specifically targeting the veteran population through their fertility practice websites. Whether or not the inclusion of military specific benefits on websites affects the use of fertility services by veterans remains to be seen.

**P-402 Wednesday, October 10, 2018 6:30 AM**


**OBJECTIVE:** To summarize evidence on long-term economic impact of assisted reproductive technology (ART).

**DESIGN:** Systematic review of studies evaluating long-term (i.e., lifetime) economic impact of ART.

**MATERIALS AND METHODS:** Two independent reviewers conducted searches on PUBMED, MEDLINE, SCOPUS and through cross-referencing. Keywords are "ART", "IVF", "IUI", "infertility care", "infertility treatment", "economic impact", "lifetime", "lifetime productivity", "generational accounting", "net present value", and "net tax". We included peer-reviewed articles in English from database inception to 30 April 2018. 9 of 3576 identified papers were selected. All of them assessed long-term economic impact by calculation of net present value (NPV) based on a generational accounting (GA) model.

We calculated return on investment (ROI) by dividing discounted lifetime NPV by the cost of in vitro fertilization (IVF) or intrauterine insemination (IUI).

**RESULTS:** NPV was reported for 11 countries; Sweden (2008), the United States (2008), the United Kingdom (2008), Denmark (2011), Brazil (2011), Greece (2013), the Netherlands (2014), Ukraine (2015), Belarus (2015), Kazakhstan (2015) and Spain (2016). Long-term economic impact was reported for IVF-conceived children in all 11 countries and for IUI-conceived children in 1 country (Spain). The ART-conceived children had positive NPV (i.e., positive ROI) in all countries except for the Netherlands.

**IVF-conceived children:** Discounted lifetime NPV of IVF-conceived children ranged from -119,734 USD (Kazakhstan) to 27,552 USD (Sweden) with the median cost of 16,159 USD. Cost of IVF per live birth ranged from 4,147 USD (the Netherlands) to 215,450 USD (Denmark). Median discounted NPV by the cost of in vitro fertilization (IVF) or intrauterine insemination (IUI).
(the Netherlands). ROI ranged from -740.98% (the Netherlands) to 1,598.95% (Spain) with the median ROI at 353.66% (Greece).

IVF-conceived children:
Discounted lifetime NPV of IVF-conceived children was 84,470 USD. Cost of IVF per live birth was 4,558 USD and the ROI was 1,853.23%.

Influential factors:
Influential factors based on sensitivity analyses were economic growth rate, healthcare expenditure growth rate and discount rate but not cost of IVF or IUI. Correlational analyses between NPV of IVF-conceived children and gross domestic product (GDP) per capita indicated almost no correlation in developed countries, $r = -0.05$ but a highly correlated relationship in developing countries, $r = -0.77$.

All studies used GA to calculate NPV; however, there were variations in model structures and input parameters. None of the studies included broader economic benefits that individuals could contribute to their national economy beyond tax payment.

CONCLUSIONS: Evidence on long-term economic impact of ART showed positive NPV and ROI of approximately 354%. Therefore, ART can be perceived as a good investment from a societal perspective. However, there are limitations to the methods used to evaluate long-term economic impact of ART.

Supported by: The study was supported by the Thai Health Promotion Foundation.

P-403 Wednesday, October 10, 2018 6:30 AM

HOW OLD IS TOO OLD? OLDER COUPLES’ OPINIONS ON IVF AGE LIMITS. A. C. Davis, R. D. Nachtigall. Cleveland Clinic, Cleveland, OH; Obstetrics, Gynecology and Reproductive Sciences, UCSF, San Francisco, CA.

OBJECTIVE: To describe older couples’ attitudes and opinions about age limits for IVF, thereby informing the debate over current practices and policies with respect to age limits.

DESIGN: Mixed-methods, qualitative, interview-overview-based study.

MATERIALS AND METHODS: Our population was recruited from two Northern California IVF practices and included families in which the woman had conceived her first child after the age of 40. Two in-depth, semi-structured interviews were conducted over 6 months. These interviews were recorded and transcribed. Subsequent thematic analysis was performed of coded interview transcripts from 56 women and 29 men. Themes were analyzed using modified grounded theory.

RESULTS: There was no consensus to the overall question of the appropriateness of age limits for IVF with 31% in favor, 28% opposed, and 41% uncertain, thereby highlighting the heterogeneity of this patient population. In addition, there was no difference in the responses of men and women. Attitudes towards age limits were informed by concerns over the welfare of the child, parents’ motivations for childbearing, the health status of the parents, and ethical issues including autonomy, justice, and gender equality. Opinions emerged reflecting discomfort with the idea of postmenopausal pregnancy. Participants strongly referenced the personal nature of reproductive decision making and a minority voiced support for regulation if administered on an ethical and scientific basis.

CONCLUSIONS: The question of age limits for IVF is not an easy one even for older IVF patients with unequivocal personal experience. This population has extremely diverse views on age limits for IVF. Additional empirical research is needed to assess longer term outcomes and opinions for both older couples and their children as well as further evaluation of attitudes and opinions of this population in other geographic areas. We believe including the opinions of this particular population to be highly relevant to the discourse on this very sensitive topic.
INCREASED ACCESS TO FERTILITY CARE THROUGH CREATION OF PRIVATE FOUNDATIONS. J. C. Hairston, a D. McQueen, a C. Hammond, b R. Gerson, c E. C. Feinberg, a Obstetrics & Gynecology, Northwestern University Feinberg School of Medicine, Chicago, IL; bTimina Q. Cade Foundation, Owings Mills, MD; cKevin J. Lederer Life Foundation, Chicago, IL.

OBJECTIVE: The objective of this study was to understand the available financial assistance for infertility treatments provided by private foundations in the United States and Canada.

DESIGN: Cross-sectional study.

MATERIALS AND METHODS: Institutional Review Board (IRB) approval was obtained. A web-based search was performed to identify private foundations that provide financial support for infertility treatments. Foundations were invited to participate in a 14-question survey via email and non-responders were contacted by email and phone to increase participation. Descriptive statistics were analyzed.

RESULTS: Thirty-eight foundations that provide grant support for infertility treatments were identified. Twenty-six of the 38 foundations (68%) completed the survey, 1 foundation declined participation, and 11 did not respond. Among the 26 foundations, 9996 grants had been awarded for infertility treatments, with 1800 grants awarded in 2016 alone. Grants were either in the form of financial assistance (range $500-$25,000) or donated services (discounted treatment, reduced cost or fully covered IVF cycles). Eighty-eight percent (23/26) of foundations provided assistance to infertile couples, 12% (3/26) provided assistance solely for fertility preservation in cancer patients and 19% (5/26) provided financial support for elective oocyte cryopreservation. Seventy-three percent (19/26) and 65% (17/26) of the foundations included lesbian women and gay men respectively among grant awardees and 50% (13/26) assisted transgender patients. The included foundations have existed for between 2 and 25 years, with half of the foundations in existence for less than 10 years (median 7.5 years). Ninety-six percent (25/26) of foundations have a governing board. Fifty-eight percent (15/26) of foundations approvals were obtained. A web-based search was performed to identify private foundations that provide financial support for infertility treatments. Foundations that provide financial support for infertility treatments provided by private foundations

CONCLUSIONS: Private foundations vary greatly in the populations they serve, the geographic regions they cover and the amount of funds and services they provide. While private foundations have made an impact on the lives of many individuals, a more permanent solution of increased insurance cover may be needed for infertility services is greatly needed.
Given evidence for superior pregnancy rates with salpingectomy (2), we sought to measure this effect in a sample that included both inpatient and outpatient cases.

**DESIGN:** Retrospective cohort study, single health system.

**MATERIALS AND METHODS:** 782 cases of patients who required surgery for ectopic pregnancy between 2006 and 2017 were identified by chart review. Data from 155 patients (n=165 cases) managed surgically without methotrexate were abstracted.

Cases were stratified by evidence of the surgeon offering salpingectomy to the patient, as supported by the progress notes, surgical consent and/or operative report.

**RESULTS:**

- **In women seeking information regarding EOC, 33 (19.0%) reported interest in EOC specifically to delay child-bearing, 32 (18.4%) reported they did not want to delay fertility but were doing so as a result of their relationship status, and 21 (12.1%) reported they did not desire children but wanted to have the option in the future.**

- **There was no significant difference in mean age between these groups (p=0.33).**

- **The high cost of EOC was the leading stated barrier with 73.0% (127/174) reporting that it was the primary concern holding them back from pursuing EOC. Other stated barriers were a lack of knowledge about EOC, perceived disruption to daily life, and fear of side effects. Mean age was significantly higher in women who stated that cost was their primary concern compared to those who reported other concerns (34.6±4.7 vs. 32.6±6.0, p=0.02).**

- **66.7% (114/174) reported they would like to proceed with EOC in the next 12 months. 80.5% (140/174) reported they wanted to schedule a complimentary fertility assessment, consisting of serum AMH and antral follicle count.**

- **Mean age was not significantly different between those that did and did not want to schedule a complementary fertility assessment (34.1±5.4 vs. 34.0±3.7; p=0.92). There was no significant difference desired fertility assessment amongst women who stated that cost was their primary barrier and those who did not (p=0.29). To date, of the 253 women who presented to these sessions, 101 (39.9%) scheduled fertility assessments and 83 (32.8%) completed EOC cycles.**

**CONCLUSIONS:** Consistent with prior studies, purposeful delay of child-bearing is not the primary motivation for the majority of women at our education sessions. The high cost of EOC was reported as the greatest barrier to pursuing treatment even in this highly motivated cohort. Age may be a factor in cost considerations. Additional studies are needed to evaluate the potential role of a cost conscious EOC model to increase access to care.

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**P-408 Wednesday, October 10, 2018 6:30 AM**

**MOTIVATIONS AND PERCEIVED BARRIER TO CARE IN WOMEN SEEKING INFORMATION REGARDING ELECTIVE OOCYTE CRYOPRESERVATION (EOC).**


**OBJECTIVE:** Interest in EOC is growing amongst reproductive-aged women. Limited data exists on why women consider EOC and what prevents them from pursuing EOC. The primary objective of this study is to evaluate and characterize stated motivations and barriers to care in women seeking information on EOC.

**DESIGN:** Retrospective Cohort.

**MATERIALS AND METHODS:** From December 2016 - March 2018, Extend Fertility Medical Practice, a large single-center oocyte cryopreservation program offering a cost-conscious EOC model, hosted monthly public educational sessions on EOC. Following the session, attendees were given an optional feedback form. Respondents were asked for session feedback, plans regarding EOC, motivation for considering EOC, and primary concern holding them back from EOC. Free text responses were collected and characterized. Associations were compared using X² and student’s t-test.

- **RESULTS:** 253 women attended the information sessions, of which 174 (68.7%) completed the form. Mean age of respondents was 34±5.1, 35.1% (61/174) reported increasing age as their primary motivation for interest in EOC, 33 (19.0%) reported interest in EOC specifically to delay child-bearing, 32 (18.4%) reported they did not want to delay fertility but were doing so as a result of their relationship status, and 21 (12.1%) reported they did not desire children but wanted to have the option in the future. There was no significant difference in mean age between these groups (p=0.33).

- **The high cost of EOC was the leading stated barrier with 73.0% (127/174) reporting that it was the primary concern holding them back from pursuing EOC. Other stated barriers were a lack of knowledge about EOC, perceived disruption to daily life, and fear of side effects. Mean age was significantly higher in women who stated that cost was their primary concern compared to those who reported other concerns (34.6±4.7 vs. 32.6±6.0, p=0.02).**

- **66.7% (114/174) reported they would like to proceed with EOC in the next 12 months. 80.5% (140/174) reported they wanted to schedule a complimentary fertility assessment, consisting of serum AMH and antral follicle count.**

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Summary of study findings

<table>
<thead>
<tr>
<th>Where patients find information regarding male infertility:</th>
<th>Male respondents</th>
<th>Female respondents</th>
<th>Universal responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Wife’s physician</td>
<td>- Oncologist</td>
<td>- OB/GYN visit</td>
<td></td>
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<tr>
<td>- Primary care physician</td>
<td>- Infertility conferences</td>
<td>- Urologist</td>
<td></td>
</tr>
<tr>
<td>- Wife</td>
<td>- Books related to infertility</td>
<td>- Female infertility specialist (reproductive endocrinologist)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Infertility support groups</td>
<td>- Male infertility specialist</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Internet search engine</td>
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<tr>
<td></td>
<td></td>
<td>- Word of mouth</td>
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</tr>
</tbody>
</table>

Challenges obtaining information regarding male infertility or access to male infertility services:

<table>
<thead>
<tr>
<th></th>
<th>Male respondents</th>
<th>Female respondents</th>
<th>Universal responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Information from doctors often impersonal or cold</td>
<td>- Physicians may not provide realistic information about prognosis</td>
<td>- Lack of online resources for male infertility</td>
<td></td>
</tr>
<tr>
<td>- Lack of guidance about next steps when treatment fails</td>
<td>- Long wait times to see specialists</td>
<td>- Many online resources are untrustworthy</td>
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<tr>
<td>- Fewer resources available for men compared to women</td>
<td>- Many resources provide contradictory information</td>
<td>- Lack of specialists for men</td>
<td></td>
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<tr>
<td>- Many doctors seem to only care about the female</td>
<td>- Information is often above patient comprehension</td>
<td>- There is no streamlined process for both men and women to enter the healthcare system for infertility evaluations</td>
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<tr>
<td>- Cost of infertility evaluation</td>
<td></td>
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<tr>
<td>- Medical specialists unfamiliar with fertility minimize fertility concerns</td>
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Ideal characteristics of a new set of educational materials for male infertility:

<table>
<thead>
<tr>
<th></th>
<th>Male respondents</th>
<th>Female respondents</th>
<th>Universal responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Centralized repository of information</td>
<td>- Information available through different entry points to the healthcare system</td>
<td>- Combined information for both men and women</td>
<td></td>
</tr>
<tr>
<td>- Resources that are easy to access and interpret</td>
<td>- Information from reputable sources</td>
<td>- Information written in simple terms</td>
<td></td>
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<tr>
<td>- Information should be given in small quantities to avoid overload</td>
<td>- Use of questionnaires or surveys to tailor information</td>
<td>- Information tailored to the individual's specific health issues</td>
<td></td>
</tr>
<tr>
<td>- Diagrams and illustrations</td>
<td>- Comprehensive resources</td>
<td>- Glossary or definitions for common fertility terminology</td>
<td></td>
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<tr>
<td>- Information about prognosis and success based on diagnosis</td>
<td>- Use of statistics as well as anecdotal stories</td>
<td>- Answers to commonly asked questions</td>
<td></td>
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<tr>
<td>- Resources to address myths and misinformation</td>
<td>- Information about types of providers and circumstances in which they are useful</td>
<td>- What to expect from a fertility evaluation</td>
<td></td>
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<tr>
<td></td>
<td>- Resources for individuals living far from a large medical center</td>
<td>- How to navigate the healthcare system</td>
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<tr>
<td></td>
<td>- Information about recent studies or clinical trials related to male fertility</td>
<td>- Explanations of commonly performed tests and treatment options</td>
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<tr>
<td></td>
<td>- Information about genetic testing</td>
<td>- Incorporation of mental health or relationship resources</td>
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<tr>
<td></td>
<td>- Financial information</td>
<td>- Normalizing the infertility experience for men</td>
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<tr>
<td></td>
<td></td>
<td>- Links to outside resources for further information and providers</td>
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</tbody>
</table>
OBJECTIVE: Information and support related to reproductive health and infertility services is primarily geared toward female partners. The goal of this study was to assess the experience and needs of male partners who are faced with either male- or female-factor infertility.

METHODS: Exploratory focus groups.

MATERIALS AND METHODS: A focus group (3 men, 4 women) and two 90-minute community engagement studios with ten couples experiencing male-factor infertility (men and women in separate groups) were conducted by trained facilitators and documented via audio recordings and written summaries. Participants were recruited via social media. The focus group discussed men’s feelings and experiences related to male- and female-factor infertility. Studio participants discussed sources of male infertility information, topics to include in educational materials about male infertility, and experiences with fertility treatment.

RESULTS: Feelings of grief and loss related to the inability to have a family were common. Men also reported problems communicating with their partners, leading to emotional isolation. With female-factor infertility, men viewed their primary role as problem solvers while with male-factor infertility, men reported frequent self-blame, loss of manhood, and feelings of guilt and isolation. Men frequently experienced barriers to treatment. All participants reported frustration with the lack of information about male infertility and difficulty finding reputable websites. Men wanted easy to understand, centralized information about male infertility while women valued comprehensive, detailed materials with links to additional resources.

CONCLUSIONS: Male partners of infertile couples experience substantial, often unrecognized, emotional and psychological distress. The experience of men facing female-factor infertility is different from those facing male-factor infertility, which highlights the need for specific support services geared toward the male partner. Normalizing the experience, improving access for men, and developing easily-understood educational materials will better serve patients and allow them to become informed participants in their care.

Supported by: ASRM Research Grant.

P-411 Wednesday, October 10, 2018 6:30 AM

IT TAKES TWO TO TANGO: COUPLES’ LONG AND EXPENSIVE PATHS TO VARICOCELE REPAIR. A. Balasubramanian, N. Thirumavalavan, J. Scovell, J. J. Lo, B. Ji, E. L. Godfrey, A. W. Pastuszak, L. I. Lipshultz. Scott Department of Urology, Baylor College of Medicine, Houston, TX.

OBJECTIVE: Since females traditionally drive a couple’s fertility workup, we characterized infertile couples requiring varicocelectomy and their delay in presentation to a male infertility clinic.

DESIGN: Descriptive retrospective review of patients who underwent microsurgical varicocelectomy by two surgeons.

MATERIALS AND METHODS: Patients whose charts included partner histories were assessed for duration of attempting conception, prior workup, and prior use of assisted reproductive technology (ART). A student’s t test was used to compare total motile sperm counts between patients who used ART to those who did not. Time trying for conception was compared between those presenting with primary versus secondary infertility.

RESULTS: A total of 376 patients were included in the study population. At presentation, the mean age was 34.6 (range 21 - 63) years for men, and 31.15 (range 19 - 43) years for women. On average, couples were trying for 22 (range 0 to 120) months prior to presenting for male evaluation. 86% (307/356) of couples presented with concerns for primary infertility while 14% (49/356) of couples presented for secondary infertility. Couples with primary infertility were trying for pregnancy for an average of 21 months, while couples with secondary infertility were trying for pregnancy for an average of 29 months prior to presentation for male workup. However, the difference did not reach statistical significance (p=0.096), 59% (198/337) of couples were first seen by a gynecologist only, 24% (83/337) a reproductive endocrinologist (REI) only, 15% (50/337) presented without a female workup, and 2% (6) couples saw both a gynecologist and REI prior to presenting to a male infertility clinic. In total, 18% underwent ART prior to presentation (38/345 underwent intrauterine insemination (IUI) (range 1-10 cycles); 30% (104) in vitro fertilization (IVF) (1 to 4 cycles); 5% underwent both IUI and IVF) Couples who had undergone IUI or IVF had similar total motile sperm counts compared to others. The majority (72.3%) of females had no abnormality in their workup, making varicocelectomy the only correctable factor for infertility. The female conditions diagnosed are in Table 1.

CONCLUSIONS: Our findings show a significant delay in referral of infertile men requiring varicocelectomy. 18% of couples underwent IUI or IVF, a costly procedure, prior to having an inexpensive (<$1000) male workup (scrotal ultrasound, semen analysis, and hormone levels). In an era of medical cost containment, early referral to a male infertility specialist is imperative.

Supported by: NIH grants K12 DK083014, the Multidisciplinary K12 Urologic Research (KULe) Career Development Program awarded to D.J. L. (NT is a K12 Scholar) and R01DK078121 from the National Institute of Kidney and Digestive Diseases to D.J.L., and by a 2017 Urology Care Foundation Research Scholars Award to AWP.

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OBJECTIVE: GU injury has emerged as a signature wound of post-9/11 conflicts due to the prevalence of improvised explosive devices (IED) and advances in battlefield medicine, yet there have been few reports on the consequences of GU trauma. This study seeks to examine the lived experience of veterans with combat-related GU injuries and subsequent reproductive quality of life.

DESIGN: A qualitative phenomenological study.

MATERIALS AND METHODS: 10 Afghanistan war veterans suffering a wide variety of genital injuries participated in in-depth, semi-structured interviews that were audiotaaped and transcribed verbatim.

RESULTS: Veterans ranged in ages of 19 to 38 at the time of injury. GU injuries included hypogonadism, testicular atrophy or loss, and total loss of genitals. 9 injuries occurred as a result of an IED and 1 was due to gunshot. Post-injury, four veterans married, and one married at the time of the injury divorced. 2 veterans had children pre-injury, and 2 veterans had children via in vitro fertilization post-injury. Interviews yielded 3 primary themes: 1) feeling unprepared for and not fully understanding the fertility implications of their injuries; 2) not understanding the implications of testosterone treatment on: physical, sexual, and mental health; fertility; and difficulties in obtaining ongoing medication; and 3) avoidance of discussing the implications of their injury on sexual functioning and fertility for both medical professionals and veterans. One veteran explained feeling “broken”, “I tell everyone that the biggest injury that I’ve had isn’t losing my legs or fingers or the scars on my arms. It’s the actual ability to not have kids...because there’s nothing I can do that can change that. Walking in prosthetics, you have to train...do this...do that...to get better. But if you lose the ability to have kids, you’re not getting it back.” An unexpected finding centered on the challenges with testosterone as one veteran noted, “I was focused on: ‘Well, maybe I just don’t have as much muscle as I used to, or my libido isn’t as high as it used to be.’ But having the right hormone balance affects your personality and can contribute to depression which, looking back on it...I think I was depressed at the time...there was no in-depth discussion of the implications of the injury, and there really should have been. It was very superficial level. It was like, ‘You lost your testicles. Here’s a bottle of gel. Put some on every day. Good luck.’”

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CONCLUSIONS: While death and amputations were considered a risk of war by these veterans, there was a lack of preparation for life-altering implications on reproductive quality of life. These veterans (and caregivers) need assistance in discussing issues of fertility impairment, sexual functioning, and the effect of testosterone on health. Further consideration is needed to address GU injury prevention, fertility preservation and salvage, and the biopsychosocial impact of penile transplant and/or reconstruction.

References:

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ARE PATIENTS Assigned A NEW PATIENT CONCIERGE MORE LIKELY TO PROCEED WITH TREATMENT? D. Soltesz,a E. Lipov,a K. D. Bergin,a D. Gounko,a A. B. Copperman.a,b aReproductive Medicine Associates of New York, New York, NY; bObstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY.

OBJECTIVE: Navigating the health care system can be an overwhelming experience for patients pursuing fertility treatment. By implementing a New Patient Concierge process at a high volume fertility center, we aimed to evaluate if patients who receive additional intervention in the weeks pre and post new patient visit are more likely to move into treatment within the first 90 days post visit.

DESIGN: Randomized Control Trial.

MATERIALS AND METHODS: Patients calling to schedule a new patient appointment were randomly assigned to a specialist new patient concierge or a generalist call center representative by a hosted voice solution. Patients assigned to the concierge group received a dedicated coordinator who scheduled the new patient appointment, checked in with the patient pre and post new patient appointment to ensure all questions were answered, and provided direct contact information for key members of the patient’s physician team. Patients assigned to control group were scheduled by a call center representative, and were then sent routine instructions regarding next steps in filling out the new patient portal. Time to treatment and likelihood to proceed with treatment was evaluated.

RESULTS: A total of 132 patients in the concierge group and 2105 patients in the control group were evaluated for time to treatment at 30days, 90days and greater than 90days. Our findings showed that while average time to treatment was almost identical between the two groups with an average of 52.2 days for the control group and 53.3 for the concierge group, time to treatment was 2105) Concierge (n=132)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Statistics</th>
<th>Level</th>
<th>Control (n=2105)</th>
<th>Concierge (n=132)</th>
<th>Parametric p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to Treatment - 30 days</td>
<td>N (Col %)</td>
<td>Control</td>
<td>1902 (90.36)</td>
<td>116 (87.88)</td>
<td>0.353</td>
</tr>
<tr>
<td></td>
<td>N (Col %)</td>
<td>Treatment</td>
<td>203 (9.64)</td>
<td>16 (12.12)</td>
<td></td>
</tr>
<tr>
<td>Time to Treatment - 90 days</td>
<td>N (Col %)</td>
<td>Control</td>
<td>1699 (80.71)</td>
<td>88 (66.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>N (Col %)</td>
<td>Treatment</td>
<td>406 (19.29)</td>
<td>44 (33.33)</td>
<td></td>
</tr>
<tr>
<td>Time to Treatment - 90 days</td>
<td>N (Col %)</td>
<td>Control</td>
<td>1913 (76.63)</td>
<td>79 (59.85)</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>N (Col %)</td>
<td>Treatment</td>
<td>492 (23.37)</td>
<td>53 (40.15)</td>
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</tr>
</tbody>
</table>

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SELF-REPORTED BARRIERS TO ACCESSING INFERTILITY CARE: PATIENT PERSPECTIVES FROM URBAN GYNECOLOGY CLINICS. L. G. Insogna, L. V. Farland, E. Hariton, M. D. Hornstein. Obstetrics & Gynecology, Brigham & Women’s Hospital and Harvard Medical School, Boston, MA.

OBJECTIVE: Given the well-documented under-representation of minority women in infertility clinics in the United States, we designed a survey instrument to capture self-reported barriers to infertility care in an effort to better qualify the challenges of accessing treatment. We hypothesized that non-Caucasian women would be more likely to wait longer to seek infertility care and to report both socioeconomic and cultural barriers to care.

DESIGN: Cross-sectional survey study.

MATERIALS AND METHODS: In this pilot study, English or Spanish speaking women, ages 18-44, were recruited from resident gynecology clinics at two Boston academic medical centers between March-April 2018 (n=70). Participants were asked to approximate how long they would wait to seek care from a physician if they were having difficulty conceiving, to report demographic characteristics, personal and family history of infertility, knowledge of infertility treatments and the Massachusetts insurance mandate, and to list any potential perceived barriers to care. Logistic regression was used to model associations between self-reported barriers to care and race, education, and insurance status.

RESULTS: Non-Caucasian compared to Caucasian women were more likely to report cost (31.7% vs 25%), and missing work (17% vs 10.7%) as a barrier to infertility care. If having difficulty conceiving, the majority of both Caucasian and non-Caucasian women would present to care within 12 months. 76.0% vs 63.2% respectively. However, 38.8% of non-Caucasian women reported they would delay presenting to care beyond 12 months, compared to only 24.0% of Caucasian women (OR 1.85, CI 0.60 - 5.72). Additionally, participants without a college degree were more likely to wait beyond 12 months to seek care, 42.3% compared to only 17.4% of college graduates (OR 3.48, CI 0.92 - 13.17). Given the small sample size of this pilot study, however, these findings did not reach statistical significance. There was no difference in reported wait time when stratified by public, private, and non-profit insurance status. All 70 subjects endorsed a belief that physicians should discuss infertility treatment with women who are having difficulty conceiving. Most, 72% (50/69) of women, were not aware that Massachusetts law generally requires certain insurance companies to cover some or all of the cost of infertility treatment. The majority, 81% (55/68) of women, reported they would undergo infertility treatment if their insurance company covered the cost and 82% (58/70) believed access to infertility care is a right.

CONCLUSIONS: Though non-Caucasian women more frequently reported socioeconomic obstacles to receiving infertility care, these data suggest that additional factors are likely at play, including lack of information about insurance coverage policies.

Supported by: Reproductive Endocrinology Discretionary Fund.

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REPEATING ANNUAL FERTILITY ASSESSMENT: IS IT REALLY NECESSARY? O. Lebowitz,a R. Orvieto,b K. James,c J. C. Petrozza.a Department of Obstetrics & Gynecology, Division of Reproductive Endocrinology & Infertility, Massachusetts General Hospital, Boston, MA; aDepartment of OB/GYN, Massachusetts General Hospital, Boston, MA.
Division of REI, Chaim Sheba Medical Center, Ramat Gan, Israel; 4Massachusetts General Hospital, Boston, MA.

OBJECTIVE: It is a common practice that patients undergoing fertility treatments repeat their diagnostic testing every 12 months. However, there is no data to support this time interval. The study aims to assess the prevalence and extent of changes over repeated fertility evaluation tests in infertile women.

DESIGN: Retrospective cohort study at an academic fertility center.

MATERIALS AND METHODS: Infertile women who underwent repeat fertility evaluation tests following one year of fertility treatments were included. All patients had been evaluated for ovarian reserve (anti-Mullerian hormone [AMH], estradiol, FSH, and antral follicular count [AFC]), and uterine cavity assessment (hysterosalpingography, hysteroscopy, or sonohysterography). Each of the women’s test results at baseline evaluation were compared to repeat testing following one year of treatment. All ovarian reserve [OR] tests were measured between day 2-4 of the menstrual cycle. Cavity assessment was done in the follicular phase.

RESULTS: Among 160 patients included in the study an abnormal uterine cavity assessment [UCA] was observed in 25 (15.6%) patients. Of these positive findings, 8.1% were observed at baseline (7.5% poly or submucosal fibroid, and 0.6% chronic endometritis), and 7.5% were detected in repeated fertility evaluation (5.6% polyp or submucosal fibroid, and 1.9% retained product of conception). One patient diagnosed with endometrial polyp had evidence of malignancy in the pathological examination. All patients diagnosed with a cavity abnormality at baseline had a normal UCA in the repeated test. Comparing between baseline evaluation and the repeated testing for OR demonstrated an overall increase of 0.89±2.87 ml/mL for the FSH levels, and a decrease of 0.45±1.2 ng/mL, and 1.8±5.2 for the AMH and AFC, respectively. The rate of change in AFC varies significantly depending on the patients’ age and the cause of infertility. AFC declined by 3.2±6.3 follicles per year in women <35 years, compared with a reduction of 1.1±5.1 and 4.2±3.1 follicles in women aged 35-39 and ≥40 years, respectively (p=0.03). Decline in AFC was 3.6±6.1 and 3.6±6.9 follicles per year for patients with anovulation or idiopathic infertility, respectively, compared to 1.3±3.1 reduction for patients with diminished ovarian reserve (p=0.02).

CONCLUSIONS: The utility of yearly reevaluation of ovarian reserve and uterine cavity seems to be limited at best and provides very little clinical value, especially in patients actively undergoing treatment. Whether or not there is an ideal interval of testing requires further evaluation.

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DESIGN AND VALIDATION OF THE TRAK® VOLUME CUP - A DUAL PURPOSE SEMEN COLLECTION AND VOLUME MEASUREMENT DEVICE FOR DIAGNOSING HYPOSPERMA. L. L. Fredriksen,4 J. Epperson,5 K. Hong,4 G. Iacovetti,5 I. Doig,6 G. Sommer,6 U. Schaff.2 Research and Development, Sandstone Diagnostics, Livermore, CA; 4University of Queensland, Brisbane, Australia; 5Sandstone Diagnostics, Inc, Livermore, CA.

OBJECTIVE: To develop a semen sample collection cup that passively measures ejaculate volume and provides an indication for hyposperma (<1.5 mL, volume according to the WHO manual 5th edition). The Volume Cup is intended for home use by lay users as part of the Trak Male Fertility Testing System.

DESIGN: The Volume Cup was designed with internal geometries that funnel the collected semen sample into a volume measurement chamber for visual interpretation. The cup is enzyme-coated to assist sample liquefaction. The cup’s analytical performance was validated via a method comparison study, an interpretive reader study, and a classroom-style user interpretation test. An additional study was conducted to determine if users could correctly interpret the semen analysis parameter test results without the aid of a healthcare professional.

MATERIALS AND METHODS: Semen samples (N=232) were collected from consented human subjects directly into the Volume Cup, and tared weight measurement was used for gold standard volume measurement. Photographs of various volume results were presented to N=52 untrained, lay test subjects. N=32 additional test subjects were each presented with volume results diagnostic for ovarian reserve (anti-Mullerian hormone [AMH], estradiol, FSH, and antral follicular count [AFC]), and uterine cavity assessment (hysterosalpingography, hysteroscopy, or sonohysterography). Each of the women’s test results at baseline were compared to repeat testing following one year of treatment. All ovarian reserve [OR] tests were measured between day 2-4 of the menstrual cycle. Cavity assessment was done in the follicular phase.

RESULTS: The highest-ranking gaps (n=66) revealed five overarching thematic parameters: child outcome, maternal morbidity and mortality, effectiveness, education and training, and universal access to care and infertility interventions.

OBJECTIVE: Involuntary childlessness impacts up to fourteen percent of heterosexual couples globally, thus the burden and impact has been defined as significant. In addition, often a high psychosocial burden is placed on these couples as well as on members of their extended families and communities, especially within societal frameworks for which parenthood is critical to recognition and acceptance. Evidence-based fertility care and infertility interventions that are able to assist those with fertility problems can help to safeguard maternal, paternal and child health outcomes when delivering and improving access to care. Furthermore, ensuring appropriate implementation of recommended interventions can often prove to be (cost-)effective and can indicate a high quality of care. However, a systematic analysis of literature during the development of a set of basic, but comprehensive global draft recommendations for the World Health Organization to consider for infertility and fertility care has exposed a large number of gaps in the evidence. A strong evidence base is required to ensure interventions will support quality care and a high level of evidence to inform access to care.

CONCLUSIONS: A mechanism was needed to identify a shortlist of and then a prioritization process for all of the identified evidence gaps in order to generate a prioritized global research agenda. A Delphi survey was initiated among groups of multi-disciplinary experts and patients, and members representing reproductive medicine societies, infertility patient organizations, UN agencies and non-governmental agencies.

MATERIALS AND METHODS: Delphi Round I identified key evidence gaps (n=127) in six prioritized clinical areas. The identified evidence gaps themselves were prioritized in Round II, and these prioritized evidence gaps were then rated for importance in Rounds III and IV, resulting in a ranking within and across the six clinical areas.

RESULTS: The highest-ranking gaps (n=66) revealed five overarching thematic parameters: child outcome, maternal morbidity and mortality, effectiveness, education and training, and universal access to care and infertility interventions.

CONCLUSIONS: This prioritized research agenda which will be presented should be able to assist decision-makers, researchers and funding agencies in the development of their respective research portfolios aiming to increase global access to care and strengthen the evidence supporting fertility care and infertility interventions.
HEALTH DISPARITIES

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ENSURING HUMAN RIGHTS IN THE PROVISION OF FERTILITY CARE AND INFERTILITY INTERVENTIONS. S. Van Der Poel,a,b J. B. Davis,a,b Population Council, WHO (retired), Vesenaz, Switzerland; cReproductive Medicine Associates of New York, New York, NY.

OBJECTIVE: There are reports that define the significant unmet need for access to fertility care and infertility interventions for heterosexual couples - those who experience involuntary childlessness and who desire a biological child. This need for access to care rarely measures those couples in non-heterosexual relationships, single individuals or in key/neglected populations. This disparity in recognition of need, and resultant lack of access to care is glaring. Universal access and attainment of the highest standard of care requires the provision of high-quality information and services that fulfills, protects and respects all individuals. The objective of this study was to identify the key principles that support access to fertility care and infertility interventions, and to provide a human rights framework to guide processes during the development of draft recommendations to the World Health Organization (WHO) for clinical practice.

DESIGN: To evaluate the public health and human rights and gender impact on infertility, a literature review and systematic analysis were conducted to look at the following questions. What are the existing policies, public health directives and research evidence gaps impacting gender and human rights in the context of involuntary childlessness and infertility; and, what human rights principles guide the development and implementation of fertility care and infertility related laws, policies and systems?

MATERIALS AND METHODS: A detailed search strategy in collaboration with the WHO-HP librarian, introducing various combinations of predetermined set of terms was undertaken to identify primary literature, systematic reviews and gray literature, including documentation regarding current status of human rights and gender equality within policy and practices.

RESULTS: Using the search strategy defined, we were able to identify 488 articles, and documents, of which 102 were found appropriate. They were then categorized using 9 principles previously identified by WHO and used to address the topic of contraception. From this process, we generated a list of 12 principles which will be presented that cover issues such as non-discrimination, non-stigmatization as well as informed-decision making and autonomy, sharing of benefits and ensuring provision of care that includes the recognition of the health and well-being of the parent or parents as well as the children born.

CONCLUSIONS: During the systematic review of the published data and evidence for the development of draft clinical recommendations to be presented to and for the World Health Organization consideration, it was clear that a human rights framework was required. Our systematic review process used research and policy evidence to support the development of a framework of principles that can better ensure different human rights dimensions are clearly and systematically integrated into the provision of fertility care information and fertility interventions and services.

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SUCCESS OF FRESH IVF CYCLES AND AREA-LEVEL DEPRIVATION INDEX. S. Choe,a,b E. Yu,c J. Hwang,d

OBJECTIVE: We analyzed 4,581 women who had undertaken one or more fresh IVF cycles at a single IVF center from January 2006 to December 2014 and lived in Seoul at the time of IVF treatment.

RESULTS: Intrauterine pregnancy rate per cycle was 34.9% and 51.3% per individual. District-level deprivation index was 0.4 on average, ranging from -5.21 (least deprived) to 2.57 (most deprived). When the population was divided into 4 groups by deprivation index quartiles, intrauterine pregnancy occurred in 39.1% (least deprived), 34.1%, 34.8%, and 35.3% (most deprived) of each group (P for trend = 0.973). In multivariable models, the probability for intrauterine pregnancy in IVF cycles was 0.97 (95% CI: 0.87, 1.08) in 2nd, 1.07 (0.96, 1.19) in 3rd, and 0.96 (0.85, 1.09) in 4th quartile of deprivation index compared to lowest quartile group.

CONCLUSIONS: We found no association between area-level deprivation index of women's residence and probability of successful IVF pregnancy. Future studies exploring environmental factors and IVF pregnancy would better use other index of social deprivation than area-level deprivation index.

References:

Supported by: This work was supported by the National Research Foundation of Korea (NRF-2016R1A1B103933410).

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FACTORS ASSOCIATED WITH DISPARATE OUTCOMES AMONG AFRICAN AMERICAN WOMEN UNDERGOING IVF. L. Ghidei,a,b C. Raker,a,b L. Brayboy,a,b cDepartment of Obstetrics and Gynecology, Women and Infants Hospital of Rhode Island, Providence, RI; cDepartment of Obstetrics and Gynecology, Division of Research, Women and Infants Hospital of Rhode Island, Providence, RI; cDepartment of Obstetrics and Gynecology, Division of Reproductive Endocrinology, Women and Infants Hospital of Rhode Island, Providence, RI.

OBJECTIVE: To determine if African American (AA) women living in the United States have worse IVF outcomes than White women and to determine which factors are associated with worse IVF outcomes of AA women.

DESIGN: This is a retrospective cohort study that utilizes de-identified data from the national eIVF database.

MATERIALS AND METHODS: The eIVF database is composed of 64 clinics. Patient charts from the database were extracted if they had at least one embryo transferred during IVF. The variables of interest include patient characteristics, cycle characteristics, and outcomes such as spontaneous abortion rate (SABR), clinical pregnancy rate (CPR), and live birth rate (LBR).

RESULTS: 175,769 patient-cycles were analyzed. 2.6% of patients were AA, 26% were White, and 3% were Hispanic/Latino. AA patients were significantly more likely to be under the age of 35 years old (61% AA vs 50% White, p<.0001) and significantly more likely to be obese (36% AA vs 22% White, p<.0001). AA women were more likely to be diagnosed with tubal factor (19.8% vs 8.6% White, p<.0001) and uterine factor (7.4% vs 3.1% White, p<.0001). AA women also were more likely to have a pre-gestational diagnosis of hypertension than White women (1.8% vs 8.8% White, p<.0001), and diabetes mellitus (3.4% vs 1.3% White, p<.0001). AA women reported more psychological stress than White women (15% vs 7% White, p<.0001). CPR was significantly lower for AA women compared to all other races (46% AA vs 55% White, p<.0001; 60% Hispanic vs. p<.0001; 62% Asian p<.0001). The odds of a live birth from all cycles were 45% less than for White women (OR 1.00 vs 1.45, p<.0001) and 30% less than for Hispanic women (OR 1.0 vs 1.3, p<.0001). This significant difference of LBR persisted even after adjusting for patient characteristics (age, BMI, infertility diagnosis, hypertension, diabetes, cycle type,
African-American women had a higher adjusted odds of adverse perinatal outcomes among African-American women after controlling for demographic factors, access to prenatal care and co-morbidities, mode of delivery and perinatal outcomes (6.92% vs. 2.55%, p < 0.001). On multivariate analysis adjusted for demographic factors, access to prenatal care and co-morbidities, there were no significant differences in maternal outcomes among racial groups. However, African-American women had a higher adjusted odds of cesarean delivery (aOR: 1.35; 95% CI: 1.31-1.39), low birth weight (aOR: 1.65; 95% CI: 1.55-1.76), preterm birth (aOR: 1.32; 95% CI 1.24-1.41) and NICU admissions (aOR: 1.29, 95% CI: 1.20-1.38).

CONCLUSIONS: Consistent with racial disparities in perinatal outcomes observed in the general population, among women utilizing fertility services, African-American race was found to be an independent risk for suboptimal perinatal outcomes even after adjusting for traditional risk factors. The reasons for these differences remain unclear and warrant further studies. Tailored approaches to counseling and pregnancy monitoring for African-American women undergoing infertility treatment may be beneficial.

Table I: Baseline characteristics and outcomes for Asian and Caucasian women undergoing ART

<table>
<thead>
<tr>
<th>Race/Ancestry</th>
<th>Age (y) P&lt;0.01*</th>
<th>BMI (kg/m²) P&lt;0.01*</th>
<th>Total dose gonadotropins p=0.36</th>
<th>Number of follicles p&lt;0.01*</th>
<th>Peak estradiol (pg/mL) P=0.02</th>
<th>Estradiol per follicle (pg/mL) P&lt;0.01*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian (n=388)</td>
<td>35.8 (±3.4)</td>
<td>23.5 (±4.1)</td>
<td>2120.0 (±832.1)</td>
<td>21.9 (±12.7)</td>
<td>2598.0 (±1594.7)</td>
<td>122.6 (±53.8)</td>
</tr>
<tr>
<td>Asians (n=302)</td>
<td>36.5 (±3.5)</td>
<td>22.7 (±3.1)</td>
<td>2181.0 (±889.0)</td>
<td>19.5 (±10.9)</td>
<td>2911.0 (±1824.6)</td>
<td>154.4 (±69.2)</td>
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<tr>
<td>Asian subgroups</td>
<td></td>
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<tr>
<td>Japanese (n=17)</td>
<td>37.1 (±2.8)</td>
<td>22.9 (±2.4)</td>
<td>2339.9 (±790.5)</td>
<td>15.2 (±8.5)</td>
<td>2378.1 (±1645.4)</td>
<td>153.1 (±57.8)</td>
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<td>Filipino (n=29)</td>
<td>35.4 (±3.7)</td>
<td>24.5 (±3.8)</td>
<td>1979.7 (±734.4)</td>
<td>20.6 (±9.5)</td>
<td>2850.4 (±1403.8)</td>
<td>147.9 (±61.0)</td>
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<td>Korean (n=33)</td>
<td>36.7 (±2.8)</td>
<td>23.7 (±3.8)</td>
<td>2042.4 (±801.5)</td>
<td>20.0 (±11.2)</td>
<td>2945.4 (±1522.7)</td>
<td>161.4 (±69.7)</td>
</tr>
<tr>
<td>Chinese/Thai (n=135)</td>
<td>36.4 (±2.7)</td>
<td>21.9 (±2.5)</td>
<td>2197.4 (±954.1)</td>
<td>20.1 (±11.0)</td>
<td>2989.5 (±1907.0)</td>
<td>154.1 (±73.5)</td>
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<tr>
<td>Indian/Pakistani (n=48)</td>
<td>36.7 (±3.4)</td>
<td>23.1 (±2.8)</td>
<td>2315 (±971.0)</td>
<td>18.4 (±12.2)</td>
<td>2870.1 (±2314.3)</td>
<td>150.6 (±71.4)</td>
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<td>Vietnamese/Thai (n=40)</td>
<td>37.0 (±3.4)</td>
<td>22.5 (±3.4)</td>
<td>2164.7 (±763.2)</td>
<td>20.0 (±10.4)</td>
<td>2937.1 (±1471.3)</td>
<td>159.1 (±64.6)</td>
</tr>
</tbody>
</table>

CONCLUSIONS: The purpose of this study was two-fold: 1) to determine if Asian women undergoing assisted reproductive technology (ART) demonstrated higher peak estradiol level per follicle compared to their Caucasian counterparts, and 2) to evaluate if the peak estradiol level per follicle varied among women in select Asian populations.

DESIGN: This was a retrospective cohort study.

MATERIALS AND METHODS: The chart review encompassed patients who underwent their first ovarian stimulation cycle for either in vitro fertilization or oocyte cryopreservation between 2010 and 2018 at a single center academic fertility practice. Only patients with self-reported race identified as Caucasian or as belonging to one of the following Asian groups were included in the study: Chinese/Taiwanese, Filipino, Indian/Pakistani, Japanese, Korean, Vietnamese/Thai. Subjects with age <21 years or body mass index (BMI) <15 kg/m² were excluded. The primary outcome variable was peak estradiol per follicle. Peak estradiol per follicle was compared between Asian and Caucasian women and between Asians in the select populations using an ANOVA to adjust for age, BMI and total dose of gonadotropins. All testing was performed at the 0.05 level of significance.

RESULTS: 302 Asian and 388 Caucasian subjects were included. The breakdown of the six Asian populations that were analyzed was as follows: Chinese/Taiwanese 44.7% (n=135), Filipino 9.6% (n=29), Indian/Pakistani 15.9% (n=48), Japanese 5.6% (n=17), Korean 10.9% (n=33), Vietnamese/Thai 13.3% (n=40). There was no difference in age, total gonadotropin dose, or number of follicles between the members of the Asian subgroups. The estradiol level in Asians was significantly higher than Caucasian women, even after controlling for age, BMI and total dose of gonadotropins. All testing was performed at the 0.05 level of significance. There was no difference in estradiol per follicle between the Asians in the select populations both before and after adjusting for age, BMI and total dose of gonadotropins (p=0.97 and p=0.98, respectively).

CONCLUSIONS: Similar to findings in other studies, Asian women were noted to have higher estradiol levels than their Caucasian counterparts. There was no difference in the peak estradiol per follicle level among the members of the select Asian populations undergoing ART.
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RUBELLA IMMUNITY IN INFERTILITY PATIENTS. J. L. Keating, K. A. Hansen, T. Von Wald. "Ob/Gyn, University of South Dakota Sanford School of Medicine, Sioux Falls, SD; "Ob/Gyn, Sanford Health, Sioux Falls, SD.

OBJECTIVE: To evaluate rubella immunity and corresponding demographics of infertility patients and identify patients at risk of rubella nonimmunity.

DESIGN: Retrospective review of electronic medical records (EMR).

MATERIALS AND METHODS: IRB approval was obtained. The study consisted of a retrospective review of the EMR for female patients, ages 18 to 50, who were new patients receiving an infertility workup at a Midwestern reproductive endocrinology clinic from January 1, 2014 through December 31, 2016. Of those patients who had RV-IgG titers noted in their EMR, the following demographics were collected: age, race, gravidity and parity, state of residence, and community size. Data were compiled using MS Excel software and statistically analyzed using SAS v 9.4. Continuous variables were compared using t-tests. Discrete variables were compared using \( \chi^2 \) tests. The analyses were deemed to be statistically significant when \( p < 0.05 \).

RESULTS: There were 750 patients included in the study. Rubella titers were drawn on 72.7% of the patients. Of those drawn, 90.8% had a positive rubella titer. Caucasians/Whites, Asians, and African Americans/Blacks had the highest rates of rubella immunity, while American Indians/Alaskan Natives had the lowest rates of immunity (\( p = 0.0006 \)). Nulligravida participants had a positive rubella titer rate of 94.1%, while primigravida participants had a rate of 89.8% (\( p = 0.04 \)). Participants living in the largest sampled communities had the lowest rates of positive rubella titers, while those living in the smallest communities had the highest rates of positive rubella titers, although these findings were not statistically significant.

CONCLUSIONS: In new infertility patients presenting for evaluation, 27.3% did not have a rubella titer drawn as part of their fertility workup. Of the 72.7% of patients for whom titers were checked, nearly 10% were not immune to rubella. The groups with the lowest immunity included the American Indian/Alaskan Native population and primigravid patients. Vaccination education and efforts should be focused accordingly.

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DOES PLACENTAL MORPHOLOGY DIFFER BY RACE IN IVF PREGNANCIES? C. R. Sacha, A. L. Harris, K. M. Basnet, K. James, I. Souter, D. J. Roberts, T. L. Toth. "Ob/GYN, Massachusetts General Hospital and Harvard Medical School, Boston, MA; "Reproductive Endocrinology and Infertility, Massachusetts General Hospital, Boston, MA; "Pathology, Massachusetts General Hospital, Boston, MA; "Massachusetts General Hospital Fertility Center and Harvard Medical School, Saint Bartholomew’s Hospital, London, England; "Obstetrics and Gynecology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston IVF, Boston, MA.

OBJECTIVE: To examine whether placental morphology in IVF pregnancies differs by race, given that the rates of obstetric complications such as hypertensive disease and preterm birth have been shown to vary amongst racial groups in the United States.

DESIGN: Retrospective cohort study

MATERIALS AND METHODS: A cohort of live births with placental pathology arising from autologous IVF cycles between 2004 and 2015 were retrospectively reviewed. Placental pathologies were categorized using the pathology reports as: anatomic (e.g. cord and membrane insertion), infectious (chorioamnionitis), inflammatory (e.g. chronic villitis of unknown etiology or plasma cell deciduitis), and vascular/thrombotic (placental abruption, intervillous thrombus, maternal or fetal vascular malperfusion). Chi square tests were used to compare placental morphology between women identifying as white, black, or Asian race. We controlled for age, body mass index (BMI), infertility diagnosis, gestational age, and number of fetuses.

RESULTS: A total of 666 placentas with associated racial demographic data were available for review, including 564 from white women, 18 from black women, and 84 from Asian women. There were no significant differences in gross placental morphology between white, black, and Asian women (Table).

CONCLUSIONS: Although limited by low numbers of black and Asian women, this foundational study suggests that racial differences in adverse obstetric outcomes cannot be explained by altered placental morphology in IVF pregnancies.

Variation in placental morphology according to race.

<table>
<thead>
<tr>
<th>Category</th>
<th>White (n=564)</th>
<th>Black (n=18)</th>
<th>Asian (n=84)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomic</td>
<td>47%</td>
<td>56%</td>
<td>57%</td>
<td>0.2</td>
</tr>
<tr>
<td>Infectious</td>
<td>22%</td>
<td>11%</td>
<td>26%</td>
<td>0.3</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>14%</td>
<td>17%</td>
<td>18%</td>
<td>0.6</td>
</tr>
<tr>
<td>Vascular/thrombotic</td>
<td>55%</td>
<td>61%</td>
<td>57%</td>
<td>0.8</td>
</tr>
</tbody>
</table>

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OBJECTIVE: While racial disparities regarding access to care are well established, differences following ovarian stimulation for IVF have not been well characterized. This study aimed to determine if women of various racial backgrounds undergoing IVF demonstrate differential ovarian response to
stimulation, and morphokinetic and chromosomal development of resulting embryos.

**DESIGN:** Retrospective

**MATERIALS AND METHODS:** IVF cycles from 2003-2018 were included. Trophodermoid (TE) biopsy and pre-implantation genetic testing for aneuploidy (PGT-A) were performed on select blastocysts. Patient demographics and cycle characteristics were recorded, including number of total, metaphase II (MII) and fertilized oocytes, TE biopsy day, number of blastocysts and euploid embryos were recorded. MII, fertilization, blastulation and euploid rates were determined. Patients were grouped by race: African American (AA), Asian, Caucasian. Data was analyzed with a T-test, Chi-square, and multivariate logistic regression.

**RESULTS:** A total of 2,171 IVF cycles were performed. Differences in baseline characteristics are in table 1. While number of oocytes and MII rate were similar, number of MII (p < .01), blastocysts (p < .01) and blastulation rate (p < .01) were highest for AA patients. The number of fertilized oocytes was highest for Caucasian patients (p = .03) but Asian patients had the highest fertilization rate (p < .01). AA women had more blastocysts biopsied (p < .01) and Caucasian women had more euploid embryos (p < .01); but, the euploid rate did not differ after adjusting for confounders (p = .26). Fertilization was 26% less likely for AA compared to Caucasian women (OR 0.7, 95% CI 0.7-0.9), yet blastulation was almost 2 times more likely for AA women (OR 1.7, 95% CI 1.4-2.0) compared to Caucasian women after adjusting for confounders. Blastulation was also approximately 15% less likely for Asian (OR 0.87, 95% CI 0.8-0.96) compared to Caucasian women.

**CONCLUSIONS:** Women of different racial backgrounds exhibit heterogeneity in ovarian response to stimulation, fertilization, and embryo development. This large study revealed a greater response to ovarian stimulation in AA women, and a lower response in Asian woman, compared to Caucasian women, but no differences in euploid rate.


**P-426**

**THE LIKELIHOOD OF IMPLANTATION FOLLOWING TRANSFER OF A EUPLOID EMBRYO IS NOT CORRELATED WITH SELF-REPORTED RACE.**

**T. G. Nazem,**<sup>1,2</sup> **L. Sekhon,**<sup>3</sup> **J. Lee,**<sup>4</sup> **D. Gounko,**<sup>4</sup> **A. B. Copperman,**<sup>4</sup> **D. Stein,**<sup>5,6</sup> **Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY; 4Reproductive Medicine Associates of New York, New York, NY; 5Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai West, New York, NY.

**OBJECTIVE:** Data are conflicting regarding the impact of a patient’s race on assisted reproductive technology treatment success. Dhillon et al. observed lower IVF pregnancy rates in African American (AA) and Asian women compared to Caucasian women; but findings were limited to cycles involving fresh, unscreened embryo transfers. The current study sought to determine differences in pregnancy outcomes in women of different racial groups who undergo a single, euploid frozen embryo transfer (FET).

**DESIGN:** Retrospective

**MATERIALS AND METHODS:** Patients who underwent IVF and single, euploid FET between 2015-2017 were included. Trophodermoid biopsy and pre-implantation genetic testing for aneuploidy (PGT-A) were performed. Patient age, body mass index (BMI), self-reported race, endometrial type/thickness at transfer, blastocyst morphologic grade and day of embryo biopsy were recorded. Clinical pregnancy (CP) was confirmed by sonographic evidence of a gestational sac. Ongoing pregnancy/live birth (OP/LB), early pregnancy loss (EPL), and clinical pregnancy loss (CPL) rate were determined. Patients were grouped by race: AA, Asian, and Caucasian. Data were analyzed using a Student’s t-test, Chi square/Fisher’s Exact test, Cochran Armitage trend test, and binary logistic regression.

**RESULTS:** A total of 812 patients underwent 1,111 single, euploid FETs. Compared to other groups, patients of AA (n=51) descent were older (38.0 ± 3.1 yrs, p = 0.0006), had a higher BMI (27.0 ± 4.2, p = 0.0001) and were more likely to have a TE grade of A (53.1%, p = 0.02). Asian (n=237) patients were more likely to be nulliparous (84.9%, p = 0.03) compared to Caucasian women. All other cycle characteristics were similar among racial groups (Table). There were no significant differences in CP (p = 0.67), OP/LB (p = 0.51), EPL (p = 0.73), or CPL (p = 0.12) rates among ethnicities, before and after adjusting for confounders.

**CONCLUSIONS:** Successful IVF outcomes following the transfer of a single, euploid embryo do not appear to differ among women of different races. Despite differences in age, BMI and parity observed among women of different races in this study, these dissimilarities did not contribute to pregnancy outcomes. Utilization of a combined PGT-A and FET protocol in a high quality laboratory results in universally high pregnancy rates and low miscarriage rates, regardless of patient race.


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**Baseline Characteristics and Demographics among Patients of Different Ethnicities**

<table>
<thead>
<tr>
<th></th>
<th>African American (n=51)</th>
<th>Asian (n=237)</th>
<th>Caucasian (n=823)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>38.0 ± 3.1±*</td>
<td>36.2 ± 3.6*</td>
<td>35.9 ± 3.9*</td>
<td>0.0006</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.0 ± 4.2*</td>
<td>23.0 ± 3.8*</td>
<td>23.7 ± 4.3*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nulligravid/Nulliparous</td>
<td>24 (48%)/38 (76%)</td>
<td>117 (50.7%)/196 (84.9%)</td>
<td>406 (49.3%)/607* (73.8%)</td>
<td>0.40/0.03</td>
</tr>
<tr>
<td>Endometrial Thickness at time of Transfer (mm)/Endometrial Type 2 at time of transfer</td>
<td>9.7 ± 2.1/11 (21.6%)</td>
<td>9.5 ± 1.8/39 (16.7%)</td>
<td>9.6 ± 1.9/155 (18.8%)</td>
<td>0.80/0.60</td>
</tr>
<tr>
<td>Embryo biopsy on Day 5</td>
<td>37 (72.6%)</td>
<td>163 (68.8%)</td>
<td>579 (70.4%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Embryo Etapamorphosis E4</td>
<td>23 (45.1%)</td>
<td>98 (41.4%)</td>
<td>320 (39.2%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Embryo Inner Cell Mass Grade A</td>
<td>33 (67.4%)</td>
<td>146 (63.5%)</td>
<td>555 (67.4%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Embryo Trophodermoid Grade A</td>
<td>26* (53.1%)</td>
<td>67* (29.1%)</td>
<td>289* (35.1%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Clinical Pregnancy Rate</td>
<td>28 (54.9%)</td>
<td>150 (63.3%)</td>
<td>511 (62.0%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Ongoing Pregnancy/Live Birth Rate</td>
<td>25 (49.0%)</td>
<td>126 (53.2%)</td>
<td>448 (54.4%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Clinical Pregnancy Loss Rate</td>
<td>3 (8.6%)</td>
<td>24 (13.4%)</td>
<td>63 (12.3%)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

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**FERTILITY & STERILITY® e279**
ED visits with a principal diagnosis (ICD-9) of EP between 2006-2014. Parameters assessed included the number of ED visits, admission rates, hospital geographic location, patient demographic characteristics, and ED charges. Z-tests were performed to compare counts and proportions across groups and years, and analysis was performed using SAS V9.4 Cary, NC.

RESULTS: Nearly 75% of all ED visits for EP were in patients belonging to the 20-34 yo age group. The estimated number of ED visits increased slightly from 44,217 to 50,607 between 2006-2014 (p < 0.028), however, the overall percentage of ED visits for EP compared to all ED visits for other diagnoses in women of the same age group remained stable at 0.13% throughout the years. The average charges per ED visit for EP increased 120%, from $4,808 to $10,557 between 2006-2014 (p < 0.0001), yielding total annual charges of $213M and $534M, respectively. During the same time period, the average charges for ED visits for all other diagnoses similarly increased 121%, from $1,336 to $2,948. Hospital admission rates for EP decreased from 51.7% to 26.2% between 2006-2014 (p < 0.0001). In 2014, admission rates were highest for women in the 40-44 yo category (34.0%), in the West region (37.7%), in metropolitan areas with population ≥1M (28.9%), in patients with Medicaid or no charge (29.7% and 28.1%, respectively), and those in the lowest quartile for household income based on zip code (27.3%).

CONCLUSIONS: Despite an almost 50% fall in admission rates, the number of ED visits for EP in women age 18-50 yo remained fairly stable between 2006-2014. The persistence in the number of visits for EP in the face of markedly declined admission rates suggests an opportunity to increase the less expensive non-ED outpatient management of EP, possibly by increasing the number of clinics equipped to dispense methotrexate and offer same day ultrasound and lab testing. Furthermore, disproportionately higher ED utilization by women with Medicaid coverage and women from zip codes in the lowest income quartile raises questions about disparities in access to care and ability to follow up, suggesting we have a need for more equitable health care in treating women with EP.

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OBJECTIVE: Racial variation in semen quality is not well studied. Investigators continue to explore racial and genetic contributions to male infertility, with the aim of defining distinct genetic biomarkers that may affect spermatogenesis. Studies suggest that racial differences in semen analysis (SA) parameters exist, but firm conclusions are limited by heterogeneity of the studied populations. This study sought to identify racial differences in semen quality among US sperm banking donors.

DESIGN: Multi-center, retrospective

MATERIALS AND METHODS: SAs performed on specimens collected between 2007-2017 from donors (ages 19-38 with 2-5 days abstinence) who self-identified as White, African American (AA), or Asian were examined. Specimens from donors reporting >1 race were excluded. Primary outcomes were semen volume, total sperm count (TSC), sperm concentration (SC), percent motility, and total motile sperm count (TMSC). Data was analyzed using one-way ANOVAs, and a general estimate equation (GEE) model with an exchangeable working correlation structure to account for repeated measures.

RESULTS: A total of 94,592 SA specimens (from 1929 donors) were analyzed. Controlling for BMI and geographic region, there were no differences in semen volume or percentage motility between specimens from men of different races. TSC was significantly lower in specimens from Asian men as compared to White men (β = -21.04, p < 0.01), but no difference was observed between specimens from Asian and AA men, or White and AA men. There was a significant decrease in SC in specimens from Asian men compared to White men (β = -5.27, p < 0.01), but no difference between specimens from Asian men and AA men or White and AA men. There was a significant decrease in TMSC in specimens from Asian men compared to White men (β = -15.4, p < 0.01), as well as in specimens from AA men compared to White men (β = 16.1, p < 0.05), but no difference between specimens from AA and Asian men.

CONCLUSIONS: Significant progress has been made in personalized reproductive medicine as advances in next generation sequencing have enabled us to make individualized treatment recommendations based on patient genotypes. Our study was the largest to date to evaluate racial variations in semen quality in infertility patients reporting. Confirming the findings of the Study for Future Families, we found that specimens from AA men had significantly lower TMSC when compared to those from White men; however, we found no difference in semen volume or SC. We also demonstrated significant differences in SA parameters of specimens from Asian men when compared to White men. Further efforts in sequencing donors may elucidate polymorphisms that are more prevalent in men of different races, providing even greater insight into differential expression of gene pathways regulating spermatogenesis.

References:

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POLYCYSTIC OVARY SYNDROME IN AMERICAN INDIAN WOMEN: AN EXPLORATORY STUDY. R. Carron, S. Koioenga, E. Gilman-Kehrer, D. K. Boyle, R. Alverno. Fay W. Whitney School of Nursing, University of Wyoming, Laramie, WY; Warren Alpert Medical School, Brown University, Providence, RI.

OBJECTIVE: To explore American Indian (AI) women’s experience in a cohort with clinically diagnosed polycystic ovary syndrome (PCOS) by examining symptoms and the effects of PCOS on their health-related quality of life (HRQL). The experience of the participants with health care providers (HCPs) in diagnosing and managing PCOS also was explored.

DESIGN: A descriptive, mixed methods study with an ethnographic lens using semi-structured interviews and three validated surveys: Polycystic Ovary Syndrome Questionnaire (PCOSQ), Short Form-12 (SF-12), Diabetes Risk Test (DRT)

MATERIALS AND METHODS: A sample of 12 AI women with PCOS clinically confirmed by the Rotterdam criteria was recruited from a reservation in the western United States. Inclusion criteria were aged 18-40, able to read and write in English, and eligible to receive services at Indian Health Services. Surveys were analyzed with descriptive statistics using SPSS. Interviews were analyzed using a constant comparison approach.

RESULTS: Mean age of participants was 30.25 years (range: 24-36 years), and mean BMI was 37.85 kg/m² ± 8.68 kg/m². Scores on the PCOSQ indicated that weight (2.47) had the poorest function, followed by menstrual problems (3.08), emotions (3.86), body hair (3.87), and infertility problems (4.00). Mean DRT score was 3.83 ± 1.19 with some women scoring 5 indicating increased risk for diabetes. For the physical component summary (PCS) on the SF-12, 42% of the sample were at the general population norm (GPN), while 8% were above, and 50% below the GPN. For the mental component summary (MCS), 67% were at the GPN, while 8% were above and 25% were below the GPN.

Interview data with the women supported these quantitative findings. Women were interested in maintaining their health and weight with holistic measures including diet and exercise. Many women discussed problems regulating their menstrual cycles. Many were worried about the long-term consequences of PCOS including diabetes. Some women experienced stigmatization in the form of teasing due to their PCOS symptoms. In some women desiring to conceive, infertility problems was the PCOSQ domain of most concern to some of them. Some women expressed a desire for large families. Women felt more community information was needed about PCOS. Some women were frustrated that it had taken so long to diagnose their PCOS or expressed relief at receiving a PCOS diagnosis. Women felt they had not been provided with enough information about PCOS, and they wanted culturally specific information.

CONCLUSIONS: The study data contribute to an evidence-based management program for AI women with PCOS. AI women need to be screened for PCOS at annual wellness visits. Providers need to be knowledgeable about PCOS. Some AI women may be interested in fertility treatments.

LGBTQ

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OVARIAN STIMULATION OUTCOMES FOR TRANSGENDER MALES. A. Adelkeyea, M. Cedars, E. Mok-Lin, University of California, San Francisco, San Francisco, CA; University of California San Francisco Center for Reproductive Health, San Francisco, CA; UCSF, San Francisco, CA.

OBJECTIVE: To describe ovarian stimulation outcomes in transgender men utilizing ovarian stimulation for assisted reproduction either before or after testosterone exposure.

DESIGN: Retrospective cohort study

MATERIALS AND METHODS: A chart review was performed for all transgender men presenting to an academic fertility clinic between January 1st 2015 and April 1st, 2018. Demographics, testosterone usage, stimulation and pregnancy outcomes were reviewed. Stimulation outcomes were compared using a Wilcoxon-Rank Sum test.

RESULTS: Four subjects presented prior to initiating testosterone, and 4 presented after discontinuing testosterone. The median age of the cohort was 26.6 years [range 19.4 to 37.4 years]. There was no difference in age between the two groups and there was a trend towards men with a history of testosterone use being older (p=0.08). The mean time of discontinuation of testosterone prior to stimulation was 8.5 months [range 6-13 months]. All subjects were stimulated with an antagonist based protocol. Three cycles were initiated on cycle day 2 and two started randomly. The remaining patients were suppressed with oral contraceptives (n=1) or estradiol (n=2) prior to gonadotropin stimulation. Peak estradiol levels, the number of oocytes retrieved and the number of mature oocytes retrieved were lower in transgender men who had previously used testosterone. However, the estradiol level per follicle and the maturity rate were not different between the two groups. Ovarian stimulation outcomes are reported as median values [25% to 75%] in Table 1.

Two subjects presented for conception; both had a history of testosterone use. One patient presented with his cis-gender male partner. Ovarian stimulation in this patient resulted in ten eggs retrieved and, six 2PNs, which survived to day three embryos. He received a fresh transfer that resulted in a spontaneous abortion and two frozen embryo transfer cycles were unsuccessful. A second patient presented with his cis-gender wife. His cycle resulted in 12 oocytes, eight 2PNs and one blastocyst transferred fresh to his partner that resulted in a successful pregnancy.

CONCLUSIONS: Successful ovarian stimulation and conception is possible for transgender men with an antagonist gonadotropin protocol. Transgender men with a history of testosterone use have fewer eggs retrieved compared to those with no prior testosterone use. Further studies with more patients are needed to evaluate the effect of testosterone duration on ART outcomes.

Table 1

<table>
<thead>
<tr>
<th>All subjects (n=8)</th>
<th>No Testosterone (n=4)</th>
<th>Testosterone (n=4)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Stimulation days</td>
<td>10 [9-12.5]</td>
<td>10.5 [9.5-12.5]</td>
<td>9.5 [8.5-12]</td>
</tr>
<tr>
<td>Total FSH</td>
<td>1687.5 [1275-2175]</td>
<td>1575 [1200-2100]</td>
<td>1762.5 [1387.5-2250]</td>
</tr>
<tr>
<td>Total LH</td>
<td>1125 [900-1350]</td>
<td>1350 [975-1500]</td>
<td>1050 [862.5-1125]</td>
</tr>
<tr>
<td>Peak Estradiol</td>
<td>2241 [1071.2-2713.5]</td>
<td>2713 [2481-3373.5]</td>
<td>1071 [676.9-1661]</td>
</tr>
<tr>
<td>Peak Estradiol per egg retrieved</td>
<td>115.8 [97.3-162.4]</td>
<td>115.8[93.2-138.8]</td>
<td>138.4 [97.3-282.7]</td>
</tr>
<tr>
<td>Eggs retrieved</td>
<td>15 [11-27.5]</td>
<td>27.5 [22.5-29]</td>
<td>11 [5.5-12]</td>
</tr>
<tr>
<td>Number of M2s</td>
<td>19 [13-29]</td>
<td>19.5 [14.3-26.5]</td>
<td>9 [1-9]</td>
</tr>
<tr>
<td>Maturity rate</td>
<td>82.1% [72.2-100%]</td>
<td>77.2% [65.7-91.1%]</td>
<td>90% [75-100%]</td>
</tr>
</tbody>
</table>

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OBJECTIVE: Reproductive health needs of patients who have undergone a gender transition are often under addressed. The goal of this study is to determine the use of fertility preservation in this population and the reasons why many are not opting to preserve their fertility.

DESIGN: Cross-sectional, survey-based study

MATERIALS AND METHODS: Transgender individuals ages 18-64 participated in an online survey. The patients were questioned about their reproductive history and desire for fertility preservation. This is an update to preliminary data presented at ASRM 2017.

RESULTS: A total of 605 transgender individuals responded. 139 individuals on the transfeminine spectrum responded. The mean age of participants was 34 (SD 14). 128 (93%) identified as white, and 128 (92%) were non-Hispanic. 90 (65%) individuals had private health insurance. 102 (74%) were currently on hormone therapy. Although 39 (29%) desired children, only 18 (14%) participants had preserved their fertility prior to starting hormone therapy. The reasons for not preserving fertility included cost (38%), no desire (58%), and unsure at the time they were asked (15%). 9 (10 %) were never presented with the option, while 6 (7%) already had children. 466 individuals on the transmasculine spectrum responded. The mean age of participants was 26.6 years [range 19.4 to 37.4 years]. There was no difference in age between the two groups but there was a trend towards men with a history of testosterone use included cost (38%), no desire (58%), and unsure at the time they were asked (15%). 9 (10 %) were never presented with the option, while 6 (7%) already had children. 466 individuals on the transmasculine spectrum responded. The mean age of participants was 26.6 years [range 19.4 to 37.4 years]. There was no difference in age between the two groups but there was a trend towards men with a history of testosterone use included cost (29%), no desire (66%), and never being presented with the option (24%). 33 (10%) were unsure at the time they were asked. Only 1 (0.3%) individual already had children. When asked if they desired to personally get pregnant, 381 (84%) said no. 9 (2%) individuals said yes, while 40 (9%) were unsure.

CONCLUSIONS: Although more than half of individuals surveyed were on hormone therapy, very few opted to preserve their fertility. More than half of individuals stated that they had no desire to preserve their fertility. Although almost half of individuals on the transfeminine spectrum either desired children or were unsure, many reported cost as well as being unsure at the time as reasons for not preserving their fertility. For individuals on the transmasculine spectrum, many reported cost or not being presented with the option as reasons for not preserving their fertility. Additionally, although the majority of them desired children or were unsure, most did not desire to carry a pregnancy. It was also noted that more individuals on the transmasculine spectrum were not presented with the option to preserve their fertility. These findings highlight the fact that this is a vulnerable population, for which there needs to be greater attention to education and access to care for fertility preservation services.

References: No references cited
BARRIERS TO FERTILITY PRESERVATION IN TRANSGENDER (TG) PATIENTS: A SURVEY

OBJECTIVE: ASRM guidelines recommend fertility preservation (FP) counseling prior to initiating treatment for gender dysphoria. Previous studies have shown that TG people have similar parenting desires to cisgender people, but barriers to pursuing biological parenthood have not been explored. The objective of this study was to examine factors and potentially modifiable barriers surrounding the desire to have children in a TG population.

DESIGN: Survey study

MATERIALS AND METHODS: Patients presenting for gender affirming hormone therapy at a single academic institution were invited to complete an anonymous survey that included questions about fertility and parenting desires, as well as validated assessments of genital self-image. Data were analyzed with chi-square tests.

RESULTS: The survey was completed by 41 transwomen (TW, median age 37 years) and 35 transmen (TM, median age 25 years), of which 13 TW and 0 TM had biological children. 85% of TW and 91% of TM were counseled about potential fertility impairment, but only 70% of TW and 60% of TM reported being counseled about FP options, and only 10% of TW and 0 TM pursued FP. Of those who had received FP counseling, 80% were counseled by reproductive/medical endocrinology, 28% by primary care, and 4% by surgery (more than one option could be selected). The most common factors cited as strongly influencing FP decision-making in TW were desire for genetic children (33%), concern over delaying transition (26%), and need to stop hormones (23%); in TM, main factors were need to stop hormones (44%), desire for genetic children (32%), and concern with taking gender incongruent hormones (29%) or undergoing pelvic exams/ transvaginal monitoring (29%). 24% of TW and 40% of TM reported it was moderately to extremely important to have a child in the future, but only 10-11% of both groups felt it was important to have a genetically related child. Desire for future children was associated with Caucasian race (p = 0.003), Christian religion (p = 0.03), current children (p = 0.02), desire for FP (p = 0.001) and higher genital comfort score (p = 0.02). Importance of having genetic children was associated with higher genital comfort score (p < 0.0001).

CONCLUSIONS: Most patients were counseled about potential fertility effects of gender affirming treatment, but only a proportion received FP counseling, and very few pursued FP. Primary concerns influencing FP decision-making were factors that may worsen gender dysphoria, and importance of having children was associated with better genital comfort. Low FP utilization may therefore be related to inadequate options for TG patients that allow them to build their desired family without gender dysphoria. These results highlight the importance of FP counseling prior to transition and improving non-hormonal techniques for FP, such as ovarian and testicular tissue cryopreservation.

FERTILITY PRESERVATION OUTCOMES IN FEMINIZING TRANSGENDER PATIENTS: EXPERIENCE AT A SINGLE INSTITUTION.

OBJECTIVE: Report our program’s fertility preservation outcomes for adolescent and young adult feminizing transgender patients undergoing semen cryopreservation.

DESIGN: Retrospective chart review.

MATERIALS AND METHODS: This study was approved by the University of Pittsburgh Institutional Research Board. Data collection was completed on all transgender patients referred for fertility preservation between 2013 and 2018. Chart abstraction included demographic information, patient age at fertility preservation consultation, age at semen cryopreservation, and semen analysis (SA) parameters.

RESULTS: Eleven feminizing transgender patients were referred for semen cryopreservation; seven patients completed at least one collection. All patients in the study were non-Hispanic Caucasians. Patients reported experiencing gender dysphoria at age 12 years (range 5-13 years). Median age at first Endocrine/Adolescent Medicine visit was 17 years (range 15-24). Fertility preservation consultation occurred approximately one year later (median age 19; range 16-24 years). Five patients had successful semen cryopreservation prior to initiating treatment with hormone blockers. Mean SA parameters were within normal limits apart from low morphology noted in all patients using the modified strict Kruger’s classification (Table 1). One patient had been treated with leuprolide acetate for 6 months and had an unsuccessful semen cryopreservation three months after discontinuing the hormone blocker; the patient did achieve a successful semen cryopreservation after being off the hormone blocker for five months. One patient had been treated with spironolactone and oral/transdermal estradiol prior to fertility preservation. SA showed no sperm 2, 3, and 4 months after discontinuation of these medications.

CONCLUSIONS: Semen cryopreservation is a viable method of fertility preservation in adolescent and young adult feminizing transgender patients. It can be performed quickly and repeated every 2-3 days to ensure adequate sperm counts prior to initiating hormone-blocking or gender-affirming hormone therapy. This study represents the first published results of a fertility preservation program for transgender adolescent feminizing clients. Our results suggest further research is needed to determine the optimal length of time off hormone blocking therapy or gender-affirming hormone therapy for successful semen cryopreservation.

Semen Analysis Parameters for Six Patients with Successful Cryopreservation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± Standard Deviation</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (cc)</td>
<td>3.12 ± 1.64</td>
<td>1.0-6.1</td>
</tr>
<tr>
<td>Density (million)</td>
<td>30.45 ± 27.91</td>
<td>0.00001-127</td>
</tr>
<tr>
<td>Motility (%)</td>
<td>58.1 ± 13.22</td>
<td>16.6-74</td>
</tr>
<tr>
<td>Morphology (%)</td>
<td>6.80 ± 1.69</td>
<td>5-10</td>
</tr>
<tr>
<td>Vials cryopreserved (count)</td>
<td>13 ± 3.47</td>
<td>4-25</td>
</tr>
<tr>
<td>Number of collections (count)</td>
<td>2.2 ± 0.45</td>
<td>2-3</td>
</tr>
</tbody>
</table>

IS INTRAVAGINAL CULTURE A MORE ECONOMICAL TREATMENT FOR LESBIAN COUPLES?

OBJECTIVE: Lesbian couples often do not fall under the definition of infertility, thus creating a financial burden on couples in pursuit of a family. The aim of this study is to determine if an IVC (intravaginal culture) cycle...
using an INVOcell device is a more cost-effective treatment for lesbian couples compared to standard dIUI (donor intrauterine insemination) cycles.

**DESIGN:** Cost-Effectiveness Analysis (CEA)

**MATERIALS AND METHODS:** We performed a cost-effective analysis to determine out-of-pocket costs for lesbian couples in fertility treatment. The mean costs for a vial of donor sperm, shipping, and one-time miscellaneous fees (e.g., 6 months of onsite storage, access to donor profiles) were calculated from pricing information available online from three sperm banks: Xytex, California Cryo Bank, and Seattle Sperm Bank. Note that prices for ART donor sperm vials are less expensive and only one vial of sperm is needed for an IVF cycle; therefore, storage fees were removed from the miscellaneous fees category. A current clinic cost sheet for self-pay patients was utilized to determine the cost of a dIUI cycle and an INVO cycle. Clinic fees for IUI included an average of 1.5 monitoring visits (i.e., follicle scans, blood work), medication, sperm preparation, and the insemination. Fees for an INVO cycle included 2 monitoring visits, oocyte retrieval, insemination, sperm preparation, INVOcell device and embryo transfer. Similarly, fees for subsequent FET (frozen embryo transfer) from an INVO cycle and subsequent dIUI cycles were determined.

**RESULTS:** Results of CEA is listed in the table below.

**CONCLUSIONS:** An IVF cycle requires more upfront money than standard treatment. However, after 3 dIUI cycles, an IVF cycle appears to be a more cost effective option. Two points for consideration is if the IVF cycle is successful, there is a possibility for a subsequent FET cycle. If the IVF cycle is unsuccessful (i.e., fertilization failure, nothing to transfer) patients can move quickly to a more aggressive therapy. More research is needed in the efficacy of IVF treatments when using donor sperm. However, pregnancy rates for dIUI compared to published IVF cycle rates should strongly be considered. Clinicians should evaluate cost-effectiveness along with pregnancy success when treating lesbian couples.

Reference:

**P-435** Wednesday, October 10, 2018 6:30 AM

**ANALYSIS OF CONCORDANCE IN BLASTULATION BETWEEN PARTNERS OF SAME-SEX MALE COUPLES USING SIBLING OOCYTES FROM A SINGLE OVUM DONOR.** S. Moskotvey, a,b T. Partch, a S. Hemalal, a,b Chamas, a N. Millman, a,b H. Balakier, a C. L. Librach, a,b,c

**CREAtE Fertility Centre, Toronto, ON, Canada; aDepartment of Obstetrics and Gynaecology, University of Toronto, Toronto, ON, Canada; bDepartment of Gynaecology, Women’s College Hospital, Toronto, ON, Canada.**

**OBJECTIVE:** Oocyte donation is increasingly utilized for treatment of numerous infertility conditions and is the only option (together with surrogacy) available for same-sex male couples or single men seeking parenthood. Prior studies have analyzed the outcomes of shared oocytes donations, mainly focusing on factors relevant to egg donors or female recipients. To our knowledge, there are no studies to date examining embryo development of sibling oocytes from a single donor, fertilized by sperm from both partners of a same-sex male couple.

**DESIGN:** Retrospective cohort study

**MATERIALS AND METHODS:** To assess differences in fertilization and embryo development rates, IVF cycles where the donor’s oocytes were shared equally by each partner of the same-sex male couple were analyzed (n = 139) between January 2015 and December 2017 at a single IVF center. The following parameters were compared by paired T testing between partners: age, sperm quality, fertilization, cleavage, and blastulation rates. Relative differences were calculated to determine any discordant results between partners. Concordant and discordant groups were compared by ANOVA.

**RESULTS:** In total, 278 men in same-sex relationships ranging from 25 to 60 years of age were included in this study. The only discordance between partners of couples was the blastulation rates with a relative percentile difference of 36.4% ± 19. Based on this cut-off of discordant blastocyst development of sibling oocytes, couples were classified as concordant (Group 1, n = 77) or discordant (Group 2, n = 62). Men from Group 1 and Group 2 were similar in terms of age (36.8 ± 5.7 vs. 36.3 ± 5.6) and semen quality (mean concentration 74.6 million/ml ± 53.7 vs. 75.6 million/ml ± 53.8 and motility 51% ± 15.8 vs. 52% ± 15.9). While groups were similar in embryo cleavage of day 3 (97.3% ± 0.9 vs. 94.9 ± 14.7, P = 0.1); significant difference in blastulation rates were observed (50.2% ± 20.5 vs. 43.2% ± 26.6%, P = 0.01).

**CONCLUSIONS:** As sibling oocytes were donated by a single donor and randomly split, egg quality should not be different between each partner. Therefore, discordant results of blastocyst development between some partners should only be explained by the contribution of each partner’s sperm to development. Paternal contribution to embryo development could be underestimated without proper embryo assessment following genome activation on day 3 of embryo development.

**P-436** Wednesday, October 10, 2018 6:30 AM

**SEGMER AMH ASSESSMENT IN FEMALEs OF REPRODUCTIVE AGE BOTH ON AND OFF ORAL CONTRACEPTION: IMPLICATIONS FOR CESSATION.** K. Marron, a D. J. Walsh, b M. Cotter, c H. Harrity, d Zentra Lab, Sims IVF, Dublin, Ireland; dClinical, Sims IVF, Dublin, Ireland; eNursing, Sims IVF, Dublin, Ireland; fObstetrics & Gynaecology, Royal College of Surgeons, Dublin, Ireland.

**OBJECTIVE:** Serum anti-Müllerian hormone (AMH) is considered an accurate marker of ovarian reserve and is heavily utilised in the world of assisted reproductive technologies (ART). Given its important role in reproduction, AMH values are highly relevant and are seen to vary extensively, with the single greatest influencer being age. Oral contraceptives (OC) are considered as confounders to the true AMH value but the full extent of this effect is largely unknown. Do general population and ART recipient’s serum AMH levels differ and to what extent do OC influence serum measurements. Over what time period are values likely to return to normal following OC cessation.

**DESIGN:** Over a 3-year period, serum AMH levels were measured in an age-matched general population cohort of 4,322 women and 1,280 ART recipients. A separate non-ART cohort (n=1,837) were identified with either current use of COCP (n=155) versus those who have never taken OC (n=337).

**MATERIALS AND METHODS:** All serum AMH measurements were conducted on the Roche Cobas automated platform. Procurement times, storage conditions and time to analysis were carefully controlled for all cohorts.

**RESULTS:** A normogram was created to demonstrate the age-related decline in serum AMH levels. Age-matched ART participants and general population means were identical (17.0 vs 17.1, P =0.77). The effect of OC was assessed and showed an average 5% depressive effect on serum AMH levels relative to those who have never taken OC (P<0.001) despite being an average 3 years younger (31.9 vs 34.9, p<0.001).

**CONCLUSIONS:** Data from this large-scale study indicates serum assessment of mean AMH levels in general population and ART cohorts are identical but vary depending on OC use. OC use depresses serum AMH levels by 5%, relative to age matched individuals with no history of OC use. AMH levels in those individuals who stop taking OC typically return to “normal” within 3 to 6 months of cessation.

Supported by: This project was entirely funded by Sims IVF and Virtus Health. There are no conflicts of interest.
OBJECTIVE: Compare bleeding patterns and amenorrhea rates over 2 years in nulliparous and parous women using a levonorgestrel 52 mg intrauterine system (IUS).

DESIGN: Prospective multicenter clinical trial

MATERIALS AND METHODS: Eligible nulliparous and parous women 16-45 years old received a levonorgestrel 52 mg IUS in the ACCESS IUS trial evaluating efficacy and safety of Liletta® for up to 10 years after insertion. Participants completed daily diaries for the first year with bleeding information, including subjective evaluation of flow. Bleeding events included no bleeding or spotting (amenorrhea), bleeding, spotting, and bleeding or spotting (B/S). We compared bleeding patterns per 28-day cycle in nulliparous and parous women over 13 cycles (1 year) and at cycle 26 (2 years). Fisher’s exact testing was performed to compare outcomes between groups.

RESULTS: The median B/S days in nulliparous (n=976) and parous (n=715) women were 15 and 13, respectively, in cycle 1. Median B/S days decreased steadily in both groups to 3 or fewer days per cycle by cycle 10 and 2 or fewer days per cycle by cycle 21. The median bleeding days per cycle were 5 for each group in cycle 1 and declined in nulliparous and parous women to a median of 0 by the 4th and 5th cycle, respectively. The median spotting days per cycle were 2 or less by cycle 6 in both groups. Amenorrhea rates increased over two years and were similar (See Table). Over 26 cycles, 13 (1.3%) nulliparous and 26 (3.4%) parous women discontinued for bleeding complaints (p=0.003).

CONCLUSIONS: Amenorrhea rates and B/S days are comparable between nulliparous and parous women using a levonorgestrel 52 mg IUS. Bleeding and spotting days decrease over time. More than half of all users experience no bleeding by the 5th cycle. Discontinuation for bleeding complaints over 2 years is low overall, but parous women are more likely to discontinue for bleeding complaints than nulliparous women.

### Amenorrhea Rates by Parity with Levonorgestrel 52 mg IUS Use

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Nulliparous</th>
<th>Parous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n(%)</td>
</tr>
<tr>
<td>1</td>
<td>976</td>
<td>5 (0.5%)</td>
</tr>
<tr>
<td>2</td>
<td>962</td>
<td>68 (7.1%)</td>
</tr>
<tr>
<td>6</td>
<td>917</td>
<td>246 (26.8%)</td>
</tr>
<tr>
<td>13</td>
<td>841</td>
<td>305 (36.3%)</td>
</tr>
<tr>
<td>19</td>
<td>753</td>
<td>290 (38.5%)</td>
</tr>
<tr>
<td>26</td>
<td>674</td>
<td>309 (45.8%)</td>
</tr>
</tbody>
</table>

P-439 Wednesday, October 10, 2018 6:30 AM

### HIGHLY EFFECTIVE CONTRACEPTIVE USE IN THE POSTPARTUM PERIOD AMONG WOMEN WITH DIABETES

J. R. Morris. Emory University, Atlanta, GA.

OBJECTIVE: The number of reproductive age women affected by diabetes is increasing. Almost half of pregnancies in the United States are unintended with a higher rate among women with chronic disease. Use of contraception, particularly highly effective methods (sterilization or long acting reversible contraception [LARC], including intrauterine devices and implants), decreases risk for unintended pregnancy and LARC’s allow for pregnancy planning when disease control is optimal. Although women with diabetes are overall less likely to use postpartum contraception, one study found they were more likely to undergo postpartum sterilization and less likely to receive LARC’s than women without diabetes among women in California. This study sought to determine the prevalence of highly effective contraceptive use and factors associated with using sterilization versus LARCs among postpartum women with diabetes and without diabetes.

METHODS: We identified 47,684 women who gave birth between January 2013 and October 2014 and who had at least two months of pharmacy coverage after delivery. We describe levels of use of most and moderately effective contraception (MMEC) (including sterilization, long acting reversible contraception [LARC] and short acting hormonal methods) and LARC use within 3 days, 60 days and 6 months post-partum. We conducted multivariate analyses to test odds of MMEC and LARC use at each time point. We also conducted survival analysis to estimate time to MMEC and LARC initiation after delivery.

RESULTS: At 3 days postpartum 10% of women had received MMEC, the percentage rising to 23% at 60 days and 40% at 6 months postpartum. LARC use was non-existent at 3 days and remained low at 60 days (1.7%). By 6 months postpartum, 5.6% of women were using LARCs, comprising 14% of the method mix of MMECs. MMEC uptake progressed more rapidly among mothers aged 15-19 years, reaching 27% at 60 days and 51% in 6 months compared to 20% and 35% among women over the age of 35. Likewise, MMEC uptake also increased more rapidly from 26% to 45% during this time period among women living in the poorest neighborhoods versus 22% to 36% among those living in the most affluent areas.

CONCLUSIONS: In 2013-14, postpartum uptake of contraception in the 3 days following delivery was low in Maryland. Use of MMEC, including LARC, increased in the 6 months after delivery, reaching 40% overall but demonstrating higher uptake among teenagers than women over 35 years of age.

Supported by: This study was funded by Bayer US, LLC
Using a hormonal contraceptive at study enrollment compared to naive users. Knowledge of the contraceptive history of women seeking a hormonal contraception may help prescribers focus their counseling.

Supported by: Funding provided by Agile Therapeutics, Inc.

MENOPAUSE

P-441 Wednesday, October 10, 2018 6:30 AM

BIOCOMPATIBILITY AND EFFICACY OF AN ISOTONIC BUFFERED GEL FOR VAGINAL PH BALANCING. B. Rizk, E. Torres. Obstetrics and Gynecology, University of South Alabama, Mobile, AL; Advanced Fertility Centers, Houston, TX.

OBJECTIVE: Vaginal freshening gels (VFG) are gaining popularity for treating vaginal pH imbalance. Elevated vaginal pH increases rates of dysbiosis, malodor and reproductive diseases. Leading VFG have osmotic levels exceeding WHO vaginal-product guidelines. Studies of a novel lactic-acid buffered, isotonic VFG (Isofresh, Fairhaven Health; IF), evaluated gel: A) vaginal pH balancing efficacy in women with malodor concerns; B) impact on beneficial lactobacillus species; and C) mucosal irritation potential.

DESIGN: A) One month, open-label, nonrandomized IRB-approved clinical study, B) Prospective in vitro study of 24 hr lactobacillus growth. C) Prospective 5-day invertebrate mucosal tolerance study.

MATERIALS AND METHODS: A) Non-pregnant women (n=16, 21-56 yrs) with vaginal malodor concerns were evaluated at: Baseline; Day 3 after initial IF therapy; and Day 30 after every 3 day IF use. Outcomes included: rating level of odor concern (OC); colposcopic findings, and vaginal pH levels. B) Two ATCC Lactobacillus Crispatus strains were incubated with and without 25% IF in MEM medium for 24 hrs to compare gel impact on growth rates (ARL, Oklahoma City). C) Total mucus production in the Slug Mucosal Irritation assay was measured following 30 min exposures over 5 days to: a) cellulose control; b) leading VFG (Represh and Stay Fresh). An established classification model for this assay is predictive of vaginal burning in women (InverteTox, Ghent, BE).

RESULTS: A) Mean ± SD OC scores (0 = no concern to 10 = high concern) decreased (p < 0.01) between baseline (6 ± 2) and Day 30 (2 ± 2) for women using IF. On Day 3 after initial IF, 50% of women reported decreased OC. Mean vaginal pH levels also declined (p<0.05) between baseline (5.5 ± 0.9) and Day 3 initial IF (5.0 ± 0.7); as well as at Day 30 with every 3 day IF use (4.9 ± 0.6). Reductions in pH at Day 30 related to decreased OC (r = 0.52; p = 0.02). All women with initial vaginal pH levels of ≥ 5.5 reported decreased OC at Day 30 IF use. No product related colposcopic changes were reported. B) Percent change in log CFUs of lactobacillus at 24 hr did not differ with IF contact (control % change = -0.10 ± 0.60; IF % change = -0.46 ± 0.30). C) The isotonic IF demonstrated no mucosal irritation potential.

CONCLUSIONS: The novel isotonic, buffered IF gel reduced women’s odor concerns and improved vaginal pH during regular use. Modeling studies found IF to be non-toxic to healthy vaginal microbes and to have no mucosal irritation potential.

Supported by: A grant from Fairhaven Health, LLC, Bellingham, WA.

Slugs Mucosal Irritation Assay

<table>
<thead>
<tr>
<th>Product</th>
<th>Mucus Production (MP) as % Slug Body Weight</th>
<th>Predictive Product Irritation Class by MP</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEC Control</td>
<td>-2.5 ± 0.6</td>
<td>None</td>
</tr>
<tr>
<td>Isofresh</td>
<td>0.3 ± 1.1</td>
<td>None</td>
</tr>
<tr>
<td>Represh</td>
<td>13.2 ± 0.6</td>
<td>Moderate</td>
</tr>
<tr>
<td>Stay Fresh</td>
<td>19.9 ± 2.1</td>
<td>Severe</td>
</tr>
</tbody>
</table>

CONCLUSIONS: The novel isotonic, buffered IF gel reduced women’s odor concerns and improved vaginal pH during regular use. Modeling studies found IF to be non-toxic to healthy vaginal microbes and to have no mucosal irritation potential.

Supported by: A grant from Fairhaven Health, LLC, Bellingham, WA.
OBJECTIVE: Vasomotor symptoms (VMS), comprising of hot flashes and night sweats, affect between 60 and 80% of menopausal women and typically persist for over seven years in the majority of women. In addition to being a source of considerable distress, it is thought that VMS may be associated with increased risk of cardiovascular disease. We performed a systematic literature review and meta-analysis to assess how VMS during menopause are associated with cardiovascular risk factors.

DESIGN: A systematic review and meta-analysis of existing literature.

MATERIALS AND METHODS: We searched the Medline (OVID), Embase (OVID), PubMed, and The Cochrane Database until December 2017. Risk of bias was assessed using the Newcastle Ottawa scale. The standardized differences in means were calculated for continuous outcomes and the risk ratio was estimated for binary outcomes by using a random effects model. The heterogeneity of the pooled studies was assessed by estimating the I-squared. The risk of publication bias and small studies effect was visually assessed with funnel plots by plotting the precision of the estimate against the size effect.

RESULTS: 5,313 citations were identified of which 973 were duplicates. 4,196 citations were excluded on the basis of screening titles and abstracts, leaving 144 texts to be read in full. Of these 115 were excluded and 29 were included in the meta-analyses. Pooled analyses showed that experiencing VMS is associated with higher BMI (0.12 kg/m2 [95% CI 0.09, 0.15]), higher total cholesterol (0.16 mmol/l [95% CI 0.12, 0.19]), higher LDL cholesterol (0.06 mmol/l [95% CI 0.02, 0.11]), lower HDL cholesterol (-0.05 mmol/l [-0.09, -0.01]), higher glucose (0.05 mmol/l [0.01, 0.08]), higher HOMA-IR (0.19 units [0.13, 0.25]), higher systolic blood pressure (0.07 mmHg [95% CI 0.04, 0.10]) and higher diastolic blood pressure (0.06 mmHg [95% CI 0.03, 0.08]) compared with women without VMS. Funnel plots were symmetrical suggesting small possibility of publication bias or small studies effect.

CONCLUSIONS: We found that experiencing VMS is associated with higher BMI, adverse lipid profile, increased insulin resistance, and increased blood pressure. However, due to the largely cross-sectional nature of included studies we cannot prove causality. We cannot dispute though that our findings adds further evidence that VMS should not be solely treated symptomatically but should trigger a more holistic work up to for earlier detection and prevention of CVD risk factors. Further longitudinal studies are needed to investigate the temporal relationship between VMS and risk factors and the impact of VMS on cardiovascular disease incidence.

References: NA

Supported by: MRC Skills Development Fellowship (MR/N015177/1).
MALE FACTOR

P-444 Wednesday, October 10, 2018 6:30 AM
WHAT MALE FACTORS PREDICT EMBRYO DEVELOPMENT TO THE BLASTOCYST STAGE? D. A. Conway, K. Maas, C. Slater, E. Gurtcheff, J. Dorais, T. Schuermann. UUtah Fertility Center, Pleasant Grove, UT; bIdaho Center for Reproductive Medicine, Boise, ID.

OBJECTIVE: To determine if there are any specific male factors that predict embryo development and the percentage of chromosomally normal embryos when cultured to the blastocyst stage, in same sex couples splitting fertilization through donor egg in vitro fertilization (IVF) cycles.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: We compared the semen analysis parameters, age, and Body Mass Index (BMI) of 31 same sex male couples undergoing split fertilization of donor egg IVF cycles, at two different treatment centers. Pearson correlations were used to determine if there were any significant predictors of high quality or euploid blastocyst development. Significance was set at a p value of 0.05.

RESULTS: The only semen analysis parameter that predicted high quality blastocyst development was motility, showing a positive correlation. No semen analysis parameters were found to predict the percent of chromosomally normal embryos. Age correlated negatively to the development of high quality blastocysts (p = 0.008). Higher BMI correlated positively to the development of high quality blastocysts (p = 0.02), however the mean BMI of the men evaluated was 24.0 (SD = 3.0), and no one evaluated had a BMI over 30. Neither age nor BMI was found to affect the percent of euploid embryos.

CONCLUSIONS: In general, the male contribution to embryo development is often underestimated. However, when comparing split fertilization between two men in donor egg IVF cycles, there are semen analysis and lifestyle factors that can be helpful in predicting the development of high quality blastocysts. However, none of the characteristics we evaluated were shown to affect the percent of euploid embryo development.

References:

P-445 Wednesday, October 10, 2018 6:30 AM
IS ICSI SUPERIOR TO CONVENTIONAL IVF IN SEVERE MALE FACTOR: A 3 YEAR PROSPECTIVE OBSERVATIONAL STUDY. R. Bhattacharya, S. Sharma, B. Chakravarty. ART, Institute of Reproductive Medicine, Kolkata, India.

OBJECTIVE: To study whether IVF (in-vitro fertilisation) yields better outcome in severe male factor infertility over Intracytoplasmic sperm injection (ICSI) in terms of live birth, obstetric outcome and congenital anomalies.

DESIGN: This prospective observational study included 253 women whose male partner had TMC (Total motile count) <1 million and underwent conventional IVF or ICSI from January 2014 to December 2016. All subjects were between 25-37 years. Records of prenatal care of mother and neonates were reviewed. Developmental wellbeing of children born after IVF/ICSI were followed for three years.

MATERIALS AND METHODS: The 253 male partners who had semen analysis on day of oocyte retrieval with <1 million motile sperm and morphology-4% after wash, were included and divided into Group A (GrA) (n=121) in which conventional insemination was done and Group B (GrB) (n=132) where ejaculated ICSI was done. Antagonist protocol was performed. Total fertilization failure were 6/121(4.9%) in GrA and 3/132(2.2%) in GrB. Rest 244 patients with 295 cycles were analysed. Other female factors-PCOS, endometriosis, tubal factors and uterine defects were excluded.

RESULTS: Both groups were comparable in terms of age of both partners, BMI, dose of gonadotropins, estradiol on day of oocyte retrieval, endometrial thickness and number of oocytes retrieved. Conventional IVF group (496/840, 59.01%) had significantly lowered fertilization rate than ejaculated ICSI (591/910, 64.94% p=0.0119), although number of day 3 embryos were comparable in both groups (GrA 407/496, 82.05% vs GrB 467/591, 79.01%).

Pregnancy rate per embryo transfer in GrA was 42.2% and GrB was 47.61% (p=ns). Pregnancy per oocyte retrieval was also comparable-38.58% in conventional IVF and 42.85% in ICSI. Live birth rate per oocyte retrieval was also similar in both groups (GrA 30.6% vs GrB 26.4%). Missed abortion, though higher in ICSI group was not significantly different than conventional IVF (GrA 26.53% vs GrB 29.1%). Amnioncentesis two patients in ICSI group had pre-eclamptic toxemia (PET) while none had the condition in IVF group. One baby in ICSI group was terminated due to chromosomal defect and two babies born after ICSI had birth defects (one hypospadias and the other imperforate anus). In IVF group one baby had posterior urethral valve. Incidence of PET and congenital anomalies could be chance findings in this study.

CONCLUSIONS: In our study conventional IVF is as good as ejaculated ICSI in terms of reproductive outcome, where male partner had <1million motile sperm in post wash sample. IVF could be the first choice over ICSI in severe male factor infertility especially in developing countries which will decrease the cost of ART.

References:

P-446 Wednesday, October 10, 2018 6:30 AM

OBJECTIVE: Utilization of testicular (TESE) sperm in cryptozoospermic patients is still controversial. There has been no established treatment strategy available for such patients. Some achieve successful outcome with ejaculated (EJ) sperm while some may require surgical sperm retrieval. In order to propose a treatment strategy we attempted to characterize cryptozoospermic patients with successful results by investigating clinical outcome according to the sperm origin and the number of ICSI attempts.

RESULTS: The only semen analysis parameter that predicted high quality blastocyst development was motility, showing a positive correlation. No semen analysis parameters were found to predict the percent of chromosomally normal embryos. Age correlated negatively to the development of high quality blastocysts (p = 0.008). Higher BMI correlated positively to the development of high quality blastocysts (p = 0.02), however the mean BMI of the men evaluated was 24.0 (SD = 3.0), and no one evaluated had a BMI over 30. Neither age nor BMI was found to affect the percent of euploid embryos.

CONCLUSIONS: In our study conventional IVF is as good as ejaculated ICSI in terms of reproductive outcome, where male partner had <1million motile sperm in post wash sample. IVF could be the first choice over ICSI in severe male factor infertility especially in developing countries which will decrease the cost of ART.

References:

MATERIALS AND METHODS: As long as motile sperm were found in ICSI samples cryptozoospermic couples underwent ICSI initially with EJ sperm, while some couples with no viable sperm available chose to use TESE sperm from their first attempt. We also included couples that had several previous failed cycles (average 4.2) with EJ sperm and subsequently underwent TESE ICSI (EJ-TESE). The rates of fertilization (FR), blastulation (BR), and live birth (LB) per cycle as well as per couple were assessed.

RESULTS: Clinical outcome of 67 cryptozoospermic couples consisted of 38 with EJ, 12 with TESE, and 17 with EJ-TESE was evaluated. Among the three groups EJ-TESE showed lowest FR (61.4% in EJ, 62.8% in TESE, and 45.1% in EJ-TESE, P < 0.01) and BR (45.4%, 43.9% and 24.6%, P < 0.05). LBs per cycle were all comparable, 45.6% in EJ, 28.9% in TESE, and 27.3% in EJ-TESE. Interestingly, LB per couple was 68.4% (26/38) in EJ, statistically similar to 91.7% (11/12) in TESE, and 53.0% (9/17) in EJ-TESE, respectively. More importantly, 88% of successful EJ couples achieved LB in less than 3 embryo transfers (ET). In TESE, 91% of couples obtained LB in 2 ETs, while 88% of LB in EJ-TESE was occurred in 2 ETs. In both EJ and EJ-TESE groups, average maternal age with LB was younger than unsuccessful couples (31.5 years vs 38.1 in EJ, 32.9 vs 38.6 in EJ-TESE, P < 0.01), while in EJ-TESE group only paternal age with LB was significantly younger (34.2 vs 41.4, P < 0.05). Finally, none of the male endocrine parameters and testicular volume was associated with ICSI results.

CONCLUSIONS: Over 80% of couples obtained live birth in two embryo transfers with EJ sperm. Interestingly, well over 90% of couples initiated with TESE achieved live birth. Thus, as far as viable spermatozoa are available, cryptozoospermic couples may undergo up to two ICSI attempts with EJ sperm when a female partner is young. In cases where no motile sperm are available in ejaculates, surgical sperm retrieval is recommended as the first line treatment option.
IS ICSI SUPERIOR TO CONVENTIONAL IVF IN SEVERE MALE FACTOR INFERTILITY: A 3 YEAR PROSPECTIVE OBSERVATIONAL STUDY. S. Batwal, a R. Bhattacharya, a S. Sharma, b R. Chattopadhyay, c I. Saha, b B. Chakravarty. c "Infertility, Institute of Reproductive Medicine, Kolkata, India; cInstitute of Reproductive Medicine, Saltlake, India.

OBJECTIVE: To study whether IVF (in-vitro fertilization) yields better outcome in severe male factor infertility over Intracytoplasmic sperm injection (ICSI) in terms of live birth, obstetric outcome and congenital anomalies.

DESIGN: This prospective observational study included 253 women whose male partner had TMC (Total motile sperm count) <1million and underwent conventional IVF or ICSI from January 2014 to December 2016. All subjects were between 25-37 years of age. Records of prenatal care of mother and neonates were reviewed. Developmental well-being of children born after IVF/ICSI were followed for three years.

MATERIALS AND METHODS: The 253 male partners who had semen analysis on day of oocyte retrieval with <1 million motile sperms and morphology<4% after wash, were included and divided into Group A (GrA) (n=121) in which conventional insemination was done and Group B (GrB) (n=132) where ejaculated ICSI was done. Antioxidant protocol was performed. Total fertilization failure were 6/121(4.9%) in GrA and 3/132(2.2%) in GrB. Rest 244 patients with 295 cycles were analysed. Other female factors-PCOS, endometriosis, tubal factors and uterine defects were excluded. Statistical analysis was performed using chi-square and t-test, as applicable.

RESULTS: Both groups were comparable in terms of age of both partners, BMI, dose of gonadotrophins, estradiol on day of oocyte retrieval, endometrial thickness and number of oocytes retrieved. Conventional IVF group (496/840, 59.01%) had significantly lower fertilization rate than ejaculated ICSI (591/910, 64.94%; P=0.0119) although number of day 3 embryos were comparable in both groups (GrA 407/496, 82.05% vs GrB 467/591, 79.01%). Pregnancy rate per embryo transfer in GrA was 42.2% and GrB was 47.61% (P=ns). Pregnancy rate per oocyte retrieval was also comparable-38.58% in conventional IVF and 42.85% in ICSI. Live birth rate per oocyte retrieval was 25.69% in both groups (GrA 30.6% vs GrB 26.4%). Miscarriage rate, though higher in ICSI group was not significantly different than conventional IVF (GrA 26.53% vs GrB 29.1%). Antenatally two patients in ICSI group had pre-eclamptic toxemia (PET) while none had the condition in IVF group. One baby in ICSI group was terminated due to chromosomal defect and two babies born after ICSI had birth defects (one hypospadias and the other imperforate anus). In IVF group one baby had posterior urethral valve. Incidence of PET and congenital anomalies could be chance findings in this study.

CONCLUSIONS: In our study conventional IVF is as good as ejaculated ICSI in terms of reproductive outcome, where male partner had <1 million motile sperms in post wash sample. IVF could be the first choice over ICSI in severe male factor infertility especially in developing countries which will decrease the cost of ART.


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CONSERVATION OF A NONRENEWABLE RESOURCE: SHAVING CRYOPRESERVED SPERM. K. W. Keefe, a M. Kathrins, b R. K. Ashby, c R. Cacowsky. c "Obstetrics and Gynecology, Brigham and Women’s Hospital, Boston, MA; bBrigham and Women’s Hospital, Boston, MA; cObstetrics and Gynecology, Brigham & Women’s Hospital, Boston, MA.

OBJECTIVE: Traditionally, one or more vials of cryopreserved sperm must be thawed per IVF/ICSI cycle for patients who are using donor or previously banked sperm. However, if a patient wants multiple children, the number of vials can be restrictive because multiple cycles are often needed to achieve each live birth. Cryopreserved sperm shaving offers an alternative for not only couples utilizing donor sperm, as previously published, but also for couples using semen banked prior to gonadotoxic therapy or for those with severe male factor infertility.

DESIGN: Retrospective case series.

MATERIALS AND METHODS: Eighty-nine ICSI cycles from 62 patients in our academic medical center from January 1998 to January 2018 were identified as using cryopreserved sperm processed using the shaving technique. The shaving technique included: 1) The cryopreserved sperm vial was thawed from the holding tank to a liquid nitrogen (LN2) reservoir in the laboratory hood; 2) A spatula was used to carefully chip small quantities of frozen sperm while the vial remained fully submerged in LN2; 3) The chips were carefully collected into warmed media; 4) Further shaving was performed as necessary to obtain enough sperm for ICSI; 5) The warmed media with the sperm was then processed as indicated.

RESULTS: Eighty cycles used shaved sperm from ejaculate. Five cycles used shaved epididymal biopsy specimens, and four used shaved epididymal aspiration specimens. Fifty-five cycles used banked semen collected prior to a male partner undergoing gonadotoxic therapy. Seventeen of these cycles resulted in clinical pregnancies: 15 live births, one 21-week loss and 1 lost to follow-up. Twenty-four cycles involved frozen donor sperm from ejaculate. Twelve of these cycles resulted in clinical pregnancy: 9 live births, 1 termination due to trisomy 21 and 2 lost to follow-up. Two of the 9 live births were in the same patient using the same donor sperm shaved twice. One cycle used shaved semen from the male partner, microsorted for X chromosomes due to a strong family history of males with autism. This cycle did not result in a pregnancy. Only 1 cycle using shaved epididymal sperm resulted in a clinical pregnancy and ultimately a live birth. None of the cycles using shaved testicular biopsy resulted in a clinical pregnancy.

CONCLUSIONS: Using the shaving technique to harvest cryopreserved sperm is a valid method to allow couples with limited quantities of nonrenewable cryopreserved sperm to pursue pregnancy via ICSI and maintain residual banked sperm for future pregnancy attempts.


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A SYNTHETIC PHOSPHATIDYLCHOLINE-BASED FREEZING MEDIUM COULD REPLACES EGG YOLK AND PRESERVES POST-THAW SPERM MOTILITY AND CHROMATIN INTEGRITY IN ASTHENOSPERMIC INFERTILE MEN: A RANDOMIZED CLINICAL TRIAL. F. Sicchieri, a A. B. Silva, a V. P. Santana, a A. A. Vireque,b M. C. Vasconcelos, a R. A. Ferriani, a R. M. Reis. a"Gynecology and Obstetrics, Ribeirao Preto Medical School of University of Sao Paulo, Ribeirao Preto, Brazil; bInvita - Assisted Reproductive Technology, Ribeirao Preto, Brazil.

OBJECTIVE: To compare two sperm freezing media: commercially available Freezing Medium TEST Yolk Buffer-Irvine Scientific - USA (TYB) and a synthetic cryoprotectant supplemented with phosphatidylcholine (PC) and antioxidante L-acetyl-carnitine (ANTIOX-PC) - designed by Invita Assisted Reproductive Technology, Ribeirao Preto Medical School - in relation to progressive motility and sperm DNA fragmentation index (IFD) in semen samples obtained from men with altered seminal parameters.

DESIGN: Non-inferiority clinical trial.

MATERIALS AND METHODS: We included semen samples with altered seminal parameters (asthenospermia) from 58 volunteers at the Clinical Hospital of Ribeirao Preto Medical School, University of Sao Paulo. Semen samples were subjected to analysis both before and after cryopreservation. The sperm motility was evaluated by the spermogram and the sperm DNA fragmentation was analyzed by the transferase-mediated dUTP nick-end labeling technique (TUNEL). Before cryopreservation, all semen samples were divided and randomized to receive the cryoprotectants TYB or ANTIOX-PC, frozen and thawed after 30 days. An exploratory data analysis was carried out through measures of central position and dispersion. The paired t-test was used to compare the groups. Comparisons between the two media ANTIOX-PC and TYB, and fresh semen were performed through orthogonal contrasts using the mixed effects linear regression model. This model was implemented in the SAS 9.3 program considering PROC MIXED.

RESULTS: Progressive motility (P = 0.78) and IFD (P = 0.06) were not different when comparing ANTIOX-PC (12.40 ± 11.49; and 13.33 ± 10.54) and TYB (11.04 ± 9.11 and 11.49 ± 10.54), respectively, evidencing that the synthetic cryoprotectant designed was not inferior in the sperm DNA protection compared to the TYB medium. In addition, ANTIOX-PC retained higher rates of overall motility (43.36 ± 10.56 ± 6.77) than TYB (34.79 ± 22.86; P<0.0001) and significantly reduced the immotile sperm rates (56.64 ± 26.77; P<0.0001) when compared with TYB (65.00 ± 23.00).

References:
CONCLUSIONS: ANTIOX-PC medium can not be considered less effective than TEST-yolk buffer relative to progressive motility and the DNA fragmentation index. Kinetic parameters observed in post-swab sperm from ANTIOX-PC extender demonstrated the positive impact of the phospholipid/antioxidant treatment on human sperm cryotolerance in the absence of animal adjuvits.

Supported by: CNpq, FAEPA and USP.

P-450 Wednesday, October 10, 2018 6:30 AM

SEMN PARAMETERS AMONG US MEN EVALUATED FOR INFERTILITY: CROSS SECTIONAL, ANALYSIS OF CLAIMS DATA. C. H. Glazer, a,b,l S. Li, c Z. Zhang, c A. Giwercman, c J. H. Bondé, d M. L. Eisenberg, e 1Occupational and environmental medicine, Bispebjerg Hospital, Copenhagen, Denmark; 2Stanford, Palo Alto, CA; 3Molecular Reproductive Genetics, Department of Translational Medicine, Lund University, Malmö, Sweden; 4Occupational and Environmental Medicine, Bispebjerg Hospital, Københavun NV, Denmark.

OBJECTIVE: To compare sociodemographic differences in semen parameters among US men evaluated for infertility.

DESIGN: Cross sectional study.

MATERIALS AND METHODS: The cohort includes 11,552 men that provided a semen sample while evaluated for infertility between 2007-2016. The men were identified from insurance claims in the Optum ClininformaticsTM Data Mart Database with de-identified lab data from ten geographically diverse regions in the US. First, analysis of variance was used to compare continuous variables of mean semen parameters (concentration, volume, morphology and motility) according several categories including age, year of semen analysis, race, region, education and income. Then descriptive statistics were applied to quantify the percentages of men with abnormal semen parameters according to WHO 5th guidelines. Last, Logistic regression was used to study the risk of having semen parameters below the WHO reference range with adjustment of age, socioeconomic status, race and region. Vasectomized men were excluded.

RESULTS: Men aged 30-39 made of 53% of the cohort. The majority of the men had a bachelor degree or equivalent (56.9%) and a yearly household salary above $100,000 per year (41.3%). White men made up the largest percent of the cohort (62.4%) followed by Hispanics (17.7%) and Asians (7.6%). Overall, the mean sperm concentration was 50.0 x10^6/mL. Men over the age of 40 had the lowest semen quality across all semen parameters with a mean sperm concentration of 43.6 x10^6/mL. Asians had the highest mean semen concentrations (65.8 x10^6/mL) whereas whites had the lowest (46.7 x10^6/mL). This trend was also accompanied by a higher percentage of White men with semen parameters below the current WHO reference range. Men from New England and Mountain region were more likely to have low sperm concentrations when compared with men from South Atlantic with risk estimates of (OR 2.51; 95% CI 1.30-4.95) and (OR 1.67; 95% CI 1.46-1.91) respectively. An inverse relationship between education and sperm concentration was observed. Men with a high school diploma or less were more likely to have low sperm concentrations (OR 1.21; 95% CI 0.72-1.98) whereas men with a bachelor degree or higher were less likely (OR 0.84; 95% CI 0.75-0.95) when compared with skilled workers.

CONCLUSIONS: We observed differences in semen quality across several sociodemographic categories. Differences in sperm concentration based on education, race, and region were observed. Further work is warranted to understand the etiology of such differences and determine if different normative reference values may apply for different populations.

Supported by: CHG was partially funded by ReproUnion.

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PRELIMINARY OBSERVATIONS ON EMBRYO MORPHOGENETICS AND SPERM DNA FRAGMENTATION ASSESSED USING THE HALO SPERM KIT. S. Ploskonka N. Desai. OB-GYN, Cleveland Clinic, Beachwood, OH.

OBJECTIVE: Sperm DNA fragmentation has been suggested to be a contributory factor in male infertility and lower pregnancy outcomes. The degree to which DNA fragmentation influences outcomes in IVF/ICSI cycles is however still controversial. Integration of time-lapse microscopy (TLM) in to IVF labs allows more in depth analysis of embryo developmental kinetics than was previously possible with conventional microscopy. This study examines sperm DNA fragmentation and its relationship to embryo morpho genetics, multicellulation and cleavage anomalies.

METHODS: Pilot study looking at DNA fragmentation (DF) and embryo morpho genetics.

MATERIALS AND METHODS: This study encompassed 77 couples undergoing IVF. Sperm specimens were prepared for ICSI using density gradient centrifugation. Mature oocytes were fertilized by ICSI and immature oocytes were incubated overnight with sperm. Normally fertilized oocytes were cultured in the EmbryoScope time lapse chamber. Timing of specific events from the point of insemination was determined using time lapse (TL) imaging and expressed in hours. The following kinetic markers were assessed: time to syngamy (t-sym), time to 2c (t2), 3c (t3), 4c (t4), 5c (t5), 8c (t8), morula (Mor-t), start of blastulation (SIB), blastocyst (BL-t), and expanded blastocyst (EVL-t). Durations of the second (cc2) and third (cc3) cell cycles as well as time to complete synchronous divisions s2 and s3 were calculated. Embryos were also observed for presence or multicellulation and cleavage anomalies. Sperm DNA fragmentation testing was performed on a aliquot of the first test sperm preparation using the Halosperm kit (Halotech/ Spectrum Technologies). The kit enabled.
microscopic detection of sperm chromatins dispersion. Sperm were embedded in agarose coated slides and exposed to acid denaturation and a lysis buffer. Following alcohol dehydration and staining with DiffQuik, slides were examined to detect presence of halos surrounding sperm. Sperm cells with large/medium sized halos characteristic of dispersed DNA loops were considered to have intact DNA. Sperm with small, degraded or absent halos were considered to have fragmented DNA. Cases were divided according to % DF in ICSI specimens. Morphokinetic parameters were compared. P value of <0.05 were considered to be statistically significant.

RESULTS: Only parameters that were significantly different are shown in the table.

### Morphokinetics and DNA fragmentation

<table>
<thead>
<tr>
<th>DNA Fragmentation</th>
<th>DNA</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total embryos</td>
<td>633</td>
<td>54</td>
</tr>
<tr>
<td>Multinucleation</td>
<td>47%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Irregular chaotic division</td>
<td>25%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Morula formation</td>
<td>79%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Start of blastulation</td>
<td>74%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Early blastocyst formation</td>
<td>66%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Expanded blastocyst formation</td>
<td>52%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>t4</td>
<td>39.6±0.3</td>
<td>42.2±1.2</td>
</tr>
<tr>
<td>t4+t3</td>
<td>2.7±0.2</td>
<td>4.8±0.7</td>
</tr>
<tr>
<td>t8</td>
<td>59.5±0.5</td>
<td>64.7±2.2</td>
</tr>
</tbody>
</table>

### RESULTS:

**CONCLUSIONS:** These SCSA test data clearly show a strong relationship between age of men attending an infertility clinic and sperm DNA fragmentation. Previous studies suggest that the SCSA test has three clinical thresholds for %DFI: 1) >20% DFI (30% of men at this level) for beginning of loss of fertility potential, especially if one or more classical semen parameters are present, 2) ≥25% DFI (20% of men) for natural and IUI fertilization, and 3) ≥40% DFI for low probability of success for IVF/ICSI fertilization. Idiopathic couples, especially those above age 41.6, as shown here, even with the man having all normal semen parameters, would be strongly advised to determine their SCSA test values and seek counsel as to a plan that increased chance of pregnancy.

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**P-453 Wednesday, October 10, 2018 6:30 AM**

**RELATIONSHIPS BETWEEN AGE OF 25K MEN ATTENDING INFERTILITY CLINICS AND SCSA TEST DATA ON SPERM DNA FRAGMENTATION (% DF) AND HIGH DNA STAINABLE (%HDS)**

**OBJECTIVE:** The purpose of this study was to determine statistical correlations of age of men with potential male factor infertility and SCSA measures of sperm DNA fragmentation (DFI) and High DNA Stainable (HDS) in 25k clinical semen samples.

**DESIGN:** 25k semen samples sent from infertility clinics and individuals signing consent forms from January 2007 to November 2017 were measured by the SCSA test. These data were statistically analyzed for determining effects of age on sperm DNA integrity.

**MATERIALS AND METHODS:** Following liquefaction, aliquots of semen were transferred to cryotubes, flash frozen in LN2 and shipped to SCSA Diagnostics, Brookings, SD by Federal Express. Individual thawed samples were independently measured twice by the SCSA test protocol. The raw data were processed through SCSAsoft software to produce a clinical report.

**RESULTS:** In brief, at ages 20-25, 40-45, 60-65, the mean [min, max] for DFI, SD DFI and HDS are shown in Fig. 1. The percent of men with mean %DFI ≥20%, 25% and 50% is 30%, 20%, and 3%, respectively. An estimate for the change point in slope of age vs. %DFI is age 41.6 with a 95% confidence interval of (40.4, 42.8). The slope before age 41.6 was estimated to be 0.39 and after age 41.6 was 0.86. An estimate for the change point in slope of age vs. SD DFI was age 40.0 with a 95% confidence interval of (36.7, 43.0). The slope before age 40.0 was estimated to be 1.51 and after age 40.0 was 2.22. According to logistic regression model, the estimated probability that the mean DFI ≥20% for ages 20, 25, 30, 35, 40, 45 and 50 were 0.10, 0.13, 0.18, 0.24, 0.33, 0.42 and 0.52 respectively; e.g., a 40-year-old man has a 1/3 mean chance to have ≥20% DFI by age factor alone.

From loess smooth, the relationship of %HDS with age is observed to be linear with an estimated slope of -0.137 (SE = 0.0062).

**CONCLUSIONS:** The Halosperm kit provided an easy inexpensive means to assay DNA fragmentation. Further study is needed on the association between sperm DNA fragmentation and embryo quality markers made possible by time lapse imaging systems.

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**P-454 Wednesday, October 10, 2018 6:30 AM**

**RISK OF CONGENITAL MALFORMATIONS IN ICSI WITH SURGICALLY OBTAINED SPERM: A US STUDY IN FOUR STATES.**

**OBJECTIVE:** To evaluate the rate of congenital malformations in children conceived via ICSI with surgically obtained sperm (aspirated or biopsied).

**DESIGN:** Cohort study, comparing birth defects resulting from ICSI with aspirated and biopsied sperm to those obtained from ejaculated sperm in couples with male factor infertility, and with results for non-male factor cases.

**MATERIALS AND METHODS:** ICSI cycles (autologous oocytes, partner sperm, fresh embryos) in SART CORS resulting in live births in 2004-13 were linked to birth certificates and birth defects registries in four States (NY, TX, MA, and NC). Risks were modeled separately by plurality using logistic regression (AOR, 95% CI), adjusted for paternal age, race, ethnicity, education, and maternal parity, pre-gestational and gestational diabetes and hypertension, State, and year of birth.

**RESULTS:** The two study groups (combined aspirated and biopsied sperm) included 1,332 singletons and 1,157 twins, while the control groups included 10,656 singletons and 9,033 twins for ejaculated male factor, and 11,527 singletons and 10,637 twins for ejaculated non male factor cases (see table). The estimated risks for these groups did not differ significantly (their 95% CIs overlap). Although the risk of birth defects was slightly, but non-significantly increased for children conceived with surgically retrieved sperm (their 95% CIs overlap), these estimates were limited by small sample size.
CONCLUSIONS: Although the risk of congenital malformations when surgically retrieved sperm were used for ICSI did not differ significantly from the controls, this risk warrants further surveillance due to the small sample size, especially in children born using epididymal and testicular sperm in cases of non-obstructive azoospermia.

Supported by: NIH Grant R01 HD84377.

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OBJECTIVE: Back ground: ICSI has emerged as a prominent tool in the treatment of male factor infertility. The success of ICSI doesn’t depend upon the parameters of conventional semen analysis, but is largely related to sperm quality1. On contrary to the earlier belief, many recent studies have reported that elevated sperm DFI (DNA fragmentation index) affects pregnancy and live birth of ICSI cycles, though to a lesser extent than IVF (In-Vitro fertilization) cycles2. In men with elevated DFI, ICSI with testicular sperms have shown to yield a higher live birth rate, than the use of ejaculated spermatozoa2. The present study is aimed at the determination of the effect of sperm DFI by sperm chromatin dispersion (SCD) assay, on the outcome of ICSI cycles.

Aim: To study the effect of sperm DNA fragmentation on the outcome of ICSI cycles.

Primary OBJECTIVE: to determine the effect of sperm DFI on the pregnancy after ICSI (Intracytoplasmic sperm injection)

Secondary OBJECTIVE: to determine the effect of sperm DFI on fertilization, implantation and miscarriage after ICSI

DESIGN: Type of study: Prospective observational study

Setting: Tertiary care University teaching hospital

Sample Size: 76 infertile couple

Duration: 2 years (June 2015- June 2017)

MATERIALS AND METHODS: Inclusion criteria: All men of the infertile couple planned to undergo ICSI, at our centre

Exclusion criteria: 1. ICSI performed by surgically retrieved sperms 2. ICSI performed by cryopreserved semen or donor sperm

Protocol: All study subjects were asked to provide a semen sample within 48-72 hours of abstinence. The sperm DFI was estimated by sperm chromatin dispersion assay. The cut off value for positive test was ≥ 30%. Based on the DFI results, the study subjects were divided into two groups: Group A (DFI positive men) and Group B (DFI negative men)

RESULTS: The study subjects were comparable in demographic characteristics viz., age, BMI, duration of infertility. There was no significant difference in semen concentration, but the motility and morphology were significantly lower in Group A compared to Group B. There was no significant difference in fertilization and embryo quality between the groups. The pregnancy and implantation rates were significantly lower in Group A compared to Group B.

Comparison of demographic characteristics and ICSI outcome in the study groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A, N=35</th>
<th>Group B, N=41</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.0 ± 4.6</td>
<td>35.5 ± 4.5</td>
<td>P=0.62, NS</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>27.9 ± 3.9</td>
<td>26.9 ± 3.3</td>
<td>P=0.32, S</td>
</tr>
<tr>
<td>Duration of infertility (years)</td>
<td>6.3 ± 2.9</td>
<td>7.3 ± 3.4</td>
<td>P=0.22, NS</td>
</tr>
<tr>
<td>Sperm concentration (millions/ml)</td>
<td>27.3 ± 28.0</td>
<td>36.4 ± 27.5</td>
<td>P=0.08, NS</td>
</tr>
<tr>
<td>Sperm motility (%)</td>
<td>33.4 ± 18.9</td>
<td>46.6 ± 19.6</td>
<td>P=0.003, S</td>
</tr>
<tr>
<td>Sperm morphology (%)</td>
<td>2.4 ± 1.5</td>
<td>3.8 ± 2.8</td>
<td>P=0.02, S</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>75.6 ± 24.7</td>
<td>81.5 ± 17.7</td>
<td>P=0.23, NS</td>
</tr>
<tr>
<td>Good quality embryos</td>
<td>7.1 ± 4.2</td>
<td>8.5 ± 5.8</td>
<td>P=0.42, NS</td>
</tr>
<tr>
<td>Pregnancy rate (%)</td>
<td>11 (32.4%)</td>
<td>23 (67.6%)</td>
<td>P=0.03, S</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>13.7 ± 25.4</td>
<td>25.2 ± 28.8</td>
<td>P=0.05, S</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>02</td>
<td>03</td>
<td>P=0.77, NS</td>
</tr>
</tbody>
</table>

CONCLUSIONS: 1. Elevated DFI significantly lowers the pregnancy rate after ICSI

2. Elevated DFI doesn’t seem to have significant effect on fertilization in ICSI cycles

3. As the number of miscarriages were lower in our group of patients, the effect of elevated DFI on this parameter needs to be evaluated further in a larger data

References:

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OBJECTIVE: Several studies evidenced that the use of MACS (Magnetic-Activated Cell Sorting - Annexin V columns) for semen samples with high levels of DNA damage could be useful to reduce it (1). However, other studies demonstrated that there was no benefits of using MACS. A few years ago, we published a retrospective study who showed that using MACS could improve the ongoing pregnancy rates (2) in a oocyte donation program. Thus, the present prospective controlled study aimed to evaluate the clinical outcomes using MACS in patients with sperm DNA fragmentation in a shared oocyte donation cycles.

DESIGN: Prospective controlled study

MATERIALS AND METHODS: Our study population included 60 ICSI cycles (egg-shared donation program). Semen samples were previously studied to determine DNA fragmentation level by TUNEL assay. The normal value considered for TUNEL assay was 15%. Each oocyte cohort were split in two or three recipients. Semen samples with altered DNA damage were considered. Two groups were considered, altered level of DNA damage treated with MACS (Treatment, N= 34 cycles) and other recipient with altered level of DNA damage without MACS (Control, N= 26 cycles).

Fertilization rate, positive hCG, clinical pregnancy, implantation rate and blastulation rate, were compared between groups. Statistical analysis was performed by ANOVA and chi-square as appropriate.

RESULTS: Results are resumed in Table 1 (* p< 0.05).

CONCLUSIONS: The use of MACS in patients with altered levels of DNA damage seems to improve the clinical outcomes. To have a better sperm quality improves embryo development and ongoing pregnancy when oocyte competence is not compromised.

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Group (MACS)</th>
<th>Control Group</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>N=34</td>
<td>26</td>
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<tr>
<td>Male age</td>
<td>43.1 ± 2.9</td>
<td>42.8 ± 2.6</td>
</tr>
<tr>
<td>Oocyte Donor age</td>
<td>27.8 ± 2.6</td>
<td>26.6 ± 2.9</td>
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<tr>
<td>Fertilization rate (%)</td>
<td>82.6</td>
<td>85.7</td>
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<tr>
<td>DNA fragmentation (%)</td>
<td>22.8 ± 4.8</td>
<td>24.8 ± 3.8</td>
</tr>
<tr>
<td>Positive hCG/transfer (%)</td>
<td>59 (20/34)</td>
<td>50 (13/26)</td>
</tr>
<tr>
<td>Clinical pregnancy/transfer (%)</td>
<td>56 (19/34)²</td>
<td>31 (8/26)</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>41 (25/61)</td>
<td>23 (10/44)</td>
</tr>
<tr>
<td>Blastulation rate (%)</td>
<td>62²</td>
<td>38</td>
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</table>

References:
OBJECTIVE: To determine statistical correlations between age of 25K men attending infertility clinics and SCSA measures of sperm DNA fragmentation (DFI) and High DNA Stainable Sperm (HDS).

RESULTS: In brief, at ages 20-25, 40-45, 60-65, the mean [min, max] for DFI, SD DFI and HDS were as seen in Table 1. The percent of men with mean DFI >20%, >25% and >50% is 30%, 20%, and 3%, respectively. An estimate for the change point in slope of age vs. DFI is age 41.6 with a 95% confidence interval of (40.4, 42.8). The slope before age 41.6 was estimated to be 0.39 and after age 41.6 was 0.86. An estimate for the change point in slope of age vs. SD DFI was age 40.0 with a 95% confidence interval of (36.7, 43.0). The slope before age 40.0 was estimated to be 1.51 and after age 40.0 was 2.22. According to logistic regression model, the estimated probability that the mean DFI for DFI, SD DFI and HDS were as seen in Table 1. The percent of men with mean DFI >20%, >25% and >50% is 30%, 20%, and 3%, respectively. An estimate for the change point in slope of age vs. DFI is age 41.6 with a 95% confidence interval of (40.4, 42.8). The slope before age 41.6 was estimated to be 0.39 and after age 41.6 was 0.86. An estimate for the change point in slope of age vs. SD DFI was age 40.0 with a 95% confidence interval of (36.7, 43.0). The slope before age 40.0 was estimated to be 1.51 and after age 40.0 was 2.22. According to logistic regression model, the estimated probability that the mean DFI >20% for ages 20, 25, 30, 35, 40, 45 and 50 were 0.10, 0.13, 0.18, 0.24, 0.73. 0.42 and 0.52 respectively; e.g., a 40-year-old man has a 1/3 mean chance to have >20% DFI by age factor alone. From loess smooth, the relationship of %HDS for %DFI: 1) present, 2) 25% DFI (20% of men) for natural and IUI fertilization, and 3) 50% DFI for low probability of success for IVF/ICSI fertilization. Idiopathic couples, especially those above age 41.6, as shown here, even with the man having all normal semen parameters, would be strongly advised to determine their SCSA test values and seek counsel as to a plan that increases chance of pregnancy.

Table 1 The result of X-chromosome STR analysis (a case of maternal origin extra-X)

<table>
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<tr>
<th>Marker</th>
<th>DXS10148</th>
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<th>DXS8378</th>
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<td>22.00</td>
<td>10.00</td>
<td>18.21</td>
<td>17.00</td>
<td>16.00</td>
</tr>
<tr>
<td>Mother</td>
<td>20.00</td>
<td>22.00</td>
<td>10.00</td>
<td>17.00</td>
<td>18.00</td>
<td>16.00</td>
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<td>18.00</td>
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<td>DXS10103</td>
<td>DXS10134</td>
<td>DXS10146</td>
<td>DXS7423</td>
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<td>Mother</td>
<td>13.00</td>
<td>29.31</td>
<td>17.19</td>
<td>36.37</td>
<td>26.32</td>
<td>15.16</td>
</tr>
<tr>
<td>Patient</td>
<td>14.00</td>
<td>29.31</td>
<td>17.19</td>
<td>36.37</td>
<td>26.32</td>
<td>15.16</td>
</tr>
</tbody>
</table>

OBJECTIVE: It has been reported that the incidence of sperms with disomic XY is higher in the testis tissue smear of KS patients and these sperms are the cause of KS. However some papers report the maternal origin. So we performed this study to investigate the origin of extra X in Klinefelter Syndrome (KS).

RESULTS: X-chromosomal STR DNA profiles were compared among KS patient and their parents. In 13 of the 21 KS patients, both two X chromosomes were maternal origin, showing that an extra X chromosome in male KS is higher in the testis tissue smear of KS patients and these sperms are the cause of KS. However some papers report the maternal origin. So we performed this study to investigate the origin of extra X in Klinefelter Syndrome (KS).
OBJECTIVE: To measure the effects of maternal and paternal variables on embryo aneuploidy based on preimplantation genetic testing (PGT-A) results.

DESIGN: Multi-center retrospective cohort.

MATERIALS AND METHODS: In vitro fertilization (IVF) cycles undergoing intracytoplasmic sperm injection with subsequent PGT-A using array-CGH (aCGH) at 2 academic centers (“A” and “B”) between 1/1/2013-6/30/2017 were eligible for inclusion in the study. Data collection included maternal and paternal age, maternal diagnosis, day 3 FSH levels, semen analysis results (concentration, motility, morphology), and PGT-A results. Exclusion criteria included sperm donors, missing data, PGT-A for unbalanced translocations, and mosaic embryos. Logistic regression was performed to assess factors associated with overall, autosomal, or sex chromosome aneuploidies for Center A, Center B, and Centers A+B. Correction for multiple hypothesis testing using Benjamini & Hochberg1 was utilized and q-values <0.05 were considered significant.

RESULTS: 577 IVF cycles were analyzed including 2747 embryos. A summary of data collected is described in the Table. 50.12% of all embryos were aneuploid, with an average of 2.15 aneuploid embryos per cycle. Logistic regression found only maternal age to be associated with overall and sex chromosome aneuploidies. In addition to the factors listed in the table, a female-factor primary infertility diagnosis was not found to be significant. This was observed when each Center was analyzed separately and together.

CONCLUSIONS: 1. There was no association of male infertility nor of paternal age and embryo aneuploidy. This is in contrast to older studies, which were smaller and relied on FISH technology.

2. As expected, we have demonstrated an association of maternal age and autosomal aneuploidy, while sex chromosome aneuploidies were not associated with maternal age.

3. The transition of PGT-A to NGS may shed a new light on the paternal contribution to aneuploidy.

CONCLUSIONS: In conclusion, this study revealed that PICSI patients with high sperm DNA fragmentation and low HA-binding ability have significantly higher blastocyst aneuploidy rates than maternally age-matched ICSI patients. Nevertheless, following a euploid FET these patients exhibited positive clinical outcomes and no pregnancy losses to date.

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OBJECTIVE: To evaluate the influence of overcome semen viscosity (SV) on clinical outcomes according to two types of insemination method (i.e., conventional in vitro fertilization or intracytoplasmic sperm injection) in fresh embryo transfer cycles.


MATERIALS AND METHODS: Cycles were divided into 4 groups according to the presence of SV and the types of insemination method (IVF: SV, n = 51 vs. no SV, n = 77 and ICSI: SV, n = 255 vs. no SV, n = 298). Cycles with poor responder, advanced maternal age (≥38 years), frozen sperm, and surgically retrieved sperm were excluded. Semen parameters were evaluated according to the WHO 2010. SV (length of 2 cm) was checked by gentle aspiration of liquefied semen into a 5-mL serological pipette and then allowing the semen to drop by gravity and observing the length of any thread. To overcome semen viscosity, a sterile 5-mL syringe fitted with a sterile 18G needle was used. The semen was gently drawn into the syringe and expelled slowly back into the tube and repeated. Semen was treated by swim-up method.

RESULTS: Patients' characteristics between SV and no SV in the IVF or the ICSI group were not statistically significant difference (p > 0.05). We observed similar rates of fertilization and good-quality embryos on day 3 between SV and no SV in IVF or the ICSI group, respectively. Moreover, the rates of biochemical pregnancy, clinical pregnancy, ongoing pregnancy, miscarriage, and implantation per cycle also did not significantly differ between SV and no SV in the IVF or the ICSI group (p > 0.05).

CONCLUSIONS: When SV was overcome, it did not affect the clinical outcomes of fresh embryo transfer cycles regardless of insemination methods.

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DOES PATERNAL AGE INFLUENCE THE FERTILIZATION RATE OF EGG DONATION CYCLES WITH MALE FACTOR?. V. Santonvena,a G. Garcia Villafana,b J. C. Rosales,c S. Alvarado,d J. R. De Leon-Lopez,c P. Galache Vega,c G. Russell Beltran,c 1IECH Fertility Center, Monterrey N.L., Mexico; 2Laboratory, IECH, Monterrey, Mexico; 3IECH, Monterrey, Mexico; 4Research, Clinical Statistical Advisor, Monterrey, Mexico; 5IECH Fertility Center, Monterrey, Mexico; 6IECH Fertility Center, Monterrey, Nuevo Leon, Mex, Mexico.

OBJECTIVE: Evaluate the impact of paternal age in egg donation cycles with male factor.

DESIGN: Observational, analytical, retrospective, transversal.

MATERIALS AND METHODS: In vitro fertilization cycles from the egg donation program in a private fertility center from January 2012 through December 2016 were reviewed. The cycle outcomes were assessed in relation to semen samples to analyze the impact of male factor and paternal age. Cycles were divided into two groups: Group 1, those who had male factor (oligo, terato, asthenospermia of any degree) and Group 2, those who had normal seminal parameters. Male age, fertilization rate, embryo development, and pregnancy rate were compared between groups.

RESULTS: From 472 samples, 213 (45.13%) had male factor (Group 1), and 259 (54.87%) had normal seminal parameters (group 2). Overall, male patients from group 2 were younger (mean 38.2 yr, ± 5.8, P = 0.002) and had a higher fertilization rate (68.22%, P = 0.005). In this group, fertilization rates didn’t fluctuate with age (r² = 0.010). However, patients from group 1 were older (mean age 40.5 a, ± 4.85, P = 0.002) and paternal age was slightly correlated with fertilization rate (r² = -0.126) with lower fertilization rates (62.51%, P=0.005) and a low probability of pregnancy when normal forms were less than 6% (AUROC = 0.677, SEN 57%, SPE 76.7%).

CONCLUSIONS: Male age mildly reduces fertilization rates in IVF cycles with male factor. In cycles without male factor, age did not correlate with fertilization rates or any seminal parameter.

Table 1. Clinical outcomes in SV versus no SV according to insemination method

<table>
<thead>
<tr>
<th></th>
<th>IVF-SV</th>
<th>IVF-no SV</th>
<th>p-value</th>
<th>ICSI-SV</th>
<th>ICSI-no SV</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycles (n)</td>
<td>51</td>
<td>77</td>
<td></td>
<td>255</td>
<td>298</td>
<td></td>
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<tr>
<td>Oocytes fertilized (%)</td>
<td>84.7 (533/629)</td>
<td>83.1 (726/874)</td>
<td>0.386</td>
<td>73.7 (2238/3037)</td>
<td>73.6 (2503/3401)</td>
<td>0.931</td>
</tr>
<tr>
<td>Good quality embryos (%)</td>
<td>18.6 (99/533)</td>
<td>21.8 (158/726)</td>
<td>0.165</td>
<td>14.3 (319/2328)</td>
<td>15.8 (396/2503)</td>
<td>0.132</td>
</tr>
<tr>
<td>Biochemical pregnancy (%)</td>
<td>60.8 (31/51)</td>
<td>50.6 (39/77)</td>
<td>0.259</td>
<td>49.8 (127/255)</td>
<td>48.3 (144/298)</td>
<td>0.728</td>
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<td>Clinical pregnancy (%)</td>
<td>51.0 (26/51)</td>
<td>36.4 (28/77)</td>
<td>0.101</td>
<td>39.6 (101/255)</td>
<td>37.2 (111/298)</td>
<td>0.569</td>
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<td>Ongoing pregnancy (%)</td>
<td>41.2 (21/51)</td>
<td>33.8 (26/77)</td>
<td>0.395</td>
<td>32.9 (84/255)</td>
<td>34.2 (102/298)</td>
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<td>Abortion (%)</td>
<td>19.2 (5/26)</td>
<td>7.1 (2/28)</td>
<td>0.243</td>
<td>16.8 (17/101)</td>
<td>8.1 (9/102)</td>
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<td>Implantation (%)</td>
<td>36.2 (38/105)</td>
<td>25.5 (41/161)</td>
<td>0.061</td>
<td>23.7 (129/544)</td>
<td>21.3 (132/621)</td>
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CLINICAL OUTCOME OF 342 ICSI CYCLES UTILIZING SPERM RETRIEVED BY 3 SURGICAL TECHNIQUES. M. Javed,a A. Kannachath,b H. Matrafi,c S. Najashi,d H. Sufyan.e 1In Vitro Fertilization Laboratory, Thorium Medical Center, Mississauga, ON, Canada; 2IVF Lab, Embryologist, Riyadh, RI, Saudi Arabia; 3Urology/Andrology, Thorium Medical Center, Riyadh, Saudi Arabia; 4REI, Thorium Medical Center, Riyadh, Saudi Arabia.

OBJECTIVE: The clinical management of men with azoospermia seeking fertility has been a challenge for andrologists, urologists, and reproductive endocrinologists. The surgical sperm retrieval and intracytoplasmic sperm injection have successfully transformed the treatment of male infertility so that now most of the men can father their own children. The aim of this study was to present outcome of 342 intracytoplasmic sperm injection (ICSI) cycles utilizing fresh and cryopreserved sperm retrieved from azoospermic men by 3 surgical techniques.

DESIGN: Comparison of ICSI cycles outcome utilizing sperm retrieved by 3 surgical techniques with fresh ejaculates and ejaculated cryopreserved sperm.

MATERIALS AND METHODS: The data from 1619 ICSI cycles performed during Jan to Dec 2017 were analysed. In 342 cycles, either fresh or cryopreserved sperm retrieved by fine needle aspiration (FNA), microsurgical epididymal sperm aspiration (MESA) or microsurgical testicular sperm extraction (Micro-TESE) were used. The female patients more than 40 years of age were excluded. The ovarian stimulation was initiated on day 3 of the cycle and GnRH antagonist was added later. The oocytes were collected 36 hours post hCG injection. They were denuded 2 hours after collection and ICSI was performed an hour later. The fertilization was checked 18-19 hours post ICSI. Embryo culture was performed in triple gas environments.
incubators at 37 degree C, in an atmosphere of 6% CO2, 5% O2 and balance nitrogen. The data were analysed using SPSS ver 23. The significance level was 0.05.

RESULTS: The fresh or cryopreserved sperm retrieved by all 3 surgical procedures were utilized successfully. The female age, number of oocytes retrieved and number of MII oocytes were similar in all groups (P<0.05). The fertilization rate was similar except in the group utilizing cryopreserved sperm from Micro-TESE. Pregnancy rates were higher in groups utilizing fresh sperm from Micro-TESE and MESA (Table 1).

CONCLUSIONS: Freshly collected testicular sperm provide highest pregnancy rate. Although sperm from any surgical procedure were used successfully, pregnancy rates of fresh sperm retrieved by FNA and cryopreserved sperm from Micro-TESE were lower.

Table 1: Patient age, oocyte number, number MII, fertilization and pregnancy rates

<table>
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<tr>
<th>n</th>
<th>FNA-Fresh</th>
<th>Micro-TESE Fresh</th>
<th>Micro-TESE Frozen</th>
<th>MESA Fresh</th>
<th>MESA Frozen</th>
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OBJECTIVE: Assess correlation of Sperm DNA fragmentation (DFI) with poor embryo development, embryo ploidy, failed implantation, and pregnancy loss.

DESIGN: IRB-approved, prospective, double-blinded study correlating DFI values on neat semen specimen provided by 81 men for use in IVF/ICSI. The remaining semen was processed with a standard gradient and wash protocol for use with either standard in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). Trophectoderm biopsy was performed using standard laser procedure on Day 5 or 6 and blastocysts (BL) were vitrified. Frozen semen aliquots were sent to an external clinical laboratory, blinded, for measurement of DFI, reported as % DNA Fragmentation Index (%DFI), using the acidine orange and flow cytometry as described in the SCFA method (SDFA test, ReproSource, Woburn,MA). Next Generation Sequencing was performed by CooperGenomics (Detroit, MI). Data from testing and clinical outcome data were simultaneously, unblinded. Statistical analysis was performed using contingency tables with Pearson’s Chi Squared test (p<0.05) or unpaired t-tests utilizing JMP 12 (SAS Institute Inc.) software.

RESULTS: Average fertilization rates with IVF/ICSI were significantly from semen with %DFI ≥ 15 vs <15% (p<0.0001). Subset analysis of IVF or IVF with ICSI showed similar correlation. BL development was slower when DFI ≥ 15% resulting in more embryos biopsied on Day 6 as compared to the DFI <15% group (p=0.019) despite a trend toward better day 3 embryo quality when DFI ≥ 15% vs <15% (P=0.061) No significant differences were observed in ploidy status of blastocysts based upon DFI, however, the study was underpowered to adequately assess this correlation.

CONCLUSIONS: This study confirms that DFI predicts performance of sperm in IVF. DFI demonstrated strong correlation to fertilization rates and speed of blastocyst development adding further evidence that DFI may play a role in disrupting paternal contribution to embryo development after the maternal zygotic transition. Although insufficient data were collected to assess DFI relationship to blastocyst ploidy, these results are from an ongoing clinical study which will provide additional IVF cycle data as well as pregnancy outcomes. Overall, the study confirms that DFI provides a clinically important measurement of sperm quality.

Supported by: ReproSource Investigator Award covering cost of testing.

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LOOKING FOR MOLECULAR BIOMARKERS OF CRYODAMAGE IN DONORS SEMEN. E. Selles, P. Hernandez-Vargas, N. Garrido, F. Vilella, I. Perez-Cano, M. Muñoz, IVIRMA Alicante, Alicante, Spain; aFundación IVI, Valencia, Spain; bResearch, Igenomix, Alicante, Spain.

OBJECTIVE: Sperm cryopreservation is a widespread tool in assisted reproduction for the management of male infertility and it is mandatory for sperm donor programs. It is well-established that cryopreservation causes loss of sperm motility, impacting on its reproductive competence. Therefore, the selection of sperm donor samples with good freezability and fertilization abilities is important for optimization of sperm banks. The molecular basis of the vulnerability to cryopreservation is still unknown. Microarray provides a powerful tool to explore the molecular mechanisms involved in cryoinjury. The objective of this study is to characterize the gene expression profiles of semen samples according to their resistance to cryopreservation and to determine the impact of cryodamage on pregnancy outcomes after donor intratruerne insemination (IUI).

DESIGN: Prospective cohort study using sperm samples from 28 donors attending IUI Alicante from 2014 to 2017.

MATERIALS AND METHODS: Donor sperm samples were categorized according to their high resistance (HR, n = 14; >0.5988 posthaw/fresh motility) or low resistance (LR, n = 14; <0.5988 posthaw/fresh motility) in cryopreservation. The mRNA was extracted with the QIAgen kit and analyzed on Agilent Bioanalyzer 2100. Whole genome microarray was individually performed and results were analyzed to detect genes differentially expressed. Limma moderated T-Statistic was used to analyze differential expression (P < 0.05). Functional analysis was performed using Gene Ontology (GO) bioinformatics tools to determine differences in tree GO terms: biological processes, molecular functions and cellular components. For cryodamage correlation with pregnancy success in IUI 16 donor’s samples were employed (6 HR; 10 LR).

RESULTS: Gene expression: No differentially expressed genes were observed between HR and LR samples among the 19619 genes analyzed. Functional analysis: Eighty six from the 5648 biological processes analyzed were found significant different between HR and LR samples (13 up-regulated (U) and 73 down-regulated (D)). In addition, significant differences were observed between those groups in 39 cellular component GO terms (3 U and 36 D) and in 2 molecular functions GO terms (1 U). Clinical outcomes: Up to now, 24 and 37 IUI have been performed with samples from HR and LR group, obtaining 9 and 13 pregnancies, respectively. Apparently, the use of samples with better freezability in IUI seem to slightly increase pregnancy success. However, differences are not significant.

CONCLUSIONS: Although no gene was found to be differentially expressed, significant changes in several biological functions were observed between samples with different freezability, probably due to the sample size.
CHARACTERIZATION OF SPERM PROTEOME AND REPRODUCTIVE OUTCOMES AFTER REDUCED MALE ABSTINENCE IN IVF TREATMENT. D. Li, T. Wang, X. Wang. *Shengjing Hospital of China Medical University, Shenyang, China; †Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale School of Medicine, New Haven, CT.

OBJECTIVE: Semen samples from short abstinence show improved sperm quality. However, whether improving the reproductive outcomes, and especially the associated molecular mechanisms remain largely unknown.

DESIGN: This study had a concurrent control trial design, with an experimental group of 167 couples and a control group of 361 couples undergoing their first round of IVF treatment.

MATERIALS AND METHODS: Participants provided a semen sample after 3-7 days of abstinence followed by another sample after only 1-3 hours. Control and experimental groups used a semen sample during IVF treatment of 3-7 days or 1-3 hours abstinence, respectively. Implementation, clinical pregnancy, early miscarriage, and live birth rates following fresh IVF and freeze-all cycles were compared. For both ejaculates, sperm physiological and biochemical parameters were analyzed, and global proteome profiling and protein modifications were assessed by proteomic techniques.

RESULTS: We report that ejaculates from short (1-3 hours) as compared to long (3-7 days) abstinence showed increases in motile sperm count, sperm vitality, normal sperm morphology, acrosome reaction capacity, total antioxidant capacity, sperm mitochondrial membrane potential and high DNA stainability, and decrease in sperm DNA fragmentation index. Sperm proteomic analysis showed 626 differentially expressed proteins, with 521 up- and 105 down-regulated. These differentially expressed proteins are highly involved in specific cellular processes, such as motion, oxidative stress, mitochondrial function, adherence, and metabolism. Gene Set Enrichment Analysis revealed multiple functional networks that are more abundant after short abstinence. Interestingly, protein trimethyllysine modification was increased, and butyryllysine, propionyllysine, and malonyllysine modifications were decreased in ejaculates from short versus long abstinence. Finally, the rates of implantation, clinical pregnancy, and live birth from IVF treatment were significantly increased using semen samples from short abstinence.

CONCLUSIONS: Our study provides preliminary mechanistic insights into the molecular mechanism underlying improved sperm quality and pregnancy outcomes associated with sperms from short abstinence.
OBJECTIVE: Sperm DNA damage has been associated with adverse reproductive outcomes. Sperm vitality is especially important to measure if sperm motility is low, so differentiate between live-motile sperm and dead sperm. L-carnitine (L-C) is essential for the normal mitochondrial oxidation of fatty acids, protects cell membrane and DNA against free oxygen radicals damage.

DESIGN: This was a randomized, double blind, placebo controlled (DBPC) study and it examined the effect of test formulation (Proxeed Plus), containing L-C 2g and acetyl-L-carnitine (ALC) 1g, in men with idiopathic oligo-asthenospermia. The protocol was 2 months wash-out and 6 months treatment (T-2, T0, T+3, T+6), with test formulation (125 patients) or placebo (50 patients).

MATERIALS AND METHODS: Analysis of ejaculate was done according to 5th guideline. Progressive sperm motility (A+B grade of rapid) was done manually. DFI was evaluated by Halosperm kit (Halotech DNA, S.L,) and sperm vitality was done by the one-step eosin-nigrosin technique.

RESULTS: The values at different time points were: sperm vitality (%): T0=0.52 (0.43-0.60), T3=0.57 (0.46-0.64) and T6=0.56 (0.56-0.65); DFI (%): T0=38.50 (32.00-48.75), T3=35.50 (25.50-44.00) and T6=31.00 (25.00-41.00); the progressive sperm motility ( %): T0=28.00% (12.00±38.00), T3=30.00% (12.00±39.00) and T6=31.00% (20.00±41.00); all parameters showed significance of p<0.001 by Friedman test. The increase of spermatozoa vitality has the best predictive and diagnostic characteristics and those men who have increased this parameter by 1% have 1,119 times more likely to have a progressive motility of spermatozoa greater than 20% after 6 months of therapy. If the spermatozoa vitality, after six months of therapy increases by 5.9% and more (cut off value), the likelihood that sperm motility is greater than 10% (AUC ¼ 0.18, p ¼ 0.022) and total motility (r ¼ 0.022) is significantly lower (p ¼ 0.027) in placebo group. If DFI drops by more than 3% (cut-off), after 6 months of therapy increases by 5.9% and more (cut off value), the likelihood that sperm motility is greater than 10% (AUC ¼ 0.793; p<0.001). DFI reduction (odds ratios ¼ 1.106 with 95% confidence intervals) independently increases the likelihood that sperm motility is >10%. In placebo group there was no significant difference in sperm motility, vitality and DFI, between T0 and T6. In the overall population, this DBPC study demonstrated that increase of percent of sperm vitality and decrease of DFI are good predictors of improvement of progressive sperm motility in oligoasthenospermic men treated with antioxidant therapy.

Supported by: NIH grants R01-ES009718, P30/ES000002.

OBJECTIVE: To examine associations between levels of cell-free DNA (cfDNA) and WHO semen parameters or sperm DNA damage, in men with low, variable and normal semen quality.

DESIGN: Prospective validation study in 194 men (18-45 years; mean age 33.3 years) from 3 subgroups, representing different semen qualities: 1) Low semen quality (men eligible for intracytoplasmic sperm injection (ICSI)), 2) Variable semen quality from couples planned for in vitro fertilization (IVF) / intrauterine insemination (IUI), and 3) Normal semen quality (fathers of infants below 30 months of age, pregnancy obtained by natural intercourse). Study samples were collected at one visit at the clinic. All subjects provided written consent and the study was approved by the local ethics committee.

RESULTS: Serum levels of cfDNA ranged from 0 to 847 ng/mL in the study population, with a median concentration of 3.1 ng/mL. A statistically significant (p = 0.001) difference in serum levels of cfDNA between the study subgroups was observed with median concentrations of 6.2 ng/mL, 2.0 ng/mL and 1.9 ng/mL in subgroups 1, 2 and 3, respectively. In the overall population, very weak but statistically significant negative correlations were observed between serum cfDNA and the WHO semen parameters progressive motility (r = -0.17, p = 0.022) and total motility (r = -0.16, p = 0.027). In addition, a very weak but significant correlation between serum cfDNA and sperm DNA fragmentation index was observed (r = 0.18, p = 0.017). Associations between sperm DNA damage and WHO semen parameters were confirmed as moderate to strong significant (p<0.001) negative correlations between sperm DNA fragmentation index and concentration
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CELL-FREE DNA IS ELEVATED IN MEN WITH ABNORMAL SEMEN. H. J. Tournaye, B. Popovic-Todorovic, S. Hamamah, B. Nilsson, H. Aasted, B. M. Klein, J. C. Arce. UZ Brussels Fertility Clinic CRG, Brussels, Belgium; University Hospital of Montpellier, Montpellier, France; Ferring Pharmaceuticals, Copenhagen, Denmark; Ferring Pharmaceuticals, Parsippany, NJ.

OBJECTIVE: To examine correlations between levels of cell-free DNA (cfDNA) and sperm DNA damage in male subjects with normal or abnormal semen quality.

DESIGN: Prospective validation study in 183 men (18-45 years; mean age 33.5 years) attending a fertility clinic, of whom 162 subjects were male part- ners of couples undergoing infertility treatment and 21 subjects were sperm donors. Subjects were grouped based on WHO criteria to have abnormal or normal semen quality based on WHO semen parameters concentration, total count, progressive motility and morphology. Data were analyzed using non-parametric methods.

RESULTS: Serum levels of cfDNA ranged from 0 to 237 ng/mL in the study population, with a median concentration of 2.5 ng/mL. Statistically significant differences (p < 0.05) were observed between serum levels of cfDNA and WHO semen parameters concentration, total count, progressive motility and morphology. Data were analyzed using non-parametric methods.

RESULTS: Levels of cfDNA were significantly different (p < 0.05) across subjects with normal semen quality compared to subjects with abnormal semen quality. The significance of these differences was confirmed using non-parametric statistical methods. Associations between sperm DNA damage and WHO semen parameters concentration, total count, progressive motility and morphology were observed. The study results suggest a potential role of cfDNA in male infertility. Even though the observed correlations between cfDNA and semen quality were weak in the overall study population, cfDNA was clearly elevated in subjects classified with severe male infertility based on semen quality/sperm DNA damage.

Supported by: Ferring Pharmaceuticals.

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PREDICTORS OF SPERM RETRIEVAL IN PATIENTS WITH CHROMOSOMAL ANOMALIES AND NON-OBSTRUCTIVE AZOOSPERMIA. A. Majzoub, M. Arafah, S. AlSaid, H. Shehadeh, K. Khalafalla, H. Elbardissi, Hamad Medical Corporation, Doha, Qatar; Hamad Medical Corporation, DOHA, Qatar; HMC, Doha, Qatar.

OBJECTIVE: Amongst the several causes of male factor infertility, genetic causes play an important role with a reported incidence of 2-8% in infertile men, increasing to about 19% in men with non-obstructive azoo- spermia (NOA). Generally, the reported surgical sperm retrieval (SSR) rate is lower in azoospermic patients with chromosomal abnormalities (ChA) in comparison to patients without ChA. This study assessed the predictors for successful SSR from infertile men with NOA due to ChA.

DESIGN: Retrospective chart review

MATERIALS AND METHODS: Patients presenting with NOA (n=483) who underwent SSR at a tertiary medical center over a period of 5 years were included in this study. Data regarding patient demographics, clinical findings, serum hormone levels, ChA, type/outcome of the sperm retrieval procedure and histopathology results was collected. All patients underwent a staged sperm retrieval procedure starting with testicular sperm aspiration (TESA) and progressing to microsurgical testicular sperm extraction (mTESE) when no sperm were retrieved after 4 aspirations from each testicle. Collected variables were examined against the sperm retrieval outcome. Chi-squared test and Mann-Whitney test were used to analyze categorical and numerical values, respectively. A p value < 0.05 was considered statistically significant.

RESULTS: 9.1% (44) patients had a ChA. Klinefelter syndrome and chromosomal translocations and Y-chromosome microdeletions were detected in 16 (36.4%), 14 (31.8%) and 14 (31.8%) cases respectively. The mean age of the study population was 44 ± 1.2 years. Their mean left testicular size, right testicular size, serum testosterone, FSH, LH and estradiol levels were 5.6 ± 0.7cm³, 6.7 ± 0.8cm³, 11.4 ± 0.7nmol/L, 17.3 ± 1.5IU/L, 9.5 ±
OBJECTIVE: Advances in chemotherapeutic treatments can achieve high remission rates in pediatric and adolescent patients with cancer, but cytotoxic chemotherapy may lead to irreversible spermatogenic dysfunction. In cancer survivors, the restoration of fertility and achievement of paternity have become important concerns. Newborns, however, are at diagnosis, patients with such serious diseases are often not concerned with reproductive issues.

DESIGN: A retrospective study in a reproductive center.

MATERIALS AND METHODS: We evaluated sperm retrieval rate (SRR) of microdissection TESE (micro TESE), two pronuclei (2PN) oocyte rates, blastocyst development rates, good-quality blastocyst (Grade 3BB and above on day 5 by the Gardner scoring) rates, and clinical pregnancy rates per embryo transfer (ET) in 44 cases with post chemotherapy NOA patients (including 8 patients with bone marrow transplantation (BMT)), 330 NOA cases with 46,XY without past history (unexplained NOA; not including after orchidopexy, Klinefelter syndrome, cryptozoospermia, mumps orchitis, etc), and 107 cases with obstructive azoospermia (OA) between September 2013 and April 2018. The cancer types included testicular cancer, colon cancer, Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, leukemia, neuroblastoma, and osteosarcoma. The age at micro TESE and chemotherapy was 33.9±5.4 and 17.3±10.4 years of age, respectively, and the ages at ICSI were 33.7±3.9 years.

RESULTS: SRR of micro TESE in post chemotherapy NOA (21/44=47.7%) was higher than unexplained NOA (92/330=27.9%) patients (P<0.01). In sperm retrieved post chemotherapy NOA, age at chemotherapy end was older (20.6±1.9 years) than failure group (14.2±10.8 years) (P<0.05). With respect to type of cancer, there was no significant difference in the SRR and no significant differences in the pregnancy and live birth rates. In 3 of 8 post BMT patients spermatooza were successfully retrieved. Two of 3 patients even showed a 46,XX karyotype (transplantation from female donor). The 23 patients who failed to obtain sperm could not find any germ cells in their testicular samples in wet preparations and histopathological sections (Sertoli cell only syndrome). 2PN oocytes, blastocysts development, and good-quality blastocyst rates were 63.2%, 55.8%, and 61.9% in post chemotherapy NOA, 58.3%, 45.2%, and 37.8% in unexplained NOA, and 66.0%, 51.6%, and 42.8% in OA. Post chemotherapy NOA showed higher clinical pregnancy rates per ET (44.9%: 22/49) than unexplained NOA (26.2% : 37/141) (P<0.05). Fourteen children have been born and 4 patients are on going pregnancy in post chemotherapy NOA couples.

CONCLUSIONS: Age at chemotherapy was an important predictive factor for successful sperm recovery. Once sperm were obtained their reproductive performance was satisfactory. These findings provides hope for men of reproductive age who have not undergone sperm cryopreservation before chemotherapy.

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THE IMPACT OF SEMEN INFECTIONS ON SPERM PARAMETERS IN PRIMARY INFERTILE MEN - RESULTS FROM A REAL LIFE, CROSS-SECTIONAL STUDY. F. Pederzoli,a E. Ventimiglia,a,b P. Capogrosso,a L. Boeri,a W. Cazzaniga,a,b M. Alfano,a F. Chierigo,ab E. Pozzi,ab N. Frega,a F. Deho,a E. Montanari,c F. Gaboardi,a F. Montorsi,a,b A. Salonia,a,b Division of Experimental Oncology/Unit of Urology, IRCCS San Raffaele Hospital, Milan, Italy; Vita-Salute San Raffaele University, Milan, Italy; Department of Urology, IRCCS Fondazione Ca’ Granda – Ospedale Maggiore Policlinico, Milan, Italy.

OBJECTIVE: Urogenital tract infections are usually considered a potentially treatable cause of male infertility (MI). Clear data about the negative impact of infections on semen parameters and MI still lack.

DESIGN: We assessed the prevalence of urogenital infections and their impact on sperm and hormonal parameters in a homogenous cohort of 2464 Caucasian-European men presenting for primary couple infertility at a single institution.

MATERIALS AND METHODS: Demographic, clinical and laboratory (including the hormonal profile) data of the entire cohort were analyzed. Health-significant comorbidities were scored with the Charlson Comorbidity Index (CCI; categorized 0 vs. ≥1). Sperm analysis was based on 2010 WHO performance was satisfactory. These findings provide hope for men of reproductive age who have not undergone sperm cryopreservation before chemotherapy.

RESULTS: Overall, 1662 patients (67.5%) underwent sperm cultures. Of these, semen cultures were positive in 271 patients (16.3%). Most commonly identified bacteria were Ureaplasma and Enterobacteriaceae spp. (32.9% and 1.7%, respectively). A concurrent infection with ≥2 agents was reported in 15.1% cases. Patients with a positive semen culture had higher mean (SD) BMI [26.1 (4.0) vs. 25.6 (3.3)], lower ejaculate volume [2.99 (1.6) vs. 3.35 (1.8) ml] and lower sperm density [21.1 (9.5) vs. 24.7 (11.1) million/ml], and lower motility (9.1 years) than failure group (14.2 years) (P<0.001). Fourteen children have been born and 4 patients are on going pregnancy in post chemotherapy NOA couples.

CONCLUSIONS: Age at chemotherapy was an important predictive factor for successful sperm recovery. Once sperm were obtained their reproductive performance was satisfactory. These findings provides hope for men of reproductive age who have not undergone sperm cryopreservation before chemotherapy.

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THE ASSESSMENT OF TESTICULAR SPERM EXTRICATION (TESE) AND INTRACYTOPLASMIC SPERM INJECTION (ICSI) IN COUPLES OF POST CHEMOTHERAPY NON-OBSTRUCTIVE AZOO-SPERMIA (NOA). T. Ishikawa,a,b S. Mizuta,a K. Yamaguchi,a,b Y. Takaya,a H. Matsubayashi,a,b T. Takeuchi,a K. Kitaya,a Reproduction Clinic Osaka, Osaka, Japan; Reproduction Clinic Tokyo, Tokyo, Japan.

OBJECTIVE: To perform semen culture in asymptomatic infertility men? hints from a cross sectional study. E. Ventimiglia,a F. Pederzoli,a,c Capogrosso,a,b C. Caprogna,a W. Cazzaniga,a,b L. Boeri,a M. Alfano,a F. Chierigo,a,b E. Pozzi,ab N. Frega,a F. Deho,a E. Montanari,c F. Gaboardi,a F. Montorsi,a,b A. Salonia,a,b Division of Experimental Oncology/Unit of Urology, IRCCS San Raffaele Hospital, Milan, Italy; Vita-Salute San Raffaele University, Milan, Italy; Department of Urology, IRCCS Fondazione Ca’ Granda – Ospedale Maggiore Policlinico, Milan, Italy; Urology, IRCCS Fondazione Ca’ Granda - Ospedale Policlinico, Milan, Italy.

OBJECTIVE: The EAU guidelines suggest performing semen culture in cases of increased leukocytes in semen. However, the clinical significance of an increased concentration of leukocytes in the ejaculate is controversial. Although leukocytoxspemia is a sign of inflammation, it is not necessarily associated with bacterial or viral infections.

DESIGN: We aimed to retrospectively validate this recommendation in a cohort of Caucasian-European men seeking medical help for male factor couples’ infertility.

MATERIALS AND METHODS: Complete socio-demographic, clinical and hormonal data from 547 consecutive infertile men and asymptomatic for genital infections were analysed. Health-significant comorbidities were scored with the Charlson Comorbidity Index (CCI; categorized 0 vs 1 vs ≥2). Semen culture was obtained in all cases. In all cases, cytotoxic chemotherapy was administered for leukemia, lymphoma, solid tumors, and osteosarcoma. The age at micro TESE and chemotherapy was 33.9±5.4 and 17.3±10.4 years of age, respectively, and the ages at ICSI were 33.7±3.9 years.

RESULTS: SRR of micro TESE in post chemotherapy NOA (21/44=47.7%) was higher than unexplained NOA (92/330=27.9%) patients (P<0.01). In sperm retrieved post chemotherapy NOA, age at chemotherapy end was older (20.6±1.9 years) than failure group (14.2±10.8 years) (P<0.05). With respect to type of cancer, there was no significant difference in the SRR and no significant differences in the pregnancy and live birth rates. In 3 of 8 post BMT patients spermatooza were successfully retrieved. Two of 3 patients even showed a 46,XX karyotype (transplantation from female donor). The 23 patients who failed to obtain sperm could not find any germ cells in their testicular samples in wet preparations and histopathological sections (Sertoli cell only syndrome). 2PN oocytes, blastocysts development, and good-quality blastocyst rates were 63.2%, 55.8%, and 61.9% in post chemotherapy NOA, 58.3%, 45.2%, and 37.8% in unexplained NOA, and 66.0%, 51.6%, and 42.8% in OA. Post chemotherapy NOA showed higher clinical pregnancy rates per ET (44.9%: 22/49) than unexplained NOA (26.2% : 37/141) (P<0.05). Fourteen children have been born and 4 patients are on going pregnancy in post chemotherapy NOA couples.

CONCLUSIONS: Age at chemotherapy was an important predictive factor for successful sperm recovery. Once sperm were obtained their reproductive performance was satisfactory. These findings provides hope for men of reproductive age who have not undergone sperm cryopreservation before chemotherapy.
predictive performance and accuracy of several clinical parameters and compared them to EAU guidelines.

RESULTS: A positive semen culture was found in 56 (10%) men. The most commonly identified pathogens belonged to Enterobacteriaceae (15% of all positive examinations). Of all, 141 (26%) patients had leukocytospermia >10^9 WBCs/mL and would have therefore deserved semen culture testing based on EAU guidelines; of them, 12 (9%) actually displayed a positive semen culture. Conversely, 44 (79%) out of 56 patients with positive semen culture would have been missed. Overall predictive accuracy, sensibility, and specificity of EAU guidelines were 48%, 21%, and 74%. No further clinical parameter was significantly associated with positive sperm culture and could be therefore used as a predictor, except for increased serum neutrophil-to-lymphocyte (NRL) ratio (predictive accuracy 60%, p=0.03 vs. EAU guidelines).

CONCLUSIONS: The vast majority (79%) of asymptomatic infertile men with a positive sperm culture may miss a proper assessment if applying EAU guidelines. Not a single parameter, except for NRL, can assist medical decision making. Therefore, a semen culture should be offered to every infertile man.

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OBJECTIVE: Studies evaluating the impact of teratospermia (<4% normal forms) and very low strict morphology (0-1% normal forms) on intrauterine insemination (IUI) outcome have relied on the primary semen analysis for classification of morphology and not the actual sample inseminated.1 As there can be significant variation in semen parameters between samples, we aim to determine the effect of sperm morphology from the specific sample used for IUI on clinical pregnancy rates (CPR). DESIGN: Retrospective cohort study of couples undergoing IUI from July 2016 to January 2017 at a university based clinic.

MATERIALS AND METHODS: The records of couples undergoing IUI were retrospectively reviewed. Semen analyses including Kruger strict morphology from the actual sample inseminated were available for 151 couples comprising 236 total treatment cycles, performed in accordance with the WHO fifth edition laboratory manual. Of these, 110 couples comprising 158 treatment cycles had normal semen parameters or isolated teratospermia. The primary outcome was CPR measured by detection of cardiac activity. Multiple logistic regression modeling was performed to determine the association of sperm morphology with CPR, controlling for other related factors.

RESULTS: Of the total 236 treatment cycles included, 9.3% resulted in clinical pregnancy. Mean post-wash total motile sperm count (TMS) was 30.1 million, ranging from 0.1 - 259 million. Of the 158 treatment cycles with otherwise normal semen parameters or isolated teratospermia, 10.1% resulted in pregnancy. Mean post-wash TMS was 38.8 million, ranging from 10.2 - 259 million. Average female age in both cohorts was 34.0 ± 4.3 years. CPR by morphology criteria are listed in Table 1.

CONCLUSIONS: Our study evaluating the morphology of the actual inseminated sample did not find any difference in CPR following IUI among couples with normal and abnormal sperm morphology. Abnormal sperm morphology should not exclude couples from attempting IUI. Future studies with larger sample sizes are needed.

Table 1

<table>
<thead>
<tr>
<th>Morphology</th>
<th># Cycles</th>
<th>CPR (%)</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>165</td>
<td>192</td>
</tr>
<tr>
<td>&lt;4%</td>
<td>49</td>
<td>56</td>
</tr>
<tr>
<td>0 - 9%</td>
<td>142</td>
<td>147</td>
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<tr>
<td>Isolated</td>
<td>100</td>
<td>104</td>
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EPIDIDYMAL SPERM RETRIEVAL BY MODIFIED OPEN FINNE NEEDLE ASPIRATION. H. Wang. Perfect Family Hospital, Beijing, China.

OBJECTIVE: To develop a method with maximally minimized injury and sufficient sperm yield on the basis of the above methods. DESIGN: For obstructive azospermia (OA), percutaneous epididymis sperm aspiration (PESA), microsurgical epididymal sperm aspiration (MESA), minimally invasive epididymal sperm aspiration (MIESA), minimicro-epididymal sperm aspiration (mini-MESA), macroscopic epididymal sperm imprint collection (MESIC) and open fine needle aspiration (OFEN) have been employed to retrieve sperm. In this study, PESA, MESA, MIESA, mini-MESA , MESIC and OFEN were performed for more than 10 cases each method in OA patients. On the basis of comparing the above methods, we developed a modified method of OFEN (MOFEN).

MATERIALS AND METHODS: MOFEN was performed under local anesthesia with 2% lidocaine in 20 OA patients. A small incision less than 1 cm in length was cut at the position corresponding to epididymis. After epididymis was exposed, the needle tip of tuberculin syringe preloaded with about 0.1 ml of sperm washing medium was pierced through tunica into the epididymal tubule which was seen faintly beneath epididymal tunic under operating microscope at 25X magnification. To minimize injury to epididymal tubule, attention was paid to inserting the needle carefully with the rear of the needle bevel just passed the tunica. Then the tubule fluid was aspirated. If no cloudy material entered into syringe, the needle was withdrawn a little and inserted again with direction adjusted. After aspiration, the content of the syringe was expelled into a culture plate. Then, the epididymis was squeezed, and the fluid milked out from the needle hole was suctioned with the nipple of the same syringe preloaded with about 0.1 ml of sperm washing medium. If no sperm was found in the aspiration, the needle hole on the epididymal tunic was enlarged as small as possible that just 2 or 3 tubes were exposed. Then, the tubule was pierced and aspirated, and the contents milked out from the needle hole of the tubule was suctioned with the same manoeuvre as described above.

RESULTS: The severity of injury ranked from MESA, MIESA to Mini-MESA in microsurgical procedure; MESIC to OFNA in macrosurgical procedure. In PESA, the epididymal tubules were punctured blindly and generally repeatedly, many tubes were injured. Considering the size of the incision and only one tubule was punctured in most condition, MOFNA injured the least in the study. As to efficiency of sperm retrieval, PESA and MIESA harvested the least and the most, respectively. In MOFNA, sperm retrieval was 100% successful and 20.8X10^6 sperm were harvested on average.

CONCLUSIONS: MOFEN is an efficient and safer method for epididymal sperm aspiration.

References:
IS PRENATAL AND POSTNATAL EXPOSURE TO HEAVY METALS ASSOCIATED WITH ALTERED SPERMATOGENESIS IN THE MOUSE?. A. Gentry, a M. Clemmer, b J. Freedman, b K. Pagidas, a Obstetrics, Gynecology, and Women’s Health, University of Louisville School of Medicine, Louisville, KY; bObstetrics and Gynecology, West Virginia University, Morgantown, WV; aPharmacology and Toxicology, University of Louisville School of Medicine, Louisville, KY.

OBJECTIVE: Lifestyle and exposure to pollutants can have detrimental effects to male fertility (1,2). It is recognized that obesity contributes to male infertility as well (3,4). Additionally, exposure to heavy metals in adults affects fertility. There is however, a paucity of data on the consequences of in utero exposure to heavy metals on spermatogenesis. The objective of this study was to evaluate the effects of prenatal and postnatal exposures to the environmental toxicants cadmium or arsenic on spermatogenesis in a mouse model. Additionally, the interaction between these pollutants and obesity was examined.

DESIGN: Basic science, bench research

MATERIALS AND METHODS: Male mice were exposed in utero and post-wean to either control, cadmium (0.5 or 5ppm), or arsenic (0.1ppm), and post-wean fed to either high fat, or regular diet. At sacrifice (10 or 24 weeks), testicular tissue was removed, embedded in paraffin, sectioned (5µm) and stained with haematoxin and eosin for histopathology. All round seminiferous tubules were examined for signs of germ cell degeneration (detachment, sloughing, and presence of neutrophils), morphometry, and assessment of progression of spermatogenesis.

RESULTS: Mice exposed to 5ppm cadmium and sacrificed at 24 weeks had a significant (P<0.01) decrease in complete spermatogenesis. Diet, 0.5ppm cadmium, and 0.1ppm arsenic did not have an effect on any markers of spermatogenesis. There was a significant increase in detachment of seminiferous tubules in animals exposed to 5 ppm cadmium that was not seen in animals exposed to 0.5ppm cadmium or 0.1ppm arsenic. The length of toxicant exposure or diet did not have a significant effect on detachment. Ten week old animals had a higher incidence of sloughing, despite either toxicant exposure, than older animals (P=0.01), while 24 week mice had a significantly (P<0.01) higher numbers of neutrophils within the lumen of seminiferous tubules. Exposure to either toxicant and high fat diet did not affect sloughing or increase the number of neutrophils. Three-way analysis of variance on the height of the epithelium revealed a significant three-way interaction between either toxicant, diet, and sacrifice time (P=0.01).

CONCLUSIONS: Exposure to high dose cadmium in utero and post-na-tally had a negative effect on spermatogenesis and showed significant germ cell degeneration. This suggests that prenatal and postnatal exposure to heavy metals can compromise the reproductive potential in the male.


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INTERACTION BETWEEN MALE ANTHROPOMETRIC PARAMETERS WITH SPERMOMGRAS. J. E. Ramirez Monterrubio, a C. A. Maldonado, a R. Santos Haliscak, a L. de la O Tamez, a IECH Fertility Center, Monterrey, Mexico; aBiologia de la Reproduccion Humana, IECH Fertility Center, Monterrey, Nuevo Leon, Mexico.

OBJECTIVE: To evaluate male body composition data that can be associated with semen analysis parameters.

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DESIGN: observational, prospective, analytic inferential study.

MATERIALS AND METHODS: A total of 186 healthy male patients were recruited. We used a bio impedance scale OMRON BF511 for somatometry and after that we classified patients into normal (n=92), high (n=43) and too high (n=51) body fat according to Gallagher et al and Body Mass Index. We analysed the results using a correlation parameter (R.3.4.1) and adjusting with multivariable regression model.

RESULTS: The mean age of the male patients was 32 yr, ±6.3, the BMI was 28.56 kg / m², ±6.2), the total body fat was 28.55%, ±8.4). The mean percentage of visceral fat was 11.1%, ±5.1, muscle (34.1%, ±6.1), basal metabolism rate (1855.73kcal, ±263.96), and metabolic age (51.08yr, ±18.62). A slight interaction amongst BMI, Abdominal Circumference, and Age was found with total sperm count (r² = 0.240) ; sperm vitality was moderately (r² = 0.424) correlated with basal metabolism, and percentage of visceral fat; Also, we observed less normal Kruger morphology (r² = -0.341) with a higher visceral fat percentage; above 9 % in visceral fat (AUROC = 0.647) there was an increased risk of abnormal Kruger morphology.

CONCLUSIONS: The somatic composition of the male, especially body fat percentage, visceral fat percentage, age, and basal metabolism rate have a mild to moderate interaction with the results of sperm vitality and Kruger morphology.


OBJECTIVE: To identify the optimal transfection parameters to ensure the viability of spermatozoa in a CRISPR-Cas9 protocol.

DESIGN: We aim to find the optimal transfection parameters for human spermatozoa to ensure the highest viability and motility of cells after transfection. To meet this goal, different sets of electroporation parameters were tested in a unique 24-well system. We plan to use CRISPR-Cas9 on sperm cells to knock out LAMA1, a gene that is upregulated in male infertility patients.

MATERIALS AND METHODS: In a 10-month period, we ran five different preliminary experiments using one donor, one frozen, and three ejaculate specimens. To test our system, we transfected embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) grown in vitro with Oct3/4 CRISPR-Cas9 knockout plasmid utilizing a GFP reporter gene. Successful transfection (Neon Transfection System, Invitrogen) was defined as the absence of GFP expression. We then began our first attempt using human sperm cells and evaluated different sets of parameters ranging from 800 V, 27 ms, 5 pulses to 1,700 V, 20 ms, 1 pulse.

RESULTS: Our test experiment using ESCs and iPSCs was highly successful, matching a threshold of 79% transfection efficiency, comparable to prior research. Oct3/4 expression was markedly decreased by 81%±2% after transfection when compared to the initial expression.

As for our experiments with human spermatozoa, 1100 V, 20 ms, 1 pulse was found to be the optimal set to successfully transfected CRISPR-Cas9 plasmid in human spermatozoa and retain their motility. For these experiments, we utilized various samples (donor, frozen, or ejaculate) with an average initial concentration of 5.2±4x10⁷/ml and an average motility of 43.2%. The ejaculate sample with the highest initial concentration and motility following processing resulted in 89.4±10⁷/ml and 19.0±4%, respectively. The motility of this sample after transfection was 49.3±3% at a concentration of 10±8x10⁷/ml using the optimal transfection settings.

Currently, we are experimenting with a microfluidic selection system in order to further isolate the motile portion of transfected spermatozoa. Moreover, we will be utilizing DNA sequencing and a custom fluorescent hybridization probe as proof of transfection.

CONCLUSIONS: Retaining motility in spermatozoa after exposing them to high-voltage pulses may facilitate the correction or induction of mutations in human gametes. The accuracy and reproducibility of this analysis might be affected by the structural peculiarities and the innate kinetic characteristics of the spermatozoan following transfection. Successful utilization of CRISPR-Cas9 on human spermatozoa may ease qualms related to the direct genetic manipulation of human embryos.
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SEMINAL GSTM3, CRISPLD2, AND RARRES1 DIAGNOSE SPERM FUNCTIONAL ALTERATIONS. P. Intasqui, M. Camargo, M. P. Antoniassi, L. B. Belardin, R. P. Bertolla. Department of Surgery, Division of Urology, Sao Paulo Federal University, Sao Paulo, Brazil.

OBJECTIVE: Sperm functional alterations are considered the main cellular mechanisms of male infertility, observed in 25% of infertile men. We have previously shown, using a shotgun proteomics approach, that Glutathione S-transferase Mu3 (GSTM3), Cysteine-rich secretory protein LCCL domain-containing 2 (CRISPLD2) and Retinoic acid receptor responder protein 1 (RARRES1) seminal proteins are associated with sperm abnormalities. Current limitations in the quantitative aspect of a shotgun proteomics approach demand these results be validated in a larger cohort. In this study, thus, we sought to evaluate, using a confirmatory method, GSTM3, CRISPLD2 and RARRES1 levels in seminal plasma in association with sperm mitochondrial activity and DNA fragmentation.

DESIGN: Prospective study.

MATERIALS AND METHODS: 197 normozoospermic men were recruited for this study. Semen was collected by masturbation following 2 to 5 days of ejaculatory abstinence. An aliquot was used for semen analysis, another for sperm functional evaluation, and the remaining semen volume was centrifuged for separation of seminal plasma. Sperm functional data were used to separate the experimental groups: High (control, n=27) and Low (study, n=27) sperm mitochondrial activity, and Low (control, n=29) and High (study, n=29) sperm DNA fragmentation. Seminal plasma of all samples was utilized to evaluate the levels of GSTM3, CRISPLD2 and RARRES1. Western blotting. Data were homogenized using triton x-protein (Ponceau S staining) and multiplied by the ejaculate volume, to obtain the total protein levels in the ejaculate. Groups were compared using an unpaired Student’s t test (t=5%).

RESULTS: GSTM3 was observed as two different bands (27 kDa, its expected molecular mass, and 38 kDa). Total levels of both bands were twice as high in samples with sperm mitochondrial alterations. CRISPLD2 was observed as three different bands (17, 28 and 58 kDa, expected molecular mass = 51 kDa), suggesting its digestion by seminal plasma proteases during semen liquefaction. Total seminal levels of the 17 and 28 kDa bands were decreased in samples with high sperm DNA fragmentation (1.6-fold and 2.6-fold decrease, respectively). Likewise, RARRES1 was identified as two bands (50 and 62 kDa, expected molecular mass = 33 kDa), suggesting post-translational modifications and/or dimer formation. The 50 kDa band was 1.9-fold decreased in the seminal plasma of men with sperm DNA fragmentation.

CONCLUSIONS: Seminal plasma proteins directly reflect sperm functional alterations and, thus, male infertility. Seminal plasma proteins may be used as markers of functional alterations. In this study, we confirmed that this is the case for GSTM3 (sperm mitochondrial activity), and CRISPLD2 and RARRES1 (sperm DNA fragmentation).


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MALES WITH HIGHLY POSITIVE ANTISPERM ANTIBODIES (ASA) ON THEIR SPERM DO NOT HAVE A GREATER FREQUENCY OF LOW HYPO-OSMOTIC SWELLING (HOS) TEST SCORES. J. H. Cheok, A. Bollendorf, E. Chang, R. Cohen, J. Cheok. "Cooper Medical School of Rowan University, Camden, NJ; Philadelphia College of Osteopathic Medicine, Philadelphia, PA.

OBJECTIVE: Males with low hypo-osmotic swelling (HOS) test scores (<50) rarely will achieve a live delivery following intercourse, intrauterine insemination (IUI) or conventional in vitro fertilization related to causing embryo implantation failure (though not adversely affecting fertilization). Two methods that markedly increase pregnancy rates with this abnormality related to a toxic protein attached to the sperm are intracytoplasmic sperm injection or avoidance of unprotected intercourse and pretreatment of sperm with the protein digestive enzyme chymotrypsin followed by IUI. Similarly, chymotrypsin pretreatment of sperm laden with ASA prior to IUI has been found to improve pregnancy rates in female partners of males with ASA. The objective of this study was to determine if the frequency of low HOS tests increases in males with highly positive ASA’s.

DESIGN: Prospective observational study.

MATERIALS AND METHODS: Subjects: a series of males enlisted when sperm tested positive for ASA’s (IgG) (>50%). The HOS test was also performed on these males. The direct immunobead test was used to measure ASA.

RESULTS: 128 males enlisted. 98/128 (70.3%) had ASA’s ≥80%. A low HOS test was found in only 5 males (3.9%) with HOS test scores of 25, 31, 43, 47, and 48%. The 48% HOS test level was found in a male with 58% ASA. Otherwise the ASA score was ≥90% in these males.

CONCLUSIONS: There is a greater percentage of low HOS test scores in males who test positive for ASA’s (3.9%) than found in males negative for ASA based on previous studies. The factor causing functional impairment of the sperm membrane resulting in low HOS scores and ASA are both proteins. Based on this study the two proteins appear separate with no overlap. Thus, the presence of ASA does not seem to cause a low HOS test score when one compares the 3.9% frequency to known frequency of low HOS test scores in the general population devoid of ASA.

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ASSOCIATION OF SINGLE NUCLEOTIDE POLYMORPHISM (SNP) OF HSPA2 GENE WITH PATERNAL FACTORS IN RECURRENT PREGNANCY LOSS: AN IN SILICO FUNCTIONAL AND STRUCTURAL ANALYSIS WITH VALIDATION AT PROTEIN LEVEL. L. Samanta, G. Mohanty, S. Kar. Redox Biology, Ravenshaw University, Cuttack, India; Zoology, Ravenshaw University, Cuttack, Odisha, India; Consultant Obstyn KCJPL, Bhubaneswar, India.

OBJECTIVE: The molecular chaperone HSPA2 plays a pivotal role in the remodelling of the sperm surface during capacitation. It is established that mice lacking HSPA2 gene are infertile and spermatozoa that fail to interact with the zona pellucida of the oocyte consistently lack HSPA2 protein expression. However, its role in post fertilization events is not fully understood. Owing to the importance of HSPA2 in male infertility, functional analysis was carried out to reveal the association between genetic mutation and phenotypic variation through various in silico approaches and its validation at protein level by western blot (WB) in idiopathic recurrent pregnancy loss (iRPL).

DESIGN: Computational and case-control study

MATERIALS AND METHODS: The present study analyzed the functional consequences of the nsSNPs in human HSPA2 gene using SIFT, PolyPhen 2, PROVEAN, nsSNPAnalyzer, SNPs&GO along with stability analysis through 1-Mutant2.0. Protein structural analysis with these amino acid variants was performed by using HOPE, ConSurf, Swiss PDB viewer, Chimera and NOMAD-Ref servers to check their solvent accessibility, molecular dynamics and energy minimization. STRING and Cytoscape softwares were used for pathway analysis. The study was further validated by WB consisting of male partners of iRPL patients (n=16) with no female factor abnormality as revealed by gynaecologic investigation including karyotyping and consistent matched fertile healthy volunteers (n=20). All samples were collected during 2013-2015 after getting institutional ethical approval and written consent from the participants.

RESULTS: 444 SNPs were synonymous and 56 were found to be non-synonymous SNPs. It was found that 18 SNPs were deleterious using a combinatorial servers-SIFT, Polyphen, PROVEAN, nsSNP analyzer and SNPs&GO. Further functional analysis suggests that screening of SNP variants of HSPA2 such as V106E, D55Y, T301R, R314P, S343P may be useful for predicting outcome. Additionally, the HSPA2 was found to be underexpressed in iRPL as compared to their fertile counterparts.

CONCLUSIONS: This pilot study however showed that in case of iRPL, HSPA2 has a confounding impact as a pivotal paternal factor inRPL patients.

Supported by: GM thanks University Grants Commission, Government of India for post-doctoral fellowship

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PROTEOMIC ANALYSIS OF SEMINAL PLASMA BIO-MARKERS IN INFERTILE MEN WITH VARICOCELE. M. Panner Selvam, A. Agarwal, L. Samanta, R. Sharma, S. Gupta, D. Durairajanayagam, B. Willard, S. C. Vij. American Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH; Redox Biology, Ravenshaw University, Cuttack, India; "Faculty of
OBJECTIVE: Alteration in expression levels of seminal plasma proteins may affect the fertilizing ability of spermatozoa. This study aimed to 1) compare seminal plasma proteome of proven fertile men with infertile varicocele patients; and 2) identify protein biomarkers in seminal plasma of infertile men with unilateral and bilateral varicocele.

DESIGN: Proteomic profiling of seminal plasma was performed using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Key differentially expressed proteins (DEPs) in varicocele (unilateral and bilateral) patients and fertile men were selected using bioinformatics analysis and evaluated using western blot (WB).

MATERIALS AND METHODS: Pooled seminal plasma samples from fertile men (n = 5), unilateral (n = 5), and bilateral (n = 5) varicocele patients were processed for quantitative proteomic analysis. Proteins identified by LC-MS/MS in both varicocele groups were combined and compared with the fertile group. Ingenuity pathway analysis software was used to narrow down key DEPs associated with normal sperm function. Four proteins namely acrosin (ACR), heat shock-related 70 kDa protein 2 (HSPA2), peroxiredoxin 2 (PRDX2) and apolipoprotein A2 (APOA2) were validated by WB and evaluated in fertile men (n = 6) and varicocele patients (n = 12). Statistical significance was calculated using Mann-Whitney test.

RESULTS: A total of 412 and 486 proteins were detected in seminal plasma of fertile men and varicocele patients respectively. Twenty eight proteins were identified as DEPs and key DEPs selected for WB validation were underexpressed, overexpressed, and overexpressed with statistical significance (P < 0.05), underexpressed, and overexpressed.

CONCLUSIONS: Irrespective of varicocele type (unilateral or bilateral), seminal plasma protein profiles of infertile varicocele patients differ from fertile patients. These biomarkers can be used as potential markers to identify sperm quality and aid in treatment decisions.

<table>
<thead>
<tr>
<th>Protein</th>
<th>Expression</th>
<th>Relative Fold Change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR</td>
<td>↓</td>
<td>0.81</td>
<td>0.3861</td>
</tr>
<tr>
<td>HSPA2</td>
<td>↓</td>
<td>0.10</td>
<td>0.0037*</td>
</tr>
<tr>
<td>PRDX2</td>
<td>↑</td>
<td>1.29</td>
<td>0.0474*</td>
</tr>
<tr>
<td>APOA2</td>
<td>↓</td>
<td>0.67</td>
<td>0.0373*</td>
</tr>
</tbody>
</table>

*Statistically significant (P < 0.05), ↓ underexpressed, ↑ overexpressed

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OBJECTIVE: Assess correlation of Sperm DNA fragmentation (SDF) after sperm gradient centrifugation with poor embryo development, and embryo ploidy status and effect on SDF of sperm processing, culture medium, and laboratory conditions.

DESIGN: IRB approved double-blinded, prospective study evaluating the effect of SDF on the day of the oocyte retrieval on blastocyst (BL) development, preimplantation genetic testing for aneuploidy (PGT-A) results, and live birth rates.

MATERIALS AND METHODS: Three aliquots of semen were immediately frozen from the semen sample provided by 85 men for IVF/ICSI as follows: aliquot 1 = neat sample, aliquot 2 = resuspended sperm immediately post density gradient centrifugation (Isolate, Irvine), and aliquot 3 = just prior to fertilization (2 to 6 hours later). Code specimens were sent to an external clinical laboratory (ReproSource, Woburn, MA) for blinded SDF measurement, reported as % DNA Fragmentation Index (%DFI), using the acridine orange and flow cytometry as described in the SCISA method (ReproSource, Woburn, MA). Trophoectoderm biopsy (Bx) was performed on Day 5 or 6 BL. Next generation sequencing (NGS) was utilized for PGT-A (CooperGenomics, Detroit, MI). Statistical analysis was performed using contingency tables with Pearson’s Chi Squared test (p < 0.05) or unpaired t-tests using JMP 12 (SAS Institute Inc.) software.

RESULTS: Sperm gradient processing improved DFI a relative 62% with a relative increase of 8% during the 2-6 hours between processing and fertilization. Outcome data was categorized by DFI of ≥ 15 (H) and < 15 (L) in aliquots 1 (neat) and 3 (at fertilization) as follows: H/H (n = 17), H/L (n = 34), L/L (n = 34). Average %DFIs were 37/33 (H/H), 25/7 (H/L), and 10/3 (L/L). As average outcome parameters in the H/L group did not differ significantly from L/L group, they were combined and compared to the H/H group as show below.

CONCLUSIONS: High DFI both pre and post sperm processing is significantly correlated with reduced fertilization rates, increased quantity of good quality day 3 embryos, and lower quantities of good quality blastocysts consistent with the biological understanding that sperm quality is important during fertilization and later blastocyst formation. This study confirms that SDF measurement provides a measurement of sperm quality which predicts performance in IVF and that SDF reduction by sperm processing may predict improved outcomes at IVF.

Supported by: ReproSource Investigator Award covering cost of testing

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LIPIDOMICS OF SPERM CELLS OF FERTILE AND SUB-FERTILE MEN BY MRM-PROFILING. E. D. Borges, A. A. Vireque, T. S. Bertelli, C. B. de Lima, T. J. Sobreira, C. R. Ferreira, P. A. Navarro, "Departmento de Ginecologia e Obstetrícia, Faculdade de Medicina de Ribeirão Preto - USP, Ribeirão Preto, Brazil; Invitral - Assisted Reproductive Technology, Ribeirão Preto, Brazil; Universidade de Sao Paulo, Sao Paulo, Brazil; "Bindley Bioscience Center, Purdue University, West Lafayette, IN; "Obstetrics and Gynecology, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil.

OBJECTIVE: Sperm lipids play a very important role in the integrity of membranes and determine many of their important physicochemical properties. However, data on the lipid profile of human sperm cells is currently very limited and mainly obtained by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, in which resulting spectra are largely dominated by phosphatidylcholine (PC) and lyso-phosphatidylcholine signals. By MRM-profiling, diverse lipid classes can be profiled using a parent ion and class fragment information to obtain multiple reaction monitoring (MRM) methods. Thus, we aimed to characterize the lipid profile of sperm of fertile and subfertile men by MRM-profiling, which may help to identify possible lipids related to male fertility.

DESIGN: Prospective experimental study.

MATERIALS AND METHODS: Semen samples from 3 fertile men and 3 subfertile men (total motile sperm count under 1 million) were obtained from the ejaculate. Lipids were extracted from samples using the Bligh & Dyer protocol adapted for sperm cells. To obtain a list of MRMs, parent masses were calculated after combining constitutional isomers listed at the Lipid-Map database and adding neutral losses or product ions expected for diverse lipid classes including phosphatidylcholine (PC), sphingomyelin (SM), phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidylserine (PS), phosphatidylglycerol (PG), triacylglycerols (TAG), sulfatides, and seminolipids. For profiling diverse classes of lipid, reference samples (pooled lipid extracts of 3 sub fertile and 3 fertile men) were directly injected to a triple quadrupole mass spectrometer equipped with electrospray ion source. Blank samples were also run to check for chemical noise.

RESULTS: Out of 1187 MRMs screened, 428 presented higher ion intensity of at least 100 units than a blank in the sperm lipid extracts, 174 lipids were exclusive to either fertile or subfertile group, with the vast majority being present only in subfertile samples (including all PC, SM, sulfatides, and seminolipids detected exclusively between the two groups).

CONCLUSIONS: This comprehensive lipidomic approach allows the assessment of the lipid profile of human sperm cells in a fast and sensitive manner by using minimal sample amount. Over 400 lipids of 8 different classes were observed in human sperm from fertile and subfertile men. Moreover, the identification of lipids exclusive to either of the groups (fertile and subfertile) is a
remarkable finding that will aid future studies in the search for possible biomarkers of sperm quality. For the next step, we will be investigating semen samples of 20 men (10 fertile, and 1 subfertile) individually, guided by our current results."

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**A THEMATIC ANALYSIS OF ONLINE DISCUSSION BOARDS FOR MALE INFERTILITY.** L. Beeder*, M. Samplaski, Keck School of Medicine of USC, Los Angeles, CA; *Institute of Urology, Keck School of Medicine of USC, Los Angeles, CA.

**OBJECTIVE:** Many patients use the Internet for medical information and emotional support. We sought to identify what information patients and partners seek online related to male infertility.

**DESIGN:** We reviewed posts from male infertility discussion boards using a structured themetic analysis.

**MATERIALS AND METHODS:** Online discussion boards were identified by searching “male factor infertility message boards”. Three forums were identified as having the most posts. Using an iterative and structured analysis process, each post was reviewed in 3 steps: open coding, axial coding and selective coding, to determine common themes. We used a single sample t test to determine significant differences in the percentages of males and females authoring posts in each selective.

**RESULTS:** 1118 posts were analyzed, dated September 2004 to October 2017. The majority of posts (20.2%, 226/1118) were related to “Questions about male fertility diagnosis and testing”, with 47.8% (108/226) asking for assistance interpreting semen analysis results. 15.7% (176/1118) of posts dealt with “Feelings associated with male infertility”, with 26.7% (47/176) expressing anger or frustration, 26.1% (46/176) encouraging hope, 21% (37/176) seeking hope and 12.5% (22/176) expressing fear. 15.4% (172/1118) of posts were about “Lifestyle factors to improve male fertility”, 24.4% (42/172) of which were about vitamins and 6.4% (11/172) about optimal intercourse timing. 15.4% (172/1118) posted asked about “Male infertility conditions”, with 43% (74/172) being about semen parameters. Other themes included “Questions about male factor treatments”, “Questions about assisted reproductive technologies (ART)”, “Relationship issues”, “Asking for advice”, “Financial concerns” and “Information sharing”.

63.6% of posts were written by female partners, t(1117)=9.451, p<0.001. Males and females differed in posted content, with statistically significant differences in feelings associated with fertility [51.4% female, t(175)=1.985, p=0.049], relationship issues [86.0% female, t(49)=7.336, p<0.001], questions about male fertility diagnosis and testing [62.8% female, t(225)=3.981, p<0.001], questions about male factor treatments [74.2% female, t(150)=6.797, p<0.001], questions about male infertility conditions [65.7% female, t(171)=4.337, p<0.001], asking for advice [91.8% female, t(20)=10.665, p<0.001], questions about ART [76.7% female, t(59)=4.892, p<0.001] and information sharing [89.5% male, t(37)=7.943, p<0.001].

**CONCLUSIONS:** Patients with male factor infertility and their partners use online forums for information and support. Males and females differ in their concerns and questions. The most common posts posed questions about interpreting semen analysis results, indicating that online information about this may be useful. Users also wrote about their feelings, suggesting that forums may serve as a support platform. These findings should help target educational efforts.

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**IS THERE A ROLE FOR PRE-IMPLANTATION GENETIC SCREENING IN COUPLES WITH MALE FACTOR INFERTILITY?.** K. C. Mantravadi, D. G. Rao. Oasis Center for Reproductive Medicine, Hyderabad, India.

**OBJECTIVE:** Will male factor infertility bring about higher incidence of Embryo Aneuploidy? Will PGS help us pick euploid embryo and optimize reproductive outcome in cases with severe male faces infertility?

**DESIGN:** This was a retrospective study of all of couples in the year 2014-2016 with severe male factor infertility and undergoing PGS for failed implantation as an indication.

**MATERIALS AND METHODS:** All couples during January 2014 - December 2016 with two-failed IVF/ICSI attempts (fresh or frozen transfers) were offered PGS at our center. All couples were subjected to trophotrope biopsy on day 5 post insemination. All embryos were vitrified post biopsy. Biopsy of embryos was subjected to comprehensive chromosome aneuploidy with Next Generation Sequencing. Male partners were divided into three groups based on age (<40yrs (n=43) and >40yrs age (n=20)), sperm counts (<5millions/ml (n=14) & >5millions/ml (n=31)) and source of sperm used (Ejaculate (n=31) & Testicular sperm (n=33)). Percentage of aneuploidy was calculated. Only couples with female age less than 35years were included to ensure we do not have bias with advanced maternal age. Euploid embryos were transferred in a frozen semen replacement cycle. Live birth rate in all groups were calculated.

**RESULTS:** Percentage of aneuploidy and Live birth rates in each group respectively were as follows: <40yrs age - 54.58% & 68.75% >40yrs age - 56.66% & 25% (p=0.0013) <5millions/ml -52.63% & 50% >5millions/ml - 54.45% & 59% Testicular sperm- 56.41% & 64% Ejaculate sperm - 54% & 59%All the groups of severe male factor infertility showed similar incidence of aneuploidy and there was no statistical significance. LBR across all groups was comparable except advanced paternal age group - 25% (p=0.001). Young couples seem to have the highest LBR compared to advanced age. Though the advanced paternal age group had similar aneuploidy rates, still LBR were statistically low. Sperm counts and source of sperm for IVF/ICSI seem to have comparable aneuploidy rates and LBR.

**CONCLUSIONS:** Severe male factor infertility does not bring about higher incidence of embryo aneuploidy. Advanced paternal age more than 30years seem to have lesser live birth rates (LBR) in spite of comparable aneuploidy rates. There seems positive trend for use of PGS in male factor infertility to pick a euploid embryo and optimize reproductive outcomes.

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**SPERM CHROMATIN FRAGMENTATION HAS NO DISCERNABLE EFFECT ON ICSI EMBRYO PLOIDY.** D. Keating, A. Parrella, M. Irani, Z. Rosenwaks, G. D. Palermo, Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medicine, New York, NY.

**OBJECTIVE:** To assess whether the chromatin integrity of the male gamete has any quantifiable effect on the chromosomal composition of the resulting embryo.

**DESIGN:** The ejaculates of 26 men were screened for sperm chromatin fragmentation (SCF). Preimplantation genetic testing for aneuploidy (PGT-A) was performed on ICSI embryos. Aneuploidy records were recorded and compared to the SCP levels.

**MATERIALS AND METHODS:** Specimens retrieved from consenting men were screened for SCP by terminal deoxynucleotidyl dUTP nick-end labeling (TUNEL) utilizing a commercial kit (In Situ Cell Death Kit, Roche). Each patient had at least 500 spermatozoa analyzed for chromatin integrity, and the average SCP was calculated. Patients were divided into 4 age groups: <35yrs age, 35-40yrs age, 40-43yrs age, and >43yrs age. Each age group was further divided into normal sperm and a SCF group. Men then provided an ejaculated semen sample on the day of retrieval. To control for confounding factors, the age of the female partner was limited to 35 years, and only first ICSI attempts were considered. After PGT-A was performed, the tested embryos were cryopreserved for potential thaw and transfer at a later date.

**RESULTS:** A total of 26 couples were included in this study. The average maternal (or donor) age was 31.7±3.3 years, and the average paternal age was 37.2±4 years. The average SCP rate in the normal group was 10.7±3.3%, while the average SCP rate in the abnormal group was 21.8±4% (P < 0.001). After ICSI, the average number of embryos tested for aneuploidy in each cycle was 6.6±5. Seventeen of these couples presented with normal levels of SCP in their ejaculates. In their ICSI cycles, they had 114 embryos deemed suitable for PGT-A, which revealed that 38 were aneuploid (33.3%). None of the couples had any SCF result that fell outside of the normal threshold. These cycles yielded a cohort of 57 embryos deemed suitable for aneuploidy testing, with 22 showing abnormal genetic composition (38.6%). For patients who replaced at least one conceptus, those with a normal DFI had a clinical pregnancy rate of 50%. For those with an abnormal DFI, only biochemical pregnancies were achieved.

**CONCLUSIONS:** From this preliminary data, it appears that SCF is not associated with embryo aneuploidy. While it has been claimed that debranded DNA breakage may play a role in embryo aneuploidy, this doesn’t seem to be the case from our observations. However, it may still have a deleterious effect on embryo implantation. These findings do not negate the impact that an altered SCP has on embryo development.
1. Practice Committee of the American Society for Reproductive Medicine, E. B. Johnstone, D. Broberg, D. T. Carrell. Obstetrics and Gynecology, University of Utah, Salt Lake City, UT; Division of Urology, Department of Surgery, University of Utah, Salt Lake City, UT; Human Genetics, University of Utah, Salt Lake City, UT.

OBJECTIVE: Fifty percent of couples with recurrent pregnancy loss (RPL) will receive no diagnosis [1]. Sperm integrity is essential for sperm-egg interaction, fertilization and early embryonic development. The sperm epigenetic program is tailored to meet the need of this highly specialized cell and it has been suggested that the integrity of the sperm epigenome is essential not only for spermatogenesis but also the initiation and maintenance of a successful pregnancy [2]. Therefore, the objective of our study is to investigate the role of sperm epigenetics in unexplained RPL.

DESIGN: Comparison study between epigenetic marks in cases of idiopathic RPL and fertile controls.

MATERIALS AND METHODS: After excluding subjects with severe oligozoospermia, azoospermia and known karyotype abnormalities, we included a total of 17 well phenotyped male partners of women with unexplained RPL less than 10 weeks gestational age as the cases in this study. We utilized 15 known fertile donors as our controls. DNA extraction was performed from sperm samples and were assessed for the absence of somatic cell contamination. DNA fragmentation levels were assessed using Illumina’s EPIC array. We utilized a novel approach to test epigenetic variability/instability at multiple genomic loci important in various cellular processes (spermatogenesis, neurodevelopment, cellular differentiation, etc.) and throughout the entire genome. Unpaired t-tests were performed in R to compare means between our cases and controls. A p value < 0.05 was considered statistically significant.

RESULTS: Our results indicate that the sperm epigenetic signature of the marks tested were quite similar between our cases and controls as a group. However, 4 of our cases corresponding to 23.5% demonstrated significant epigenetic instability compared to our controls in all the epigenetic marks tested, most importantly in spermatogenesis (p = 0.02884), neurodevelopment (p = 0.03171) and cell differentiation (p = 0.02753).

CONCLUSIONS: While preliminary and with small numbers, our data suggests that some cases of unexplained RPL are associated with a severely altered epigenetic signature compared to controls. Although, we cannot confirm that this signature difference is independently causative of unexplained RPL, these findings are interesting and more work is required to fully understand their biological implications.

References:
1. Practice Committee of the American Society for Reproductive Medicine, E. B. Johnstone, D. Broberg, D. T. Carrell. Obstetrics and Gynecology, University of Utah, Salt Lake City, UT; Division of Urology, Department of Surgery, University of Utah, Salt Lake City, UT; Human Genetics, University of Utah, Salt Lake City, UT.

ABNORMAL SPERM EPIGENETIC SIGNATURE MAY BE ASSOCIATED WITH UNEXPLAINED RECURRENT PREGNANCY LOSS. Y. Ibrahim, T. Jenkins, E. B. Johnstone, D. Broberg, D. T. Carrell. Obstetrics and Gynecology, University of Utah, Salt Lake City, UT; Division of Urology, Department of Surgery, University of Utah, Salt Lake City, UT; Human Genetics, University of Utah, Salt Lake City, UT.

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CONCLUSIONS: While preliminary and with small numbers, our data suggests that some cases of unexplained RPL are associated with a severely altered epigenetic signature compared to controls. Although, we cannot confirm that this signature difference is independently causative of unexplained RPL, these findings are interesting and more work is required to fully understand their biological implications.

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VEry long chain polyunsaturated fatty acids in sperm are not associated with sperm progression or morphology. L. B. Craig, R. S. Brush, M. Agbaga, M. T. Zavy, M. T. Sullivan, R. E. Anderson. "OhGyn; Section of Reproductive Endocrinology and Infertility, The University of Oklahoma Health Sciences Center, Oklahoma City, OK; Department of Ophthalmology, The University of Oklahoma Health Sciences Center, Oklahoma City, OK; Department of Ophthalmology and Cell Biology, The University of Oklahoma Health Sciences Center, Oklahoma City, OK.

OBJECTIVE: Lipids play a major role in sperm structure and function. The lipids of sperm are relatively unique in that they contain very long chain polyunsaturated fatty acids (VLC-PUFA; ≥ 28 carbons), which are synthesized via ELOVL4 from dietary essential fatty acids and incorporated into sphingolipids, primarily sphingomyelin (SM). Our lab has previously shown that VLC-PUFA-SM levels have a strong positive correlation with sperm count and motility. Our objective was to determine if levels of VLC-PUFA in the sperm of infertile males correlate with sperm progression or morphology, since lipids play integrals roles in energy production and membrane structure.

DESIGN: Prospective Cohort

MATERIALS AND METHODS: Males age 18-45 who presented for semen analysis at an academic fertility clinic were offered participation in the study. Subjects were excluded if they were unable to provide a sample, had a current history of sexually transmitted disease, used testosterone or anabolic steroids in the last 2 years, had a history of vasectomy or known testicular obstruction, or had a history of retrograde ejaculation. Following clinical semen evaluation, the remaining sample was stored at -80°C. For lipid analysis, samples were thawed, centrifuged, and the seminal fluid removed from the cell pellet. Total lipids were extracted from the cell pellet and the sphingolipids were enriched. SM species were measured using tandem mass spectrometry. Pair-wise Pearson and linear regression analyses were used to compare VLC-PUFA-SM levels to sperm morphology and progression.

RESULTS: VLC-PUFA-SM species having 28-34 carbon fatty acids were detected in sperm samples (n = 70), with 28 and 30 carbon VLC-PUFA being the most abundant. The sum of all VLC-PUFA-SM species made up anywhere from 0 to 6.1% of the overall SM pool, with the average being 2.1%. Pair-wise Pearson and linear regression analyses showed that VLC-PUFA-SM levels in sperm cells were not correlated with sperm Kruger morphology or sperm progression. There was no statistical correlation of VLC-PUFA levels with race or age.

CONCLUSIONS: Although lipids play an integral role in energy production and membrane structure, we did not find a correlation between levels of VLC-PUFA and sperm progression or morphology. However, our previous work showed a strong positive correlation between the levels of VLC-PUFA in sperm cells and both sperm count and motility and therefore these fatty acids may be involved in infertility and warrant further study.

GAMETE BIOCOMPATIBILITY OF A PARaben-FREE FERTILITY LUBRICANT. A. Agarwal R. Sharma. American Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH.

OBJECTIVE: Food and Drug Administration (FDA) created a new product code namely PEB, for the new class of fertility lubricants, which are gamete, fertilization and embryo compatible. To date, Baby Dance (BD) is the only FDA cleared fertility lubricant which is paraben free. The current study evaluates biocompatibility of a recently FDA cleared paraben-free lubricant (BD) on sperm motility and DNA fragmentation.

DESIGN: Prospective studies to test the biocompatibility of BD on sperm motility, DNA fragmentation, and cervical mucus penetration.

MATERIALS AND METHODS: Sperm biocompatibility of BD (Fairhaven Health, Bellingham, WA) was evaluated as follows. 1) Unprocessed semen samples from normozoospermic (n = 10) and oligozoospermic (n = 10) men were incubated with human tubal fluid (HTF; Controls) or HTF plus 10% BD (Treated) for 30 min to determine sperm progressive motility (PM) according to WHO criteria and DNA fragmentation index (DFI) using the SCSA. 2) Washed human sperm (normospermic men, n = 11) were incubated for 120 min. with or without 10% BD in HTF, followed by computer-assisted semen analysis (CASA) to evaluate Total Motile Sperm (TMS) counts. 3) Bovine cervical mucus assay was performed using cow mucus columns and bull sperm, to evaluate sperm penetration ability following 30 min incubation with or without 10% BD in Tris extender.

RESULTS: Data is expressed as mean ± SD. 1) Sperm PM and DFI did not differ between treatments in either group. Normozoospermic: PM - Treated 72 ± 9% vs Control 73 ± 9%; DFI - Treated 8.8 ± 4.5% vs Control 9.0 ± 4.8%; Oligozoospermic: PM - Treated 62 ± 3% vs Control 63 ± 3%; DFI - Treated 10.6 ± 3.6% vs Control 10.6 ± 3.5%. 2) Numbers of TMS did not differ after exposure to BD (Treated TMS 11 ± 5 x 10⁶/mL vs Control TMS 12 ± 4 x 10⁶/mL). 3) Exposure to BD did not change sperm penetration into cervical mucus columns, although more sperm swam further into columns following BD contact (Table 1).

CONCLUSIONS: These studies suggest that the recently cleared PEB paraben-free fertility lubricant does not interfere with sperm function such as progressive sperm motility, DNA fragmentation and penetration ability in cervical mucus columns.
**P-496** Wednesday, October 10, 2018 6:30 AM

**IDENTIFICATION OF TESTIS- AND GERM CELL-SPECIFIC PROTEINS AS BIOMARKERS OF SPERM MATOGENESIS AND TARGETS FOR SPERM SELECTION.** A. P. Drabovich,a,b J. Zhang,a M. Kanoato,v S. Moskovtseva,b,c L. Librach,a,b CREATe Fertility Centre, Toronto, ON, Canada; vUniversity of Toronto, Toronto, ON, Canada; aSinai Health System, Toronto, Toronto, ON, Canada.

**OBJECTIVE:** We previously identified and verified testis-specific proteins as seminal plasma biomarkers for the differential diagnosis of azoospermia and male infertility [1, 2]. Our studies provided us with unique criteria to identify human testis- and germ cell-specific proteins. Here, our objective was to identify a comprehensive panel of testis-, germ cell-, spermatozoa- and organelle-specific proteins and demonstrate the value of these proteins as biomarkers of spermatozoa maturation, tools to evaluate sperm integrity, and targets to select sperm for assisted reproduction.

**DESIGN:** Cross Sectional Study

**MATERIALS AND METHODS:** Reproductive age men evaluated for infertility were enrolled in this institutional REB approved research study. Semen samples with 2010 WHO sperm reference values were collected. Human Protein Atlas and NexProt databases were mined for testis-, germ cell-, spermatozoa- and organelle-specific proteins. Testis-specificity and expression in spermatozoa were experimentally verified by mass spectrometry-based targeted proteomic assays. Top candidates were evaluated by antibody-based immunofluorescence, ELISA and flow cytometry assays.

**RESULTS:** Mining of the Human Protein Atlas revealed nearly 1,500 proteins with highly specific or enhanced expression in testis and male germ cells versus all human tissues. The list was narrowed down to 129 cell-

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**TABLE 1. Cervical mucus penetration of bull spermatozoa after exposure to 10% BD**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>CASA Motility (%)</th>
<th>Vanguard Sperm (cm)</th>
<th>Sperm Density (2 cm)</th>
<th>Sperm Density (3 cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>10</td>
<td>40.0 ± 2.0</td>
<td>5.6 ± 0.2</td>
<td>27.9 ± 1.1</td>
<td>14.4 ± 0.9*</td>
</tr>
<tr>
<td>BabyDance</td>
<td>10</td>
<td>42.0 ± 1.0</td>
<td>5.8 ± 0.2</td>
<td>29.7 ± 0.6</td>
<td>16.6 ± 0.6*</td>
</tr>
</tbody>
</table>

*Means differ between treatments at p=0.03
surface or secreted proteins previously identified in the spermatozoa protein. Following verification by targeted proteomic assays, 45 proteins expressed exclusively by spermatogonia (n=1), spermatocytes (n=6), spermatids (n=10) and spermatozoa (n=3) were selected. Localization of selected proteins including ADAM20 and ADAM29 (post-acrosomal cell-surface proteins), ACRV1 (intra-acrosomal secreted protein) and AKAP4 (sperm tail-specific protein) was confirmed by immunofluorescence in testicular and mature spermatozoa. Acrosome-specific protein ACRV1 was evaluated by ELISA in seminal plasma and spermatozoa, and emerged as a non-invasive biomarker to evaluate acrosome integrity.

CONCLUSIONS: Our panel of testis-, germ cell-, spermatozoa- and organelle-specific proteins will facilitate evaluation of spermatogonia and acrosome integrity and selection of rare sperm for assisted reproduction. Selected panel is a unique and comprehensive toolbox for basic and clinical andrology research.

References:

Supported by: None.

P-497 Wednesday, October 10, 2018 6:30 AM
CORRELATION BETWEEN SPERM MORPHOLOGY AND DNA INTEGRITY AT A SINGLE CELL LEVEL. W. Y. Wang, B. Nguyen, Y. Xu, J. B. You, A. Lagunov, T. G. Hannah, K. Jarvi, D. Sinton. *Mechanical and Industrial Engineering, University of Toronto, Toronto, ON, Canada; ²Hannam Fertility Centre, Toronto, ON, Canada; ³University of Toronto, Toronto, ON, Canada.

OBJECTIVE: In this work, we aim to elucidate the relationship between sperm morphology and DNA integrity at a single cells level.

DESIGN: Single sperm morphological parameters (such as sperm head size, aspect ratio, circularity, middle piece width, etc.) and DNA fragmentation index (DFI) were obtained from differential interference contrast (DIC) and fluorescence images, respectively. A linear model was used to analyze the relationship between sperm morphology and DNA integrity for single sperm.

MATERIALS AND METHODS: Single sperm samples were prepared by a non-destructive drying method. Raw semen sample after washing were seeded onto a hyaluronic acid (HA) modified glass cover slide, followed by air-drying and Acridine Orange (AO) staining.[1] Images of identical sperms under DIC and fluorescence mode were obtained with laser-scanning confocal microscopy. Analysis of variance was conducted in JMP software with DFI as the response variable.

RESULTS: Our method of sperm sample preparation allows sperm imaging with high efficiency and quality, especially for protocols requiring multi-step staining. The preliminary results from ~200 sperms reveal that there is a significant correlation between sperm head area and DNA integrity. Other sperm morphological parameters, such as head aspect ratio and circularity, are also correlated with sperm DFI.

CONCLUSIONS: The study of sperm morphology and DNA integrity suggests that sperm morphology and DNA integrity is correlated at a single cell level.

References:

Supported by: None.

P-498 Wednesday, October 10, 2018 6:30 AM
PIERCING ROLES FOR FOXA TRANSCRIPTION FACTOR IN EMBRYONAL STEM AND PROGENITOR SPERMATOGENESIS. D. Prokai, A. Moeliman, K. Chapman, J. Chaudhary, A. Pudasaini, F. Hamra, Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas, TX; ²Cecil H. & Ida Green Center for Reproductive Biology Sciences, University of Texas Southwestern Medical Center, Dallas, TX; ³Neurosence, University of Texas Southwestern Medical Center, Dallas, TX; ⁴Biophysics, University of Texas Southwestern Medical Center, Dallas, TX; ⁵Advanced Imaging Center, University of Texas Southwestern Medical Center, Dallas, TX.

OBJECTIVE: Our goal was to investigate the potential for FOXA family proteins to regulate genetic programs in the germline that impact male fertility.

DESIGN: Experimental Study
MATERIALS AND METHODS: Adult rat seminiferous tubules and spermatogonial stem cell lines were subjected to co-immunolabelling to evaluate the presence of FOXA-family proteins in undifferentiated spermatogonia and spermatogenic cells progressing through S-phase. Spermatogonial stem cell lines were used to assess the abundance of FOXA-family transcripts and proteins before and after treatment with retinoic acid to drive spermatogonial differentiation. FOXA2-deficient donor spermatogonial stem cell lines were generated using CRISPR/Cas9, clonally expanded in culture and then transplanted into recipient rat testes to assess their ability to regenerate spermatogenesis in vivo.

RESULTS: FOXA2 was most abundant in “A-single” spermatogonia subtypes before promptly declining in “A-paired” and “A-aligned” progenitor spermatogonia initiating spermatogenesis. Similarly, FOXA2 transcripts and protein were abundant in spermatogonial stem cell cultures, prior to being rapidly down-regulated upon differentiation in response to retinoic acid (RNA-Seq, western, ICC). Interestingly, a relatively high proportion of FOXA2+, GFP+1- type A-single spermatogonia displayed robust EDU labeling. FOXA2-deficient spermatogonia (CRISPR knockout) were ineffective at forming colonies of donor-derived spermatogenesis in rat testes. Like FOXA2, FOXA3 was abundant in spermatogonial stem cell cultures and down-regulated in response to retinoid acid. In contrast, FOXA1 was uniquely localized to A-aligned spermatogonia.

CONCLUSIONS: Rat spermatogonia are endowed with FOXA family proteins and FOXA2 is critical for donor spermatogonial stem cells to regenerate spermatogenesis. Nuclear FOXA2 protein concentrations in the rat germ line are of fascination interest and FOXA family proteins function as ‘pioneer’ transcription factors in somatic cells that de-condense heterochromatin and program euchromatin for transitioning through distinct cellular states. A deep understanding into the molecular mechanisms by which FOXA family proteins enhance the functional robustness of spermatogonial stem and progenitor cells is needed, as it may translate into the identification of clinically relevant environmental and/or genetic factors required to precisely classify and formulate treatments for specific types of spermatogenic arrest and severe oligospermatogenesis.

References:

Supported by: Research supported by grants from NIH/NICHD (R01HD053889) to F.K.H.

P-499 Wednesday, October 10, 2018 6:30 AM
COPIR IS ASSOCIATED WITH MIWI AND MODULATED THE PIRNA PATHWAY, A POSSIBLE MECHANISM INVOLVED IN THE HUMAN TERATOZOOOSPERMIA SPERM PHENOTYPE. C. Innocenti, E. Fabbrizio, D. Haouzi, C. Sardet, S. Hamamah, CHU Montpellier, Inserm U1203, Montpellier, France; Université Montpellier-Institut de Recherche en Cancérologie de Montpellier, Inserm U1194, Montpellier, France; CHU Montpellier, Inserm U1203, 34295, France; University Hospital of Montpellier, Montpellier, France.

OBJECTIVE: Protein arginine methyl transferase 5 (Prmt5) was implicated in genome defense in primordial germ cells (PGCs) via a PRMT5-dependent methylation of the Piwi protein family that participates within the piRNA pathway in promoting transposon silencing. However, the role of the Prmt-5 and histone-associated protein Copri in the regulation of the piRNA pathway remains unknown. Is the Prmt-5-associated factor Copri implicated in spermatogenesis? We reported for the first time that the Prmt-5-piRNA pathway regulates spermatogenesis.

DESIGN: Testes from Copri knockout (KO) mice and wild type (WT) (n=3 per group) were used for immunoprecipitation, western blot analyses, immunohistochemistry (IHC) and RQ-PCR experiments. Ten human sperm samples were collected from patients with normozoospermia (n=3) and teratozoospermia (n=7) for RqPCR experiments.

MATERIALS AND METHODS: Proteins, total RNA and paraffin-embedded testis sections were extracted and/or prepared from the Copri-
KO and WT mice. 200 μl of each semen were used for total RNA extraction using the miRNasy serum/plasma kit (Qiagen).

RESULTS: Pmr5- and histone-associated protein Copr5 is highly expressed in testis and its depletion impacted on the maturation of spermatogonia in mice. Although Copr5 KO animals were fertile, the fertilization rate of Copr5 in mite tests leads to a down-regulation of the level of Miwi protein, as confirmed by western blot analyses and immunohistochemistry of WT and KO mice testis whole cell extracts and paraffin-embedded testis sections, respectively. In addition, the mRNA level of three pre-puchyphere piRNAs, prepiR1, prepiR2 and prepiR3 was decreased in KO Copr5 compared to WT mice, whereas in KO mice the expression level of the LINE1 mRNA, the mRNA level of two retroelements that was used as a read out of deregulation of the piRNA pathway, was increased. Using both human GEO data and patients with teratozoospermia, the present study reports a correlation between a low level of Copr5 mRNA and teratozoospermia, a human pathology characterized by abnormally shaped sperm that can negatively affect fertility.

CONCLUSIONS: Copr5 KO in mice perturbed some genome surveillance mechanisms in germ cells by an alteration of the expression level of two major components present in the Pwi-interacting RNA (piRNA) pathway, the Miwi and the LINE1. In addition, low level of Copr5 mRNA correlates with human teratozoospermia sperm.

Supported by: This work was supported by grants from the Ligue Contre le Cancer (CS) and the Association pour la Recherche contre le Cancer (EF). The authors declare no competing or financial interests.

**OOCYTE BIOLOGY**

**P-500** Wednesday, October 10, 2018 6:30 AM

**OOCYTE DEVELOPMENTAL POTENTIAL FOLLOWING STANDARD HCG OR COMBINED HCG AND GnRH-AGONIST TRIGGER.** N. Pereira, a N. J. Shah, b C. Mostisser, b R. Elias, a Z. Rosenwaks. a aWeill Cornell Medicine, New York, NY; bObstetrics and Gynecology, Weill Cornell Medicine, New York, NY.

OBJECTIVE: Recent studies have highlighted that the beneficial effects of combined hCG and GnRH-agonist triggers may extend beyond OHSS prevention. In this context, we investigate whether a combined hCG and GnRH-agonist trigger improves the developmental potential of oocytes when compared to a standard hCG trigger in ICSI cycles.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: All patients <40 years, with baseline FSH <12.0 mIU/mL, AMH >1 ng/mL, and antral follicle counts (AFC) ≥8 undergoing their first ICSI cycle with fresh ejaculated sperm. Patients received either a standard hCG trigger (3,350 IU-10,000 IU) or a combined hCG (1,500 IU) and GnRH-agonist (2 mg) trigger for OHSS prevention. Baseline demographics, ICSI cycle characteristics, and ovarian stimulation parameters were recorded. Oocyte developmental potential was determined by the rate of 2-PN embryos per M-II oocyte and blastulation per M-II oocyte and 2-PN embryo. Abnormal fertilization (3-PN) per M-II oocyte was also recorded. The blastulation rate per M-II oocyte was considered the primary outcome of interest. A multivariate regression model was constructed for the primary outcome, while controlling for confounders of interest.

RESULTS: A total of 401 patients were included - 318 (79.3%) and 83 (20.7%) received the standard and combined trigger, respectively. There was no difference in the baseline demographics, AMH levels or AFCs of the two groups. Patients in the combined trigger group had more robust ovarian stimulation parameters compared to the hCG trigger group. Although the combined trigger group had a higher number of total oocytes retrieved (22.2 ± 10.8 vs 17.8 ± 10.3), the percentage of mature oocytes was similar in both groups (83±14 vs. 83.8±14.3; P=0.65). The combined trigger group had a higher number of 2-PN embryos. The blastulation rate per M-II oocyte (29.7 ± 18.9%; P<0.001) and per 2-PN embryo (36.8 ± 24.4%; P<0.001) was significantly higher in the combined trigger group compared to the standard trigger group. The combined trigger was also associated with lower abnormal fertilization (6.4% vs. 11.3%; P=0.05). Overall, the blastulation rate per M-II oocyte was 11.6% (95% CI 4.8-20.4; P=0.01) higher in the combined hCG and GnRH-agonist trigger group compared to the standard hCG trigger, after controlling for potential confounders.

CONCLUSIONS: Compared to a standard hCG trigger, a combined hCG and GnRH-agonist trigger increases the blastulation rate per M-II oocyte and 2-PN embryo and decreases the rate of abnormal fertilization in patients undergoing their first ICSI cycle.

**Baseline demographics, ovarian stimulation parameters and oocyte developmental potential of patients**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Combined Trigger (n=83)</th>
<th>hCG Trigger (n=318)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>32.8</td>
<td>33.3</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>23.6</td>
<td>22.9</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline AMH</td>
<td>3.9</td>
<td>3.2</td>
<td>NS</td>
</tr>
<tr>
<td>Total Stimulation Days</td>
<td>10.1</td>
<td>9.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak Estradiol</td>
<td>3187.5</td>
<td>1799.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of oocytes</td>
<td>22.4</td>
<td>13.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mature oocytes(%)</td>
<td>83%</td>
<td>83.8%</td>
<td>NS</td>
</tr>
<tr>
<td>2-PN embryos</td>
<td>14.7</td>
<td>8.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal fertilization rate (%)</td>
<td>6.4</td>
<td>11.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blastulation rate/Mature oocyte (%)</td>
<td>29.7</td>
<td>18.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blastula tion rate/2-PN embryo(%)</td>
<td>36.8</td>
<td>24.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
OBJECTIVE: Even though assisted reproductive technology (ART) has evolved drastically over the years, in vitro fertilization (IVF) remains the treatment that yields the highest chance of pregnancy. The medication protocol and gonadotropin dosing are customized according to ovarian reserve and the unique hormonal profile of patient. Anti-mullerian hormone (AMH), a newer “sexy” assay, has recently been added to this hormonal profile. AMH is exclusively produced by the ovaries and reflects the ovarian follicular pool. Ideally, AMH values above 1 ng/mL are considered optimal, and many claim that higher levels of AMH are better indicators of ART success. However, too high of an AMH level can indicate impaired reproductive outcomes, as evidenced in patients with polycystic ovary syndrome (PCOS). We sought to determine the effect of elevated serum AMH levels (>5 ng/mL) on egg quality.

DESIGN: Retrospective chart review at a private infertility center.

MATERIALS AND METHODS: All patients with a serum AMH level greater than 5.0 ng/mL were included. All ICSI cycles from this group from 2016 to 2018 were analyzed for oocytes retrieved, maturation rate, fertilization rate, and blastocyst rate, and compared against nationally available data. One sample t-tests, binomial tests, and logistic regressions to calculate adjusted odds ratios were used to analyze the data using SPSS.

RESULTS: A total of 119 cases were identified. The average number of oocytes retrieved per cycle for patients with an AMH greater than 5.0 was 17.3 oocytes. Oocyte quality was not affected by AMH status.

CONCLUSIONS: Cycles in which the entire oocyte cohort is affected with both large PVS and AMH granularity have compromised implantation and pregnancy rates.

References: N/A.

Supported by: None.

Supported by: Intramural funds from The Center for Human Reproduction and grants from The Foundation for Reproductive Medicine.

P-506 Wednesday, October 10, 2018 6:30 AM

ASSOCIATION BETWEEN CHARACTERISTICS OF INFERTILE PATIENTS AND OOCYTE MEASUREMENTS. A. Weghofer, a,b V. A. Kushnir, a S. K. Darmon, a H. Jafri, b E. Lazzaroni-Tealdi, b L. Zhang, D. F. Albertini, a D. H. Barad, a,b N. Gleicher, a,b,c,d eDepartment of Obstetrics and Gynecology, Medical University Vienna, Vienna, Austria; eCenter for Human Reproduction, New York, NY; fStem Cell Biology and Molecular Embryology Laboratory, Rockefeller University, New York, NY; gFoundation for Reproductive Medicine, New York, NY; hMedical University Vienna, Vienna, Austria.

OBJECTIVE: Oocyte sizes were previously reported to be smaller in obese women with polycystic ovary syndrome (PCOS). Whether oocyte size and morphology are associated with patient characteristics in non-PCOS women was the subject of this study.

DESIGN: Prospective cohort study in academically affiliated private fertility center.

MATERIALS AND METHODS: We prospectively investigated whether female age, body mass index (BMI), anti-Mullerian hormone level and AMH and oocyte yield are related to the total oocyte and oolemma diameter, enlarged perivitelline space (PVS), and ooplasm granulation in 308 MII oocytes from 77 couples undergoing IVF. Total oocyte diameter was measured as the maximum diameter of the zona pellucida. Oolemma diameter was measured as the maximum diameter of the oolemma. AMH levels were unevenly distributed and therefore log converted.

RESULTS: Patients presented with a mean age of 37.7±6.1 years, BMI of 24.9±5.1 kg/m2. AMH levels of 3.1±3.4 ng/ml and produced a median of 12.46, the area under curve - 0.845, sensitivity -90.5%, specificity-70.6%).

CONCLUSIONS: In non-PCOS infertile women, advancing age and increasing BMI are associated with smaller total oocyte diameter. These results expand on previously observed association between oocyte size and BMI in women with PCOS. Ooplasm granulation appears to be reflective of decreasing ovarian function (i.e. advancing age, lower AMH levels and lower oocyte yield). These findings indicate the importance of detailed oocyte assessments, which may aid the currently used criteria for embryo selection.

Supported by: Intramural funds from The Center for Human Reproduction and grants from The Foundation for Reproductive Medicine.

Table 1

<table>
<thead>
<tr>
<th>CC genes mRNA expression</th>
<th>I group</th>
<th>II group</th>
<th>III group</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCAN</td>
<td>17.63* (14.25-17.63)</td>
<td>16.76* (13.38-22.00)</td>
<td>8.57 (5.7-14.56)</td>
</tr>
<tr>
<td>HAS2</td>
<td>0.44* (0.32-0.52)</td>
<td>0.44 (0.36-0.60)</td>
<td>0.24 (0.17-0.31)</td>
</tr>
<tr>
<td>ITPKA</td>
<td>0.31* (0.23-0.42)</td>
<td>0.31 (0.18-0.53)</td>
<td>0.602 (0.22-0.71)</td>
</tr>
<tr>
<td>PTGS2</td>
<td>2.61* (0.22-0.41)</td>
<td>1.481 (0.75-3.19)</td>
<td>0.871 (0.52-1.29)</td>
</tr>
</tbody>
</table>

References:
TARGETED GENETIC MODIFICATIONS IN A PARTHENOGENETIC MOUSE MODEL. A. A. Kiesling, A. Chatterjee, J. Lawitts, M. Kearnan. Bedford Research Foundation, Bedford, MA.

OBJECTIVE: Develop gene editing techniques in parthenogenetically activated eggs to take advantage of the potential to derive uniformly modified, hypo-immunogenic stem cells resistant to infection by human immunodeficiency virus (HIV). To make this clinically feasible with human eggs, the efficiency of targeted genetic modification of unfertilized eggs needs to be improved over published reports of approximately 10% of mouse eggs.

DESIGN: Mouse eggs were parthenogenetically activated with strontium and cultured without and with specific guide RNAs (sgRNA) while pronuclei formed. Pronuclei were microinjected with Cas9 enzyme complexed with guide RNAs and cultured. B2M, BCR, and CCR5 were targeted. B2M is essential to expression of the major histocompatibility complex on the cell surface, and guide RNAs designed to disruptCCR5, an essential receptor for infection by HIV. Parthenogenes were analyzed for mutations at various stages of development to assess mutation frequency.

MATERIALS AND METHODS: Eggs were collected from super ovulated B6C3H female mice and cultured in 10mM strontium in calcium-free medium for 2 hours, then washed free of strontium and transferred to fresh culture dishes without and with three guide RNAs, two targeting CCR5 and one targeting B2M. Following an additional 2 hours, the pronuclei of the parthenogenes were injected with complexes of Cas9 enzyme and the three guide RNAs, and placed in culture.

DNA was isolated from groups of one to three injected eggs at the two-cell to blastocyst stages and analyzed for PCR products with primers that bracketed the targeted genomic regions. PCR products were then subjected to restriction enzyme digestion and/or Sanger-sequencing to detect mutations.

RESULTS: The first strategy employed 2 sgRNAs targeting CCR5 plus 1 sgRNA targeting B2M, all individually pre-incubated with Cas9 to form the standard sgRNA/Cas9 complex. This approach led to mutation rates of 5% to 22%. The second strategy was to pre-load the sgRNAs into the eggs by incubating them in culture medium supplemented with the 3 sgRNAs, followed by micro-injection of Cas9 enzyme. This strategy led to mutation rates of 63-70%. The third strategy was to pre-inject the three sgRNAs into pronuclei, followed by a second injection of Cas9 enzyme. This strategy led to similar mutation rates as the second strategy. Importantly, it was noted: (1) that mutations frequently disrupted PCR primer binding sites located within 100 bases of guide RNA sequences. Making it difficult to obtain sequences for analysis, and (2) repair of the Cas9 cleavages appeared to take place over one or two cell cycles.

CONCLUSIONS: These results suggest that the efficiency of Cas9-sgRNA mediated cleavage of B2M and CCR5 target genes can be increased to clinically relevant frequencies for the derivation of modified human parthenogen stem cells.

P-507 Wednesday, October 10, 2018 6:30 AM

MIRNA FROM FOLLICULAR EXTRACELLULAR VESICLES TARGET CELL PROLIFERATION IN YOUNG WOMEN WITH DIMINISHED OVARIAN RESERVE. S. Thomas, a T. H. Kitapci, b D. Campo, c I. Woo, d K. Bendikson, e K. Chung, f R. J. Paulson, g A. Ahmady, h L. K. McGinnis,i aUniversity of Southern California, Los Angeles, CA; b USC Genomic Core, Los Angeles, CA; c California Center for Reproductive Health, Encino, CA; d USC Fertility, Los Angeles, CA.

OBJECTIVE: Extracellular vesicles (ECVs) play an important role in the cellular communication between the oocyte, and the surrounding granulosa cells. ECVs carry microRNA (miRNA), which are post-transcriptional gene regulators that influence oocyte development. Oocytes from women with diminished ovarian reserve (DOR) have a reduced oocyte developmental competence compared to women with normal ovarian reserve (NOR). There is limited data on how signaling pathways that are important for ovarian follicle development, may be dysregulated in patients with idiopathic DOR. The primary aim was to determine if there are differences in expression of miRNA in the ECVs between young women with DOR and NOR. The secondary aim was to identify molecular signaling pathways that are regulated by these miRNA that may impact oocyte developmental competence.

DESIGN: A pilot prospective cohort study. Women <38yo were recruited into two groups. Group 1: DOR group (n=4) defined as AMH<1.5 and Group 2: NOR group (n=4), defined as AMH>2.

MATERIALS AND METHODS: At oocyte retrieval, follicular fluid from the first punctured follicle was collected from each ovary. ECVs were isolated from the follicular fluid using standard differential centrifugation, ultracentrifugation, and qE (IZON) protocol. RNA extraction from the ECVs, and miRNA library preparation were done using the Qiagen miRNAeasy kit and the QIAseq miRNA library kit respectively. The latter includes adaptors with Unique Molecular Identifiers (UMIs), designed to avoid amplification bias. Sequencing was done in a rapid flow cell in an Illumina HiSeq 2500. The results were analyzed using Qiangen online portal, which included read trimming, mapping, and counting of the UMIs. All miRNAs with less than 6 UMI counts in all samples at least one of the groups were excluded. The resulting counts were used for differential expression analysis. Significance was set at p<0.05.

RESULTS: 119 miRNA were differentially expressed between the two groups. Thirty-nine were upregulated and 80 downregulated in the DOR group compared to NOR. After correction for multiple comparisons, only two miRNAs held statistical significance (False Discovery Rate<0.05); miRNA-29b-2-5p upregulated and miRNA-144-5p downregulated in the DOR group, p<0.01. These miRNA have been shown to regulate genes critical for cellular proliferation, differentiation, and apoptosis.

CONCLUSIONS: We observed distinct miRNA fold change expression in the ECVs from young women with DOR compared to healthy controls. These miRNA may have a significant role in the physiological pathways for oocyte and follicular development, and their aberrant expression profile may contribute to the pathogenesis of idiopathic DOR in young women.

Supported by: Grant HD082484 and research award from the Goldhirsh-Yellin Foundation

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IDENTIFICATION AND CHARACTERIZATION OF AMYLOID-LIKE SUBSTANCE IN IMMATURE AND MATURE HUMAN'S OOCYTES. R. Pimentel, a,b P. Navarro, a F. Wang, b L. Robinson, a M. Cammer, a Y. Kramer, a d L. D. Keefe, a Faculty of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil; b New York University, New York, NY.

OBJECTIVE: Recent studies have shown that amyloid has a functional role during reproduction, participating in the process of gametogenesis and conclusion of meiosis I with a prion predicted domain. Since amyloid-like molecules can accelerate aging in long-lived, post-mitotic cells, we sought to verify the presence and characterize developmental timing of amyloid-like substance in immature and mature human's oocytes.

DESIGN: A prospective pilot study, using 46 immature and in vitro mature human oocytes from 11 patients, obtained according to the IRB approval study H6902.

MATERIALS AND METHODS: A total of 46 immature oocytes (28 GV and 18 MI) donated for research from women ages 18-45 were collected and in vitro matured for up 48 hours following the subjects’’ retrieval. Samples were fixed and immunostained for evaluation of amyloid-like substance, using an anti-amyloid antibody (Fibrils OC Antibody [AFOC], Millipore). Imaging was performed using a confocal microscopy (Zeiss 880) for the quantification of amyloid-like substances. SAS version 9.4 was used to perform data analyses. Data were compared by one-way analysis of variance, with the Least Square-MEANS post-test, Pearson correlation coefficients (r) and Bivariate analyses (r-tests). Differences were considered to be statistically significant if p<0.05.

RESULTS: In all samples, immunostaining for amyloid-like substance appeared throughout the zona pellucida, as well as in the cytoplasm and nucleus of oocytes and polar bodies. Quantitative analysis showed that fresh GV's possess the most intense signal of the anti-amyloid antibody (164.74088/C6 1143.70), followed by arrested GV (2967.66667/C6 1775.88), MII (2495.2500/C6 986.36). Fresh GVs showed, statistically significant differences between the Anti-amyloid (F-32.33; p=0.0007) and Bivariate analyses (r-tests). Differences were considered to be statistically significant if p<0.05.

CONCLUSIONS: In all samples, immunostaining for amyloid-like substance appeared throughout the zona pellucida, as well as in the cytoplasm and nucleus of oocytes and polar bodies. Quantitative analysis showed that fresh GV's possess the most intense signal of the anti-amyloid antibody (164.74088/1573.46), followed by arrested GV (2967.66667/659.06), fresh MI (2601.5710/1143.70), MI (2495.2500/1775.88), and arrested MI (2511.8000/986.36). Fresh GVs showed, statistically significant differences between the Anti-amyloid (F-32.33; p=0.0007) and Bivariate analyses (r-tests). Differences were considered to be statistically significant if p<0.05.

CONCLUSIONS: We demonstrate for the first time the presence and distribution of immunostaining for an amyloid-like substance in immature and mature human’s oocytes, and its correlation with clinical characteristics. Since amyloid-like substances can produce age related cellular pathology, further studies should be focused on the role of amyloid-like substance in oocyte aging, and potential roles in female infertility.

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**P-510 Wednesday, October 10, 2018 6:30 AM**

**COQ10 DECREASES ANEUPOLOIDY RATE AND INCREASES MITOCHONDRIAL MASS DURING IN VITRO MATURATION OF HUMAN IMMATURE OOCYTES.** L. Ma,a M. Hu,b X. Ma,c Y. Cui,d J. Liu,a

"The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; bNanjing Medical University, Nanjing, China; cReproductive Medicine, Nanjing, China; dBasic Research in Reproductive Medicine, Nanjing, China.

OBJECTIVE: To evaluate the effect of CoQ10 supplementation on the post-meiotic oocyte aneuploidy rate and mitochondrial mass during in vitro maturation (IVM) of human immature oocytes.

DESIGN: Clinical laboratory observation.

MATERIALS AND METHODS: Total of 64 germinal vesicle (GV) stage oocytes from 32 women were collected at aged 35-46 years and cultured in IVM media with or without 50 μM CoQ10 for 24-48 h of IVM. The number of mature oocytes were compared between two groups, also we compared the post-meiotic aneuploidy rate using polar body and next generation sequencing (NGS). Oocyte micrographs were quantitated for mitochondrial mass by Mitotracker Red staining. Statistical analyses were performed using SPSS, version 16.0 (SPSS, Inc.), and the percentage of mature oocytes and aneuploidy rate between groups were compared using the χ² test. The differences in means of mitochondrial mass data were calculated by t test.

RESULTS: There were no statistically significant differences in the number of mature oocytes between two groups. However, CoQ10 supplementation significantly decreased the post-meiotic oocyte aneuploidy rate and increased the number of mitochondria. There was a 1.7-fold more mitochondrial mass at 50 μM CoQ10, and CoQ10 supplementation also decreased the post-meiotic oocyte aneuploidy rate when the women have a high body mass index (BMI) over than 25.0 kg/m².

CONCLUSIONS: CoQ10 supplementation decreases the post-meiotic oocyte aneuploidy rate and increases the number of mitochondria during IVM of human immature oocytes, and CoQ10 supplementation may have high efficiency for women who are with obesity.

**References:**

**Supported by:** NO

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**P-511 Wednesday, October 10, 2018 6:30 AM**

**HIGH-GLUCOSE CONCENTRATIONS CHANGE DNA METHYLATION LEVELS IN HUMAN IVM OOCYTES.** Q. Wang,a Z. Ge,a C. Zhang,a "Henan Provincial People’s Hospital, Zhengzhou, China; bDepartment of Biology, Institute of Reproductive Science & Key Laboratory of Animal Reproduction and Germplasm Enhancement, Qingdao, China.

OBJECTIVE: What are the effects of high-glucose concentrations on DNA methylation of human oocytes?

DESIGN: Immature metaphase I (MI) stage oocytes of good quality were retrieved from patients who had normal ovarian potential and who underwent ICSI in the Reproductive Medicine Center of People’s Hospital of Zhengzhou University. MI oocytes were cultured in medium with different glucose concentrations (control, 10 mM and 15 mM) in vitro and 48 h later, oocytes with first polar body extrusion were collected to check the DNA methylation concentrations (control, 10 mM and 15 mM) in vitro and 48 h later, oocytes with first polar body extrusion were collected to check the DNA methylation levels.

MATERIALS AND METHODS: MI oocytes underwent in vitro maturation (IVM) at 37°C with 5% mixed gas for 48 h. Then the mature oocytes were treated with bisulfite buffer. Target sequences were amplified using nested or half-nested PCR and the DNA methylation status was tested using combined bisulfite restriction analysis (COBRA) and bisulfite sequencing (BS).

RESULTS: High-glucose concentrations significantly decreased the first polar body extrusion rate. Compared to controls, the DNA methylation levels of Peg3 in human IVM oocytes were significantly higher in 10 mM (P < 0.001) and 15 mM (P < 0.001) concentrations of glucose. But the DNA methylation level of H19 was not affected by high-glucose concentrations in human IVM oocytes. We also found that there was a decrease in DNA methylation levels in the promoter of adipoonectin in human IVM oocytes between controls and oocytes exposed to 10 mM glucose (P = 0.028).

CONCLUSIONS: This is the first time that the effects of high-glucose concentration on DNA methylation of human oocytes have been elucidated. Our result indicates that in humans, the high risk of chronic diseases in offspring from diabetic mothers may originate from abnormal DNA modifications in oocytes.

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**P-512 Wednesday, October 10, 2018 6:30 AM**

**PERFORMANCE OF RETRIEVED OOCYTES THAT MATURE FROM METAPHASE I (MI) TO METAPHASE II (MII) AFTER A GnRH AGONIST TRIGGER.** P. N. Godiwala,a K. C. Humm,b I. A. Comstock,a J. Witmyer,a D. Peak,b A. D. Sparks,a S. I. Lalwani,a D. Frankfurter.b "Department of Obstetrics and Gynecology, Division of Fertility and IVF, The George Washington University School of Medicine and Health Sciences, Washington, DC; bFertility and IVF Center, Medical Faculty Associates, Washington, DC; cDepartment of Surgery, Medical Faculty Associates, Washington, DC.

OBJECTIVE: Current understanding of the clinical value of MI oocytes maturing to MII oocytes in the lab is limited to IVF cycles utilizing a hCG trigger. Our objective was to evaluate the developmental potential of MI oocytes that matured to the MII stage in vitro following a GnRH agonist trigger.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: We collected data on demographics, treatment protocols, and the embryologic outcomes for women who underwent their first fresh non-donor IVF cycle between 01/01/2012 and 04/30/2017 and produced at least one MII oocyte. Patients underwent an egg retrieval 36 hours after GnRH agonist trigger administration. MI oocytes and MI-MII oocytes were inseminated using intracytoplasmic sperm injection (ICSI) and fertilization was confirmed 18 hours later. The cleavage and developmental progression of the resulting zygotes were evaluated daily. The development of MI-MII oocytes was compared to oocytes that were MII at the time of retrieval. MI conversion rate is the number of MII-MII oocytes / total MI oocytes. Cleavage and blastulation rates were calculated using fertilized oocytes as a denominator. Cleavage stage grading was based on cell number and percent fragmentation with grade 1 indicating < 10% fragmentation. Blastulation was defined by evidence of blastocoel formation and blastocyst grading was based on the Gardner system. Chi-square testing was used for statistical analysis and p value < 0.05 was considered statistically significant.

RESULTS: A total of 1399 oocytes (1181 MII and 218 MI) from 103 women who received a GnRH agonist trigger were included. Mean age was 36.3 (±4.3) years. Median number of total oocytes retrieved was 14 (IQR 12, 19), MII oocytes was 11 (IQR 8, 14), MI oocytes was 2 (IQR 1, 3). A total of 70 MI oocytes matured spontaneously to the MII stage resulting in a conversion rate of 24%. Performance of MI oocytes versus MI-MII oocytes is reported in Table 1. There was no significant difference in fertilization, cleavage, or blastulation. There was no difference in high quality blastocyst formation.

CONCLUSIONS: In the setting of a GnRH agonist trigger, approximately 24% of MI oocytes will spontaneously mature to MII. These MI-MII oocytes have comparable fertilization, cleavage, and blastulation rates to MII oocytes and therefore the utility of these oocytes should not be disregarded.

<table>
<thead>
<tr>
<th>Oocytes</th>
<th>MII Oocytes</th>
<th>MI-MII Oocytes</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertilization (2pn)</td>
<td>67.1%</td>
<td>55.5%</td>
<td>0.26</td>
</tr>
<tr>
<td>High quality Day 2 (4cell, grade 1)</td>
<td>66.0%</td>
<td>49.6%</td>
<td>0.23</td>
</tr>
<tr>
<td>High quality Day 3 (8cell, grade 1)</td>
<td>61.1%</td>
<td>44.0%</td>
<td>0.09</td>
</tr>
<tr>
<td>Blastulation</td>
<td>53.3%</td>
<td>40.0%</td>
<td>0.40</td>
</tr>
<tr>
<td>Fertilization (2pn)</td>
<td>27.3%</td>
<td>26.7%</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Developmental Potential of MI Oocytes versus MI-MII Oocytes
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GROWTH FACTORS IMPROVE MOUSE OOCYTE DEVELOPMENTAL POTENTIAL VIA INCREASED MAPK AND MTOR SIGNALING ACTIVITIES IN CUMULUS CELLS DURING IN VITRO MATURATION. J. C. Becker, R. Pasquariello, S. K. Rajput, W. B. Schoolcraft, R. L. Krisher, Y. Yuan. Colorado Center for Reproductive Medicine, Lone Tree, CO.

OBJECTIVE: Oocyte in vitro maturation (IVM) is an emerging technology in human ART that has several potential advantages over traditional ovarian stimulation. Our previous work demonstrated a combination of human growth factors (GFs) resulted in better oocyte quality in pig and mouse, yielding increased blastocyst formation as well as improved fetal development after embryo transfer. The objective of this study is to understand how metabolic pathways were affected by these GFs in mouse cumulus cells (CCs) and oocytes.

DESIGN: Research Study.

MATERIALS AND METHODS: Cumulus-oocyte complexes (COCs) were obtained from outbred CF1 mice and randomly allocated into groups either with or without the combination of GFs (FGF2, 40 ng/ml, LIF, 20 ng/ml, and IGFI, 20 ng/ml). Oocytes were matured for 18h in 6.5% O2/7.5% CO2 at 37.0 °C and then completely denuded from their surrounding CCs. CCs from 10 COCs and oocytes were frozen separately for subsequent analysis. The concentrations of phosphorylated MAPK (p-MAPK), p-mTOR, and p-AKT, and total MAPK (t-MAPK), t-MTOR and t-AKT were examined by Western blotting and the ratio of phosphorylated form relative to total protein concentrations was used to determine the activity of each signaling pathway (three replicates). In addition, genes correlated with changes in MAPK activation in CCs, including AREG, EREG, BTC, HAS2, TNAIP6, were examined by quantitative PCR (three replicates). Protein data were analyzed by one-way ANOVA, and qPCR data were analyzed by REST 2009 software to determine relative expression levels between treatments (significance, p < 0.05).

RESULTS: The ratios of p-MAPK/MAPK, p-mTOR/mTOR, and p-AKT/AKT were measured and compared between the two treatment groups. On the other hand, both p-MAPK/MAPK and p-mTOR/mTOR were elevated in the GF treated CCs compared to control CCs, while p-AKT/t-AKT was not different. The EGF-like factor, EREG, and the cumulus expansion factor, TNAIP6, were significantly upregulated in CCs treated by GFs.

CONCLUSIONS: COCs treated with GFs during IVM exhibited greater MAPK and mTOR signaling activities in CCs, as well as upregulation of genes involved in cumulus-oocyte signaling and cumulus expansion. This work suggests that the improved oocyte quality previously observed following the addition of these growth factors may be mediated by enhanced metabolism and cell communication in CCs.

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OBJECTIVE: To identify the role of nuclear and/or cytoplasmic maturity within the retrieved cohort on embryo developmental competence and subsequent live birth rate.

DESIGN: ICSI couples were placed into the following four groups based on their percentage of mature oocytes: complete (100-75%MII), adequate (76-50%MII), partial (51-25%MII), and minimal (26-0% MII). ICSI cycles were divided into quartiles according to the decreasing proportion of mature oocytes to identify its effect on fertilization rate, embryo development, implantation rate, and pregnancy outcome.

MATERIALS AND METHODS: Couples treated by ICSI between September 1993 and April 2017 were included in this study. To control for maternal age or male factor, only women ≤35 years of age using ejaculated spermatozoa with adequate parameters were included. Ovarian stimulation was performed with a GnRH-agonist/antagonist and gonadotropins, with oocytes retrieved approximately 36 hours after hCG administration. ICSI was then performed only on MII oocytes in the standard fashion. Fertilization was assessed 16-18 hours after insemination, and good-quality embryos were transferred to the patient either on day 3 or day 5.

RESULTS: A total of 7,672 ICSI cycles, in which 95,667 MII oocytes were injected using ejaculated spermatozoa, were allocated into the following four oocyte maturity ratio groups: optimal: 4.838; adequate: 2.252; partial: 518; and minimal: 64. The overall average of paternal age was 35.3 ± 5 years. Maternal age was comparable among the four groups (31.9 ± 31.9 ± 32.1 ± 2, and 31.6 ± 3 years, P = NS). The overall average of paternal age was 35.3 ± 5 years. The mean numbers of injected oocytes were 10.8, 8.8, 4.9, and 1.7, respectively (P < 0.0001). The decreasing proportion of MII oocytes was associated with a significant decrease in normal fertilization (2-pronuclei) (78% to 71%; P < 0.0001), with a corresponding increase in oocyte lysis and abnormal fertilization (P = 0.003). The implantation rate gradually fell from 33% to 17% with the declining proportion of MII oocytes (P < 0.0001). Similar trends were observed for the clinical pregnancy (63.6% to 37.5%; P < 0.0001) and live birth rates (49.2% to 26.6%; P < 0.0001; OR = 2.6; 95% CI = 1.5-4.7). Furthermore, the pregnancy losses were higher in the minimal maturation group compared to the optimal maturation group (29.1% vs. 22.6%; P = 0.001).

CONCLUSIONS: From this study, it appears that a suboptimal nuclear and/or cytoplasmic maturation rate affects fertilization, implantation, and delivery rates in an inverse relationship. These findings suggest that achieving the highest oocyte nuclear maturation rating grants higher ooplasmic readiness, yielding conceptuses with higher embryo developmental competence.

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DOUBLE DUTY?: IMPACT OF A DELAYED DOSE OF GONADOTROPIN-RELEASING HORMONE AGONIST (GnRHa) AFTER A DUAL TRIGGER ON OOCYTES RETRIEVED AND RISK OF OVARIAN HYPERSTIMULATION SYNDROME (OHSS). J. K. Blakemoore, D. H. McCullogh, P. A. Grifo. a New York University, New York, NY; bNYU Langone Fertility Center, New York, NY; cOb/Gyn, NYU Langone Medical Center, New York, NY.

OBJECTIVE: Use of a dual trigger (low dose hCG + GnRha) is common for patients with good response to antagonist COH since it adequately triggers oocyte maturation and lowers the risk of OHSS compared to hCG alone. Our objective was to determine if a second dose of GnRha, 12 hours later, had an impact on oocytes retrieved and risk of OHSS.

DESIGN: Retrospective cohort study of cycles utilizing a dual trigger between 1/1/2017 - 1/31/2018 at our center (total n = 917).

MATERIALS AND METHODS: 163 patients used a second dose of GnRha-a (G2) and 754 patients used a single dose (G). Primary outcomes compared were number of oocytes retrieved, % mature, and incidence of OHSS. Secondary outcomes from a subgroup analysis of PGS cycles were the number of PNs, % of PNs biopsied as blastocysts, and ploidy. Statistical analysis included χ² tests and t-tests with or without adjustments for patient age.

RESULTS: The number of oocytes retrieved was significantly greater in the G2 (21.7) than in the G group (19.8) even adjusted for age. Maturation and demographics were not different (Table 1). OHSS incidence was unaffected, although moderate and severe (ModSev) cases of OHSS (defined by the ASRM practice committee) were significantly lower in the G2 group. A subgroup analysis of cycles utilizing PGS (95 G2, 362 G) adjusted for age revealed a higher number of 2PNs for G2 (13.5 v 11.7, p < 0.01) but no difference in the % of 2PN biopsied as blastocysts (55.0% v 59.1%, p < 0.10), number of euploid embryos (2.5 v 2.3, p < 0.01) or % euploid of biopsied embryos (29.8% v 31.5%, p < 0.53).

![Cycle Characteristics with single and double GnRha-a triggers.](image-url)
CONCLUSIONS: Use of G2 results in more oocytes retrieved but does not result in increased maturity. While the number of euploid embryos was not different, the higher rate of 2PNs seen with G2 suggests a possible enhanced oocyte quality. The overall incidence of OHSS was not different between groups, yet there was a lower incidence of Mod&Sev OHSS with use of G2. This study suggests the need for further prospective analysis of the effect of a second delayed dose of GnRH-a.

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THREE-DIMENSIONAL CULTURE OF FRESH AND VITRIFIED OVARIAN TISSUE IN A NOVEL TYRAMINE SUBSTITUTED HYALURONAN GEL.
M. Spangler, P. Gill, A. Upadhye, A. Gishio, N. Desai. OB-GYN, Cleveland Clinic, Beachwood, OH.

OBJECTIVE: Follicle culture in matrices that allow 3-D growth may better mimic in vivo conditions by preserving follicle architecture and critical granulosa-oocyte interactions. This study explores methodology for culturing fresh and vitrified ovarian tissue. We further describe the application of a relatively new biomaterial for in vitro follicle maturation and the production of functional metaphase II oocytes.

DESIGN: Mouse pre-antral follicle model for IVM and testing of a hyaluronan matrix.

MATERIALS AND METHODS: Ovaries from 12 to 14 day B6D2F1 pups were removed. Ovaries were vitrified using an ethylene glycol (EG)/DMSO protocol. Ovaries were equilibrated in chilled vitrification solutions (VS) containing 5, 10, 15 and finally 20% EG/DMSO in L-15 with 20% SSS. Ovaries were loaded on a nylon mesh and plunged in to a specially vented cryovial filled with LN2. Pre-antral follicles (FL) and ovarian follicle clusters were collected from fresh and vitrified-warmed ovaries either by mechanical isolation using needles or by enzymatic digestion in collagenase. The HA hydrogel (3 mg/ml) cross-linking was initiated by mixing with 0.03% hydrogen peroxide in a 25:1 ratio. HA gel was then quickly pipetted into the culture dish. Isolated preantral follicles or intact clusters with 4-6 follicles were rapidly seeded into the HA before gelling was completed. Follicle culture was performed in α-MEM supplemented with 5% FBS, 100 mIU/ml FSH, and ITS. Dishes were incubated at 37°C with 6% CO2. Final maturation was triggered with hCG (1.5 IU/ml) and EGF (5 ng/ml) after 12 days of growth. Outcome parameters monitored were follicle morphology, survival in culture, germinal vesicle breakdown, oocyte maturation and meiotic spindle retardance using Oosight Imaging system.

RESULTS: Vitrified-warmed ovarian tissue was easily dissected into clusters with 4-5 intact follicles without exposure to enzyme. In contrast, enzymatic follicle isolation was more efficient and preferable for fresh tissue. With fresh ovaries, maturation rate in FL-clusters was similar to that observed with isolated follicles. Meiotic spindle retardance in ovulated oocytes from both culture types did not differ. The overall percent oocyte maturation observed with isolated follicles. Meiotic spindle retardance in ovulated oocytes from both culture types did not differ. The overall percent oocyte maturation was triggered with hCG (1.5 IU/ml) and EGF (5 ng/ml) after 12 days of growth. Outcome parameters monitored were follicle morphology, survival in culture, germinal vesicle breakdown, oocyte maturation and meiotic spindle retardance using Oosight Imaging system.

CONCLUSIONS: Use of G2 results in more oocytes retrieved but does not result in increased maturity. While the number of euploid embryos was not different, the higher rate of 2PNs seen with G2 suggests a possible enhanced oocyte quality. The overall incidence of OHSS was not different between groups, yet there was a lower incidence of Mod&Sev OHSS with use of G2. This study suggests the need for further prospective analysis of the effect of a second delayed dose of GnRH-a.

TABLE 1. IVM summary data for fresh and vitrified tissue

<table>
<thead>
<tr>
<th>Description</th>
<th>Frozen</th>
<th>Fresh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicles observed during IVC</td>
<td>69</td>
<td>130</td>
</tr>
<tr>
<td>Antrum formation</td>
<td>na</td>
<td>51% (66/130)</td>
</tr>
<tr>
<td>Ovulated complexes after hCG</td>
<td>93% (64/69)</td>
<td>71% (92/130)</td>
</tr>
<tr>
<td>GVBD (MI)</td>
<td>52% (33/64)</td>
<td>30% (28/92)</td>
</tr>
<tr>
<td>Maturation to MII</td>
<td>34% (22/64)</td>
<td>59% (54/92)</td>
</tr>
<tr>
<td>Spindle Retardance (Range)</td>
<td>na</td>
<td>1.34-3.64</td>
</tr>
</tbody>
</table>

*Mechanically isolated follicle cluster. †Enzymatic isolation.
A MORE ACCURATE SYSTEM FOR MEIOTIC CLASSIFICATION OF HUMAN OOCYTES IN CLINICAL IVF. D. Zhang, a,b J. Patel, a L. V. Farland, a A. M. Thomas, a C. Racowsky, a Obestetrics & Gynecology, Brigham & Women’s Hospital and Harvard Medical School, Boston, MA; a,b Key Laboratory of Reproductive Genetics, Women’s Hospital, School of Medicine, Zhejiang University, Hangzhou, China.

OBJECTIVE: Oocytes exhibiting the 1st polar body (PB) are typically classified as meiotically mature (i.e. metaphase II, [MII]). While the extent of PB extrusion likely reflects both nuclear and cytoplasmic maturity, this is not typically recorded when grading maturity. This study was performed to determine whether a more precise system for meiotic staging of human oocytes enables more accurate prediction of fertilization potential and embryo quality than the meiotic staging system currently used in clinical IVF.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: A retrospective cohort study was conducted of 210 fresh ICSI cycles performed in our program from 8/15/2014 to 9/30/2017 to identify oocytes with very early onset of PB emission (a discernible bulge in the oolemma but no evidence of PB extrusion; early telophase I, ETI), partially emitted PB (late ETI, LTI) or complete PB emission (MII). Cycles with a minimum of one ETI or LTI oocyte and at least one MII were included. ETI, LTI and MII oocytes were compared for proportions of normally fertilized oocytes (2PN), good quality embryos on day 3 and day 5, and freezable and usable (i.e. freezable and transferred) blastocysts. Comparisons were performed using multivariable logistic regression.

RESULTS: The results are shown in the table. Compared with MII oocytes, ETI oocytes were associated with significantly reduced 2PN and Day 3 good quality embryo rates. No significant differences were observed for Day 5 embryos regarding incidence of good quality, freezable, or usable embryos. LTI oocytes were not associated with differences in 2PN rate, or good quality embryo rates on either Day 3 or Day 5, compared with MII oocytes. Day 5 freezable and usable (i.e. freezable and transferred) blastocyst rates were significantly lower in LTI than in ETI and MII oocytes.

CONCLUSIONS: Our findings support a refinement of the current classification for oocyte meiotic maturity to include the extent of PB extrusion when oocytes are classified as mature. Such a refinement will assist in inter- preting cycle outcomes and, in the setting of a previous high incidence of ETI or LTI oocytes, may suggest benefit of increasing exposure time to the ovulatory trigger prior to a subsequent retrieval.

OVARIAN FUNCTION

P-518 Wednesday, October 10, 2018 6:30 AM

PEROXIREDOXIN4, A PROTEIN WHICH SHOWS PROTECTIVE EFFECT ON OVARIAN FUNCTION. Y. Meng, Z. Yan, X. Liang. The First Affiliated Hospital, Nanjing Medical University, Nanjing, China.

OBJECTIVE: Peroxiredoxin4 (Prdx4) is a member of Prdx family. As revealed by our previous research work, the expression of Prdx4 was in close contact with ovary-aging. Furthermore, we also discovered that it was located in endoplasmic reticulum (ER) of granular cell and involved in regulating the endoplasmic reticulum stress (ER stress) in granulosa cell. This research work aimed at exploring the protective effect and the molecular mechanism of Prdx4 on ovarian function.

DESIGN: Mice were divided into two groups: Prdx4-KO and wild type group. The indicators of ovarian function, oxidative stress and ER stress pathways-associated markers were compared between the two groups.

MATERIALS AND METHODS: We established mice model with gene prdx4 knock out by the CRISPR/Cas9 technology. All mice aged 8 months were sacrificed and then blood was collected by removing eyeball. The left ovary was immediately excised and stored at -80°C for biochemical analysis and the right ovary was fixed in 4% paraformaldehyde for histological studies. For the purpose of evaluating the protective effect of Prdx4 on ovarian function, we calculated ovary-to-body weight ratio. Secondly, we detected the level of AMH and expression of senescence-associated protein P16 with the help of real-time PCR and immunohistochemistry correspondingly. Thirdly, the number of different types of follicles were counted by hematoxylin and eosin (H&E) staining for the assessment of ovarian reserve. Eventually, the levels of 4-HNE, 8-OHdG, NTY, and three ER stress pathways related markers were examined by immunohistochemistry and real-time PCR. All the statistical analyses were performed using SPSS v.16. software. All the statistical comparisons between the two groups were analysed by t test.

RESULTS: In comparison with the control group, the prdx4-KO group presented significantly smaller ovary weight/body weight ratio (p<0.05), lower level of AMH, higher expression of senescence-associated protein P16, and lower proportion of primordial follicles (p<0.05). In addition, the prdx4-KO group expressed higher 8-OHdG, 4-HNE, NTY. By screening three pathways of ER stress, we found that ATF4 changed obviously. The level of ATF4 and CHOP were up-regulated in ER.

CONCLUSIONS: Prdx4 may contribute to the ovarian function protection. As for the molecular mechanism of Prdx4 on ovarian function, we hypothesized that Prdx4 may inhibit ER stress through PERK-eIF2α-ATF4-GADD153/CHOP pathway in granulosa cells.

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PEROXIREDOXIN4, A PROTEIN WHICH SHOWS PROTECTIVE EFFECT ON OVARIAN FUNCTION. Y. Meng, Z. Yan, X. Liang. The First Affiliated Hospital, Nanjing Medical University, Nanjing, China.

OBJECTIVE: Peroxiredoxin4 (Prdx4) is a member of Prdx family. As revealed by our previous research work, the expression of Prdx4 was in close contact with ovary-aging. Furthermore, we also discovered that it was located in endoplasmic reticulum (ER) of granular cell and involved in regulating the endoplasmic reticulum stress (ER stress) in granulosa cell. This research work aimed at exploring the protective effect and the molecular mechanism of Prdx4 on ovarian function.

DESIGN: Mice were divided into two groups: Prdx4-KO and wild type group. The indicators of ovarian function, oxidative stress and ER stress pathways-associated markers were compared between the two groups.

MATERIALS AND METHODS: We established mice model with gene prdx4 knock out by the CRISPR/Cas9 technology. All mice aged 8 months were sacrificed and then blood was collected by removing eyeball. The left ovary was immediately excised and stored at -80°C for biochemical analysis and the right ovary was fixed in 4% paraformaldehyde for histological studies. For the purpose of evaluating the protective effect of Prdx4 on ovarian function, we calculated ovary-to-body weight ratio. Secondly, we detected the level of AMH and expression of senescence-associated protein P16 with the help of real-time PCR and immunohistochemistry correspondingly. Thirdly, the number of different types of follicles were counted by hematoxylin and eosin (H&E) staining for the assessment of ovarian reserve. Eventually, the levels of 4-HNE, 8-OHdG, NTY, and three ER stress pathways related markers were examined by immunohistochemistry and real-time PCR. All the statistical analyses were performed using SPSS v.16. software. All the statistical comparisons between the two groups were analysed by t test.

RESULTS: In comparison with the control group, the prdx4-KO group presented significantly smaller ovary weight/body weight ratio (p<0.05), lower level of AMH, higher expression of senescence-associated protein P16, and lower proportion of primordial follicles (p<0.05). In addition, the prdx4-KO group expressed higher 8-OHdG, 4-HNE, NTY. By screening three pathways of ER stress, we found that ATF4 changed obviously. The level of ATF4 and CHOP were up-regulated in ER.

CONCLUSIONS: Prdx4 may contribute to the ovarian function protection. As for the molecular mechanism of Prdx4 on ovarian function, we hypothesized that Prdx4 may inhibit ER stress through PERK-eIF2α-ATF4-GADD153/CHOP pathway in granulosa cells.

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POI followed by a few years of normal function, yet ultimately developed ovarian failure 6 years post-transplant. Remaining patients had post-transplant periods of hypogonadotropic hypogonadism and either normal function or POI. Of the 14 patients with post-transplant AMH values, only 1 patient had normal AMH (>1 ng/mL). Five patients had spontaneous pregnancies post-transplant. Four of the 5 were in the matched transplant cohort.

CONCLUSIONS: SCD patients undergoing transplant should be counseled about the high likelihood of altered ovarian function. While 20% of patients maintained normal ovarian function, 26.7% lost function permanently. None of the patients in the haplo-identical group maintained normal ovarian function, which may be due to the use of Cyclophosphamide in the transplant regimen. Women are at risk for post-transplant progression to POI, even if they initially have normal post-transplant ovarian function. Conversely, some patients with initial post-transplant POI may have return of ovarian function and should be counseled on contraception. Medical centers performing transplants should help facilitate affordable and efficient oocyte vitrification if patients wish to preserve fertility.

Supported by: Supported in part by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health.

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SMN1 HETEROZYGOSITY IS ASSOCIATED WITH DECREASED ANEUPLOIDY RATES. D. Aharon, a L. Sekhon, b a T. Mukherjee, b a A. B. Copperman. b, a Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY; b Reproductive Medicine Associates of New York, New York, NY.

OBJECTIVE: Spinal muscular atrophy (SMA), a neuromuscular disorder caused by biallelic mutations in the survival of motor neuron 1 (SMN1) gene. Patients with neuromuscular disorders demonstrate impaired responsiveness to controlled ovarian hyperstimulation. In a mouse model, SMN1 mutation was associated with reduced testis size and impaired spermatogenesis, but no difference was shown in ovarian size or function. The objective of this study was to examine the ovarian reserve and ART outcomes of SMN1 mutation carriers.

DESIGN: Retrospective

MATERIALS AND METHODS: Female patients who underwent expanded carrier screening (2012–2018) were included. Baseline demographics, ovarian reserve, IVF laboratory outcomes, embryonic aneuploidy and transfer outcomes were compared between SMN1 heterozygotes and controls. A sub-analysis assessed single, euploid FETs outcomes. Student's t-test, chi-square test, and multivariate linear and binary logistic regression models were used for data analysis.

RESULTS: SMN1 mutation carriers (n=76) were compared to controls (n=1214). Baseline demographics and clinical factors are shown in Table 1. When controlling for age, SMN1 heterozygosity did not impact AMH (β=0.7, p=0.19) or BAFC (β=0.7, p=0.4). When controlling for age and AMH, SMN1 carrier status was not found to impact oocyte yield (β=-0.8, p=0.4), fertilization (β=0.01, p=0.74), or blastulation (β=0.03 p=0.4). SMN1 carriers had a significantly lower degree of embryonic aneuploidy (β=0.1, p=0.045). A subanalysis restricted to patients undergoing single, euploid FETs included heterozygous SMN1 carriers (n=28) vs. controls (n=437). SMN1 heterozygosity did not significantly impact the odds of implantation (OR 0.93 [95% CI 0.45-1.92], p=0.9), ongoing pregnancy (OR 0.84 [95% CI 0.41-1.71], p=0.6), live birth (OR 0.91 [95% CI 0.38-2.17], p=0.8), or clinical pregnancy loss (OR 2.2 [95% CI 0.48-9.8], p=0.3).

CONCLUSIONS: SMN1 carrier status was not associated with suboptimal ovarian reserve, oocyte yield, or euploid FET outcome. A significant decrease in the rate of embryonic aneuploidy may represent a potential a heterozygote advantage in SMN1 carriers. If human gonads exhibit a similar response to low SMN protein found in mouse testes, with enrichment in early cell-line genes and upregulation of pro-apoptotic proteins, SMN1 mutation could protect against meiotic errors and prevent aneuploidy by eradicating abnormal oocytes.

References:
OBJECTIVE: There have been studies about the effect of macrophage colony stimulating factor (M-CSF) and its receptor (M-CSFR) on folliculogenesis and ovulation. In our previous study, we detected the expression of M-CSF and M-CSFR by human ovary and luteinized granulosa cells (GCs). The purpose of this study is to understand the functional role of M-CSF and its receptor in luteinized GCs and their results are compared with IVF-ET pregnancy outcome.

DESIGN: Cross-sectional study

MATERIALS AND METHODS: We investigated expression levels of M-CSF and M-CSFR genes in luteinized GCs from 166 IVF patients. These genes were divided into four groups according to their expression patterns (M-CSF P/M-CSFR P vs. M-CSF P/M-CSFR N vs. M-CSF N/M-CSFR P vs. M-CSF N/M-CSFR N) and their results were compared with clinical outcome. To confirm the autocrine and paracrine control mechanisms of the M-CSF and M-CSFR during folliculogenesis, GC was cultured for one week in culture medium supplemented with rhM-CSF. Cell proliferation was assessed by MTT assay and the expression of M-CSFR and NPR2 mRNA were analyzed by RT-PCR.

RESULTS: The M-CSF and M-CSFR were detected in GCs of human ovarian follicle through immunohistochemistry, and their mRNAs were highly expressed in GCs derived from pregnant patients compared to those from non-pregnant women. The pregnancy rate according to gene expression was significantly higher in M-CSF P/M-CSFR P group (M-CSF P/M-CSFR P vs. M-CSF P/M-CSFR N vs. M-CSF N/M-CSFR P vs. M-CSF N/M-CSFR N: 85.7% vs. 25.0% vs. 40.5% vs. 0.0%), These groups were comparable with respect to patients’ characteristics such as age of patients, infertility duration. The growth rate of GC cells grown in the medium supplemented with rhM-CSF was increased (126±40.02 vs. 145.75±50.87) and M-CSFR gene expression was increased, while NPR2 gene expression was decreased.

CONCLUSIONS: In this study, we confirmed that the expression of M-CSF and M-CSFR has positively correlated with IVF-ET pregnancy outcome. In rhM-CSF-treated group, GC proliferation rate and M-CSFR expression were increased and NPR2 expression was decreased. These results indicate that M-CSF influences folliculogenesis through direct action on GCs, also may regulate follicular development by controlling autocrine and paracrine mechanisms. Our study suggests that M-CSF is involved in folliculogenesis and partly promotes ovulation by influencing ovarian macrophages.

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THE OVARIAN SENSITIVITY INDEX (OSI) PREDICTS EMBRYO QUALITY IN OOCYTE DONORS. A. Weghofer, V. A. Kushnir, N. Gleicher | Departments of Obstetrics and Gynecology, Medical University Vienna, Vienna, Austria; Center for Human Reproduction, New York, NY; Obstetrics & Gynecology, Wake Forest University, Winston-Salem, NC.

OBJECTIVE: Ovarian response to exogenous gonadotropin stimulation is essential for the success of in vitro fertilization (IVF). The ovarian sensitivity index (OSI), defined as the amount of gonadotropins utilized per oocyte retrieved, was recently introduced to account for different gonadotropin requirements among high, normal and poor responders, and demonstrated superiority to oocyte numbers in predicting pregnancy potential in younger patients undergoing FSH stimulation. This is the first study to demonstrate that, like in autologous IVF, OSIs are also in oocyte donation cycles predictive of embryo quantity and quality. That pregnancy and live birth rates did not differ in luteinized GCs should not surprise since even donors with higher OSI likely, still produce excellent embryos. Differences with low OSI donors will, therefore, only become apparent in cumulative pregnancy rates. This observation, however, also suggests that, among currently considered well qualified donors, distinct differences exist, with their causes and consequences still largely unknown.

Supported by: Intramural funds from The Center for Human Reproduction and grants from The Foundation for Reproductive Medicine.

THE OVARIAN SENSITIVITY INDEX (OSI) IS PREDICTIVE OF LIVE BIRTH CHANCES AFTER IVF IN INFERTILE PATIENTS WITH RELATIVE POOR PROGNOSIS. A. Weghofer, V. A. Kushnir, N. Gleicher | Departments of Obstetrics and Gynecology, Medical University Vienna, Vienna, Austria; Center for Human Reproduction, New York, NY; Obstetrics & Gynecology, Wake Forest University, Winston-Salem, NC; Stem Cell Biology and Molecular Embryology Laboratory, Rockefeller University, New York, NY; Foundation for Reproductive Medicine, New York, NY; Medical University Vienna, Vienna, Austria.

OBJECTIVE: The ovarian sensitivity index (OSI), defined as the amounts of gonadotropins utilized per oocyte retrieved, was recently introduced to account for different gonadotropin requirements among high, normal and poor responders and demonstrated superiority to oocyte numbers in predicting pregnancy potential in younger patients undergoing FSH stimulation. We here evaluated whether the OSI is also superior to age and oocyte yields in predicting embryo quality, pregnancy potential and live births in an older, more unfavourable patient population undergoing combined FSH/hMG stimulation for IVF.

DESIGN: Retrospective cohort study in academically affiliated private fertility center.

MATERIALS AND METHODS: We retrospectively investigated the relationship between baseline characteristics, total gonadotropin dosages, OSIs, oocyte yields, embryo development, pregnancy rates and live births in 1934 fresh IVF cycles in 1282 women. According to ovarian function, patients were grouped into daily gonadotropin dosage of up to 600 IU of gonadotropins in 3:1 FSH/hMG distribution. Cycles were divided according to their OSIs, OSIs were then stratified into tertiles to compare low, medium and high OSI donors.

RESULTS: Patients who received a daily gonadotropin dosage of 5357±2411 IU and produced 17.9±6.5 oocytes. Pregnancy and live birth rates were 22.0±16.5%, respectively. Women in with low, medium and high OSIs were 36.4±5.6, 40.3±4.4 and 41.1±4.5 years old (P = 0.001). After controlling for age and egg numbers, patients with lower OSIs (less gonadotropin requirement per oocyte retrieved) produced significantly more high-quality embryos than patients with medium and high OSIs (1.2±1.8 vs. 2.3±1.8; P = 0.001 and also demonstrated higher pregnancy (30.9% vs. 20.4% vs. 12.8%) and live birth rates (24.7% vs. 14.3% vs. 8.8%) than their counterparts (P = 0.005 and P = 0.02, respectively). These results indicate that M-CSF influences folliculogenesis through direct action on GCs, also may regulate follicular development by controlling autocrine and paracrine mechanisms. Our study suggests that M-CSF is involved in folliculogenesis and partly promotes ovulation by influencing ovarian macrophages.
The effect of ovarian follicle size on the formation of good quality blastocysts.

B. S. Shapiro, a, A. Raman, a, F. C. Garner, b, M. C. Aguirre, c, C. Morrison, d, S. J. Thomas, a, A. Bill, a, C. E. Bedient, a, Fertility Center of Las Vegas, Las Vegas, NV; University of Nevada Las Vegas, Las Vegas, NV; Ovation Fertility, Las Vegas, NV.

**OBJECTIVE:** Assess relationships, if any, between good-quality blastocyst formation and the diameter of the follicle from which the oocyte originated.

**DESIGN:** IRB-approved prospective observational cohort study.

**MATERIALS AND METHODS:** Patients underwent controlled ovarian stimulation with exogenous gonadotropins. During oocyte collection, follicle diameters were sonographically measured on two perpendicular axes, and the mean diameter was calculated for each follicle. Embryos were group-cultured to the blastocyst stage according to ranges of mean follicle diameter (≤9.5, 10-12.5, 13-15.5, 16-18.5, 19-21.5, 22-24.5, 25-27.5, and ≥28mm). Good blastocyst formation rates (A or B grade inner cell mass and trophectoderm, no C grades) were calculated for each follicle diameter group of each oocyte retrieval. Wilcoxon’s test was used to compare good blastocyst formation rates among follicle diameter groups. Statistically significant overall differences were followed by comparisons of group means.

**RESULTS:** There were 4462 follicle punctures, 2152 collected oocytes, 1633 M2 oocytes, 1126 2pn oocytes following ICSI, and 566 good-quality blastocysts. Weighted averages of oocytes collected, M2 oocytes, 2pn oocytes, and good-quality blastocysts per punctured follicle are shown in Table 1, along with 95% confidence intervals. Wilcoxon’s test revealed differences in good-quality blastocyst formation rates per follicle among all groups (P<0.0001) and that follicles ≤12.5mm in diameter were least likely to yield good blastocysts, those ≥16mm or greater were the most likely to yield good blastocysts, and intermediate-sized follicles 13-15.5mm had intermediate probability of yielding good blastocysts.

**CONCLUSIONS:** Mean follicle diameter predicted formation of good-quality blastocysts, with a plateau starting at 16mm and with no significant evidence of diminution in good-quality blastocyst formation rate even beyond 28mm mean diameter.

---

**Table 1**

<table>
<thead>
<tr>
<th>Mean follicle diameter</th>
<th>Punctures</th>
<th>Oocytes per puncture</th>
<th>M2 oocytes per puncture</th>
<th>2pn oocytes per puncture</th>
<th>Good blastocysts per puncture</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤9.5mm</td>
<td>493</td>
<td>0.249 (0.205-0.294)</td>
<td>0.099 (0.070-0.129)</td>
<td>0.075 (0.050-0.100)</td>
<td>0.030 (0.017-0.044)</td>
</tr>
<tr>
<td>10-12.5mm</td>
<td>718</td>
<td>0.409 (0.366-0.453)</td>
<td>0.223 (0.187-0.258)</td>
<td>0.171 (0.138-0.204)</td>
<td>0.060 (0.041-0.079)</td>
</tr>
<tr>
<td>13-15.5mm</td>
<td>795</td>
<td>0.472 (0.425-0.519)</td>
<td>0.332 (0.291-0.374)</td>
<td>0.240 (0.203-0.277)</td>
<td>0.113 (0.088-0.138)</td>
</tr>
<tr>
<td>16-18.5mm</td>
<td>887</td>
<td>0.538 (0.492-0.583)</td>
<td>0.439 (0.394-0.483)</td>
<td>0.310 (0.270-0.350)</td>
<td>0.160 (0.132-0.188)</td>
</tr>
<tr>
<td>19-21.5mm</td>
<td>744</td>
<td>0.590 (0.545-0.635)</td>
<td>0.512 (0.470-0.554)</td>
<td>0.323 (0.280-0.364)</td>
<td>0.161 (0.131-0.191)</td>
</tr>
<tr>
<td>22-24.5mm</td>
<td>491</td>
<td>0.550 (0.499-0.600)</td>
<td>0.495 (0.444-0.546)</td>
<td>0.330 (0.283-0.376)</td>
<td>0.191 (0.154-0.229)</td>
</tr>
<tr>
<td>25-27.5mm</td>
<td>219</td>
<td>0.525 (0.454-0.596)</td>
<td>0.447 (0.378-0.517)</td>
<td>0.320 (0.258-0.382)</td>
<td>0.192 (0.141-0.243)</td>
</tr>
<tr>
<td>≥28mm</td>
<td>115</td>
<td>0.513 (0.416-0.610)</td>
<td>0.426 (0.333-0.519)</td>
<td>0.243 (0.167-0.320)</td>
<td>0.174 (0.105-0.243)</td>
</tr>
</tbody>
</table>

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**ASRM Abstracts Vol. 110, No. 4, Supplement, September 2018**
MATERIALS AND METHODS: Acclimatized 52-weeks old female SD rats were randomly assigned to a cell therapy group or non-treated group. Rats in cell therapy group were received a single tail vain injection of 5x10^5 hPD-MSCs. At various time-points following transplantation (e.g. 1, 2, 3, 5 weeks after hPD-MSCs therapy), the body weight and organs weight in hPD-MSCs treated vs control animals. The ovarian structures and follicle numbers were also confirmed histologically. Level of hormones, circulating miRNAs, mRNAs and miRNA copy numbers were detected by ELISA and quantitative real-time RT-PCR.

RESULTS: Body weight significantly decreased after hPD-MSCs injection. Human DNA (Alu) sequences were found in different organs (lung, liver, spleen and ovary) after hPD-MSCs therapy. The mean total number of secondary and antral follicles was significantly increased in ovaries at 1 week after hPD-MSCs injection. Genes associated with follicle formation and growth, including Bmp13, Cyp19a1, Gdf9, Mki67, Sirt1 and Zp3, were markedly increased in ovaries, starting from the second week after cell therapy. Levels of miR-21, miR-34a, miR-145 and miR-191, known as associated with ovarian reserve and aging, were changed in serum. In addition, hPD-MSCs therapy led reduction of mtDNA content and improved mitochondrial condition by increasing levels of Atp5a1, Esr2 and Tomm7.

CONCLUSIONS: Our study verified that the hPD-MSCs injection via tail vein led to the improved folliculogenesis through gene expression involved in follicle assembly in the aged rats. We also observed that hPD-MSCs therapy maged aging phenotypes through weight loss, improved mitochondrial function and growth of circulating miRNAs involved in ovarian reserve and aging process. Our findings suggest the future therapeutic potential of hPD-MSCs transplantation for women in advanced age to improve their ovarian function and keep youthfulness.

Supported by: This research was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) & funded by the Korean government (MSIT) (NRF-2017M3XAB4061854).

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OBJECTIVE: Functional analysis of microarray data obtained in human primary cumulus granulosa cells (hGCs) revealed for the first time the expression and regulation of DDIT4 and CYR61 by gonadotropins and oocyte-secreted factors (1). In cancer cells, DDIT4 has been shown to promote proliferation and survival; while CYR61 promotes cell apoptosis. Because oocyte-secreted factors influence GC growth, the purpose of this study was to determine the role of the OSFs growth differentiation factor 9 (GDF9) and bone morphogenetic protein 15 (BMP15) on DDIT4 and CYR61 expression in primary hGCs.

DESIGN: Prospective in vitro studies using human primary cumulus granulosa cell cultures.

MATERIALS AND METHODS: Follicular aspirates from 20 women undergoing in vitro fertilization at a University clinic were used. Cumulus cells were mechanically separated from the oocyte, seeded at a density of 6x10^4 cells/ml on culture dishes pre-coated with extracellular matrix and cultured for 24-72 hours before treatment. Cells were treated with a combination of GDF9, BMP15, recombinant follicle stimulating hormone (FSH), and SMAD inhibitors for 48 hours. Cells were harvested for analysis. DDIT4 and CYR61 mRNA and protein levels were quantified using real-time PCR and Western Blot respectively. Data were analyzed by two-way ANOVA and P<0.05 was considered significant.

RESULTS: Treatment with GDF9 or BMP15 alone, or in combination (G+B) had no effects on DDIT4 and CYR61 mRNA and protein levels, compared to the untreated control group (C). FSH-stimulation of DDIT4 mRNA expression was significantly potentiated in the presence of G+B (GDF9 + BMP15). DDIT4 mRNA fold increase relative to control: FSH: 2.4±0.3 vs. FSH+G+B: 4.6±1.2, P<0.01). Similarly, FSH-inhibition of CYR61 mRNA expression was significantly potentiated in the presence of G+B (CYR61 mRNA relative expression: C: 26.2±6.4 FSH: 21.2±6.0 vs. FSH+G+B: 7.0±2.0, P=0.002). The regulation of DDIT4 and CYR61 was confirmed by Western Blot (P<0.05). G+B inhibition of CYR61 followed a dose-dependent pattern with maximal inhibition observed at 5ng/ml for each GDF9 and BMP15. The addition of SMAD2/3 and SMAD1/5/8 inhibitors had no effect on the potentiation of DDIT4 stimulation by G+B. In marked contrast, the addition of either of these inhibitors attenuated the expression of CYR61 strongly even in the presence of FSH and G+B (P<0.0001).

CONCLUSIONS: Our data highlight the expression and regulation by OSFs of two genes involved in proliferation and survival. The findings provide a novel mechanism by which the oocyte, via the secretion of GDF9 and BMP15, potentiates the protective effects FSH on GC survival and proliferation.


Supported by: NIH NIGMS-T32GM08307, NIH NICHD-R21HD084802
LNCRNA LNC-GULP1-2:1 IS INVOLVED IN HUMAN GRANULOSA CELL PROLIFERATION BY REGULATING COL3A1 GENE. Y. Kong, G. Yao, J. He, G. Yang, D. Kong, Y. Sun. Reproductive Medical Center, the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China.

OBJECTIVE: Long non-coding RNAs (lncRNAs) are defined as transcripts longer than 200 nucleotides that are not translated into protein. Many studies have identified the association between abnormal expression of lncRNAs and specific disease states, especially in tumor-related studies. However, the precise functions of these lncRNAs are not clear. In our previous study, both Inc-GULP1-2:1 and its potential target COL3A1 were significantly downregulated in ovarian cortical tissues of POI patients compared with normal control patients. The results of GO and KEGG analysis also showed that changes in extracellular matrix-related genes play an important role in the development of POI. Therefore, we speculate that Inc-GULP1-2:1 may participate in the development of ovarian follicles by regulating the COL3A1 gene.

DESIGN: Basic research study.

MATERIALS AND METHODS: The lenticillar vessels were used to construct a KGN cell line with stable high expression of Inc-GULP1-2:1. Real-time PCR and western blot were used to analyze the expression of COL3A1 and Inc-GULP1-2:1. Cell proliferation was analyzed by using CCK-8 kits.

RESULTS: The stable over-expression of Inc-GULP1-2:1 in KGN cells could significantly inhibit granulosa cell proliferation. Treatment of KGN cells with chemotherapeutic agents (cisplatin and paclitaxel) dose-dependently inhibited granulosa cell proliferation and promoted the expression of Inc-GULP1-2:1, whereas the cytokine TGFα, which promoted granulosa cell proliferation, inhibited the expression of Inc-GULP1-2:1. These results suggest that Inc-GULP1-2:1 may be involved in proliferation regulation of granulosa cells. Further studies found that the protein levels of COL3A1 were significantly increased in KGN cells with stable over-expression of Inc-GULP1-2:1, indicating that Inc-GULP1-2:1 regulates the expression of COL3A1. mRNA levels of Inc-GULP1-2:1 can be down-regulated by miRNAs (5, 10, 15, 20) in different concentrations of COL3A1 in KGN cells, and silencing COL3A1 could also significantly inhibit KGN cell proliferation.

CONCLUSIONS: The results of this study suggest that the involvement of Inc-GULP1-2:1 in the regulation of KGN granulosa cells might partly be mediated through the regulation of its target gene COL3A1. The regulation effect of Inc-GULP1-2:1 on granulosa cell proliferation was consistent with the occurrence of POI in clinical chemotherapeutic agents, suggesting that Inc-GULP1-2:1 may be involved in the regulation of granulosa cell function in POI patients. This is the first study to discover the regulation of Inc-GULP1-2:1 in ovarian granulosa cells, which is of great significance for the further investigation of IncRNA regulation in ovarian follicle development.

Supported by: National Natural Science Foundation of China (Grant No. 81501128)

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MINICHROMOSOME MAINTENANCE COMPLEX COMPONENT 8 AND 9 GENE EXPRESSION IN THE MENSTRUAL CYCLE AND UNEXPLAINED PRIMARY OVARIAN INSUFFICIENCY. Y. Donkik, Z. Lei, J. Gaskins, K. Pagidas. University of Louisville, Louisville, KY.

OBJECTIVE: DNA repair genes Minichromosome maintenance complex component (MCM) 8 and 9 have been linked with gonadal development, primary ovarian insufficiency (POI), and age at menopause. Our objectives were to characterize MCM 8/9 gene expression in the menstrual cycle and to compare MCM 8/9 expression in POI subjects with normo-ovulatory controls.

DESIGN: Prospective cohort study.

MATERIALS AND METHODS: Normo-ovulatory controls (n=11) and unexplained POI subjects (n=6) were recruited. For 5 of 11 controls, 3 blood samples were taken within a single menstrual cycle: 1) early follicular phase, 2) ovulation, 3) mid-luteal phase. Controls who were unable to provide multiple blood samples (n=6/11) were drawn only in the follicular phase. All POI patients were amenorrheic and provided a single, random blood sample. RNA was extracted from whole blood and cDNA synthesis performed. MCM8 and 9 mRNA expression was assessed with quantitative real-time PCR. To compare differences across different menstrual cycle phases, a random effects ANOVA analysis was performed. Two-sample t-tests were used to compare two groups. All analyses were performed using delta-Ct measurements; group differences were transformed to a fold change (FC) and confidence interval (CI) for interpretation.

RESULTS: In normo-ovulatory subjects (n=5) who submitted 3 samples within the same cycle, significantly higher MCM8 gene expression was noted in the early follicular phase (FC=1.49, CI=0.50, 0.85). No significant change in MCM9 gene expression was noted throughout the menstrual cycles phases. The FC=0.84 in the luteal vs follicular phase (p=0.53, CI=0.67, 0.70). There was a statistically significant difference seen in MCM8 or 9 gene expression when comparing MCM8/9 intervention (P<0.0001) and confidence interval (CI) for interpretation.

RESULTS: Microarray gene expression analysis of murine ovarian tissue revealed significant transcription changes in the acai intervention group, with the most enriched pathways belonging to apoptotic signaling and oxidation redox (P<0.005). PCR validation confirmed a decrease of pro-apoptotic genes (Fas, Casp9, Bik and Tnf) and increases of pro-survival cell death regulators (Bcl2 and Bcl2l1), as well as increases of antioxidant enzymes (Gclm and Sod2, among others) with acai intervention (P<0.005). Murine MI oocytes in the acai intervention group were also found to have increased antioxidant gene expression (Gss, Gpx1, Gsr, Gst01, Gclm, Sod1 and Sod2). Ongoing clinical results continue to show significant improvements in oocyte yield (17.4 ±10.1 vs. 13.7±8.2; P<0.0001) and proportion of euploid blastocysts (43.6% vs. 30.3%; P<0.0001) for female patients with ≥1 prior failed IVF cycle. Euploid FET (n=138) outcomes for these intervention patients have resulted in a 76.1% live birth rate.

CONCLUSIONS: In conclusion, following antioxidant intervention with natural aging, the murine ovarian transcriptome revealed an environment promoting cell survival alongside a decrease in apoptotic signaling, and an increase in antioxidant activity that could be resulting in restoration of ovarian function and oocyte quality. Taken together this offers a molecular explanation for the clinical improvements observed for women with a history of IVF failures, following antioxidant intervention prior to infertility treatment.

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ANTIOXIDANT INTERVENTION PROMOTES CELL SURVIVAL AND REDOX BALANCE WITHIN THE OVARY AND SUBSEQUENT OOCYTE RESULTING IN IMPROVED IVF OUTCOMES. I. Patsalos, A. McCallie, A. Patton, N. I. McCubbin, W. B. Schoolcraft, M. Katz-Jaffe. Colorado Center for Reproductive Medicine, Lone Tree, CO; University of Kent, Canterbury, United Kingdom.

OBJECTIVE: The damaging effect of oxidative stress and reactive oxygen species in ovarian aging has been associated with a decrease in follicular quantity and quality. Previously we have reported that antioxidant intervention prior to infertility treatment benefits patient outcomes. The objective of this study was to utilize a murine model to explore the molecular mechanisms underlying this observed clinical benefit.

DESIGN: Research study.

MATERIALS AND METHODS: Female CF-1 mice were naturally aged for 9 months prior to a daily oral diet intervention of 4 grams/animal for 12 weeks of Euterpe oleracea (açaí; sourced from Brazil and biochemically tested for high antioxidant activity). Control mice received the same balanced nutritional feed but without the intervention. Aged mouse ovaries (n=12) were processed for CodeLinkTM Mouse Whole Genome (Applied Microarrays) with Ingenuity Pathway Analysis (Qiagen). QPCR was utilized for microarray validated genes (n=12) and MiR probe gene expression (n=19) with REST-2009 statistical software (Qiagen). Infertility patients (n=209; mean 38.0 ±4.0 years) presenting with ≥1 prior failed IVF cycle, ingested 600mg of natural açaí three times a day for 8-12 weeks prior to routine ovarian stimulation. Live birth outcomes were analyzed for each patient, with and without açaí, using Fisher’s exact test, with significance at P<0.05.

RESULTS: Microarray gene expression analysis of murine ovarian tissue revealed significant transcription changes in the acai intervention group, with the most enriched pathways belonging to apoptotic signaling and oxidation redox (P<0.005). PCR validation confirmed a decrease of pro-apoptotic genes (Fas, Casp9, Bik and Tnf) and increases of pro-survival cell death regulators (Bcl2 and Bcl2l1), as well as increases of antioxidant enzymes (Gclm and Sod2, among others) with acai intervention (P<0.005). Murine MI oocytes in the acai intervention group were also found to have increased antioxidant gene expression (Gss, Gpx1, Gsr, Gst01, Gclm, Sod1 and Sod2). Ongoing clinical results continue to show significant improvements in oocyte yield (17.4 ±10.1 vs. 13.7±8.2; P<0.0001) and proportion of euploid blastocysts (43.6% vs. 30.3%; P<0.0001) for female patients with ≥1 prior failed IVF cycle. Euploid FET (n=138) outcomes for these intervention patients have resulted in a 76.1% live birth rate.

CONCLUSIONS: In conclusion, following antioxidant intervention with natural aging, the murine ovarian transcriptome revealed an environment promoting cell survival alongside a decrease in apoptotic signaling, and an increase in antioxidant activity that could be resulting in restoration of ovarian function and oocyte quality. Taken together this offers a molecular explanation for the clinical improvements observed for women with a history of IVF failures, following antioxidant intervention prior to infertility treatment.
**OVARIAN RESERVE**

**P-534 Wednesday, October 10, 2018 6:30 AM**


OBJECTIVE: Systemic levels of bioactive omega-3 (n-3) fatty acids (FA) are positively associated with ovarian reserve in animal models, however, little is known about the relationship between follicular fluid (FF) FA and ovarian reserve. We aimed to assess differences in FF FA levels from patients with diminished (DOR) and normal ovarian reserve (NOR) undergoing in vitro fertilization (IVF).

DESIGN: Prospective cohort study.

MATERIALS AND METHODS: Patients undergoing IVF at a single academic center were eligible. DOR was defined as either: AMH < 1.0 ng/mL, antral follicle count (AFC) ≤ 10, ≤ 10 oocytes retrieved, or FSH > 10 mIU/mL. NOR controls had tubal or male factor infertility. PCOS patients were excluded. Leftover FF from oocyte retrieval was collected. The non-esterified FA in the total lipid extract were quantified by mass spectrometry and normalized to total protein. Student’s t-test and Pearson’s correlations were performed, as appropriate.

RESULTS: As expected, DOR patients (N = 10) had lower AMH levels, lower AFC, fewer oocytes retrieved, and higher FSH levels than NOR controls (N = 10) (table). There was no difference in age (DOR 35.6 ± 3.2 years, NOR 32.9 ± 5.0 years, p = 0.2) or BMI (DOR 26.4 ± 3.8 kg/m², NOR 24.2 ± 2.8 kg/m², p = 0.2) between groups. The overall ratio of saturated FA to unsaturated FA was positively associated with AFC (r = 0.55, p = 0.012). Arachidonic acid (C20:4) was the saturated FA most significantly reduced in FF from DOR patients as compared to NOR controls (table). AMH levels were also positively associated with FF C20:0 (r = 0.48, p = 0.03). No differences in bioactive n-3 or n-6 FA levels in FF were observed between DOR and NOR patients (table).

<table>
<thead>
<tr>
<th>FA</th>
<th>DOR (mean ± SD)</th>
<th>NOR (mean ± SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMH (ng/mL)</td>
<td>1.5 ± 0.7</td>
<td>3.5 ± 1.2</td>
<td>0.0002</td>
</tr>
<tr>
<td>AFC</td>
<td>10.6 ± 2.0</td>
<td>20.0 ± 8.4</td>
<td>0.006</td>
</tr>
<tr>
<td>Oocytes retrieved</td>
<td>8.3 ± 3.9</td>
<td>19.7 ± 7.0</td>
<td>0.0003</td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>8.3 ± 1.7</td>
<td>6.6 ± 1.7</td>
<td>0.04</td>
</tr>
<tr>
<td>Linoleic Acid (C18:2; n-6) (nmol/mL FF/mg protein)</td>
<td>134.5 ± 35.0</td>
<td>127.0 ± 58.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Alpha-Linolenic Acid (C18:3; n-3) (nmol/mL FF/mg protein)</td>
<td>38.7 ± 15.5</td>
<td>32.4 ± 20.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Arachidonic Acid (C20:4; n-6) (nmol/mL FF/mg protein)</td>
<td>4.3 ± 1.8</td>
<td>4.0 ± 1.8</td>
<td>0.7</td>
</tr>
<tr>
<td>EPA (C20:5; n-3) (nmol/mL FF/mg protein)</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.3</td>
<td>0.8</td>
</tr>
<tr>
<td>DHA (C22:6; n-3) (nmol/mL FF/mg protein)</td>
<td>2.9 ± 2.0</td>
<td>4.2 ± 3.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Ratio of total n-6/n-3</td>
<td>3.2 ± 0.6</td>
<td>3.4 ± 0.7</td>
<td>0.5</td>
</tr>
</tbody>
</table>
CONCLUSIONS: Decreased ratios of saturated to unsaturated FA and decreased levels of C20:0 in FF are associated with DOR. Interestingly, we found no correlation between FF n-3 FA and ovarian reserve. Further work is needed to understand the role of arachidonic acid and other saturated fats in female fertility.

References:

Supported by: AAOFG Grant to MS-W; Resident Research Fund Grant, University of Colorado to ISL

P-535 Wednesday, October 10, 2018 6:30 AM

RECOVERY OF OVARIAN FUNCTION BY HUMAN EMBRYONIC STEM CELLS DERIVED MESENCHYMAL STEM CELLS IN CISPLATIN INDUCED PREMATURE OVARIAN FAILURE IN MOUSE. S. Yoon, J. Yoon, D. Shim, M. Park, J. Eum, H. Song, J. Lee, D. Lee, W. Lee, S. Lyu. Fertility Center of CHA Gangnam Medical Center, Seoul, Korea, Republic of; CHA University, Seongnam-si, Gyeonggi-do, Korea, Republic of.

OBJECTIVE: Mesenchymal stem cells (MSC) [Unsuppoted Character - Codename ]]represent a population of multipotent adult stem cells capable of differentiating into mesodermal and nonmesodermal lineages. Recent MSC have been introduced in various clinical trials for transplantation therapy. However, harvesting MSC requires invasive procedures, limited number of cells and obtains uniform populations for clinical use. Human embryonic stem cells derived MSC (hESC-MSC) can differentiate into three germ layers, and possess immunosuppressive effects in vitro. In this study we investigated the effect of hESC-MSC on recovery of ovarian function in cisplatin-induced premature ovarian failure in mice.

DESIGN: Animal experiment

MATERIALS AND METHODS: Eight weeks ICR or C57BL/DBA F1 hybrid female mice were intraperitoneally injected with 2mg/kg cisplatin for 10 days. Control group received same amount of saline (con). On the 12th day, hESC-MSC (5x10^6/mouse) or PBS were transplanted into cisplatin administered mice by tail vain injection. All mice were sacrificed on the 4 weeks day of the experiment. hESC-MSC were generated form CHA15 hESC (CHA stem cell institute, Korea). MSC characterizations were performed by flow cytometry and mesodermal lineage differentiation (adipogenic, osteogenic and chondrogenic differentiation). The bilateral ovaries were removed at 28 day transplantation, fixed, and assessed of ovarian histology and immunostaining. For in vitro fertilization and embryonic development, the female mouse were superovulated and fertilized epidymal sperm from fertile male mouse. Fertility test were performed with fertile male for 10 days. Statistical data analysis was performed using Graphpad program by t-test or one way ANOVA test.

RESULTS: Three days after the treatment we observed a reduction of 66.3% in the small follicles density for the group treated with the highest dose of cyclophosphamide compared to control group (p<0.001). The density of small follicles for the lower doses was similar to the control group at day 3. Seven days after the treatment the density of the small follicles is significantly reduced for all the treated mice compared to the control, even in the groups receiving the lowest doses. We observed a reduction in small follicles density of 34.5% in the group treated with 50mg/Kg (p<0.01) and 56% in the group treated with 75mg/Kg (p<0.001). For the group treated with 100mg/Kg a reduction of 70.2% was registered (p<0.01). The follicle density was calculated as the total number of small follicles divided by the area of ovarian tissue examined. The study was approved by the regional ethics committee for animal experiments.

RESULTS: Three days after the treatment we observed a reduction of 66.3% in the small follicles density for the group treated with the highest dose of cyclophosphamide compared to control group (p<0.001). The density of small follicles for the lower doses was similar to the control group at day 3. Seven days after the treatment the density of the small follicles is significantly reduced for all the treated mice compared to the control, even in the groups receiving the lowest doses. We observed a reduction in small follicles density of 34.5% in the group treated with 50mg/Kg (p<0.01) and 56% in the group treated with 75mg/Kg (p<0.001). For the group treated with 100mg/Kg a reduction of 70.2% was registered (p<0.001).

CONCLUSIONS: Our data seem to indicate that the ovarian damage caused by CPA is progressive and suggest that potential protective therapeutic interventions might be applied after initiation of chemotherapy treatment, in particular if low doses of CPA had been administered (window of opportunity for a few days but shorter than one week). Our data also confirmed that the pre-pubertal status is not itself protective against ovarian follicle depletion.

Supported by: The Swedish Childhood Cancer Foundation, Radiumhemmet's research grants, the Stockholm County Council and Karolinska Institutet.

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TIMING OF FOLLICLE DAMAGE AFTER LOW DOSES OF CHEMOTHERAPEUTICS IN PRE-PUBERTAL MICE. A. Anastacio, S. Alonzo de Mena, R. Kuiper, K. A. Rodriguez-Walberg. Oncology-Pathology, Laboratory of Translational Fertility Preservation, Karolinska Institutet, Stockholm, Sweden; Embryologist, Malaga, Spain; Karolinska Institutet, Stockholm, Sweden; Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden.

OBJECTIVE: Assess the effect of low doses of cyclophosphamide in the ovarian follicular pool of prepubertal mice.

DESIGN: Three weeks old C57BL/6N mice (n=45) were randomly distributed in 4 groups: three groups treated with different doses of cyclophosphamide (CPA) and a control group. The animals were sacrificed 3 or 7 days after the treatment and the ovaries dissected for histological analysis. Follicle density of small size follicles was calculated.

MATERIALS AND METHODS: The animals were injected (IP) on two consecutive days with a) 100mg/Kg; b) 75mg/Kg or c) 50 mg/Kg. The ovaries were collected for histological analysis 3 or 7 days after the first injection of CPA. Follicles were counted by two independent observers on scanned (3DHistech®) 5 μm HE-stained sections using the classification of Pedersen & Peters [1]. Follicle density was calculated as the total number of small follicles divided by the area of ovarian tissue examined. The study was approved by the regional ethics committee for animal experiments.

RESULTS: Three days after the treatment we observed a reduction of 66.3% in the small follicles density for the group treated with the highest dose of cyclophosphamide compared to control group (p<0.001). The density of small follicles for the lower doses was similar to the control group at day 3. Seven days after the treatment the density of the small follicles is significantly reduced for all the treated mice compared to the control, even in the groups receiving the lowest doses. We observed a reduction in small follicles density of 34.5% in the group treated with 50mg/Kg (p<0.01) and 56% in the group treated with 75mg/Kg (p<0.001). For the group treated with 100mg/Kg a reduction of 70.2% was registered (p<0.001).

CONCLUSIONS: Our data seem to indicate that the ovarian damage caused by CPA is progressive and suggest that potential protective therapeutic interventions might be applied after initiation of chemotherapy treatment, in particular if low doses of CPA had been administered (window of opportunity for a few days but shorter than one week). Our data also confirmed that the pre-pubertal status is not itself protective against ovarian follicle depletion.

Supported by: The Swedish Childhood Cancer Foundation, Radiumhemmet’s research grants, the Stockholm County Council and Karolinska Institutet.

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OBJECTIVE: Wilson’s disease is a disorder of copper metabolism caused by homozygous mutations in the ATPase Copper Transporting (ATP7B) gene. Multiple organs experience oxidative damage from copper deposition, including the reproductive system. One study found an association between elevated serum copper levels and reduced implantation in patients undergoing frozen embryo transfer (FET). Single-allele ATP7B mutations have been shown to result in elevated urinary copper levels. Data on the effect of ATP7B mutation heterozygosity on female reproduction is limited. The study aimed to determine ovarian reserve and clinical outcomes of Wilson’s disease carriers undergoing IVF.

DESIGN: Retrospective cohort

MATERIALS AND METHODS: Patients underwent expanded carrier screening and IVF between 2012-2018. Demographics and cycle outcomes
were compared between ATP7B mutation carriers and negative controls. A sub-analysis restricted to single, euploid FETs was done. A student’s t-test, chi-square, and linear and logistic regression were used.

RESULTS: A total of 48 ATP7B mutation carriers and 1214 non-carriers were compared (Table 1). Controlling for age, AMH (β=1.1, p=0.1) and BAFc (β=0.07, p=0.9) were unaffected in carriers. Controlling for age and AMH, ATP7B carrier status did not impact oocyte yield (β=1.5, p=0.2), fertilization (β=0.02, p=0.6), blastulation (β=-0.02 p=0.7) or embryonic arrest (β=0.03, p=0.6). A subanalysis of heterozygous ATP7B carriers (n=36) and controls (n=437) undergoing single euploid, euploid FET showed no association between ATP7B heterozygosity and odds of implantation (OR 1.2 [95% CI 0.5-2.9], p=0.6), ongoing pregnancy (OR 0.96 [95% CI 0.4-2.3], p=0.9), live birth (OR 1.5 [95% CI 0.5-4.6], p=0.5), or clinical pregnancy loss (OR 0.5 [95% CI 0.1-1.6], p=0.2).

CONCLUSIONS: While there is evidence that a partial loss of ATP7B function can result in some degree of impaired copper metabolism and clinical sequelae, our study is the first to show that despite reduced ATP7B function, carriers of Wilson’s disease have IVF outcomes comparable to that of non-carriers. It is possible that the modest reduction in copper metabolism in carriers does not meet the threshold required to affect hypothalamic-pituitary-ovarian function or the environment surrounding embryo implantation. Further research is required to confirm these findings in a non-ART population, and to investigate whether there are copper level thresholds beyond which reproductive function is affected.


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THE PSYCHOLOGICAL AND EMOTIONAL IMPACT OF AMH TESTING. Y. O’Brien,1,2,3,4 C. Kelleher,1,2 M. Wingfield,1,2,3,4,5 Merrion Fertility Clinic, Dublin, Ireland; 2National Maternity Hospital, Dublin, Ireland; 3University College Dublin, Dublin, Ireland; 4Department of psychology, Royal College of Surgeons in Ireland, Dublin, Ireland; 5Trinity College Dublin, Dublin, Ireland.

OBJECTIVE: The aim of this study was to use psychological scales to evaluate the impact of Anti-Mullerian Hormone (AMH) testing on women. From the findings of a previous qualitative study by our research group, we hypothesised that knowledge of one’s ovarian reserve test has a psychological impact which could be measured by assessing pre-and post AMH (i.e. Time 1 and 2) test measures of depression, affect, fertility quality of life and stigma.

MATERIALS AND METHODS: Women who were having AMH testing as part of gynaecological investigations, mostly subfertility, were recruited over a 6-month period. Five psychological scales were used to measure pre and post testing levels of depression (Patient Health Questionnaire depression scale (PHQ-8)), affect (The Positive and Negative Affect Schedule (PANAS)), stigma (The Adapted Stigma Consciousness Questionnaire), resilience (The 25-item Resilience Scale) and fertility quality of life (The Fertility Quality of Life (FertiQoL) tool). For this study we defined an AMH result of 7 pmol/l as a ‘low’ AMH result reflecting low ovarian reserve. A mixed within-between subjects analysis of variance was conducted to assess the impact of the AMH result on the psychological scale scores before and after AMH testing. The interaction effect was described. P<0.05 was considered statistically significant. This study was approved by the Medical Research and Ethics committee of the National Maternity Hospital, Holles Street, Dublin.

RESULTS: The response rate (fully completed response) for the Time 1 and 2 questionnaires respectively was 79% (79/100) and 71.2% (52/73). There was a significant interaction between the change in scores in the PHQ-8 and the PANAS scales over the two questionnaires and the normal and low AMH groups. There was no significant interaction between Fertiqol, resilience or stigma scores and the AMH level. See Table 1.

CONCLUSIONS: We have demonstrated that a low AMH level has a significant impact in terms of levels of depression and positive and negative affect before and after AMH testing. This study demonstrates a need for appropriate information and counseling prior to and after AMH testing. It should be extended to evaluate the impact of AMH testing on a cohort of women from the general population prior to the introduction of ovarian reserve screening for all young women.

TABLE 1. Baseline and Post AMH scores for all psychological scales

<table>
<thead>
<tr>
<th>Scale</th>
<th>Low AMH group Mean +/- SD</th>
<th>Low AMH group Mean +/- SD</th>
<th>Normal AMH group Mean +/- SD</th>
<th>Normal AMH group Mean +/- SD</th>
<th>Partial Eta squared</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHQ-8</td>
<td>2.0 +/- 2.0</td>
<td>5.6 +/- 5.6</td>
<td>5.9 +/- 4.1</td>
<td>4.5 +/- 3.8</td>
<td>0.118</td>
<td>0.013*</td>
</tr>
<tr>
<td>PAS</td>
<td>28.1 +/- 9.9</td>
<td>22.8 +/- 7.4</td>
<td>28.5 +/- 7.4</td>
<td>30.6 +/- 7.7</td>
<td>0.103</td>
<td>0.021*</td>
</tr>
<tr>
<td>NAS</td>
<td>20.5 +/- 7.2</td>
<td>23.0 +/- 11.7</td>
<td>25.5 +/- 7.0</td>
<td>19.7 +/- 7.4</td>
<td>0.127</td>
<td>0.009*</td>
</tr>
<tr>
<td>FertiQol</td>
<td>75.4 +/- 28.3</td>
<td>55.7 +/- 16.3</td>
<td>64.6 +/- 11.9</td>
<td>65.7 +/- 12.0</td>
<td>0.010</td>
<td>0.534</td>
</tr>
<tr>
<td>Resilience</td>
<td>131.0 +/- 17.1</td>
<td>130.7 +/- 15.1</td>
<td>130.3 +/- 14.8</td>
<td>133.1 +/- 14.6</td>
<td>0.018</td>
<td>0.345</td>
</tr>
<tr>
<td>Stigma</td>
<td>29.0 +/- 12.5</td>
<td>27.0 +/- 10.2</td>
<td>28.6 +/- 8.5</td>
<td>29.6 +/- 8.6</td>
<td>0.026</td>
<td>0.255</td>
</tr>
</tbody>
</table>

FERTILITY & STERILITY®
P-539 Wednesday, October 10, 2018 6:30 AM

PREGNANCY RATES FOLLOWING IN VITRO FERTILIZATION-EMBRYO TRANSFER (IVF-ET) IN WOMEN WITH DIMINISHED OOCYTE RESERVE WHO ONLY HAD ONE DAY 3 FRESH EMBRYO TO TRANSFER. J. H. Cheok, E. Chang, R. Cohen, J. Choe, C. Wilson, D. Summers. Cooper Medical School of Rowan University, Camden, NJ; Philadelphia College of Osteopathic Medicine, Philadelphia, PA.

OBJECTIVE: To determine the pregnancy outcome following IVF-ET according to age in women with diminished oocyte reserve (DOR) having only one embryo available to be transferred on day 3.

DESIGN: Retrospective review.

MATERIALS AND METHODS: All IVF-ET cycles in which the female partner had diminished oocyte reserve as evidenced by a day 3 serum follicle stimulating hormone (FSH) >12 mIU/mL and/or a serum anti-mullerian hormone (AMH) level <1 ng/mL, in which there was only a single embryo developing to day 3 to be transferred, were enlisted in the study. The data was stratified according to 5 age groups. Only mild controlled ovarian stimulation was used.

RESULTS: Pregnancy rates for patients with diminished ovarian reserve having a single day 3 embryo transferred are seen in the table below.

<table>
<thead>
<tr>
<th>Age</th>
<th># transfers</th>
<th>Average age</th>
<th>% clinical pregnancy/transfer</th>
<th># live delivered</th>
<th>% delivered</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤35</td>
<td>165</td>
<td>33.2</td>
<td>28.5%</td>
<td>41</td>
<td>24.8%</td>
</tr>
<tr>
<td>36-39</td>
<td>285</td>
<td>38.2</td>
<td>18.6%</td>
<td>37</td>
<td>13.0%</td>
</tr>
<tr>
<td>40-42</td>
<td>452</td>
<td>41.6</td>
<td>11.7%</td>
<td>26</td>
<td>5.8%</td>
</tr>
<tr>
<td>43-44</td>
<td>295</td>
<td>43.9</td>
<td>4.4%</td>
<td>5</td>
<td>1.7%</td>
</tr>
<tr>
<td>45-46</td>
<td>129</td>
<td>45.9</td>
<td>3.9%</td>
<td>2</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

CONCLUSIONS: Women aged 36-39 (average 38.2) with DOR are 52% as likely to have a live baby following a single embryo transfer on day 3 compared to women aged ≤35 (average 33.2). Women aged 40-42 (average age 41.6) are 23% as likely to conceive as women aged <35 and are 44% as likely to deliver a live baby as women aged 36-39. The younger the age, despite DOR, the greater the chance of reaching a clinical pregnancy (ultrasound evidence of pregnancy at 8 weeks) and the lower the chance of miscarriage in those whose DOR is so severe that there is only one embryo to transfer on day 3. For women aged 43-46 the live delivered pregnancy rates are <2% per transfer, but interestingly they were the same in women aged 45-46 (average 45.9) vs. those 43-44 (average 43.9).

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OBJECTIVE: To determine the predictive value of discordant (FSH) and anti-Müllerian hormone (AMH) levels on blastocyst yield and ploidy results during in-vitro fertilization cycles.

DESIGN: Retrospective, cohort analysis of a large database at a single IVF center. Primary outcome: euploid blastocyst yield. Secondary outcomes: number of mature oocytes retrieved, number of fertilized oocytes, total number of usable blastocysts (prior to genetic screening).

MATERIALS AND METHODS: A retrospective cohort of patients who underwent ovarian stimulation and oocyte retrieval followed by trophoblast biopsy for pre-implantation genetic screening from 2012 to the present. The patients were divided into four groups based on their FSH and AMH levels: normal FSH and normal AMH (group A); elevated FSH and normal AMH (group B); normal FSH and decreased AMH (group C); and elevated FSH and decreased AMH (group D). The cutoff values were 12 IU/L for FSH and 1.5 ng/mL for AMH. Outcomes were quantified and compared using ANOVA, with a p-value significance threshold of 0.05. Linear regression was employed to investigate covariates which may have impacted outcome. The most parsimonious model was selected to compare the impact of AMH/FSH levels on the average rate of embryo euploidy when controlling for age.

RESULTS: Of the 3898 patients, 2486 were assigned to group A, 49 to group B, 1137 to group C, and 226 to group D. Average mature oocytes retrieved per cycle were 14.6 ±8.2 in group A, 8.8 ±4.1 in group B, 7.5 ±4.4 in group C, and 4.9 in group D (p<0.01). A significant difference in fertilization paralleled the above findings (p<0.01). The percentage of usable blasts were similar for groups B and C but were significant for all other comparisons (p=0.04, P<0.01). In the adjusted linear regression, both groups with an elevated FSH level (B and D) had a lower rate of euploid blastocysts in comparison to group A, no difference was seen in group C. This suggests that FSH is a better predictor of the likelihood of obtaining a euploid blastocyst.

CONCLUSIONS: Values of a low AMH and high FSH are well correlated with diminished ovarian reserve. This is the first study to look at discordant AMH/FSH values as a predictor of embryologic parameters. This data suggests that in patients with discordant values a high FSH is a better predictor of the diminished likelihood of obtaining a euploid blastocyst. This information may be helpful in counseling patients with diminished ovarian reserve in the prediction of a successful outcome.

P-541 Wednesday, October 10, 2018 6:30 AM

ANTIMULLERIAN HORMONE (AMH): HOW HIGH IS TOO HIGH? A 2012-2014 NATIONAL STUDY. K. S. Acharya, B. S. Harris, T. Truong, R. Lerebours, C. F. Pieper, J. L. Eaton. Division of Reproductive Endocrinology and Infertility, Duke University, Durham, NC; Department of Biostatistics & Bioinformatics, Duke University Medical Center, Durham, NC.

OBJECTIVE: Serum antimullerian hormone (AMH) is positively correlated with oocyte yield among women undergoing controlled ovarian hyperstimulation for in vitro fertilization (IVF). However, elevated serum AMH may contribute to abnormal follicular development and decreased implantation rates.1, 2 There is a paucity of data for women with severely elevated, or “ultrahigh,” AMH.2, 3 The objective of our study was to assess the association between ultrahigh AMH and live birth among women undergoing IVF.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: We utilized the Society for Assisted Reproductive Technologies-Clinical Outcomes Reporting System (SART-CORS) 2012-2014 data to identify all first, fresh, autologous IVF cycles with AMH ≥ 5.0 ng/ml, subdividing patients into those with “elevated” AMH (5.0-9.99 ng/ml) and those with “ultrahigh” AMH (≥ 10 ng/ml). Exclusion criteria were age >44 and preimplantation genetic testing. Differences between the groups were compared using the Student’s t-test or Wilcoxon rank sum test for continuous variables, or the Chi-square test for categorical variables. Logistic regression was used to test the effect of ultrahigh AMH on live birth rate while adjusting for age, race, BMI, parity, infertility diagnosis, smoking status, FSH dose, intracytoplasmic sperm injection
(ICSI), assisted hatching, number of embryos transferred, and blastocyst transfer. A subgroup analysis of patients with polycystic ovary syndrome (PCOS) as their only infertility diagnosis was performed using the same model.

RESULTS: Our cohort included 8,430 patient cycles with elevated AMH and 2,186 patient cycles with ultrahigh AMH. Compared with women with elevated AMH, women with ultrahigh AMH were younger (31.1 vs 31.9 years, P < 0.0001), more likely to be nulliparous (86.6% vs 83.2%, P < 0.0002), and were almost twice as likely to carry the diagnosis of PCOS (67.5% vs 37.5%, P < 0.0001). Women with ultrahigh AMH required less gonadotropins (1,688 vs 1,950 IU, P < 0.0001) and had more oocytes retrieved (20 vs 18, P < 0.0001), but they had higher rates of cycle cancellation due to concern for OHSS, and they have significantly lower outcomes with this procedure was listed in Table 1.

CONCLUSIONS: Compared with women with elevated AMH, women with ultrahigh AMH (≥ 10 ng/ml) are more likely to carry the diagnosis of PCOS. Ultrahigh AMH patients require less gonadotropin stimulation and have a higher oocyte yield; however, they are more likely to have cycle cancellation due to concern for OHSS, and they have significantly lower odds of live birth. We conclude that with elevated AMH, more is not always better for patient outcomes.

References:

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SUCCESSFUL DRUG-FREE IVA (IN VITRO ACTIVATION) APPROACH WITH LAPAROSCOPY TO INCREASE VIABLE EMBRYOS IN POOR RESPONDER (POR) PATIENTS. A. Tanaka,a M. Nagayoshi,a I. Tanaka,a T. Yamaguchi,a T. Ichiyama,a M. Ohno,b M. Shimada,b K. Kawamura. aSaint Mother Hospital, Kitakyushu, Japan; bHiroshima University Graduate School of Biosphere Sciences, Higashi-Hiroshima, Japan; cInternational University Health and Welfare School of Medicine, Narita, Japan.

OBJECTIVE: The success of IVF treatment in poor responder (POR) patients is low due to decreases in the number of retrieved oocytes. A recent study demonstrated that suppression of Hippo signaling in somatic cells of ovarian follicles induced secondary follicle growth, resulting in successful follicle growth in patients with primary ovarian insufficiency though in vitro activation (IVA). The aim of this study is to improve clinical outcome of IVF treatment in POR patients through induction of secondary follicle growth leading to increases in number of viable embryos by Drug-free IVA.

DESIGN: Prospective cohort study to improve clinical outcome of IVF treatment in POR patients.

MATERIALS AND METHODS: Under ethical approval for clinical study of Drug-free IVA, 79 patients who received written informed consent and met the Bologna criteria were enrolled from February 2016 to December 2017. For Drug-free IVA, we excised partial ovarian tissues from one side of ovary under laparoscopic surgery. The ovarian cortex was dissected into 1-2 mm squares and cultured them overnight to suppress Hippo signaling pathway. After culture, these cubes were auto-transplanted beneath the serosa of Fallopian tubes and ovaries. Simultaneously, we made 7-9 linear cuts on the surface of contralateral side of ovary. After the surgery, patients received ovarian stimulation under short protocol with maintaining normal LH levels (<10 mIU/ml) for oocyte retrieval. The effects of Drug-free IVA were evaluated by counting the number of follicles at oocyte retrieval under trans-vaginal ultrasound monitoring and the number of retrieved oocytes, fertilization rate, cleavage rate, cryopreservation rate, clinical pregnancy rate, and miscarriage rate. The oocytes were allowed to fertilize either cIVF or ICSI and all embryo transfers were performed using freeze-thawed embryos under hormone replacement protocol.

RESULTS: The median age of enrolled patients was 43.6 [38-48].Clinical outcome with this procedure was listed in Table 1.

CONCLUSIONS: The Drug-free IVA increased the number of mature follicles and also tend to increase the quality of oocytes. These data suggest a potential of Drug-free IVA to improve clinical outcome of IVF treatment in POR patients.

P-543 Wednesday, October 10, 2018 6:30 AM
MIDKINE CAN BE EVALUATED AS A NEW OVARIAN RESERVE MARKER AT POLYCYSTIC OVARY SYNDROME CASES EXCEPT FOR UNEXPLAINED INFERTILITY CASES. M. Erguvan a T. Irez, b Istanbul Aydın University, Istanbul, Turkey; cHistology&Embryology, Biruni University Medical Faculty, Istanbul, Turkey.

OBJECTIVE: The purpose of this study was to evaluate the levels of midkine (MK), a growth factor with a cytokine role, as a new biomarker for predicting ovarian reserve with the Anti-Müllerian Hormone (AMH) in patients with polycystic ovary syndrome (PCOS) and underwent ICSI procedures.

DESIGN: A prospective, multicentered clinical study.

MATERIALS AND METHODS: The study prospectively included 120 patients (aged 22-43 years; the UI group, n = 60; the control group (fertile women), n = 60; the PCOS group, n = 60) who underwent ICSI process. Serum levels of MK and the hormones FSH, LH, E2, PRL, AMH were measured on the 3rd day of menstrual cycle.

RESULTS: Mean values of hormones and MK levels for the control group were FSH 6.0 mIU/ml (p < 0.05), LH 6.0 mIU/ml (p < 0.05), E2 41.8 pg/ml (p < 0.05), AMH 2.99 ng/ml (p < 0.05) and MK 250 pg/ml (The cut-off value, p < 0.05). MK oocyte and the fertilisation rates for UI were found 75 % and 93 %, respectively. These values for UI were FSH 6.0 mIU/ml (p > 0.05), LH 2.99 mIU/ml (p > 0.05), E2 41.8 pg/ml (p > 0.05), PRL 15.46 ng/ml (p > 0.05), AMH 2.99 ng/ml (p > 0.05) and MK 250 pg/ml (The cut-off value, p > 0.05). MK oocyte and the fertilisation rates for UI were detected 62 % and 80 %, respectively.

Table 1Clinical outcome following laparoscopically modified in vitro activation

<table>
<thead>
<tr>
<th>Patients (n=79)</th>
<th>Average number of follicles at oocyte retrieval</th>
<th>Average number of retrieved oocytes</th>
<th>Fertilization rate (%)</th>
<th>Cleavage rate (%)</th>
<th>Cryopreservation rate (%)</th>
<th>Clinical pregnancy rate (%)</th>
<th>Miscarriage rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pre-op (240 cycles)</td>
<td>1.45ᵃ</td>
<td>1.39</td>
<td>58.3% (130/223)</td>
<td>57.0% (127/223)</td>
<td>63.9% (159/249)</td>
<td>19.7% (25/127)</td>
<td>3.7% (1/27)</td>
</tr>
<tr>
<td>post-op (226 cycles)</td>
<td>1.79ᵇ</td>
<td>1.54</td>
<td>64.7% (161/249)</td>
<td>13.8% (22/159)</td>
<td>18.4% (7/38)</td>
<td>42.9% (3/7)</td>
<td></td>
</tr>
</tbody>
</table>

(a-a': p<0.05, t-test)

FERTILITY & STERILITY®
For the PCOS group, these were FSH 5.7 mIU/ml (p < 0.05), LH 6.5 mIU/ml (p < 0.0001), E2 43.8 pg/ml (p < 0.05), PRL 15.47 ng/ml (p > 0.05), AMH 5.89 ng/ml (p < 0.0000) and MK 423 pg/ml (The cut-off value; p < 0.0000). MI oocyte and the fertilisation rates for PCOS were detected 46% (p < 0.00001) and 53% (p < 0.0000), respectively.

CONCLUSIONS: Midkine can be evaluated as a new ovarian reserve marker at the PCOS cases except for the UI cases. MK levels were proportionally changed with AMH levels.

P-544 Wednesday, October 10, 2018 6:30 AM

IS ANTI-MULLERIAN HORMONE A MARKER FOR CARDIO-METABOLIC HEALTH IN REPRODUCTIVE AGE EUENORRHEIC WOMEN? J. Sroga-Rios,1 E. Greenwood,1 H. Huddleston,1 M. Cedars,1 M. Diamond,1 H. Zhang,1 N. Santoro,1 M. Pavone,1 Obstetrics and Gynecology, University of Cincinnati College of Medicine, West Chester, OH; Obstetrics, Gynecology & Reproductive Sciences, UCSF, San Francisco, CA; Obstetrics and Gynecology, University of California San Francisco, San Francisco, CA; University of California San Francisco Center for Reproductive Health, San Francisco, CA.

OBJECTIVE: Menopause is associated with increased risk of cardiovascular disease however the relationship between reproductive and cardiometabolic aging is unclear. Our objective is to determine if anti-mullerian hormone (AMH), antral follicle count (AFC) and AMH/AFC ratio are markers of cardio-metabolic disease in reproductive age women with and without infertility. DESIGN: Cross sectional cohort study in eumenorrheic women age 25-40 from two independent populations including a secondary analysis of 870 infertile women who participated in the AMIGOS (AMIG) trial and 951 regular-cycling community controls (OVA).

MATERIALS AND METHODS: Women (ages 25-40) were enrolled into either study population and baseline demographics, ovarian reserve markers (AMH and AFC), and cardio-metabolic measures (CMM) were collected including body mass index (BMI), waist circumference (WC), blood pressure (BP) (AMG only), fasting glucose and insulin, lipids, and C reactive protein. We performed a multivariable linear regression to investigate the association of between ovarian reserve markers and CMM.

RESULTS: Several CMM were found to be negatively associated with AMH and AMH/AFC in the OVA population including BMI, WC, insulin, homeostasis model assessment-insulin resistance (HOMA-IR) and there was a positive association with high density lipids (HDL) and AMH/AFC (Table 1). Only BMI was negatively associated with AMH in the AMG cohort while AFC was not associated with any metabolic features in either group. Adjusting for BMI removed all AMH-CMM associations in the OVA group but in the AMG cohort increased diastolic BP was associated higher AMH (0.30, p < 0.03).

CONCLUSIONS: Cross-sectional evidence suggests that a less favorable cardio-metabolic risk profile is mainly mediated by BMI rather than AMH in regularly cycling women despite infertility status. BMI appears to directly impact AMH since no association was seen on AFC. Future longitudinal studies are needed in order to determine relationship between AMH and BMI and the development of cardiovascular disease.

Supported by: R25HD075377, 3U10HD055925-02S1, 5U10HD055925, 3U10HD039005-08S1, 5U10HD039005, ARRA, R01HD044876

OVARIAN RESERVE STATUS AND CARDIOVASCULAR FUNCTION IN WOMEN AFTER A HYPERTENSIVE COMPLICATED PREGNANCY. L. M. Jorissen1, D. A. Pattni2, J. A. Bons3, O. Valkenburg4, M. E. Spanjerd2, R. V. Golde1. 1Reproductive Medicine, Maastricht University Medical Centre, Maastricht, Netherlands; 2Central Diagnostic Laboratory, Maastricht University Medical Centre, Maastricht, Netherlands; Obstetrics and Gynaecology, Maastricht University Medical Centre, Maastricht, Netherlands; 3Obstetrics and Gynecology, Maastricht, Netherlands; 4Obstetrics and Gynecology, Maastricht, Netherlands.

OBJECTIVE: There is evidence for a close relation between markers of vascular (dys)function and ovarian reserve status. Also, pre-existent vascular dysfunction is highly associated with the occurrence of preeclampsia (PE) during pregnancy. Therefore, it is speculated that cardiovascular dysfunction may be similarly involved in processes that regulate depletion of the ovarian follicle pool and the occurrence of PE. The objective of the present study is to evaluate ovarian reserve status and markers of vascular function among women with a history of PE.

DESIGN: This was a hospital-based observational cohort study, conducted at a tertiary referral center at the Maastricht University Medical Center in The Netherlands.

MATERIALS AND METHODS: The study group consisted of 162 women with a history of hypertensive disease during pregnancy (gestational hypertension, preeclampsia and/or HELLP-syndrome). Controls constituted 80 healthy women with previous uncomplicated pregnancies. Both groups were included at least six months postpartum. Exclusion criteria were a current pregnancy, breastfeeding, hormonal medication and/or a history of ovarian surgery. Primary and secondary outcome parameters were serum AMH level, vascular function parameters i.e., body mass index (BMI), blood pressure (BP) and fasting serum levels of insulin, glucose and lipid profile. Baseline characteristics, ovarian reserve status and vascular function parameters were compared between both groups by Student t-test or Mann-Whitney U test. Linear regression analysis using log-transformation was used to adjust for known confounders, such as age.

RESULTS: Median serum AMH levels were 20% higher among patients vs. controls (respectively 2.40±3.20 µg/L and 2.00±2.90 µg/L). Univariate analysis showed no significant difference in AMH levels between both groups. Cardiovascular function parameters were significantly higher in the patient group vs. controls, systolic BP 4%, diastolic BP 5%, triglycerides 32%, glucose 4% and insulin levels 99%, whereas HDL cholesterol was 6% lower in patients.

CONCLUSIONS: PE cases were clearly associated with unfavorable changes in cardiovascular function and lipid parameters. However, no difference in ovarian reserve status was observed between the study group and control group.

Linear regression models for CMM and ovarian reserve markers, adjusted for age and site

<table>
<thead>
<tr>
<th>AMH: Coefficient (p-value)</th>
<th>AFC: Coefficient (p-value)</th>
<th>AMH/AFC: Coefficient (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AMH</td>
<td>AMH</td>
</tr>
<tr>
<td></td>
<td>AMG</td>
<td>OVA</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>-0.27 (0.02)</td>
<td>-0.42 (&lt; 0.001)</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>-0.31 (0.27)</td>
<td>-0.98 (&lt; 0.001)</td>
</tr>
<tr>
<td>Fasting insulin (mg/dL)</td>
<td>-0.20 (0.45)</td>
<td>-0.17 (0.02)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>-0.06 (.33)</td>
<td>-0.05 (0.02)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>0.11 (0.37)</td>
<td>0.38 (0.05)</td>
</tr>
</tbody>
</table>
trols. Therefore, we observe no evidence for the hypothesis that cardiovascu-
lar dysfunction might also contribute to accelerated depletion of the ovarian
follicle pool.

References: No references cited in the abstract.

P-546 Wednesday, October 10, 2018 6:30 AM

ASSOCIATION BETWEEN HISTORY OF DEPRESSION AND ANTI-MULLERIAN HORMONE AMONG LATE REPRODUCTIVE-AGED WOMEN. S. W. Golenbock, a L. A. Wise, a G. M. Lambert-Messerlian, a E. E. Eklund, a B. L. Harlow. aDepartment of Epidemiology, Boston University School of Public Health, Boston, MA; aDepartment of Pathology and Laboratory Medicine, Alpert Medical School at Brown University, Providence, RI.

OBJECTIVE: We investigated the association between a history of depression and ovarian reserve, as measured by anti-mullerian hormone (AMH), among premenopausal women.

DESIGN: The Harvard Study of Moods and Cycles (HSMC) was a prospective cohort study of women aged 36-45 years living in the Boston, MA metropolitan area (1995-1999). The aims were to examine associations between a history of depression and ovarian reserve. Early follicular phase blood specimens were collected at baseline and every 6 months for 36 months to measure reproductive hormones.

MATERIALS AND METHODS: Participants were sampled from seven Boston metropolitan area communities. Using Structured Clinical Interviews for DSM-IV, 332 of 976 women were classified as having a depression history. From this larger cohort, we performed a cross-sectional analysis among 141 depressed and 228 non-depressed women at baseline. Depression severity was measured using the Hamilton Rating Scale (HAM-D). Serum AMH was measured via the picoAMH kit (Ansh Labs, Webster TX) (sensitivity limit 6 pg/mL). Demographic and lifestyle characteristics were self-reported at baseline. Log-binomial regression was used to calculate prevalence ratios (PR) for the association between depression history and low AMH levels (≤ 1.4ng/mL), while adjusting for age, age at menarche, cycle regularity, oral contraceptive use, parity, body mass index and smoking. We excluded women (n=33) with physician-diagnosed polycystic ovary syndrome (PCOS) and AMH levels above 5.0 ng/mL (a marker of subclinical PCOS).

RESULTS: The prevalence of low AMH was similar for depressed (57.5%) and non-depressed (57.9%) women. Depression history showed a modest inverse association with low AMH (PR=0.90, 95%CI: 0.75, 1.08). Results were similar for depressed women who ever used antidepressants and depressed women with comorbid anxiety. A slightly stronger inverse association was seen among depressed women with lower HAM-D scores (< 8) (PR=0.81, 95%CI: 0.59, 1.11) and with later depression onset (age ≥30: PR=0.81, 95%CI: 0.61, 1.09). Stronger associations were seen among women aged 36-45 years (PR=0.75, 95%CI: 0.52, 1.09) than women aged 41-45 years (PR=1.16, 95%CI: 0.59, 1.40), and among nulliparous women (PR=0.77, 95%CI: 0.59, 1.00).

CONCLUSIONS: In a cohort of premenopausal women, those with a history of depression had a slightly reduced risk of low AMH. The inverse association appeared stronger among younger and nulliparous women, but a dose-response association with depression severity was not evident. Interpretation of findings remains difficult due to the cross-sectional nature of the analysis, low numbers of women in analyses of depression severity, and the differences in effect by age.

Supported by: The Harvard Study of Moods and Cycles was supported by NIH Grants R01-MH50013 and R01-MH69732. We thank Ansh Labs for the generous provision of assay reagents.

P-547 Wednesday, October 10, 2018 6:30 AM

THE TELOMERE LENGTH OF LEUKOCYTES AND CUMULUS CELLS ARE NOT DIFFERENT BETWEEN POOR RESPONDERS AND GOOD RESPONDERS TO CONTROLLED OVARIAN HYPERSTIMULATION FOR IVF. S. Morin, a D. Marin, a X. Tao, c J. Landis, d R. Scott, b E. Seli, a TVI RMA New Jersey, Basking Ridge, NJ; a Thomas Jefferson University, Basking Ridge, NJ; b Reproductive Medicine Associates of New Jersey, Basking Ridge, NJ, c Foundation for Embryonic Competence, Basking Ridge, NJ, d Yale School of Medicine, New Haven, CT.

OBJECTIVE: Decreasing telomere length (TL) has been proposed as a mechanism to explain reproductive aging. Indeed, leukocyte telomere length (LTL) has been correlated with the duration of the reproductive lifespan from menarche to menopause. Furthermore, cumulus cell telo-
meres length (CCTL) has been proposed as a biomarker for oocyte and embryo quality in ART cycles. However, there are no current studies that analyze the relationship between TL and response to controlled ovarian stimulation in an IVF cycle. In this study, we aimed to determine: 1) whether patients with abnormal response to stimulation exhibited different LTL or CCTL compared to patients with age appropriate response. and 2) whether TL differed between leukocytes and cumulus cells from the same patient.

DESIGN: Prospective Cohort

MATERIALS AND METHODS: Patients in one of the following four categories were recruited for inclusion: Group A) < 35 yo with good response (> = 15 follicles maturing 15mm [mature foll] on day of trigger), Group B) < 35 yo with poor response (< 5 mature foll), Group C) > 40 yo with poor response (< 4 mature foll), and Group D) > 40 yo with good response (> = 12 mature foll). Blood and CC were collected at time of oocyte retrieval and genomic DNA was isolated and stored at -80 C. Telomere DNA quantity was measured by a quantitative real time PCR method. The AluYa5 gene was targeted as endogenous control in all samples. CCTL and LTL comparisons were made between good and poor responders in each age group (Group A vs. B and C vs. D, respectively). CCTL was also compared to LTL in all age groups. Analysis was performed via T-tests and Wilcoxon-Mann-Whitney tests where appropriate.

RESULTS: A total of 77 patients enrolled in the study. All patients had sufficient quantities of leukocyte DNA for analysis. Fourteen of the pooled cumulus samples were unable to be analyzed due to poor DNA yield. The CCTL and LTL were no different between patients with good response to stimulation and patients with poor response to stimulation in both the < 35 year old group (CC Fold Change: 0.86 +/- 0.35, p = 0.22; L Fold Change: 0.88, +/- 0.3 p = 0.14) and > 40 year old group (CC Fold Change: 1.03 +/- 0.21, p = 0.1385; L Fold Change: 1.01 +/- 0.32, p = 0.94). In the 66 patients with evaluable samples in each sample type, telomeres were significantly longer in CC than leukocytes in white blood cells, with a mean 2.16 fold change (+/-0.2, p < 0.0001).

CONCLUSIONS: Neither CC or leukocyte telomere length is correlated with response to ovarian stimulation. While telomeres may play a role in the reproductive aging process, CCTL and TL do not appear to influence the pool of gonadotropin responsive follicles in an ART cycle. Interestingly, CC appear to feature longer telomeres than leukocytes. This is consistent with findings from prior findings by our group that the methylation profile of CC is younger than chronologic age would predict in other somatic cells.

References:

Supported by: Foundation for Embryonic Competence
OVARIAN STIMULATION

P-548 Wednesday, October 10, 2018 6:30 AM

CAN ANTI-MÜLLERIAN HORMONE (AMH) PREDICT THE OUTCOME OF GONADOTROPIN INDUCTION/INTRAUTERINE INSEMINATION (GN/IUI) CYCLES AMONG INFERTILE WOMEN? G. Christou, I. Dimitriadis, J. Y. Hu, K. James, C. L. Bormann, I. Souter, Massachusetts General Hospital, Boston, MA; OB/GYN, Massachusetts General Hospital-Harvard Medical School, Boston, MA; Harvard Medical School-Massachusetts General Hospital Fertility Center, Boston, MA.

OBJECTIVE: To evaluate the ability of AMH to predict treatment outcomes among infertile women undergoing Gn/IUI, given emerging evidence suggesting otherwise among women of normal fertility[1].

MATERIALS AND METHODS: Sample size/Intervention: 1110 Gn/IUI cycles (from 503 women) at a large academic center were analyzed (11/2007-10/2017). Cycles were stratified by AMH serum concentration cut-offs, based on previously published literature: low (<0.7 ng/ml, n=273) and normal (≥0.7 ng/ml, n=837). Outcomes measures: Cumulative probability of achieving (i) positive pregnancy test (PPr) and (ii) clinical pregnancy (CPr) over a maximum of 4 completed cycles per attempt. Statistics: Pearson’s χ², t-test, or nonparametric tests were used as appropriate. Cumulative probabilities of achieving the outcomes of interest were determined via the Kaplan-Meier failure function. Cox proportional hazard models (adjusted for age and BMI) were used to determine fecundability ratios (FR) for each AMH group. P<0.05 was considered significant.

RESULTS: As expected, mean (SD) age, day-3 FSH, total gonadotropin dose, and duration of stimulation were different between groups: 37.5 (3.8) vs. 35.3 (3.9) years, p<0.01; 10.2 (5.1) vs. 7.0 (2.3) IU/L, p<0.01; 1836.5 (1541.1) vs. 750.8 (582.2) IU, p<0.01; and 10.2 (5.1) vs. 12.2 (4.4) days, p<0.01, for low vs. normal AMH groups, respectively. Conversely, BMI (25.3 [5.1] vs. 24.1 [5.1]) kg/m², p=0.17 and peak estradiol (508.1 [237.6] vs. 462.5 [286.4] pg/ml, p=0.15) did not differ significantly. Women with AMH <0.7 ng/ml were more likely to have either a PPr or CPr with an unadjusted cumulative probability (95%CI) of 31.4% (20.4-46.4) vs. 46.3% (37.4-56.3), p<0.005, and 19.9% (11.6-32.7) vs. 29.3% (21.9-38.3), p=0.017, for low vs. normal AMH groups, respectively. Following the same trend, the estimated adjusted FRs revealed that women with AMH <0.7 ng/ml were more likely to have a PPr (adjusted FR: 1.52, 95%CI: 0.99-2.35) and CPr (adjusted FR: 1.47, 95%CI:1.92-2.35). Similarly, when further stratified to low (<0.7 ng/ml), normal (0.7-8.4 ng/ml) and high (≥8.5 ng/ml) AMH groups, women with AMH ≥8.5 ng/ml were more likely to have a PPr (adjusted FR: 1.90, 95%CI:1.09-3.28) and CPr (adjusted FR: 1.76, 95%CI: 0.96-3.20) when compared to women with AMH <0.7 ng/ml.

CONCLUSIONS: Despite the recent evidence that low AMH in a population of fertile women was not associated with reduced fecundability, our findings suggest that among infertile women undergoing Gn/IUI cycles, lower AMH might be associated with lower probability of a successful treatment outcome.

References:

Supported by: None.

P-550 Wednesday, October 10, 2018 6:30 AM

A COMPARISON OF BLASTOCYST FORMATION BETWEEN JAPANESE AND WHITE VOLUNTARY EGG DONORS. H. Chen, E. Wu, N. Besic, H. Ahn, V. Y. Fujimoto, T. Kosasa, T. Huang, B. Kessel. Department of OB/GYN, University of Hawaii, Honolulu, HI; University of Hawaii, John A. Burns School of Medicine, Honolulu, HI; N/A, Waipahu, HI; Complementary and Integrative Medicine, University of Hawaii John A. Burns School of Medicine, Honolulu, HI; UCSF, San Francisco, CA; Division of Reproductive Endocrinology, University of Hawaii School of Medicine, Honolulu, HI; OB/GYN, Honolulu, HI; University Of Hawaii, Honolulu, HI.

OBJECTIVE: Some studies indicate lower autologous IVF success rates in Asian vs White women. If this is true, the underlying etiology is unclear. We chose to compare rates of blastocyst formation between Japanese and White young, healthy voluntary egg donors to seek explanations for lower IVF success rates in Asian women.

DESIGN: Japanese and White voluntary egg donors underwent gonadotropin stimulation followed by egg retrieval. The rates of high quality blastocysts were compared between the groups.

MATERIALS AND METHODS: Japanese and White voluntary egg donors donated gonadotropin stimulation based on age and basal follicle count. GnRH antagonist was initiated with a lead follicle of 15mm. Final oocyte retrieval occurred 36 hours later and mature oocytes were fertilized by intracytoplasmic sperm injection. The mature fertilized oocytes were graded on Day 5 and 6. Blastocyst grading was made using a scoring system, in which high quality blastocysts were expanded blastocysts at grade 4+, and inner cell mass and trophectoderm at grade A or B.

RESULTS: The mean age of Japanese egg donors (n=101) was 26.0, and the mean age of White egg donors (n=53) was 24.5 (p=0.0002). The groups were similar with regard to gravidity, parity, prior miscarriage, or abortion. BMI was not significantly different. Estradiol on day of trigger was higher in Japanese donors (p=0.0127). The primary end point of number of high quality blastocysts per cycle (Japanese 7.3 vs. White 8.6, p=0.093) was not significantly different. Similarly, number of high quality blastocysts

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Oocyte Donor Cycle Outcomes (mean values)

<table>
<thead>
<tr>
<th></th>
<th>Japanese</th>
<th>White</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Oocytes</td>
<td>21.9</td>
<td>24.2</td>
<td>0.2210</td>
</tr>
<tr>
<td>Total Mature Oocytes</td>
<td>18.0</td>
<td>19.5</td>
<td>0.3357</td>
</tr>
<tr>
<td>Oocytes Fertilized</td>
<td>13.9</td>
<td>15.8</td>
<td>0.1440</td>
</tr>
<tr>
<td>High Quality Blastocysts/cycle</td>
<td>7.3</td>
<td>8.6</td>
<td>0.0930</td>
</tr>
<tr>
<td>High Quality Blastocysts/mature oocyte</td>
<td>0.4</td>
<td>0.4</td>
<td>0.3017</td>
</tr>
<tr>
<td>High Quality Blastocysts/fertilized oocyte</td>
<td>0.5</td>
<td>0.6</td>
<td>0.6440</td>
</tr>
</tbody>
</table>

per mature oocyte and per fertilized oocyte were not statistically different between Japanese and White donors. Multivariate analysis correcting for age, gonadotropin dose, estradiol, and number of embryos transferred, showed similar results. Clinical pregnancy rates of recipients were also not statistically different between Japanese and White recipients.

CONCLUSIONS: Formation of high quality blastocysts occurs at the same rate in Japanese vs White voluntary egg donors. This suggests that the lower autologous IVF success rates in Japanese women is not related to oocyte, fertilization, or embryo development.

References:

**P-551 Wednesday, October 10, 2018 6:30 AM**

**IS THERE A JUSTIFICATION FOR AN EXTRA STIMULATION DOSE THE DAY OF MATURATION TRIGGERING IF TRIGGERING IS GOING TO HAPPEN LATE IN THE DAY?**

OBJECTIVE: Spontaneous ovulation is preceded by a surge of both FSH and LH. This combined gonadotropin surge is thought to be necessary for final oocyte nuclear maturation (meiosis) and initiation of follicular rupture. In an IVF stimulation cycle, trigger medication is administered 36 hours before oocyte retrieval to simulate the LH surge and promote final oocyte maturation. Yet, the last stimulation dose of FSH may be given before oocyte retrieval to simulate the LH surge and promote final oocyte maturation.

In an IVF stimulation cycle, trigger medication is administered 36 hours after the last stimulation dose. After comparing stimulation response and laboratory parameters, there is no evidence to suggest that late trigger impacts ovarian stimulation outcome.

Supported by: None.

**P-552 Wednesday, October 10, 2018 6:30 AM**

**ULTRASONOGRAPHICALLY DIAGNOSED DERMOID CYSTS DO NOT INFLUENCE OVARIAN STIMULATION RESPONSE IN IVF.**

OBJECTIVE: Dermoid cysts (DC) are the most common ovarian germ cell tumor (OGCT) in reproductive age. Because OGCTs derive from the primordial germ cells of the ovary, it is essential to recognize whether a DC impacts controlled ovarian stimulation (COS) during IVF

DESIGN: Retrospective

MATERIALS AND METHODS: Infertility patients with a DC diagnosed by ultrasound that underwent IVF between Jan 09-Dec 16 were included. A cystic mass with mixed echogenicity, internal echoes similar to thick bands, fatty-fluid level or an echogenic tubercle with anecic shadow (Rokitansky nodule) within 2 years of the cycle characterized the diagnosis. To compare COS response to a “normal” population mean, a nomogram (expected oocytes minus oocytes obtained divided by the standard deviation), adjusted for age and oocytes retrieved, was used. When utilizing 1520 cycles, the mean number of total oocytes (8.6±8.5 vs. 8.5±7.7, p=0.43) and MIIs (6.7±4.7 vs. 7.0±6.7, p=0.74) retrieved were similar between groups. When cycles with and without a DC were compared to the nomogram (z-score of 0), cycles with a DC presented a z-score for ovarian response of -0.1921 SDs from the mean, and patients without DC presented a z-score difference from a reference proportion of 80% in fertilization rate with 80% power (alpha=0.05).

RESULTS: Patients in the 8h-10h group (n=1033) and in the ≥13h pm group (n=176) were identified. Age (38.7±4.1 vs. 38.9±4.1), BMI (23.2±3.9 vs. 22.9±3.8), AMH (1.0±1.2 vs. 1.4±1.7), starting dose (217.1±117.9 vs. 210.2±117.2), days of stimulation (10.7±2.1 vs. 10.9±1.5) and total GND dose (2860.7±1247.2 vs. 2706.9±958.1) were similar between groups. All variables observed statistically significant (shown in table 1) were included in a logistic regression model. After adjusting for AFC, peak estradiol, follicles at trigger, oocytes retrieved and MIIs in the model, there was no difference between groups if the retrieval was performed after 1pm when compared to before 10am.

CONCLUSIONS: Concern was raised for patients triggered more than 24 hours after the last stimulation dose. After comparing stimulation response and laboratory parameters, there is no evidence to suggest that late trigger impacts ovarian stimulation outcome.

Patient Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>37.0±4.2</td>
<td>0.765</td>
</tr>
<tr>
<td>BMI</td>
<td>27.5±11.1</td>
<td>0.257</td>
</tr>
<tr>
<td>AMH</td>
<td>1.5±1.8</td>
<td>0.341</td>
</tr>
<tr>
<td>AFC</td>
<td>10.9±6.8</td>
<td>0.569</td>
</tr>
<tr>
<td>Stimulation Days</td>
<td>10.9±2.8</td>
<td>0.857</td>
</tr>
<tr>
<td>Stimulation Dose</td>
<td>2598.8±1160.3</td>
<td>0.766</td>
</tr>
<tr>
<td>Estradiol at trigger</td>
<td>2042.9±1139.9</td>
<td>0.641</td>
</tr>
<tr>
<td>Oocytes Retrieved</td>
<td>8.6±5.8</td>
<td>0.428</td>
</tr>
<tr>
<td>MIIs</td>
<td>6.7±4.7</td>
<td>0.736</td>
</tr>
<tr>
<td>Follicle Output Rate</td>
<td>83.0% (77.6-88.5)</td>
<td>0.636</td>
</tr>
</tbody>
</table>

Supported by: None.
endoplasmic reticulum cluster, and zona pellucida abnormalities have been observed. Antagonist cycles had significantly lower incidence of dark cytoplasm when undergoing IVF. Questions arise to whether remove the cyst before COS vs. the impact of surgery on ovarian reserve. After building a population “normal” response as a template, patients with and without a DC responded similarly to COS. Patients can be reassured that the presence of a DC does not impact negatively the outcome of their cycle.

OBJECTIVE: To study the effect of the pituitary suppression regimen - GnRH agonist or antagonist - on oocyte morphology and ovarian response to controlled ovarian stimulation (COS) in consecutive intracytoplasmic sperm injection (ICSI) cycles.

RESULTS: Mean interval between cycles was 235.78 ± 323.9 days. Maternal age, BMI and total dose of FSH administered were similar in both patients’ cycles. The type of GnRH analogue did not influence the estradiol level on hCG trigger day, number of follicles, number of oocytes, or oocyte yield, however a higher mature oocyte rate was observed in GnRH antagonist cycles (81.35 ± 2.21% vs. 74.73 ± 2.82% p = 0.039). GnRH antagonist cycles had significantly lower incidence of dark cytoplasm (0.67 ± 1.27% vs. 4.37 ± 1.41%, p = 0.039), smooth endoplasmic reticulum cluster (3.77 ± 1.50% vs. 8.04 ± 1.50%, p = 0.046), and zona pellucida dysmorphisms (4.69 ± 2.77% vs. 12.44 ± 2.52%, p = 0.041).

CONCLUSIONS: Oocyte dysmorphisms, such as dark cytoplasm, smooth endoplasmic reticulum cluster, and zona pellucida abnormalities have been previously associated with impaired embryo development and implantation potential. Our findings suggest that the GnRH antagonist inhibitory effect on the ovaries in consecutive ICSI cycles results in optimized ovarian function, represented by improved oocyte maturity and morphology, which may lead to a more favorable treatment outcome.

References:
4. J. Zuzuarregui, S. Iliodromiti, S. M. Nelson. "Human Reproduction, IVI-RMA Valencia, Valencia, Spain; 0Obstetrics and Gynaecology, University of Glasgow, Glasgow, United Kingdom; "School of Medicine, University of Glasgow, Glasgow, United Kingdom.

OBJECTIVE: To define the predictive capability of ovarian response of an automated AMH assay (Elecys®) in GnRH antagonist cycles performed with a GnRH antagonist protocol between January 2015 and January 2017, in women in which serum AMH was determined within 6 months before stimulation with the Elecsys® automated assay.

MATERIALS AND METHODS: A cohort of 1248 women aged 18-48, undergoing 1448 ovarian stimulation cycles for IVF (n=1119), fertility preservation (n=252) or oocyte donation (n=77) in a private infertility center. Serum AMH was determined in house with a fully-automated platform based AMH assay (Elecys®) within 6 months before treatment. Ovarian stimulation was performed in all cases with a GnRH antagonist protocol, and a customized dose according to doctor’s judgment of recombinant FSH, HMG, or a combination of both.

RESULTS: Patients’ age was 36.4±5.0 and the mean ovarian response was 11.0±5.0 oocytes. From 1448 cycles, 270 (18.6%) were low responders (0-3 oocytes), 539 (37.2%) were suboptimal (4-9 oocytes), 341 (23.5%) had an optimal response (10-15 oocytes), and 298 (20.6%) were high responders (>15 oocytes). AMH was correlated with the number of oocytes retrieved ( spearman rho = 0.74). The ROC curve analysis of AMH to exclude each ovarian response category showed an AUC (95% CI): of 0.85 (0.83-0.88) for low; 0.67 (0.64-0.69) for suboptimal; 0.66 (0.63-0.69) for optimal, and 0.89 (0.87-0.91) for high response (p<0.001 for all categories). The median (Interquartile range) of AMH for each ovarian response category were: 3.6 (1.7-6.5) for low (1.7-6.5), 7.8 (4.9-12.1) for suboptimal (4.9-12.1), 15.2 (9.5-21.8) for optimal (9.5-21.8), and 27.6 (18.8-41.6) pmol/L for low suboptimal, optimal and high response respectively. Optimal AMH cutpoints for excluding a low, suboptimal or excessive response were 6.4, 13.4 and 14.2 pmol/L respectively. The multivariable regression analysis showed that serum AMH by itself explained 47% (R²=0.470) of the variation of ovarian response. The addition of age, body weight and total dose of gonadotrophins showed a limited impact on the model, as increased this value to 50.9% (R²=0.509).

CONCLUSIONS: The assay shows high capability for the exclusion of a low (≤3 oocytes) and high (>15) ovarian response, and good for suboptimal (4-9) and optimal (10-15) responses. Serum AMH determination with an automated assay allows physicians to counsel properly to patients when planning to undergo ovarian stimulation, as the number of estimated oocytes to be retrieved can be defined with high precision. Decisions regarding prognosis and/or gonadotrophins doses can be based on these findings.
**P-556 Wednesday, October 10, 2018 6:30 AM**


**OBJECTIVE:** It was previously reported that mixed gonadotropin stimulation protocols improve euploidy rates, however this was evaluated using older preimplantation genetic testing (PGT) modalities. We compared euploidy rates in in vitro fertilization (IVF) cycles stimulated with either follicle stimulating hormone (FSH) only or FSH and human menopausal gonadotropin (hMG) utilizing PGT performed exclusively by Next-Generation Sequencing (NGS).

**DESIGN:** Retrospective cohort study

**MATERIALS AND METHODS:** 477 cycles performed at a large university-based center during a three-year period were evaluated. IVF cycles stimulated with either FSH only preparations (n=344) or a mixed protocol containing FSH and hMG preparations (n=133) were included for analysis. PGT was performed by NGS. PGT results were reported as euploid, aneuploid, or not performed. Secondary outcomes included maximum estradiol level, age, BMI, number of oocytes, number of embryos, and clinical pregnancy rate.

**RESULTS:** There were no differences in baseline characteristics between the two groups. Patients who received early hCG supplementation demonstrated no differences in number of oocytes retrieved, number of mature oocytes, or total gonadotropin consumption when compared to those who did not.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Early hCG (n=47)</th>
<th>Placebo (n=44)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>24.4 (2.6)</td>
<td>24.8 (2.8)</td>
<td>0.44</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.7 (3.3)</td>
<td>23.3 (3.0)</td>
<td>0.33</td>
</tr>
<tr>
<td>AMH (ng/ml)</td>
<td>5.3 (2.6)</td>
<td>5.8 (2.9)</td>
<td>0.39</td>
</tr>
<tr>
<td>Gonadotropin</td>
<td>2698 (803)</td>
<td>2661 (767)</td>
<td>0.82</td>
</tr>
<tr>
<td>Consumption (IU)</td>
<td>5401 (2626)</td>
<td>4761 (2041)</td>
<td>0.20</td>
</tr>
<tr>
<td>Maximum estradiol (pg/ml)</td>
<td>26.3 (9.4)</td>
<td>29.7 (15.1)</td>
<td>0.20</td>
</tr>
<tr>
<td>Number of mature oocytes</td>
<td>19.4 (2.3)</td>
<td>19.3 (3.1)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

**CONCLUSIONS:** In oocyte donor ovarian stimulations, early hCG supplementation after 14 days of oral contraceptives in a GnRH antagonist cycle does not increase oocyte yield or decrease gonadotropin consumption.

**References:**

**FERTILITY & STERILITY® e331**
THE PROFILE OF FREE AND EXOSOMAL MiRNAs IN FOLLICULAR FLUID OF OHSS WOMEN. K. Liu D. Zhang. The First Affiliated Hospital, Nanjing Medical University, Nanjing, China.

OBJECTIVE: With the increasing incidence of infertility, the controlled ovarian hyperstimulation (COH) becomes a major method in assisted reproductive technology (ART). Unfortunately, some patients after receiving COH may suffer from the ovarian hyperstimulation syndrome (OHSS). OHSS not only affects the embryonic implantation and development, but also endangers patients’ lives. mRNAs in exosomes can be delivered to other cells and modulate the function of recipient cells. However, the mechanisms underlying the association with exosomal miRNAs and OHSS remain poorly understood. Here we aimed to investigate the profiles of miRNAs in follicular fluid and exosomes of OHSS women, and screen some key miRNAs and the molecular mechanism that may be involved in pathogenesis of OHSS. This study may be helpful for understanding pathophysiology of OHSS and for finding potential therapeutic targets in future.

DESIGN: Patients undergoing IVF for IVF/intercytoplasmic sperm injection (ICSI) from June 2017 to November 2017 were recruited for this study. The patients participating in this study followed a long GnRH agonist protocol. The criteria for OHSS classification defined by Navot et al. Sixty patients with or without OHSS were divided into three groups according to their OHSS grading.

MATERIALS AND METHODS: Follicular fluid samples were collected from the first punctured follicle. Exosomes were obtained by ultracentrifugation. The samples of exosome and follicular fluid were stored respectively. The expression profiles of exosomes miRNAs were tested using Illumina HiSeq 2500 platform.

RESULTS: A total of 526,626 and 672 miRNAs were detected in the severe OHSS group and the mild group when compared with the control group. After RT-qPCR verification, the relative content of the first eight differential high expression miRNAs was consistent with the sequence result. The miRNA-10b-5p, miRNA-423b, miRNA-125a-5p were highly expressed only in severe group. mir-195 was up-regulated in both severe and mild group. miRNA-16 and miRNA-92-3p were only down-regulated in severe group compared with control. MiRNA-21-5p, miRNA-27b-3p were down-regulated in severe and mild group (p < 0.05). Bioinformatic analysis of those miRNAs indicated that their potential target genes were involved in the main pathways including cAMP signaling pathway, calcium signaling pathway and PI3K-Akt signaling pathway.

CONCLUSIONS: Our data provides the expression profiles of exosomal miRNAs in follicular fluid, which may have a potential role in regulating some genes. That may help us to understand more about the mechanism of OHSS.

Efficacy of Interventions to Reduce Risk of Ovarian Hyperstimulation Syndrome. A. Gadson,*, J. A. Politch,*, V. A. Escott,* W. Kuohung,* 1 Boston Medical Center, Boston, MA; 2 Obstetrics and Gynecology, Boston University School of Medicine, Boston, MA; 3 Software Development, Practice Highway.com, Inc., Farmers Branch, TX; 4 Boston University School of Medicine, Boston, MA.

OBJECTIVE: Ovarian hyperstimulation syndrome (OHSS) is a rare but serious complication of IVF. Strategies to reduce the risk of OHSS have been described, including metformin use, triggering oocyte maturation with GnRH agonist (GnRHa), high-dose dopamine agonist administration post-trigger, and freeze-all of embryos. There are no studies comparing the incidence of OHSS in high-risk patients based on multiple risk-reducing interventions, alone or in combination. The objective of this study is to determine the efficacy of different treatments, alone and in combination, in reducing risk in IVF patients at high risk for developing OHSS.

DESIGN: Retrospective case-control study

MATERIALS AND METHODS: Patients aged 35 and younger with PCOS undergoing a first IVF cycle were included from the deidentified eIVF database. Oocyte donors and patients undergoing fertility preservation or PGD/PGS were excluded from analysis. Patient data (age, BMI, gravidity/parity, smoking status), OHSS risk-reducing strategy (metformin use, carbogel use in the absence of hyperprolactinemia, GnRHa trigger, freeze-all of embryos), and cycle data (protocol type, maximum FSH dose, peak estradiol level, number of follicles at trigger, number of oocytes retrieved, number of MII oocytes, number of 2PN embryos) were collected for each patient. Chi square analysis was used to determine the efficacy of various risk reduction methodologies in reducing incidence of OHSS.

RESULTS: A total of 23,309 charts (13,595 with OHSS; 9,203 without OHSS) were included in our initial analysis. Overall OHSS incidence in this cohort was 59.6%. Patients who only received one or two specific risk reducing interventions were extracted from the database and subjected to analysis. Compared to the OHSS incidence of 56.8% in patients in whom no risk-reducing strategy was employed, the OHSS incidence with GnRHa trigger was 45.7% (p < 0.0005), with metformin use was 55.8% (p = 0.06; NS), with post-trigger high-dose carbogel was 76.9% (p < 0.0005), and with embryo freeze-all was 56.7% (p = 0.93; NS). GnRHa trigger combined with one other risk-reducing intervention (GnRHa trigger + carbogel = 67.2% OHSS, GnRHa + metformin = 48.0% OHSS, GnRHa trigger + freeze-all = 60.8% OHSS) did not decrease OHSS incidence more than GnRHa trigger alone (45.7%).

CONCLUSIONS: We found that GnRHa agonist trigger was the sole intervention that significantly reduced the incidence of OHSS in this group of high-risk patients. Combining GnRHa trigger with one other risk-reducing treatment did not improve OHSS outcome over that of GnRHa trigger alone. These findings affirm the primary role of hCG trigger in causing OHSS and suggest that interventions other than GnRHa agonist should be subjected to further prospective studies to confirm efficacy.

Supported by: New England Fertility Society/Practice Highway Honorable Mention Grant

Understanding the Pathophysiology of OHSS: The Role of TGF-B and sENG. E. Minis,* A. Athanasiou,* D. Nasios,* M. Ianni,* S. S. Witkin,* S. D. Spandorfer,* OB/GYN, Weill Cornell Medicine, New York City, NY; 3Department of Obstetrics and Gynecology, Hospital of the University of Pennsylvania, Philadelphia, PA; 4OB/GYN, Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, New York City, NY.

OBJECTIVE: Soluble endoglin (SEng) decreases angiogenesis by binding to pro-angiogenic transforming growth factor beta (TGF-b). It also increases vascular permeability by decreasing the activation of endothelial nitric oxide synthase. Irregular angiogenesis and elevated vascular permeability have been implicated in the pathogenesis of Ovarian Hyperstimulation Syndrome (OHSS). The aim of this study is to investigate the association between serum levels of sENG and TGF-b and the subsequent development of OHSS.

DESIGN: Retrospective case-control study including 21 women who developed OHSS and did not undergo embryo transfer (ET) and 38 women who did not develop OHSS and underwent ET. All patients were considered at risk for OHSS by virtue of having anti-Mullerian hormone (AMH) levels ≥2 ng/ml.

MATERIALS AND METHODS: Sera were collected on day 2 of the IVF cycle, before stimulation, and tested for levels of sENG and TGF-b by ELISA. Subjects were matched for age, body mass index (BMI), number of harvested oocytes and AMH. Associations between the levels of these markers and outcomes were calculated by Student's t-test or Mann-Whitney-U and expressed as mean±SD and median (interquartile range) as appropriate.

RESULTS: There were no significant differences between the two groups regarding age (34±1 vs 32±1 or 34.3 vs 32.2; p = 0.23), BMI (23.5 (21.1-25.5) vs 22.2 (20.3-24.9); kg/m², p = 0.399) and number of harvested oocytes (23.5 (22-29) vs 23 (19-34), p = 0.28). Levels of circulating sENG were significantly higher in women who developed OHSS (34.5±5.2 vs 28.6±6.4 ng/ml, p = 0.001). Serum levels of TGF-b did not differ between the two groups.

CONCLUSIONS: Increased levels of sENG at baseline may predict a predisposition for increased vascular permeability following stimulation. Alternatively, this increase could be reflective of a compensatory mechanism to sequester excess TGF-b, in women prone to OHSS. If confirmed by larger studies, sENG may have utility as a predictive marker for the development of OHSS in high risk women.
COMPARISON OF EFFICACY OF TWO DIFFERENT DOSES OF RECOMBINANT HUMAN CHORIONIC GONADOTROPIN IN IN-VITRO FERTILIZATION CYCLES TO IMPROVE FINAL OOCYTE QUALITY: A PROSPECTIVE STUDY.

P. Girish N. Singh, Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi, India.

OBJECTIVE: The primary objective of our study is to assess the effect on the number of oocytes retrieved per follicle and number of mature metaphase II oocytes after triggering final follicular maturation using either 250 μg or 500 μg of r-hCG (Ovitrelle®, Serono, Spain) in IVF-ET cycles. The secondary objective was to compare clinical pregnancy rates and occurrence of ovarian hyperstimulation syndrome between the two groups.

DESIGN: This was a prospective, randomized, single-centre, open-label study performed between June 2017 to August 2017 at the in-vitro fertilization unit in a tertiary care centre in North India.

MATERIALS AND METHODS: Seventy-six normal and poor-responder women planned for IVF-ET were included and underwent treatment with standard long GnRH agonist, antagonist or microdose-flare regimen according to baseline ovarian reserve. When two or more follicles had attained a maximum mean diameter of 18mm, follicular maturation was achieved by subcutaneous administration of either 250mcg (group 1-38 women) or 500mcg (group 2-38 women) of r-hCG (Ovitrelle®, Serono, Spain).

RESULTS: Baseline demographic parameters were similar between the groups, however, basal serum anti-Mullerian hormone (AMH) level (5.32±2.20ng/dl versus 5.19±1.85ng/dl, respectively, P=0.008) and basal antral follicle count (AFC) were found to be significantly higher in group 1 compared to group 2 (17.03±7.23 versus 12.20±4.07, respectively, P=0.02). Mean number of oocytes retrieved per follicles were 67.40±23.95 and 77.57±23.36 in 250 μg r-hCG and 500 μg r-hCG groups, respectively, which was significantly higher with 500 μg r-hCG than the lower dose (P=0.02). No significant differences were seen between the groups in terms of implantation rate and clinical pregnancy rates. Three women (8.5%) in group 1 and 2 women (5.7%) in group 2 had cycle cancellation due to failure of retrieval of oocytes. OHSS occurred in 2 patients, both of whom received 250mcg r-hCG. Due to heterogeneity between the groups with regard to ovarian reserve, we performed subgroup analysis in poor responder women, identified as subjects with antral follicle count (AFC) <11 and AMH ≤ 1.1 ng/ml. In this population, the mean number of metaphase II oocytes per total oocytes was 33.71±26.45 in group 1 and 51.97±28.25 in group 2, and this was significantly higher in women who received 500mcg r-hCG (P=0.03).

CONCLUSIONS: In our study, double dose of r-hCG when used to trigger final follicular maturation resulted in higher yield of oocytes per follicles and increased yield of metaphase II oocytes, especially in poor responders. However, further large randomized studies are needed to confirm our findings.

References: Nil

P-563 Wednesday, October 10, 2018 6:30 AM

INCREASED SERUM IGF-1 AND SFLT-1 LEVELS AT BASELINE PREDICT CYCLE CANCELLATION IN IVF PATIENTS. E. Minis,1 M. Irani,1 A. Athanasiou,2 S. S. Witkin,3 S. Spandorfer.1 1Weill Cornell Medicine, New York, NY; 2Center for Reproductive Medicine and Infertility, Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medicine, New York, NY; 3Obstetrics and Gynecology, Weill Cornell Medicine, New York, NY; 4Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medicine, NYC, NY.

OBJECTIVE: The aim of this study is to confirm preliminary findings from previous studies that soluble fms-like tyrosine kinase-1 (sFLT-1) and insulin-like growth factor-factor 1 (IGF-1) levels predicted IVF cycle cancellation. Increased serum levels of sFLT-1 and IGF-1 on day 2 of an IVF cycle were associated with a cancelled cycle due to poor ovarian response. sFLT-1, a soluble receptor for vascular endothelial growth factor (VEGF) that sequesters this compound, and IGF-1 have been shown to play a role in perifollicular angiogenesis, follicular luteinization during follicular maturation.

DESIGN: Prospective cohort study.

MATERIALS AND METHODS: Sera were obtained from 273 women undergoing an IVF cycle at our institution, prior to ovulation induction (day 2) and assayed by ELISA for levels of IGF-1 and sFLT-1. Cycle outcomes (cancellation or progression) were followed prospectively. Associations between concentrations of serum components and outcome were evaluated by the Mann-Whitney test. Receiver operator curves were constructed to evaluate the strength of the correlations between markers and outcomes, by area under the curve (AUC). Logistic regression was used to construct ROC curves for combined biomarkers.

RESULTS: Thirty-four women (12.5%) had their cycles cancelled due to a poor response to ovarian stimulation. Patients who had a cycle cancellation and those who proceeded with their IVF cycle had comparable age and BMI (p=0.086 and 0.42). Anti-Mullerian hormone (AMH) (1.4 vs 0.8 ng/mL, p=0.0001) and antral follicular count were higher in women who had an ongoing IVF cycle. Median concentrations of IGF-1 (14.6 vs 21.5 ng/ ml, p=0.031) and sFLT-1 (0.8 vs 0.4 ng/ml, p<0.0001) were increased in women that had a cancelled cycle, when compared to those who proceeded with their IVF treatment. AUC for IGF-1 and sFLT-1 were 0.62 and 0.70, respectively. When combined, sFLT-1 and AMH yielded an AUC of 0.91 and was superior to the AUC of 0.864 for AMH alone.

CONCLUSIONS: Elevated circulating levels of IGF-1 and sFLT-1 prior to stimulation are potential predictive markers of IVF cycle cancellation.
Higher levels of sFLT-1 could be indicative of poor perifollicular angiogenesis due to the sequestration of VEGF, while increased IGF-1 could be reflective of an enhanced endocrine response to a poor ovarian reserve. Confirmation in other populations could ultimately have an important clinical value to predict poor responders with the aim of modulating their stimulation protocols and provide them with realistic expectations.

**P-564 Wednesday, October 10, 2018 6:30 AM**

**PROGESTERONE VARIATION ON THE DAY OF OOCYTE TRIGGERING: A PROSPECTIVE STUDY WITH REPEATED MEASUREMENTS WITHIN THE SAME PATIENT. IS THE PROGESTERONE ELEVATION "STORY" STILL VALID?**


OBJECTIVE: To determine daily variation of progesterone levels on the day of ovulation triggering in women undergoing controlled ovarian stimulation (COS).

DESIGN: This is a prospective cohort study with repeated measurements conducted in a University-Affiliated Fertility unit. Overall, 22 oocyte donors were recruited between November 2017 and January 2018. Progesterone circulating levels were evaluated at 4 different times on the day of oocyte triggering (08:00 am, 12:00 pm, 04:00 pm and 08:00 pm) in healthy oocyte donors using the Progesterone Elecsys Gen III assay. Oocyte donors were treated with recombinant FSH in a flexible antagonist protocol.

MATERIALS AND METHODS: The sample size was calculated to detect a difference of 15% between the first and the last progesterone measurement with a false positive rate of 5% in a two-sided test (80% statistical power, 95% confidence interval [CI]). Progesterone percentage pairwise differences within each patient were calculated. An analysis of variance for repeated measures was performed to compare the change in progesterone levels between 4 times.

RESULTS: Mean (SD) progesterone levels were 1.75 (0.90) ng/ml at 08:00 am, 1.40 (0.76) ng/ml at 12:00 pm, 1.06 (0.53) ng/ml at 04:00 pm and 0.97 (0.55) ng/ml at 08:00 pm. Overall, there was a 44% decline between 08:00 pm (n=22).

Comparison of the differences of progesterone determinations from 08:00 am to 08:00 pm (n=22).

<table>
<thead>
<tr>
<th>08:00 pm</th>
<th>≤ 1.5 ng/ml</th>
<th>&gt; 1.5 ng/ml</th>
<th>Total</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:00 am</td>
<td>12 (100%)</td>
<td>0 (0%)</td>
<td>12</td>
<td>0.016</td>
</tr>
<tr>
<td>12 (100%)</td>
<td>7 (70%)</td>
<td>3 (30%)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>3</td>
<td>22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The first morning measurement (08:00 am) and the last determination of the day (08:00 pm) (p < 0.001). Of interest, among patients considered as women with elevated progesterone at baseline (08:00 am) based on currently accepted thresholds (progesterone ≥ 1.5 ng/ml), the vast majority, 70% presented levels below the threshold of <1.5 ng/ml on the last determination of the day (08:00 pm) (p = 0.012).

CONCLUSIONS: Progesterone levels demonstrate a remarkable clinically and statistically significant decline of up to 44% between 08:00am and 08:00 pm on the day of oocyte maturation. This study seriously questions the proposed progesterone thresholds utilized to clinically suggest lower implantation rates in fresh embryo transfer cycles. Based on the robust within-patient decline in serum progesterone levels, great caution is needed given that none of the available studies specify the exact timing of sampling determination.

References: NA

Supported by: Funding was granted from Fundació Santiago Dexeus Font.

**P-565 Wednesday, October 10, 2018 6:30 AM**

**THE EFFECT OF GONADOTROPIN DOSAGE AND DURATION OF OVARIAN HYPERSTIMULATION ON EUPLOIDY AND LIVE BIRTH RATES: AN ANALYSIS OF 12,298 TROPHECTODERM BIOPSIES.**


OBJECTIVE: A recent study reported a remarkable difference in the euploidy rates (range: 39.5%-82.5%) between young oocyte donors from 42 fertility centers, suggesting a potential iatrogenic etiology resulting from different stimulation methods (1). Therefore, we aim to determine whether ovarian hyperstimulation methods affects the embryo euploidy rates and/or live birth rates (LBRS) of euploid embryos transferred in subsequent frozen-thawed single-embryo transfer cycles (FET).

DESIGN: This is a retrospective cohort study including 2,230 IVF/PGT-A cycles followed by 930 single FET cycles between 2013 and 2017.

MATERIALS AND METHODS: IVF cycles were divided into the five SART age groups (<35, 35-37, 38-40, 41-42, and >42 years old), Euploidy rates and LBRS were compared between different durations of stimulation (<10, 10-12, and ≥13 days), total gonadotropin dosages (<4,000, 4,000-6,000, and >6,000 IU), numbers of oocytes retrieved (<10, 10-19, and ≥20 oocytes), peak estradiol (E2) levels (<2,000, 2,000-3,000, and >3,000 pg/ml), and sizes of the largest follicles on the day of trigger (<20 and ≥20 mm).

RESULTS: A total of 12,298 embryos were analyzed for ploidy status. Within the same age group, euploidy rates and LBRS were comparable between cycles of different total gonadotropin dosages, durations of stimulation, numbers of oocytes harvested, sizes of the largest follicles, or peak estradiol levels (Table 1). For instance, euploidy rates in women aged 41-42 years old (n=1,823 embryos) were not significantly different between cycles of different total gonadotropin dosages (18.4% for <4,000 IU vs. 22.6% for ≥6,000 IU; P=0.3), durations of stimulation (18.2% for <10 days vs. 16.6% for ≥13 days; P=0.8), numbers of oocytes retrieved (16.9% for <10 oocytes vs. 17.2% for ≥20 oocytes; P=0.5), sizes of the largest follicles (16.6% for <20 mm vs. 19.8% for ≥20 mm; P=0.1), or peak estradiol levels (Table 1).

CONCLUSIONS: The findings of this study should reassure providers and patients that a higher gonadotropin dosage, longer ovarian hyperstimulation, higher estradiol levels, follicular size at trigger, and a higher number of

**Table 1**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Outcomes</th>
<th>Peak estradiol &lt;2000 pg/mL</th>
<th>Peak estradiol &lt;2000 pg/mL</th>
<th>Peak estradiol &gt;3000 pg/mL</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>Euploidy rate (%)</td>
<td>55.7</td>
<td>55.4</td>
<td>54.8</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>LBR (%)</td>
<td>57.9</td>
<td>72.6</td>
<td>67.2</td>
<td>NS</td>
</tr>
<tr>
<td>35-37</td>
<td>Euploidy rate (%)</td>
<td>46.2</td>
<td>44.7</td>
<td>41.8</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>LBR (%)</td>
<td>59.3</td>
<td>54.4</td>
<td>43.3</td>
<td>NS</td>
</tr>
<tr>
<td>38-40</td>
<td>Euploidy rate (%)</td>
<td>31.2</td>
<td>33.0</td>
<td>35.1</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>LBR (%)</td>
<td>57.4</td>
<td>50</td>
<td>61.7</td>
<td>NS</td>
</tr>
<tr>
<td>41-42</td>
<td>Euploidy rate (%)</td>
<td>16.5</td>
<td>21.2</td>
<td>18.2</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>LBR (%)</td>
<td>63.4</td>
<td>51.2</td>
<td>39.1</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;42</td>
<td>Euploidy rate (%)</td>
<td>8.8</td>
<td>8.7</td>
<td>7.5</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>LBR (%)</td>
<td>62.9</td>
<td>78.6</td>
<td>53.8</td>
<td>NS</td>
</tr>
</tbody>
</table>
OBJECTIVE: Human growth hormone (hGH) in poor responders has been shown to improve oocyte yield, embryo development and in some studies, clinical outcomes including live birth rate. However, the effect of hGH on embryo euploidy rates in patients undergoing in vitro fertilization (IVF) has not been studied. Our objective was to determine if adjuvant hGH during IVF improves euploidy and other IVF outcomes.

RESULTS: A total of 60 women underwent 77 cycles during the study period and met inclusion criteria. All cycles were GnRH antagonist protocol. The study included all patients who underwent IVF at a single academic center between December 2016 and February 2018. All patients who underwent IVF with trophoderm biopsy and preimplantation genetic testing with next generation sequencing for aneuploidy (PGT-A) were included. A comparison was performed between patients who received adjuvant hGH (40IU per day, from the first day of stimulation until the day of trigger) and those who did not receive adjuvant therapy. Because the use of hGH is more common in women of advanced reproductive age, the patients were segregated into two age groups based on their age at the time of oocyte retrieval: ≥ 35 years old, and > 35 years old. IVF outcomes were compared between the treatment and control group, segregated by age. Statistical analysis was performed using the student t-test with p-value < 0.05 considered significant.

RESULTS: Compared with the natural cycle, all ovarian stimulation protocols were associated with a significantly increased risk for PTD, LBW and SGA (aOR = 2.60, 95% CI 1.49 to 4.53, P < 0.001 and aOR = 1.82, 95% CI 1.57 to 2.11, P < 0.001, respectively), and was associated with CS (aOR = 1.13, 95% CI 1.02 to 1.24, P = 0.02) and VLBW (aOR = 2.60, 95% CI 1.49 to 4.53, P = 0.001). Ovarian stimulation using CC+gonadotropin had the highest increased risks for LBW and SGA (aOR = 1.68, 95% CI 1.47 to 1.90, P < 0.001 and aOR = 1.82, 95% CI 1.57 to 2.11, P < 0.001, respectively), and was associated with CS (aOR = 1.13, 95% CI 1.02 to 1.24, P = 0.02) and VLBW (aOR = 2.60, 95% CI 1.49 to 4.53, P = 0.001). Ovarian stimulation using CC alone had similar significant associations. Sensitivity analysis using a sample subgroup with a maternal age under 35 demonstrated similar significant associations between ovarian stimulation and pregnancy and neonatal outcomes.

CONCLUSIONS: Ovarian stimulations, especially those using clomiphene citrate, were significantly associated with adverse perinatal outcomes compared with natural cycles for fresh ET.

OBJECTIVE: To compare perinatal outcomes following ovarian stimulation with natural cycles in fresh embryo transfers (ETs).

RESULTS: Compared with the use of Clomiphene citrate (CC) as an ovulation trigger, aOR = 1.49, (95% CI 1.02 to 2.15, P = 0.03), and was associated with CS (aOR = 1.13, 95% CI 1.02 to 1.24, P = 0.02) and VLBW (aOR = 2.60, 95% CI 1.49 to 4.53, P = 0.001). Ovarian stimulation using CC alone had similar significant associations. Sensitivity analysis using a sample subgroup with a maternal age under 35 demonstrated similar significant associations between ovarian stimulation and pregnancy and neonatal outcomes.

CONCLUSIONS: Ovarian stimulations, especially those using clomiphene citrate, were significantly associated with adverse perinatal outcomes compared with natural cycles for fresh ET.
delaying the start of a subsequent cycle was detrimental to cycle outcome as measured by oocyte yield.

DESIGN: Retrospective cohort study of all patients who completed >1 oocyte retrieval at the NYU Langone Fertility Center between 1/2014 and 12/2017.

MATERIALS AND METHODS: All paired cycles were identified and included which comprised of oocyte cryopreservation, oocyte donation, IVF and both medical and elective indications. Patients with one cycle or canceled cycles were excluded. If a patient underwent greater than two cycles, comparisons were made between subsequent cycles. The primary outcome was the number of oocytes retrieved. Statistical analysis was performed using direct paired two-tailed Students t-test.

RESULTS: 2068 paired cycles were reviewed from 1330 patients. Age at first cycle ranged from 16 to 48 years. Cycle intervals ranged from 21 days to 44.7 months. The average difference of oocytes in the second cycle was significantly greater with a 1,2,3 or 4-6 month delay in women 44.7 months. The average difference of oocytes in the second cycle was 16 to 48 years. Cycle intervals ranged from 21 days to 44.7 months. The average difference of oocytes in the second cycle was significantly greater with a 1,2,3 or 4-6 month delay in women >40 yrs (Ta-ble 1); whereas, there was no significant change for women over 40 yrs. There was no significant decline in the average number of oocytes regardless of the delay for women of any age. A subgroup analysis of only patients’ first and second cycle also demonstrated no significant decline in number of oocytes regardless of delay or age and a similar increase in number of oocytes retrieved with an earlier cycle.

CONCLUSIONS: Over the range of delays between cycles observed, there was no significant decline in the average number of oocytes retrieved. More surprising was the average increase in egg numbers for patients 40 years during the six months following the first egg retrieval. This information is important for patients who wish to, or must, delay their second cycle start.

P-569 Wednesday, October 10, 2018 6:30 AM

NO DIFFERENCE IN CLINICAL OUTCOMES USING FOLLITROPIN ALFA (BIOSIMILAR) COMPARED TO FOLLITROPIN ALFA OR FOLLITROPIN BETA FOR CONTROLLED OVARIAN STIMULATION (COS) IN OOCYTE DONATION-RECIPIENT CYCLES. E. Bosch a, C. Howles b, C. K. Johnston a, aHuman Reproduction, IVI-RMA Valencia, Valencia, Spain; bARIES Consulting, Geneva, Switzerland; cUniversity of Edinburgh, Edinburgh, United Kingdom.

OBJECTIVE: To assess the safety and effectiveness of a recently available biosimilar follitropin alfa (Bemfola®) compared to established recombinant FSH preparations (follitropin alfa, Gonal-F®; follitropin beta, Puregon®) in an ART program.

DESIGN: Retrospective anonymized cohort analysis on all donor oocyte cycles using only r-hFSH for COS and clinical follow up data on recipient transfers carried out during 2016-2017.

MATERIALS AND METHODS: In total, there were 2499 COS cycles in a donor population using different FSH preparations. Of these, 1547 were stimulated with FSH alone and of these, 1341 received r-hFSH for COS, of which 671 cases were with biosimilar follitropin alfa, 79 with follitropin alfa, and 591 with follitropin beta. Following a course of birth control pill or lutal phase oestradiol valerate, donors were stimulated from menstrual day 2-3 with daily r-hFSH (150-225 IU), with daily GnRH antagonist commenced from cycle day 6. Final follicular maturation was triggered using a GnRH agonist (0.2 mg) and oocytes were collected approximately 36 hours later. Oocytes were vitrified or fertilized in vitro and cultured to the blastocyst stage. Routinely one blastocyst was replaced in the recipient who was receiving hormone replacement to facilitate synchronization of the transfer procedure. Demographic, stimulation variables and pregnancy data were analysed using SPSS (Version 21.0). The main outcome measure was ongoing clinical pregnancy (week 12). Statistical analysis employed chi-squared with Pearson correction and logistic regression analysis for factors associated with ongoing pregnancy.

RESULTS: Overall mean donor and recipient age were 24.4 ± 4.4 and 41.3 ± 4.1 respectively. The total r-hFSH doses were 2014 ± 529, 1824 ± 559 and 2084 ± 677 for follitropin alfa, beta and biosimilar follitropin alfa respectively. (p<0.05 for the comparisons between follitropin beta vs both follitropin alfa preparations). The number of oocytes retrieved were 21 ± 10, 25 ± 11 and 26 ± 10 (p<0.05 for the comparisons between follitropin alfa vs its biosimilar and vs follitropin beta), resulting in a FSH dose per oocyte retrieved of 117 IU, 89 IU and 98 IU for follitropin alfa, beta and biosimilar follitropin alfa respectively (p<0.05 for all comparisons). The number of embryos transferred were: 1.5 ± 0.5 for follitropin alfa; 1.4 ± 0.5 for follitropin beta, and 1.3 ± 0.5 for the biosimilar of follitropin alfa (p<0.05 for the comparison between follitropin alfa and its biosimilar). The ongoing clinical pregnancy rate in donor recipients was 52.8 % for biosimilar follitropin alfa (n=579), 50.7% (n=73) for follitropin alfa and 51.5% for follitropin beta (n=520) (p>0.05). All preparations were well tolerated at the site of injection.

CONCLUSIONS: This large retrospective study in a donor oocyte-recipient program demonstrates similar clinical efficacy for biosimilar follitropin alfa compared to established recombinant follitropins.

References: "None"

Supported by: This study was supported by an unrestricted educational grant from Preglem SA Switzerland

P-570 Wednesday, October 10, 2018 6:30 AM


OBJECTIVE: To explore whether a single luteal dose of long-acting GnRH-antagonist can downregulate endogenous LH during controlled ovarian stimulation for IVF and produce fertilizable oocytes and implantable blastocysts.

DESIGN: This proof of concept case control trial studied the efficacy of a single dose of long-acting antagonist, Degarelix. The study was performed during March-December 2017. The same 10 oocyte donors underwent two consecutive ovarian stimulation and IVF for oocyte donation.

MATERIALS AND METHODS: The first stimulation (control group) followed a classic fixed-day 6 GnRH-antagonist protocol with 225 units of recombinant gonadotropin whereas, in the second IVF trial six months later, the same women underwent the new protocol (study group-Long Antagonist group). In the new protocol a single dose of 0.5 ml degarelix was administered on day 24 of preceding cycle and after the period all donors allowed to start gonadotropin stimulation (225 units) from day 3 of the cycle up to the 10th day of the cycle, in order to prove the flexibility of this new protocol.

RESULTS: The mean age of participants was similar among groups (27 years). Stimulation ranged from 9-10 days in control group, whether in the Long Antagonist group ranged from 10-12 days. No LH rise was noticed
in any groups. All patients in the Long Antagonist group were triggered with agonist triggering. Similar number of oocytes (13.2 vs 15, p>0.05) and blastocysts produced in both groups (6.0 vs 7.7, p>0.05). After embryo transfer, in egg recipients the clinical pregnancy rate was similar among the two groups; 50% (n=5/10) in classic antagonist and 50% (n=6/10) in the new Long Antagonist group.

CONCLUSIONS: This novel concept for IVF couples addresses security (OHSS avoidance) and flexibility (up to 10 days later in the follicular phase possible start of stimulation. This new Long-Antagonist protocol allows cycle programming that was missing, with antagonist protocols and might eradicate OHSS since the GnRH-agonist triggering is applied. However, the limitation of this study is the small size, however this is a proof of concept trial. Additionally, other doses of Degarelix could be tested to investigate differences in ovarian stimulation.

P-571 Wednesday, October 10, 2018 6:30 AM

EFFECT OF ROUTE OF ESTROGEN PRIMING IN LUTEAL PHASE ON IN VITRO FERTILIZATION OUTCOMES. V. Sundaram1 H. G. Huddleston2 1Reproductive Endocrinology & Infertility, UCSF, San Francisco, CA; 2OBGYN, UCSF, San Francisco, CA.

OBJECTIVE: To determine whether the route of estrogen priming (oral versus patch) has a significant effect on various in vitro fertilization (IVF) parameters.

DESIGN: Retrospective cohort study

MATERIALS AND METHODS: Using an electronic health query in IDEAS, we identified women who underwent in-vitro fertilization cycles (egg cryopreservation, in vitro fertilization, intracytoplasmic sperm injection, and oocyte donation) between June 2012-June 2017 at the University of California, San Francisco Center for Reproductive Health. Those who received estrogen priming in the luteal phase were identified and further subdivided by mode of estrogen use (oral estradiol versus Vivelle Dot transdermal patch). The mean ratios of the following parameters were compared using a paired t-test: mature follicles per antral follicle (AFC) at baseline ultrasound, total eggs collected per AFC, MII (mature oocytes) per AFC, and 2PN (fertilized embryos) per AFC. Further linear regression models evaluated the relationship between these IVF parameters and mode of estrogen priming, while controlling for age, cycle length, and starting dose of follicle stimulating hormone.

RESULTS: 1450 patients were identified with IVF cycles using estrogen priming in the luteal phase. 759 had priming with the transdermal patch and 701 with oral estradiol. The table below shows the comparison of means using a paired t-test for each of the considered IVF outcomes. While those women who underwent oocyte cryopreservation were included in the mature follicles/AFC and eggs collected/AFC outcomes, only those patients undergoing IVF with embryo transfer were considered when analyzing MII/AFC and 2PN/AFC. Estrogen priming with estradiol transdermal patch in the luteal phase does not have a significant increase from oral estradiol when comparing the ratios of mature follicles per AFC, total eggs collected per AFC, MII's per AFC, and 2PN per AFC (though mature follicles per AFC and MII's per AFC approach significance). A multivariate linear regression shows MII/AFC is significantly greater in the estrogen patch cohort when controlled for age, but not significant with respect to cycle length and initial dose.

CONCLUSIONS: There appears to be no significant difference between estrogen priming with transderal versus oral modes, when comparing the outcomes of mature follicles/AFC, eggs collected/AFC, MII's/AFC, and 2PN/AFC.

References: None - included in background section upon oral/poster.

Comparison of mean ratios of various in vitro fertilization parameters

<table>
<thead>
<tr>
<th>IVF Outcome</th>
<th>Observations (N)</th>
<th>Mean</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patch</td>
<td>Pill</td>
<td>Patch</td>
</tr>
<tr>
<td>Mature Follicles/AFC</td>
<td>713</td>
<td>670</td>
<td>0.6991</td>
</tr>
<tr>
<td>Eggs collected/AFC</td>
<td>613</td>
<td>564</td>
<td>0.7660</td>
</tr>
<tr>
<td>MII's/AFC</td>
<td>609</td>
<td>562</td>
<td>0.4260</td>
</tr>
<tr>
<td>2PN/AFC</td>
<td>605</td>
<td>557</td>
<td>0.4048</td>
</tr>
</tbody>
</table>

P-572 Wednesday, October 10, 2018 6:30 AM

KNOWLEDGE, ATTITUDES, AND PRACTICES REGARDING THE USE OF OVULATION INDUCTION AND OVARIAN STIMULATION WITHOUT IN VITRO FERTILIZATION (IVF): HEALTHCARE PROVIDER SURVEY. D. Kissin, A. D. Kulkarni, A. C. Dieke, J. F. Kawwass, C. Ayala, L. Warner, S. Boulet, Division of Reproductive Health, Centers for Disease Control and Prevention, Atlanta, GA; *Gynecology and Obstetrics, Emory Reproductive Center, Atlanta, GA.

OBJECTIVE: To assess provider practices of recommending non-IVF fertility treatments to patients, their knowledge about treatment safety, and their attitudes about using non-IVF fertility treatments.

DESIGN: Cross-sectional, web-based survey of U.S. healthcare providers.

MATERIALS AND METHODS: We used data from the 2017 DocStyles survey of a random sample of providers with respondents’ distribution of age, sex, and region matching the American Medical Association’s master file (39.5% response rate). We assessed responses of family practitioners, internists, nurse practitioners, and obstetrician-gynecologists who provided care for infertility patients in the past year. Non-IVF fertility treatments were defined as ovulation induction or ovarian stimulation with timed intercourse or insemination with no intention of performing IVF.

RESULTS: Of 1,510 respondents, 603 (40%) reported providing care for infertility patients in the past year, including 182 family practitioners, 118 internists, 72 nurse practitioners, and 231 obstetrician-gynecologists. The most commonly recommended non-IVF fertility treatments were natural cycle insemination (66%), clomiphene citrate (57%), and Metformin (57%). Primary reasons for recommending non-IVF fertility treatments were patient or couple’s prior success in conceiving a pregnancy (41%), duration of infertility (39%), and infertility diagnosis (38%). Most providers (53%) recommended non-IVF fertility treatments before IVF because they considered them less risky. While 44% of providers believe non-IVF fertility treatments were associated with more adverse infant outcomes than IVF, 18% considered IVF to be safer. Only 35% of providers considered oral fertility drugs to be safer than injectable drugs, while 18% disagreed; 47% had no opinion. Nearly one-third (29%) of obstetrician-gynecologists and the majority of family practitioners (68%), internists (55%), and nurse practitioners (74%) reported not using any specific strategy to limit the risk of multiple births when using non-IVF fertility treatments. The most common strategies of preventing multiple births were beginning treatment with clomiphene citrate (29%), monitoring hormone levels and adjusting treatment protocols (16%), and monitoring follicular size using ultrasound and aspirating excess follicles if needed (14%).

CONCLUSIONS: While study generalizability may be limited, many providers involved in infertility care may not be aware of the risk of adverse infant outcomes for non-IVF versus IVF fertility treatments, and do not attempt to limit the risk of multiple births while using these treatments. These results can inform provider education efforts.

Supported by: Centers for Disease Control and Prevention

P-573 Wednesday, October 10, 2018 6:30 AM


OBJECTIVE: During controlled ovarian stimulation, final oocyte maturability can be triggered with human chorionic gonadotropin (hCG) or gonadotropin-releasing hormone agonist (GnRHa); however, each process functions by different biologic mechanisms and their effects on oocyte quality and subsequent pregnancy outcomes are a topic of ongoing debate. Although prior studies suggest that GnRHa may adversely affect oocyte quality, none has controlled for the contribution of aneuploidy on subsequent pregnancy outcomes. By evaluating pregnancy outcomes after euploid embryo transfer, the effect of each trigger on IVF outcomes can be more clearly elucidated.

DESIGN: A retrospective study was performed at a private fertility clinic. Patients were included if they completed PGT-A cycles performed between 2014-2017 and hyper-responder to stimulation (defined by 15 or more mature follicles at the time of trigger). Outcomes were stratified by GnRHa or hCG trigger.
The association between oocyte maturation trigger type and IVF outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>hCG-only trigger n=765 (ref)</th>
<th>Dual-trigger n=439</th>
<th>RR/OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34.7 (3.7)</td>
<td>33.6 (3.4)</td>
<td>–</td>
</tr>
<tr>
<td>AMH (ng/mL)</td>
<td>4.9 (3.9)</td>
<td>6.2 (4.5)</td>
<td>–</td>
</tr>
<tr>
<td>Oocytes Retrieved</td>
<td>13.6 (6.9)</td>
<td>18.1 (8.1)</td>
<td>1.31 (1.23, 1.38)***</td>
</tr>
<tr>
<td>Fertilized oocyte rate (fertilized/retrieved)</td>
<td>60.2% (21.3)</td>
<td>60.6% (19.8)</td>
<td>0.98 (0.94, 1.02)</td>
</tr>
<tr>
<td>Blastocyst conversion rate (blastocysts/2Pns)</td>
<td>39.6% (32.9)</td>
<td>54.8% (30.5)</td>
<td>1.22 (1.15, 1.29)***</td>
</tr>
<tr>
<td>Number of embryos transferred</td>
<td>1.7 (0.7)</td>
<td>1.2 (0.5)</td>
<td>0.77 (0.74, 0.81)***</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>41% (45)</td>
<td>41% (48)</td>
<td>0.95 (0.82, 1.10)</td>
</tr>
<tr>
<td>Biochemical pregnancy</td>
<td>76 (9.9%)</td>
<td>64 (14.6%)</td>
<td>1.84 (1.28, 2.63)***</td>
</tr>
<tr>
<td>Clinical pregnancy</td>
<td>383 (50.1%)</td>
<td>181 (45.5%)</td>
<td>0.69 (0.54, 0.89)***</td>
</tr>
<tr>
<td>Live birth</td>
<td>327 (42.9%)</td>
<td>147 (33.6%)</td>
<td>0.61 (0.47, 0.79)***</td>
</tr>
</tbody>
</table>

Mean (SD) or n (%) *Controlled for age and number embryos transferred **p<0.05

RESULTS: The dual-trigger group was younger (mean 33.6 vs 34.7 years), had a higher AMH (6.2 vs 4.9 ng/mL) and a higher rate of day 5 embryo transfer (74.7% vs 44.4%) compared to the hCG-only trigger group. The dual-trigger group had more oocytes retrieved (18.1 vs 13.6) and a better blastocyst conversion rate (54.8% vs 39.6%). Yet, the dual-trigger group was more likely to have an unsuccessful biochemical pregnancy (14.6% vs 9.9%) and a lower probability of clinical pregnancy (presence of a gestational sac, 43.5% vs 50.1%) and live birth (33.6% vs 42.9%), all of which reached the threshold of statistical significance. There were only 3 cases of OHSS, all in the hCG-only trigger group.

CONCLUSIONS: The dual-trigger group had a better prognosis based on age and AMH levels and had better stimulation outcomes. Despite this observation, pregnancy outcomes were significantly worse in this group, suggesting that the low dose hCG (1,000u) in the dual-trigger protocol may not provide adequate luteal support compared to an hCG-only trigger (10,000u hCG/250u Ovidrel). Further studies are needed to establish the optimal dose of hCG to both support early pregnancy development and offer an acceptably low risk of OHSS.

References: N/A

P-574 Wednesday, October 10, 2018 6:30 AM

THE EFFECT OF LOW DOSE HCG/GNRH AGONIST DUAL-TRIGGER ON PREGNANCY OUTCOMES. M. Shapiro, P. Romanski, A. M. Thomas, L. V. Farland, E. Yanushpolsky. Obstetrics & Gynecology, Brigham & Women’s Hospital and Harvard Medical School, Boston, MA.

OBJECTIVE: The use of a GnRH agonist (GnRHa) to trigger final oocyte maturation has been shown to eliminate ovarian hyperstimulation syndrome (OHSS) but is also associated with lower pregnancy and live birth rates compared to hCG triggers due to inadequate luteal phase support. The use of a dual-trigger with both low-dose hCG and GnRHa can help provide the necessary luteal phase support, but the optimal hCG dose is unknown. Our objective was to assess pregnancy and OHSS rates following dual-trigger with GnRHa and low-dose hCG compared to hCG-only trigger.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: Fresh IVF/ICSI GnRHa antagonist cycles from 1/1/2012 to 5/31/2017 at our institution were reviewed. Patients who received a dual-trigger with a GnRHa (2 mg) and low-dose hCG (1,000u) were compared to women who received an hCG-only trigger (10,000u hCG/250u Ovidrel). Freeze-all cycles and predicted poor responders (≥ 41 years old, BMI <18 or >40 kg/m2, AMH <2.0) were excluded. Demographics, stimulation and pregnancy outcomes were analyzed. Logistic and Poisson regression were used to estimate the odds ratio (OR) and relative risk (RR).

OBJECTIVE: After the early follicular phase, the elevated serum follicle stimulating hormone (FSH) level gradually declines as the estrogen level increases. However, in women with diminished ovarian reserve, an elevated FSH level tends to remain or even increase regardless of an elevated estrogen level. The aim of the present study was to evaluate the developmental competence of oocytes retrieved in these cases in a minimal stimulation program.

DESIGN: This was a retrospective, single-center, cohort study.

MATERIALS AND METHODS: This study included women who underwent oocyte retrieval (OR) with a clomiphene citrate in minimal stimulation IVF between April 2016 and March 2017. A GnRH agonist was used to trigger oocyte maturation 34-36 hours before OR. A mature oocyte (MII) was retrieved from a single dominant follicle and was inseminated by conventional IVF or ICSI. A total of 831 cycles were divided into group A (418 cycles, mean patient age: 39.2 ± 3.5 years, with increased FSH level) and group B (413 cycles, mean patient age: 39.4 ± 3.6 years, with decreased FSH level) according to the shifting pattern of the FSH levels from the third day of menstruation (day 3) to the day of oocyte maturation trigger. All fertilized oocytes were cultured to blastocysts and cryopreserved when the blastocysts reached 160 μm or larger in diameter and met Gardner’s criterion (≥ 3 CC). The primary outcome measures were fertilization, cleavage, and blastocyst cryopreservation rates. The secondary outcome measure was morphological evaluation of blastocysts. The Student t-test and chi-square test were performed, and a P-value of <0.05 was considered statistically significant.

RESULTS: The mean day 3 FSH levels (mIU/ml) were 12.8 ± 7.0 (group A) and 13.4 ± 5.6 (group B) at baseline and 24.8 ± 16.2 (group A) and 9.2 ±
4.2 (group B) on the day of maturation trigger. The duration from the begin-
ning of menstruation to OR in group A was significantly longer than that in
group B (15.2 ± 3.2 vs 13.7 ± 1.7). The rate of normal fertilization in group A
(75.6%, 313/414) was significantly lower than that in group B (82.6%, 341/
413). No significant difference in the rate of abnormal fertilization was found
between the groups (group A: 7.9%, 33/418, group B: 6.5%, 27/413). No sig-
nificant difference in cleavage rate was observed (group A: 55.7%, 233/418,
group B: 59.3%, 245/413). The blastocyst cryopreservation rate in group A
(28.9%, 121/418) was significantly lower than that in group B (35.6%, 147/
413). We found no significant difference in the good morphology of blast-
cysts (≥4 AA) cryopreserved between groups A (19.0%, 23/121) and B
(17.7%, 26/147).

CONCLUSIONS: Increased serum FSH level on the day of maturation
trigger as compared with the day 3 FSH level showed a negative influence on
the developmental competence of oocytes even if mature oocytes were
retrieved. Attention needs to be paid to not only day 3 FSH levels but also
the shifting pattern of FSH levels to retrieve oocytes with better develop-
mental competence.

References:
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2. LaPolt PS, et al. Gonadotropin-induced up- and down-regulation of
ovarian follicle-stimulating hormone (FSH) receptor gene expression in
immature rats: effects of pregnant mare’s serum gonadotropin, human chori-
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P-576 Wednesday, October 10, 2018 6:30 AM
CONTROLLED OVARIAN HYPERSTIMULATION (COH) PARAMETERS ASSOCIATED WITH DONOR
EUPLOIDY RATES. S. B. Santiago Blanco Munne,1,a D. H. McCulloch,1,a S. S. Sawarkar,2 M. Alikani,2,3 J. Norian,2
K. Anderson1, K. Anderson2, K. Anderson3,3 J. Riley4, C. WoolFolk4, T. P. Jimenez5, S. Gunderson6, K. Anderson7, J. Riley8, C. WoolFolk9,
P. T. Jimenez10, S. Gunderson6, 1Department of Obstetrics and Gynecology, University of California, San Diego, CA; 2NYU Langone Fertility Center, New York, NY; 3Research, CooperGenomics, Livingston, NJ; 4Laboratory Professional, CooperGenomics, Livingston, NJ; 5Laboratory Professional, Reproductive Science Center of NJ, Eatontown, NJ; 6Laboratory Professional, Huntington Reproductive Center, Pasadena, CA.

OBJECTIVE: The report that euploidy rates using donor oocytes vary
among clinics led us to question what causes these differences in euploidy. We
considered donors at one clinic that performed over 400 donor PGS cy-
cycles using the same embryology lab and the same genetics lab but in which
there were significant differences of euploidy rates among the 6 different
clinics leading us to question what causes these differences in euploidy.

MATERIALS AND METHODS: In November of 2017 a protocol change
was implemented in our institution and an additional dose of a GnRH antagonist
was given on the day of hCG trigger in an effort to prevent premature
ovulation. The primary objective of our study was to determine if this
addition of a GnRH antagonist on the day of hCG trigger. Our secondary objective was to determine if this
protocol change increased clinical pregnancy rates.

DESIGN: IRB approved, retrospective cohort study of couples with
various infertility diagnoses undergoing an antagonist cycle in a single insti-
tution from 2016-present.

RESULTS: A total of 246 couples were analyzed. The two cohorts were
similar with the exception of a higher proportion of patients with an infertility
diagnosis of “other” seen in the standard antagonist protocol group.

<table>
<thead>
<tr>
<th>Antigen on Day of Trigger</th>
<th>Antigen Day Prior to Trigger</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics and cycle outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antigen on Day of Trigger N=82</td>
<td>Antigen Day Prior to Trigger N=164</td>
<td>p</td>
</tr>
<tr>
<td>Maternal Age</td>
<td>33.0 (30.0, 36.0)</td>
<td>32.5 (29.0, 35.0)</td>
</tr>
<tr>
<td>Maternal BMI</td>
<td>24.5 (21.9, 30.4)</td>
<td>24.1 (21.2, 30.2)</td>
</tr>
<tr>
<td>Diagnosis: Male (%)</td>
<td>28 (34.2)</td>
<td>44 (26.8)</td>
</tr>
<tr>
<td>Diagnosis: DOR (%)</td>
<td>6 (7.3)</td>
<td>14 (8.5)</td>
</tr>
<tr>
<td>Diagnosis: Unexplained (%)</td>
<td>16 (19.5)</td>
<td>27 (16.5)</td>
</tr>
<tr>
<td>Diagnosis: Tubal (%)</td>
<td>8 (9.8)</td>
<td>18 (11.0)</td>
</tr>
<tr>
<td>Diagnosis: Other (%)</td>
<td>19 (23.2)</td>
<td>66 (40.2)</td>
</tr>
<tr>
<td>Antimullerian hormone level</td>
<td>2.7 (1.4, 4.9)</td>
<td>2.7 (1.4, 5.0)</td>
</tr>
<tr>
<td>Antral follicle count</td>
<td>29.0 (17.0, 44.5)</td>
<td>25.0 (17.0, 40.0)</td>
</tr>
<tr>
<td>Lead follicle at start of antagonist</td>
<td>14.0 (13.5, 15.5)</td>
<td>14.0 (13.0, 15.0)</td>
</tr>
<tr>
<td>Estradiol at start of antagonist</td>
<td>613.0 (358.5, 869.0)</td>
<td>557.0 (341.0, 819.0)</td>
</tr>
</tbody>
</table>

FERTILITY & STERILITY®
e339
(table 1). The number of oocytes retrieved for either protocol was not significantly different (9.5 oocytes (6-14) in the new protocol group and 10 oocytes (6-14) in the standard protocol group, p=0.92). Using the standard antagonist protocol as a reference there was no significant difference in clinical pregnancy rates when comparing the two protocols using chi-square analysis (χ² = 0.98; 95% CI (0.51-1.90)). No premature ovulation events were observed in the analyzed patients.

CONCLUSIONS: The addition of a GnRH antagonist on the day of HCG trigger does not appear to impact oocyte yield or clinical pregnancy rates when compared to the standard antagonist protocol. To our knowledge this is the first study analyzing the impact of GnRH antagonist on the day of HCG trigger. The addition of GnRH antagonist on the day of final maturation trigger does not appear to impact cycle outcome and may not be necessary to prevent premature ovulation in patients with normal ovarian reserve.

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ARE OUTCOMES FROM FRESH DONOR OOCYTES STILL SUPERIOR TO FROZEN DONOR OOCYTES?1, S. Hosseini Nasab, a W. H. Wang, b S. Bello, b M. A. Clapp, a D. B. Williams, a University of Texas, UT Health Houston, Houston, TX; b Houston Fertility Institute, Houston, TX; c Houston Fertility Institute, Tomball, TX.

OBJECTIVE: To compare pregnancy outcomes from assisted reproductive technology (ART) cycles using fresh donor oocytes versus frozen donor oocytes.

DESIGN: Retrospective cohort study within a private practice setting.

MATERIALS AND METHODS: All donor egg cycles at Houston Fertility Institute from January 2012 to December 2017 were examined. Data collected included demographic information, age, parity, number of oocytes, blastulation rate, embryo transfer number, and pregnancy outcomes (in particular, clinical pregnancy and ongoing pregnancy rate per embryo transfer). Patients using frozen donor eggs received 6-8 mature oocytes from the internal egg bank at Houston Fertility Institute. Only the first embryo transfer cycle was used for data analysis of pregnancy outcome. Descriptive statistics were computed and bivariate analysis was performed with the appropriate tests.

RESULTS: A total of 1,054 donor oocyte cycles were analyzed, including 501 fresh cycles and 553 frozen cycles. A total of 704 cycles had immediate blastocyst transfer with “freeze-all” for other cycles due to biopsy for PGT-A or other reasons. As expected more eggs were inseminated from fresh versus frozen groups (14.5 ±9.2 vs. 8 ±1.9, p < 0.0001). Fertilization and blastulation rates were significantly higher in the fresh group compared with the frozen group (85% vs. 81%; 65% vs. 54%, p < 0.0001). Frozen oocytes had a post-thaw survival rate of 97% (See Table 1). There was no significant difference in clinical pregnancy rate per transfer between fresh and frozen groups (64% (151/237) vs. 60% (280/467), p = 0.3). Ongoing pregnancy rates per transfer were also similar between the groups (fresh 52% (123/237) vs. frozen 51% (239/467), p = 0.8).

CONCLUSIONS: Although fresh donor oocyte cycles had a higher fertilization and blastulation rate compared to frozen donor oocyte cycles, the pregnancy outcomes between the two groups were similar with no statistically significant differences. Therefore, frozen donor oocytes should be considered as a valuable alternative to fresh donor oocytes.

<table>
<thead>
<tr>
<th>Donor oocyte cycle characteristics and outcomes</th>
<th>Fresh (n=501) Mean (SD)</th>
<th>Frozen* (n=554) Mean (SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age (years)</td>
<td>41(6.2)</td>
<td>41.7(5.4)</td>
<td>0.046</td>
</tr>
<tr>
<td>No. Mature Oocytes (n)</td>
<td>14.5(9.2)</td>
<td>8(1.9)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Survival Rate Post-thaw (%)</td>
<td>97.9(5.8)</td>
<td>81(18)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Fertilization Rate (%)</td>
<td>85(15)</td>
<td>8(18)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Blastulation Rate (%)</td>
<td>65(25)</td>
<td>54(26)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>No. Blastocysts Transferred (n)</td>
<td>1.6(0.7)</td>
<td>1.8(0.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>No. Blastocysts Frozen (n)</td>
<td>6.2(5.1)</td>
<td>1.8(1.8)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

References:

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A RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL ASSESSING THE EFFECTS OF A VAGINALLY ADMINISTERED PHARMACOBIOTIC OVULE ON THE VAGINAL MICROBIOME IN WOMEN UNDERGOING OVARIAN STIMULATION.

J. A. Garcia-Velasco, a A. Requena, a M. Piro, a A. Fabris, a S. Matey, b A. Alvarez. a "Reproductive Endocrinology & Fertility, Madrid, Spain; b Registered Nurse, Madrid, Spain.

OBJECTIVE: To evaluate the effect of Lactobacillus rhamnosus CECT 8800 vaginal ovule on the vaginal microbiome in healthy women undergoing ovarian stimulation (OS).

DESIGN: Randomized double-blind, placebo-controlled, parallel-group, single center Phase-II trial. Ethic Committee approval and AEMS authorization 589/15/EC. Oocytes donor undergoing OS were randomized to receive L. rhamnosus CECT 8800 vaginal ovule (n=25) (Probiotic group) or placebo ovule (n=25) (Placebo group) daily from day 4-6 of ovarian stimulation until the day 3-5 after oocyte retrieval (OR) in a 1:1 ratio. Luteal phase support by progesterone 25 mg daily subcutaneous injection provided from day 3/5 after OR until 7-9 days after for all subjects.

MATERIALS AND METHODS: Women 18-35 years randomized on day 4-6 of OS to Probiotic or Placebo group. Blood samples, vaginal swabs (VS) and vaginal pH measured at 5-7 days before expected menses (T1), on day 4-6 of stimulation (T2), at the end of stimulation (T3), 3-5 days after OR (T4) and 7-9 days after OR (T5). Local tolerability and acceptability of the ovule assessed. Sequencing of the 16S rDNA microbiome used to identify the bacteria on VS.

RESULTS: Similar Shannon index evolution is found in both groups. OS reduces Lactobacillus genus presence at T2 in all subjects. Probiotic ovule increases significantly the Lactobacillus genus presence at T3 in probiotic ovule vs placebo group (p=0.04), descending in T4 in both groups due to routinely administration of azithromycin 1000 mg to all patients at OR. Lactobacillus rhamnosus CECT 8800 presence with high level expression at T3 and T4, descending to basal numbers at T5 due to no administration from T4. Probiotic ovule affects vaginal microbiota with differences in 16S rDNA microbiome at T3 and T4 in probiotic group vs placebo group. The vaginotype IV (diverse group) is reduced in probiotic group vs placebo group (p<0.0001) and vaginal pH measured at 5-7 days before expected menses (T1), on day 4-6 of stimulation (T2), at the end of stimulation (T3), 3-5 days after OR (T4) and 7-9 days after OR (T5).

Conclusions: Tolerability and acceptability of the ovule assessed. Sequencing of the 16S rDNA microbiome used to identify the bacteria on VS.
CONCLUSIONS: First time to asses the effect of a well documented probiotic strain on vaginal microbiota and as well as its variations during an OC cycle. L. rhamnosus CECT 8800 vaginal colonization and safety are shown: it is well-tolerated, increases significantly Lactobacillus presence and has an influence in vaginal microflora evolving it into healthier vaginotypes. All this may be useful in IVF cycles.

Supported by: Ferring Pharmaceutical Sponsored Trial

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OBJECTIVE: Progesterone-primed (PP) stimulated cycles are a safe and effective alternative to antagonist cycles for controlling the endogenous LH rise in any clinical situation in which endometrium receptiveness is not an issue, i.e. oocyte donors (OD). Some concern may exist regarding the quality of the endocrine response to the final oocyte maturation trigger when performed with a GnRH agonist bolus. The objective is to describe the endocrine response to GnRH agonist trigger in antagonist (ANT) versus PP stimulated cycles in OD.

DESIGN: Retrospective

MATERIALS AND METHODS: OD underwent ovarian stimulation with gonadotropins at a private, university-based infertility clinic between Jan’17-Mar’18. Serum estradiol evaluation and ultrasound scans were performed for monitoring response. Endogenous LH peak was controlled with either daily injections of GnRH antagonist starting between Jan’17-Mar’18. Serum estradiol evaluation and ultrasound scans were performed for monitoring response. Endogenous LH peak was controlled with either daily injections of GnRH antagonist starting between Jan’17-Mar’18.

RESULTS: A total of 404 OD cycles were included. There were no differences in mean age. AMH between groups. After agonist trigger, significantly lower P before and after agonist trigger when oral desogestrel was used for the control of endogenous LH compared to the use of GnRH antagonist. It is hypothesized that differential endogenous LH inhibition during stimulation with a GnRH antagonist or PP could be associated to the different outcomes.

CONCLUSIONS: Pregnancy outcomes after ART do not differ in euthyroid patients even with fluctuations in TSH. Despite higher blastulation rate in patients with TSH > 2.5 mIU/L, there were no differences in ovarian stimulation or pregnancy outcomes after FET. Euthyroid patients can be reassured that while thyroid dysfunction may cause hormonal disturbance, subtle changes do not impair IVF outcomes.

References:

<table>
<thead>
<tr>
<th>Estradiol, progesterone and LH values on Triggering day and day after trigger, and cycle outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP Group (n=207)</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Estradiol at trigger (pg/ml)</td>
</tr>
<tr>
<td>Days of stimulation</td>
</tr>
<tr>
<td>Follicles at trigger</td>
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<tr>
<td>P4 at trigger</td>
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<tr>
<td>P4 at trigger+1</td>
</tr>
<tr>
<td>LH at trigger</td>
</tr>
<tr>
<td>LH at trigger+1</td>
</tr>
<tr>
<td>MII oocytes</td>
</tr>
<tr>
<td>Recipient Fresh cycles</td>
</tr>
<tr>
<td>Total Number of usable embryos</td>
</tr>
<tr>
<td>Clinical Pregnancy Rate</td>
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</tbody>
</table>

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OBJECTIVE: The thyroid is critical in metabolism, steroidogenesis and development. While treatment of thyroid abnormalities in reproductive-aged women is universally accepted, the threshold for thyroid stimulating hormone (TSH) is still debated. The American Society for Reproductive Medicine suggests 2.5 mIU/L while the American Thyroid Association recommends 4.12 mIU/L. Fertility, particularly ovulation, implantation and miscarriage risk, is impacted by thyroid dysfunction, but there is limited understanding of artificial reproductive technologies (ART) outcomes in euthyroid women. This study aimed to determine how TSH impacts cycle outcomes after controlled ovarian stimulation for IVF.

DESIGN: Retrospective

MATERIALS AND METHODS: Patients who underwent IVF from 2005-2018 were included. Patient age, gravidity, parity, day 3 TSH, basal antral follicle count (BAFC), serum estradiol (E2) and progesterone (P4), total gonadotropin dose (GND), total number of oocytes and metaphase II (MII) oocytes retrieved, number of oocytes fertilized, number of blastocysts, day of biopsy and oocyte insemination method were determined. Patients were grouped by TSH: Group A=0.4-2.5, Group B=2.5-4.12 mIU/L. Frozen embryo transfer (FET) cycles with/without preimplantation genetic testing for aneuploidy (PGT-A) were sub-analyzed. Clinical pregnancy (CP), ongoing pregnancy (OP), and clinical pregnancy loss (CPL) rates were determined. CP was considered sonographic evidence of a gestational sac. Data was analyzed with a T-test, Chi square, Fishers Exact test and multivariate logistic regression.

RESULTS: Data from 861 IVF and 358 FET cycles was included. Both groups had similar age, gravidity, parity, BAFC, serum E2/P4, total GND, oocyte insemination type and biopsy day. No differences in MII, fertilization or blastulation rates were found. After adjusting for confounders, blastulation was higher in Group B (OR 1.5, 95% CI 1.2-1.7). Patients who underwent FET had no differences in CPR (58.9 vs 63.8%, p=0.4), OPR (44.9 vs 51.1%, p=0.3) or CPL (23.9 vs 20.0%, p=0.8), before and after adjusting for confounders.

CONCLUSIONS: Pregnancy outcomes after ART do not differ in euthyroid patients even with fluctuations in TSH. Despite higher blastulation rate in patients with TSH > 2.5 mIU/L, there were no differences in ovarian stimulation or pregnancy outcomes after FET. Euthyroid patients can be reassured that while thyroid dysfunction may cause hormonal disturbance, subtle changes do not impair IVF outcomes. Supported by: Ferring Pharmaceutical Sponsored Trial
with a persistent number of aneuploid embryos that cannot be solely attributed to the female partner may benefit from the selection of spermatozoa with intact chromatin to increase the chances of conceiving a child.


SPERM PREPARATION

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OBJECTIVE: We tested a novel approach for treating couples with complete and persistent embryo aneuploidy. Using a microfluidic device, we selected spermatozoa with the highest progressive motility and genomic integrity, capable of generating euploid embryos.

DESIGN: In a 19-month period, seven couples with a history of high sperm chromatin fragmentation (SCF) and persistent embryo aneuploidy underwent a cycle of ICSI in which semen specimens were processed in a standard fashion or by microfluidics. SCF was assessed by TUNEL. Fertilization and clinical pregnancy rates were assessed and compared between the two preparation methods, and preimplantation genetic testing for aneuploidy (PGT-A) was performed on the resulting embryos.

MATERIALS AND METHODS: Consent ing men had their ejaculates screened by standard semen analysis according to WHO 2010 criteria. Specimens were processed by density gradient and microfluidic sperm selection (MFSS). SCF was measured by TUNEL utilizing a commercial kit (In Situ Cell Death Detection Kit, Roche). At least 500 spermatozoa were counted under fluorescent microscopy, with an established threshold of 70% with intact chromatin to increase the chances of conceiving a child.

RESULTS: Seven couples (average maternal age, 38.3 ± 6 years; average paternal age, 44.2 ± 11 years) underwent 19 ICSI cycles. An average semen concentration of 11.5 ± 16x10^6/mL, 18.5 ± 16% motility, 2.0 ± 0% normal morphology, and an SCF of 29.2 ± 10% were found. After selection by density gradient, the total motility of the sperm samples was 34.2 ± 26%, resulting in a 60.4% fertilization rate. These cycles only generated 5 euploid embryos out of 2,3 which yielded two pregnancies, both resulting in miscarriage. Couples subsequently underwent 7 ICSI cycles in which the spermatozoa were processed by MFSS, which generated 98% ± 4 P < 0.0001 motility and an increased 4% morphology, while the SCF dropped to only 1.6 ± 1 P < 0.0001. Although the fertilization rate was 67.7%, 7 euploid blastocysts out of 14 (50%) were obtained, yielding 5 out of 7 ongoing clinical pregnancies (71.4%; P < 0.001).

CONCLUSIONS: Selecting a genomically competent male gamete may enhance the chances of obtaining a euploid conceptus for transfer. Couples with a persistent number of aneuploid embryos that cannot be solely attributed to the female partner may benefit from the selection of spermatozoa with intact chromatin to increase the chances of conceiving a child.

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OPTIMIZING SPERM CRYOPRESERVATION AND RECOVERY (OSCAR). R. Sabouhi, K. J. Presa, L. Stadtmuhr. Obstetrics and Gynecology, Jones Institute for Reproductive Medicine, Norfolk, VA.

OBJECTIVE: The objective of this study is to compare three common sperm freezing methods and two common thawing methods to one another to determine if there is a superior method to enhance post-thaw sperm survival.

DESIGN: Prospective cohort study.

MATERIALS AND METHODS: Twelve discarded fresh semen samples were obtained with patient consent. Each fresh sample was washed with mHTF (LifeGlobal, Guilford, CT) and centrifuged for 15 minutes at 400G. The pellet was resuspended in a 3:1 ratio of mHTF to Artic (Irvine Scientific, Santa Ana, CA). Motility was evaluated manually and each participant’s sample was divided into six aliquots for cryopreservation Medium (Irvine Scientific, Santa Ana, CA). Motility was evaluated manually and each participant’s sample was divided into six aliquots containing 0.5mL of specimen. Two aliquots of each specimen underwent one of 3 different freezing methods: (a) plunge into liquid nitrogen (LN2), (b) suspension in LN2 vapor for 15 minutes followed by plunge into LN2 or (c) suspension in LN2 vapor for 15 minutes followed by plunge into liquid nitrogen. Each of the freezing methods was subject to two different thawing methods: (a) 37°C dry bath for 20 minutes followed by 40 minutes at room temperature or (b) room temperature (RT) for 1 hour. Following recovery, a second evaluation of motility was performed for each aliquot as a measure of sperm viability (percent motility versus initial). Analysis by two way repeated measures ANOVA was utilized with a p-value of 0.05 to determine significance.

RESULTS: The mean motility for plunge sperm thawed at RT and 37°C were 22.9 ± 0.04% and 20.3 ± 0.04%, respectively. The mean motility for 15 minutes vapor then plunge thawed at RT and 37°C were 31.7 ± 0.06% and 31.5 ± 0.07%, respectively. For 1 hour in vapor then plunged, the mean motility at RT and 37°C were 43.8 ± 0.07% and 48.1 ± 0.06%, respectively. Survival rates between all freezing methods varied significantly, with greater recovery noted in the 1 hour vapor phase when compared both plunge (p < 0.001) and 15 minutes in vapor (p = 0.005). The shorter vapor phase of 15 minutes also demonstrated statistically greater viability compared to plunge (p = 0.027). Thawing methods did not significantly affect sperm recovery.

CONCLUSIONS: The recovery of motile sperm varied directly with the length of cooling prior to plunge in LN2 with an hour suspension in vapor resulting in greatest motility compared to the initial sample. Recovery was not dependent on the thaw method used, with either of the two methods producing similar results for a given cryopreservation method. Interestingly, it was also noted that samples plunged directly from room temperature into LN2 retained appreciable, if diminished viability.
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OBJECTIVE: To test a novel selection method capable of identifying spermatozoa that retain the highest chromatin integrity and have the highest progressive motility and improved morphology.

DESIGN: From October 2016 to April 2018, semen samples from infertile men (n = 30) were processed simultaneously by density gradient centrifugation (DGC) and by a new microfluidic sperm sorter (MFSS) chamber to allow selection of the most forwardly progressive motile sperm. Sperm chromatin fragmentation (SCF) was measured on the raw spermatozoa and on the fraction retained after DGC and MFSS. Some of these patients underwent ICSI.

MATERIALS AND METHODS: Fresh ejaculate specimens from consenting men were analyzed according to WHO 2010 criteria. DGC and MFSS were used to isolate motile spermatozoa based on cell motility and fluid dynamics. SCF was assessed by TUNEL on at least 500 spermatozoa under a fluorescent microscope utilizing a threshold of ≥15.

RESULTS: A total of 30 men with an average age of 39.7 ± 9.2 years had a sperm concentration of 52.5 ± 38 x10^6/mL, 33.5 ± 15% motility, and 2.4 ± 1% morphology. After DGC and MFSS, sperm concentration became 39.7 ± 26 and 13.8 ± 12 x10^6/mL, with 67.7 ± 30.4% and 98.1 ± 2% motility, respectively (P < 0.0001). The raw sample sperm morphology decreased from 23% in raw samples to 13% following DGC, and 1.8% after MFSS processing (P < 0.0001). Couples (n = 7) who underwent ICSI had an SCF of 1.6 ± 1% after MFSS, which was remarkably lower than their ejaculates (29.1 ± 10; P < 0.0001), and reported a CPR of 71%.

CONCLUSIONS: Microfluidic selection yields the most progressive motile portion of the male gamete with better morphology, characterized by the highest genomic integrity. Spermatozoa selected in this manner appear to be associated with higher ongoing pregnancy rates.

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LABORATORY AND CLINICAL OUTCOMES OF SPERMATOZA PREPARED THROUGH A MICROFLUIDIC DEVICE: A PROSPECTIVE PILOT SIBLING OOCYTE STUDY. B. Akcay, N. Findikli, T. Aksoy, B. Teke, E. Oral, M. Kavrut, M. Bahceci, IVF Laboratory, Bahceci Fulya IVF Centre, Istanbul, Turkey; Infertility Clinic, Istanbul University Cerrahpasa School of Medicine, Istanbul, Turkey; Infertility Clinic, Bahceci Fulya IVF Centre, Istanbul, Turkey.

OBJECTIVE: Selection of the most viable spermatozoa in conventional ART treatments is still a challenge. Recent studies have shown that involvement of multiple centrifugation steps in conventional sperm separation techniques can also artificially induce increased DNA damage, implying that more nature-like sperm selection methodologies such as microfluidic-based sperm selection (MFSS) are needed. Although such devices are currently being tested for their biological potential, data related to MFSSs laboratory and clinical performance are scarce. The aim of this study is to evaluate the laboratory and clinical outcomes of sperm preparation and selection via Fertile®, a MFSS device which is recently introduced in the ART market.

DESIGN: Prospective sibling oocyte study.

MATERIALS AND METHODS: This study was performed between January - March 2017 and included 30 ART cycles in which female age was ≤ 38, ≥ 10 oocytes collected and males showing normal sperm concentration & motility but having poor morphology (isolated teratozoospermia). In each case, semen sample was processed by density gradient sperm preparation (DG) and MFSS sperm preparation methods in parallel. After hyaluronidase treatment, m2 sibling oocytes were randomly (and equally where available) allocated either in DG group or MFSS group for intracytoplasmic morphologically selected sperm injection (IMSI). Resulting embryos were cultured up to blastocysts stage. All embryo transfers were performed as frozen embryo transfer (FET). Main outcome measures were fertilization rate, cleavage rate, percent of grade I embryos on day 3 of embryo development, blastocyst development rate and clinical outcome.

RESULTS: A total of 540 cumulus oocyte complexes (COCs) and 439 m2 oocytes were collected from 30 patients. No statistically significant differences were found with respect to main laboratory performance indicators including fertilization rates (73.7% vs. 77.4%), early cleavage rate (98.8% vs. 99.4%), grade Embryos on day 3 (71.5% vs. 74.7%) as well as blastocyst development rate (45.8% vs. 48.4%) between DG and MFSS groups respectively (p > 0.05).

In 26 cycles, P-586 Wednesday, October 10, 2018 6:30 AM

OPTIMIZATION OF SPERM CULTURE CONDITIONS FOR ASSISTED REPRODUCTIVE TECHNOLOGIES. L. Borrann, C. Cucvo. OB/GYN, Massachusetts General Hospital-Harvard Medical School, Boston, MA; San Diego Fertility Center, San Diego, CA.

OBJECTIVE: Optimizing sperm performance is essential for maximizing clinical outcomes in Assisted Reproductive Technology (ART) programs. Maintaining optimal conditions during sperm handling is subject to atmospheric conditions. Commercial handling media use buffering agents to regulate pH between 7.2-7.4. HEPES and MOPS are zwitterionic buffering agents used to maintain stable conditions for oocytes and embryos at atmospheric conditions. Individually, HEPES has been shown to be safe and effective for sperm storage. Additionally, in animal models MOPS has been shown to preserve motility at lower temperatures. Combining buffers in solution has previously been shown to stabilize external and internal pH in biologic systems, although less evidence is available in the human literature. The objective of this study was to evaluate whether dual-buffer culture media such as Multipurpose Handling Medium (MHM) improves sperm viability parameters when compared to conventional handling media: Sperm Washing Media (SPWASH, Irvine Scientific) and Quinn’s Sperm Washing Medium (QUINN, CooperSurgical).

MATERIALS AND METHODS: Twenty-one men undergoing semen analysis for diagnostic purposes were enrolled and served as their own controls. Patients with normal parameters by WHO 5th edition guidelines were included in this study. Specimens were processed per institutional guidelines. Processed sperm motility and concentration was calculated and evenly distributed to MHM, SPWASH and QUINN media to yield a final concentration of 5 million/ml motile sperm per treatment. Samples were maintained at room temperature and assessments were performed at 8, 24 and 48 hrs. Computer Assisted Sperm Analyzer (CASA; CEROS II, Hamilton Thorne) was used to evaluate concentration, percent motility and percent progression. Statistical analysis was performed using linear mixed regression modeling.

RESULTS: At 48 hours, MHM had better performance with sperm viability, total motility and rapid forward progression compared to controls. The estimated mean percent motility was lower in QUINN media (17.04% lower, p < 0.001) and SPWASH (17.14% lower, p < 0.001) than to MHM, figure 1. A similar reduction in percent rapid progression was found in mean rapid progression SPWASH (13.16% lower, p < 0.001) and QUINN (10.6% lower, p < 0.001).

CONCLUSIONS: Sperm processing in dual-buffer culture media such as Multipurpose Handling Medium results in higher sperm viability and improved sperm motility dynamics following sperm isolation and extended culture.

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FERTILITY & STERILITY®

P-588 Wednesday, October 10, 2018 6:30 AM

OPTIMIZATION OF SPERM CULTURE CONDITIONS FOR ASSISTED REPRODUCTIVE TECHNOLOGIES. C. L. Borrann, C. Cucvo. OB/GYN, Massachusetts General Hospital-Harvard Medical School, Boston, MA; San Diego Fertility Center, San Diego, CA.

OBJECTIVE: Optimizing sperm performance is essential for maximizing clinical outcomes in Assisted Reproductive Technology (ART) programs. Maintaining optimal conditions during sperm handling is subject to atmospheric conditions. Commercial handling media use buffering agents to regulate pH between 7.2-7.4. HEPES and MOPS are zwitterionic buffering agents used to maintain stable conditions for oocytes and embryos at atmospheric conditions. Individually, HEPES has been shown to be safe and effective for sperm storage. Additionally, in animal models MOPS has been shown to preserve motility at lower temperatures. Combining buffers in solution has previously been shown to stabilize external and internal pH in biologic systems, although less evidence is available in the human literature. The objective of this study was to evaluate whether dual-buffer culture media such as Multipurpose Handling Medium (MHM) improves sperm viability parameters when compared to conventional handling media: Sperm Washing Media (SPWASH, Irvine Scientific) and Quinn’s Sperm Washing Medium (QUINN, CooperSurgical).

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CONCLUSIONS: Sperm processing in dual-buffer culture media such as Multipurpose Handling Medium results in higher sperm viability and improved sperm motility dynamics following sperm isolation and extended culture.
objective of this study was to determine if two established semen processing techniques in men with proven ZIKV infection of semen could clear the semen of the virus.

**DESIGN:** Observational study.

**MATERIALS AND METHODS:** Subjects were men with confirmed ZIKV infection and presence of the virus in semen, who were recruited by a private fertility clinic in Trinidad during the 2016 Caribbean epidemic. Semen assessment was of ZIKV load by RT-PCR on raw samples and semen samples processed by gradient wash and swim up technique.

**RESULTS:** Of 23 men testing positive for ZIKV infection, 3 men were ZIKV RT-PCR positive in semen, with RNA viral loads high in 2 men with cycle threshold (Ct) values of 17.9 and 18.6 in 2 and low in 1 man with Ct of 34.7. Viral clearance by gradient washing was only achieved in one sample, which had a low viral load and from which ZIKV could not subsequently be isolated. Swim-up and gradient washing failed to reduce ZIKV loads in 2 culture positive samples.

**CONCLUSIONS:** Currently utilised semen washing techniques are not effective in reducing ZIKV viral load in semen containing a high viral load, although it has been possible to clear a low viral load.

**References:**

**Supported by:** European Union’s Horizon 2020 research and innovation programme under ZikaPLAN grant agreement No 734584

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### Comparing Sperm Collections

<table>
<thead>
<tr>
<th>Sample collected n days post symptom onset</th>
<th>ZIKV isolation</th>
<th>RT-PCR R (Ct-values)</th>
<th>RT-PCR GW (Ct-values)</th>
<th>RT-PCR SU (Ct-values)</th>
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<tbody>
<tr>
<td>E</td>
<td>17 positive</td>
<td>17.9</td>
<td>21.2</td>
<td>21.1</td>
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<tr>
<td>V</td>
<td>6 positive</td>
<td>18.6</td>
<td>19.5</td>
<td>ND</td>
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<tr>
<td>R</td>
<td>2 ND</td>
<td>34.7</td>
<td>0</td>
<td>36.0</td>
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</table>

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**P-588 Wednesday, October 10, 2018 6:30 AM**

**DOUBLE COLLECTION TO IMPROVE IUI PREGNANCY RATE WITH VERY POOR INITIAL SPECIMEN: IS IT WORTH THE TROUBLE?**  

D. R. Grow; D. Hernandez-Aranda, C. Bartels, A. J. Loza, U. Sward, A. Bartolucci, C. Benadiva, ObGyn, UConn Health, Farmington, CT; ObGyn, St Francis Hospital, Hartford, CT; Uconn Health Center, Farmington, CT; Center for Advanced Reproductive Services, Farmington, CT.

**OBJECTIVE:** IUI is a useful treatment for mild-moderate male factor infertility, especially when paired with super-ovulation. When an IUI sample reveals less than 1 million (M) total motile sperm (TMS), this severely oligospermic specimen is unlikely to result in a pregnancy. Recent data shows that double collections with very short abstinence times can produce improved specimens, suggesting clinical benefit. (Bahadur et al) but to date, no pregnancy data have been reported. This is the first report of pregnancy outcome after double collection IUI for oligospermia.

**DESIGN:** Retrospective cohort study

**MATERIALS AND METHODS:** During the study period 8/1/16 through 3/31/18, there were 1982 IUI’s performed in our center. If the collected sample revealed < 10 M total motile sperm, the patient was asked to return to produce a second ejaculate. The sperm was prepared with a gradient using Isolate (Irvine), Sperm Wash (Irvine) and the pellet suspended in 0.5 mL of Sperm Wash. If the second sample revealed adequate sperm concentration, it was similarly prepared and added to the sperm wash solution for the IUI. Sperm parameters were compared with the paired t-test. Pregnancy rates were compared with Fisher’s exact test.

**RESULTS:** During the study period, 39 men produced a second sample. This group of men had on average 35+/- 37 M TMS in the complete semen analysis most recent to the treatment cycle. Of these cycles, there were 23 using Clomiphene, 7 using rFSH, 5 using letrozole, and 4 natural cycle. TMS available for IUI nearly tripled after the second collection, with improved concentration and motility after only 1-3 hours of abstinence. Following double collection IUI treatment, there was a single clinical pregnancy, and no ongoing pregnancies. In comparison, ongoing pregnancy rates for our general IUI population are 13.6% for Clomiphene/IUI and 14.6 % for Letrozole/IUI. For the population of male factor IUI (defined as with original TMS < 35), the OPR is 12.1%, better than with double IUI (P<0.05). Pregnancy rates with TMS < 5 M and < 1 M were 0% and 0% respectively.

**CONCLUSIONS:** Collection of a second sample when the initial unprepied TMS is less than 10 M, improves the IUI sample, nearly tripling the TMS in the combined, prepped specimen. There were no ongoing pregnancies in 39 treatment cycles. This preliminary report suggests the inconvenience of bringing patients back for a second collection on the morning of the IUI may outweigh the limited clinical benefit.

**References:**

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### Comparing Sperm Collections

<table>
<thead>
<tr>
<th>Conc</th>
<th>Vol</th>
<th>Mot</th>
<th>TMS (post-prep)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>6.5 +/- 6.3</td>
<td>3.2 +/- 1.8</td>
<td>33 +/- 14</td>
</tr>
<tr>
<td>Second</td>
<td>10.4 +/- 10.0</td>
<td>1.8 +/- 1.1</td>
<td>39 +/- 17</td>
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<tr>
<td>Combined</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
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<td>P-value</td>
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</tbody>
</table>

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**References:**
DENSITY GRADIENT OUTPERFORMS SWIM-UP WHEN EXAMINING DIFFERENT SPERM NUCLEAR DNA INTEGRITY AND MEMBRANE CHARACTERISTICS. D. Vaughan, a D. Sakkas, b B. Leader, c E. E. Tirado, a OBGYN, Beth Israel Deaconess Medical Center, Boston, MA; bBoston IVF, Waltham, MA; cClinical Research Division, ReproSource, Inc, Woburn, MA; D. Andrology, Director of Andrology Department, Woburn, MA.

OBJECTIVE: Male factor contributes to 30-40% of infertility cases. In addition, infection and inflammation of the male reproductive tract are significant causes of male factor infertility. The objective of this study was to compare sperm quality, after two commonly used sperm preparation methods, using a series of commercially available clinical tests for male factor infertility.

DESIGN: Prospective cohort study

MATERIALS AND METHODS: Twenty discarded samples from patients attending a single, university-affiliated infertility clinic were utilized for the study, following routine processing of semen using either swim-up or PureSperm (Nidacon) density gradients. The following sperm characteristics were examined to evaluate nuclear integrity: DNA fragmentation index (DFI), high DNA stainability (HDS) and decondensation, performed by measuring head area after 30 minutes of exposure to dithiothreitol (DTT). Sperm membrane integrity tests included hypersonomic swelling test (HOST), viability and apoptosis (Annexin). The acrosome was evaluated using an anti-acrosome-monoconal human antibody (Sigma) and the presence of CD46. Lastly, CD45 was used to identify the presence of leukocytes by flow cytometry.

RESULTS: Compared to raw sperm (27%), both swim-up and density gradients doubled percentage of sperm which were fully decondensed in 30 minutes (62.5% and 56.3% respectively). Density gradient preparation was superior to swim-up in improving both nuclear DNA and membrane integrity parameters (Table 1). There was a significant difference in mean DFI between density gradient preparation and swim-up (5.9 and 17.0 respectively, p<0.05). HOST was also significantly different between the density gradient preparation and both the swim-up and the raw samples. There was a significant difference in acrosomal characteristics (anti-acrosome-monoconal human antibody and CD46) between the groups. Lastly, CD45 levels were similar across groups.

CONCLUSIONS: There is a longstanding debate about the merits of density gradient and swim-up in sperm selection. In this study, density gradient was superior to swim-up in selecting higher proportions of high quality spermatozoa. Clinical correlates are ongoing.

Table 1. Comparison of commercially available, clinical laboratory test results in semen from raw, post swim-up, and post density-gradient (PureSperm 100) samples. Data are presented as means (standard deviations).*P<0.05 compared to Raw and †P<0.05 comparing gradient versus swim up.

Supported by: ReproSource Investigator Award.

FERTILITY & STERILITY

P-590 Wednesday, October 10, 2018 6:30 AM

THE HAMSTER EGG PENETRATION TEST CAN DECREASE ICSI UTILIZATION WHILE MAINTAINING HIGH MICRODROPLET FERTILIZATION RATES. Y. Ibrahim, a B. Emery, b D. Carrell, a,b,c E. Johnstone, c Obstetrics and Gynecology, University of Utah, Salt Lake City, UT; Division of Urology, Department of Surgery, University of Utah, Salt Lake City, UT; Human Genetics, University of Utah, Salt Lake City, UT.

OBJECTIVE: Intracytoplasmic sperm injection (ICSI) is indicated primarily for the treatment of male factor infertility but is also widely used with IVF in men with borderline semen parameters [1]. ICSI has been associated with increased risks of certain birth defects and imprinting disorders [2]. Our practice utilizes the hamster egg penetration test (HEPT) to select couples for ICSI, and maintains ICSI utilization rates at least 10% lower than national averages [3]. The objective of our study is to determine if the HEPT compares to WHO-V morphology in predicting successful microdrop-fertilization rates.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: We included 502 subjects who underwent IVF cycles at the University of Utah utilizing partner sperm between May 2013 and November 2017. There were 260 subjects where both the HEPT and semen analysis were performed within two years prior to the IVF cycle. These subjects were stratified into 4 groups as presented in the table below based on HEPT and morphology results. The mean microdrop and ICSI fertilization rates were calculated for each group. Unpaired t-tests were used to calculate differences in mean fertilization rates between clinically interesting groups. A p-value <0.05 was considered statistically significant.

RESULTS: As shown in Table 1, 36% of patients had an abnormal HEPT, while 59% of patients had an abnormal WHO-V morphology. Among patients with a normal HEPT, there was no statistically significant difference in mean microdrop fertilization rates between those with normal and abnormal morphology (95.81% vs 91.41%, p = 0.0763). Forty-five percent of subjects with abnormal morphology (70/155) were able to avoid ICSI due to a normal HEPT and have a mean microdrop fertilization rate of 91.41%. There were 71 subjects who did not have the HEPT performed and had microdrop-fertilization due to a normal morphology and there were 171

Mean and 95% Confidence Interval fertilization rates by HEPT and WHO-V Morphology

<table>
<thead>
<tr>
<th>HEPT&lt;80%</th>
<th>HEPT&gt;80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO-V Morphology&lt;4%</td>
<td>Group 1</td>
</tr>
<tr>
<td>ICSI Fertilization rate (%)</td>
<td>87.95 (84.10 - 91.81) N=73</td>
</tr>
<tr>
<td>Microdrop fertilization rate (%)</td>
<td>81.25 (44.19 - 118.32) N=2</td>
</tr>
<tr>
<td>WHO-V Morphology&gt;4%</td>
<td>Group 3</td>
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<tr>
<td>ICSI Fertilization rate (%)</td>
<td>88.94 (81.97 - 95.91) N=19</td>
</tr>
<tr>
<td>Microdrop fertilization rate (%)</td>
<td>N/A N=0</td>
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</table>
P-591 Wednesday, October 10, 2018 6:30 AM
IFV OR ICSI: WHICH IS BETTER IN WOMEN WITH ENDOMETRIOSIS ASSOCIATED INFERTILITY?

L. Tan, K. C. Brown, H. Dhanani, L. Hughes, F. Tekpetey, A. Abu Rafea, Obstetrics and Gynaecology, Western University, London, ON, Canada; The Fertility Clinic, London Health Sciences Centre - Victoria Hospital, London, ON, Canada; Schultich School of Medicine and Dentistry, Western University, London, ON, Canada.

OBJECTIVE: Endometriosis is associated with infertility. Between 25 - 50% of infertile women have endometriosis and 30 - 50% of women with endometriosis are infertile (1). Many of these women will have to undergo IVF. Abnormal folliculogenesis, impaired oocyte and embryo quality due to radical oxidative stress and imbalances in the levels of cytokines and interleukins have been described as potential contributors to infertility in women with endometriosis (2). We wondered if utilizing ICSI may overcome these stressors and improve fertilization rate and pregnancy rate in women with endometriosis associated infertility.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: 262 conventional IVF cycles and 260 ICSI cycles from 2006 - 2016 at the Fertility Clinic in London, Ontario, Canada. Women were surgically staged according to the ASRM revised classification of endometriosis: 1996 and were classified as no endometriosis (control group), minimal to mild (Stage I & II) endometriosis or moderate to severe (Stage III & IV) endometriosis. Women with a legitimate reason for ICSI were excluded from the study. Linear and logistic regression analyses were performed to examine the association between stages of endometriosis and method of fertilization on various reproductive outcomes. Outcomes were adjusted for age, BMI, FSH, and number of embryos transferred.

RESULTS: No statistically significant differences in reproductive outcomes were noted between women with no endometriosis and those with minimal to mild (stage I & II) endometriosis whether conventional IVF or ICSI was utilized. However, ICSI was associated with a 71% decrease in clinical pregnancy rate (OR = 0.29, p = 0.046) and approached statistical significance for a 69% decrease in live birth rate (OR = 0.31, p = 0.0796) in women with moderate to severe (stage III & IV) endometriosis.

CONCLUSIONS: The findings of this study suggest that there is no added benefit and it is potentially detrimental to recommend ICSI in women diagnosed with endometriosis associated infertility especially in moderate to severe (Stage III & IV) endometriosis. Further study with a larger sample size will need to be done. However, at this time caution should be practiced against recommending ICSI when there is no clear indication of failed fertilization with conventional IVF or male factor infertility, especially in women diagnosed with endometriosis associated infertility.

P-592 Wednesday, October 10, 2018 6:30 AM
THE IMPACT OF MEIOTIC SPINDLE ASSESSMENT IN EMBRYO DEVELOPMENT. M. d. Lopez Rioja, A. Chavez Badiola, R. Garcia Sanchez, P. Zavala Gonzalez, Y. Recio, M. Sanchez Gonzalez; New Hope Fertility Center, Guadalajara, Mexico, Mexico; New Hope Fertility Center, Mexico, Mexico.

OBJECTIVE: The meiotic spindle (MS) is a direct indicator of physiological behaviour, and certainly may be a good prognostic marker of oocyte viability. In the present work, we propose a predictive model of oocyte viability based on morphologic and topologic features of the meiotic spindle.

DESIGN: This is a retrospective study in which 450 MII oocytes obtained from patients eligible for IVF with intracytoplasmic sperm injection (ICSI) were subject to spindle located ICSI (SL-ICSI) prior to fertilization and embryo development follow-up. All patients attended New Hope Centers located in Guadalajara and Mexico City, Mexico from November 2014 to August 2016.

MATERIALS AND METHODS: Controlled ovarian stimulation was performed with a minimal stimulation protocol. MS visualization was performed just before ICSI with a polarizer filter (make), under 40x magnification. The oocytes were rotated until polar body was positioned at 12 o’clock. The spindle position and intensity was recorded by embryologist as 0/+;++;+++; with 0 being assigned to spindle absence and +++ to maximum spindle intensity when compared against the most birefringent area in zona pellucida.

RESULTS: A QUEST decision tree for predicting fertilization and viable embryos showed that the majority of 2 pronuclei embryos are found when MS intensity is higher than 0 with spindle positioned at 11,12 and 1 o’clock. The model adequately predicted 79% of cases, and the most important independent variable in this model was the intensity of the MS. A binary logistic regression model was performed to assess if age, as a numerical variable, meiotic spindle location and intensity could predict fertilization. The model was statistically significant (p<0.000) with an effect size of 7.9% (Nagelkerke R^2). Hosmer and Lemeshow test for expected and observed event rates was not statistically significant (X^2 = 13.34, p=0.101) which indicated the goodness of fit of the model. The model correctly predicted 77.8% of cases. Meiotic spindle location at 11,12 and 1 o’clock predicted embryo viability with an OR 2.071. MS intensity ++ and +++ predicted fertilization with an OR 2.0 and 2.5 respectively. MS intensity +++ was not significant due to small sample size and will be eliminated as a category in further analyses

CONCLUSIONS: Our proposed algorithm suggests a combination of parameters such as MS characteristics, patients’ age and PN status could effectively predict an oocyte’s chance to become a viable embryo. Whether this could be included as a measure to better select the one embryo to transfer or not is yet to be assessed as is the potential this algorithm has to be added into already existing models to predict one embryo’s chance to become a blastocyst and a successful pregnancy.

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FERTILIZATION BY ICSI RESULTS IN SIGNIFICANTLY HIGHER ANEUPLOIDY RATES COMPARED TO IFV, IN EMBRYOS ANALYSED BY NEXT GENERATION SEQUENCING (NGS) OR COMPARATIVE GENOME HYBRIDIZATION (CGH) ARRAY. H. K. Swearman, G. Liperis, J. Crittenden, C. Sjoblom; Institute for Reproductive Medicine, University of Sydney, Sydney, Australia; Westmead Fertility Centre, Westmead, Australia.

OBJECTIVE: The objective of this study was to understand if the method of fertilization (IFV vs. ICSI) influences the aneuploidy rate in embryos from patients of the same age group.

DESIGN: This was a retrospective cohort study of consenting patients undergoing PGS at Westmead Fertility Centre between February 2014 and June 2017. Indicators for PGS included advanced maternal age of more than 36 years, recurrent implantation failure of ≥3 embryo transfers with high-quality embryos, unsuccessful implantation following transfers of ≥10 embryos and recurrent miscarriage of ≥2 miscarriages.

MATERIALS AND METHODS: The study included data from 131 couples undergoing an average of 2.3 banking cycles ahead of embryo biopsy
and aneuploidy screening using NGS or aCGH (ICSI n=31, average 10.55 embryos per couple and IVF n=100, average 13.02 embryos per couple). Fresh ejaculated sperm samples were used for fertilization in both groups. Patients with poor sperm (<5×10^6/ml and <10% motility) and those with known translocations were excluded from analysis to avoid any influence on ploidy rates. GEE models were used to compare ploidy rates per couple in the IVF and ICSI cohorts, taking into account female age at oocyte retrieval.

RESULTS: ICSI cycles resulted in a significantly higher embryo aneuploidy rate per couple compared to IVF, 79.1% vs. 70.9% respectively (p=0.001) adjusting for female age, which was not significantly different between the two groups (ICSI 36.9 yrs, IVF 38.3 yrs; p=0.13). Aneuploidy rates were not affected by the incidence of banking with no significant difference in the data between those embryos which were frozen-thawed before biopsy and those which were biopsied as part of a fresh cycle. Considering that only euploid embryos were transferred, there was no significant difference in clinical pregnancy rate between each fertilization method (45.7% ICSI vs. 46.1% IVF). However, blastulation rates were significantly higher in euploid IVF embryos (47.7% vs. 23.0%), so utilisation rate improved compared to ICSI which could indicate higher cumulative pregnancy rates in the future.

CONCLUSIONS: Embryo aneuploidy rate (per couple) was significantly higher when oocytes were fertilized by ICSI, compared to those that were fertilized by IVF. ICSI was initially developed to overcome male factor infertility, accounting for 40% of couples seeking ART. However, the proportion of ICSI cycles worldwide is 66%, with some regions almost exclusively doing ICSI. There is currently no evidence that ICSI is beneficial for couples with no underlying male factor. The use of ICSI is increasing, often being utilized even when sperm is suitable for IVF; where embryo selection is based on morphological development alone without PGS, this could unknowingly increase the risk of an aneuploid embryo being transferred, and be a contributing factor to cycle outcome.

Supported by: This study was kindly supported by Westmead Fertility Centre.

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LONG-TERM FOLLOW UP OF THE BABIES BORN FROM ICSI WITH CALCIUM IONOPHORE ACTIVATION. M. Irie, S. Tarui, H. Matsumoto, S. Mizuno, A. Fukuda, Y. Morimoto, IVF Osaka Clinic, Gashiosaka, Japan; IVF Osaka Clinic, Osaka, Japan; IVF Osaka Clinic, Hi-gashiosaka, Japan; HORAC Grand Front Osaka Clinic, Osaka, Japan.

OBJECTIVE: Repeated fertilization failures in ICSI are rare but distressful events for patients. Therefore, oocyte activation by calcium (Ca) ionophore following ICSI has been applied to enhance fertilization. However, few follow up studies regarding children born after Ca ionophore have been reported and no statistically significant differences in fetal development at birth were indicated compared to those without artificial oocyte activation. The present study was conducted to clarify whether Ca ionophore activation affected the babies development until 5 years old.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: Development of 24 babies born from ICSI treated with Ca ionophore for repeated fertilization failures from 2004 to 2016 were investigated by sending questionnaires to their parents. Sex ratio, gestational age, congenital abnormalities at birth, birth weight and height were compared to the data of national growth survey on preschool children collected by Ministry of Health, Labor and Welfare (MHWL) of Japan. Height, weight and congenital abnormalities diagnosed at the age of 1 and a half, 2, 3 and a half and 5 were also followed up in 6 babies out of Japan. Height, weight and congenital abnormalities diagnosed at the age of children collected by Ministry of Health, Labor and Welfare (MHLW) and height were compared to the data of national growth survey on preschool

RESULTS: The sex ratio (f/m) was 0.6 (15 males and 9 females, respectively). Average gestational age (days) was 272.5±11.9. 21 trisomy was confirmed in one baby. Average birth height (cm) of males and females were 48.35±1.85 and 49.17±2.50, respectively. Average birth weight (kg) of males and females were 2.89±0.43 and 2.92±0.42, respectively. Birth height of all babies were plotted between the 97th and 3rd percentile curves of the national growth survey. Birth weight of 20 babies were plotted between the 97th and 3rd percentile curves, but 4 babies were out. Except for one male, height and weight of all 5 babies at the age from 1 to 5 were plotted between the 97th and 3rd percentile curves. There were no significant differences in physical development between the data of babies born from ICSI with Ca ionophore and national average by MHWL. Any abnormalities were not diagnosed until 5 years old.

CONCLUSIONS: The present study demonstrates that oocyte activation with Ca ionophore does not influence physical development of children. However, the safety of Ca ionophore should not be concluded from the present study due to sample size. 21 trisomy was confirmed in one baby. It is known as the result of a chromosome abnormality which occurs in the first meiotic cell cycle and is also known to be caused by chromosome nondisjunction during the early stages of embryo cleavage. Further scrutiny is required to determine the influence of Ca ionophore on the prognosis of babies.

P-595 Wednesday, October 10, 2018 6:30 AM

INVESTIGATION OF FERTILIZATION AND CLINICAL OUTCOMES FOLLOWING ICSI IN PATIENTS WITH PRIMARY DYSKINESIA. H. Ishimoto, S. Mizuta, K. Yamaguchi, H. Matsubayashi, K. Kitaya, T. Takeuchi, T. Ishikawa, Reproduction Clinic Tokyo, Tokyo, Japan; Reproductive Medicine, Reproduction Clinic Osaka, Osaka, Japan; Reproduction Clinic Osaka, Osaka, Japan.

OBJECTIVE: This retrospective study investigated the testicular sperm extraction (TESE)-ICSI outcomes of 9 couples with male Primary Ciliary Dyskinesia (PCD) between September 2013-December 2017 at one fertility clinic. Two pronuclei (2PN) rate, blastocyst development rate, good-quality blastocyst (Grade 3BB and above on day 5 by the Gardner scale) rate, clinical pregnancy rate (CPR), and live birth rate were investigated and compared between embryos derived from motile testicular spermatozoon, immotile testicular spermatozoon and ejaculated sperm.

DESIGN: A retrospective study in a reproductive center.

MATERIALS AND METHODS: TESE was performed on 9 PCD patients following semen analysis. Oocytes for TESE-ICSI were collected over a total of 18 oocyte retrieval cycles. All testicular spermatozoon retrieved were immotile and treated with pentoxifylline. The HOST was conducted on spermatozoon in which stimulating motility was unsuccessful to ensure viable spermatozoon was used for ICSI. All embryos were transferred by single frozen-thawed embryo transfers (FET). All patients involved gave written consent and international review board approval was granted. Statistical significance was calculated by application of the student T-test with a p-value of <0.05.

RESULTS: The mean female and male ages were 32.5±3.8 and 36.2±5.4, respectively. Sperm retrieval rate was 100% (9/9) with 22.2% (2/9) motile sperm retrieval following pentoxifylline treatment. Of the 9 patients who underwent TESE, motile sperm could be confirmed in the ejaculate of 1 patient. No significant differences in TESE-ICSI results using motile testicular spermatozoon, immotile spermatozoon and ejaculated sperm were reported in terms of 2PN rate (71.1%, 65.4%, 73.7%, respectively), blastocyst development rate (37.5%, 23.4%, 53.8%, respectively) and good-quality blastocyst rate (6.3%, 10.9%, 38.5%, respectively). CPR was 27.3% (3/11), 36.4% (4/11) and 50.0% (2/4), respectively, with no significant difference between the groups. Live birth rate using motile sperm, immotile sperm and ejaculated motile sperm were 33.3% (1/3) with 1 couple reporting miscarriage and 1 ongoing pregnancy, 75.0% (3/4), 50.0% (1/2), respectively. There are currently four female infants from testicular spermatozoon and one male infant from ejaculated sperm. No perinatal anomalies were reported.

CONCLUSIONS: Our results indicate sperm derivation does not affect fertilization or clinical outcomes following TESE-ICSI for patients with PCD. We therefore suggest that ejaculated motile sperm is used as first means of treatment, followed by fresh TESE and sequential HOS test following failed attempts.
EMBRYO BIOLOGY

Wednesday, October 10, 2018 6:30 AM

EMBRYO MORPHOLOGY ON DAY 3 OF EMBRYOGENESIS IS PREDICTIVE OF ANEUPLOIDY IN GENETICALLY TESTED EMBRYOS. M. Pasternak, M. Thompson, Z. Rosenwaks, S. Sandorfer. Weill Cornell Medical College, New York, NY; Reproductive Medicine, Physician. New York, NY; Cornell University Medical College, NYC, NY.

OBJECTIVE: The ability to accurately predict embryo quality while minimizing invasive testing is one of the most active pursuits in reproductive medicine; this study aims to assess whether embryo morphology in the cleavage stage on day 3 of embryogenesis is a useful prognostic indicator of aneuploidy.

DESIGN: This is a retrospective single institution study. Demographics of patients undergoing IVF with preimplantation genetic testing (PGT) during a 4-year period were recorded, as well as characteristics of their resultant embryos.

MATERIALS AND METHODS: 10,837 embryos from 2164 IVF cycles were included in the analysis. Patient age, body mass index (BMI), and anti-mullerian hormone (AMH) were recorded. Embryo characteristics prior to biopsy, genetic testing results, and ultimate frozen embryo transfer outcomes were documented for all patients. Embryo cell number and fragment percent of day 3 cleavage stage embryos were obtained by time-lapse microscopy. Chi-square analysis was used to test for the significance of embryo morphology on day 3 as a predictor of PGT outcome.

RESULTS: After stratifying day 3 embryos by cell number, embryos with ≥8 cells on day 3 had a significantly higher correlation with euploid status, compared to day 3 embryos with <7 cells (P = 0.00). 78% of euploid embryos were found to have ≥8 cells on day 3, while only 21.8% of euploid embryos had <7 cells on day 3 (P = 0.00). We subsequently stratified patients by age (<39yo, ≥40yo), to assess whether there was a difference in the ability of day 3 morphology to predict chromosomal status in younger versus older reproductive-age women. Women in the age group of ≥8 cells had a higher association with euploid embryos in patients <39yo (50.7%), versus in patients ≥40yo (19.4%). In patients ≥40yo, only 18.7% of total embryos were noted to be euploid, and of these embryos, 78% had ≥8 cells on day 3 (P = 0.038). Women in this age group with <7 cells on day 3 had an 83.6% rate of embryo aneuploidy (P = 0.038). Percent fragmentation on day 3 (<20% or >20%) did not appear to significantly predict aneuploidy.

CONCLUSIONS: IVF outcomes are heavily influenced by the ability to select and transfer the single best embryo with the highest potential for success. Cellular morphology and division in early embryos may be indicative of abnormal DNA replication, and thereby potentially useful as a screening tool to predict chromosomal abnormality. Our findings in women ≥40 yo appear to be especially predictive, as the percentage of euploid embryos in this population with ≥8 cells on day 3, is essentially equal to the percentage of euploid embryos in women in this age group. Our data demonstrate that day 3 embryo cell number is a strong predictor of aneuploidy, and suggests that using time-lapse microscopy to determine cellular morphology is an effective early non-invasive way to assess embryo quality and the second after embryos frozen-thawed replacement from the same in vitro fertilization (IVF) cycle.

MATERIALS AND METHODS: A first cohort (Fresh/FET) included all IVF cycles where fresh embryo transfer that resulted in a singleton live birth (fresh group n = 158) was followed by FET that led to a singleton live birth (FET group n = 158). A second cohort (FET/FET) included all siblings pairs where FET resulting in a singleton live birth (FET1 group n = 25) was followed by transfer of one or two frozen embryos from the same cohort that resulted in a singleton live birth (FET2 group n = 25). Twin pregnancies and stillbirths were excluded. The embryos were frozen either by slow freezing or vitrification. Birth weight were adjusted for gestational age and the adjusted birth weight in the two groups were compared with the Wilcoxon test.

RESULTS: In the Fresh/FET cohort, the mean adjusted birth weight of the FET group was significantly higher (by 271.2 g) than that of the fresh group (3508.9 g vs 3237.7 g respectively; p < 0.01). This difference still remains regardless of the number of embryos transferred, the stage of transfer, either freezing method (slow freezing or vitrification). In the Fresh/FET cohort, the mean adjusted birth weight was higher for the younger baby by 24.4 g but this difference is not significant (3383.7 g vs 3371.4 g; p = 0.632).

CONCLUSIONS: As both embryos in the Fresh/FET cohort (fresh and frozen) were from the same IVF cycle to avoid confounding factors and the only difference between groups was the absence/presence of the cryopreservation step, our results strongly suggest that the cryopreservation procedure affects the birth weight of sibling embryo cohort. Moreover, comparing birth weight between both FET groups, the difference between Fresh/FET cohort and the FET/FET one, our study suggests that parity is not involved in this difference and increases the role of cryopreservation step in birth weight variation. At our knowledge, this is a first large observational study which compares cryopreservation impact on birth weight in an embryo sibling cohort.

EMBRYO CRYOPRESERVATION PROCESS IS ASSOCIATED WITH SIGNIFICANTLY HIGHER BIRTH WEIGHT IN A SIBLING EMBRYO COHORT: A MULTICENTRIC STUDY. M. Pasternak, S. Phillips, A. Fernieres, Hoa, A. Cala, A. Fournier, E. Maris, C. Grysole, S. Brouillet, I. Kadoch, S. Hamaamah, ART/PGD Department, Montpellier, France; ART/PGD, University Hospital Montpellier, Montpellier, France; CHU Montpellier, Montpellier, France; Gynecology Department, Montpellier, France; Obstetrics and Gynecology, Faculty of Medicine, University of Montreal, Montreal, QC, Canada; Ovo Fertility, Montreal, QC, Canada; ART/PGD Department, La Tronche, France; Clinique ovo, Montreal, QC, Canada; University Hospital of Montpellier, Montpellier, France.

OBJECTIVE: To determine if the freeze-thaw procedure itself in a sibling embryo cohort, is involved in birth weight difference between singleton born after fresh embryo transfer and those born after frozen embryo transfer.

DESIGN: Retrospective multicentric cohort study. The cohort included 158 sibling pairs where the older sibling was born after fresh embryo transfer and the second after embryos frozen-thawed replacement from the same in vitro fertilization (IVF) cycle.

MATERIALS AND METHODS: A first cohort (Fresh/FET) included all IVF cycles where fresh embryo transfer that resulted in a singleton live birth (fresh group n = 158) was followed by FET that led to a singleton live birth (FET group n = 158). A second cohort (FET/FET) included all siblings pairs where FET resulting in a singleton live birth (FET1 group n = 25) was followed by transfer of one or two frozen embryos from the same cohort that resulted in a singleton live birth (FET2 group n = 25). Twin pregnancies and stillbirths were excluded. The embryos were frozen either by slow freezing or vitrification. Birth weight were adjusted for gestational age and the adjusted birth weight in the two groups were compared with the Wilcoxon test.

RESULTS: In the Fresh/FET cohort, the mean adjusted birth weight of the FET group was significantly higher (by 271.2 g) than that of the fresh group (3508.9 g vs 3237.7 g respectively; p < 0.01). This difference still remains regardless of the number of embryos transferred, the stage of transfer, either freezing method (slow freezing or vitrification). In the Fresh/FET cohort, the mean adjusted birth weight was higher for the younger baby by 24.4 g but this difference is not significant (3383.7 g vs 3371.4 g; p = 0.832).

CONCLUSIONS: As both embryos in the Fresh/FET cohort (fresh and frozen) were from the same IVF cycle to avoid confounding factors and the only difference between groups was the absence/presence of the cryopreservation step, our results strongly suggest that the cryopreservation procedure affects the birth weight of sibling embryo cohort. Moreover, comparing birth weight between both FET groups, the difference between Fresh/FET cohort and the FET/FET one, our study suggests that parity is not involved in this difference and increases the role of cryopreservation step in birth weight variation. At our knowledge, this is a first large observational study which compares cryopreservation impact on birth weight in an embryo sibling cohort.

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EUPLOID EMBRYOS THAT REACH THE BLASTOCYST STAGE ON DAY 5 OF DEVELOPMENT HAVE A SIGNIFICANTLY HIGHER CHANCE OF IMPLANTATION. S. McCormick, C. Pospisil, R. Smith, W. B. Schoolcraft, M. Katz-Jaffe, Colorado Center for Reproductive Medicine, Lone Tree, CO.

OBJECTIVE: In programmed frozen embryo transfers (FET), hormonal priming of endometrial receptivity is not dependent on the characteristics of blastocyst development. There are conflicting reports in the literature regarding whether blastocyst morphology has any impact on clinical outcomes. The aim of this study was to evaluate single, euploid, frozen, blastocyst transfer in association with blastocyst development and implantation potential.

DESIGN: Retrospective analysis of a large dataset of single euploid blastocyst transfers.

MATERIALS AND METHODS: In vitro fertilization (IVF) cycles with Preimplantation Genetic Testing for Aneuploidy (PGT-A) followed by a single, euploid blastocyst transfer (n = 2,428) were included for analysis. Blastocysts were biopsied on either day 5 (D5) or day 6 (D6) of embryonic development upon identification of an inner cell mass (ICM), with removal of approximately 3-6 trophectoderm (TE) cells prior to vitrification using the Cryotop method. Standard protocols for a hormone replacement FET were utilized. Single, euploid blastocyst transfer was performed and outcome recorded as negative, biochemical (positive hCG), non-viable implantation or ongoing implantation (fetal heart tone). Statistical analysis included ANOVA, Student’s t-test and Fisher’s exact test where appropriate, significance at P < 0.05.

RESULTS: The timing of blastocyst development, which is directly related to the existence of an ICM and therefore the day of TE biopsy, was significantly associated with single, euploid blastocyst transfer outcomes (P < 0.05). Specifically, the contribution of D5 biopsied blastocysts to positive outcomes was significantly greater than to negative outcomes (69.9% vs 54.8%, respectively; P < 0.0001), independent of embryo grade. Further evaluation of the three different negative outcomes revealed a significantly higher proportion of D5 biopsied blastocysts associated with biochemical or clinical signs of implantation (negative = 46.3%, biochemical = 58.8%, non-viable implantation = 67.3%; P < 0.001), once again independent of embryo grade. In contrast, outcome of D6 biopsied blastocysts was correlated with embryo quality and grade, as well as significantly associated with a negative outcome (P < 0.05).
CONCLUSIONS: This study has demonstrated a highly significant association between embryo morphology and euploid FET outcomes in regards to the timing of blastocyst development and therefore the day of TE biopsy. D5 biopsied blastocysts had a significantly higher probability of achieving ongoing implantation with fetal heart tone or showing signs of implantation than a D6 biopsied blastocyst, regardless of embryo quality. This would indicate embryonic factors, independent of chromosome numeration, are compromised in these slower developing D6 human blastocysts.

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ASSOCIATION BETWEEN EMBryo QUALITY AND ANEUPLOIDY AFTER A STANDARDIZED CONTROLLED OVARIAN STIMULATION (COS) PROTOCOL. S. Anderson,1,2, a R. Sethuraman,1,2 T. Hartlein,1,2 D. Brasile,3,4 b M. J. Glassner,1,2, a I. J. Orris,1,2 Main Line Fertility Center, Bryn Mawr, PA; 1Ob/gyn, Drexel University College of Medicine, Philadelphia, PA.

OBJECTIVE: There is growing evidence of a correlation between embryo development kinetic markers and ploidy status. The objective of this study was to examine the relationship between day 3 and day 5 embryo quality and aneuploidy after a standardized COS protocol.

DESIGN: This was a subgroup analyses within a prospective, randomized, and controlled study that was set at a university-affiliated fertility center between 2016-2018.

MATERIALS AND METHODS: Women aged 21-41 years pursuing in vitro fertilization were screened using strict inclusion/exclusion criteria. Inclusion criteria included: B. Good follicle stimulating hormone (FSH) < 10 IU/mL, estradiol < 12 IU/mL, estradiol < 50 pg/mL, and anti-Mullerian hormone (AMH) > 1.0 ng/mL on day 2-4 of menstrual cycle, and antral follicle count between 10 to 20, body weight < 12 IU/ml, estradiol < 50 pg/mL, and anti-Mullerian hormone (AMH) > 1.0 ng/mL on day 2-4 of menstrual cycle, and antral follicle count between 10 to 20, body weight < 50 kg, and BMI > 18 and < 32 kg/m². All 100 enrolled patients received 300IU start dose FSH in an antagonist cycle for the first 5 days, and then up to 450 IU per day at 75 IU increments until day of human chorionic gonadotropin (hCG) trigger injection, when at least 3 follicles reached 17 mm. Oocyte retrieval was conducted 36 hours after hCG trigger. Embryo morphology was graded using the Society for Assisted Reproductive Technology (SART) standardized system. A total of 347 blastocysts, from 91 patients, of good (Grade A) or fair quality (Grade B) were biopsied on day 5 or day 6 of culture for preimplantation genetic testing for aneuploidy (PGT-A) using next generation sequencing from a single genetics lab. End points analyzed were cell number, percent fragmentation, and cell symmetry in day 3 embryos. However, there was a significant difference for Assisted Reproductive Technology (SART) standardized system.

RESULTS: When comparing the embryo morphology between euploid and aneuploid embryos, no significance difference was found in cell number and cell symmetry in day 3 embryos. However, there was a significant difference for blastocyst quality and inferior blastocyst quality when compared to euploid embryos after a standardized controlled ovarian stimulation protocol.

CONCLUSIONS: There was a significant difference for blastocyst quality and inferior blastocyst quality when compared to euploid embryos after a standardized controlled ovarian stimulation protocol.

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OBJECTIVE: The introduction of time-lapse imaging has enabled dynamic embryo observations such as cleavage-type and development-speed determinations in addition to the conventional morphological assessments. Direct cleavage (DC) represents a chromosomal abnormality rather than a normal cleavage (NC) and reportedly affects embryo development. This study aimed to investigate whether DC embryos influence the outcomes of embryonic development and single frozen-thawed embryo transfer (SFET).

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EMBRYO BIOPSY DOES NOT AFFECT THE RATE OF MULTIPLES AFTER SINGLE EMBRYO TRANSFER (SET): A REVIEW OF THE SOCIETY FOR ASSISTED REPRODUCTIVE TECHNOLOGY (SART) REPORTED OUTCOMES. A. Peyser,1,2 S. L. Palen,3 T. Leung,3 M. Lesser,4 M. J. Blitz,5 N. Vohra,6 A. Hershlag,7 Northwell Fertility, Zucker School of Medicine at Hofstra/Northwell, Manhasset, NY; 3Biostatistics Unit, Feinstein Institute, Manhasset, NY; 2Biostatistics Unit, Feinstein Institute for Medical Research, Manhasset, NY.

OBJECTIVE: It has been hypothesized that embryo manipulation such as the artificial breach of the zona pellucida and blasmoner biopsy may result in an increased risk of multiples. However, most of these studies were performed on day 3 embryos before blastocyst biopsy. The objective of this study was to determine the incidence of monzygotic twins and triplets or more after embryo biopsy and SET.

DESIGN: Population-based retrospective cohort study of cycles from the Society for Assisted Reproductive Technology (SART) database.

MATERIALS AND METHODS: All 2005-2015 SART cycles were reviewed. Selection criteria included SET cycles where the number of fetal heart beats was reported as well as information regarding embryo biopsy. Those with no embryo biopsy information were excluded. The association between embryo biopsy and the number of fetal heart beats detected (none, singletons, twins, and triplets or more) was calculated by the Chi Square test.

RESULTS: A total of 40,016 cycles were included in the analysis. 10.5% (n = 4219) had embryo biopsy performed (n = 4427) with no biopsy. Of the SET that resulted in twins (n = 818), 12.9% (n = 106) had undergone embryo biopsy versus 87.1% (n = 712) with no biopsy. For triplets or more (n = 26), embryo biopsy was performed in 15.3% of cases (n = 4) and not performed in 84.6% (n = 22) of cases. There was no evidence

The number of twins and triplets in biopsied and not biopsied embryos

<table>
<thead>
<tr>
<th>Biopsied</th>
<th>Twins n (%)</th>
<th>Triplets n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>106</td>
<td>12.9</td>
<td>4</td>
</tr>
<tr>
<td>Not Biopsied</td>
<td>712 (87.1)</td>
<td>22 (84.6)</td>
</tr>
</tbody>
</table>
of an association between embryo biopsy and the four groups of ultrasound heartbeats (p=0.11).

CONCLUSIONS: 1. Embryo biopsy does not increase the chance of monosomygetic multiple pregnancies.2. The precise mechanism of monosomygetic twinning following ART remains unclear, however this information is important when counseling patients about the risks associated with embryo biopsy.

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EMBRYO MORPHOLOGY ON DAY 3 OF EMBRYOGENESIS IS PREDICTIVE OF PREGNANCY AND LIVE BIRTH RATES IN EUPLOID EMBRYOS; ANALYSIS OF 1112 EUPLOID EMBRYO TRANSFERS. M. Pasternak,1 M. Thompson,1 Z. Rosenwaks,2 S. Spandorfer.1 1Weill Cornell Medical College, New York, NY; 2Reproductive Medicine, Physician, New York, NY; 1Cornell University Medical College, NYC, NY.

OBJECTIVE: This study aims to assess whether embryo morphology, specifically the number of cells present in cleavage stage embryos on day 3 of embryogenesis, is a useful prognostic indicator of pregnancy and live birth rates in genetically tested euploid embryos.

DESIGN: This is a retrospective single institution study. Demographics of patients undergoing IVF with preimplantation genetic testing (PGT) during a 4-year period were recorded, as well as characteristics of their resultant embryos and subsequent obstetrical outcomes after euploid single embryo transfer (SET).

MATERIALS AND METHODS: 1112 euploid SET cycles were included in analysis. Patient age at retrieval, embryo characteristics prior to biopsy, results of chromosomal testing, and frozen embryo transfer outcomes were documented for all patients. Embryo cell number and percent fragmentation of day 3 cleavage stage embryos were obtained by time-lapse microscopy. Statistical analysis was conducted to assess significance of embryo morphology on day 3 as a predictor of pregnancy and live birth rates.

RESULTS: The euploid SET, our data demonstrated a 68.1% pregnancy rate, and a 49.9% live birth rate. 69.9% of patients that achieved pregnancy had a subsequent pregnancy loss. These results were similar independent of patient’s age at retrieval. After stratifying day 3 embryos by morphology, we analyzed SET outcomes from embryos with ≥8 cells on day 3, as our previous data analyses had established these were significantly less likely to be chromosomally abnormal, compared to day 3 embryos with ≤7 cells (P<0.01). Of 609 total live births, 85.9% resulted from the transfer of an embryo with ≥8 cells on day 3, with only 14.1% resulting from an embryo with <7 cells. Live Birth was achieved by 57.6% of euploid embryos with ≥8 cells on day 3 morphology, compared to only 42.6% with ≤7 cells (P<0.01).

CONCLUSIONS: Our data demonstrate that day 3 embryo morphology is a strong predictor of successful obstetrical outcome after SET. Despite the exclusive transfer of euploid embryos based on PGT, cellular morphology at the day 3 cleavage stage was highly significant and predictive of live birth rate. IVF outcomes are heavily influenced by the ability to select and transfer the single best embryo with the highest potential for a successful reproductive outcome. Cellular morphology and division in an early embryo may be indicative of abnormal DNA replication. Our data suggests that day 3 embryo morphology is an effective and non-invasive method of assessing chromosomal quality early in the embryogenic pathway. These embryonic parameters may prove potentially useful as a screening tool (either synergistically with PGT-A, or potentially independently) to predict obstetrical outcomes and live birth rate after embryo transfer.
OBJECTIVE: The objective of the study was to determine the rate of embryonic mosaicism in 21,212 clinical PGS cases utilizing trophectoderm biopsy and NGS.

DESIGN: Retrospective.

MATERIALS AND METHODS: A retrospective review was conducted of all embryos that underwent PGS by NGS over a 27-month period ending in April 2018 by a large genetics reference laboratory. All patients underwent standard in vitro fertilization (IVF) and preimplantation genetics screening (PGS). All embryo biopsies were performed at the blastocyst stage. 69% (14,636) of the embryo biopsies were performed on day 5 of development and 31% (6,576) of the embryo biopsies were performed on day 6 of development. Next generation sequencing (NGS) was performed on 50ng of DNA from each TE sample. First, the sample underwent enzymatic shearing, fragment stabilization and size selection. Then, sequencing primers and polymerase were added, the samples were loaded onto a sequencing cartridge and analyzed at a depth of 1X across the genome. Amniotic cells underwent routine G-banded karyotyping and NGS sequencing for chromosomes. Different tissues were analyzed for mosaicism.

RESULTS: 21,212 clinical PGS cases utilizing trophectoderm biopsy and NGS were identified. Of all samples, 763 (9.6%) mosaic embryos were identified. 29,449 (96.4%) non-mosaic embryos were identified. Of all samples, 763 (9.6%) mosaic embryos were identified. Of all samples, 763 (9.6%) mosaic embryos were identified.

CONCLUSIONS: Utilizing a robust data set, this data suggests that the rate of aneuploidy is higher among embryos that are slow to develop. While faster growing embryos are hypothesized to have a higher likelihood of being euploid, there is limited literature on the ploidy rate in day 5 versus day 6 biopsies after standardized controlled ovarian stimulation (COS) cycles.

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DAY 6 BLASTOCYSTS HAVE HIGHER ANEUPLOIDY RATES COMPARED TO DAY 5 BLASTOCYSTS AFTER STANDARDIZED CONTROLLED OVARIAN STIMULATION PROTOCOL. R. Sethuram, a D. Brasile, b,a B. Gociak, b M. J. Glassner, b J. J. Orris, a S. Anderson, a Drexel University College of Medicine, Philadelphia, PA; a Main Line Fertility Center, Bryn Mawr, PA.

OBJECTIVE: Blastocysts are biopsied for preimplantation genetic testing for aneuploidy (PGT-A) either on day 5 or day 6 of culture, depending on the rate of embryo development. While faster growing embryos are hypothesized to have a higher likelihood of being euploid, there is limited literature on the ploidy rate in day 5 versus day 6 biopsies after standardized controlled ovarian stimulation (COS) cycles.

DESIGN: This was a prospective observational study after a standardized COS protocol set at a university-affiliated fertility center between 2016-2018.

MATERIALS AND METHODS: Women 21 to 41 years of age were screened using strict inclusion criteria including anti-mullerian hormone (AMH) \(>1.0 \text{ ng/mL} \), follicle stimulating hormone (FSH) \(<10 \text{ IU/mL}\), luteinizing hormone (LH) \(<12 \text{ IU/mL}\), estradiol \(<50 \text{ pg/mL}\) on day 2-4 of menstrual cycle. One hundred women were enrolled in the study. Subjects received 300 IU/day of FSH for the first five days of COS in an antagonist cycle. After that, patients were adjusted either down or up to a maximum of 450 IU/day to optimize ovarian response until trigger with human chorionic gonadotropin (hCG). Oocyte retrieval was performed 36 hours after hCG trigger when at least three follicles reached 17 mm. Nine patients either dropped out of the study or did not have embryos that grew to blastocyst stage and hence could not be biopsied. From 91 patients a total of 347 blastocysts of good or fair quality were biopsied when they reached the blastocyst stage on day 5 or day 6 of embryo culture. PGT-A was performed on the biopsied embryos using next generation sequencing at a single genetics lab. Aneuploidy rates in day 5 and day 6 blastocysts were analyzed by an independent statistician using SPSS version 24. Aneuploidy rates were compared between day 5 and day 6 blastocysts using Mantel-Haenszel method (with Cochran's statistic for a p-value). Level of statistical significance was set at P<0.05.

RESULTS: The demographics of the patients such as age, AMH concentrations, amount of FSH received were similar between the day 5 and day 6 groups. The percent aneuploidy in embryos that reach the blastocyst stage on day 5 (49.3%) was found to be significantly higher (p<0.023) than the percent aneuploidy in faster growing embryos that reached the blastocyst stage on day 5 (36.9%).

CONCLUSIONS: In this study, day 6 blastocysts were more likely to be aneuploid when compared to day 5 blastocysts. Slower growing embryos may be at higher risk of aneuploidy.

Supported by: Ferring Pharmaceuticals, Inc.

The descriptive % aneuploidy by age between day 5 and day 6 blastocysts.

<table>
<thead>
<tr>
<th>Maternal age</th>
<th>% aneuploidy day 5</th>
<th>% aneuploidy day 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35 (n=174)</td>
<td>28.1</td>
<td>32.8</td>
</tr>
<tr>
<td>35=37 (n=98)</td>
<td>46.0</td>
<td>60.0</td>
</tr>
<tr>
<td>&gt;38 (n=75)</td>
<td>50.0</td>
<td>64.4</td>
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OBJECTIVE: Trophectodermal (TE) biopsy of a blastocyst typically occurs on the fifth day after egg retrieval (D5), however delayed blastulation may require that TE biopsy occur on Day 6 (D6) or Day 7. It has been proposed that the rate of aneuploidy is higher among embryos that are slow to blastulate. Our aim was to assess euploidy rates in expanded blastocysts at different time points during the course of extended embryo culture.

DESIGN: Retrospective cohort study involving all non-donor egg, IVF cycles with preimplantation genetic screening (PGS) between 01/01/2013 to 05/31/2017.

MATERIALS AND METHODS: All intracytoplasmic sperm injection (ICSI) derived embryos undergoing TE-PGS during the study interval were included. Embryos were assessed for quality at three time intervals: AM D5 post retrieval; PM D5 post retrieval and AM D6 post retrieval. High quality blastocysts, defined as a Gardner 3-BB or better, were then biopsied and vitrified. TE-PGS testing was accomplished using comparative genomic hybridization (CGH) or next generation sequencing (NGS) for 24 chromosomes. The primary outcome of the study was the euploidy rate as a function of the biopsy time point.

RESULTS: 119 patients underwent 176 fresh IVF cycles. The mean age of study patients was 38±0.7 years with a mean of 15±2.4 total oocytes retrieved. The fertilization rate was 73.5% with 38.6% of zygotes becoming high quality blastocysts. A total of 654 blastocysts were biopsied. Of biopsied embryos, 52% were biopsied on Day 5 AM, 24.2% on Day 5 PM, and 22.7% on Day 6. AM D5 blastocysts had a euploidy rate of 53.2% (181/340), compared to those biopsied on PM D5 having a euploidy rate of 41.1% (65/158) (p=0.01) and those biopsied on D6 having a euploidy rate of 40.9% (61/149) (p=0.01). There was no statistically significant difference between euploidy rates of PM D5 and D6 blastocysts (p=0.9).

CONCLUSIONS: The majority of embryos developed to a stage appropriate for biopsy by the morning of Day 5 and these embryos had a significantly higher euploidy rate than embryos blastulating at a later time. However, late blastulating embryos still had an approximately 41% euploidy rate. This warrants extended culture of embryos but indicates that there is no clear value to biopsying embryos at two different time points on Day 5.
MATERNAL STAT3 REGULATES OOCYTE MATURATION AND DEVELOPMENT OF EARLY EMBRYOS THROUGH AUTOGRAPHY. Y. Kawagoe,a,b Y. Sato,b N. Okamoto,a,b, B. Ishizuka,a K. Kawamura,a *Rose Ladies Clinic, Tokyo, Japan; aInternational University of Health and Welfare, Narita, Japan.

OBJECTIVE: JAK2/STAT3 signaling is known as an intracellular signaling pathway. JAK2 is the member of Janus protein tyrosine kinase family and recruits and phosphorylates STAT3. Phosphorylated STAT3 is dimerized and translocated into the nucleus to regulate transcriptional activity. In addition, cytoplasmic STAT3 regulates the autophagy machinery in cells. In preimplantation embryos, STAT3 is constitutively active during fetal stage and shown to be important for embryonic development as demonstrated by embryonic lethality in STAT3 knockout mice. However, its role during early cleavage stage embryos is unknown due to the presence of maternal STAT3 in early embryos before zygote gene activation. The purpose of this study is elucidate the role of maternal STAT3 signaling in preimplantation embryonic development.

DESIGN: GV-stage oocytes and preimplantation embryos were obtained from ICR mice (3-4 weeks of age) for quantification of STAT3 expression. In addition, these oocytes and embryos were used to examine the role of maternal STAT3 in oocyte maturation and embryonic development by inhibiting phosphorylation of JAK2 and STAT3 using selective inhibitors of both genes.

MATERIALS AND METHODS: The expression levels of STAT3 in oocyte and embryos at different stages were measured using real-time RT-qPCR. GV-stage oocytes, zygote and cell stage embryos were cultured with different inhibitors to compare the proportions of oocytes undergoing maturation and embryonic development. The spindle structure in cultured oocytes was examined using tubulin staining. To assess the autophagy activity, expression of microtubule-associated-protein-light-chain 3 (LC3) at mRNA and protein levels were measured by real-time RT-qPCR and immunofluorescence staining, respectively.

RESULTS: The expression levels of STAT3 peaked in oocytes and gradually decreased toward 4-cell stage embryos. It was not detected after 8 cell-stage embryos, suggesting its maternal origin. In GV-stage oocytes, nuclear maturation rate was significantly decreased when both JAK2 and STAT3 signaling were inhibited. When embryos were cultured with the STAT3 inhibitor Soti-201, embryo development was significantly suppressed at 4 cell-stage, whereas JAK2 inhibitor Febratinib showed a weaker suppressive effect. If both JAK2 and STAT3 inhibitors were used, they showed synergistic effect on suppression of embryonic development from 2 cell-stage embryos onwards. Of note, embryo development was not affected when phosphorylation of JAK2 or/and STAT3 was inhibited after 8 cell-stage embryos. Furthermore, LC3 expression was significantly decreased in these embryos.

CONCLUSIONS: Although similar studies using human oocytes are required to confirm the importance of STAT3 activity, our findings may provide a new strategy to help the patients with impaired oocyte maturation by culturing their GV-stage oocytes with STAT3 activators to induce oocyte maturation.

References:

NORMAL GROWTH VERSUS EARLY DEVELOPMENTAL ARREST OF THE HUMAN EMBRYO: UNDERSTANDING MOLECULAR NETWORK PERTURBATIONS. L. Sekhon,a,b J. Lee,b Y. Wang,c C. Briton-Jones,c, E. Schadt,e R. P. Sebra,c, A. B. Copperman,b,a,Obstetrics, Gynecology and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, NY; cGenetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY; dSema4, Stamford, CT.

OBJECTIVE: Despite our ability to enhance transfer selection and pregnancy outcomes using preimplantation genetic testing for aneuploidy (PGT-A), certain embryos do not blastulate and some euploid embryos fail to implant, suggesting other causes of developmental arrest. This study aimed to characterize variations in molecular networks associated with human embryonic arrest.

DESIGN: Prospective cohort.

MATERIALS AND METHODS: Patients donated fresh arrested and ongoing embryos (day 3-7) from IVF in 2016. Approximately 2-4 cells were removed for aneuploidy screening by next generation sequencing (NGS), prior to RNA sequencing. Differential gene expression (DE) was calculated using DESeq2 (significance at adjusted p value <0.05). Likelihood ratio tests were accounted for heterogeneity due to patient, batch, ploidy status, and developmental stage. Pathway analysis was performed and grouped according to major cellular functions (Table).

RESULTS: A total of 33 ongoing (32 blastocysts/10 euploid) and 48 arrested embryos (11 blastocysts/6 euploid) were compared. Of 20,553 protein-coding transcripts, 38 were found to be DE. Ongoing embryos had pervasive gene downregulation, involving all function categories. Upregulated genes (n=5) involved metabolism and biosynthesis, immune function, cell division and proliferation. In a sub-analysis of euploid embryos (n=16), ongoing embryos had 6 DE genes, only one of which was upregulated (SNRNP70; codes for spliceosome proteins). Notable downregulated genes in ongoing, euploid embryos were: ZNF33A (DNA binding transcription factor promoting increased S phase entry) COMMD6 (immune response, cellular growth
and apoptosis) E4FEBP3 (repressor of translation initiation) and MMAB (vitamin B metabolism).

CONCLUSIONS: As an adaptive mechanism to stress, embryos in danger of developmental arrest may compensate for loss of embryonic cells by up-regulating gene expression that drives key cellular processes. Arrested euploid embryos may enter S phase more rapidly as a mechanism to counteract cellular apoptosis. While the blockage of vitamin B12 metabolism has been implicated in mouse embryonic arrest, this is the first study implicating cobalamin metabolism in human embryonic arrest. Elucidating the transcriptome of abnormal embryogenesis may improve our ability to assess developmental competence and optimize culture conditions.


Tuesday, October 10, 2018 6:30 AM

KEY MOLECULAR EMBRYONIC SIGNALING NETWORKS ARE COMPROMISED WITH MATERNL REPRODUCTIVE AGING. B. McCallie, a,b J. Parks, a,b G. D. Trahan, a K. Jones, a B. B. Coate, a D. Griffin, a W. B. Schoolcraft, a, b M. Katz-Jaffe, c "Colorado Center for Reproductive Medicine, Lone Tree, CO; "University of Kent, Canterbury, United Kingdom; "University of Colorado, School of Medicine, Aurora, CO; "Oregon Reproductive Medicine, Portland, OR.

OBJECTIVE: Female reproductive aging impacts both oocyte number and quality, independent of chromosome constitution. Together, this results in increased risks for infertility, pregnancy complications, and decreased live birth rates. The objective of this study was to investigate the underlying embryonic molecular networks in association with advanced maternal aging.

MATERIALS AND METHODS: Cryopreserved, transferrable quality, human blastocysts were donated to research under IRB approval and patient consent: young, fertile, oocyte donor (DON<30 years old; n=12), and advanced maternal age (AMA≥42 years old; n=12). RNA sequencing libraries were prepared using the SMARTer RiboZero System (Illumina) and sequenced on the Illumina HiSeq 4000. Derived sequences were processed and analyzed using a 2-sided independent Student’s t-test followed by Ingenuity® Pathway Analysis (Qiagen). 

RESULTS: RNA sequencing revealed 1247 significant differentially expressed genes between DON and AMA blastocysts (P<0.05). 1134 (91%) of these genes were decreased and 113 (9%) genes displayed increased transcription in the blastocysts from older women, representing an overall global decrease of gene expression with maternal aging. Pathway analysis revealed three distinct, interrelated, molecular signaling networks known to be critical for embryo and fetal development: CREBBP, ESR1 and SP1. 23 genes regulated by the CREBBP network were found to be significantly decreased in AMA blastocysts, in addition to 33 genes regulated by ESR1 and 31 genes regulated by SP1 (P<0.05). Validation of genes within these networks confirmed the global decreased transcription. CREBBP, vital for embryonic-maternal crosstalk during the window of implantation, exhibited statistically significant decreased gene expression in AMA blastocysts (fold change = -0.36; P<0.05). TSPAN9, a trophoblast gene which is part of the ESR1 network, as well as MAKP3IP1 and SP1 which both play key roles in development, were also found to have decreased transcription in blastocysts from older women (fold change = -0.25, -0.2 and -0.62 respectively; P<0.05).

CONCLUSIONS: In conclusion, our study reveals, independent of chromosomes, that embryo competence is significantly compromised with female reproductive aging. Three key molecular signaling networks for embryo and fetal development show global decreased expression that may explain the lower implantation rates observed after a euploid embryo transfer for women ≥42 years old. Ongoing investigations will further elucidate our understanding of the biological impacts of aging on reproductive health.

P-610

Wednesday, October 10, 2018 6:30 AM

BLASTOCOELE CELL-FREE DNA CONTENT IS RELATED TO CHANGES IN PLOIDY STATUS (CHROMOSOMAL LOSS/GAIN) IN DAY-5 EMBRYOS. R. Jeelani, a R. J. Chosed, b S. Zimmerman, c T. Chang, a R. D. Robinson, a W. E. Roudebush, b "Vios Fertility Institute, Chicago, IL; "Biomedical Sciences, UCSOM Greenville, Greenville, SC; "Vios Fertility Institute, Swansea, IL; "Obstetrics and Gynecology, University of Texas Health Science Center, San Antonio, TX; "University of Texas Health Science Center, San Antonio, Saint Barthélemy.

OBJECTIVE: The presence of cell-free DNA (cfDNA) in blastocoeal fluid is most likely due to cell lysis (e.g. apoptosis) or tissue remodeling. Apoptosis is a regulated cellular death mechanism characterized by nuclear condensation, cell shrinkage, membrane blebbing and DNA fragmentation, and all of these characteristics can be found during preimplantation embryonic development. Apoptosis may play a significant role in the self-correction mechanism for chromosomal abnormalities during preimplantation embryo development. This study compared day-5 blastocyst ploidy status ( euploid vs. gain/loss) with blastocoel cfDNA content.

MATERIALS AND METHODS: Following laser-assisted trophectoderm biopsy of IVF-generated day-5 blastocysts, each individual blastocoele fluid was conditioned medium (25µL) was saved. Trophectoderm biopsied cells were assessed for ploidy status (grouped by chromosome loss, gain vs euploid) via next-generation sequencing. Blastocoeal fluid cfDNA was quantified via fluorospectrometry. Ploidy status and cfDNA content were compared by analysis of variance (ANOVA) and Students’ t-test.

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RESULTS: A total of 78 blastocyst stage embryos were evaluated. Normal, euploid blastocyst stage embryos (N=45) had a mean cfDNA content of 44.9 ng/mL. Blastocyst embryos (N=18) exhibiting a chromosomal loss had a mean cfDNA content of 35.6 ng/mL. Blastocyst embryos (N=15) exhibiting a gain in chromosome number had a mean cfDNA content of 38.1 ng/mL. There was a significant (p<0.05) difference in cfDNA content between euploid (44.9 ng/mL) and aneuploid (36.8 ng/mL) day-5 blastocysts. ANOVA revealed a significant (p<0.05) difference between chromosomal status (gain/loss/euploid) and cfDNA. As ploidy status deviated from the norm, cfDNA content significantly decreased.

CONCLUSIONS: This study provides further evidence that cfDNA is present in blastocoeel fluid, is quantifiable, and correlates with embryonic ploidy status. There is also evidence that blastocoeel fluid in day-5 euploid embryos contains significantly more cfDNA than similar developmental stage aneuploid embryos and is chromosome number dependent. Additional studies are warranted to determine the mechanism by which embryos may self-correct for incidences of aneuploidy (e.g., via apoptosis) and to determine the relationship with cfDNA content, embryonic ploidy status and implantation potential.

P-612 Wednesday, October 10, 2018 6:30 AM

OBJECTIVE: Early prediction of the viability and quality of in vitro developed embryo is still challenging. After that, various kinds of evaluation methods for embryo such as morphological analysis, proteomics, and metabolomics were reported. Time lapse system is also a good option to know the embryo quality. However, more objective method for the embryo evaluation is needed. To evaluate oxygen consumption, that is embryo respiration, evaluation is needed. To evaluate oxygen consumption, that is embryo respiration, the embryo or not.

DESIGN: A prospective study.

MATERIALS AND METHODS: Sixty-nine normal fertilized frozen-thawed 2 pronucleus stage embryos from 11 patients, all of them had successfully conceived by IVF and delivered, had enrolled in this study. All study subjects had signed informed consents prior to entering the study, in accordance to local IRB protocol. Oxygen consumption of each embryo was evaluated by cell respiratory assay system every day for 6 days. Embryo morphology was also evaluated every day for 6 days.

RESULTS: Oxygen consumption of the morphologically good quality embryo at day 4 and day 5 was significantly higher than that of the morphologically poor quality embryo (p<0.05 and p<0.01, respectively). Moreover, oxygen consumption of the morphologically poor quality embryo decreased on day 4. However, no decrease was observed for the morphologically good quality embryo. So, it was possible to classify the morphologically good and poor quality embryo by setting the cutoff value of the embryo oxygen consumption to 4.93 x 10^15/mol s^-1. Further analysis of oxygen consumption of the embryo that later had become good quality blastocyst, appropriate oxygen consumption on day 3 embryo was 4.80-7.18 x 10^15/mol s^-1. Good quality blastocyst rate in good quality embryo on day 2 and appropriate oxygen consumption (4.80-7.18 x 10^15/mol s^-1) on day 3 was 46.2% (12/26) and it was significantly higher than others (2.7% (1/37), p<0.01). Moreover, there was a significant positive correlation between blastocyst oxygen consumption and embryo oxygen consumption of the embryo (r^2=0.583, p<0.01).

CONCLUSIONS: Embryo morphological analysis on day 2 and the investigations of day 3 or day 4 oxygen consumption of the embryo become good predictor to detect the good quality blastocyst.

May make a contribution to clinical success in IVF treatment. Hance embryonic ability more than the current single step medium, and it

P-

The pregnancy rates for IUI performed in the same calendar year were 13% and 12% respectively for patients in the same age bracket with a total of 869 cycles performed.

CONCLUSIONS: IVC with day 5 blastocysts transfers appears to offer an appreciable pregnancy rate increase when compared with IUI cycles. While IVC cannot compete with full IVF cycles, due to inherent treatment limitations, it may offer a more efficacious first treatment option for infertility patients that meet the selection criteria than several rounds of IUIs. However, cell requirements for a large HeLa culture and L cells in 1959, which don’t reflect the requirements of embryos. This may have caused to limit the ability of human embryos in vitro. Efficacy of media composed of amino acid concentrations of human oviductal fluid has yet to undergo analysis because there is no medium with the amino acid concentrations similar to human oviductal fluid. In this study, we confirm whether human oviductal amino acid medium is more effective in human IVF compared with current single step medium.

DESIGN: randomized control study.

MATERIALS AND METHODS: Human oviductal fluid samples were collected laparoscopically from 28 women aged 26-39 years, and were analyzed in helping to formulate new embryo culture media. In 2017, medium composed of amino acid concentrations of most these media are the concentrations set by Dr. Eagle on the basis of required for a large HeLa culture and L cells in 1959, which don’t reflect the requirement of embryos. This may have caused to limit the ability of human embryos in vitro. Efficacy of media composed of amino acid concentrations of human oviductal fluid has yet to undergo analysis because there is no medium with the amino acid concentrations similar to human oviductal fluid. In this study, we confirm whether human oviductal amino acid medium is more effective in human IVF compared with current single step medium.

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We conclude similar observations in this randomized comparative validation
Miri with 269 zygotes while 451 zygotes from 41 patients were cultured in the
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tool has yet to be determined.
significant differences, the added value of time-lapse as a patient engagement
cess and morphokinetic data in relation to embryo ploidy did not result in sig-
time-lapse incubator. Journal of assisted reproduction and genetics,
clinical trial comparing embryo culture in a conventional incubator with a
Materials and Methods: Sibling oocytes were divided into two groups after sperm injection. The 1st group was dry culture which included 286 oocytes. The 2nd group was the humid culture which included 285 oocytes.

RESULTS: In the dry culture group, 286 MII oocytes from 21 women were cultured inside dry chambers from day 0 to day 5 or 6. In the humid culture group, 285 MII sibling oocytes were cultured in humid chambers from day 0 to day 5 or 6. Humid culture negatively affected the high-quality blastocyst rate as it was significantly lower in the humid culture group (43.5%) than the dry culture group (62.9%) (P = 0.0032). However, there were no significant difference in cleavage rate in the humid culture group (75.4%) than the dry culture (78.67%) (P = 0.3577), neither was significant difference in blastocyst formation rate in humid culture group (50.23%) than the dry culture Group (55.11%) (P = 0.3060).

CONCLUSIONS: Humidification didn’t affect fertilization, Cleavage, or Blastocyst formation rates, but there was a significant difference in high-quality blastocyst rate favoring dry culture.


P-620 Wednesday, October 10, 2018 6:30 AM
A COMPARISON OF PGS EUPLOIDY RATES BETWEEN DAY 5 AND DAY 6 BLASTOCYSTS. G. Abdo,4 M. R. Goodwin, 4 M. G. Abdo, 4 F. Sharara, 4 5 6 Virginia Center for Reproductive Medicine, Reston, VA; 2George Washington University, Washington, WA.

OBJECTIVE: Aneuploidy screening of blastocysts is being used to improve live birth rates and reduce the number of embryos for transfer. A primary observation indicates that embryo culture and development speed of blastocyst stage can affect PGS results. The current study tests the hypothesis that faster embryo development and blastocyst formation on day 5 can lead to higher euploidy rate.

DESIGN: A retrospective study of PGS results from blastocyst biopsied on day 5 versus day 6 was conducted to identify differences in euploidy rates in PGS cases.

MATERIALS AND METHODS: A total of 818 blastocyst biopsies (693 day 5 blastocyst biopsies and 125 day 6 blastocyst biopsies) were included in this analysis. Assisted hatching was performed on day 3, and trophecto- derm biopsy took place on days 5 or 6. Euploidy and aneuploidy rates, struc-
tural segmental abnormal, complex abnormal and no-results rates were
CONCLUSIONS: Euploidy rate tends to be higher in day 5 biopsied blastocysts. Slower developing embryos that are biopsied on day 6 have significantly higher euploidy rates compared to embryos biopsied on day 5 but still 35% were euploid. The data support the hypothesis that there is a relationship between embryo development speed, day of blastocyst biopsy and euploidy rate. While our findings disagree with a previous study that found no difference in euploidy rate between day 5 and day 6 biopsies (Grunert et al., 2014), they are supported by another study that examined only euploidy rate between day 5 and day 6 biopsies (Grunert et al., 2014). Larger studies are needed to confirm our findings.

References:
1. Park J.K, Singh S., Berchuck S., Conchman G., and Meyer W; Aneuploidy prevalence is no different between embryos biopsied on day 5 vs day 6. Fertility and Sterility 2013; vol 100 Issue 3 S197.

Supported by: Non

P-621 Wednesday, October 10, 2018 6:30 AM

THE COMPARISON OF STANDARD INCUBATOR AND TIME-LAPSE MONITORING INCUBATOR PRODUCED HUMAN EMBRYOS BY TRANSCRIPTOME AND DNA METHYLATION ANALYSIS. J. Li1
H. Guoning.b aChongqing Reproductive and Genetics Institute, Chongqing, China; bChongqing Genetic and Reproductive Institute, Chinese Society of Reproductive technology.

OBJECTIVE: Compare the effects of time-lapse monitoring (TLM) culture on gene expression and DNA methylation of D3 human embryos with that of standard incubator (SI).

DESIGN: Randomized controlled trial.

MATERIALS AND METHODS: Using single-cell RNA sequencing (RNA-seq) and whole-genome bisulphite sequencing (WGBS) technology to investigate the gene expression and DNA methylation profiles in three groups of embryo in human: ICSI zygote, SI and TLM produced 8-cell embryo.

RESULTS: RNA-Seq data showed that the SI embryos have higher variability of gene expression patterns than TLM. It might indicate that the frequent embryo handling and several exposures to non-optimal conditions outside the incubator when culturing in SI cause the great variability of gene expression during embryonic genome activation. In addition, more genes involved in RNA splicing and DNA repair were activated in SI group. We analyzed the DNA methylation data and found global demethylation from zygotes to SI or TLM produced 8-cell embryos. Relatively higher methylation was observed in TLM group. Additionally, differentially methylated regions analysis identified several genes whose methylation could be critical, such as IGFB2 and PEG10.

CONCLUSIONS: This study provides the first comprehensive comparison between SI and TLM via transcriptome and DNA methylation analysis, and will serve as a basis for assessing the safety of TLM application in assisted reproductive technology.

P-622 Wednesday, October 10, 2018 6:30 AM

MELATONIN ATTENUATES POST OVULATORY OOCYTE DYSFUNCTION BY REGULATING SIRT 1 EXPRESSION. Q. Yang Y. Sun Reproductive Medical Center, the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China.

OBJECTIVE: To explore the underlying mechanisms of melatonin improves the quality of post-ovulatory aged oocytes.

DESIGN: Immunofluorescent staining, RT-PCR and western blotting were employed to investigate the protective mechanisms of melatonin on delaying post-ovulatory oocytes aging.

MATERIALS AND METHODS: 6-week-old ICR female mice were stimulated with an intraperitoneal injection of 7.5 IU of Pregnant Mares Serum Gonadotropin (PMSG), and 5 IU human Chorionic Gonadotropin (hCG) to induce superovulation. Mouse metaphase-II (MII) oocytes were in vitro aged for 0, 6, 12 and 24 h, respectively. And the oocytes were treated with different concentrations of melatonin (10-7 M, 10-5 M and 10-3 M) for 24 h group. In vitro fertilization and embryo culture were evaluated. Immunofluorescent staining, Real-time RT-PCR and western blotting were employed to investigate the protection mechanisms of melatonin on delaying post-ovulatory oocytes aging.

RESULTS: There were elevated ROS levels and impaired mitochondrial function demonstrated by reduced mitochondrial membrane potential (∆Ψm) and increased mitochondrial aggregation in oocytes aged 24 h, accompanied by an increased number of meiotic errors, unregulated autophagy-related proteins and early apoptosis, which led to decreased oocyte quality and disrupted developmental competence. However, all of these events can be largely prevented by supplementing the oocyte culture medium with 10-3 M melatonin. Additionally, we found that the expression of sirtuin family members (SIRT1, 2, 3) was dramatically reduced in aged oocytes. In addition, in vitro supplementation with melatonin significantly upregulated the expression of SIRT1 and antioxidant enzyme MnSOD, but this action was not observed for SIRT2 and SIRT3. Furthermore, the protective effect of melatonin on the delay of oocyte aging vanished when the SIRT1 inhibitor EX527 was used to simultaneously treat the oocytes with melatonin. Consistent with this finding, we found that the post-ovulatory oocyte aging process was markedly attenuated when the oocytes were treated with the SIRT1 activator SIRT1/720.

CONCLUSIONS: In conclusion, our data strongly indicate that melatonin delays post-ovulatory mouse oocyte aging via a SIRT1-MnSOD-dependent pathway, which may provide a molecular mechanism support for the further application of melatonin in the assisted reproductive technology (ART) field.

P-623 Wednesday, October 10, 2018 6:30 AM

THE EFFECTS OF TEMPERATURE VARIATION TREATMENTS ON IN VITRO MOUSE EMBRYO QUALITY: A CHANGE OF TEMPERATURE EVERY 12 HOURS MIMICKING FEMALE BASAL BODY TEMPERATURE. D. F. Moriyama, a G. F. Moraes, a M. O. Pinheiro, a E. G. Lo Turco. " Surgery Division of Urology, Human Reproduction Section, Sao Paulo Federal University, Sao Paulo, Brazil; "Departamento de Cirurgia, Disciplina de Urologia, Yrea de Reproduaoo Humana, Unifesp, Sao Paulo, Brazil.

OBJECTIVE: This study compared two temperature variation treatments with a control group on in vitro mouse embryo culture to estimate the effects on blastocyst rate and embryo quality.

DESIGN: Prospective study.

MATERIALS AND METHODS: Female mouse C57BL/6J (4 weeks) were superovulated with PMSG and hCG. Males and females were placed to mate for natural fertilization. Zygotes were collected from the tubes and then cultivated (15 embryos/droplet) for 96 hours in continuous culture medium incubated at 37°C in control group (C group), in Treatment 1 group (T1 group) at 37°C during the day and 35.5°C during the night and Treatment 2 group (T2 group) at 38.5°C during the day and 37°C during the night, 90% humidity and 6% CO2 (N=270). Number of blastocysts and the assessment of embryo quality were analyzed on day 5 of development. Blastocyst quality was assessed using In Situ Cell Death Detection kit (TUNEL test). Data was statistically analyzed using IBM SPSS software. Differences in the frequencies of blastocysts were analyzed by Pearson’s Chi Square Test. One-way ANOVA was used for analyzing differences between the number of total cells, apoptotic cells and apoptotic rate in the blastocysts.

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RESULTS: T2 group presented a significant (p=0.001) higher blastocyst rate (38.82%), when compared to T1 group (13.33%) and C group (22.82%). Additionally, considering the TUNEL test, T2 group presented a significant (p=0.001) higher number of total cells (130.36±38.20) when compared to T1 group (70.40±34.82) and C group (122.50±45.68). T2 group also presented a significant (p=0.003) lower apoptotic rate (0.06±0.03) when compared to T1 group (0.15±0.09) and C group (0.09±0.06).

CONCLUSIONS: Our preliminary data suggested that temperature variation, in contrast to a consistent temperature, may improve blastocyst rate and embryo quality in vitro. This study may contribute to further investigations, which aim to elucidate how in vitro culture, among other ART procedures, affects embryo development.

References: Not applicable.

Supported by: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

P-624 Wednesday, October 10, 2018 6:30 AM


OBJECTIVE: To determine whether the type of media used for in vitro fertilization (IVF) culture is dependent on maternal age.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: IVF cycles between 1/2015-12/2017 with embryos fertilized via ICSI that reached at least 5 days were included in the study. Subjects were stratified by SART age group (<35, 35-37, 38-40, >40) and the type of media used to culture embryos (Sequential-Sage versus Continuous Single Culture(CSC)-Irvine). For each retrieved oocyte the following data were collected: maturity; fertilization; day 2, 3, 5, and 6 morphology; and whether embryo was transferred/cryopreserved or discarded. Student’s t-tests and Chi Square tests assessed differences between the age groups based on the media used for embryo culture. P < 0.05 was considered significant.

RESULTS: A total of 380 cycles with 5286 resulting embryos were included in the study. The sequential media group included 140 cycles (2719 embryos) while the CSC group included 140 cycles (2567 embryos). In the <35-year-old group, the percentage of embryos that were either transferred or cryopreserved was significantly higher in the sequential media compared to CSC (43% vs. 39%, p=0.0002) (Table). In the 35-37 and 38-40 age groups, the transfer/frozen rate was significantly higher in the CSC media compared to the sequential (35-37 - 35% vs. 27%, p=0.0002; 38-40 - 30% vs. 22%, p=0.00006) (Table). There was no significant difference for patients older than 40 years old between the two media types. The development rate from Day-2 to Day-5 was significantly higher in the sequential media compared to the CSC in the <35 (20% vs. 9%, p=0.0000); 35-37 (16% vs. 7%, p=0.0001) and 38-40 (6% vs. 3% p=0.0187). There was no significant difference for patients older than 40 between the two media types for Day-2-Day5 development.

CONCLUSIONS: 1. Patients <35 had better embryo development when cultured in Sequential media compared to CSC. While CSC was better for >35-40, media did not make a difference for >40. 2. To our knowledge, this is the first study to identify maternal age as a factor in the choice of culture system. 3. It is unclear, at this point, whether pre-embryos have different metabolic requirements (e.g. glucose; phosphate) at different maternal ages. This hypothesis can be further investigated if additional studies confirm our observations.

P-625 Wednesday, October 10, 2018 6:30 AM

MATERNAL SERUM CONCENTRATIONS OF FOLLICLE STIMULATING HORMONE AND ANTI-MULLERIAN HORMONE AS PREDICTORS OF SUCCESSFUL BLASTOCYST DEVELOPMENT DURING IVF TREATMENT. S. Sadruddin, B. D. Barnett, L. T. Ku, D. L. Havemann, S. J. Mucowski, R. S. Herrington, W. W. Burggren, Embryology, Dallas IVF; Frisco, TX; Developmental and Integrative Biology, University of North Texas, Denton, TX; Reproductive Endocrinology, Dallas IVF, Frisco, TX; Statistics, University of North Texas, Denton, TX.

OBJECTIVE: Women with elevated basal FSH are reported to still achieve reasonable pregnancy rates, but few studies report correlations with blastocysts development. The purpose of the current study is to understand the interactions between the number of mature follicles at trigger, AMH and basal FSH values with blastocysts development in patients presenting with diminished ovarian reserve (DOR) as compared to good prognosis patients. The current study examines the correlation between diagnostic findings of basal FSH and AMH values and their predictive value in embryo development and identifies characteristics of IVF cycles and blastocyst developmental rate thresholds that influence IVF treatment success.

DESIGN: Prospective cohort study.

MATERIALS AND METHODS: One hundred and six women undergoing IVF regardless of prognosis were included in the study at a medical practice. Clinical parameters evaluated included: basal FSH value, AMH value, patient age, partner age, insemination method, days of gonadotropins, IU’s of gonadotropins, trigger type and number of mature follicles at trigger. Game related to two culture parameters included included number of oocytes retrieved, mature oocytes, normally fertilized oocytes, high quality cleavage stage embryos and high quality usable blastocysts. The main outcome measure was the rate of high-quality blastocyst production, including blastocysts determined usable for ET or vitrification, per normally fertilized oocyte. Treatment was determined successful when outcome was ≥ 40% high-quality blastocysts. Statistical computation of a decision tree was constructed using the evolutionary tree algorithm using R software which maximizes discrimination between groups at each node of the decision tree with minimal homogeneity in each split rule resulting from subset of the predictors.

RESULTS: Individuals that present with an AMH of >3.15 ng/ml, good prognosis, had a lower success per treatment (n=11, 0% success) when total gonadotropin doses were >3325 IU. Individuals that presented with an AMH of <1.78 ng/ml, poor prognosis, exhibited a greater success per treatment (n=11, 80% success). The accuracy of the statistical analysis (decision tree, etvtree methodology) was 86.5% with an error rate of 13.5%.

CONCLUSIONS: AMH is a superior indicator of ovarian stimulation response and embryo development than basal FSH. Women who are “good responders,” expected to have >12 mature follicles (>16mm) at trigger have lower rate (<40%) of high quality blastocyst development when gonadotropin doses exceed 3325 IU given an AMH of ≥ 3.2 mg/ml. IVF cycles for individuals who present with infertility due to DOR, can result in higher rate of usable blastocyst production per treatment when decision tree is utilized, thus increasing success.

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Sequential Vs. Continuous Culture

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<th>Age Group</th>
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OBJECTIVE: The ability to track performance of an IVF laboratory using statistical process controls has not been validated and remains an important goal for an early warning signal of shifts in laboratory conditions. The Vienna consensus report recently defined Key Performance Indicators (KPIs) for managing fresh IVF cycles for the first time. The objective of this study was to detect shifts in laboratory performance that result in changes in clinical outcomes.

DESIGN: Retrospective, multicentre, analysis of KPIs for fresh IVF and ICSI cycles. Three consecutive 5-month periods of embryo culture media were investigated: 1) embryo culture in Continuous Single Culture Complete (CSCM-C) (Irvine Scientific) 2) embryo culture in G-TL (Vitrolife) 3) embryo culture returned to CSCM-C (Irvine Scientific).

MATERIALS AND METHODS: Six primary embryology KPIs were tracked for 1523 cycles from June 2016 to August 2017; ICSI fertilization rate, IVF fertilization rate, usable day 5 blastocyst rate, overall usable blastocyst rate, clinical pregnancy rate and cumulative clinical pregnancy rate. Meaningful KPI shifts were identified by upper and lower warning (2-sigma) and control (3-sigma) limits. KPI shifts were analyzed by ANOVA and multivariate regression.

RESULTS: During the 15 months analyzed, the novel KPI, usable day 5 blastocyst rate, fell below the 3-sigma lower control limit for 5 months. The decrease in usable day 5 blastocyst rate, from 43% to 32%, occurred following a change from CSCM-C (Irvine Scientific) to G-TL (Vitrolife) and was detected one week after the change (p < 0.0001). Usable day 5 blastocyst rate subsequently recovered after a change back to CSCM-C (p < 0.0001). A decrease in clinical pregnancy rate (54% vs 41%) was also observed, but this was not detected until 3 months after the usable day 5 blastocyst rate shift (p = 0.01). Although culture media type independently affected usable day 5 blastocyst rate and clinical pregnancy rate, the cumulative clinical pregnancy rate was similar among the three time periods. Importantly, overall usable blastocyst rate (day 5-7) remained within control limits (52%) for all three periods, indicating that the overall rate alone may not sufficiently monitor embryology laboratory performance.

CONCLUSIONS: This study validates a statistical KPI monitoring system to provide systematic, early detection of culture condition shifts in ART laboratories. Usable day 5 blastocyst rate is identified as an important KPI, which complements overall usable blastocyst rate (day 5-7).

References:

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36 DEGREES CELSIUS IS THE OPTIMAL EMBRYO CULTURE TEMPERATURE FOR BLASTOCYST FORMATION. S. Thomas, a K. Rhodes-Long, b S. Salvatian, b H. C. Baltimore b L. K. McGinnis, b A. Ahmady, a University of Southern California, Los Angeles, CA; bUSC Fertility, Los Angeles, CA.

OBJECTIVE: To achieve successful embryo development, embryos must be maintained in a controlled in vitro environment for several days prior to transfer. There is conflicting data about the ideal temperature for embryo culture. This study aimed to evaluate the optimal temperature for embryo cellular proliferation and blastocyst development.

DESIGN: Mouse embryo study.

MATERIALS AND METHODS: One-cell stage mouse embryos (n= 668; B6C3F1xB6D2F1 strain) were thawed and randomly divided into 4 culture treatment groups (35 degrees celsius (C) (n=152), 36C (n=170), 37C (n=172), and 38C (n=174)). Embryos were cultured to blastocyst in Continuous Single Culture Complete (CSCC, Irvine Scientific) in an incubator (Heracell 160i) with 5%CO2, 8%CO2 and pH of 7.3. Embryo development was scored daily for 5 days. Embryos that reached blastocyst were fixed in 2% formalin and labeled for cell counts with Hoechst dye and CDX2 antibody to differentiate trophoderm (TE) from inner cell mass (ICM). Chi square and ANOVA were used for comparison between the groups with a P-value <0.05 considered significant.

RESULTS: 65% (435/668) of all embryos cultured reached blastocyst. Embryos cultured at 36C had the largest proportion developed to blastocyst compared to the other culture temperatures, (83%, p<0.01). By day 5, embryos cultured at 35C had the lowest proportion of hatching blastocysts and largest proportion in morula, compared to other culture temperatures, 11% and 63%, respectively, p<0.01. Of the embryos that reached blastocyst, the TE and total cell count were significantly reduced at 35C and 36C compared to other temperatures, p<0.01. At 35C, ICM cell counts were significantly reduced compared to all other temperatures, p<0.01. There were no significant differences between all TE, ICM and total cell counts of embryos cultured at 37C and 38C.

CONCLUSIONS: Culture of mouse embryos at temperatures of 36C confers the greatest proportion of total blastocyst formation than at other temperatures, but with significantly fewer cells than 37C or 38C. However, embryos cultured at temperatures of 35C lead to overall poor embryo growth outcomes (reduced blastocyst development, hatching, and lower cell counts).

Embryo Growth at Day 5

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8</th>
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<tbody>
<tr>
<td>35C</td>
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<td>36C</td>
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<tr>
<td>37C</td>
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<tr>
<td>38C</td>
<td></td>
<td></td>
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</tbody>
</table>

*n=40 for all groups, mean counts calculated. SD= standard deviation
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AUTOMATIC PREDICTION OF EMBRYO CELL STAGES USING ARTIFICIAL INTELLIGENCE CON-VOLUTATIONAL NETWORK. J. Malmsen,a N. Zaninovic,c Q. Zhan,a M. Toschi,a Z. Rosenwaks,a J. Shan.a,b Reproductive Medicine, Weill Cornell Medicine, New York, NY; Pace University, NYC, NY.

OBJECTIVE: The objective of this study is to identify the times of embryo cell division (up to 8-cell) by applying an artificial intelligence-based (AI) approach using time-lapse microscopy (TLM) images. Our hypothesis is that the unbiased AI approach would identify embryo division times without relying on human intervention.

DESIGN: We built a stand-alone framework with a convolutional neural network (CNN) as the core to predict cell division times for mouse and human embryos, respectively, based on raw time-lapse digital images.

MATERIALS AND METHODS: This study used 31,120 images of 100 mouse embryos from a public dataset. We also used 661,060 images of 11,898 human embryos cultured in the TLM system (EmbryoScope, Vitrolife, Sweden) at various cell stages post-insemination/ICSI. Images were separated randomly into training, validation, and test sets with a ratio of 70:15:15 for mouse and 80:10:10 for human. Separation was done on an embryo basis, such that all images from the same embryo belonged to the same set. We applied deep convolutional neural networks for cell-stage image analysis on both datasets. The networks included Google’s Inception architecture (V3) with and without transfer learning. An additional 233,954 images were acquired from the TLM system to reproduce complete TLM sequences of 100 embryos from the test set. These images were used to predict cell division times. We compared the AI outcome on individual images and complete TLM sequences to the embryologists’ manual annotations of division times.

RESULTS: First, the Inception V3 CNN model was used to classify individual images up to the 4-cell stage. The test sets were used to validate the results, achieving average accuracies of >99% for mouse and 90% for human embryos. All accuracies are comparing the model’s outcome to the embryologists’ annotations. Second, a modified version of the model was used to further classify human embryos using images up to the 8-cell stage in seven focal planes. Classification performance on the test set showed an average accuracy of 82%. Transfer learning was not possible with the modified model, but earlier tests had shown no significant gain from transfer learning except for a slightly shorter training time. Third, to identify division times, we selected 100 embryos from the test data to reproduce whole time-lapse sequences. After applying constraints given by the natural development of embryos, cell division times were predicted accurately within five frames of the embryologist’s annotation in 91% of the cell-stage transitions.

CONCLUSIONS: We successfully applied AI to predict cell division times with high accuracy. Our approach provides a novel way to assess the cell stage of the embryo as well as a platform for an automatic annotation to improve the consistency and quality of embryo evaluation using time-lapse systems.

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BLASTOCYSTS CRYOPRESERVED ON DAY 5 HAVE HIGHER LIVE BIRTH RATES THAN THOSE CRYOPRESERVED ON DAY 6 IN FROZEN EMBRYO TRANSFER (FET) CYCLES. M. Shear,a,b D. Vaughan,a,b A. Modest,a L. Murphy,a,b E. Seidler,a M. Hacker,a D. Sakkas,b A. S. Penzias,a,b Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; Boston IVF, Waltham, MA.

OBJECTIVE: With improved cryopreservation techniques, frozen embryo transfer (FET) cycles have at least equivalent reproductive outcomes to fresh IVF cycles.1,2 We sought to compare live birth incidence from blastocysts vitrified on day 5 (D5) versus day 6 (D6) in FET cycles.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: We reviewed all homologous, single blastocyst, FET cycles from January, 2012 to December, 2016 at a large, university-affiliated infertility clinic. All embryos were cryopreserved by vitrification. We performed log-binomial regression to compare outcomes, controlling for age at retrieval, number of oocytes retrieved during fresh cycle, BMI, embryo quality, and PGT-A.

RESULTS: We included 1092 IVF transfers with embryos cultured to and cryopreserved on D5 and 546 transfers with embryos cultured to and cryopreserved on D6. Baseline characteristics were similar in each group, with 95% of D5 embryos and 93% of D6 embryos classified as high quality. Primary and secondary clinical outcomes are shown in Table 1. Transfer of a cryopreserved D5 embryo was associated with a significantly higher incidence of live birth compared to transfer of a cryopreserved D6 embryo (52.5% versus 39.4%, p < 0.0001; adjusted risk ratio (ARR) 0.79, 95% CI 0.70 - 0.89). The incidence of clinical pregnancy also was significantly higher with transfer of a D5 embryo (66.7% versus 52.4%, ARR 0.83 95% CI 0.76 - 0.91).

Table 1Clinical outcomes

<table>
<thead>
<tr>
<th>Cell Stage</th>
<th>Day 5 n=1092</th>
<th>Day 6 n=546</th>
<th>P value</th>
<th>Crude RR (95% CI)</th>
<th>Adjusted RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical pregnancy</td>
<td>728 (66.7)</td>
<td>286 (52.4)</td>
<td>&lt;0.001</td>
<td>0.79 (0.72-0.86)</td>
<td>0.83 (0.76-0.91)</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>79 (10.9)</td>
<td>41 (14.3)</td>
<td>0.12</td>
<td>1.3 (0.93-1.9)</td>
<td>1.44 (0.98-2.1)</td>
</tr>
<tr>
<td>Live birth</td>
<td>573 (52.5)</td>
<td>215 (39.4)</td>
<td>&lt;0.0001</td>
<td>0.75 (0.67-0.84)</td>
<td>0.79 (0.70-0.89)</td>
</tr>
</tbody>
</table>

Data are presented as n (%), risk ratio (RR) and 95% confidence interval (CI).

*Adjusted for age at retrieval, number of oocytes retrieved during fresh cycle, BMI, embryo quality, and PGT-A.

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OBJECTIVE: In this study, we utilize discarded human zygotes with three pronuclei to investigate a novel system for human embryo culture. Our objective was to determine the efficacy of a medium with significantly reduced nutrient concentrations for human embryo culture to the blastocyst stage, and to investigate quality of the resulting embryos in a peri-implantation extended culture system.

Supported by: This work was conducted with support from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health Award U1L TR001102) and financial contributions from Harvard University and its affiliated academic healthcare centers.
DESIGN: Research Study.

MATERIALS AND METHODS: Human zygotes with 3 pronuclei (PN) were cryopreserved with consent, thawed, and placed into control (CON; n=23) or reduced nutrient (RN; n=25) sequential culture medium, both supplemented with 10% FCS. Embryos were cultured individually in an EmbryoScope and were assessed for blastocyst development on D5 and D6. On D6, blastocysts were placed into fibronectin coated dishes for outgrowth culture in IVC1 (Cell Guidance Systems) medium, along with thawed D6 human blastocyst controls donated to research after culture under standard clinical conditions (Sage CM/BM with SPS; CBL). After 48h in outgrowth, attachment was assessed and media was replaced with IVC2. Media was replaced daily (96h of outgrowth (D10)), at which point embryos were fixed and imaged to measure outgrowth area. Embryos were then stained with F-actin, DAPI, and POUF51, and imaged using confocal microscopy to determine outgrowth volume, total cell number, and epithelial cell number, respectively.

RESULTS: Blastocyst development was not different between 3PN embryos cultured in CON and RN medium on D5 (30.4% and 24.0%) or D6 (34.7% and 28.0%). All embryos placed into outgrowth were attached by 48h (CON n=11; RN n=7; CBL n=7). There was no difference in the area of outgrowth between treatments, either at 48h (0.05±0.02mm², CON; 0.09±0.04mm², RN; 0.06±0.02mm², CBL) or 96h (0.12±0.06mm², CON; 0.23±0.10mm², RN; 0.20±0.10mm², CBL). Of embryos placed into outgrowth, 73% CON, 60% RN, and 100% CBL had a 3D volume that was assessed using confocal microscopy. Of these embryos, 50% of CON, 67% of RN, and 40% of CBL embryos contained a visible epithelial blastocyst; these embryos had similar average numbers of epiblast cells (59, CON; 41, RN; 67, CBL).

CONCLUSIONS: This data demonstrates that an environment of reduced nutrient concentration successfully supports the development of human zygotes to the blastocyst stage, with equal developmental potential to both those cultured in control medium and those cultured in standard clinical conditions. In addition, 3PN zygotes developed to the blastocyst stage and successfully organized peri-implantation embryonic development equivalent to normally fertilized embryos. This innovative approach to safely investigating novel culture conditions for human embryos could significantly enhance research in the development of more effective embryo culture media for human ART.


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OBJECTIVE: Numerous commercial embryo culture media are now available for IVF, raising the question of whether any medium is superior to others. Notably, the ability of a medium to yield a high embryo development percentage in vitro does not necessarily mean that the embryos are viable. For example, previously it was common to add blood serum to animal embryo culture media to stimulate blastocyst formation, but this impaired embryonic, fetal, and offspring health. Given the importance of culture media in treatment outcome, well-designed RCTs are needed, but the existing data are insufficient to select the best medium. In this study, we report updated data of an RCT conducted to compare the clinical outcome between three embryo culture media systems widely used in IVF.

DESIGN: Single-center RCT.

MATERIALS AND METHODS: This study included 795 healthy patients undergoing their first IVF treatment cycle at our clinic between February 2016 and August 2017. They were randomized by computer-generated tables into three groups and underwent our standard oocyte retrieval and IVF/ICSI procedures. Embryos were then divided into three culture media systems: Global To-LifeGlobal (B), or Sequential Cleav/Blast (Origio) (C) media. Thirty-seven patients with no 2PN oocytes 18 h after insemination were excluded from the study. During embryo culture (1-5/0 μL), for cycles where the patients had only one good-quality (GQ) embryo by D3, the embryos were vitrified on D2/3. When the patients had ≥ 2 GQ embryos by D3, ≥ 2 GQ embryos were vitrified on D2/3, culture period of the remaining embryos was extended, and all GQ blastocysts were vitrified on D5/6. Data for vitrified ET performed until the end of March 2018 were analyzed.

RESULTS: Patient age (y) and vitrified D2/3 embryo percentages/cultured 2PN oocytes were similar for Groups A (36.4 ± 0.3 and 339/1646 (20.6%), respectively, n = 251), B (36.2 ± 0.3 ± 352/1749 (20.1%), respectively, n = 256), and C (36.3 ± 0.3 and 339/1681 (20.2%), respectively, n = 251). Vitrified D5/6 blastocyst percentages/2PN oocytes were 26.1% (A), 36.9% (B), and 30.6% (C) (A vs. B, P < 0.0001; A vs. C, P = 0.0039; B vs. C, P > 0.0001). Groups A, B, and C underwent 316 (D2/3 ET, 133; D5/6 ET, 183), 346 (D2/3 ET, 107; D5/6 ET, 239), and 318 (D2/3 ET, 107; D5/6 ET, 211) vitrified ET cycles, respectively (ET cancellation: A, 0.6%; B, 0.6%; C, 0.3%). The mean number of embryos transferred, implantation rates, clinical PRs/ET, and ongoing/ delivered PRs/ET did not differ for Groups A (1.12 ± 0.02, 40.5%, 43.6%, and 32.8%, respectively), B (1.07 ± 0.02, 42.9%, 44.8%, and 32.0%, respectively), and C (1.11 ± 0.02, 77.7%, 40.1%, and 28.1%, respectively). CONCLUSIONS: Overall PR of a culture system yielding fewer blastocysts was comparable to or slightly better than those of other systems. Differentiation of the ability of culture media to support preimplantation development with its ability to yield viable embryos would be important. Follow-up on perinatal and long-term health of children born after embryo culture with more participants is required.

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KEY PERFORMANCE INDICATORS (KPIS) BASED ON POOR PROGNOSIS PATIENTS ARE MORE SENSITIVE TO THE EVALUATING EFFECTIVENESS OF DIFFERENT EMBRYO CULTURE INCUBATORS. Y. Du, Y. Geng, Y. Zhang. Department of Reproductive Medicine, Tianjin Central Hospital of Gynecology Obstetrics, Tianjin, China.

OBJECTIVE: To study whether it is better to follow the poor-prognosis patients compared with the gold standard patients in IVF before further integrating a change into routine human IVF practice.

DESIGN: A prospective cohort study.

MATERIALS AND METHODS: This study included 1260 infertile patients from April 2017 to March 2018. Patients were categorized as poor prognosis patients and gold standard patients group based on age and function parameters. Embryo culture parameters (ESI) and preg- nancy rates were analyzed using a two-part prospectively study in IVF. Part A involved 202 infertile poor prognosis patients; Part B involved 1058 infertile gold standard patients. After oocyte collection, randomization was carried out and all of the patients’ oocytes were allocated to culture in either a conventional incubator (control group) or a Flat Bed incubator (FBC) until embryo transfer on Day 3. The primary KPIs of this study was the implantation rate (IR) per embryo transferred. We then compared pregnancy-, ongoing pregnancy- and good quality embryos rate on day-3 after fertilization. Statistical analysis was performed using χ² test for categorical data and Student’s t-test for continuous data with p < 0.05 considered statistically significant.

RESULTS: In Part A revealed in poor prognosis patients no significant difference in the good quality embryos rate between groups: the control group and FBC group. The IR per embryo cultured in Flat Bed incubator (28.0% / 23/ 82) was significantly higher after transfer than the control group (16.4% / 40/244), p = 0.031; χ² = 6.626). Similarly, a significantly higher rate in pregnancy-, ongoing pregnancy was found in the FBC group compared with the control group (46.2 and 29.7%, p = 0.043, χ² = 4.088; 42.3 and 24.8%, p = 0.016, χ² = 5.033). In Part B (the gold standard patients’ group), the data displayed that no significant differences were found in the rate of GQEs on day 3 embryos, or implantation-, pregnancy-, and ongoing pregnancy rate between two embryo culture incubators groups.

CONCLUSIONS: The poor-prognosis patients may be a more sensitive group on evaluating the effectiveness of implementing a change in IVF laboratory process.

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OBJECTIVE: Advances in embryo culture strategies seeking to mimic in vivo conditions raise questions regarding the adequacy of the current use of dry incubators combined with oil covered media systems. The aim of the present study is to determine the effects of atmospheric humidity on embryo development by performing a continuous embryo monitoring assessment and an oxidative stress profiling.

DESIGN: Prospective randomized controlled trial including a total of 1,734 embryos from 176 patients.

MATERIALS AND METHODS: Embryos were cultured in the time-lapse incubator G1/G2 Plus (Vitrolife) in G1/G2 Plus (Vitrolife) (A), Global To-LifeGlobal (B), or Sequential Cleav/Blast (Origio) (C) media. Thirty-seven patients with no 2PN oocytes 18 h after insemination were excluded from the study. During embryo culture (1-5/0 μL), for cycles where the patients had only one good-quality (GQ) embryo by D3, the embryos were vitrified on D2/3. When the patients had ≥ 2 GQ embryos by D3, ≥ 2 GQ embryos were vitrified on D2/3, culture period of the remaining embryos was extended, and all GQ blastocysts were vitrified on D5/6. Data for vitrified ET performed until the end of March 2018 were analyzed.

RESULTS: Part A revealed in poor prognosis patients no significant difference in the good quality embryos rate between groups: the control group and FBC group. The IR per embryo cultured in Flat Bed incubator (28.0% / 23/ 82) was significantly higher after transfer than the control group (16.4% / 40/244), p = 0.031; χ² = 6.626). Similarly, a significantly higher rate in pregnancy-, ongoing pregnancy was found in the FBC group compared with the control group (46.2 and 29.7%, p = 0.043, χ² = 4.088; 42.3 and 24.8%, p = 0.016, χ² = 5.033). In Part B (the gold standard patients’ group), the data displayed that no significant differences were found in the rate of GQEs on day 3 embryos, or implantation-, pregnancy-, and ongoing pregnancy rate between two embryo culture incubators groups.

CONCLUSIONS: The poor-prognosis patients may be a more sensitive group on evaluating the effectiveness of implementing a change in IVF laboratory process.
with lower oxidative stress levels in humid culture conditions. This could be explained by culture increased stability in a humid environment, directly affecting osmolarity and pH levels. Further studies with larger sample sizes are required to confirm our findings.

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WHAT STAGE OF IN VITRO EMBRYO DEVELOPMENT IS AFFECTED BY OXYGEN TENSION? A RANDOMIZED CLINICAL TRIAL (RCT). C. Herbemont,a P. Maurin,a I. Cedrin-Durierin,a M. Gryenberg,a C. Sifer,a bIV Unit Jean Verdier, Bondy, France; bHopital Antoine Beclere, Clamart, France.

OBJECTIVE: In mammals, uterine environment is at low oxygen concentration (2-8% O2). Thus, human embryo culture under low O2 is recommended by ESHRE revised guidelines for good practices in IVF labs. Indeed, hypoxia seems to improve embryo quality at cleavage and blastocyst stages, presumably by reducing damages of oxidative stress (OS). Nevertheless, recent meta-analyses concluded with a low evidence to a superiority of hypoxia on IVF/ICSI outcomes. Furthermore, a study on mouse embryos suggested a negative impact of OS only at cleavage stage. This hypothesis has still never been investigated in humans.

DESIGN: From 01/2016 to 12/2017, 721 IVF/ICSI cycles were included in this RCT. At Day 0 (D0), cycles were randomized using a 1:2 allocation ratio: group 20% O2 (n = 241); group 5% O2 (n = 480). Extended culture (EC) was performed when ≥5 D2 good quality embryos were available (n = 83 in subgroup A (20% O2)). In subgroup 5% O2, 175 EC cycles were randomized among 2 groups using a 1:1 ratio: group B: 5% O2 until D6 (n = 88); or C: switch to 20% O2 from D3 to D6 (n = 87).

MATERIALS AND METHODS: Inclusion criteria were: intra-couple IVF/ICSI using fresh/frozen ejaculate; female age <40 years; absence of hydrosalpinx; ≥8 cumulus-oocyte complexes retrieved. Oocytes were fertilized and cultured in similar benchmark incubators, under 5% or 20% O2. Fertilization rate, cleavage-stage quality (D2 top quality embryo (D2 TQE) = 4 blastomeres, <20% cytoplasmic fragmentation), blastocyst quality, hatching rates and hatching blastocysts, were compared between groups 20% and 5% (=cleavage-stage analysis), or A (20%), B (5%) and C (5% to 20%) (=EC analysis).

RESULTS: In cleavage-stage analysis, all characteristics were similar between groups 20% and 5% O2. A significantly higher number of early-cleaved embryos was obtained under 5% O2 (3.3 vs. 2.4 under 20%; p = 0.0009). A trend towards higher D2 TQE rate was achieved under 5% O2 (40.8% vs. 37.9%; p = 0.067). Then, overall IR was comparable whatever the culture condition applied from D0 to D3 (5% O2: 29.7% vs. 20% O2: 27.8%). Considering EC analysis, both demographic and clinical parameters of the cycles were also comparable. Blastulation rates were similar in groups A, B and C (68.1%, 70.4% and 71.6%, respectively). Regarding blastocyst quality, embryo culture under 20% O2 from D0 to D6 (A) resulted in significantly lower D5 TQB rates/blastocyst (15.2%), than in both groups B (23.4%; p = 0.0029) and C (20.1%; p = 0.04). Furthermore, blastocyst quality was statistically equivalent between groups B and C. Finally, blastocysts IR were similar in groups A, B and C (43.4% vs. 39.4% vs. 42.7%, respectively).

CONCLUSIONS: Hypoxia during embryo culture improves embryo quality and development ability. However, late pre-implantation embryo development seems to be less vulnerable to OS.

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COMMERCIAL PROTEIN SUPPLEMENTS SIGNIFICANTLY AFFECT MOUSE EMBRYO DEVELOPMENT AND MAY IMPACT BLASTOCYST IMPLANTATION POTENTIAL. A. F. Ermisch, D. M. Logsdon, W. B. Schoolcraft, Y. Yuan, R. L. Krisher, Colorado Center for Reproductive Medicine, Lone Tree, CO.

OBJECTIVE: An array of protein supplementation is available for use in human embryo culture. Our objective was to analyze several types of protein for their ability to support mouse embryo development and implantation competence using an in vitro embryo culture and extended outgrowth model.

DESIGN: Research Study.

MATERIALS AND METHODS: In vivo matured IVF mouse zygotes were cultured in sequential, medium containing 5 mg/ml of our standard re-combinant albumin (Albix; ALB), and compared to 5 mg/mL albumin from four commercially available protein supplements: Vitrolife GMM (GMM), Vitrolife human serum albumin (HSA), Vitrolife HSA supplemented with additional fatty acids and carnitine (HSA+), or Quinn’s Serum Protein Substitute (SPS). On D3.5 of culture, morulae and blastocysts were placed into four commercially available dishes containing ICV1 (Cell Guidance Systems) medium for outgrowth. Media was replaced with IVC2 after 72h in outgrowth and embryo attachment assessed. At 120h (D8.5), embryos were fixed and measured for outgrowth area (n=40-56 per treatment). Outgrowth embryos were also stained with F-actin, DAPI and POUF51, and then imaged using confocal microscopy to determine outgrowth volume, total cell number, and epiblast cell number, respectively (n=15-19 per treatment).

RESULTS: Development to blastocyst on D3.5 was significantly lower in SPS than GMM, HSA+, and HSA (44±3.9%, 71±1.3%, 62±3.9%, 66.9±3.8%, respectively). Similarly, ALB, GMM, HSA+, and HSA all had significantly more hatching blastocysts than SPS (29.8±3.7%, 34.9±3.9%, 35.9±3.9%, 29.9±3.7%, 15.1±2.8%, respectively). There was a trend (p = 0.07) towards larger outgrowth area in HSA+ and GMM compared to SPS (0.63±0.03mm², 0.67±0.05mm², 0.51±0.03mm², respectively). More (p = 0.05) HSA+ embryos had epiblast cells (94.4%) than those in GMM (57.9%), HSA (52.6%), or SPS (46.7%), although the average number of epiblast cells in these embryos, including those in ALB, was not different (197.5±57.5, 257.1±94.8, 202.5±91.0, 141.1±27.5, 332.8±133.8, respectively). Likewise, total cell number (589±264.4, 684±150.7, HSA+; 556.8±155.2, HSA: 526.9±90.1, GMM: 561.2±181.7, SPS) and total outgrowth volume (6.7±1.9x10⁶ μm³, ALB; 6.1±1.8x10⁶ μm³, HSA+; 3.8±0.9x10⁶ μm³, GMM; 3.6±1.2x10⁶ μm³, SPS) were not significantly different between treatments.

CONCLUSIONS: While differences were seen in developmental outcomes, type of protein supplementation did not have a statistically significant impact on implantation competence as measured in our extended outgrowth model. However, those embryos cultured in ALB and HSA+ successfully proliferated in outgrowth culture, suggesting that these two protein supplements better support blastocyst implantation potential—a hypothesis we are currently studying. This data could have an important translational impact on the choice of protein supplementation for use in human embryo culture media.

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MEDIA EVAPORATION IN A DRY CULTURE INCUBATOR; EFFECT OF DISH, DROP SIZE AND OIL ON MEDIA OSMOLARITY. J. E. Swain, C. Graham, R. Kile, W. B. Schoolcraft, R. L. Krisher, Colorado Center for Reproductive Medicine, Lone Tree, CO.

OBJECTIVE: Modern benchtop incubators typically lack humidity, a significant difference compared to traditional big box incubators. Combined with the recent popularity of single step culture systems, media evaporation resulting in an increase in osmolality during the culture period is a legitimate concern. The objective of this study was to evaluate variables that may impact evaporation over the time course of normal human embryo culture in a dry benchtop incubator.

DESIGN: Prospective Study.

MATERIALS AND METHODS: 1) Cleavage medium (Sage) + 10% SPS was used for all experiments. Dishes for each treatment were prepared and placed into the same chamber of a K Systems G185 incubator. After 6 days, media from microdrops in each treatment was recovered and osmolality measured on a Wescor 5600 Vapor Pressure osmometer. All experiments were repeated 3 times, with a minimum of 13 drops measured per treatment. Media prior to incubation was used as a control. In experiment 1. 30 ul drops were prepared under 3.5 mL of oil (OvOil) in a Falcon 35 mm dish and under 4.5 mL of oil in a mini-GPS dish. In experiment 2, drop volume was examined in the mini-GPS dish (20UL, 40UL and 60UL). In experiment 3, 30UL drops in a mini-GPS dish were covered with 3, 4 or 5 mL of oil. In experiment 4, 30 ul drops in a mini-GPS dish were covered with 4.5mL OvOil, light oil, or heavy oil. Results are presented as mean ± SEM in mOsm. Significance was determined at p<0.01.

RESULTS: Uninterrupted culture for 6 days in a benchtop incubator resulted in a significantly increase in medium osmolality regardless of dish type (Falcon control: 275.8± 1.5; Falcon 6 day: 300.7 ± 2.0; GPS control: 275.9 ± 1.7; GPS 6 day: 293.1 ± 1.5). Although evaporation occurred in both types of dishes, GPS dishes resulted in a significant improvement in osmolality on D6. Evaporation resulting in increased osmolality occurred in all drop sizes control: 271.0 ± 1.4; 20 ul: 306.6 ± 2.6; 40 ul: 292.4 ± 2.6; 60 ul: 302.4 ± 3.3), although 40 ul drops resulted in lower osmolality than 20 or 60 ul drops. Elevated osmolality also resulted regardless of oil
**HUMAN UTERINE FLUID COMPOSITION IS DISTINCT FROM CLINICALLY USED PREIMPLANTATION EMBRYO CULTURE MEDIA.** M. Tarahomi, F. Vaz, S. Zafardoust, F. Fatemi, M. vanWely, A. Mohammadzadeh, S. Repping, G. Hamer, S. Mastenbroek, Center for Reproductive Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands; Laboratory Genetic Metabolic Diseases, Academic Medical Center, university of Amsterdam, Amsterdam, Netherlands; Reproductive Biotechnology Research Center, Avicenna Research Institute, ACECR, Tehran, Iran, Islamic Republic of.

**OBJECTIVE:** To compare the composition of human uterine fluid on the third day after ovulation with the composition of embryo culture media used in IVF treatments.

**DESIGN:** Between April 2015 and March 2016, we conducted a cross sectional clinical study to determine the composition of human uterine fluid at the time of implantation, i.e. three days after ovulation. The uterine fluid composition was compared with the composition of commonly used human preimplantation culture media.

**MATERIALS AND METHODS:** Fertile women of reproductive age with normal uterine anatomy were included. Uterine fluid was aspirated on the third day after ovulation in a normal non-stimulated menstrual cycle. All pre-implantation culture media were tested directly from the supplied bottle, well before the expiry date. In total, 37 components were tested. For quantification of ions, metabolites, immunoglobulins, proteins and amino acids, liquid chromatography-tandem mass spectrometry and gas chromatography-mass spectrometry were used. The effects of potential confounders, such as female age and BMI, were evaluated using linear mixed models and the Mann-Whitney U test was used for comparing the concentrations of different components in uterine fluid with concentrations in culture media.

**RESULTS:** The uterine fluid composition of 22 women on the third day of the luteal phase of the menstrual cycle was analyzed. Similarly, the composition was compared with the composition of commonly used human preimplantation culture media.

<table>
<thead>
<tr>
<th>Component</th>
<th>Uterine Fluid</th>
<th>Culture Media</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>37.6 ± 4.3</td>
<td>37.5 ± 4.6</td>
<td>0.56</td>
</tr>
<tr>
<td>AMH (ng/mL)</td>
<td>2.9 ± 4.0</td>
<td>2.7 ± 3.1</td>
<td>0.21</td>
</tr>
<tr>
<td>BAFC</td>
<td>11.3 ± 6.4</td>
<td>11.3 ± 6.8</td>
<td>0.99</td>
</tr>
<tr>
<td>Surfact E2 (pg/mL)</td>
<td>2067 ± 1176</td>
<td>2039 ± 1141</td>
<td>0.68</td>
</tr>
<tr>
<td>Number of Oocytes Retrieved</td>
<td>13.1 ± 8.8</td>
<td>13.2 ± 9.0</td>
<td>0.98</td>
</tr>
<tr>
<td>Number of MII / MII Rate</td>
<td>10.2 ± 7.4</td>
<td>10.3 ± 7.4</td>
<td>0.85 / 0.85</td>
</tr>
<tr>
<td>Types of Insemination: Conventional / ICSI / Split</td>
<td>111 (7.3%) / 1395 (92.3%) / 6 (0.4%)</td>
<td>162 (6.9%) / 2188 (92.9%) / 5 (0.2%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Number of Fertilized Oocytes / Fertilization Rate</td>
<td>7.9 ± 6.0 / 76.8 ± 20.0%</td>
<td>7.8 ± 6.0 / 76.2 ± 20.0%</td>
<td>0.76 / 0.41</td>
</tr>
<tr>
<td>Number of Blastocysts / Blastulation Rate</td>
<td>6.0 ± 5.0 / 69.5 ± 27.1%</td>
<td>5.9 ± 5.0 / 68.3 ± 27.8%</td>
<td>0.51 / 0.21</td>
</tr>
<tr>
<td>Day of Blastocyst Biopsy: Day 5 / Day 6 / Day 7</td>
<td>721 (67.6%) / 303 (28.4%) / 42 (3.9%)</td>
<td>1004 (62.0%) / 543 (33.5%) / 73 (4.5%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Number of Euploid Embryos / Euploidy Rate</td>
<td>2.1 ± 2.4 / 43.9 ± 34.2%</td>
<td>2.1 ± 2.4 / 43.4 ± 34.5%</td>
<td>0.61 / 0.71</td>
</tr>
</tbody>
</table>

**CONCLUSIONS:** Analysis of 37 components showed that the concentration of 32 components differed between human uterine fluid and human embryo culture media used in routine IVF practice. These differences suggest that current in vitro culture conditions might be suboptimal to provide support for the developing human preimplantation embryo in vitro. Our findings provide valuable information for the improvement of embryo culture media.

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**OBJECTIVE:** With the rise in IVF cycles over the years, optimizing incubator space is a priority of the modern embryology laboratory. High volume centers are challenged by incubator use and maintenance of culture conditions for optimal embryo development. The study aimed to determine if differences in incubator capacity are associated with laboratory outcomes following extended blastocyst culture.

**DESIGN:** Retrospective.

**MATERIALS AND METHODS:** Patients who underwent IVF from 2016-2018 were included. Embryos were cultured up to day 7, and select blastocysts underwent pre-implantation genetic testing for aneuploidy (PGT-A). All oocytes/embryos were stored in Panasonic MCO-5M incubators. Groups were separated by incubator capacity: Group A: 1 shelf, with oocyte/embryos from up to 3 patient cycles; Group B: 2 shelves, with oocyte/embryos from up to 6 patient cycles. Patient age, body mass index (BMI), anti-Müllerian hormone (AMH), basal antral follicle count (BAFC), estradiol (E2) and progesterone (P4) at surge, cumulative gonadotropin (G DN) dose, total number of oocytes and metaphase II (MII) oocytes retrieved, number of fertilized oocytes, type of fertilization method, number of blastocysts, day of trophoderm(T) biopsy, and number of euploid blastocysts were determined. The rate of MII development, fertilization, blastulation, and euploidy were also measured. Data were analyzed using a Student’s T-test, Chi-squared and multivariate logistic regression.

**RESULTS:** Of 3867 cycles, approximately 39% were in group A (n=1512) and 61% were in group B (n=2355). Patient age, BMI, AMH, BAFC, Surge E2, Cure P4, and cumulative GDN did not differ between groups. The total number of oocytes, MII oocytes, fertilized oocytes, blastocysts, blastocysts biopsied, and euploid blastocysts were similar between groups. The MII rate, fertilization rate, blastulation rate, and euploid rate did not differ between groups A and B, before and after adjusting for confounders.

**CONCLUSIONS:** Embryonic development was not associated with the amount of specimens contained in an incubator. Embryologists can be reassured that increased embryo storage per incubator unit is not detrimental to oocyte/embryo development. While environmental exposures, temperature fluctuations, and pH shifts within the IVF laboratory are vital to the culture of embryos, high volume programs can be reassured that modern incubators are clinically efficient and can yield consistently good outcomes.
OBJECTIVE: To evaluate the effects of different culture media on embryonic development and morphokinetic parameters in the same culture condition by sibling oocyte study.

DESIGN: Retrospective analysis: randomized, sibling oocyte study in a private assisted reproductive technology clinic. This study was approved by the Ladies Clinic Kyono Ethics Committee.

MATERIALS AND METHODS: The experiments were performed in an Embro卵子 from 66 cycles from which at least six oocytes were retrieved at clinical embryos were monitored by EmbryoScope+TM with 6% CO2 and 5% O2. We analyzed embryonic development and morphokinetic parameters in the same culture conditions by sibling oocyte study. The results were analyzed according to different age groups.

RESULTS: Some clinics do not have access to time-lapse systems and try to mimic undisturbed culture by not removing the embryos from the standard incubator. This study shows the results from this approach. There were no significant differences in terms of patient's demographics between both groups (including BMI and sperm concentration). For all groups, the average ongoing pregnancy rate was higher in TS (non PGT-a 49.5% and PGT-a 46.5%) than in SI (non PGT-a 44.4% and PGT-a 42.5%) although not significant. Table 1 shows results according to different age groups.

CONCLUSIONS: Pseudo undisturbed culture with SI does not achieve the same results as real undisturbed culture in TS. Although not significant, clinical outcomes are 5% better in the TS group than in SI. Results are only shown for different patients in the non PGT-a. However, significance may be achieved by increasing the number of cycles in each group. Further studies are needed.

Supported by: None.

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DEVELOPMENT OF A CLINIC-SPECIFIC PREDICTIVE EMBRYOKINETIC PATIENT MODEL IN AN ACADEMIC CENTER. L. Yang, M. Peavey, K. Kaskar, N. Chappell, L. Zhu, D. Devlin, C. Valdes, A. K. Schutt, T. L. Woodard, P. Zarutskie, R. Cochran, W. Gibbons. Baylor College of Medicine, Houston, TX; University of North Carolina, Chapel Hill; NC; Rice University, Houston, TX; Obstetrics and Gynecology, Baylor College of Medicine, Houston, TX; Reproductive Endocrinology and Infertility, Baylor College of Medicine, Houston, TX; Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX.

OBJECTIVE: To develop and examine the feasibility of a clinic-specific embryo morphokinetic assay by time-lapse microscopy (TLM) to predict clinical pregnancy rate.

DESIGN: Retrospective cohort analysis of TLM of embryos with clinical pregnancy data (Phase I), and a prospective, blinded cohort analysis of TLM of embryos that were transferred at an academic fertility center (Phase II).

MATERIALS AND METHODS: Embryos that underwent EmbryoScope™TLM and subsequent frozen transfer with or without clinical pregnancy (defined by fetal heart beat after 6 weeks) were included from 2014 to 2016. For phase II, embryos that were transferred in 2017-2018 were included and with blinded pregnancy outcomes from the annotator. All morphokinetic parameters from fertilization to blastocyst formation were manually annotated. Data were analyzed by multivariate analysis of covariance, Fisher’s exact, Chi-square tests, and binomial logistic regression with SPSS.

RESULTS: In the phase I study, embryos that resulted in clinical pregnancy (n=94) were faster to develop to 4-cell stage (37.8h vs 40.2h, p=0.057, OR 0.74) compared to embryos that did not result in clinical pregnancy (n=121). A logistic regression prediction model (Chi-square=26.3, p=0.010) using morphokinetic parameters, termed the Yang-Peavey Embryo Enhancement Algorithm (YPEEA). A receiver operating characteristic curve was developed and found to be significant with area under the curve 0.757 (95% CI 0.667-0.848, p<0.001). In the phase II prospective cohort study, the algorithm was applied to 132 embryos that were transferred, which were manually annotated and blinded from the pregnancy outcome. When applied to a subset of patients under the age of 35 (n=63), the YPEEA algorithm yielded positive predictive value (PPV) of 70% vs 60% pregnancy rate of euploid embryos. When applied to the total cohort, the YPEEA algorithm yielded 68% sensitivity and 53% PPV.

CONCLUSIONS: This study shows the feasibility and development of a clinic-specific, novel embryo morphokinetic predictive model with as few as 200 embryo outcomes, applicable to a prospective cohort of embryos. The predictive value of the algorithm is comparable or even superior in a subset of patients to that of preimplantation genetics testing and therefore is a valuable non-invasive technology to predict clinical pregnancy in IVF.

Supported by: Baylor College of Medicine Department of Obstetrics and Gynecology, the Division of Reproductive Endocrinology and Infertility, the 2016 Robert and Janice McNair Medical Scientist Training Program Scholarship

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DETERMINING OXYGEN EQUILIBRATION DYNAMICS IN ART CULTURE MEDIA. T. O’Leary, A. Krieg. Oregon Health Science University, Portland, OR; Oregon Health Science University, Beaverton, OR.

OBJECTIVE: The culture of human embryos in low oxygen conditions (5% O2) has become common practice in ART laboratories. Despite this, little is known about the dynamics of oxygen de-saturation and re-saturation during embryo culture and manipulation. The objective of this study was to determine the time needed to equilibrate ART culture media from atmospheric conditions (21% O2) to 5% O2 or vice versa.

DESIGN: ART media was aliquoted in a manner consistent with that used in the clinical setting, and allowed to equilibrate to 5% O2. Changes in oxygen concentration were tracked in real-time using an oxygen-sensing microprobe during the equilibration and reoxygenation process.

MATERIALS AND METHODS: Room temperature Global Total media was distributed as microdroplets (30 microliter per droplet, 4 per dish) overlaid with 6 mL of room temperature Global light culture oil. Organ well culture dishes containing 3 mL of media overlaid with 3 mL of oil were analyzed in parallel. Media and oil was distributed at room temperature without prior equilibration of reagents. Dishes were placed in a humidified hypoxia glove box incubator (Coy Labs, Inc.) equilibrated to 5% O2; 5% carbon dioxide, and 37 degrees Celsius. Changes in oxygen tension were measured within 15 seconds with a Microx4 oxygen meter equipped with a needle-type fiber optic oxygen sensing microprobe (PreSens, GmbH). Reoxygenation dynamics from 5% O2 were measured on the bench top at room temperature in atmospheric conditions.

RESULTS: Both media droplets and media layers were fully equilibrated to 5% O2 within 20 hours. Loss of oxygen followed a monophasic exponential decay with a half-life of 60 minutes. The majority of the equilibration occurred within 8 hours, with only an additional 10% loss in oxygen concentration (change of 0.5%) occurring throughout the remainder of the measurements. Following return of media to 21% O2, reoxygenation occurred with a doubling time of 36 minutes. Media O2 levels had risen to over 7% O2 within 15 minutes. Within 4.5 hours, media had returned to full oxygen saturation.

CONCLUSIONS: Temporary exposure of culture dishes to CO2-only isolettes/incubators or to atmospheric conditions should consider these parameters for maintaining stable low O2 conditions. Further studies comparing these results with different media types, culture volumes, and oil viscosity will further inform efforts to minimize introduction of reactive oxygen species during ART procedures.

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EARLY PREGNANCY OUTCOMES DO NOT DIFFER BASED ON THE TYPE OF INCUBATOR USED FOR EMBRYO CULTURE IN CRYOTHAW SINGLE EMBRYO TRANSFER CYCLES. I. Dimitriadis, G. Christou, I. Souter, C. L. Borrowman. Massachusetts General Hospital, Boston, MA; Harvard Medical School-Massachusetts General Hospital Fertility Center, Boston, MA; OB/GYN, Massachusetts General Hospital-Harvard Medical School, Boston, MA.

OBJECTIVE: To evaluate the difference in early pregnancy outcomes between vitrified blastocysts thawed for single embryo transfer (SET) cultured in a closed-system time-lapse incubator (Embryoscope®) versus a conventional incubator.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: A total of 119 embryos from SET cryothaw cycles completed between 8/2015-12/2016 at a large academic institution were analyzed. Fifteen percent of embryos were cultured in a conventional and 60 in an Embryoscope® incubator. Positive pregnancy (PPR), implantation (IMPR), clinical pregnancy (CPR) and spontaneous abortions (SABR) rates were compared between the two groups.

Statistics: Chi-square and multivariate generalized fixed and random effect logistic regression models [adjusted for age, body mass index (BMI), anti-mullerian hormone levels (AMH), and infertility diagnoses] were used as appropriate.

RESULTS: The patients from which the embryos of the two groups originated, did not differ in age, BMI, ovarian reserve markers (day-3 FSH and AMH levels), or endometrial thickness. However, polycystic ovarian syndrome and decreased ovarian reserve were more prevalent diagnoses among patients whose embryos were cultured in the conventional incubators when compared to those cultured in the Embryoscope® (10.2% vs 1.7%, and 13.6% vs 6.7%, respectively, p<0.05 for both comparisons). PPR, IMPR, CPR, and SABR did not differ between groups (OR 0.70 vs 0.35, 0.46, and 0.40, respectively). The odds for implantation, positive and clinical pregnancy, as well as spontaneous abortion did not differ, when the cryothaw SET cycles from the closed-system time-lapse incubators were compared to those from the conventional ones (OR (95% CI): 1.26 (0.59, 2.68), p=0.54; 1.33 (0.52, 3.43), p=0.55; 1.26 (0.58, 2.68), p=0.55; 2.25 (0.20, 24.03), p=0.52), for IMPR, PPR, CPR, and SABR respectively.

CONCLUSIONS: Among cryothaw single embryo transfers, no difference in early pregnancy outcomes, including PPR, IMPR, CPR and SABR, were noted when embryos from a closed-system time-lapse incubator were compared to those cultured in conventional ones, a finding consistent with that of studies involving fresh embryo transfers.
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COST-EFFECTIVENESS ANALYSIS OF ENDOMETRIAL INJURY ON FROZEN-THAWED BLASTOCYST TRANSFER FOR ASSISTED REPRODUCTIVE TECHNOLOGY: A MARKOV MODEL ANALYSIS.

M. Funabiki, S. Taguchi, N. Amano, Y. Nakamura. Oak Clinic, Osaka, Japan.

OBJECTIVE: To perform a cost-effectiveness analysis of endometrial injury on frozen-thawed blastocyst transfer for assisted reproductive technology (ART).

DESIGN: Cost-effectiveness analysis of endometrial injury on frozen-thawed blastocyst transfer for ART.

MATERIALS AND METHODS: A Markov decision analytic model was developed to simulate endometrial injury plus an in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) strategy or the IVF/ICSI strategy alone in hypothetical cohorts of 10,000 patients undergoing IVF/ICSI with frozen-thawed blastocyst transfer using data from published randomized clinical trials.

RESULTS: The cost per live birth was estimated at €12,145 and at €15,147 for the IVF/ICSI strategy alone and the endometrial injury plus IVF/ICSI strategy, respectively, using efficacy data from published randomized clinical trials. The resulting incremental cost-effectiveness ratio (ICER) was €11,616 per live birth. The ICER for the endometrial injury plus IVF/ICSI strategy versus the IVF/ICSI strategy alone was estimated at €7,500 per live birth, with a savings of about €8.52 million and 1000 additional live births. The sensitivity analyses showed that the main ICER drivers were the pregnancy rate and the live birth rate. The probabilistic sensitivity analysis indicated that the endometrial injury plus IVF/ICSI strategy was the dominant strategy in 60.3% of cases using the randomized clinical trial data.

CONCLUSIONS: The present analysis indicates that compared with the IVF/ICSI strategy alone, the endometrial injury plus IVF/ICSI strategy is less costly for managing IVF/ICSI-related procedures from a healthcare payer's viewpoint.

References: "None"

Supported by: "None"

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PREGNANCY AND NEONATAL OUTCOMES OF INFERTILE PATIENTS UNDERGOING FROZEN-THAWED EMBRYO TRANSFER AFTER ARTIFICIAL OOCYTE ACTIVATION: A SIX-YEAR POPULATION-BASED RETROSPECTIVE STUDY. Z. Yan. Shanghai Ninth People’s Hospital, Shanghai, China.

OBJECTIVE: To evaluate the clinical outcomes and safety of artificial oocyte activation (AOA) in patients with frozen-thawed embryo transfer (FET).

DESIGN: This was a retrospective single-center cohort study from January 2011 to December 2016. A total of 6806 patients of FET were divided into two cohorts: (1) routine ICSI group includes 6605 patients transferred embryos from ICSI. (2) ICSI-AOA group includes 201 patients transferred embryos from ICSI combined with AOA. Data were collected from the first FET cycle of each patient.

MATERIALS AND METHODS: All participants provided informed consent after receiving counseling concerning infertility treatments. Based on the published literatures, patient treated with AOA according to the following criteria: (1) ICSI fertilization rate ≤50 (in-house and out-house cases); (2) good quality embryo rate ≤50% (in-house and out-house cases); (3) severe oligoasthenoteratozoospermia or teratozoospermia; and (4) testicular sperm aspi-ration (TESA) or percutaneous epididymal sperm aspiration (PESA). AOA was performed by exposure to 10 μM of ionomycin for 10 minutes after 1 hour of ICSI. The procedures of ovarian stimulation, ICSI, embryo assessment, freezing, and thawing, endometrial preparation, and FET have been described in previous studies The Pregnancy and neonatal outcomes were assessed according to the terms defined based on the International Committee for Monitoring Assisted Reproductive Technology and the World Health Organization revised glossary of ART terminology. Compare differences of rates were performed by the Chi-square test or Fisher’s exact test as appropriate. Compare differences in mean values were performed by Student’s t-test. P < 0.05 was considered statistically significant.

RESULTS: The pregnancy outcome in two cohorts of 6605 patients with routine ICSI and 201 patients with ICSI-AOA showed no statistically significant difference in the rates of clinical pregnancy, implantation, abortion, ectopic pregnancy, multiples pregnancy and live birth. Moreover, when compared to the neonatal outcomes, no statistically significant differences were found in the birth defect rate, birth weight, low birth weight rate, birth length, gestational age, and fetal sex ratio among 3213 babies and 93 babies born from routine ICSI group and ICSI-AOA group, respectively.

CONCLUSIONS: The application of AOA in specific infertility patients could yield comparable FET pregnancy and neonatal outcomes to patients with routine ICSI. Moreover, AOA with ionomycin does not increase the risk of birth defects for the offspring born from FET. This is the first clinical outcome and safety assessment of AOA on FET patients in a large retrospective cohort.

Table 1 The pregnancy outcomes of FET cycles between routine ICSI and ICSI-AOA patients

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Routine ICSI</th>
<th>ICSI-AOA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical pregnancy(%)</td>
<td>47.72(3152/6605)</td>
<td>47.26(95/201)</td>
<td>0.898</td>
</tr>
<tr>
<td>Implantation(%)</td>
<td>32.48(4010/12346)</td>
<td>32.60(118/362)</td>
<td>0.963</td>
</tr>
<tr>
<td>Miscarriage(%)</td>
<td>14.94(471/3152)</td>
<td>16.64(169/95)</td>
<td>0.609</td>
</tr>
<tr>
<td>Ectopic pregnancy(%)</td>
<td>1.43(45/3152)</td>
<td>2.11(29/135)</td>
<td>0.913</td>
</tr>
<tr>
<td>Live birth rate (%)</td>
<td>39.20(259/6605)</td>
<td>37.31(75/201)</td>
<td>0.59</td>
</tr>
<tr>
<td>Multiples birth rate(%)</td>
<td>24.10(624/2589)</td>
<td>24.00(18/75)</td>
<td>0.984</td>
</tr>
<tr>
<td>No. of children</td>
<td>3213</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Birth Weight (g)</td>
<td>3018.4±201/3264.7</td>
<td>3019.6±605.6</td>
<td>0.986</td>
</tr>
<tr>
<td>Body Gestational age (weeks)</td>
<td>37.99±2.07</td>
<td>37.92±2.41</td>
<td>0.78</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>1614/1599</td>
<td>43/50</td>
<td>0.447</td>
</tr>
<tr>
<td>Live birth defect rate(%)</td>
<td>1.21%(39/3213)</td>
<td>1.08%(19/193)</td>
<td>0.904</td>
</tr>
</tbody>
</table>

References:

Supported by: This work was supported by The National Nature Science Foundation of China (grant nos. 81571486 and 81771649). None of the authors declare any conflict of interest.
EFFECT OF ENDOMETRIAL INJURY ON REPRODUCTIVE OUTCOMES OF FROZEN-THAWED EMBRYO TRANSFER CYCLES IN WOMEN WITH ONE IMPLANTATION FAILURE. T. Chen a, Y. Su a. a The Reproductive Medical Center, The First Affiliated Hospital of Zheng Zhou University, Zhengzhou, China; b The Reproductive Center, The First Affiliated Hospital of Zheng Zhou University, Zheng Zhou, China.

OBJECTIVE: Endometrial injury (EI) is a recently proposed, relatively simple procedure that may improve endometrial receptivity. However, the subgroup of patients and the timing and type of embryo transfer (ET) cycles needed to achieve an optimal effect remain uncertain. The purpose of our study is to investigate whether EI improves reproductive outcomes in patients with one implantation failure in a previous fresh or frozen-thawed ET (FET) cycle.

DESIGN: This is a retrospective study including a total of 300 patients who underwent artificial-cycle FET. All subjects were divided into an EI group and a control group. The EI group underwent EI in the proliferative phase of the subsequent FET cycle, and the control group was not treated with EI. The outcome measures included the rates of biochemical pregnancy, implantation rate, clinical pregnancy, multiple pregnancy, miscarriage (early, late) and live birth (per transfer, per pregnancy).

MATERIALS AND METHODS: A total of 300 patients were divided into an EI group (n = 150) and a control group (n = 150). All the patients were analyzed in subgroups based on previous implantation failure type. Patients with one implantation failure in the fresh ET cycle were classified into group A (EI group, n = 62) and group C (control group, n = 62). Patients with one implantation failure in the FET cycle who did not undergo ET during the fresh ET cycle were classified into group B (EI group, n = 88) and group D (control group, n = 88).

RESULTS: No significant differences were found in the baseline characteristics or in the rates of implantation, biochemical pregnancy, clinical pregnancy, multiple pregnancy or live birth rate per transfer between the EI and control groups. The EI group exhibited a significantly lower rate of miscarriage compared to the control group, with the main difference manifested in early miscarriage. The live birth rate per pregnancy was higher in the EI group than in the control group. The rates of implantation, biochemical pregnancy, clinical pregnancy, multiple pregnancy, miscarriage, live birth per transfer or live birth per pregnancy in groups A and C were similar. The rates of implantation, biochemical pregnancy, clinical pregnancy, multiple pregnancy or live birth transfer were not significantly different in groups B and D, but the patients in group B demonstrated a significantly lower miscarriage rate, early miscarriage and higher live birth rate per pregnancy than did those in group D. Moreover, EI was shown to be an independent protective factor that decreased the miscarriage rate as assessed by logistic regression analysis.

CONCLUSIONS: These results reveal that EI fails to improve the rates of implantation and clinical pregnancy compared with a control group, but is beneficial in decreasing the miscarriage rate and increasing the live birth rate per pregnancy, especially in women with one implantation failure in a previous frozen-thawed ET cycle.

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OBJECTIVE: To compare pregnancy outcomes between natural and programmed cycles in patients undergoing STEET after in vitro fertilization with preimplantation genetic testing for aneuploidy (IVF/PGT-A) with NGS. DESIGN: Retrospective cohort study

MATERIALS AND METHODS: All STEET cycles after IVF/PGT-A with NGS between 2015-2017 were included. Patients were stratified into those who underwent programmed cycles with exogenous estrogen and progesterone replacement or natural cycles. Patients undergoing a programmed cycle took oral estradiol fentanyl per day followed by either progesterone in oil 50-75mg intramuscular per day or vaginal progesterone suppository twice daily. Patients were scheduled for transfer when the lining reached 7mm or greater. Patients undergoing natural cycle were monitored until a dominant follicle reached 18mm. Human chorionic gonadotropin 5,000 international units was then administered and vaginal progesterone suppository twice daily. Data was collected including age, gravidity, parity, infertility diagnosis, and number of prior frozen embryo transfer cycles. Statistical analysis was performed using 1-test and Fisher’s exact test with P<0.05 deemed statistically significant. RESULTS: 124 STEET cycles met inclusion criteria, including 109 natural cycle and 133 programmed cycles. There were no significant differences in the age at time of IVF/PGT-A cycle between the natural cycle and the programmed cycle groups (36.9 ± 3.89, 36.7 ± 4.4, p = 0.57). There was no significant difference in IR, OPR, or SABR between groups, see table 1. Estradiol levels were significantly higher in programmed cycles, and progesterone levels 5 days prior to embryo transfer were significantly higher in natural cycles.
DAY-3 QUALITY IS NOT A VALUABLE PARAMETER FOR PREDICTING PREGNANCY OUTCOMES AFTER VITRIFIED-WARMED SINGLE BLASTOCYST TRANSFER. G. Li, P. Chen, Q. Sun, F. Xiong, C. Wan, Y. Zeng. Shenzhen Zhongshan Urology Hospital, Shenzhen, China.

OBJECTIVE: The aim of the present study is to determine whether day-3 (D3) quality of the blastocyst can predict pregnancy outcomes in the vitrified-warmed single blastocyst transfer cycles in a good prognosis population.

DESIGN: The alpha error level was fixed at 0.05 and the power was set at 80%. Assuming that the difference in clinical pregnancy rate would be 10% (40% and 50%), the optimum sample size should be at least 388 cases in each group. According, a total of 1109 vitrified-warmed single blastocyst transfer cycles were retrospectively analyzed. Patients were divided into two groups: D3 good quality group (D3-GQ group, n=593) and D3 poor quality group (D3-PQ group, n=516).

MATERIALS AND METHODS: All cycles met the following inclusion/exclusion criteria. Inclusion criteria: 1) female age ≤ 37; 2) previous OPU cycle ≤ 3; 3) single blastocyst transfer cycle; 4) Day 1 score of the transferred blastocyst: 2PN; 5) ovarian stimulation protocol: luteal-phase gonadotrophin releasing hormone agonist protocol. Exclusion criteria: 1) no blastocyst survived after warming; 2) lost to follow-up. Patients underwent the hormone replacement cycles and received the same treatment in the whole cycle, and were followed up to March 2018. Clinical outcomes were retrospectively evaluated according the quality of the transferred blastocyst at D3. Statistical differences between the two groups were analyzed by Wilcoxon-Mann-Whitney and Fisher's exact tests.

RESULTS: Clinical pregnancy rate was significantly higher (P < 0.001) of vitrified-warmed single blastocysts. The overall clinical and neonatal outcomes following transfer of thawed cleavage-stage embryos was more suited for women of advanced age.

CONCLUSIONS: Cleavage-stage FET was found to be more suitable for younger women, while FET of blastocysts cultured from cleavage-stage embryos was more suited for women of advanced age.


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CLINICAL AND NEONATAL OUTCOMES OF PATIENTS OF DIFFERENT AGES FOLLOWING TRANSFER OF THAWED CLEAVAGE EMBRYOS AND BLASTOCYSTS CULTURED FROM THAWED CLEAVAGE-STAGE EMBRYOS. Q. Zhou. Institute of Reproductive and Stem Cell Engineering, School of Basic Medical Science, Central South University, Changsha, China.

OBJECTIVE: Frozen-thawed embryo transfer (FET) has become a routine procedure in assisted reproductive technology (ART). In FET, blastocysts cultured from thawed cleavage-stage embryos are associated with fewer miscarriages and better perinatal outcomes than cleavage-stage FET. However, culture of cleavage-stage embryos to the blastocyst stage may increase cycle cancellation. The overall clinical and neonatal outcomes following transfer of thawed cleavage-stage FET and blastocysts cultured from thawed cleavage-stage embryos in young and advanced age patients remains unclear. Therefore, in this study we aimed to identify the optimal FET strategy in young and advanced age women who undergo FET.

DESIGN: This is a retrospective study.

MATERIALS AND METHODS: It included 20,411 thaw cycles. We retrospectively analyzed date of couples who had completed at least one FET from January 2010 to December 2015 at the Reproductive and Genetic Hospital of CITIC-Xiangya. Two FET strategies were studied: transfer of thawed cleavage-stage embryos (strategy A) or blastocysts cultured from these thawed cleavage-stage embryos (strategy B). The clinical and neonatal outcomes of two FET strategies were compared in young (<35 years) and advanced (≥35 years) age women, respectively.

RESULTS: In young women, the implantation rate (48.49% vs. 40.47%, P < 0.001), clinical pregnancy rate (63.45% vs. 58.39%, P < 0.001) and live birth rate (52.68% vs. 48.41%, P < 0.001) in per transfer cycle were significantly higher in strategy B than strategy A. While, the clinical pregnancy (57.46% and 52.30%, respectively) and live birth rates per thaw cycle were significantly higher in strategy A than in strategy B (47.64% and 43.42%, respectively). In women of advanced age, the implantation (40.54% vs. 23.07%, P < 0.001), clinical pregnancy (54.48% vs. 39.99%, P < 0.001) and live births rates per transfer cycle (41.27% vs. 24.32%, P < 0.001) were significantly higher in strategy B than in strategy A. The clinical pregnancy and live birth rates per thaw cycle were still significantly higher in strategy B cycles (41.43% and 31.39%, respectively) than in in strategy A cycles (33.56% and 23.39%, respectively).

CONCLUSIONS: Cleavage-stage FET was found to be more suitable for younger women, while FET of blastocysts cultured from cleavage-stage embryos was more suited for women of advanced age.


Supported by: This work was supported by the National Natural Science Foundation of China (31401069), and the National Science Foundation of Hunan Province of China (2017JJ13237).

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EMBRYO TRANSFER STRATEGY OF BLASTOCYSTS WITH VARIOUS GRADES: IVF OUTCOMES FROM 1306 FROZEN-THAWED EMBRYO TRANSFERS. D. Park, J. Eum, J. Kim, J. Hwang, J. Kim, W. Lee, S. Lyu. Fertility Center of CHA Gangnam Medical Center, CHA University, Seoul, Korea, Republic of.

OBJECTIVE: Until now, there are no well-established embryo transfer strategies when there are blastocysts with various grades. Therefore, we aimed to compare pregnancy outcomes and neonatal outcomes of three different frozen-thawed embryo transfer (FET) protocols with various graded blastocysts.

DESIGN: A retrospective cohort study.

MATERIALS AND METHODS: We evaluated 1306 FET cycles of blastocysts performed between January 2014 and December 2015 at the Fertility Center of CHA Gangnam Medical Center. All cycles underwent natural endometrial preparation and used vitrified-warmed blastocysts. FET cycles split into 3 groups according to grades of blastocysts:

<table>
<thead>
<tr>
<th>Natural (n=109)</th>
<th>Programmed (n=1133)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR 78 (71.6%)</td>
<td>777 (68.6%)</td>
<td>0.6</td>
</tr>
<tr>
<td>OPR 71 (65.1%)</td>
<td>696 (61.4%)</td>
<td>0.51</td>
</tr>
<tr>
<td>SABR 7 (8.97%)</td>
<td>81 (10.4%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Estradiol 227.3±98.6</td>
<td>526.9±511.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progesterone 0.54±0.94</td>
<td>0.33±0.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endometrial Thickness 9.08±1.59</td>
<td>8.8±1.54</td>
<td>0.12</td>
</tr>
</tbody>
</table>
1. Group GG: two good blastocysts transfer
2. Group GP: one good and one poor blastocysts transfer
3. Group GS: one good blastocyst transfer

Blastocysts were graded according to the Gardner-Schoolcraft blastocyst grading system before freezing on day 5 or 6. Good blastocysts were defined as those meet all of the following three criteria at least: expansion of blastocyst fills the embryo completely [grade 3], the inner cell mass is loosely grouped with several cells [grade B], and the trophectoderm has few cells forming a loose epithelium [grade B]. Lower than grade 3BB quality blastocysts were defined as poor blastocysts.

RESULTS: There were no significant differences with baseline characteristics, including maternal age, paternal age, body mass index, infertility duration and endometrial thickness among three groups. IVF outcomes and neonatal outcomes are presented in the Table.

Implantation rate (IR) was significantly lowest in group GP, and it was similar between group GG and group GS. Clinical pregnancy rate (CPR) and live birth rate (LBR) were significantly highest in group GG, but there are no significant differences between group GP and group GS. Multiple pregnancy rates (MPR) were significantly higher in order of group GG, group GP and group GS. Preterm birth (PTB) rate and low birth weight (LBW) rate was significantly lowest in group GS.

CONCLUSIONS:
1. Group GS was not worse than group GP in terms of CPR and LBR. Rather, MPR, PTB rate and LBW rate were increased in group GP. Therefore, transferring a good blastocyst with a poor one is not recommended.
2. Compared with group GS, CPR and LBR were higher in group GG. However, IR was similar between two groups and MPR, PTB rate and LBW rate were significantly increased in group GG. Therefore, two consecutive single good blastocysts transfers may be recommended rather than double good blastocysts transfer.

REFERENCE:

OBJECTIVE: Several studies have shown improved pregnancy rates following frozen-thawed embryo transfer in women with elevated progesterone. However, little is known whether transfer of good quality blastocyst can improve pregnancy outcomes in patients who had high progesterone levels. Therefore, we compared the pregnancy rate of frozen-thawed with fresh embryo transfer by transferring a single good quality blastocyst in patients with elevated progesterone.

DESIGN: A retrospective cohort study.

MATERIALS AND METHODS: From January 2015 to December 2017, a total of 176 in vitro fertilization (IVF) cycles in patients whose progesterone levels (P4) were more than 1.5 on the day of trigger were included. Frozen-thawed blastocyst transfer (n = 87) and fresh blastocyst stage embryo transfer (n = 89) were compared. Also, frozen-thawed single blastocyst transfer (n = 37) and fresh single blastocyst stage embryo transfer (n = 25) were compared. In each group, there was no significant difference in P4 levels (2.19 ± 0.96 vs. 2.44 ± 1.44, P = 0.30). Subgroup analysis was performed by dividing blastocyst grade into good or poor based on ICM and TE grade. Data analyzed using Student’s T-tests and P value < 0.05 was considered to be statistically significant.

RESULTS: Frozen-thawed blastocyst transfer resulted higher clinical pregnancy rate as compared to fresh blastocyst embryo transfer (54.02% vs. 39.33%, P = 0.02). In single embryo transfer, frozen-thawed blastocyst transfer resulted higher pregnancy rate than fresh blastocyst transfer, respectively (48.65% vs. 28.00%, P < 0.05). The pregnancy rate of single good quality frozen-thawed blastocyst was significantly higher than in fresh good quality blastocyst (57.14% vs. 31.82%, P = 0.04).

CONCLUSIONS: In women with elevated progesterone level more than 1.5, we confirmed freeze-all at the blastocyst stage can achieve higher clinical pregnancy rates. Among those, selecting a single good quality blastocyst can significantly augment the pregnancy rate in frozen-thawed embryo transfer cycles in patients with elevated progesterone.

Supported by: None.

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EMBRYO MORPHOLOGIC GRADING AND MITO-SCORE: ARE THEY RELATED? I. Collazo, M. Bustillo, J. Ricard, J. Eisermann, N. Hendon, H. Arora. IVFMD, South Florida Institute for Reproductive Medicine, Miami, FL; Urology, IVFMD, South Florida Institute for Reproductive Medicine, Miami, FL; Urology, University of Miami, Miami, FL.

OBJECTIVE: The number of copies of mitochondrial genes (mtDNA or "MitoScore") is related to the energy supply of the embryo, which may affect its ability to implant in the maternal uterus. However, it is important to understand the potential significance of MitoScore to establish its relevance with respect to assisted reproduction (ART). In ART, there are multiple factors that are considered to affect outcome; embryo quality is considered critical. There is no specific literature to show if embryo quality (EQ) could be reliably associated with the embryo’s MitoScore. This information could be critical to successfully maximize the success rate of single embryo transfer in ART. In the present study we compared MitoScore and EQ in patients in the years 2016 and 2017.

DESIGN: A retrospective study of 384 cases from year 2016 and 2017 at IVFMD.

MATERIALS AND METHODS: Data from a total of 384 women: 192 in the year 2016 and 192 in the year 2017, undergoing ART with pre-implantation genetic testing for aneuploidy (PGT-A) was analysed. PGT-A and MitoScore testing (on euploid embryos) was performed by Igenomix with a change of MitoScore methodology in the beginning of 2017. Embryos were classified on the basis of EQ utilizing Gardner’s criteria into three groups: Good (AA, AB, BA), Fair (BB, AC) and Poor (BC). CC embryos were not biopsied. 2016 data included 59 patients with good EQ, 72 with fair and 61 with poor EQ. 2017 data included 65 patients with good EQ, 78 with fair and 49 with poor EQ respectively. GraphPad Prism (GraphPad Software) was used for statistical analysis. All data are analysed as the mean ± SEM. The statistical significance between two groups was estimated by unpaired two-tailed t test. In all cases, p < 0.05 was considered statistically significant.

RESULTS: Results showed that there is no statistical difference in clinical pregnancy rates when transferring embryos in the cleavage or blastocyst stage (p-value = 0.8352). However, there is an important reduction in the multiple pregnancies achieved when transferring only one blastocyst (1%) compared with double embryo cleavage stage transfer (33%) and double blastocyst stage transfer (33%). The independence between groups and multiple pregnancies was rejected (p-value < 0.0001). The comparison of proportions were significant between G1 and G3 (p-value < 0.0001), and between G2 and G3 (p-value < 0.0001). In addition, as we expected the implantation rate was highly improved when only one embryo in the blastocyst stage was transferred (41%) in comparison to two blastocysts (26%) or two cleavage embryos (24%) transfers. The independence was rejected (p-value < 0.0001). The comparison of proportions were significant between G1 and G3 (p-value = 0.0007), and between G2 and G3 (p-value = 0.0375). The odds ratio for implantation rates obtained, with G1 as reference, were 1.1129 for G2 and 2.0967 for G3. Finally, the decrease in the abortion rate was striking, 20% for G1, 5% for G2 and 10% for G3. There is not a statistical significance among the groups (p-value = 0.1352), however, these proportions show a tendency, transferring in blastocyst stage suffers fewer abortions than in cleavage stage. The main limitation of this study is the difference in the number of patients in each group.

CONCLUSIONS: We conclude that single day-five transfer in fresh IVF cycles decreases multiple pregnancy and abortion rates and increases implantation rates without affecting the number of clinical pregnancies achieved.
BMI, infertility diagnosis, implantation rate, are underway to evaluate the significance of MitoScore in helping to choose the embryo for most successful outcome in ART.

References: NA

Supported by: This work was supported in part by the IVFMD, South Florida Institute for Reproductive Medicine

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OBJECTIVE: Currently, standard morphological evaluation represents the most widespread approach for blastocyst selection, and it is still the main strategy applied in the Gardner-Schoolcraft grading system. Recently, some reports have shown that an expanded blastocyst size and some morphokinetic parameters which are obtained from time-lapse monitoring (TLM) are associated with successful clinical pregnancy outcomes. The aim of the present study was to determine whether morphokinetic parameters assessed by TLM associate with clinical outcomes when using morphologically good quality frozen-thawed blastocysts in single embryo transfer (SET).<br><br>DESIGN: Retrospective observational study.<br><br>MATERIALS AND METHODS: We targeted 234 patients (300 blastocysts) who underwent conventional IVF or ICSI from January to September 2017. The embryos obtained were cultured in a time-lapse incubator (EmbryoScope plus, Vitrolife, Sweden) for 5/6 days. Good quality blastocysts were defined as ≥4BB (according Gardner-Schoolcraft grading) with an internal diameter of ≥170 μm at day 5/6 and were used for frozen-thawed SET. The observed morphokinetic parameters included period of pronuclear fading (tPNF), onset of 2- to 5-cell divisions (t2 to t5), starting blastulation (tSB), full blastocyst stage (tB), and expanded blastocyst stage (tEB; internal diameter ≥170 μm). The association of morphokinetic parameters (the interval for each morphokinetic event or the elapsed time between each morphokinetic event) with clinical outcomes (clinical pregnancy [CP], ongoing pregnancy [OP], or pregnancy loss) was investigated. Statistical analysis was performed using the Mann-Whitney U test and a P-value of <0.05 was considered statistically significant.<br><br>RESULTS: The overall CP and OP rates were 40.0% (120/300) and 31.0% (93/300), respectively. Comparison of CP vs. non-pregnancy in terms of the tEB−tB interval (mean hours ± standard deviation) (10.8 ± 5.7 vs. 12.3 ± 5.7, P = 0.023) and the tEB−tSB interval (17.1 ± 5.1 vs. 19.1 ± 6.1, P = 0.003) showed significantly shorter duration in the CP group. Comparing OP vs. pregnancy loss, the t3−t2 interval (10.7 ± 2.5 vs. 11.3 ± 2.5, P = 0.026) showed a significantly shorter duration in the OP group. These data indicate that the interval between the start of blastulation to the expanded blastocyst was associated with CP outcomes, and the interval between the 2-cell to 3-cell stage was associated with OP outcomes.<br><br>CONCLUSIONS: This study revealed that specific morphokinetic parameters were associated with CP and OP outcomes in morphologically good quality frozen-thawed blastocyst transfers. Therefore, we suggest that size and morphology-based blastocyst grading with morphokinetic assessment will enable clinicians to select blastocysts with high clinical potential in SET procedures.

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APPLICATION OF ARTIFICIAL INTELLIGENCE TECHNOLOGY TO INCREASE THE EFFICACY OF EMBRYO SELECTION AND PREDICTION OF LIVE BIRTH USING HUMAN BLASTOCYSTS CULTURED IN A TIME-LAPSE INCUBATOR. N. Zaninovic, C. J. Rocha, Q. Zhan, M. Toschi, J. Malmsten, M. Nogueira, M. Meseguer, Z. Rosenwaks, C. Hickman, CRM, Reproductive Medicine, Weill Cornell Medicine, New York, NY; Department of Biological Sciences, Sao Paulo State University, Assis, Brazil; Cornell Reproductive Med, New York, NY; Weill Cornell Medical College, New York, NY; Sao Paulo State University, Assis, Brazil; IVI, Barcelona, Valencia, Spain; Reproductive Medicine, Physician, New York, NY; Imperial College London, London, United Kingdom.

OBJECTIVE: To apply artificial intelligence (AI) technology on time-lapse (TLM) morphokinetic parameters and TLM embryo images to enhance embryo selection and prediction of live birth.

DESIGN: The morphokinetic parameters (n= 303, ICSI only) of embryos associated with live births resulting from single blastocyst transfers, along with 386 TLM images of embryos at 111.5 hours post ICSI were used to train (70%), validate (15%), and blindly test (15%) for the ability to predict live birth by an AI feature-extraction system. Inclusion criteria involved good-prognosis patients with single blastocyst transfer and non-PGD/S.

MATERIALS AND METHODS: Absolute and interim cleavage time points (t2 to t8) were used, along with 33 independent numerical variables extracted from standardized EmbryoScope images (Virtolife, Sweden) as input data. The artificial neural network (ANN) architecture associated with this study was create complex machine learning (ML) model that can accurately predict the reproductive potential of a particular euploid embryo to establish viable pregnancy in IVF PGT cycles with single embryo transfer (SET).

RESULTS: A retrospective study of NGS PGT outcome data from blastocysts biopsied on day 5 or day 6 (2013-2017) was conducted using supervised and unsupervised ML algorithms to identify differences in clinical pregnancy rates (PR).

MATERIALS AND METHODS: 1383 cycles (7120 embryos) of IVF PGT followed by 1108 SETs were included in the study (842 patients). From 320 original features (175 clinical and 145 morph. and kinetic parameters of embryo development), 6470 synthetic features were created (by_weight of evidence, Encoding of categorical levels, Target Encoding, etc.), tested and 357 features were selected. 73 statistical models were trained and ensembled in the final model. Predictive accuracy was evaluated by 5-fold cross-validation. Clinical PR was defined by the presence of a fetal heartbeat at 6-7 weeks of pregnancy.

RESULTS: Analysis of the combined predictions from multiple weak learners (GLM, random forest, gradient boosting, etc.) processed by Generalized Model Stacking produced a predictive performance of AUC = 0.8103, Logloss = 0.5356. The probability of positive clinical outcome was calculated for each euploid embryo and ranged from 0.194 to 0.838 (baseline prediction - 0.645). The variable of highest importance were the morphological characteristics of the blastocysts, the history of previous failed IVF cycles, and when blastocysts became available for biopsy (0.372, 0.233, and 0.118 respective). Generalized linear model intercept estimate for embryo morphology was 0.957 (Std. Error = 0.36, Pr (z) = 0.008), intercept estimate for the history of previous failed IVF cycles was -0.625 (Std. Error = 0.1, Pr (z) = 3.1e-10), and intercept estimate for biopsy day was -0.416 (Std. Error = 0.133, Pr (z) = 0.002). These results were confirmed by univariate analysis: the ongoing PR after SET was considerably higher when the transferred euploid embryos were graded as good quality embryos (AA/AB/BA) vs fair (BB) or borderline fair (-B or B-) quality: 68.6% (493/719) vs 56.9% (161/283) and 42.5% (45/106) respectively, χ² = 4.31, OR = 0.338, CI = 0.223 - 0.513, p<0.05.

CONCLUSIONS: Analysis of the data proved that Machine learning algorithms applied to large clinical data sets could predict the outcome of the IVF treatment with high accuracy. In order to achieve high accuracy predictions in IVF PGT, clinical parameters were defined, ranked, and evaluated. Ensemble methods of statistical learning offer superior performance over their singleton counterparts and essentially help to transform medical records into medical knowledge.
with the genetic algorithm was used to produce a predictable output of live birth. The efficacy of prediction of live birth was quantified and assessed using ROC curves, AUC, and confusion matrices (true positive, TP; true negative, TN; false positive, FP; and false negative, FN).

**RESULTS:** Using morphokinetic data, we achieved 83% overall accuracy of predicting live birth by AI (215/258; TP = 99, TN = 106, FP = 22, FN = 21; AUC = 0.91). In the training dataset, the accuracy was 85% (181/213, AUC = 0.91), and in the blind test data set, the accuracy was 76% (34/35, AUC = 0.77). The overall accuracy of live birth by AI using image analysis was 85% (280/328, TP = 138, TN = 142, FP = 25, FN = 23, AUC = 0.90). In the training dataset, the accuracy was 97% (235/250, AUC = 0.92), and in the blind test data set, the accuracy was 78% (45/58, AUC = 0.67-0.80). For morphokinetics, the AUC for positive and negative live birth was similar (0.90); however, for image analysis, the negatives (0.67) were harder to predict compared to the positives (0.80).

**CONCLUSIONS:** This is the first time that AI has been used to evaluate human embryo quality using morphokinetic and morphological assessment in a controlled dataset of single embryo transfers with known live birth. Our data suggest that AI can be used to enhance the efficacy of embryo selection beyond the limits of current practice. Applying AI in conjunction with morphokinetic and image analysis has the potential the become the universal platform, as exhibited by its consistency, efficacious embryo selection, and can be prospectively applied in any clinic, regardless of its practice or patient base.

**P-664** Wednesday, October 10, 2018 6:30 AM

**IS AI ASSESSMENT OF MORPHOKINETIC DATA AND DIGITAL IMAGE ANALYSIS FROM TIME-LAPSE CULTURE PREDICTIVE OF IMPLANTATION POTENTIAL OF HUMAN EMBRYOS?** C. Rocha, M. G. Nogueira, N. Zaninovic, C. Hickman. 1Department of Biological Sciences, Sao Paulo State University, Assis, Brazil; 2Biological Sciences, SYo Paulo State University (UNESP), Assis, Brazil; 3CRM, Reproductive Medicine, Weill Cornell Medicine, New York, NY; 4Imperial College London, London, United Kingdom.

**OBJECTIVE:** This work aimed to use variables extracted from morphokinetic data and blastocyst image to predict the implantation potential of human embryos.

**DESIGN:** Time-Lapse data (quality controlled by two independent practitioners) from a single IVF clinic. Implantation established as ultra-sound detectable foetal heart at 6-8 weeks. Morphokinetic data from 660 ICSI and 244 IVF-derived embryos with known implantation potential (KID+n=282, KID-n=622) and the respective images at 110 hpi of a subset of 238 embryos were assessed using AI. Data divided as training (70%), validation and blind testing (30%).

**MATERIALS AND METHODS:** Absolute and interim cleavage time points from 0-12 h to 1-11 h were used, along with 33 numerical variables extracted from the standardised images which formed the input of the ANN architecture associated with the genetic algorithm to produce a predictable output of implantation. This AI was assessed using ROC, confusion matrix and Kappa Index.

**RESULTS:** The confusion matrix for IVF (AI as the output class and implantation as the target class) demonstrated agreement of 98.2% in training and 94.6% in blind validation. For ICSI, agreement of 96.1% in training and 71.7% in blind validation. Image analysis led to an agreement of 95.8% in training and 88.9% in blind validation. ROC curves demonstrated excellent performance of the AI when applied with image analysis (AUC training 0.9788-0.9818, and blind validation 0.8381-0.8190) and with IVF morphokinetic data (AUC training 0.9995-0.9995 and blind validation 0.9484-0.9524), which was higher than with ICSI (AUC training 0.9781-0.9947 and blind validation 0.7066-0.7192). Excellent agreement was demonstrated when AI was used to predict implantation using morphokinetics (IVF: Kappa Index = 0.878; ICSI: 0.782) and image analysis (0.765).

**CONCLUSIONS:** Artificial Intelligence (AI) in conjunction with time-lapse technology has a potential 85% accuracy of predicting known implantation of human embryos. AI provides a powerful solution for turning the abundance of information available using time-lapse into an embryo selection method that is more objective, simplified, consistent and predictive of implantation than any other previously published method of diagnosing embryo viability. Patients can therefore be better informed of their chance of pregnancy.

**P-665** Wednesday, October 10, 2018 6:30 AM


**OBJECTIVE:** The primary objective of this study was to determine if Reproductive Endocrinology and Infertility (REI) fellow confidence in performing an embryo transfer (ET) improved with simulation.

**DESIGN:** A descriptive cross-sectional study evaluated whether the American Society for Reproductive Medicine (ASRM) ET simulation certificate course improved fellow confidence in ET.

**MATERIALS AND METHODS:** A total of 7 fellows (2 first year, 2 second year, and 3 third year) worked through a 6 week training course with reading materials, course proctors, and individual practice sessions. Each fellow performed a total of 120 ET simulations using 3 different transfer techniques with 4 uterine models with different levels of difficulty under real time ultrasound guidance. Each attempt was graded by the simulator. There was opportunity for feedback after each session. Fellows completed a confidence survey before and after the certificate course and were assessed on experience level based on previous performance of live or mock ET and intratuerine insemination (IUI). Confidence was graded on a scale from 0 (not confident) to 5 (expert confidence). Fellows were also tested on knowledge of ET types as well as trouble shooting difficult ET cases. Descriptive analysis was performed.

**RESULTS:** Clinical experience was similar among all fellowship years at initiation of the simulation course. The pre-course confidence survey scores
increased with each year of fellowship, however at the completion of the course all fellowship years had similar average confidence scores 43.5, 46.5, 43.3 per year respectively. First year fellows confidence scores increased most by 163.64%, followed by 102.14% for second years, and 46.97% for third years. Specific questions on confidence in their skills of performing ET, even proficiency in difficult transfers. This simulator gives fellows the opportunity to increase their confidence in ET techniques prior to finishing fellowship.

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FELLOWS’ PERFORMANCE ASSESSMENT AFTER COMPLETION OF THE AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE EMBRYO TRANSFER SIMULATION CERTIFICATE COURSE. M. Barsky, C. Valdes, W. Gibbons, A. K. Schutt. Reproductive Endocrinology and Infertility, Baylor College of Medicine, Houston, TX.

OBJECTIVE: The primary objective of this study was to determine if Reproductive Endocrinology and Infertility (REI) fellow performance of embryo transfer (ET) improved with simulation.

DESIGN: A descriptive cross-sectional study evaluated whether the American Society for Reproductive Medicine (ASRM) ET simulation certificate course improved fellow performance in ET.

MATERIALS AND METHODS: A total of 7 fellows (2 first years, 2 second years, and 3 third years) worked through a 6 week training course with reading materials, course proctors, and individual practice sessions. Each fellow performed a total of 120 ET simulations using three different transfer models each increasing in level of difficulty under real time ultrasound guidance. Uterus A was a midline short uterus, uterus B was sharply anteverted, uterus C had a tortuous cervical canal, and uterus D had a false passage. Each simulation was graded based on ability to virtually place an embryo more than 1 cm from the fundus, without touching the fundus, within two minutes of starting simulation, and without more than two passes of the inner catheter through the internal os. There was opportunity for feedback after each session. Descriptive analysis was performed comparing average scores per fellow during the first 5 transfers performed to the last 5 transfers performed for each uterine model and overall.

RESULTS: Overall each fellowship year had improvement in ET scores upon completion of the course when comparing the average score for all uterine models for the first 5 transfers simulations to the last 5 (0.67%, 8.19%, and 15.56% for years 1, 2, 3 respectively). Comparing the first 5 transfer simulations to the last 5 for uterus A showed ET score improvement by 1.18%, 3.67%, and 38.44% respectively for each increasing fellowship year. For uterus B fellowship year 1, 2, 3 also improved by 1.91%, 9.25%, and 9.44% respectively. For uterus C there was no change in the scores for year 1, however year 2, 3 improved by 12.21% and 4.97% respectively. For uterus D year 1 fellows decreased scores by 0.5% while year 2 and 3 increased scores by 8.09% and 13.31% respectively.

CONCLUSIONS: Level of training did not reflect experience with ET prior to the start of the course. The ASRM ET certificate course improved performance for each fellowship year overall, regardless of ET difficulty, with more accurate placement of the embryo in the ideal location. However, the benefit of the course was more evident in fellowship year 2 and 3. This data suggests that use of this simulator will enhance fellow capability of performing ETs and standardize training in REI fellowships.

P-667 Wednesday, October 10, 2018 6:30 AM  
COMPASSIONATE TRANSFER: PROVIDER PRACTICES AND PERSPECTIVES. J. C. Hairston E. C. Feinberg, Northwestern University Feinberg School of Medicine, Chicago, IL.

OBJECTIVE: To assess board-certified reproductive endocrinologists’ knowledge and experience with compassionate transfer. Compassionate transfer is an embryo transfer at a time or location where implantation is unlikely to occur.

DESIGN: Cross-sectional study

MATERIALS AND METHODS: Institutional Review Board approval was obtained. A Research Electronic Data Capture survey was distributed via email to all members of the Society for Reproductive Endocrinology and Infertility (SREI). Descriptive statistics were analyzed for provider knowledge and experience with compassionate transfer.

RESULTS: Seven-hundred and forty-four members of SREI were sent the survey and 197 (26.5%) responded. Of the 163 (82.7%) providers who had heard of compassionate transfer, 73 (44.7%) had offered the service to a patient. Four providers stated that they always offer compassionate transfer, 24 stated they offered it sometimes, and 44 offered it only once or twice. Seventy-eight percent stated they would offer compassionate transfer South University was patient demand; 73 (44.8%) would offer if there were ASRM guidelines. Forty respondents wrote robust comments in support of (n=24; “should offer more often”) or against (n=16; “wasteful,” “not a real alternative”) compassionate transfer. Among providers who did not routinely offer compassionate transfer, 94 (59%) cited lack of patient interest as a barrier. Other reasons included: provider conclusion that it is not a worthwhile choice (n=50, 31.4%), providers’ personal/moral/religious beliefs (n=17, 10.6%) and fear of reducing the frozen embryo transfer success rate (n=17, 10.6%). Fifty-three providers have performed compassionate transfer since completing fellowship with a range of 0 to 8 (median = 2) being performed within the past two years. The majority of providers (75.4%) have placed the embryos in the endometrium, 26.4% in the vagina, and 7.54% on the cervix. There was no consensus on timing of compassionate transfer: 28% have transferred during the 1st week, 31% during the 2nd week, 32% during the 2nd and 3rd. Nineteen percent transferred during the patient’s period and 23% transferred with some form of contraception. Most providers (n=23) restricted the number of embryos transferred, ranging from 1 to 3. Others (n=14) transferred all remaining embryos and 5 providers allowed patients to select the number. Seventy-two percent of providers charged less than a frozen embryo transfer and 28.3% charged an amount equal to a frozen embryo transfer. Charges ranged from $0 to $450. Three providers reported pregnancies from compassionate transfer, none were ectopic.

CONCLUSIONS: Embryo abandonment is an increasing problem as couples struggle with decision-making regarding supernumerary embryos after completion of treatment. Disposition options such as discard, donation to research, or donation to another couple are most commonly offered. Compasionate transfer is another option that could be offered to couples. This may facilitate closure and decrease embryo abandonment. Guidelines should be created regarding compassionate transfer.
CONCLUSIONS: Although the cumulus. Unclinical pregnancy rate per transfer was lower in the SET cycles, SET could decrease the rates of multi- ple pregnancy and low birthweight without compromising the live birth rate. Therefore, high-quality SET is recommended for women with a unicornuate uterus.

REGENERATIVE MEDICINE AND STEM CELLS

P-669 Wednesday, October 10, 2018 6:30 AM
INTRA-GONADAL DELIVERY OF FIRST TRIMESTER HUMAN UMBILICAL CORD PERIVASCULAR CELLS (FTM HUCPVC) PRIOR TO CHEMOTHERAPY HAS A PROTECTIVE EFFECT IN RODENT MODELS OF ALKYLYATING AGENT-INDUCED TESTICULAR AND OVARIAN DAMAGE. L. Lopez, a K. Zohni, a,b,c M. Garcia, a M. Filice, a P. Szaraz, a S. Baram, a,b,c K. Glass, a A. S. Gauthier-Fisher, a C. Librach, a,b,c,d,e CREAtE Fertility Centre, Toronto, ON, Canada; b Department of Reproductive Health & Family Planning, National Research Centre, Cairo, Egypt; c Obstetrics and Gynecology, University of Toronto, Toronto, ON, Canada; d Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada; e Obstetrics and Gynecology, Women’s College Hospital, Toronto, ON, Canada.

OBJECTIVE: FTM HUCPVCs have increased capacity for regeneration when compared to older sources of mesenchymal stromal cells (MSCs), promote restoration of germ cell lineages in a phthalate-induced testicular damage mouse model, are resistant to cyclophosphamide (CTX)-induced cytotoxicity, and maintain their regenerative properties when exposed to CTX in vitro. As such, we hypothesize that they may be a good cell therapy candidate for fertility preservation. Our objective was to determine whether FTM HUCPVCs engraft and prevent loss of fertility in rodent models of alkylating agent-induced gonadotoxicity when delivered to the testis or ovary prior to chemotherapeutic treatment.

DESIGN: Pre-clinical study of male and female rodent models administered with FTM HUCPVCs prior to receiving gonadotoxic doses of alkylating chemotherapy.

MATERIALS AND METHODS: Busulfan (20mg/kg) was administered to CD1 mice 3 days after intra-testicular delivery of 50,000 FTM HUCPVCs. CTX (150-200mg/kg) was administered to Wistar rats following intra-ovarian delivery of 50,000 FTM HUCPVCs. Control groups included: untreated animals, animals untreated with chemo receiving intra-gonadal media injection, and animals treated with chemo following intra-gonadal injection of media. HUCPVC survival, ovarian follicles (female model) and tubules with active spermatogenesis (male model) were assessed using histological methods. Fertility profiles, sperm concentration and motility were assessed in the male study.

RESULTS: When compared to media controls, female and male models receiving FTM HUCPVCs prior to CTX or busulfan treatment, showed a significant recovery in the number of primordial follicles (P<0.001) and proportion of tubules with active spermatogenesis (P<0.05), respectively. FTM HUCPVC-treated animals showed improved mating profiles and sperm parameters when compared to busulfan-treated controls (P<0.05). FTM HUCPVCs were detected in the testicular interstitial space and near blood vessels in the ovarian stroma.

CONCLUSIONS: FTM HUCPVCs administered pre-alkylating drug therapy prevent gonadal damage in vivo. FTM HUCPVCs are therefore promising candidates for fertility preservation.

Supported by: This study was funded by CREAtE Program Inc and supported in part by a studentship from the University of Toronto.

P-670 Wednesday, October 10, 2018 6:30 AM
NEW INSIGHTS INTO THE GENIC AND METABOLIC CHARACTERISTICS OF INDUCED PLURIPOTENT STEM CELLS FROM POLYCYSTIC OVARY SYNDROME WOMEN. Z. Min Y. Yu. Peking University Third Hospital, Beijing, China.

OBJECTIVE: Through the iPSC (induced pluripotent stem cells) technology, to generate a PCOS (polycystic ovary syndrome) patient-specific iPSC disease modelling for study the pathogenic mechanism of PCOS in vitro.

DESIGN: The selected genes were verified by RT-PCR in iPSCs and granulosa cells from PCOS patients. Mitochondrial biogenesis, mitochondrial respiration ability, and testosterone levels in iPSCs were analysed. PCOS-derived iPSCs were treated with metformin to investigate disease rescue. Also, iPSCs were differentiated to neural stem cells (NSC) for functional study.

MATERIALS AND METHODS: The mRNA abundance of iPSCs was analysed by RNA microarray and RT-PCR. Karyotyping of iPSCs was performed with cytogenetic analysis. The mitochondrial respiration ability was measured using an oxygen consumption rate analyser. The expression of iPSC-associated markers was identified by immunofluorescence and RT-PCR. The testosterone level was measured by ELISA.

RESULTS: A PCOS-derived iPSC model was established from somatic cells of PCOS patients. By comprehensive transcriptional profiling of RNA microarray, PCOS-derived iPSCs showed metabolic abnormalities and mitochondrial dysfunction compared with non-PCOS-derived iPSCs in vitro. A total of 3300 genes were differentially expressed between the two iPSC populations, of which 1600 genes were up-regulated and 1700 genes were down-regulated (fold change>2, p<0.01). The PCOS-derived iPSCs demonstrated decreased mitochondrial respiration function (p<0.05) but increased mitochondrial numbers and biogenesis (p<0.05). The up-regulated genes were enriched in metabolic processes and mitochondrial activities, which were implicated in the tricarboxylic acid (TCA) cycle, the respiratory electron transport chain (ETC) and glycogenolysis. On the other hand, the down-regulated genes were related to glucose uptake, cell communication, neurogenesis and endocrine. The testosterone level was decreased in PCOS-derived iPSCs cultured medium. Treatment with metformin rescued some of the genes related to glucose metabolism in PCOS-derived iPSCs. However, metformin had little effect on mitochondrial respiration function. Further more, the iPSCs were differentiated to neural stem cells. The mitochondrial respiration ability of granulosa cells from PCOS patients, the PCOS-derived iPSCs and the PCOS-derived NSC were down-regulated consistently.

CONCLUSIONS: iPSCs derived from women with PCOS had abnormal changes in metabolic process, mitochondrial function and neuroendocrine in vitro, which could be used for in vitro disease modelling. The study provided a novel disease model in vitro for studying the clinical causes and molecular mechanisms of PCOS.

References:
15. Moran LJ, Noakes M, Clifton PM, Norman RJ, Fenec MF. Genomic instability is increased in lymphocytes of women with polycystic ovary syndrome and is correlated with insulin resistance. Mutat Res 2008;639:55-63.

Supported by: This work was supported in part by the National Key R&D Program of China (2017YFC1001003, 2016YFC1000601), the National Natural Science Funds for general program (81671419, 81571400, 81771580).

P-671 Wednesday, October 10, 2018 6:30 AM

HUMAN FOLLICULAR FLUID PROMOTES EXPRESSION OF OVARIAN MARKERS IN DIFFERENTIATING iPSCs. R. M. Anchan, K. Dam, N. Ng, M. Stewart, A. Milne, M. Ng. Center for Infertility and Reproductive Surgery, OB/GYN, Brigham and Women's Hospital, Boston, MA.

OBJECTIVE: Human follicular fluid (HFF) bathes the oocyte within the follicle and contains vital factors for oocyte development; thus, we investigated whether HFF promotes preferential differentiation of stem cells into ovarian cells and oocytes in vitro.

DESIGN: Basic science research.

MATERIALS AND METHODS: We previously showed that mouse granulosa cell-derived induced pluripotent stem cells (mGrIPSC) differentiate into functional endocrine tissue that produces estradiol and progesterone, as well as expressing ovarian and oocyte markers. iPSC differentiation into ovarian cells was confirmed by immunocytochemistry (ICC) for the ovarian antigens INH-B, FSHR, and GJA1. Differentiated oocytes were confirmed by ICC for the oocyte antigens ZP1, DAZL, and DDX4. Following IRB approval, HFF was obtained as discarded tissue from consenting patients undergoing fertility treatment at the IVF laboratory. Briefly, the experimental design comprised of culturing iPSCs for 3-4 days prior to generating embryoid bodies (EBs, three-dimensional aggregates of pluripotent stem cells) in suspension culture. Various concentrations of HFF (0.5-20%) were added to our EB cultures. After 14 days in suspension, EBs were attached and grown for an additional 15 days. Following attachment, conditioned media was collected every three days from the culture wells for endocrine analysis by ELISA. Cells were then fixed in 4% PFA and processed for ICC. Mann-Whitney U tests were used to analyze ICC cell count data. RNA extractions were performed to be used for RT and QRT PCR (Cyp19, Gja1, Zp1, Foxl2). Fluorescence activated cell sorting (FACS) was employed to confirm the presence of differentiated ovarian cell populations (DDX4 and FSHR).

RESULTS: ICC showed that EBs cultured with 1% and 5% HFF expressed significantly greater levels of the ovarian marker GJA1 (28.0% in control, 44.4% in 1% HFF, 57.1% in 5% HFF, P<0.05) and the oocyte marker ZP1 (3.6% in control, 19.0% in 1% HFF, 42.7% in 5% HFF, P<0.05). ELISA revealed that EBs exhibited a dose-dependent increase in estradiol synthesis with increasing concentrations of HFF in media (0.5, 1, and 2%). While control EBs produced 25-200 pg of estradiol over 15 days of EB culture, EBs in HFF media produced estradiol ranging from 900-2,300 pg. PCR and FACS confirmed the expression of tissue specific transcripts and subpopulations of ovarian cells.

CONCLUSIONS: In summary, our data supports the hypothesis that HFF increases the differentiation of mGrIPSCs into steroidogenic, ovarian-like and oocyte-like cells. This experimental paradigm may prove useful for improving the in vitro maturation of oocytes.

References:

Supported by: This study was funded by The Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA.
presence of VASA-positive and DAZL-positive cells, strongly indicates that the cells reached the spermatogonia/spermatocyte cell stage. Cells that were positive for VASA and DAZL without OCT4 expression also suggest that a fraction of cells were able to progress to the advanced meiotic stages of in vitro spermatogenesis.

CONCLUSIONS: Our attempt to use the HD method together with the two-step culture system to induce the appearance and eventual maturation of male germ cells has shed light on the mechanisms of spermatogenesis in vitro. Using pluripotent stem cells to generate germ cells may benefit men afflicted by spermatogenic failure.

P-673 Wednesday, October 10, 2018 6:30 AM

WNT/BETA-CATENIN SIGNAL PATHWAY PLAYS A ROLE IN THE PROCESS OF HUMAN EMBRYONIC STEM CELLS DIFFERENTIATING INTO ENDOMETA-rial CELLS. Y. Liu N. Liu. Department of Reproductive Medicine, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing, China.

OBJECTIVE: To determine whether Wnt/beta-catenin signal pathway play a role in the process of human embryonic stem cells differentiating into endometrial cells.

DESIGN: An experiment study.

MATERIALS AND METHODS: Human embryonic stem cells were cultured with co-culture method or condition medium method in vitro. On the time point of culture day 7, 14, 21, differentiated cells were collected and subjected to fluorescence activated cell sorting (FACS) and analyzed by FlowJo software. Alternatively, differentiated cells were fixed in paraffin-embed for immunofluorescence study. The expression of Wnt/beta-catenin signal pathway related genes during differentiation was detected by immunofluorescence and qRT-PCR.

RESULTS: Flow cytometry analysis revealed that the expression of CK-18 and VIM was the highest at day 14 of differentiation. Immunofluorescence analysis showed that the terminal differentiation stage cells didn’t express embryonic stem cell marker OCT4, but did express the surface markers of embryonic stem cells. Real-time PCR revealed that the expression of CK-18, VIM and PR. Moreover, the gene expression of Wnt5a, beta-catenin and AXIN2 of Wnt/beta-catenin signal pathway were higher in the co-culture group and conditioned culture group than those in the control group (P<0.05).

CONCLUSIONS: hESC can differentiate into endometrium cells in the co-culture method and condition medium method. Wnt/beta-catenin signal pathway was found to be significantly upregulated in the differentiated cells induced in both of the co-culture method and condition medium method.

Supported by: The study was supported by the National Natural Science Foundation of China (81471520), Beijing Natural Science Foundation (7182054), and Project Training High-Level Medical Technical Personnel in the Health System in Beijing (2014-3-075).

P-674 Wednesday, October 10, 2018 6:30 AM

IN VITRO NEOSPERMATOGENESIS OF HUMAN INDUCED PLURIPOTENT STEM CELLS. M. Irani, a A. Parrella, a C. O’Neill, b V. La, b D. Choi, c D. Choi, c G. D. Palermo, c a Center for Reproductive Medicine and Infertility, Weill Cornell Medicine, New York, NY; bCenter for Reproductive Medicine, Weill Cornell Medicine, New York, NY; cCRM, Weill Cornell Medicine, New York, NY; dWeill Cornell Medicine, New York, NY; eReproductive Medicine, Physician, New York, NY.

OBJECTIVE: We have previously cultured and differentiated mouse spermatogonia in the presence of growth factors and ROCK inhibitor. After becoming confluent, colonies were trypsinized and cells were cultured in 25uL droplets (n=80) at a concentration of 1x10^5 cells/mL. The medium contained Activin A, bFGF, and KSR in the first three days followed by BMP4, BMP9b, EGF, LIF, and SCF for 9 days. In the third step, the medium was mainly composed of retinoid acid for 4 days. Cells were stained for OCT4, VASA, and BOULE. After disaggregating EBs by collagenase IV, RNA were isolated and sequenced by Illumina HiSeq at 2x150 bp concentration per lane. A log fold change of >2 with FDR P<0.05 was considered significant.

RESULTS: A total of 80 EBs were formed in hanging drops. The staining of undifferentiated HiPSC was 84% positive for OCT4 and negative for VASA, and BOULE. After completing the three steps of culture with differentiating factors, the staining showed that 45% were positive for OCT4, 40% positive for VASA, and 5% positive for BOULE, which suggests that HiPSC differentiated and reached the meiotic stages. This was validated by the significant over-expression of genes related to stem cell differentiation (HOXD4), cell growth (BCL2 and TGFb2), and most importantly spermatogenesis (TMEM119, CELF3, and GTF3F1) in cells cultured with differentiating factors compared to HiPSC that were preserved undifferentiated. There was also a significant under-expression of genes involved in the maintenance of stemness (KLIF4, FGFI4, and GDF3F3) in the cells coaxed toward differentiation compared to controls.

CONCLUSIONS: Hanging drops provide a 3D culture condition for HiPSC to differentiate and generate male germ cells in the presence of several growth and differentiating factors. A progress in reproducing spermatogenesis in vitro may help to understand gamete development and assist non-obstructive azoospermic men with spermatogenic arrest and germ cell aplasia to have biological children.

P-675 Wednesday, October 10, 2018 6:30 AM

DEVELOPMENTAL REPROGRAMMING OF PRO-INFLAMMATORY PATHWAY MEDIATES ADULT ONSET OF UTERINE FIBROIDS. Q. Yang, a L. S. Trevino, b A. El Andaloussi, a N. Ismail, c C. L. Walker, a A. Al-Hendy, a OB/GYN, University of Illinois at Chicago, Chicago, IL; Molecular & Cellular Biology and Medicine, Baylor College of Medicine, Houston, TX; Pathology, University of Illinois at Chicago, Chicago, IL.

OBJECTIVE: Inflammation is well recognized as a hallmark feature linked to the development of many diseases, including various types of tumors. However, there remains a gap in our knowledge regarding the role of inflammation in the development of uterine fibroids (UFs). The objective of this study was to determine if developmental exposure to xenoestrogens activates pro-inflammatory processes to decipher the underlying mechanism.

DESIGN: Laboratory research studies using the Eker rat fibroid model (Tsc2 mutant Eker (Tsc2Δ20/+); myometrium tissues as well as corresponding myometrial stem cells (MSCs).

MATERIALS AND METHODS: Female newborn rats were treated S.C. with vehicle (VEH) or 1 μg/kg of diethylstilbestrol (DES) on postnatal days (PND) 10-12, a key period of uterine development. MSCs were isolated from adult (5 month old) myometrium tissue (N=5) using density gradient and CD44 flow cytometry. Flow cytometry and immunohistochemistry were used to determine the levels of a panel of pro-inflammatory mediators. To identify targets of epigenomic reprogramming in MSCs, whole genome RNA-sequencing and ChIP-sequencing (with an anti-H3K4me3 antibody) were performed. DiffReps G-Test and EdgeR (pair-wise comparisons) were used for statistical analysis of ChIP-seq and RNA-seq, respectively.

RESULTS: Our studies demonstrated that myometrium from adult Eker rats PND 10-12 exposed to DES exhibited significantly higher expression of pro-inflammatory markers (TNF-α, NF-kB and IL1β). Notably, macrophage numbers detected by immunostaining with a CD11b antibody was also significantly increased in DES-exposed myometrium (p<0.05). The production of key inflammatory cytokines, TNF-α and IL-6 was significantly increased in DES-MSCs vs VEH-MSCs (p<0.05). By ChIP-seq analysis, we identified 66 of 123 inflammatory responsive genes (IRGs) with greater enrichment of H3K4me3 at their promoters in DES-MSCs vs VEH-MSCs. By RNA-seq analysis of IRGs, 28.3% and 9.7% genes exhibited upregulation and downregulation in DES-MSCs vs VEH-MSCs, respectively. Importantly, the increased expression of IRGs was positively correlated with the elevated H3K4me3 mark (p<0.05). Reprogrammed key cytokining genes that contribute to the reprogramming process/macrophage, including Ccl2, Ccl-7, Csf1, exhibited 10.1-, 9.0- and 2.8-fold changes, respectively in mRNA expression. In addition, the expression of inflammatory responsive genes, including Pdcd7, Pdmp, Cxcl10, Cd40, Piger2, and Ereg, were also increased concomitant with H3K4me3 enrichment in DES-MSCs vs VEH-MSCs.
CONCLUSIONS: These data strongly suggest that developmental exposure to DES alters the inflammatory microenvironment in the myometrium and increases the risk of adult onset of UFs by permanently reprogramming pro-inflammatory genes in MSCs towards a pro-fibroid epigenetic landscape.


Supported by: This work was supported in part by the National Institutes of Health grant ES028615-01.

P-676 Wednesday, October 10, 2018 6:30 AM

MITOCHONDRIAL INHIBITION DURING 20% O2 CULTURE IS SUFFICIENT TO EMULATE HYPOXIC-STRESS INDUCED POTENCY LOSS AND TGC DIFFERENTIATION IN MTSC. E. Puscheck, Y. Yang, D. A. Rappolee. Wayne State University School of Medicine, Detroit, MI.

OBJECTIVE: Stress induces differentiation of multiple stem cell types despite culture conditions that should maintain stemness. Mouse placental trophoblast stem cells (mTSCs) are capable of differentiating into all placental lineages. Hypoxic stress (0.5% O2) induces differentiation of mTSCs despite the presence of mTSC stemness-maintaining growth factors FGF4. CDX2, ID2 and ERRB are stemness transcription factors that indicate mTSC stemness. What is the link between hypoxic stress and mTSC stemness-factor loss? Our objective is to compare the sufficiency of mitochondria inhibition in inducing mTSC stemness loss and differentiation in the presence of FGF4.

DESIGN: Experimental design MATERIALS AND METHODS: Four mitochondria inhibitors (KCN, FCCP, NaN3 and Antimycin A) were added to cultured mTSCs to investigate the sufficiency of mitochondria inhibition in inducing mTSC stemness loss and differentiation gain. Western blots detected the relative levels of stemness factors +/- mitochondria inhibitors. Immunofluorescence nuclear stainings were measured for nuclear size (TGC are measured by firefly luciferase-based luminescence measurement using a miRTnics kit). Putrescine delays postovulatory aging of mouse embryos. Western blotting showed that putrescine treatment decreases nuclear size.

RESULTS: NaN3 and Antimycin A during normoxia and in 0.5% O2 decreased mTSC stemness and both differentiated TGC. Unexpectedly, [ATP] at 0.5% O2 culture and with NaN3 was higher than normal mTSC culture control (20% O2). Inhibition of GSK3 reversed ERRB or ID2 decrease by ~50%, and p38MAPK inhibition reversed ERRB by ~25%. Inhibition of other PKs did not reverse 0.5% O2-induced stemness loss.

CONCLUSIONS: Mitochondria inhibition is sufficient to decrease mTSC stemness and increase TGC% at 20% O2, but isn’t associated with ATP decrease, GSK3 is good candidate for testing PR-mediated mTSC stemness decrease during hypoxia.

REPRODUCTIVE BIOLOGY: ANIMAL AND EXPERIMENTAL MODELS

P-677 Wednesday, October 10, 2018 6:30 AM

IN VITRO FERTILIZATION AND CULTURE ALTERS CHROMATIN ACCESSIBILITY IN THE MOUSE INNER CELL MASS. E. Ruggeri, E. Grow, X. Liu, A. Donjacour,* P. Rinoado, *University of California San Francisco, San Francisco, CA; HCL, Salt Lake City, UT.

OBJECTIVE: Define genome-wide chromatin accessibility changes occurring in ICM of mouse embryo following in vitro fertilization and culture.

DESIGN: While several studies have examined DNA methylation changes in embryo following IVF, limited knowledge is available on the effect of IVF on chromatin changes in blastocysts. To increase sensitivity, we focused on ICMs and studied if male and female embryos have different chromatin characteristics following culture.

MATERIALS AND METHODS: Expanded blastocysts (CF-1 females x B6D2F1 males) were obtained by IVF or flushed out of the uterus (FB = flushed blastocyst = control). IVF was performed using KSOM with amino acids and 5% O2. Individual ICM were isolated using complement and chromatin status assessed using an ATAC-seq protocol. Cells were lysed and nuclei incubated with the Ta5 transposome and tagmentation buffer (Nexera). After the tagmentation, PCR amplification (15 cycles), mitochondrial depletion and library purification were performed. Sex of the embryo was assigned based on MSY (Male sex region on the Y chromosome) and total Y chromosome aligning reads. Samples were divided into four groups, male IVF (n=7), female IVF (n=12), male FB (n=13), and female FB (n=13). Sequencing was completed using Illumina HiSeq 2500. MACS2 was used for peak identification from the sequencing results and DESeq2 was used for statistical analysis.

RESULTS: Overall there were 134,000 open chromatin peaks identified in FB samples and 94,000 peaks in IVF samples. We found 2124 regions that were significantly different when comparing IVF vs. FB samples (630 increased and 1494 decreased in IVF). GREAT analysis indicates that these regions were enriched for genes associated with inflammation (IL 17) ectoderm formation, mesenchymal morphology, and abnormal placental development. Surprisingly, sub-analysis by sex revealed that 1043 regions were different between IVF and FB females while only 72 regions were different between IVF vs FB males.

CONCLUSIONS: Our data are the first to analyze genome-wide chromatin accessibility changes in the ICM of mouse embryos generated spontaneously of by IVF. Importantly, these results indicate that IVF impacts the chromatin status of the inner cell mass in a sex dependent fashion providing insight into epigenetic and sexual dimorphic changes present in IVF embryos.

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P-678 Wednesday, October 10, 2018 6:30 AM

PUTRESCINE DELAYS POSTOVULATORY AGING OF MOUSE OOCYTES BY REGULATING PDK4 EXPRESSION AND MITOCHONDRIAL ACTIVITY. W. Xu, Z. Yan, L. Gao, C. Mao, Y. Cui. *State Key Laboratory of Reproductive Medicine, Clinical Center of Reproductive Medicine, First Affiliated Hospital, Nanjing Medical University, Nanjing, China; Reproductive Medicine Center, First Affiliated Hospital of Soochow University, China, Suzhou; China; Embryology, Nanjing, China.

OBJECTIVE: If fertilization does not occur for a prolonged time following ovulation, oocytes will deteriorate, as the so-called postovulatory aging, disrupting oocyte developmental competence. Putrescine, one of the biogenic amines, improves the oocyte quality of aged mice during IVM, suggesting that postovulatory aged oocytes may be reactivated by putrescine. Pyruvate dehydrogenase kinase-4 (PDK4) is one of key factors in the regulation of energy homeostasis and is increased during oocyte meiotic maturation. The study was designed to explore the effect of putrescine on postovulatory aging and the potential mechanism associated with PDK4.

DESIGN: Metaphase II (MII) oocytes from sexually mature CD1 female mice were demed and postovulatory aged in the culture medium-M2. We investigated whether putrescine to arrest the aging process by regulating PDK4 expression and the mitochondrial function.

MATERIALS AND METHODS: The denuded MII oocytes were layed in the putrescine treatment group, while ROS accumulation was significantly decreased in the putrescine treatment group, while ROS accumulation was significantly decreased.
decreased (P<0.01). Analysis of MII oocytes after 24 h of aging showed that the proportion of abnormal spindles, chromosomal distribution and mitochondrial distribution were reduced in the putrexine treatment group (P<0.05). The percentages of TUNEL-positive and autophagy aged oocytes were lowered in putrexine-supplemented cultures (P<0.01). The increased MMP in the oocytes treated with putrexine showed the increase in mitochondrial activation (P<0.05). The expressions of p-ERK1/2, p-AKT and Bcl2 were increased in the putrexine treatment group (P<0.05). Meanwhile, down-regulation of SOD2, SIRT1, PDK4 and HIF1a genes in aged oocytes was prevented by oocyte treatment with putrexine (P<0.01).

CONCLUSIONS: Putrexine, as a small molecule, may be a useful tool in a clinical setting to prevent the deterioration of oocyte quality following prolonged culture by regulating PDK4 expression and mitochondrial activity. Supported by: The study was supported by projects from NNSF of China (2017YFC0101602, 81730041).

P-679 Wednesday, October 10, 2018 6:30 AM
DOSE DEPENDENT DECREASED FERTILITY IN RESPONSE TO THE BURDEN OF ENDOMETRIOSIS IN A MURINE MODEL. A. J. Rosa-e-Silva,1 J. C. Rosa-e-Silva,1 A. Tal,1 R. Mamillapalli,1 H. S. Taylor.2 ·1Gynecology and Obstetrics, School of Medicine of Ribeirao Preto-University of Sao Paulo, Ribeirao Preto, Brazil; 2Department of Obstetrics, Gynecology and Reproductive Sciences, Yale School of Medicine. New Haven, CT; 3Ob/Gyn, Yale University School of Medicine, New Haven, CT; 4Yale School of Medicine, New Haven, CT.

OBJECTIVE: To determine if endometriosis can cause infertility and the burden of disease required in a mouse model.

DESIGN: Experimental endometriosis was induced in mice using varying amounts of endometrial tissue followed by breeding studies.

MATERIALS AND METHODS: Endometriosis was induced in 6 to 8 weeks old C57BL/6 female mice (n=28) by suturing varying amounts of uterine tissue in the peritoneal cavity. Group one (EMS1, n=6) received the equivalent of one uterine horn, group two (EMS2, n=6) received two horns while group three (EMS3, n=9) received four horns from syngenic donors. Sham group (N=7) received sutures equivalent to the amount of material used for EMS group. Four weeks after surgery animals were bred with proven males for four weeks. Pregnancy rates, time to delivery (number of days from D1 of breeding to delivery) and litter size was evaluated.

RESULTS: Animals from the Sham and EMS1 groups had higher cumulative pregnancy rates than those from groups EMS 2 and 3; 100% and 100% vs 67% and 57%, respectively (p<0.001); the rates were similar between Sham and EMS1 and between EMS2 and 3. Endometriosis did not interfere in time to delivery or in the litter size or birth weight.

CONCLUSIONS: Endometriosis leads to infertility in a mouse model. The infertility was dose responsive and apparent only with a moderate burden of disease (2 uterine horns). There was no increase in the rate of pregnancy complications. Murine endometriosis models should include functional outcomes such as fertility in addition to measures of lesion size.

References: NA

Supported by: Financial support by NIH HD052668.

P-680 Wednesday, October 10, 2018 6:30 AM
PERIVASCULAR STEM CELLS FROM HUMAN UMBILICAL CORDS AMELIORATE FIBROTIC UTERINE DAMAGE TO IMPROVE POOR PREGNANCY OUTCOMES IN A MURINE MODEL OF ASHERMAN’S SYNDROME. M. Park,1 J. Kim,1 J. Hwang,2 S. Lyu,2 H. Song,1 CHA University, Seongnam-si, Gyunggido, Korea, Republic of; 2Tertiary Center of CHA Gangnam Medical Center, Seoul, Korea, Republic of.

OBJECTIVE: Asherman’s Syndrome (AS) is representative of intrauterine adhesions and fibrosis resulting from scarring on the endometrium. There is no clear consensus about management and treatment to patients who suffer from infertility as a result of AS. Perivascular stem cells (PVSCs) from human umbilical cords (HUCs) are known to be one of the most effective cells to respond rapidly in the lesion.

DESIGN: Thus, we investigated whether PVSCs from HUCs could facilitate restoration of impaired endometrial structure and function, and improve poor pregnancy outcomes in a murine model of AS which was made by a physical insult.

MATERIALS AND METHODS: The mice with AS had similar phenotypes to those of patients with AS, including irregular cycle and poor uterine environment with defective embryo development.

RESULTS: For example, severe fibrosis with reduced cell proliferation was observed in the uterine horns of AS, and the number of implantation sites and postimplantation embryo development was significantly compromised during pregnancy. However, PVSCs extensively restored poor uterine environments and improved pregnancy outcomes in mice with AS. The mean weights of embryos from AS mice with PVSCs transplantation were significantly higher than without PVSCs on day 12 of pregnancy (118.8±0.10±0.86 vs 94.5±0.81, p<0.01). Mice with AS did not produce any pups whereas PVSCs enabled them to produce pups in a dose-dependent manner. In addition, we observed infiltration of significant numbers of immune cells such as macrophages and neutrophils into the uterine horns with AS while PVSCs modulated this event. Interestingly, the number of PVSCs was extremely low in the stroma of uterine horns with AS while we found PVSCs only in the uterine horns but not in the sham control.

CONCLUSIONS: Collectively, PVSCs transplantation gives us a promising option to facilitate restoration processes of impaired endometrium and improve poor pregnancy outcomes in the uterus with AS.

P-681 Wednesday, October 10, 2018 6:30 AM
ABSTRACT WITHDRAWN

P-682 Wednesday, October 10, 2018 6:30 AM
CHARACTERIZATION OF AMYLOID-LIKE SUBSTANCE DURING EMBRYO DEVELOPMENT USING MURINE MODEL. P. Pimentel,1,2,3,4 P. Navarro,4 F. Wang,1 L. Robinson,1 F. Liang,1 D. L. Keefe.1 1New York University, New York, NY; 2Faculty of Medicine of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, Brazil.

OBJECTIVE: Amyloid-like substances are elongated, unbranched protein fibrils which have the ability to polymerize to form a cross-beta diffusion pattern. They have been linked to various diseases in humans, especially those related to cellular aging. Interestingly, in budding yeast amyloid-like substance plays a critical role in meiosis. Since reproductive aging shares many features with aging of somatic tissues, we used the anti-human monoclonal antibody which stains germ cells in buddy yeast, to search for amyloid-like substance during early mouse development using electronic microscopy and immunostaining.

DESIGN: This experimental pilot study employed 192 mouse oocytes and pre-implantation embryos at different stages of development.

MATERIALS AND METHODS: Cryopreserved metaphase II mouse oocytes and in vivo fertilized embryos (1-cell, 2-cells, 4-cells, 8-cells, and blastocysts) (n=32 for each stage) were obtained from Embryotech Laboratories (Wilmington, MA). Samples were thawed, fixed, immunostained and submitted to electronic microscopy, for evaluation of amyloid-like substance, using an anti-amyloid antibody (Fibris OC, Millipore) and fluorophore labeled secondary antibody. Primary antibody was omitted as a negative control. Imaging was performed using a confocal microscopy (Zeiss 880) and (Philips CM-12) electron microscope. SAS version 9.4 (SAS Institute) was used to perform data analyses. Data were compared by one-way analysis of variance (ANOVA), with the LeastSquare-MEANS post-test. Differences were considered to be statistically significant if P<0.05.

RESULTS: Quantitative analysis showed that there are high levels of amyloid in oocytes (56232479.7 ± 5362949.38), and 1-cell embryos (58544435.0 ± 7823810.44), followed by a sharp increase in 2-cell embryos (6900187.4 ± 6733098.07), then a steady decline where the amyloid levels reach their lowest in blastocysts (24423606.2 ± 4882808.37). There were significant differences among the various stages, peaking at 2-cell embryo and blastocyst (p: <.0001). Electronic Microscopy images also identified sheet-like structures and filament-like structures representing amyloid protein aggregate. An interesting finding in 8 cells embryo stage was the presence of amyloid inside the autophagosome, which is the key structure responsible for the clearing abnormal proteins and damaged organelles. All controls exhibited only faint, non-specific labeling.

CONCLUSIONS: We demonstrate for the first time, using 2 different methodologies, that levels of amyloid-like substance vary across mouse development, and peak in embryos at the 2-cell stage. Subcellular analysis by transmission electron microscopy demonstrate its presence in...
autophagosomes, suggesting that oocytes and embryos work to clear amyloid like substance. Future studies should evaluate amyloid like substance as a biomarker of oocyte and embryo viability.

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GASDERMIN D-MEDIATED CELL PYROPTOSIS PRESENTS IN THE OVARY OF HYPERANDROGEN-INDUCED PCOS RATS. D. Wang; Y. Wang. Basic Medicine, Nanjing, China.

OBJECTIVE: Our study aimed to investigate that pyroptosis was associated with hyperandrogen-induced ovarian dysfunction. Furthermore, we would like to provide therapeutic strategies in improving the reproductive function of PCOS patients through exploration of the mechanisms of pyroptosis.

DESIGN: The ovary of DHEA-induced PCOS rats were obtained to analyze gasdermin D-mediated pyroptosis signaling pathway.

MATERIALS AND METHODS: Female Sprague-Dawley (SD) rats were treated daily with or without DHEA for 28 days. Altogether about 16 rats were included (n=8 in each group). DHEA-exposed rats were hypodermically injected with DHEA daily (6 mg/kg/100 g). Vehicle control rats were hypodermically injected with oil. Paraffin slices were stained with hematoxylin and eosin in order to examine the pathological structures of the rat ovary under an optical microscope. In addition, samples were left to incubate overnight at 4°C with specific antibodies against GSDMD and caspase-1 at a dilution of 1:200 in PBS, and observed under an optical microscope. The expression of androgen receptor (AR), GSDMD, caspase-1 and the proinflammatory factors, including interleukin (IL)-1β, IL-18, TNF-α and IL-6, were measured by western blot and RT-PCR.

RESULTS: As expected, ovarian cystic expansion, numbers of multiple immature follicles, granular cell layer thinning and the thickening of theca cell layer, and the vast majority of no corpus luteum formation were observed in the DHEA-induced PCOS rats. Chronic inflammation has recently been considered as important components in the pathophysiology of PCOS. Pyroptosis is rapidly emerging as a mechanism of extracellular release of the inflammasome-dependent cytokines IL-1β and IL-18, which contributes to autoimmune and inflammatory pathways. In this study, we further demonstrated that the GSDMD and caspase-1 were mainly expressed in ovarian granular cells, and had higher expression in DHEA-induced PCOS rats. To determine whether lymphocyte infiltration existed in ovary of PCOS rats, CD3 and CD45 were analyzed by immunohistochemistry. Our results confirmed that CD3 and CD45 were dramatically up-regulated in DHEA-induced PCOS rats, and mainly expressed in ovarian granular cells. In addition, the mRNA levels of IL-1β and IL-18, and the protein of TNF-α and IL-6 in ovary of PCOS rats were remarkably up-regulated compared with vehicle control. Furthermore, NLRP3 and ASC, as important components in innate immunity, play a central role in regulation of IL-1β and IL-18, and promoting the inflammatory reaction. In this study, mRNA of NLRP3 and ASC in ovary was increased in DHEA-induced PCOS rats compared with vehicle control.

CONCLUSIONS: Pyroptosis was presented in hyperandrogenic ovary of PCOS rats, and it was supposed that hyperandrogenic, pyroptosis is a lytic type of programmed cell death that mainly expressed in the ovarian granular cells. It suggested that the thinning granular cell layer was associated with increased inflammasome, which has an essential function on ovarian dysfunction.

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FUNCTIONAL INVESTIGATION OF THE HUMAN PRIMITIVE SYNCYTUM AT THE MATERNAL-BLASTOCYST INTERFACE. L. A. Kaye; L. Sun; P. Kumar; M. Bolisetty; J. McDonough; W. Skarnes; J. C. Nulsen; P. Robson. *University of Connecticut, Farmington, CT, †Single Cell Biology, The Jackson Laboratory - Genomic Medicine, Farmington, CT; §Computational Sciences, The Jackson Laboratory - Genomic Medicine, Farmington, CT; ¶Genome Editing, The Jackson Laboratory - Genomic Medicine, Farmington, CT.

OBJECTIVE: To explore the functional effects of transcription factor GCM1 in regulating primitive syncytium formation in a human induced pluripotent stem (iHPS) cell model, and to identify novel genes involved in human implantation.

DESIGN: Laboratory based experimental study

MATERIALS AND METHODS: iHPS cells were differentiated to primitive syncytium over six days and the bulk and single cell transcriptomes were collected and analyzed. A GCM1 knockout iHPS cell model was created using CRISPR/Cas9 and differentiated to primitive syncytium for analysis of comparative bulk and single cell transcriptomes. Additionally, structure and endocrine function were compared using quantitative real-time PCR, ste- riodogenesis and enzyme-linked immunosorbent assays, and immunohistochemistry.

RESULTS: Using single cell resolution to analyze differentiation time points and cellular subtypes within the primitive syncytium, we have developed a list of genes that may be integral for primitive syncytium function beyond invasion and endocrinology, including fatty acid metabolism (GPR32, TRPV2), microvilli formation (TBC1D10A), immunosuppression (HLA-G, Env(Ph) or “syncytin-3”), directing further differentiation (LMO2, TWIST2, TRX2), and regulating normal and abnormal pregnancy. GCM1 plays an important role in regulating many functionally downstream genes involved in primitive syncytium formation, hCG production, and possibly maternal immune modulation. Significant differences in cell morphology and endocrine function result from GCM1 knockout iHPS cell lines: knockouts had fewer multinucleated (syncytiotrophoblast) cells on confocal microscopy (p=0.004), decreased mRNA for syncytiotrophoblast genes such as CGA, PGE, and ERVW-1, and lower levels of androgen aromatization. PRRY is a gene that has not been previously examined in the context of primitive syncytium but was found to be upregulated on days 3-6 of differentiation. It may serve as a novel marker for this cell type and provide direction for future work.

CONCLUSIONS: Human implantation and early pregnancy are difficult to access for study, but are integral to improving the treatments for infertility and early pregnancy loss. iHPS cell models serve as a useful tool for evaluating these processes. Further, GCM1 plays an important role as master regulator of primitive syncytium formation and is necessary for the normal structural and endocrine functions of this cell type at the interface between blastocyst and maternal endometrium.

Supported by: The Jackson Laboratory internal funding; New England Fertility Society Fellowship grant, sponsored by Ferring, Inc.

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AN IMPROVED 3D IN VITRO EMBRYO IMPLANTATION MODEL WITH NONHUMAN PRIMATE EMBRYO CULTURE BEYOND DAY 7 AND EFFECT OF CULTURE CONDITIONS. T. Chang; G. Bondareno; B. Gerami-Naini; J. Drenzek; S. Rippenfort; T. G. Golos. Obstetrics & Gynecology, University of Texas Health Science Center, San Antonio, TX; Covance Laboratories, Madison, WI; School of Dental Medicine, Tufts University, Boston, MA; Illumina, Madison, WI; Comparative Biosciences; Obstetrics & Gynecology, University of Wisconsin, Madison, WI.

OBJECTIVE: To optimize a three-dimensional (3D) in vitro extended embryo culture microenvironment on embryo growth and trophoblast interaction with extracellular matrix (ECM) to study embryo implantation and pregnancy initiation/loss.

DESIGN: In vitro study, animal model.

MATERIALS AND METHODS: Nonhuman primate (NHP) embryo can serve as the closest model to human embryo to study implantation and post-implantation embryo development without ethical dilemma. Rhesus macaque IVF-derived embryos were cultured in vitro throughout Day 7, then assisted hatched and embedded into Matrigel ECM droplets with or without additional feeder cell co-culture to mimic three-dimensional (3D) embryo implantation, and cultured for another 2.5-3 weeks (3.5-4 weeks post-fertilization). Embryonic growth and trophoblast cell outgrowth were monitored daily. After the extended culture, embryos were sectioned for immunohistochemistry (IHC) staining to study differentiated structures. Spent medium was collected during the culture period for monkey chorionic gonadotropin (mCG) secretion analysis. Culture medium composition and feeder cell co-culture were evaluated for their effects on embryonic development and trophoblastic outgrowth: buffalo rat liver (BRL), irradiated BRL mouse embryonic fibroblast (MEF), human uterine fibroblast (HUF), Ishikawa, a combination of BRL-HUF-Ishikawa (BHI), and embryoid body (EB) medium. Sequential recovery effect of switching from EB medium to BHI feeder, high vs. low serum supplement concentration, and embryo growth on 2D plating vs. 3D embedding were evaluated as well.

RESULTS: Based on our extended embryo culture and implantation models using rhesus macaque embryos and baboon embryos, in this study we further tested various conditions to optimize the microenvironment on promoting embryo growth and trophoblast invasion. Embryos co-cultured with BHI combination feeder showed a better formation of post-implantation structures compared to embryos in EB medium or with single type feeder.
Secretion profile of mCG was different among culture conditions. IHC staining with markers including CG, Ki67, caspase-3, cytoketatin, vimentin, CD31, and NeuN, on embryos also found a more advanced development in those co-cultured with BHI feeder. In addition, BHI feeder provided a recovery effect on extent cultured in EB medium, and 2D plating showed a poorer development than 3D embedding.

CONCLUSIONS: This improved extended culture model provides a novel platform to examine effect of various conditions during the window of embryonic implantation and peri-implantation stage. This platform can be further used to test hypotheses in pregnancy initiation, pregnancy loss, toxicity, as well as supplemental effect of new compounds and therapeutic approaches.

Supported by: NIH R24 RR14040, R21 HD053925, R01 RR021876, and P51 OD011106.

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DIFFERENTIAL EXPRESSION OF REPRODUCTIVE HORMONE RECEPTORS AND CONTRACTION-ASSOCIATED GENES IN UTERINE ESTROUS CYCLE OF PORCINE. K. Lee,a J. Joo,a M. Jo,b S. Han,c K. Yun,b S. Hwang.a

aObstetrics and Gynecology, Pusan National University School of Medicine, Busan, Korea, Republic of; bObstetrics and Gynecology, Pusan National University Hospital, Busan, Korea, Republic of.

OBJECTIVE: Contraction of uterus tissue frequently occurs throughout the estrus cycle and is regulated by several endogenous factors, including estradiol, progesterone, luteinizing hormone, follicle-stimulating hormone, oxytocin (OXT) and contraction-associated proteins (CAPs). Contraction activity of uterus tissue according to the estrus cycle is important, due to the fact that it is directly associated with balanced implantation and stable pregnancy.

DESIGN: Rabbit anti-β-actin (no. 4967) was purchased from Cell Signaling Technology, Inc. (Danvers, MA, USA). Rabbit anti-estrogen receptor 1 (ESR1; sc-542), ESR2 (sc-8974), rabbit anti-progestrone receptor (PGR; sc-538), rabbit anti-luteinizing hormone/choirogenadotropin receptor (LHGR; sc-25828) goat anti-OXTR (sc-8102) and rabbit anti-HPGD (sc-98907) antibodies were purchased from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA, USA). Rabbit anti-GLA1 (ab11370) was purchased from Abcam (Cambridge, MA, USA). Mouse anti-OXT (MAB5296) was purchased from Merck Millipore (Darmstadt, Germany).

MATERIALS AND METHODS: Uterus tissues were fixed with 10% formalin, embedded in paraffin wax, routinely processed, then sectioned into 4-μm-thick slices. Tissue sections were deparaffinized and rehydrated through graded alcohol using standard procedures and then stained with hematoxylin & eosin (H&E; Sigma-Aldrich; Merck Millipore). Images were captured at a magnification of x40 using a model BX50F-3 optical microscope (Olympus Corporation, Tokyo, Japan) and examined for histological analysis. Results are presented as the mean ± standard deviation. Data were analyzed using Sigma Plot, version 10.0 (Systat Software, Inc., San Jose, CA, USA), P<0.05 was considered to indicate a statistically significant difference.

RESULTS: To investigate regulation of contraction-associated factors according to the estrous cycle, mRNA and protein expression levels of reproductive hormonal receptors, including estrogen receptors, progesterone receptor, oxytocin receptor and luteinizing hormone/choirogenadotropin receptor in addition to CAPs including OXT, OXT receptor (OXTR), hydroxyprostaglandin de-hydrogenase 15-(NAD) and gap junction a1 protein, were examined in the porcine uterus according to the follicular and luteal phases. For the results, hormonal receptors and CAPs were dynamically regulated depending on the estrous cycle.

CONCLUSIONS: In conclusion, genes associated with uterine contraction and its regulatory hormonal receptors in the porcine uterus were differently regulated in the follicular and luteal phases, suggesting that these genes are critically involved in the remodeling and contraction of uterine tissue and may be required to modulate the physiological status of the uterus.

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PROLONGED USE OF PAUSINYSTALIA YOHIMBE AFFECTS ESTRU CYCLE, REPRODUCTIVE HORMONES AND FOLLICULOGENESIS IN RATS. L. C. Ajonuma,a S. A. Bamiro,a S. L. Makanjuola.b

aDepartment of Physiology, Lagos State University College of Medicine (LASUCOM), Lagos, Nigeria; bDepartment of Pharmacology, Lagos State University College of Medicine (LASUCOM), Lagos, Nigeria.

OBJECTIVE: Pausinystalia yohimbe (P. yohimbe) has long been used by West African tribes, as an aphrodisiac among men and for the treatment of erectile dysfunctions. More recently, women use it to enhance arousal and libido while infertile women use it to improve chances of conceiving. However, there are no studies on the effects of P. yohimbe on rat reproductive organs and estrus cycle.

RESULTS: This improved extended culture model provides a novel platform to examine effect of new compounds and therapeutic approaches.

MATERIALS AND METHODS: Eighteen adult female Sprague-Dawley rats were randomly allocated into three groups. Group A was the control while groups B and C served as the treatment groups. Group A received 0.5ml normal saline daily while groups B and C received 150mg/kg and 300mg/kg body weights of aqueous extracts of P. yohimbe respectively via oral gavage for 6 weeks. Vaginal smear of the rats were taken daily for 4 weeks after the first week of drug administration to determine their estrous cycles. After six weeks, rats were sacrificed and sera obtained from the rats were assayed for gonadotropic hormones; Follicle Stimulating Hormone (FSH) and Luteinizing hormone (LH) and sex steroid hormones; Estradiol (E2) and Progesterone. ovaries and uteri were removed for histological processing and antral follicle counting.

RESULTS: Estrous cycle was irregular in groups B and C. Serum hormonal levels of E2, Progesterone, FSH and LH for the test groups were different from those of the control, but not significant. follicles including corpus lutea were significantly decreased and degenerative changes were observed in some areas of the ovaries and uteri of groups B and C.

CONCLUSIONS: P. yohimbe despite its usefulness in enhancing arousal and libido, it affects reproductive hormones, estrus cycle and folliculogenesis. Its prolonged use may lead to reduced fertility.
ENDOMETRIOSIS

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ENDOMETRIOSIS-ASSOCIATED INFERTILITY IN THE "EIVF" DATABASE. K. Bollig,a E. Drobnis,a A. Hsu,b Obstetrics and Gynecology, Resident Physician, Columbia, MO; cUniversity of Missouri Columbia, Columbia, MO; dWomen’s and Children’s Hospital, Columbia, MO.

OBJECTIVE: To determine whether surgically-confirmed endometriosis is associated with decreased implantation, pregnancy, or live birth rates in women undergoing in vitro fertilization (IVF).

DESIGN: Retrospective multivariable analysis of 34,278 fresh IVF cycles in Massachussets between 2003-2006, from the "eIVF" database.

MATERIALS AND METHODS: Fresh IVF cycles in women with surgically-confirmed endometriosis were compared with those in couples with male factor infertility only. Women with "suspected endometriosis" (not surgically confirmed) and couples with both endometriosis and male factor infertility were excluded. Implantation rate was calculated in two ways: (1) gestational sacs (GS) per embryos transferred (ET), and (2) heartbeats (HB) per ET. Clinical pregnancy and live birth rates per cycle were also calculated. Medians were compared with Wilcoxon t-tests; pregnancy and live birth rates were compared using Chi-square tests, and multivariable analyses were performed using logistic regression. NCSS version 11.0.2 (NCSS, Kaysville, Utah) was used for all analyses.

RESULTS: 423 IVF cycles in women with surgically-confirmed endometriosis were compared with 3,762 IVF cycles in couples with male factor infertility only. Women with endometriosis were significantly younger and leaner, with lower AMH and fewer oocytes retrieved.

On univariable analysis, no differences were found in implantation, pregnancy, or live birth rates. Using multivariable analysis (adjusting for age, BMI, day 3 FSH, AMH, maximum estradiol levels, and maximum progesterone levels) detected a statistically-significant decrease in implantation rates was found in women with endometriosis vs women with male factor infertility only. Controlling for age, BMI, Day 3 FSH, AMH, maximum estradiol and maximum P4, endometriosis was related to lower implantation rates (number of transfer cycles resulting in a fetus with a heartbeat).

Above, median (95% Confidence Intervals of the median). Below, percentages

<table>
<thead>
<tr>
<th>Endometriosis (n=423)</th>
<th>Male factor (n=3762)</th>
<th>Difference</th>
<th>P-value, univariate analysis</th>
<th>P-value, multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36 (35-36)</td>
<td></td>
<td>-1.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.9 (23.5-24.1)</td>
<td></td>
<td>-1.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Day 3 FSH (mIU/mL)</td>
<td>6.9 (6.5-7.1)</td>
<td></td>
<td>-0.2</td>
<td>0.25</td>
</tr>
<tr>
<td>AMH (ng/mL)</td>
<td>1.4 (0.96-1.6)</td>
<td></td>
<td>-0.1</td>
<td>0.0064</td>
</tr>
<tr>
<td>Oocytes retrieved (#)</td>
<td>7 (7-8)</td>
<td></td>
<td>-2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Implantation rate 1 (GS/ET)</td>
<td>26%</td>
<td></td>
<td>-3%</td>
<td>0.16</td>
</tr>
<tr>
<td>Implantation rate 2 (HB/ET)</td>
<td>25%</td>
<td></td>
<td>-4%</td>
<td>0.12</td>
</tr>
<tr>
<td>Pregnancy rate</td>
<td>31%</td>
<td></td>
<td>-1%</td>
<td>0.83</td>
</tr>
<tr>
<td>Live birth rate</td>
<td>19%</td>
<td></td>
<td>n/a</td>
<td>0.91</td>
</tr>
</tbody>
</table>

CONCLUSIONS: Surgically-confirmed endometriosis may be associated with decreased implantation rates for infertile couples undergoing IVF. However, this was not reflected in clinical pregnancy or live birth rates.

Supported by: Support: eIVF/NEFS Research Award Grant; departmental support

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CIRCULATING CELL-FREE DNA CONCENTRATION IN PATIENTS WITH ENDOMETRIOSIS: IMPACT OF LESIONS LOCATION. D. Haouzi,a E. Vintejoux,a C. Vincens,a A. Torre,a A. Fournier,a M. Anav,b S. Hamamah,b CHU Montpellier, Inserm U1203, Montpellier, France; aUniversity Hospital, Gyneco-Obstetrian, Montpellier Cedex, France; cCha Montpellier, Montpellier, France; dDepartment of Obstetrics and Gynecology, Division of Child Health, Obstetrics & Gynecology, University of Nottingham, Nottingham, United Kingdom; eART/PGD Department, CHU Montpellier, Inserm U1203, Montpellier, France; fUniversity Hospital of Montpellier, Montpellier, France.

OBJECTIVE: Is there an association between the circulating Cf-DNA (CCI-DNA) and the location of the endometriotic lesions ?

DESIGN: This was an retrospective study using serum prospectively collected from non-pregnant patients from the Cochin Hospital who were between 18 and 41 years of age (mean ± sem: 31.5 ± 0.6 years), and who underwent surgery for symptomatic benign gynecological conditions between January 2011 and December 2013.

MATERIALS AND METHODS: Surgery was performed on 76 patients with signed consent and available preoperative MRIs. After a thorough surgical examination of the abdomino-pelvic cavity, 55 women with histologically proven endometriosis and/or adenomysis were allocated to the endometriosis group and 52 symptomatic women without evidence of endometriosis with or without adenomysis to the endometriosis free group. CCF-DNA was extracted from 200 µl of serum and quantified by quantitative PCR using specific primers amplifying ALU115 sequences in both groups and according to surgical endometriosis phenotypes (superficial peritoneal, ovarian and deep pelvic endometriosis).

RESULTS: CCI-DNA concentrations were similar in the endometriosis free group with or without adenomysis. The concentration of CCI-DNA (mean±SEM) was significantly higher in the endometriosis group than in the control group (311±60 vs 144±13 fg/µL, p=0.002). ROC analysis demonstrated a good sensitivity (78.1) and specificity (71.1) (AUC=0.78, p<0.0001). In addition, according to the location of the endometriotic lesions, the CCI-DNA concentrations was significantly increased in the deep pelvic endometriosis (359±110 vs 144±13 fg/µL, p=0.0031) and the superficial peritoneal endometriosis (289±43 vs 144±13 fg/µL, p=0.01) compared with control group, but not in ovarian endometriosis 207±20 vs 144±13 fg/µL, p=0.08).

CONCLUSIONS: These findings of significantly increased concentrations of CCI-DNA in serum of patients with endometriosis suggests that CCI-DNA might be a potential biomarker for developing non-invasive diagnostic test in endometriosis.

Supported by: This work was partially supported by a grant from the Ferring Pharmaceutical Company.

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HIGH MOBILITY GROUP BOX-1 INCREASES CELL PROLIFERATION, EXPRESSION OF ADHESION MOLECULES, AND SECRETION OF CYTOKINES IN HUMAN ENDOMETRIAL Stromal CELLS IN ENDOMETRIOSIS. Y. Won,a,b I. Lee,a,b J. Yoon,a,b J. Lee,a,b S. Seo,a,b S. Cho,c,b Y. Choe,a,b B. Lee,a,b B. Yun,a,b aDepartment of Obstetrics and Gynecology, Severance Hospital, Seoul, Korea, Republic of; bInstitute of Women’s Life Medical Science, Yonsei University College of Medicine, Seoul, Korea, Republic of; cDepartment of Obstetrics and Gynecology, Gangnam Severance Hospital, Seoul, Korea, Republic of.

OBJECTIVE: To determine if endogenous ligands such as High mobility group box 1 (HMGB-1) signaling plays a pathogenic role in developing endometriosis through the inflammatory pathway in ectopic endometrial stromal cells.

DESIGN: Experimental study.

MATERIALS AND METHODS: Human endometrial stromal cell (HESC) culture was done using ectopic endometrial tissue from the surgical
specimen. HESCs were examined to ascertain cell proliferation and HMGB-1 release after inducing cellular necrosis through H2O2 treatment. Then, HESCs were treated with recombinant HMGB-1 (rHMGB-1) in a dose dependent fashion. The supernatants acquired were examined to measure inflammatory cytokines such as Tumor necrosis factor-α (TNF-α), Interleukin (IL)-1β, IL-6, and IL-10. Adhesion molecules, angiogenic markers, and Damage-associated molecular pattern (DAMP) receptors such as E-Cadherin, Inter-cellular adhesion molecule-1 (ICAM-1), Vascular endothelial growth factor (VEGF), Toll like receptor 4 (TLR4), and receptor for advanced glycation end products (RAGE) were measured by real time PCR and western blotting. RESULTS: HESCs showed a decrease in cell viability and an increase in HMGB-1 release under H2O2 treatment. Cell proliferation and invasion was significantly increased when treated with rHMGB-1. TLR4, RAGE, VEGF, ICAM-1 mRNA and protein expression was significantly increased when treated with escalating concentrations of rHMGB-1. Inflammatory cytokines also showed a significant increase in the HESC supernatant. Conversely, E-Cadherin showed a decrease in mRNA and protein expression with higher doses of rHMGB-1 treatment.

CONCLUSIONS: Endometriosis progression may be preceded by oxidative stress and endogenous stimuli that result in the chronic inflammatory pathway. Our study is limited in that we only performed in vitro analyses using HESCs so in vivo studies are required. HMGB-1 increases cell proliferation and the secretion of cytokines which demonstrates an indisputable relationship between endometriosis and HMGB-1 signaling.

References:

Supported by: This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science, and Technology (NRF-2012R1A1A1013167).

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PROGESTERONE RECEPTOR STATUS AS A PREDICTOR OF RESPONSE TO PROGESTINS IN ENDOMETRIOSIS. V. A. Flores, A. Vanhie, T. Dang, H. S. Taylor. Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale School of Medicine, New Haven, CT.

OBJECTIVE: Progesterin-based therapy is first-line in the management of endometriosis-associated pain. However, response to progestins is highly variable and currently unpredictable. A test that predicts response to progestin-based therapy would allow for a personalized approach to treating endometriosis. We hypothesize that progestrone receptor (PR) expression levels in endometriotic lesions regulates response to progestin-based therapy.

DESIGN: Retrospective cohort study at a single academic center.

MATERIALS AND METHODS: Paraffin embedded endometriotic lesions were obtained from 52 subjects undergoing surgical evaluation. Twenty-one subjects had more than one lesion obtained at the time of surgery. Immunohistochemistry (IHC) was performed using a monoclonal IgG for detection of PR-A/B. The Histo (H)-score was used for quantifying PR status. Two investigators blinded to patient response independently scored IHC specimens. When multiple lesions were present, the highest H-score was used. Response to progestin-based therapies (including OCs) was determined from review of the electronic medical record. Student’s t-test, Receiver Operator Characteristics (ROC) curve analysis, and Chi-square test were used for statistical analysis.

RESULTS: H-score was significantly higher in responders compared to non-responders (p < 0.0001). Based on ROC curve analysis subjects were categorized into three groups: high (H-score > 80, n=7), medium (H-score 50-80, n=28) and low (H-score < 5, n=17) PR status. The threshold of PR >80 was associated with a 100% positive predictive value. The threshold of PR <5 was associated with a 94% negative predictive value. Response rates were: High PR = 100%, Medium PR = 21%, and Low PR = 6% (p < 0.0001).

CONCLUSIONS: Progestrone receptor status is strongly associated with response to progestin-based therapy. Receptor status in endometriosis could be used in a manner analogous to the use of ER/PR status in breast cancer for tailoring hormonal-based regimens. Such an individualized approach to endometriosis management would negate trialing progestin-based therapy to determine resistance. PR status may allow for a novel, targeted, precision approach to treating endometriosis.

References: N/A

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OBJECTIVE: To characterize nationally representative patterns of inpatient admissions and surgeries among women with endometriosis in the United States from 2006 to 2014.

DESIGN: Pooled cross-sectional study.

MATERIALS AND METHODS: Three cohorts of inpatient admissions for women aged 18–49 were extracted from the Health Care Utilization Project Nationwide Inpatient Sample for 2006, 2010 and 2014. Endometriosis was identified by a principal diagnosis code of 617.x as defined by the International Classification of Disease, 9th Edition. Discharges with a diagnosis of malignant neoplasm of female genital organs were excluded. Outcomes of interest included counts of admissions, rates of hysterectomy, laparoscopy, laparotomy and oophorectomy procedures, inpatient surgical complication rates (among women undergoing one of the four procedures), and total hospital charges (inflated to 2014 US dollars). Survey weights were applied to produce nationally representative estimates. Chi-squared tests and analysis of variance were used to compare baseline characteristics and outcomes across years.

RESULTS: Inpatient admissions for endometriosis across the United States declined from 55,117 in 2006 to 31,745 in 2010 and 16,680 in 2014. Mean age was 38 years and did not vary over time. The share covered by private payers decreased from 80.1% to 66.1% (P < 0.001). The share of admissions with at least one Elixhauser comorbidity increased from 39.2% in 2006 to 50.9% in 2014 (P < 0.001). Although hysterectomy and oophorectomy remained the most common inpatient surgical procedures for endometriosis patients, their use declined over time (P < 0.001) (Table). Inpatient complication rates after the four procedures of interest grew from 12.9% to 16.1% (P < 0.001). Mean total hospital charges approximately doubled over time for all four inpatient procedures (P < 0.001).

CONCLUSIONS: Between 2006 and 2014, the size and composition of inpatient admissions for endometriosis changed dramatically. As the number of endometriosis hospital admissions declined, the shares that were covered by Medicaid, had a comorbid condition, and had a surgical complication increased. Hysterectomy and oophorectomy remained widespread even as their use decreased. Over the study period, mean hospital charges increased substantially.

Supported by: The design and financial support for the study were provided by AbbVie. AbbVie participated in data analysis, interpretation of

Outcome rates and mean total charges per inpatient admission by year

<table>
<thead>
<tr>
<th>Admissions with a:</th>
<th>2006 (N=55,117)</th>
<th>2010 (N=31,745)</th>
<th>2014 (N=16,680)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hysterectomy Rate</td>
<td>79.0%</td>
<td>74.2%</td>
<td>67.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Charges $17,133</td>
<td>$26,367</td>
<td>$36,592</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Laparoscopy Rate</td>
<td>2.6%</td>
<td>2.4%</td>
<td>2.9%</td>
<td>0.42</td>
</tr>
<tr>
<td>Charges $19,928</td>
<td>$30,285</td>
<td>$46,279</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Laparotomy Rate</td>
<td>11.0%</td>
<td>11.5%</td>
<td>12.4%</td>
<td>0.20</td>
</tr>
<tr>
<td>Charges $20,091</td>
<td>$32,384</td>
<td>$44,784</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oophorectomy Rate</td>
<td>63.6%</td>
<td>60.8%</td>
<td>58.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Charges $17,692</td>
<td>$26,968</td>
<td>$39,025</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surgical complication Rate</td>
<td>12.8%</td>
<td>13.0%</td>
<td>16.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Charges $21,850</td>
<td>$33,251</td>
<td>$46,951</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
data, review, and approval of the abstract. Medical writing services were provided by Julia Bond of Medicus Economics. Medical writing services were funded by Abbvie.

**P-694** Wednesday, October 10, 2018 6:30 AM

**SERUM METABOLOMIC PROFILING AS A NOVEL APPROACH FOR THE DIAGNOSIS OF GRADE III AND IV ENDOMETRIOSIS.** D. P. Braga,^1,2^ D. A. Montani,^1^ B. F. Zanetti,^1^ A. S. Setti,^1^ E. G. Lo Turco,^1^ D. O. Silva,^1^ A. Iaconelli, Jr.,^1^ E. Borges, Jr.,^1^ Fertility Medical Group, Sao Paulo, Brazil;^2^ Associação Instituto Sapientiae, Sao Paulo, Brazil;^2^ Departamento de Cirurgia, Disciplina de Urologia, Area de Reprodução Humana, UNIFESP, Sao Paulo, Brazil; Grupo de Bio-Orgânica e Bioanalítica, Instituto de Ciências Ambientais, Químicas e Farmacêuticas, UNIFESP, Diadema, Brazil.

**OBJECTIVE:** To make use of the analytical power of mass spectrometry to diagnose grade III and IV endometriosis.

**DESIGN:** Case-control study.

**MATERIALS AND METHODS:** Serum samples were collected from 100 patients under 38 years of age undergoing intracytoplasmic sperm injection (ICSI) in a private university-affiliated in vitro fertilization center. Samples, collected from Jan/2017 to Dec/2017, were split into groups according to the cause of infertility: Endometriosis Group (n = 50), samples derived from patients with grade III and IV endometriosis only, and Control Group (n = 50), samples derived from patients with isolated male factor infertility. The mass spectra were acquired in the positive and negative ionization modes, using a micrOTOF-QII mass spectrometer, equipped with an Apollo II electrospray ion source and coupled to a UPLC Prominence binary liquid chromatograph. Data for Endometriosis and Control groups were compared using the MetaboAnalyst 3.0 software. Principal component analysis (PCA) and partial least square discriminant analysis (PLS-DA) were used to detect intrinsic clusters based on the metabolic profile and to maximize the discrimination of groups, respectively. A “variables influence on the projection” (VIP) list, pointing the most important ions responsible for the discrimination of groups, was obtained. A ROC curve was built considering the VIP values, and metabolites were tentatively identified in Metlin database. The sample size calculation suggested that 95 samples would be enough to demonstrate a 25% effect with 80% power and 5% significance level.

**RESULTS:** Both PCA and PLS-DA were able to clearly distinguish the Endometriosis from the Control Group. Five ions in the positive and 15 ions in the negative ionization modes, selected according to their importance in the prediction model, were hyper-represented in the Endometriosis group. These ions were used to build the ROC curve (AUC: 95.6%, 95% CI: 89.9 - 99.3%, p = 0.009) and were considered potential serum biomarkers for endometriosis. Metabolites attributed by the Metlin database included: fatty acids, sulfenyl compounds, and compounds derived from essential and non-essential amino acids.

**CONCLUSIONS:** The presented method has proven to be a fast and easy approach to assist in the diagnosis of endometriosis with almost 100% accuracy. The suggested biomarkers could be used as diagnostic tool for endometriosis in the future, avoiding the inconvenience of invasive methods, especially for infertile patients, in which earlier diagnosis is of pivotal importance.

References: N/A.

Supported by: None.

**P-695** Wednesday, October 10, 2018 6:30 AM

**CHANGES IN EXPRESSION OF THIOREDOXIN AND THIOREDOXIN BINDING PROTEIN-2 ACCORDING TO HISTONE DEACETYLASE INHIBITOR TREATMENT IN HUMAN ENDOMETRIAL CELLS FROM PATIENTS WITH ENDOMETRIOSIS.** I. Lee,^1^ Y. Won,^1^ J. Yun,^1^ J. Lee,^1^ B. Yun,^1^ S. Cho,^2^ Y. Choi,^2^ B. Lee,^2^ S. Seo.^[4]^ Department of Obstetrics and Gynecology, Severance Hospital, Seoul, Korea, Republic of;^[4]^ Department of Obstetrics and Gynecology, Gangnam Severance Hospital, Seoul, Korea, Republic of.

**OBJECTIVE:** Thioredoxin (TRX) is a redox regulating antioxidant protein that prevents cell damage from oxidative stress and TRX binding protein (TBP)-2 are regulatory protein of TRX. Altered TRX and TBP-2 expressions in endometrium are known to be associated with the development of endometriosis. The aim of the study was to identify a role of Histone deacetylase inhibitor (HDACi) in human endometrial cells that may reverse inflammatory changes and intracellular oxidative stress status, by modifying TRX and TBP-2 expression.

**DESIGN:** Experimental study using human endometrial stromal cell (primary culture) and ishikawa cell.

**MATERIALS AND METHODS:** From July, 2015 to June, 2016, eutopic endometrium was obtained from the patients who had undergone hysterectomy, and ectopic endometrium from the patients who had undergone ovarian cyst enucleation due to endometriosis. Primary stromal cell culture was performed using eutopic and ectopic endometrial cells in vitro. The cultured human endometrial stromal cells (HESCs) and ishikawa cells were treated with HDACi (suberoylanilide hydroxamic acid, SAHA) for 48 hours. Cell proliferation was assessed by a CCK-8 proliferation assay kit, and cell viability was assessed by MTT assay. Real time PCR and western blot were used to quantify TRX and TBP-2 mRNA and protein levels. After inducing cell inflammation adding oxidative stress on the cells, SAHA treatment and following changes of cell proliferation, viability and TRX, TBP-2 expression were examined. Inflammatory cytokines including Interleukin (IL)-1β, IL-6, IL-10 and Tumor necrosis factor-α were measured by ELISA from the supernatants of the cultured cell treated with SAHA.

**RESULTS:** Expression of TBP-2 was significantly increasing according to the increase of SAHA concentration in eutopic, ectopic endometrial stromal cell and ishikawa cell. Cell proliferation was shown according to the recombinant high mobility group box1 (HMGB-1) treatment in cultured eutopic, ectopic endometrial cells. Expression of TBP-2 was significantly decreased after inducing oxidative stress by HMGB-1 on the endometrial cells, which recovery was shown by treating SAHA, resulting in TBP-2 increase and decreased TRX/TBP-2 ratio. The degree of TRX/TBP-2 decrease was significantly high in ectopic endometrial cells. Inflammatory cytokine secretion was decreased according to the SAHA treatment by concentration in endometrial cells.

**CONCLUSIONS:** SAHA may affect the inflammation induced by oxidative stress in development of endometriosis, via resuming the TRX and TBP-2 expression, leading a potential treatment option in endometriosis.

Supported by: This study was supported by a faculty research grant of Yonsei University College of Medicine for 6-2015-0073.

**P-696** Wednesday, October 10, 2018 6:30 AM

**RISK FACTORS FOR LOW BONE MINERAL DENSITY IN PREMENOPAUSAL WOMEN WITH ENDOMETRIOSIS IN THE NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES).** S. E. Chiuve,^1^ N. Chicago, IL; P. Peloso, D. Chand, M. Patwardhan, M. Snares, R. Kilpatrick, Abbvie, N. Chicago, IL.

**OBJECTIVE:** Women with endometriosis have a higher preponderance of demographic and lifestyle risk factors associated with low postmenopausal bone mineral density (BMD). However, it is unclear whether endometriosis confers an additional risk of low BMD or fracture after menopause. Further, data on risk factors for low premenopausal BMD are limited. We aimed to compare premenopausal BMD and the risk of major osteoporotic fracture (in women ≥ 40 years old) between women with and without endometriosis, accounting for known postmenopausal risk factors. We also aimed to identify risk factors for low premenopausal BMD in women with and without endometriosis.

**DESIGN:** A cross-sectional analysis was conducted in 2770 premenopausal women aged 20-54 years who participated in either NHANES 2005-06, 2007-08 and 2009-10 cycles. Data on endometriosis (available in 2005-06 only) and potential risk factors for low BMD were collected through in person interviews and physical exams by trained medical professionals. Circulating 25-OH D levels were measured in blood samples collected during the exam. Femoral neck BMD was measured via dual-energy X-ray absorptiometry (DXA) densitometers. The 10-year risk of major osteoporotic fracture was estimated through the validated FRAX® score.

**MATERIALS AND METHODS:** NHANES survey analysis procedures were used to account for the complex sampling design. Least-squares mean femoral neck BMD and FRAX® scores were estimated by linear regression in women with endometriosis (N = 43) and menopausal age and race were included as confounders in all analyses. Odds ratios for risk of low BMD (lowest decile) were calculated by logistic regression in all women (N = 2770).

**RESULTS:** Accounting for age and race, femoral neck BMD in women with endometriosis (mean = 0.826 g/cm²) was lower, but not significantly different from BMD in women without endometriosis (mean BMD =
IL-1B IN ENDOMETRIAL SECRETIONS IS A PREDICTOR OF MODERATE TO SEVERE ENDOMETRIOSIS. N. C. Llarena, A. P. Muninarayana, E. Richards, D. Fletcher, T. Bonfield, N. Desai, R. Flyckt. Cleveland Clinic, Cleveland, OH; Case Western Reserve University, Cleveland, OH; OB-GYN, Cleveland Clinic, Beachwood, OH.

OBJECTIVE: Noninvasive methods for the detection of endometriosis are desirable to reduce the potential morbidity of diagnostic surgery. The objective of this study is to identify growth factors and cytokines in endometrial secretions which may be predictive of endometriosis.

DESIGN: Prospective cohort study.

MATERIALS AND METHODS: This prospective cohort study included 58 premenopausal patients undergoing laparoscopic gynecologic surgery for benign indications. Prior to surgery, 0.5 mL of endometrial fluid was aspirated for analysis. Multiplex immunoassay was used to quantify 7 cytokines and growth factors with Luminex Magpix technology, using replicates of 50 beads per/analyte per sample. Data was analyzed using Student’s t-test and 1-way ANOVA for normally distributed continuous data, and the Mann Whitney and Kruskal-Wallis tests for non-normally distributed data. Combustions of cytokines were calculated using logistic regression analysis.

RESULTS: Endometrial fluid was aspirated from 58 patients. 29 patients had no endometriosis, 15 had minimal to mild endometriosis, and 14 had moderate to severe disease. There were no significant differences in demographical factors between groups. All 7 cytokines were found to be in detectable ranges within endometrial fluid samples. IL-1B was found to be significantly elevated in the endometrial secretions of women with moderate to severe endometriosis compared to women with none - mild endometriosis (17 ± 25.8 pg/mL versus 2.4 ± 6.2 pg/mL, p = 0.004). A receiver operating curve was generated demonstrating an area under the curve of 0.78. Using a threshold value of IL-1B greater than 1.6 pg/mL, the presence of IL-1B in endometrial secretions has a sensitivity of 75% and specificity of 79% for the diagnosis of moderate to severe endometriosis.

CONCLUSIONS: Aspiration of endometrial fluid is a safe and effective approach for evaluating the endometrial profile of women with endometriosis. The presence of IL-1B in endometrial secretions is a predictor of moderate to severe endometriosis and may have potential as a screening tool for the diagnosis of moderate to severe endometriosis. Data collection is ongoing to adequately power the analysis.

Supported by: Cleveland Clinic Internal Funds

Mean Cytokine Levels by Endometriosis Stage

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Mean Cytokine Level (pg/mL) ± Standard Deviation: None - Stage 2 (n = 44)</th>
<th>Mean Cytokine Level (pg/mL) ± Standard Deviation: Stage 3-4 (n = 14)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1A</td>
<td>45.6 ± 107.8</td>
<td>57.9 ± 72.8</td>
<td>0.09</td>
</tr>
<tr>
<td>IL-1B</td>
<td>2.4 ± 6.2</td>
<td>17 ± 25.8</td>
<td>0.004</td>
</tr>
<tr>
<td>IL-6</td>
<td>140.7 ± 39.5</td>
<td>505.5 ± 916.6</td>
<td>0.04</td>
</tr>
<tr>
<td>IL-8</td>
<td>717.6 ± 1051.4</td>
<td>1394.7 ± 1636.3</td>
<td>0.2</td>
</tr>
<tr>
<td>TNF-Alpha</td>
<td>13.5 ± 25.7</td>
<td>37.5 ± 55.6</td>
<td>0.3</td>
</tr>
<tr>
<td>VEG-F</td>
<td>242.5 ± 508.2</td>
<td>228.7 ± 420.3</td>
<td>0.8</td>
</tr>
<tr>
<td>MCP-1</td>
<td>2173.2 ± 2393.8</td>
<td>2578.4 ± 2391.8</td>
<td>0.9</td>
</tr>
</tbody>
</table>
controls [matched on age (±2 yrs, overall mean 17.7±1.3 y) and hormone use <12 weeks from blood collection (y/n)] were included. Controls had no endometriosis history. WERF EPHect patient questionnaires were completed online by participants, blood processing protocols were applied, and surgical forms were completed intraoperatively by one of 4 surgeons (1-3). Discovery included plasma from 10 cases and 10 controls (50% using hormones) analyzed via Real-Time quantitative PCR using TaqMan® Low Density Array Human MicroRNA A+B Cards v3.0 (Life Technologies) and data normalized by GeneEx v.6 (MultiD Analyses AB). Fold expression was determined Panel of miRNAs may provide insight into the pathogenesis of Stage I-II endometriosis in AYA and/or allow for a diagnostic test in the future.

### Dysregulated miRNA by hormone status

<table>
<thead>
<tr>
<th>MiRNA</th>
<th>Fold change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsa-miR-219a-5p</td>
<td>-18.03 / -6.88</td>
<td>0.003 / 0.05</td>
</tr>
<tr>
<td>hsa-miR-1296-5p</td>
<td>-7.18 / -18.99</td>
<td>0.05 / 0.02</td>
</tr>
<tr>
<td>hsa-let-7i-3p</td>
<td>3.88 / 3.45</td>
<td>0.05 / 0.03</td>
</tr>
<tr>
<td>hsa-miR-651-5p</td>
<td>-3.56 / -6.03</td>
<td>0.002 / 0.04</td>
</tr>
<tr>
<td>hsa-miR-33a-5p</td>
<td>2.51 / 12.06</td>
<td>0.02 / 0.004</td>
</tr>
</tbody>
</table>

Only in hormone users, MiRNA (fold change)

| hsa-miR-626 (-75.9); 1298-5p (46.8); 589-5p (-22.1); 542-3p (-20.6); 122-3p (19.4); 337-3p (-19.3); 376b-3p (-13.9); 422a (12.7); hsa-let-7a-3p (-12.0); hsa-miR-567 (-10.1); 193a-3p (-8.6); 124-3p (-7.9); 30c-1-5p (-6.4); 891a-5p (-4.5); 23b-5p (2.8); 154-5p (2.4); 455-5p (2.3) |

### References:


### OBJECTIVE:

To investigate whether women with endometriosis achieving singleton pregnancies through IVF have a higher risk of miscarriage.

### DESIGN:

Matched case-control study in Reproductive Medicine Center.It is a retrospective analysis of women undergoing IVF.

### MATERIALS AND METHODS:

The study included women who achieving singleton pregnancies with the use of IVF. The study group were women with a history of surgery for endometriosis and those who have ovarian endometrioma at the time of IVF cycle (n=1338). The control group were matched 1:2 according to age, type of cycle (fresh or frozen cycle) and study period (n=2676).

### RESULTS:

The miscarriage rate between the women with and without endometriosis was similar, (22% and 19.5%, respectively, p = 0.067). The odd ratio adjusted for body mass index (BMI), parity, age, duration of infertility, and male factor infertility was 0.95 (95% confidence interval 0.977-1.372). There is no significant difference in the subgroup analyses according to the type of cycle, the number of embryos transferred and in vitro fertilization technique used.

### CONCLUSIONS:

The risk of miscarriage did not increase in women with endometriosis achieving pregnancy through IVF.

### P-701 Wednesday, October 10, 2018 6:30 AM

### RISK OF MISCARRIAGE IN WOMEN WITH ENDOME- TRIOSIS ACHIEVING PREGNANCY THROUGH IVF.

P. Yang, C. Ma, Y. Wang. Reproductive Medicine Center of Peking University Third Hospital, Beijing, China.

### OBJECTIVE:

To investigate whether women with endometriosis achieving singleton pregnancies through IVF have a higher risk of miscarriage.

### DESIGN:

Matched case-control study in Reproductive Medicine Center. It is a retrospective analysis of women undergoing IVF.

### MATERIALS AND METHODS:

The study included women who achieving singleton pregnancies with the use of IVF. The study group were women with a history of surgery for endometriosis and those who have ovarian endometrioma at the time of IVF cycle (n=1338). The control group were matched 1:2 according to age, type of cycle (fresh or frozen cycle) and study period (n=2676).

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### CONCLUSIONS:

The risk of miscarriage did not increase in women with endometriosis achieving pregnancy through IVF.
miR-451 expression at 1, 2 and 4 weeks after induction of experimental endometriosis. Mature forms of miR-451 were greater than pri- and mature miR-451 levels were greater compared to mature miR-451 expression in endometriotic lesion tissue versus eutopic endometrium. To test this hypothesis, we utilized wild-type mice (expressing miR-451 functions to limit endometriotic lesion survival, leading to demise of the ectopic tissue).

Supported by: Supported by NIH R01 HD069043 to WBN

P-703 Wednesday, October 10, 2018 6:30 AM

COMPLETE AND PARTIAL POUCH OF DOUGLAS OBLITERATION: ASSOCIATION WITH SEXUAL PAIN. P. Yong a M. A. Bedaiwy. a University of British Columbia, BC Women’s Hospital, Vancouver, BC, Canada; bObstetrics and Gynecology, University of British Columbia, Vancouver, BC, Canada.

OBJECTIVE: To determine whether degree of posterior compartment disease (i.e. partial versus complete pouch of Douglas obliteration) was specifically associated with deep dyspareunia.

DESIGN: Prospective registry of women with endometriosis (ClinicalTrials.gov: NCT02911090).

MATERIALS AND METHODS: Inclusion criteria: 1) New or referral to our tertiary referral center between December 2013 to December 2016; 2) Subsequent prospective surgery with diagnosis of partial or complete pouch of Douglas obliteration, with excision and histological confirmation of endometriosis. Exclusion criteria: 1) age > 50 and/or 2) menopausal. Patients were divided into 1) partial obliteration or 2) complete obliteration. We then tested for associations between partial versus complete obliteration and severity of deep dyspareunia (rated 0-10), as well as severity of other pelvic pain symptoms and scores on validated psychological questionnaires (for depression, anxiety, and pain catastrophizing).

RESULTS: 106 patients met the study criteria: 54 with complete obliteration and 52 with partial obliteration. The cases with complete obliteration had significantly worse deep dyspareunia compared to cases with partial obliteration: 6.8 ± 2.7 vs. 5.1 ± 3.2 (t = 2.71, p = 0.008). In contrast, there were no significant differences between complete and partial obliteration for superficial dyspareunia, dysmenorrhea, chronic pelvic pain, dyschezia, age, gravidity, body mass index, depression, anxiety, or catastrophizing.

CONCLUSIONS: Complete pouch of Douglas obliteration had a specific association with more severe posterior compartment disease and deep dyspareunia in women with endometriosis.

Supported by: Canadian Institutes of Health Research (MOP-142273)

P-704 Wednesday, October 10, 2018 6:30 AM

NEGATIVE SLIDING SIGN PREDICTS LOW ENDOMETRIOSIS FERTILITY INDEX(EFI) DURING DYNAMIC ULTRASONOGRAPHY. S. A. Alfaraj, b C. Yong, b C. Allaire, c C. Williams, d S. Lisonkova, e H. Noga, e M. A. Bedaiwy. a Obstetric and Gynecology, Reproductive Endocrinology and Infertility, The University of British Columbia, Vancouver, BC, Canada; bBC Women’s Hospital, Vancouver, BC, Canada; cReproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, BC Women’s Hospital and Research Center, Vancouver, BC, Canada; dDepartment of Obstetrics and Gynaecology, The University of British Columbia, Vancouver, BC, Canada; eObstetrics and Gynecology, University of British Columbia, Vancouver, BC, Canada.

OBJECTIVE: To determine whether a negative sliding sign predicts low endometriosis Fertility Index (EFI) during dynamic ultrasonography.

METHODS: Patients with a pelvic examination consistent with endometriosis were recruited from the Reproductive Endocrinology and Infertility clinics at the British Columbia Women’s Health Centre, Vancouver, Canada. Subjects were recruited over a period of 6 months from January 2016 to July 2016. The study was approved by the University of British Columbia and Women’s Hospital Research Ethics Board.

RESULTS: 108 patients met the study criteria: 54 with complete obliteration and 52 with partial obliteration. The cases with complete obliteration had significantly worse deep dyspareunia compared to cases with partial obliteration: 6.8 ± 2.7 vs. 5.1 ± 3.2 (t = 2.71, p = 0.008). In contrast, there were no significant differences between complete and partial obliteration for superficial dyspareunia, dysmenorrhea, chronic pelvic pain, dyschezia, age, gravidity, body mass index, depression, anxiety, or catastrophizing.

CONCLUSIONS: Complete pouch of Douglas obliteration had a specific association with more severe posterior compartment disease and deep dyspareunia in women with endometriosis.

Supported by: Canadian Institutes of Health Research (MOP-142273)
OBJECTIVE: Endometriosis Fertility Index (EFI) is a robust and externally validated tool to predict pregnancy rate in endometriosis patients who attempt non-in vitro fertilization conception. However, to calculate EFI, surgical confirmation via laparoscopy is mandatory. Dynamic ultrasound can predict anatomic and functional aspects of disease, including Pouch of Douglas (POD) obliteration with high degree of accuracy. The objective of this study is to evaluate the relationship between negative sliding and the EFI. We also sought to explore its utility to triage patients with high versus low chance of conception with EFI cut-off of 7.

DESIGN: Retrospective review of a prospectively collected data from 2010 onwards among women with suspected endometriosis using a new real-time dynamic transvaginal ultrasound (US) staging system.

MATERIALS AND METHODS: Forty-eight infertile patients underwent preoperative dynamic transvaginal sonography to assess organ mobility and had their EFI calculated during laparoscopy. The sliding sign was recorded positive when anterior rectum and rectosigmoid colon glided freely across the posterior cervix and upper posterior uterus, respectively. The sliding sign was negative when there was attachment at least one site between the colon and uterus-cervix. Mann-Whitney test was used to assess the differences in the EFI score between negative and positive sliding sign groups. Spearman’s correlation coefficient was used to assess correlation between EFI and historical factors score. Logistic regression was used to obtain ROC area under the curve (AUC) using historical factors and the sliding sign. Significance was p<0.05.

RESULTS: Patients with negative sliding sign tend to be older (p<0.014), have a longer duration of infertility (p<0.017) and severe stage (n=53) endometriosis (p<0.005). A negative sliding sign was associated with significantly lower EFI (median=4, q range=2–6) versus positive sliding sign (median=8, q range=6–9) (p<0.001). Spearman correlation coefficient between EFI score and historical factors was 0.83 (p<0.001). Utilizing the sliding sign and historical factors could potentially predict EFI<7 with sensitivity of 81% and specificity of 81.8%. The AUC was 92 (95%CI 85–99).

CONCLUSIONS: Sliding sign and fertility historical factors could potentially predict EFI score. Thus, it may be possible to estimate EFI without preceding to surgery in some patients, and to triage these patients to either surgery or assisted reproduction.

References:
using chronic oral progestin (MPA 2.5 mg/day or DNG 2 mg/day) treatment at the time of surgery. Pain Recurrence rate at one-year was 19%. Higher ER-α expression increased the likelihood of experiencing moderate to severe dysmenorrhea (p<0.04) and deep dyspareunia (p<0.03) at the time of surgery in women not receiving hormonal treatment. Progestin treatment was associated with diminished ER expression. In women receiving progestin therapy, persistently high ER-α expression increased the likelihood of deep dyspareunia, severe dischezia as well as pain recurrence at one-year (p<0.02).

CONCLUSIONS: ER expression correlated with symptom severity in deep endometriosis. Failure of progestin therapy to lower ER predicted pain recurrence within one year. ER expression may serve as a prognostic biomarker of aggressive endometriosis. Estrogen modifying rather than progestin based therapies may be targeted to patients with high ER-expression to lower ER for precision medicine in endometriosis care.

References:

P-707 Wednesday, October 10, 2018 6:30 AM

A DISCRETE CHOICE EXPERIMENT STUDY OF PATIENT PREFERENCES REGARDING TREATMENTS FOR ENDOMETRIOSIS-ASSOCIATED PAIN. C. Poulos, a A. M. Soliman, c C. Renz, c J. Posner, d M. Bhattacharya, a S. K. Agarwal, a RTI Health Solutions, RTP, NC; b AbbVie Inc., North Chicago, IL; cAbbVie, North Chicago, IL; dYale School of Management, Research Triangle Park, NC; ePharmacovigilance and Patient Safety, AbbVie, Inc., North Chicago, IL; fOb/Gyn and Reproductive Sciences, UCSD, La Jolla, CA.

OBJECTIVE: Quantify patient preferences for outcomes of treatments for endometriosis-associated pain and patients’ tolerance for treatment-related risks of side effects.

DESIGN: Online discrete choice experiment (DCE) survey.

MATERIALS AND METHODS: Respondents with a self-reported physician diagnosis of endometriosis and moderate or severe dysmenorrhea (DYS) and nonmenstrual pelvic pain (NMPP) completed an online DCE survey. Each of a series of choice questions had a pair of hypothetical treatments for endometriosis-associated pain characterized by 7 attributes with varying levels: improvements from severe DYS (to moderate, mild, or no pain), severe NMPP (to moderate, mild, or no pain), and severe dyspareunia (DYS) (to moderate or mild, or no improvement); mode of administration (oral or injectable); treatment-related risks of pregnancy-related problems like miscarriage or birth defects (unknown, 0%, 2%, 7%), bone fracture later in life (in addition to age-related risk) (unknown, 0%, 2%, 5%, 10%), and moderate to severe hot flashes (0%, 30%, 50%, 65%, 85%). A mixed logit model was used to quantify preferences and conditional relative importance of each attribute (the difference between the preference weights for the most and least preferred levels of the same attribute). Sub-group analysis explored how preferences varied with respondent characteristics.

RESULTS: Two hundred fifty women from the Endometriosis Association and a web panel completed the survey. Average respondent age was 34 years, 34% were interested in becoming pregnant, 47% had a personal or family history of bone problems, and 51% had experienced moderate to severe hot flashes. The relative importance of attributes, in order of decreasing importance, were risk of moderate to severe hot flashes; improvements in DYS, NMPP, and DYS; risk of pregnancy-related problems; mode of administration; and risk of bone fracture (Table 1). Treatment preferences varied with experience with moderate to severe hot flashes. None of the preference weights corresponding to levels of bone fracture risk studied were statistically significantly different from the others.

CONCLUSIONS: Women with endometriosis differentiate between types of endometriosis-associated pain, placing the greatest weight on improvements in DYS, followed by NMPP and DYS. The risk of bone fracture did not drive preferences.

Supported by: AbbVie, Inc. funded the study and participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication.

TABLE 1. Conditional Relative Importance of Attributes of Treatments for Endometriosis-Associated P

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Conditional Relative Importance (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased risk of moderate to severe hot flashes while on treatment</td>
<td>Among respondents who had experienced moderate to severe hot flashes: 3.66 (2.51-4.81) Among respondents who had not experienced moderate to severe hot flashes: 3.58 (2.50-4.66)</td>
</tr>
<tr>
<td>Improvement in dyspareunia</td>
<td>1.70 (1.20-2.20)</td>
</tr>
<tr>
<td>Improvement in nonmenstrual pelvic pain</td>
<td>1.49 (1.0-1.97)</td>
</tr>
<tr>
<td>Improvement in dysmenorrhea</td>
<td>1.48 (1.04-1.92)</td>
</tr>
<tr>
<td>Increased risk of pregnancy-related problem if pregnancy occurs during treatment</td>
<td>0.60 (0.20-1.00)</td>
</tr>
<tr>
<td>Mode and frequency of administration</td>
<td>0.53 (0.22-0.83)</td>
</tr>
<tr>
<td>Increased risk of bone fracture later in life</td>
<td>0.50 (0.19-0.9)</td>
</tr>
</tbody>
</table>

*Conditional relative importance was calculated as the difference between the preference weight for the most preferred level and the least preferred level of the same attribute. Larger values for conditional relative importance correspond to greater relative importance.

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that the CD44/hyaluronic acid (HA) system plays a role in the development and invasion through a monolayer of PMCs on a matrigel matrix. Results were established using a telomerase vector, and verified by genotyping. CD44 KD in iEECs was created by knockdown (KD) on endometrial epithelial cells (EECs) through attachment of CD44 standard and CD44 variants were carried out using Lipofectamine and their expression verified with qRT-PCR. Established results were analyzed with ANOVA and student t-tests as appropriate.

RESULTS: In primary EECs, CD44s, CD44v3 and CD44v6 overexpression increased comparison to plasmid control (p<0.05). In primary ESCs, CD44s, CD44v3 and CD44v6 overexpression did not affect attachment compared to plasmid control. In primary ESCs, CD44v3 overexpression increased invasion (p<0.05), but CD44s and CD44v6 overexpression had no effect on invasion compared to plasmid control.

CONCLUSIONS: Overexpression of CD44s, CD44v3 and CD44v6 increases adhesiveness and invasiveness of EECs. CD44s, CD44v3 and CD44v6 overexpression did not alter ESC attachment and only CD44v6 increased ESC invasiveness. These findings suggest menstrual endometrial cell type and CD44 variants play a complex role in the development of the early endometriotic lesion.

Reference:

Supported by: NIH KL2 TR001116 (JK), ASRM grant (JK), Endometriosis Foundation of America Grant(JK), School of Medicine Womens Grant (RTT)

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OBJECTIVE: Menstrual endometrial cells (MECs) from women with endometriosis have increased adhesion and also express higher levels of CD44 variant 6 (v6) than v3, compared to MECs from women without endometriosis. Here, we assessed the effects of CD44 standard (CD44s), CD44v3 and CD44v6 overexpression on endometrial epithelial (EECs) and stroma cells (ESCs) in vitro attachment to and invasion through a peritoneal mesothelial cell monolayer (PMC).

MATERIALS AND METHODS: Primary EECs and ESCs were isolated from menstrual endometrial biopsies. EECs were immortalized (iEECs) using a telomerase vector, and verified by genotyping. Transient overexpression of CD44 standard and CD44 variants were carried out using Lipofectamine and their expression verified with qRT-PCR. Established results were used to assess EEC and ESC attachment to PMCs and invasion through a monolayer of PMCs on a matrigel matrix. Results were analyzed with ANOVA and student t-tests as appropriate.

RESULTS: In primary EECs, CD44s, CD44v3 and CD44v6 overexpression increased attachment and invasion compared to plasmid control (p<0.05). In primary ESCs, CD44s, CD44v3 and CD44v6 overexpression did not affect attachment compared to plasmid control. In primary ESCs, CD44v3 overexpression increased invasion (p<0.05), but CD44s and CD44v6 overexpression had no effect on invasion compared to plasmid control.

CONCLUSIONS: Overexpression of CD44s, CD44v3 and CD44v6 increases adhesiveness and invasiveness of EECs. CD44s, CD44v3 and CD44v6 overexpression did not alter ESC attachment and only CD44v6 increased ESC invasiveness. These findings suggest menstrual endometrial cell type and CD44 variants play a complex role in the development of the early endometriotic lesion.

Reference:

Supported by: NIH KL2 TR001116 (JK), ASRM grant (JK), Endometriosis Foundation of America Grant(JK), School of Medicine Womens Grant (RTT)

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OBJECTIVE: To consolidate and critically review studies that investigate the association between endometriosis and cardiovascular disease (CVD) risk, including evaluation of clinical and pre-clinical markers of atherogenic dyslipidemia, endothelial dysfunction (ED), and subclinical atherosclerosis which reflect an increased predisposition to CVD independent of other known risk factors.

DESIGN: Systematic review with pooled analysis.

MATERIALS AND METHODS: We systematically searched the following electronic databases: Pubmed, Embase, Medline, Cochrane Central Register, and Grey literature from inception to February 2018. Included studies were divided into two categories: 1) those that investigated the incidence of CV events in patients with a history of surgically confirmed endometriosis, and 2) those that evaluated CVD risk in patients with endometriosis through assessment of serum and non-invasive markers of dyslipidemia, atherosclerosis, and endothelial dysfunction.

RESULTS: Among 14 included studies, 2 large prospective-cohort studies found an overall increased risk of CV events (RR 1.14-1.62) in women with surgically confirmed endometriosis. Among the remaining 12 studies, brachial ankle pulse wave velocity (baPWV), a marker of vascular damage and arterial stiffness, was significantly higher in the endometriosis group, while flow mediated dilatation (FMD), an indirect marker of ED, was found to be lower compared to controls (mean difference: −4.62, 95% CI: −6.52, −2.73; P < 0.001 and 8.39 ± 0.43% vs 10.79 ± 0.54%, P = 0.001, respectively). No linear association was found between FMD and severity of endometriosis. Although one study noted a significant increase in FMD in patients post-surgical resection of endometriosis. Conversely, carotid intimal media thickness (cIMT) was not significantly different and studies that evaluated markers of dyslipidemia revealed varying associations in women with endometriosis, although limitations in study design limit the validity of the findings.
CONCLUSIONS: Although further studies are required to investigate the causal relationship between CVD and endometriosis, currently available evidence suggests that women with endometriosis are at a higher lifetime risk of CVD. This study supports the need for CVD screening and prevention in women with endometriosis.

RESULTS: Endometriosis was associated with higher BMI, waist circumference, and systolic blood pressure. Women with endometriosis had lower HDL cholesterol and higher fasting insulin levels compared to controls.

OBJECTIVE: To assess the association between endometriosis and cardiovascular risk factors in a large population-based cohort study.

DESIGN: Prospective observational cohort study.

MATERIALS AND METHODS: The study included women aged 35-74 years from the General Practice Research Database in the United Kingdom. Endometriosis was diagnosed based on clinical and imaging criteria. Cardiovascular risk factors were assessed at baseline and follow-up.

CONCLUSIONS: Women with endometriosis had higher cardiovascular risk factors compared to controls. These findings suggest the need for further research to investigate the potential mechanisms underlying this association and to develop targeted interventions.

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DETECTION AND FUNCTIONAL ANALYSIS OF HOXC8 AS AN UPSTREAM REGULATORY GENE IN OVARIAN ENDOMETRIOMA. R. Maekawa, H. Tamura, N. Sugino. Department of Obstetrics & Gynecology, Yamaguchi University Graduate School of Medicine, Ube, Japan.

OBJECTIVE: As demonstrated in recent direct reprogramming studies, cell specificity or pathogenesis of diseases is determined by a few key upstream regulators. We hypothesized that the aberrant expression of upstream regulatory genes is associated with the formation of ovarian endometrioma by altering the expression of the downstream genes.

DESIGN: Basic research.

MATERIALS AND METHODS: In order to extract the upstream regulatory genes, Significance-based Modules Integrating the Transcriptome and Epigenome (SMITE) analysis was performed using the transcriptome data of ovarian endometrioma and the functional interaction gene network data which is publicly available. In SMITE analysis, HOXC8 was extracted as a candidate gene of upstream regulatory genes. To clarify the function of HOXC8, HOXC8-overexpressing cells were established using human endometrial stromal cells, and transcriptome analysis and functional assays (wound healing assay, cell migration assay and gel contraction assay) were performed.

RESULTS: The expression statuses of 582 genes were altered by HOXC8-overexpression. Gene Ontology analysis revealed that genes associated with cell proliferation and expression of extracellular matrix were increased and 10 intra-cellular signaling pathways were altered (KEGG pathway analysis). When these pathways were compared with the pathway that is actually activated in ovarian endometrioma, 6 pathways including TGFβ, MAPK- and TNF-signaling pathways were activated as well as in ovarian endometrioma. It is known that activation of TGFβ, MAPK- and TNF-signaling pathways is characteristic of ovarian endometriosis, and is involved in the invasion and adhesion. In the functional analysis, cell migration and cell adhesion activities were enhanced in the HOXC8-overexpressing cells.

CONCLUSIONS: HOXC8 can be an upstream regulatory gene in ovarian endometrioma. Aberrant overexpression of HOXC8 is associated with the onset and development of ovarian endometrioma by inducing the aberrant expression of the downstream genes which are associated with TGFβ-, MAPK- and TNF-signaling.

Supported by: JSPS KAKENHI

P-713 Wednesday, October 10, 2018 6:30 AM

THE ENDOMETRIAL STUDY: COMPARISON OF VAGINAL, CERVICAL AND INTESTINAL MICROBIOTA COMPOSITION BETWEEN WOMEN WITH HISTOLOGY PROVEN ENDOMETRIOSIS AND HEALTHY CONTROLS. B. Aiu,~ S. Yildiz,~ E. Turkgeldi,~ V.P. Brocal,~ E. C. Dinleylec,~ A. Moya,~ B. Urman.~ Obstetrics and Gynecology, Koc University School of Medicine, Istanbul, Turkey;~ Obstetrics and Gynecology, Koc University Hospital, Istanbul, Turkey;~ Genomics and Health, Fundacion para el Fomento de la Investigacion Sanitaria y Biomedica de la Comunidad Valenciana (FISABIO), Valencia, Spain;~ Pediatrics, Osmangazi University School of Medicine, Eskisehir, Turkey.

OBJECTIVE: To investigate whether there is an association between endometriosis and microbiota composition in humans.

DESIGN: Prospective cohort study.

MATERIALS AND METHODS: Vaginal, cervical and faecal samples were collected from reproductive aged 14 women with histologically proven endometriosis and 14 healthy controls. Gravid, obese, postmenopausal women, as well as those who received antibiotics or probiotics in the last 8 weeks, with

inflammatory bowel disease, history of gastrointestinal cancer or surgery, or abnormal Pap smears were excluded. All samples were stored at -80°C until DNA extraction. A region of the 16S rRNA gene was selected and sequencing was performed on the Illumina MiSeq platform at the Sequencing and Bioinformatics Service of FISABIO foundation. Alpha and beta diversity was assessed.

RESULTS: Microbiota diversity was similar between endometriosis and control groups at all 3 sites. Yet, there are some differences of bacteria groups between endometriosis and controls. Absence of Atopobium, in endometriosis is noteworthy despite being present in the vagina and cervix of controls. In contrast, Gardnerella were significantly more abundant in endometriosis. In the gut, Streptococcus, Escherichia and Shigella were more abundant in endometriosis group, whereas Prevotella, Atopobium, Dialister, Mega- sphera were decreased or disappeared. Some patients in endometriosis group, had Escherichia/Shigella dominance in stool, and they later required segmental colon resection due to deep bowel involvement by endometriosis.

CONCLUSIONS: This is the first human study of microbiota composition in endometriosis. Strict selection criteria with pathway proven endometriosis, reflected by stability of microbiota, is a strength. Our observations are consistent with a prior study in a primate endometriosis model, i.e. higher proportion of Escherichia/Shigella species in the gut.~ Vagina and cervix have Lactobacilli dominance, and detailed analyses of vaginal and cervical microbiome are ongoing at the time of writing. If confirmed by other series, testing for existence or absence of Atopobium in a cervical sample, or assessing the percentage of Escherichia/Shigella in the stool microbiome can prove as a potential biomarker in endometriosis. Consistency between the findings of the former primate and the present human study suggests there can be a genuine association between microbiome and endometriosis. Whether any of observed associations are causal, or the direction of causality is unclear yet.


Supported by: This study is funded by an unconditional research grant from the Turkish Society of Reproductive Medicine.

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OBJECTIVE: Hyaluronic Acid (HA) plays a role in the early development of the endometriotic lesion.~ 4-Methylumbelliferone (4-MU), a coumarin, has been shown to inhibit endometriotic lesion formation in mice.~ Here, we assessed the effects of 4-MU treatment of endometrial epithelial (EEC) andstromal cell (ESC) on: (1) expression of hyaluronic acid synthases (HAS), and (2) invasion of EECs and ESCs.

DESIGN: In vitro studies.

MATERIALS AND METHODS: EECs and ESCs were isolated from menstrual endometrial biopsies. Cell viability after treatment was previously confirmed. EEC and ESC mRNA expression of HAS 2 and HAS 3 were quantified by RT-PCR with and without 4-MU (2mM). An established in vitro assay using peritoneal mesothelial cell (PM) monolayers on a Matrigel matrix was used to assess EEC and ESC invasion of 4-MU treated and untreated cells. Results were analyzed with unpaired t-tests.

RESULTS: RT-PCR confirmed a significant decrease in HAS 2 and HAS 3 mRNA expression in 4-MU treated EECs and ESCs (p < 0.01). EECs invasion to PMCs decreased with the addition of 4-MU compared to control (668 ± 37

vs 1217 ± 51; p<0.0001). ESC invasion to PMCs with addition of 4-MU also decreased compared to control (765 ± 47 vs 1187 ± 64; p<0.004).

CONCLUSIONS: 4-MU decreases HAS 2 and HAS 3 expression and invasiveness of EECs and ESCs. These findings further suggest that the CD44/HA system is involved in the development of the early endometriotic lesion and may serve as a therapeutic target to prevent the disease.


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BASELINE CHARACTERISTICS FROM >27,000 WOMEN WITH ENDOMETRIOSIS ENROLLED IN THE VIPOS STUDY. I. Bruno,* L. Marions,† S. H. Moehner,** K. Becker,*** T. Faustmann,†† K. Heinemann,‡ Reproductive Endocrinology, University Hospital Zurich, Zurich, Switzerland; Obstetrics and Gynecology, Stockholm, Sweden; Project Manager, Berlin, Germany; †Statistician, Berlin, Germany; §GMW Womens Health, Bayer AG, Berlin, Germany; **ZEG-Berlin, Berlin, Germany.

OBJECTIVE: The Visanne Post-approval Observational Study (VIPOS) aims to assess the safety of dienogest 2 mg/day (Visanne) and other hormonal treatments for endometriosis in routine clinical practice. Additionally, it provides a valuable opportunity to gain further insight and knowledge of women living with endometriosis, the disease landscape and its management across Europe.

DESIGN: VIPOS is a prospective, non-interventional, real-world study with a design similar to EURAS/INAS, which directly asks study participants about their experiences living with endometriosis. VIPOS is the largest real-world study examining the hormonal management of endometriosis.

MATERIALS AND METHODS: Since 2010, more than 27,000 women initiating a new therapy regimen for endometriosis have been enrolled in VIPOS, with a follow-up of up to 7 years that will end in 2018. Women were enrolled via gynecologists or specialized endometriosis centers from six European countries (Germany, Hungary, Poland, Russia, Switzerland and Ukraine). Participants provided their self-reported medical and gynecological history, endometriosis-related symptoms, and characteristics of their diagnosis, treatment and demographics via questionnaires at baseline.

RESULTS: Before initiating hormonal treatment for their endometriosis, women self-reported their endometriosis-related symptoms, and the frequency of each symptom type in the entire VIPOS cohort was calculated. Pain during menstruation was the most frequently reported symptom of endometriosis, experienced by 61.8% of women enrolled in VIPOS. Women frequently reported experiencing other types of pain, including pelvic pain (37.2% of women) and pain during/after intercourse (26.1%). In addition, a considerable minority of women reported pain when passing urine (10.2%) and when opening their bowels (9.5%). As well as the painful symptoms of endometriosis, half of women in VIPOS experienced heavy and/or irregular menstrual bleeding (50.7%), and more than a quarter of women (27.0%) reported feeling fatigued (tired and lacking energy). 12.7% of women self-reported their endometriosis-related symptoms, and the frequency of each symptom type in the entire VIPOS cohort was calculated. Pain during menstruation was the most frequently reported symptom of endometriosis, experienced by 61.8% of women enrolled in VIPOS. Women frequently reported experiencing other types of pain, including pelvic pain (37.2% of women) and pain during/after intercourse (26.1%). In addition, a considerable minority of women reported pain when passing urine (10.2%) and when opening their bowels (9.5%). As well as the painful symptoms of endometriosis, half of women in VIPOS experienced heavy and/or irregular menstrual bleeding (50.7%), and more than a quarter of women (27.0%) reported feeling fatigued (tired and lacking energy). 12.7% of women self-reported their endometriosis-related symptoms, and the frequency of each symptom type in the entire VIPOS cohort was calculated. Pain during menstruation was the most frequently reported symptom of endometriosis, experienced by 61.8% of women enrolled in VIPOS. Women frequently reported experiencing other types of pain, including pelvic pain (37.2% of women) and pain during/after intercourse (26.1%). In addition, a considerable minority of women reported pain when passing urine (10.2%) and when opening their bowels (9.5%). As well as the painful symptoms of endometriosis, half of women in VIPOS experienced heavy and/or irregular menstrual bleeding (50.7%), and more than a quarter of women (27.0%) reported feeling fatigued (tired and lacking energy).

CONCLUSIONS: The VIPOS study extends our understanding of women’s experience of the living with endometriosis in the real-world. The baseline characteristics presented here are a valuable dataset in describing the patient journey, disease, and its impact in a real-world setting across Europe. The results of the primary endpoint and follow-up are pending.

Supported by: VIPOS was funded by an unconditional grant from Bayer AG.

P-716 Wednesday, October 10, 2018 6:30 AM

FERTILITY IN MACAQUES WITH INDUCED ENDOMETRIOSIS. O. D. Slayden,* E. C. Mishler,† L. D. Martin,‡ Division of Reprod. & Develop. Sciences, Oregon National Primate Research Center, OHSU, Beaverton, OR; ‡Division of Reprod. & Develop. Sciences, ONPRC; OHSU, Beaverton, OR; ‡Division of Comparative Medicine, Oregon National Primate Research Center, Beaverton, OR.

OBJECTIVE: Endometriosis is the presence of endometrium-like tissue outside of the uterus. Infertile women are 6-8 times more likely to have endometriosis than fertile women (1). In cases of severe disease, scar tissue and adhesions can distort normal pelvic anatomy leading to infertility. However, the effect of mild disease on fertility remains unclear. Our goal was to determine if experimentally induced [mild] endometriosis reduces fertility in macaques.

DESIGN: In vivo, nonhuman primate study.

MATERIALS AND METHODS: Female rhesus macaques were monitored for menstrual cyclicity. On cycle day 2-3 (day 1 = first day of menses) menstrual endometrium was collected by needle aspiration of the endometrial space and immediately transferred into the intraperitoneal cavity (n=8). This procedure was repeated for 3 consecutive menstrual cycles. Thereafter, the animals were laparoscopically inspected during menses for 3 more cycles and the development of endometriosis noted. Four of the animals underwent necropsy in the mid-luteal phase and endometrium and endometriotic lesions were collected for histological analysis and immunohistochemistry (IHC) for markers of estrogen and progesterone action. Four additional (control) animals underwent sham surgery with no menstrual seeding and reproductive tracts were collected in the mid-luteal phase for comparison. The remaining 4 [induced-endometriosis] animals were paired with males following an established time-mating protocol (2). Pregnant animals underwent necropsy on gestation day 28-30 and the endometriosis collected for IHC.

RESULTS: None of the control animals developed endometriosis. Endometrium from these animals displayed normal secretory differentiation with minimal staining for epithelial estrogen receptor 1 (ESR1) and progesterone receptor (PGR). All 8 animals undergoing menstrual seeding developed at least two endometriotic lesions >4 mm in diameter. Laparoscopic assessment revealed that one of the animals developed a large endometriotic cyst (~10 cm in diameter) in the pelvic cul de sac. The remaining animals developed small red lesions (3-8 mm in diameter) with minimal adhesions that were associated with the oviducts (n=4) omentum (n=2) bladder (n=4) and cul de sac (n=8).

The unmated animals displayed 4.7+0.79 lesions per animal (lesion weight range was 1.8-0.4g). The lesions consisted of ESR1, ESR2 and PGR positive glands and stroma. The endometriotic animals displayed normal secretory endometrial histology and minimal glandular ESR1 and PGR. All 4 of the mated animals all became pregnant. Necropsy of the pregnant animals revealed 3.5±0.15 lesions per animal. Lesion weight range was 6.0+0.3g. No major abdominal adhesions were noted in the pregnant animals.

CONCLUSIONS: The presence of mild induced endometriosis, without adhesions, failed to induce infertility.


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OBJECTIVE: To describe nationally representative patterns of outpatient medication prescribing for endometriosis in the United States in 2011-2015.

DESIGN: Pooled cross-sectional study.

MATERIALS AND METHODS: Physician office visits and emergency department (ED) visits for women aged 18-49 were drawn from the 2011-2015 National Ambulatory Medical Survey (NAMCS) and National Hospital Ambulatory Medical Survey (NHAMCS) databases. Endometriosis was identified by an International Classification of Disease, 9th Edition diagnosis code (617.x) in any position. Study outcomes included proportions of visits with prescriptions for analgesics (opioids, non-steroidal anti-inflammatory drugs [NSAIDs]) and hormonal treatments (combined estrogen/progestins, gonadotrophin releasing hormone [GnRH] agonists, aromatase inhibitors, and progesterin-only pill and other medications). Outcomes were compared between obstetrician/gynecology [Ob/Gyn] vs. general medical/pediatric [Med/Peds] office visits, and all physician office visits vs. all ED visits using analysis of variance and nationally representative survey weights.

RESULTS: During 2011-2015, women with endometriosis had approximately 128,000 ED visits and 4.1 million office visits, of which 72% (3 million) were to Ob/Gyn and 15% (600,000) were to Med/Peds clinicians. Prescribing varied across practice settings (Table). Analgesic prescribing was higher in ED visits particularly for opioids (P<0.001) and was nominally higher in Med/Peds than in Ob/Gyn visits (P=0.16). Rates of prescribing hormonal treatments overall (P=0.02), progesterin-only pills (P=0.005) and other progesterin-only medications (P=0.04) were higher in Ob/Gyn visits. (Table notes: [Opoid, NSAID, other, [Progestin pill and other progestin [implant, injection, IUD or vaginal]; **Combined estrogen/progestin, GnRH agonist, aromatase inhibitor, progesterin pill, other progesterin [implant, injection, IUD or vaginal].)
CONCLUSIONS: Outpatient prescribing for women with endometriosis varied across settings during 2011-2015. Compared with Med/Peds, Ob/Gyn visits had nominally lower rates of analgesic prescribing and statistically significantly higher rates of prescribing hormonal therapies, including progestin-only treatments. Prescribing in Med/Peds office visits was most commonly for analogics and never for progestin-only treatments, and only analogics were prescribed in ED visits.

Supported by: The design and financial support for the study were provided by AbbVie. AbbVie participated in data analysis, interpretation of data, review, and approval of the abstract. Medical writing services were provided by Julia Bond of Medicus Economics. Medical writing services were funded by AbbVie.

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TCF21 REGULATION OF PERIOSTIN IN THE PROGRESSION OF ENDOMETRIOTIC FIBROSIS. U. Ganieva, a T. Nakamura, a P. X. Nguyen, a W. Wei, a M. Murakami, a N. Miyake, a N. Nakajishi, a Y. Katsahara, b N. Takasaki, a A. Muraoka, a S. Hayashi, b T. Nagai, b T. Murase, c S. Osuka, d M. Goto, e A. Iwaso. aDepartment of Obstetrics and Gynecology, Nagoya University, Nagoya, Japan; bDepartment of Obstetrics and Gynecology, Bell Research Center for Reproductive Health and Cancer, Nagoya University, Nagoya, Japan; cDepartment of Obstetrics and Gynecology, Gunma University, Maebashi, Japan.

OBJECTIVE: To study the involvement of transcription factor 21 (TCF21) in the development of endometriosis as an upstream regulator of periostin.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: Formalin fixed paraffin embedded 55 tissue samples (normal endometrial stroma, ES, n=12, endometriotic endometrial stroma eES, n=13, chocolate cyst stroma, CS, n=15, deep infiltrating endometriotic stroma, DS, n=15) of women in reproductive age were analyzed. Cells from respective tissue types were examined for mRNA and protein expression by RT-qPCR and western blotting (n=12). Periostin and TCF21 localization was analyzed by immunofluorescence and immunocytochemistry. Immunohistochemistry revealed the distribution of these proteins in tissue samples. TCF21 siRNA was utilized in CS and DS cells for knockdown. TCF21/Flag tagged plasmid vector was transfected into ES cells for overexpression of TCF21 in ES cells. Overexpression of TCF21 in ES cells, which originally never for periostin and TCF21, resulted in the induction of both TCF21 and periostin.

RESULTS: Although TCF21 expression was undetected and periostin expression was faint in ES, they were weakly positive in eES, moderately positive in CS, and strongly positive in DS. TCF21 and periostin were co-localized in the stromal compartment of CS and DS. Treatment with TCF21 siRNA suppressed periostin expression in CS and DS cells. Overexpression of TCF21 in ES cells, which originally never expressed either periostin or TCF21, resulted in the induction of both TCF21 and periostin.

CONCLUSIONS: TCF21 may regulate fibrosis through induction of periostin.

Supported by: This study was supported in part by College Women’s Association of Japan Scholarship (Tokyo, Japan) to U. Ganieva.

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THE ESTIMATED PREVALENCE AND INCIDENCE OF ENDOMETRIOSIS WITH ADMINISTRATIVE DATA IN KOREAN WOMEN: A NATIONAL POPULATION BASED STUDY. M. Kim, a H. Hwang, a J. Namkung, b Department of Obstetrics and Gynecology, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea, Republic of; bDepartment of Obstetrics and Gynecology, St. Paul’s Hospital, The Catholic University of Korea College of Medicine, Seoul, Korea, Republic of.

OBJECTIVE: To estimate prevalence and incidence of endometriosis in nationwide general population in Korea.

DESIGN: Retrospective cohort study using administrative data provided by the Korean National Health Insurance Service (NHIS).

MATERIALS AND METHODS: Data corresponded to approximately 1 million individuals selected randomly from overall Korean population, totaling 4.5 million people, with national claims data for the period from January 1, 2002, to December 31, 2013. We selected patients with endometriosis as primary or secondary diagnosis code from the NHIS sample cohort data and estimated prevalence and incidence rate of endometriosis according to age and age group. The diagnoses of endometriosis were identified by ICD-10 codes N80, except adenomyosis (N80.0).

RESULTS: Among women aged 15-54 selected from the NHIS cohort database from 2002 to 2013, 8765 women were diagnosed as endometriotic. The overall prevalence of endometriosis was increased from 1.2 per 1000 person in 2002 to 3.5 per 1000 women in 2013. The age-specific prevalence was increased sharply in twenties, highest in the 30-34 age group with 3.6 per 1000 women and decreased as the age increased. Comparing the age-specific incidence rate with 5-year internal (2003, 2008, and 2013), we found a significant trend towards an increase in diagnosis for endometriosis in Korean women with time. The peak age of incidence rate in 2013 was the group 26-46 years at 23.7 per 1000 women, and the cumulated incidence rate was highest in 26-30 age group at 23.5 per 1000 within 12 years.

CONCLUSIONS: The prevalence and incidence of endometriosis in Korean women were lower than previous reports in high-risk population studies. We found a significant trend of increase in diagnosing endometriosis in Korean women with time, especially in young age group. Considering that endometriosis is associated with subfertility and has high incidence rate in young age in Korean women, it is very important to detect and treat endometriosis earlier for improvement of fecundability.


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THE SERUM LEVEL OF CX3CL1 IS LOWER IN WOMEN WITH ENDOMETRIOSIS. Y. Chou1 C. Tzeng,6 T’aipei Medical University Hospital, Taipei City 110, Taiwan; 7Taipei Medical University Hospital, Taipei, Taiwan.

OBJECTIVE: Chemokines have been reported to play important roles in pathogenesis of endometriosis. CX3CL1 is the first CX3C-chemokine and combines both chemo-attractant and adhesion molecule properties. CX3CL1 is upregulated in several inflammatory diseases, including rheumatoid arthritis, inflammatory bowel disease and neuroinflammatory disease. Previous study demonstrated that CX3CL1 expression is lower in the peritoneal fluids of endometriosis than non-endometriosis. Other report showed that CX3CL1 expression is significantly higher in the foci of endometriosis than eutopic endometrium in endometriosis patient and control group. Controversial results were found in the role of CX3CL1 in endometriosis. In this study, we evaluate the expression level of CX3CL1 in the serum of endometriosis patients.

MATERIALS AND METHODS: In this study, we measured serum CX3CL1 expression using Bio-plex assay. Receiver-operating characteristic curve was analyzed in control and endometriosis groups. Statistical significance was analyze by paired Student’s t test. P < 0.05 is considered significant.

RESULTS: The serum level of CX3CL1 of endometriosis women (80.7±45.5 pg/mL) was significantly lower than non-endometriosis group (114.8±40.0 pg/mL), P=0.0021. After analysis of receiver operating characteristic curve, we found that area under curve of CX3CL1 was 0.71.

CONCLUSIONS: The serum level of CX3CL1 was lower in endometriosis patients and CX3CL1 may be a potential biomarker of endometriosis.

P-721 Wednesday, October 10, 2018 6:30 AM

FERTILITY OUTCOMES IN WOMEN POST SURGERY FOR ENDOMETRIOSIS. M. R. Palep-Singh1 S. B. Patil,1 2Reproductive Medicine & Surgery, Head of Infertility and Minimal Access Surgery, Fortis Hospital, Bangalore, India; 3Reproductive Medicine & Surgery, Associate Consultant Fortis Hospital, Bangalore, India.

OBJECTIVE: To evaluate fertility outcomes post excisional surgery for endometriosis.

DESIGN: An ongoing prospective longitudinal study of women undergoing surgery for endometriosis in a tertiary centre since January 2015. Fertility was analysed in relation to the stage of disease at the time of surgery and mode of pregnancy.

MATERIALS AND METHODS: All the infertile patients involved in this study were diagnosed with endometriosis according to the ESHRE 2013 guidelines. The presence of MTHFR c677T mutation was determined from a venous blood sample, using real time PCR with the RealFast™ assay (ViennaLab Diagnostic GMBH, Vienna, Austria).

RESULTS: Among the endometriosis population of our study, 60% (18/30) of the patients are carrying the MTHFR mutation (46.7% in a heterozygous state, 13.3% in a homozygous state). This proportion is significantly more important (p<0.05) than the proportion of patients carrying MTHFR mutations in the general population: 50.5% (Zappacosta, 2014). Furthermore, after we treated infertile couples with endometriosis and recurrent ART failures (2 to 7) carrying MTHFR mutations, we significantly improved their ART outcomes: average ongoing pregnancy rate per cycle: 23.4% before treatment; 29.6% after treatment, p<0.05.

CONCLUSIONS: Endometriosis can be explained by MTHFR mutations. On the one hand, polymorphisms of MTHFR induces oxidative stress through the increased homocysteine level (Gao, 2010). On the other hand, the oxidative stress is implicated in the pathophysiology of endometriosis by causing a general inflammatory response in the peritoneal cavity (Aguiré, 2009) and therefore impairs the fertility of the female patients. To our knowledge, these preliminary results are the first in the literature showing the role played by MTHFR in the endometriosis genesis of infertile patients.

Therefore, by improving the methylation and decreasing the oxidative stress of the endometriosis patients, treating MTHFR mutation carriers improves the quality of the gametes and their ART outcomes.
P-723 Wednesday, October 10, 2018 6:30 AM

WHOLE EXOME SEQUENCING OF 137 ENDOMETRIOSIS PATIENTS WITH A COMMON ANCESTOR IN SHAKESPEARE’S ENGLAND. K. Ward, R. N. Chettier, V. Argyle, Juneau Biosciences, Salt Lake City, UT; 3Juneau Biosciences Inc, Salt Lake City, UT.

OBJECTIVE: We have identified a large endometriosis family spanning 19 generations with 218 women with surgically confirmed disease in recent generations. For a common disease like endometriosis, we cannot assume that all of these distant cousins share a single causative mutation; however, segregation analyses suggest that an autosomal major gene effect is likely. In this study, we used whole exome sequencing (WES) to search for pathogenic mutations.

DESIGN: Cohort study, whole exome sequencing.

MATERIALS AND METHODS: Whole exome sequencing was performed on 137 women previously identified as descendants of common ancestor who was born in 1608. Ampliseq was used on Ion Proton system (Thermo Fisher Inc). Variants were discovered using Thermo Fisher’s Torrent variant caller and annotation was performed using ANNOVAR (Thermo Fisher Inc). Variants were discovered using Thermo Fisher’s Taster, FATHMM, LRT, and MetaLR. The excess variant burden in this large family was compared against the Non-Finnish cohort of 55,860 population samples. Variants deemed damaging if they were predicted in-silico by at least one of these algorithms (Polyphen 2, Sift, Mutation Accessor, Mutation Taster, FATHMM, LRT, and MetaLR). The excess variant burden in this large family was compared against the Non-Finnish cohort of 55,860 population samples from gnomAD database.

RESULTS: tHESCs with ERβ KD invasion through PMCs decreased in ERβ KD demonstrated decreased protein expression of ERβ and protein 10 fold higher compared to the general population (p< 0.001). ERPβ KD attachment to and invasion of PMCs was decreased in ERβ KD compared to WT (264 ± 16 vs 404 ± 22, respectively; p<0.005).

CONCLUSIONS: ERβ knock down decreases attachment and invasion through PMCs. ERPβ may serve as a future therapeutic target to decrease early endometriotic lesion formation.

Supported by: Juneau Biosciences

P-724 Wednesday, October 10, 2018 6:30 AM

ENDOMETRIUM METABOLOMIC PROFILING REVEALS POTENTIAL BIOMARKERS FOR DIAGNOSIS OF ENDOMETRIOSIS AT MINIMAL-MILD STAGES. J. Li, X. Liang. 6th Hospital of Sun Yat-sen University, Guangzhou, China.

OBJECTIVE: Sensitivity and specificity of non-invasive diagnostic methods for endometriosis, especially at early stage, is not optimal. Clinical diagnostic indicator of cancer antigen 125 (CA125) performs poorly in diagnosing minimal endometriosis with a sensitivity of 24%. Therefore, it is urgent to explore novel diagnostic biomarkers.

DESIGN: We evaluated metabolomic profile variation of eutopic endometrium between minimal-mild endometriosis patients and healthy women by ultra high performance liquid chromatography coupled with electrospray ionization high-resolution mass spectrometry (UHPLC-ESI-HRMS).

MATERIALS AND METHODS: Our study comprised 29 patients with laparoscopically confirmed endometriosis at stage I-II and 37 infertile women who underwent diagnostic laparoscopy combined with hysteroscopy from January 2014 to January 2015. Eutopic endometrium was collected by pipelle endometrial biopsy. The metabolites were quantified by UHPLC-ESI-HRMS. The best combination of biomarkers was then selected by performing step-wise logistic regression analysis with backward elimination.

RESULTS: 12 metabolites were identified as endometriosis-associated biomarkers. The eutopic endometrium metabolomic profile of endometriosis patients was characterized by significant increase in concentration of hypoxanthine, L-arginine, L-tyrosine, leucine, lysine, inosine, omega-3 arachidonic acid, guanosine, xanthosine, lysophosphatidylethanolamine and asparagine. In contrast, concentration of uric acid was decreased. Metabolites were filtered by step-wise logistic regression with backward elimination and a model containing uric acid, hypoxanthine, and lysophosphatidylethanolamine were constructed. Receiver-operating characteristic (ROC) analysis confirmed the prognostic value of these parameters in diagnosing minimal/mild endometriosis with a sensitivity of 66.7%, a specificity of 90.0%.

CONCLUSIONS: Metabolomics analysis of eutopic endometrium in endometriosis was effectively characterized by UHPLC-ESI-HRMS based metabolomics. Our study supports the importance of purine and amino acids metabolites in the pathophysiology of endometriosis and provides the potential biomarkers for semi-invasive diagnose of endometriosis at early stage.

Supported by: This study was financially supported by the National Natural Science Foundation of China (No. 81601347, 81503156, 81471507), National Science Foundation of Guangdong Province (No. 2014A030310096) and Public Welfare Research and Capacity Building Fund of Guangdong (No. 2016A02018006).


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OBJECTIVE: Endometriosis requires estrogen for development and growth. Levels of estrogen receptor beta (ERβ) in endometriosis are reported to be 100 times higher than normal endometrial tissue and inhibition of ERβ activity by an ERβ selective antagonist suppresses endometriotic lesion growth in mice. Here, we assessed the role of ERβ in the development of the early endometriotic lesion by examining the effect of ERβ knock down on endometrial stromal cell (ESC) cell attachment and invasion.

DESIGN: In vitro study.

MATERIALS AND METHODS: ERβ was knocked down (ERβ KD) with lipofectamine using shRNA in an immortalized human ESC line (iHESC). Western blot and densitometric analysis were used to assess protein expression. Established in vitro assays were used to assess WT and ERβ KD/iHESC attachment to peritoneal mesothelial cells (PMCs) and invasion through a monolayer of PMCs. Results were analyzed with unpaired t-tests.

RESULTS: iHESCs with ERβ KD demonstrated decreased protein expression by Western blot and densitometric analysis. ERβ KD attachment to PMCs decreased in comparison to WT (42% vs 67%, respectively; p<0.001). ERβ KD invasion through PMCs decreased in ERβ KD compared to WT (264 ± 16 vs 404 ± 22, respectively; p<0.005).

CONCLUSIONS: ERβ knock down decreases iHESCs adhesion to and invasion through PMCs. ERβ may serve as a future therapeutic target to decrease early endometriotic lesion formation.

P-727 Wednesday, October 10, 2018 6:30 AM

SEGREGATION ANALYSES OF 123 FAMILIES: DOMINANT GENES COMMONLY CONTRIBUTE TO PATHOGENESIS OF ENDOMETRIOSIS. K. Ward V. Argyle. Juneau Biosciences, Salt Lake City, UT.

OBJECTIVE: At the 2018 Society for Reproductive Investigation meeting, we described the largest endometriosis family reported to date: spanning 19 generations with 218 women with surgically confirmed disease. An autosomal major gene effect is likely in this family. In this study, we examine the risk of endometriosis in 123 smaller families with probands selected from the same time period and unrelated to the index pedigree.

DESIGN: Genetic segregation analysis.

MATERIALS AND METHODS: 123 probands are surgically affected women with a birth date between 1960 and 1995 (this date range chosen to focus on adult women with the highest likelihood of a surgical diagnosis). These probands have no known ancestral relationship to the large index pedigree by genealogy records or DNA ancestry methods. Three-generation family histories were collected and any reported endometriosis was confirmed with surgical records. Segregation analyses were performed.

RESULTS: Prevalence of endometriosis in close relatives is much higher than the 2-3% prevalence of surgically diagnosed endometriosis in the general population. The rates observed are also much higher than expected with multifactorial polygenic inheritance.

CONCLUSIONS: Analysis of larger number of families confirms that autosomal dominant, high penetrance risk alleles for endometriosis segregate in some families. The heritability of endometriosis may be higher than estimated by older twin studies.

References: Ward, K, Argyle V. A family with over 200 women with confirmed endometriosis suggesting autosomal dominant inheritance. Society for Reproductive Investigation, 2018

Supported by: Juneau Biosciences

P-728 Wednesday, October 10, 2018 6:30 AM

THE ROLE OF L-CARNITINE AND OMEGA-3 FATTY ACIDS IN PREVENT MEIOTIC DAMAGES TO BOVINE OOCYTES MATURED IN VITRO WITH FOLLICULAR FLUID FROM WOMEN WITH DIFFERENT STAGES OF ENDOMETRIOSIS. V. S. Giorgi,a R. A. ferriani.2 P. Navarro.3 Department of Gynecology and Obstetrics, Faculty of Medicine of Ribeirao Preto USP, Ribeirao Preto, Brazil; 2Obstetrics and Gynecology, University of Sao Paulo, Ribeirao preto, Brazil; Obstetrics and Gynecology, Faculty of Medicine of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, Brazil.

OBJECTIVE: To investigate the impact of follicular fluid (FF) from infertile women without endometriosis (control) and with endometriosis in different stages supplemented or not with L-carnitine (LC) and n-3 fatty acids to in vitro maturation (IVM) medium of bovine oocytes on stage of nuclear maturation, chromosome/spindle organization analyzed by confocal microscopy.

DESIGN: Experimental study.

MATERIALS AND METHODS: FF samples were obtained from 32 infertile women undergoing stimulated cycles for ICSI (8 control (FFControl), 8 endometriosis I/II (FFEI/II), 8 endometriosis III/IV without endometrioma (FFEIII/IV) and 8 endometriosis III/IV with endometrioma (FFEndometrioma). Immature bovine oocytes were submitted to IVM in medium with/without FF (no-FF), containing FF and/or 0.6 mg/mL of LC plus 0.4 μM of docosahexaenoic acid plus 0.6 μM eicosapentaenoic acid (LC+n3). After IVM, oocytes were immunostained for visualization of microtubules and chromatin by confocal microscopy.

CONCLUSIONS: It is concluded that endometriosis in women with infertility is associated with higher prolactin levels compared to women without this condition. Whether this association is a causal relationship remains to be determined. We have also found that women with endometriosis are less insulin resistant and have also, lower blood glucose levels and lower prevalence of uterine fibroids than our control group.

References: "none"

Supported by: "None"
RESULTS: FF samples were obtained from 32 infertile women undergoing stimulated cycles for ICSI (8 control [FFControl], 8 endometriosis III (FFEIII), 8 endometriosis III/IV without endometrioma [FFEIII/IV] and 8 endometriosis III/IV with endometrioma [FFEendometrioma]). Immature bovine oocytes were submitted to IVM in medium without FF (no-FF), containing FF and/or 0.6 mg/mL of LC plus 0.4 µM of docosahexaenoic acid plus 0.6 µM eicosapentaenoic acid (LC+n3). After IVM, oocytes were immunostained for visualization of microtubules and chromatin by confocal microscopy.

CONCLUSIONS: FF from infertile women with endometriosis causes mitotic abnormalities in bovine MI oocytes, independently of stage of dis- ease, and FF from women with endometrioma compromise nuclear oocyte maturation. LC and n3 have antioxidant properties and are important to β- oxidation (mitochondrial metabolic pathway which use fatty acids for ATP synthesis) and prevented these damages caused by FF from endometriosis.

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P-729 Wednesday, October 10, 2018 6:30 AM

LIVE BIRTH RATE AFTER SURGICAL AND EXPECTANT MANAGEMENT OF ENDOMETRIOMAS IN IN VITRO FERTILIZATION CYCLES: A SYSTEMATIC REVIEW AND META-ANALYSIS. C. Q. Wu, a A. Albert, b S. Alfaraj, b O. Taskin, b G. M. Alkusayer, c J. Havelock, b P. Yong, c C. Allaire, d M. A. Bedaiwy. e Department of Obstetrics and Gynecology, University of Saskatchewan, Regina, SK, Canada; bDivision of Reproductive Endocrinology and Infertility, University of British Columbia, Vancouver, BC, Canada; dDepartment of Obstetrics, Gynecology and Reproductive Sciences, University of Manitoba, Winnipeg, MB, Canada.

OBJECTIVE: Controversies exist regarding the surgical management of endometriomas in infertile women prior to in vitro fertilization (IVF). Growing evidence indicates that endometrioma surgery may impair ovarian response. Our objective is to compare the effect of surgical versus expectant management of endometriomas on IVF outcomes.

MATERIALS AND METHODS: We systematically searched the Cochrane Library, EMBASE, and MEDLINE databases from inception to January 2018. Prospectively and retrospectively controlled studies comparing fertility outcomes in infertile women with endometriomas undergoing surgical and expectant treatment prior to IVF were selected for inclusion. Study selection, data extraction and quality assessment were conducted indepen- dently by 2 reviewers. The primary outcome was live birth rate following IVF; secondary outcomes include the number of total and mature oocytes retrieved, antral follicle count, clinical pregnancy, fertilization, miscarriage and cycle cancellation rates.

RESULTS: Fourteen studies (1 randomized controlled trial [RCT] and 13 observational studies; n = 3,539) meeting the inclusion criteria were pooled in the meta-analysis. For the primary outcome, similar live birth rate was observed between the surgically and expectantly managed groups (odds ratio [OR] = 1.21; 95% CI = 0.73 to 2.02, p = 0.46). Clinical pregnancy rates (OR = 0.93; 95% CI = 0.71 to 1.22, p = 0.14), number of mature oocytes retrieved, and miscarriage rates were not statistically different between the two study groups. The total number of oocytes retrieved was however lower in the surgery group (mean difference = -1.23; 95% CI = -2.28 to -0.19, p = 0.02).

CONCLUSIONS: Our meta-analysis suggests that surgical management of endometriomas prior to IVF therapy yields similar live birth rate as expectant management. However, well-designed RCTs are needed.

P-730 Wednesday, October 10, 2018 6:30 AM

THE USE OF VAGINAL MISOPROSTOL PRIOR TO OFFICE HYSTEROSCOPY IS ASSOCIATED WITH LOWER PAIN AND TENACULUM UTILIZATION DURING THE PROCEDURE. P. Sarkar, a E. P. New, a E. Mikhail, e E. Sappenfield, a S. M. Plosker, a I. Imudia, b OBGYN, University of South Florida Morsani College of Medicine, Tampa, FL; eUniversity of South Florida, Tampa, FL; aReproductive Endocrinology and Infertility, University of South Florida Morsani College of Medicine, Tampa, FL.

OBJECTIVE: To evaluate the effectiveness of vaginal misoprostol in reducing patient’s pain and tenaculum utilization during office hysteroscopy (OH) performed for various gynecologic indications.

DESIGN: Prospective study performed in an academic center.

MATERIALS AND METHODS: A retrospective analysis of prospectively collected data of patients undergoing OH between October 2015 to March 2018 was performed. The primary outcome was the effect of vaginal misoprostol used pre-operatively on patient’s global pain score during OH. Pain scores were assessed post-procedure using a visual analogue scale from 0-10. Secondary outcomes were rate of tenaculum utilization and volume of saline used for cavity distention during the procedure.

RESULTS: There were 462 patients that had OH and 206 (44.6%) received 50 mcg of vaginal misoprostol the night prior to the procedure while the remaining 256 (55.4%) patients did not have pre-procedure cervical ripening. The reported pain score following OH was significantly lower among patients who received misoprostol [4.0(10)- vs. 5.0(10); p = 0.001]. Women treated with misoprostol had a significantly lower risk for tenaculum utilization (13.6% vs 21.5%; p = 0.03). However, the pre-procedure administration of misoprostol was associated with higher volume of saline (mL) used for cavity distention [100 (10-920) vs. 60 (10-560)]. The majority of patients (78.2%) did not report any misoprostol related side effects. Reported side effects were bleeding (2.4%), cramping (12.1%), both cramping and bleeding (7.3%).

CONCLUSIONS: The use of vaginal misoprostol prior to OH for various gynecologic indications is associated with lower reported pain and tenaculum utilization during the procedure.

P-731 Wednesday, October 10, 2018 6:30 AM

COMPARISON OF OPERATIVE OUTCOMES FOR ABDOMINAL AND LAPAROSCOPIC MYOMECTOMIES. A. S. Garneau, a S. L. Lababidi. b J. W. Akin. c aObstetrics and Gynecology, University of Ken- tucky, Lexington, KY; bObstetrics &Gynecology, University of Kentucky, Lexington, KY; cBluegrass Fertility Center, Lexington, KY.

OBJECTIVE: The objective of this study was to compare the rate of intraoperative and postoperative complications associated with surgical approach to myomectomy.

DESIGN: We performed a retrospective cohort study using the National Surgical Quality Improvement Program database.

MATERIALS AND METHODS: Patients who had open or laparoscopic myomectomies between Jan 1, 2008 and December 21, 2016 were included in analysis. Patients were identified using CPT codes for total laparoscopic or abdominal myomectomies. Variables studied included preoperative factors, surgical operative times, intraoperative complications, and postoperative complications. Data analysis was performed using Chi square and T-test with significance set at p < 0.05. All analyses were completed in SPSS Version.

RESULTS: A total of 12,252 patients were included in analysis. Of those, 7,202 had an abdominal laparoscopy and 5,050 had a laparoscopic myo- mectomy. The two populations were similar in age, BMI, and tobacco use. Frequency of diabetes was slightly higher in the laparoscopic group (4.0%) than abdominal group (2.9%), p = 0.003. Racial distribution was also found to be different between the groups, with African Americans

Patient Characteristics and Procedure Details

<table>
<thead>
<tr>
<th>Variables</th>
<th>Vaginal misoprostol (n=206)</th>
<th>No vaginal misoprostol (n=256)</th>
<th>p-value</th>
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<tr>
<td>Age (years)</td>
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<td>36.5±6.5</td>
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<td>0 (0-1)</td>
<td>0.65</td>
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<tr>
<td>Findings at OH, Normal F &lt; 20</td>
<td>111 (53.9%)</td>
<td>156 (60.9%)</td>
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<td>Fibroid</td>
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<td>35 (13.7%)</td>
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<tr>
<td>Polypl</td>
<td>45 (21.8%)</td>
<td>37 (14.5%)</td>
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<td>Adhesions</td>
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<td>5 (2%)</td>
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</tr>
<tr>
<td>Others</td>
<td>15 (7.3%)</td>
<td>23 (9%)</td>
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</tr>
</tbody>
</table>

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comprising 40.1% of open myomectomies vs 7.7% of laparoscopic myomectomies, \( p < 0.001 \). A trend towards laparoscopic surgery was also observed chronologically, with laparoscopic surgery surpassing open surgery in 2014, \( p = 0.0001 \). Laparoscopic myomectomy was associated with a significantly longer operative time (191 minutes) when compared to abdominal myomectomy (118 minutes), \( p = 0.0001 \). In the abdominal myomectomy cohort, there were 952 (13%) bleeding events requiring transfusion compared to 180 (3.5%) in the laparoscopic myomectomy cohort, \( p < 0.0001 \). Other perioperative and postoperative complications, including superficial surgical site infections, deep surgical site infections, organ space infections, peripheral nerve injury, and wound dehiscence were comparable between the two groups.

CONCLUSIONS: Laparoscopic approach to myomectomy was associated with a higher operative time by approximately 70 minutes. Open myomectomy, though found to have shorter operative time, was found to have a significantly higher risk of bleeding event requiring transfusion. Both modes of surgery demonstrate benefits and risks, however given the significant clinical impact of prolonged OR time in patient risk, it is necessary to counsel patients appropriately pre-operatively. It is also important to note that complications traditionally associated with open procedures, such as wound infections and dehiscence, were comparable in this population. It is unclear what effect the baseline difference in race between the two modes of procedure has on outcomes and warrants further study.


P-732 Wednesday, October 10, 2018 6:30 AM

SURGICALLY MANAGED ECTOPIC PREGNANCIES TREATED FIRST WITH METHOTREXATE ARE NOT ASSOCIATED WITH DECREASED SALPINGOSTOMY SUCCESS RATES. J. A. Gingold,\(^a\) I. Janney,\(^b\) L. Gemmell,\(^c\) T. Falcone.\(^d\)

\(^a\)Women's Health Institute, Cleveland Clinic Foun-
dation, Cleveland, OH; \(^b\)Case Western Reserve University School of Medicine, Cleveland, OH; \(^c\)Case Western Reserve University School of Medicine, Cleveland, OH.

OBJECTIVE: Many patients diagnosed with ectopic pregnancy who desire future fertility will prefer tube-sparing treatment (1). It is unknown whether initial treatment of ectopic pregnancy with methotrexate (MTX) affects the success rate of salpingostomy when surgery is required. We hypothesized that in patients who ultimately require surgery and are candidates for salpingostomy, increased difficulty of dissecting ectopic pregnancy tissue exposed to MTX would lead to lower salpingostomy success rates compared with patients treated with surgery alone.

DESIGN: Retrospective case-control study.

MATERIALS AND METHODS: 782 cases of patients who required surgery for ectopic pregnancy between 2006 and 2017 were identified by chart review. Data from 165 cases primarily managed with surgery (n=155 patients) and all 90 cases who required surgery after failing MTX (n=90) were abstracted.

Cases were stratified by date of ectopic pregnancy. Baseline characteristics recorded included demographics, ectopic risk factors, hCG levels and sonographic features. The primary outcomes were salpingostomy attempt and success rate. Secondary outcomes included salpingostomy failure reason, surgical time and evidence of hemoperitoneum or rupture. Differences were compared across the groups by ANOVA of logistic regression using a generalized linear model or t-test.

Study was powered at 90% with \( p < 0.05 \) to detect a difference between a 25% salpingostomy success rate with MTX exposure and a 50% rate without exposure.

RESULTS: No significant differences in baseline characteristics between the groups were noted. Salpingostomy was ultimately performed in 22 (43%) of the MTX-treated patients and 32 (41%) of the untreated patients (OR 1.091, 95% CI (0.531,2.229), NS). Reasons for failure were not significantly different. Rates of hemoperitoneum or ectopic rupture at the time of laparoscopy were comparable. Total surgery time was 65.5 min vs 63.2 min (2.4 min difference, 95% CI (−6.8,11.5 min), NS).

CONCLUSIONS: This study failed to find a significant negative effect of MTX treatment on salpingostomy completion rate or surgical time, suggesting that primary medical management of ectopic pregnancy in patients desiring fertility does not compromise the ability to perform a salpingostomy if surgery is required. Because of the limited number of patients available in this study, smaller effects on success rate cannot be excluded.


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TRENDS IN SALPINGOSTOMY ATTEMPT AND COMPLETION RATE BETWEEN 2006 AND 2017. J. A. Gingold,\(^a\) L. Gemmell,\(^b\) I. Janney,\(^b\) T. Falcone.\(^\d\)

\(^a\)Women's Health Institute, Cleveland Clinic Foun-
dation, Cleveland, OH; \(^b\)Case Western Reserve University School of Medicine, Cleveland, OH.

OBJECTIVE: Salpingostomy rates for inpatient surgically managed ectopic pregnancies have been reportedly decreasing nationally from 17% in 1998 to 7% in 2011 (1), alongside an increase in medical management with methotrexate (MTX) (2). It is unclear whether this trend reflects improved outpatient management or loss of surgical skill in salpingostomy, which some studies suggest offers superior intrauterine pregnancy rates (3).

We therefore sought to measure the rate of attempted and completed salpingostomy for ectopic pregnancies using a sample that included both inpatient and outpatient surgeries.

DESIGN: Retrospective cohort study, single health system.

MATERIALS AND METHODS: 782 cases of patients who required surgery for ectopic pregnancy between 2006 and 2017 were identified by chart review. Data from 165 cases primarily managed with surgery (n=155 patients) and all 90 cases who required surgery after failing MTX (n=90) were abstracted.

Cases were stratified by date of ectopic pregnancy. Baseline characteristics recorded included demographics, ectopic risk factors, hCG levels and sonographic features. The primary outcomes were salpingostomy attempt and success rate. Secondary outcomes included salpingostomy failure reason, surgical time, and evidence of hemoperitoneum or rupture.

Differences between the first and second temporal half of the cohort were compared by ANOVA of logistic regression using a generalized linear model or t-test.
Study was powered at 80% with \( p < 0.05 \) to detect a difference between a 45% and a 30% salpingostomy attempt rate and a 17% versus 7% salpingostomy success rate.

RESULTS: Patients treated surgically for ectopic pregnancy were slightly older in the second versus first half of the cohort (29.7 ± 5.6 vs 31.3 ± 5.7 years, \( p < 0.05 \)) but were otherwise comparable across all baseline characteristics. Cases representing failed MTX use were stably represented in the sample (34% vs 36%, OR 1.084, 95% CI (0.648,1.151), NS). Salpingostomy was attempted (49% vs 53%, OR 1.171, 95% CI (0.716,1.918), NS) and completed (23% vs 20%, OR 0.828, 95% CI (0.451,1.512), NS) at comparable rates. Gestational age, hCG levels, surgical time, evidence of hemoperitoneum or rupture and reported reasons for salpingostomy failure also remained stable.

CONCLUSIONS: Salpingostomy attempt and completion rates have remained stable at our institution over the past 10 years, suggesting that interest and surgical skill in fertility-sparing surgery has not waned. Completion rates at 21% were slightly higher than expected.


P-734 Wednesday, October 10, 2018 6:30 AM


OBJECTIVE: Uterus transplantation (UTx) is an evolving curative therapy for uterine factor infertility (UFI). While live births have been achieved at a handful of centers around the world, estimating the need for UTx is essential prior to expansion of this innovative therapy. Results from uterus transplant programs at Baylor University Medical Center at Dallas and Cleveland Clinic Foundation suggest great interest in UTx from the community. The purpose of this study was to quantify and characterize candidacy and interest in UTx at a high-volume transplant center in the Northeast.

DESIGN: Chart Review.

MATERIALS AND METHODS: The Penn Uterus Transplantation for Uterine Factor Infertility (UNTIL) Trial began enrolling subjects in November 2017. Interested subjects complete a three-step screening and evaluation process. Candidates initially completed an online questionnaire, which solicited both demographic information and medical/surgical/psychosocial information. Subjects that were 21-40 years old, had a body mass index (BMI) less than 35 kg/m² and had no significant medical, surgical and/or psychiatric history were asked if they would be willing to relocate for the duration of the trial (potentially five or more years) as this was a stipulation for participation.

RESULTS: From November 2017-April 2018, 91 potential recipients completed the online screening questionnaire. The mean age of respondents was 32.8 years (range: 20-47). The mean BMI was 28.4 kg/m² (range: 18.0-47.1). Half of the respondents had given birth previously. Women with congenital UFI represented 29.2% of the population and were generally younger (mean age: 29.0 years) than respondents with acquired UFI (mean age: 34.1 years). Among those with acquired UFI, two thirds had undergone a hysterectomy for a gynecologic indication (n=37) and one third had their uterus removed in an obstetric setting (n=19). The candidates resided in 28 different states, spanning all four regions of the country: Northeast (38.2%), Midwest (16.9%), South (39.3%), and West (5.6%). Of those in the Northeast, the vast majority were in states immediately adjacent to the trial site state (88.2%). Willingness to relocate was assessed in 35 candidates. Of these, 23 were willing to relocate or lived within two hours of the trial site, while the other 13 candidates were unwilling or unable to commit to relocation.

CONCLUSIONS: The demographics of patients who have expressed interest in UTx are similar across all three centers in the United States. The most common reasons for exclusion from the trial were BMI of 35 kg/m² or greater, renal anomalies, endometriosis, and surgical history. One third of candidates who meet basic screening criteria are unwilling or unable to relocate. Broad geographic demand coupled with exclusion of potential UTx recipients based on barriers to relocation highlights the need for increased regional access to UTx programs.

P-735 Wednesday, October 10, 2018 6:30 AM

ADENOMYOSIS. S. J. Silber. Infertility Center of St. Louis, Chesterfield, MO.

OBJECTIVE: The usual treatment for severe adenomyosis has been hysterectomy, because its removal is complicated by infiltrative tissue destruction of normal uterine myometrium. Yet many women wish to retain their uterus to preserve their ability to become pregnant and carry babies. Our objective was to see if it is possible to remove very large, symptomatic adenomyomas with a technique that allows safe future childbearing.

DESIGN: Complete excision of adenomyotic tissue and reconstruction of the uterine wall by a triple-flap method to prevent uterine rupture in subsequent pregnancies.

MATERIALS AND METHODS: From June 1998 to August 2017, 113 women with very severe adenomyosis who desired pregnancy, and all of whom had severe and debilitating symptoms were enrolled and followed for relief of symptoms and successful pregnancy and live birth.

RESULTS: A dramatic reduction of menstrual symptoms occurred immediately and 69.5% of women delivered a healthy baby at term without any incidence of uterine rupture.

CONCLUSIONS: Adenomyosis is a disabling disease in women that until recently had only been treated by hysterectomy. However, many patients wish to preserve their uterus for childbearing, necessitating the need for a more effective conservative approach in treating this disease. The “triple-flap method”
described here has not only significantly decreased the symptoms of adeno-
myosis but has also increased fertility in these patients with no incidence of
uterine rupture. A successful live baby delivery rate of 69.5% has been
achieved in these women who otherwise would have undergone hysterec-
tomy.

P-736 Wednesday, October 10, 2018 6:30 AM

CRYOPRESERVATION AND TRANSLANTATION OF
OVARY TISSUE: RESULTS FROM ONE CENTER IN
THE UNITED STATES. S. J. Silber S. Goldsmith. Infer-
tility Center of St. Louis, Chesterfield, MO.

OBJECTIVE: To report the first series in the United States of cryopre-
served ovary tissue transplantation using slow freeze or vitrification, for leu-
kemia and other cancers.

DESIGN: 13 patients over a 10 year period underwent thaw and transplanta-
tion of ovarian tissue that had been cryopreserved up to 20 years earlier
when they were 20 years of age or younger.

MATERIALS AND METHODS: A single fertility center in a commu-
nity hospital in the United States with a single team over 20 years, 108
females between age 6 and 35 were referred for possible ovary tissue
cryopreservation over a 20 year period. Before 10 years ago only slow
freeze was utilized, and after that only vitrification. Thus far only 13 pa-
tients whose tissue was frozen prior to age 35 returned up to 20 years
later to have their tissue transplanted back, and have more than 2 years
of post-transplant follow-up. No other ancillary treatment was adminis-
tered.

RESULTS: Detailed follow of hormones, menstruation, pregnancies, and
live birth. All 13 cases had return of ovarian function 5 months post transplant
with regular menstrual cycling. AMH rose to very high levels as the FSH
declined to normal, 4 months later the AMH again declined to very low
levels. Nonetheless the grafts remained functional for up to 5 years or longer.
Ten of the 13 (85%) became spontaneously pregnant at least one, resulting in
13 healthy babies.

CONCLUSIONS: Ovarian tissue cryopreservation and transplantation in
young patients is a robust method of fertility preservation. Cortical tissue
pressure may be a key regulator of primordial follicle recruitment and
ovarian longevity.

P-737 Wednesday, October 10, 2018 6:30 AM

HYSTEROSCOPY IMPROVES PREGNANCY OUT-
COMES IN WOMEN WITH ADVANCED MATERNAL
AGE PRIOR TO IVF/ICSI. M. Wang, L. Hu, R. Xie.
*Reproductive Medicine, The First Affiliated Hospital of
Zhengzhou University, Zhengzhou, China; 2Center for Reproductive Medi-
cine, The First Affiliated Hospital of Zhengzhou University, Reproductive
Medicine, Zhengzhou City, Henan Province, China.

OBJECTIVE: To explore the relationship between hysterectomy and preg-
nancy outcomes with assisted reproductive technologies (ART).

DESIGN: A single-centre, retrospective study.

MATERIALS AND METHODS: In total, 10,109 patients who underwent
their first IVF/ICSI-embryo transfer cycles between December 2013 and
June 2016 were divided by age into an AMA group(n=2528) and a young
maternal age (YMA) group(n=7581). Each group was divided into subgroups: group I (patients without office hysterectomy (OH)) and group II (patients with OH).

RESULTS: In the YMA group, no significant difference was found
regarding the clinical pregnancy rate, live birth rate, miscarriage rate and
implantation rate of patients between groups I and II. In the

P-738 Wednesday, October 10, 2018 6:30 AM

ROUTINE KETOROLAC FOLLOWING OOCYTE
RETRIEVAL REDUCES POST-OPERATIVE
NARCOTIC USE BY MORE THAN 50%. E. Seidler, D. Sakkas, L. Murphy, D. Vaughan, A. S. Penzias. Boston IVF, Waltham, MA; Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

OBJECTIVE: Opioid addiction is a public health epidemic, and narcotics
used in the surgical setting contribute significantly.1 The use of non-steroidal
anti-inflammatory drugs (NSAIDs), such as ketorolac, has been avoided in
the setting of IVF procedures due to theoretical concerns of the effect on
fertility and implantation. We are reassured, however, that ketorolac does
not increase post-operative bleeding.2 The objective of our study is to deter-
mine if the routine use of ketorolac at vaginal oocyte retrieval (VOR) has
resulted in decreased narcotic use while maintaining the fresh embryo transfer
(ET) pregnancy rate (PR).

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: The study was performed at a large, academically affiliated fertility clinic that utilizes IV sedation for all oocyte retrievals. Intraoperative ketorolac 30mg IV was institutionally added between November 2016 and April 2017. Patients with known renal insufficiency or NSAID allergy were excluded. Patients undergoing VOR between April 2017 and August 2017 were included in the ketor-
olac group (KG), while patients with VORS between July 2016 and
November 2016 were included in the non-ketorolac group (NGK). Pa-
rameters evaluated include percentage of patients receiving any narcotics
post-operatively, dose of narcotics required for pain control, hospitaliza-
tion/surgery following VOR for pain or hemoperitoneum, and PR
following fresh ET. Chi-squared test was used to compare mean PR be-
tween the two groups.

RESULTS: We found a significant decrease in the use of post-operative
narcotics following VOR in the group receiving ketorolac (25.1% in KG and 11.7% in NGK) (Table 1). There was no significant change in preg-
nancy rate after fresh ETs following our intervention with ketorolac (NGK
PR 76/233 (32.6%), KG PR 220/679 (32.4%), p=0.95). Furthermore,
following intervention, there was no increase in hospitalizations/surgeries
related to post-operative bleeding complications.

CONCLUSIONS: The routine use of ketorolac at VOR safely decreased the
use of post-operative narcotics by 53.1% without impacting the fresh
ET pregnancy rate. Given the current opioid epidemic, clinicians should
choose non-narcotic analgesics whenever possible.


Table 1Post-operative narcotic use following VOR; Data presented as n (%)

<table>
<thead>
<tr>
<th>Patients receiving any post-op narcotics</th>
<th>Fentanyl 25-50 mcg</th>
<th>Fentanyl 75-100 mcg</th>
<th>Vicodin, Percocet, or Tylenol#3 1-2 tabs</th>
<th>Dilaudid 2mg 1 tab</th>
<th>Demerol 50mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ketorolac group (n=685)</td>
<td>175 (25.1)</td>
<td>95 (13.9)</td>
<td>61 (8.9)</td>
<td>44 (6.4)</td>
<td>9 (1.3)</td>
</tr>
<tr>
<td>Ketorolac group (n=1752)</td>
<td>211 (11.8)</td>
<td>100 (5.7)</td>
<td>87 (5.0)</td>
<td>37 (2.1)</td>
<td>2 (0.1)</td>
</tr>
</tbody>
</table>
OBJECTIVE: To investigate the association between antimullerian hormone (AMH) level and maternal age with frozen transfer outcomes for euploid embryo transfers.

DESIGN: Retrospective cohort study from 2014 to 2018 of patients undergoing in-vitro fertilization (IVF) with 24-chromosome day 5/6 preimplantation genetic screening (PGS) at an academic medical center.

MATERIALS AND METHODS: We used multivariable logistic regression to investigate the associations between AMH (<1, 1 to <2, 2 to <5, and ≥5 ng/mL) and ongoing pregnancy and miscarriage outcomes for euploid single embryo frozen transfers. Ongoing pregnancy was defined as continued pregnancy at 8-12 weeks with transfer to obstetrical care; miscarriage included both biochemical and clinical miscarriage. Our analysis controlled for the following patient and cycle confounders: IVF indication, gravidity, parity, history of miscarriage, age at retrieval, age at transfer, AMH, body mass index (BMI), ICSI, oocyte number, cohort size, morphology (expansion, inner cell mass, and trophectoderm), medicated versus natural frozen embryo transfer, and endometrial thickness.

RESULTS: In our cohort of 389 cycles (including 284 unique patients), the overall ongoing pregnancy rate was 52.7% and the miscarriage rate was 16.2%. The average age at retrieval of the cohort was 35.7 years (standard deviation SD 3.7) and the average AMH was 3.60 ng/mL (SD 3.52). The leading indications for IVF were male factor (26.2%), diminished ovarian reserve (DOR, 18.8%) and ovulatory dysfunction (11.6%). In terms of cycle characteristics, an average of 15.8 oocytes (SD 8.2) were retrieved and the average blastocyst cohort size was 5.7 (SD 3.9). Our analysis found that compared to the reference group of AMH <1 ng/mL, AMH 1-2, 2-<5 and ≥5 did not have any significant difference in ongoing pregnancy rates on multivariate analysis. AMH 1-2 and 2-<5 had statistically significant higher miscarriage rates compared to the reference group (see Table). Neither age at retrieval or age at transfer were significantly associated with either ongoing pregnancy (p=0.42 for retrieval, 0.53 for transfer) or miscarriage (p=0.097 for retrieval, 0.10 for transfer).

CONCLUSIONS: In our cohort, after adjustment for potential confounders, AMH level was not associated with ongoing pregnancy for euploid embryo transfers. However, when compared with AMH<1, AMH 1-5 had a statistically increased chance of miscarriage. Maternal age was not associated with euploid transfer outcomes.

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### Euploid transfer outcomes in relation to AMH

<table>
<thead>
<tr>
<th>AMH group (ng/mL)</th>
<th>Number of patients</th>
<th>Maternal age at retrieval (yrs)</th>
<th>Unadjusted ongoing pregnancy (OP) rate</th>
<th>Adjusted odds ratio OP, OR (95% CI)</th>
<th>Unadjusted miscarriage rate</th>
<th>Adjusted odds ratio miscarriage, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>68</td>
<td>36.3</td>
<td>54.4%</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>1 to &lt;2</td>
<td>85</td>
<td>36.5</td>
<td>56.5%</td>
<td>0.78 (0.36-1.68), p=0.51</td>
<td>13.2% Reference</td>
<td>3.07 (1.08-8.74), p=0.036</td>
</tr>
<tr>
<td>2 to &lt;5</td>
<td>150</td>
<td>35.5</td>
<td>50.0%</td>
<td>0.68 (0.31-1.50), p=0.34</td>
<td>16.7% Reference</td>
<td>3.26 (1.11-9.63), p=0.032</td>
</tr>
<tr>
<td>≥5</td>
<td>86</td>
<td>34.6</td>
<td>52.3%</td>
<td>0.88 (0.33-2.34), p=0.80</td>
<td>16.3% Reference</td>
<td>3.20 (0.81-12.73), p=0.098</td>
</tr>
</tbody>
</table>

and ≥5 did not have any significant difference in ongoing pregnancy rates on multivariate analysis. AMH 1-2 and 2-<5 had statistically significant higher miscarriage rates compared to the reference group (see Table). Neither age at retrieval or age at transfer were significantly associated with either ongoing pregnancy (p=0.42 for retrieval, 0.53 for transfer) or miscarriage (p=0.097 for retrieval, 0.10 for transfer).

CONCLUSIONS: In our cohort, after adjustment for potential confounders, AMH level was not associated with ongoing pregnancy for euploid embryo transfers. However, when compared with AMH<1, AMH 1-5 had a statistically increased chance of miscarriage. Maternal age was not associated with euploid transfer outcomes.

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### Euploid transfer outcomes in relation to miscarriage

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Unadjusted ongoing pregnancy (OP) rate</th>
<th>Adjusted odds ratio OP, OR (95% CI)</th>
<th>p-value</th>
<th>Unadjusted miscarriage rate</th>
<th>Adjusted odds ratio miscarriage, OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No miscarriage</td>
<td>234</td>
<td>53.8%</td>
<td>Reference</td>
<td>14.3% Reference</td>
<td>1.94 (0.71-5.26), 0.20</td>
<td></td>
</tr>
<tr>
<td>History of 1 miscarriage</td>
<td>155</td>
<td>49.5%</td>
<td>0.93 (0.43-2.02), 0.85</td>
<td>22.8%</td>
<td>1.47 (0.35-6.28), 0.60</td>
<td></td>
</tr>
<tr>
<td>History of 2 or more miscarriages (RPL)</td>
<td>65</td>
<td>43.9%</td>
<td>0.91 (0.26-3.17), 0.69</td>
<td>22.0%</td>
<td>1.94 (0.71-5.26), 0.20</td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSIONS: In our cohort, there was no significant association between miscarriage history and euploid transfer outcomes (ongoing pregnancy, miscarriage) after adjustment for potential confounders. However, women with a history of miscarriage had elevated odds of having a miscarriage after euploid embryo transfer (though not statistically significant); further study in larger data sets is warranted.
P-741 Wednesday, October 10, 2018 6:30 AM

MEDICATED VERSUS NATURAL FROZEN EMBRYO TRANSFER FOR EUPLOID EMBRYOS. A. Wang,1 J. Kort,1 L. M. Westphal.2 1Stanford University School of Medicine, Menlo Park, CA; 2Stanford Fertility and Reproductive Health, Sunnyvale, CA.

OBJECTIVE: The literature on treatment protocols for frozen transfer of euploid embryos is limited. The goal of this study is to investigate medicated versus natural frozen embryo transfer outcomes (ongoing pregnancy, miscarriage) for euploid embryos. DESIGN: Retrospective cohort study at an academic medical center of patients undergoing in-vitro fertilization (IVF) with 24-chromosome day 5/6 preimplantation genetic screening (PGS) from 2014 to 2018. MATERIALS AND METHODS: Multivariable logistic regression was used to study the association between ongoing pregnancy and miscarriage outcomes with type of frozen euploid embryo transfer (medicated versus natural). Ongoing pregnancy was defined as continued pregnancy at 8-12 weeks with transfer to obstetrical care, and miscarriage included both biochemical and clinical miscarriage. Medicated transfers utilized estrogen and progesterone replacement for endometrial preparation prior to transfer. The multivariable analysis controlled for the following patient and cycle characteristics: IVF indication, AMH, body mass index (BMI), ICSI, oocytes retrieved, age at retrieval, AMH, body mass index (BMI), ICSI, oocytes retrieved, count, and endometrial thickness.

RESULTS: In our cohort of 389 cycles, 45.0% of cycles were medicated and 55.0% of cycles were natural. The average age at retrieval of the cohort was 35.1 years (standard deviation SD 3.5) for the medicated group, and 36.1 (SD 3.7) for the natural cycle group. In the medicated group, 22.9% of patients reported ovulatory dysfunction, while 4.7% of patients reported ovulatory dysfunction in the natural cycle group. We found when compared to medicated frozen embryo transfer, natural cycle frozen embryo transfer had significantly higher ongoing pregnancy rates after adjustment for confounders (adjusted odds ratio OR 2.08, 95% confidence interval CI 1.15-3.75, p<0.015). There was no significant difference in miscarriage rates between the two groups (adjusted OR for natural 0.70, 95% CI 0.37-1.34, p=0.29).

CONCLUSIONS: After adjustments for potential confounders including ovulatory dysfunction, we found that natural cycle single euploid frozen embryo transfer was associated with significantly higher ongoing pregnancy rates than medicated transfer. There was no significant difference in adjusted miscarriage rate between the two groups.

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Euploid transfer outcomes for medicated versus natural frozen embryo transfer

<table>
<thead>
<tr>
<th>Type of transfer</th>
<th>Number of patients</th>
<th>Unadjusted ongoing pregnancy (OP) rate</th>
<th>Adjusted odds ratio OP, OR (95% CI)</th>
<th>p-value</th>
<th>Unadjusted miscarriage rate</th>
<th>Adjusted odds ratio miscarriage, OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicated</td>
<td>175</td>
<td>42.9%</td>
<td>Reference</td>
<td>2.08 (1.15-3.75)</td>
<td>0.015</td>
<td>21.5%</td>
<td>Reference</td>
</tr>
<tr>
<td>Natural cycle</td>
<td>214</td>
<td>60.7%</td>
<td></td>
<td></td>
<td>15.0%</td>
<td>0.70 (0.37-1.34)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

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"MORPHOGENETIC MAPPING" WITH TIME LAPSE IMAGING: A NEW CONCEPT TO NON-INVASIVELY ASSESS BLASTOCYST QUALITY BASED ON BLASTOCYST EXPANSION KINETICS ANALYSIS IN PGD-A CASES. T. Huang,a,b B. Walker,a C. Huang,c C. Arnett.c aPacific IVF Institute, Honolulu, HI; bStanford Fertility and Gynecology and Women’s Health, University of Hawaii School of Medicine, Honolulu, HI; cAdvanced Reproductive Center of Hawaii, Honolulu, HI.

OBJECTIVE: To describe a new concept of “Morphogenetic Mapping” of blastocysts based on a standard assay of blastocyst expansion in PGD-A cases to select embryos more likely to be euploid without biopsy. DESIGN: A retrospective observational study of trophoderm biopsy cases from a single IVF center.

MATERIALS AND METHODS: The study involved 43 sequential PGD-A cases from January 2017–January 2018 which evaluated a total of 209 blastocysts. The median ages of patients was 36 (range 23–42). All fertilized eggs were cultured in an Embryoscope after ICSI for up to 6 days. On Day 2 a derived Eeva Score was annotated as HIGH, MEDIUM, or LOW using published P2 and P3 metrics. The cross sectional area of a blastocyst and its cavity was annotated at 2 hour intervals beginning at the time of initial blastocyst formation (tB) using the Embryoscope software. Biopsies were performed on D5 or D6 and analyzed by Genesis Genetics without mosaic calls. The median number of blastocysts biopsied per patient was 5 (range: 1-11). The overall rate of euploidy was 35%. A "Morphogenetic Map" was constructed as a scatterplot of each embryo based on its 1) degree of expansion at 10 hours and 2) blastocyst formation time in hrs from ICSI and 3) derived Eeva score.

RESULTS: This “standard assay” described the total area of the blastocyst (TE and cavity) over the initial 10 hours of expansion from tB. The total population Map showed a differential distribution of Aneuploids and Euploids. In the map’s vertical plane, Euploids were enriched >2:1 in regions representing those embryos most expanded, while Aneuploids were enriched >3:1 in regions representing those least expanded. Map regions enriched in Euploids were also de-enriched in single chromosome trisomies, monosomies, and complex abnormalities involving 2 or more chromosomes. The class of duplications and deletions showed no clear localization within map regions. There was no strong correlation between Eeva derived scores and ploidy overall; however, Euploids in the euploid-enriched region were mostly Eeva HIGH and MEDIUM. Eeva LOW scores characterized >50% of trisomies, further supporting the usefulness of this metric. Patient specific cohort maps showed the practical value of this approach in choosing embryos for transfer: The enrichment of Euploids among the highest ranks was greatest (approaching 90%) in patients <35 yrs, suggesting that this non-invasive approach for embryo selection could be most efficacious in this group as well as for egg donors.

CONCLUSIONS: This study defines a new standard assay of blastocyst expansion to create Morphogenetic Maps useful for non-invasive embryo selection. These maps can be used to rank embryos for transfer and may be of particular value for single embryo transfer in patients <35 yrs without biopsy.

Supported by: This work was supported by the Division of Research of the Department of Obstetrics and Gynecology and Women’s Health of the John A. Burns School of Medicine.

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P-743 Wednesday, October 10, 2018 6:30 AM

DO BLASTULATION RATES CORRELATE WITH EMBRYO PLOIDY? A COMPARISON OF 1,552 IVF CYCLES WITH PREIMPLANTATION GENETIC TESTING STRATIFIED BY AGE AND PERCENT BLASTULATION. V. Gunnula, C. C. Canon, L. Kong, J. C. Wan, M. Irani, P. Chung, Z. Rosenwaks. Center for Reproductive Medicine, Weill Cornell Medicine, New York, NY.

OBJECTIVE: To investigate if embryo blastulation rates correlate with euploidy in patients undergoing IVF with preimplantation genetic testing (PGT-A).

DESIGN: Retrospective cohort study
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MATERIALS AND METHODS: 1,552 IVF PGT-A cycles were reviewed from January 2011 to June 2017. Only patients who underwent tropho-derm biopsy with comprehensive chromosome screening (CCS) and cryo-preservation were included for analysis. Patients who underwent PGT-M for micronuclei were not included as this test was not performed in CCS cycles and was performed in 2014 onward. Patients were stratified into age groups (25-32 y, 33-35 y, ≥35 y) and embryo type: non-mosaic, mosaic only, or aneuploid. CCS results were only considered if all 24 chromosomes were reviewed.

RESULTS: A significant difference in the rate of mosaic only embryos was appreciated between age cohorts (p < 0.01). Table 1 shows the rate of mosaic only embryos compared to the older age groups. Differences in cycle characteristics were appreciated between cohorts including AMH, prior live birth, total FSH dose, total hMG dose, mixed gonadotropin protocol, IVF stimulation protocol and trigger modality. Multivariate linear regression was performed to account for these potential confounding factors; age remained the only predictive factor for mosaicism (p < 0.01).

CONCLUSIONS: Patients younger than age 35 have higher rates of mosaic only embryos compared to older patients. Rates of mosaic only em-bryos did not differ above age 35. This likely reflects the higher rate of both aneuploid and mosaic embryos in the older age group rather than a higher rate of mitotic errors in the younger age group. As patients generally have a high implantation rate in this younger age group, more research is needed to assess the actual implantation potential and ultimate outcome of the mosaic em-bryos in these patients.
REANALYSIS OF BLASTOCYSTS PREVIOUSLY DIAGNOSED AS ANEUPLOID DEMONSTRATES THAT ONE IN FOUR ARE RECLASSIFIED AS EUPLOID. T. H. Taylor, a D. Das, b M. Johnson, b J. G. Whelan, a J. L. Patrick, a S. Katz, a Reproductive Endocrinology Associates of Charlotte, Charlotte, NC; REACH, Charlotte, NC; Embryology, REACH, Cornelius, NC; REACH, Charlotte, NC.

OBJECTIVE: To determine the degree of concordance between the biopsy piece of trophectoderm and the whole embryo in blastocysts diagnosed as aneuploid.

DESIGN: Observational

MATERIALS AND METHODS: Previously vitrified blastocysts that were diagnosed as aneuploid by array comparative genomic hybridization (aCGH) that had been donated to research were included in this study. Upon warming, the blastocyst was mechanically removed from the zona pellucida (ZP) and the ZP was discarded. The entire blastocyst was washed three times in wash buffer, placed in a PCR tube and assessed using high resolution next generation sequencing.

RESULTS: A total of 43 blastocysts from 34 patients (35.3±2.4 years) were analyzed. Of these, 24 (55.8%) exhibited full concordance between the trophectoderm sample and the blastocyst, six (11.6%) had at least one aneuploid chromosome that was discordant between the trophectoderm and blastocyst, two (4.7%) were non concordant but both the trophectoderm and blastocyst were aneuploid. Remarkably, 11 (25.6%) displayed a euploid result. No blastocysts displayed mosaicism. Of the 65 aneuploidies detected in the trophectoderm, 37 (56.9%) were detected in the whole blastocyst.

CONCLUSIONS: In approximately one quarter of the blastocysts deemed aneuploid by aCGH, analysis of the whole blastocyst via NGS revealed euploidy. Possible explanations for this finding are low levels of mosaicism, mitotic non-disjunction, post-zygotic errors with sequestering of the aneuploid cells to the trophectoderm, and/or technical errors. Our findings suggest that further study is needed to determine the accuracy of blastocyst biopsy and its impact on preimplantation genetic testing results.

Supported by: Genesis Genetics

P-747 Wednesday, October 10, 2018 6:30 AM

SINGLE EMBRYO TRANSFER UTILIZING HIGH RESOLUTION OR LOW RESOLUTION NEXT GENERATION SEQUENCING FOR PREIMPLANTATION GENETIC TESTING IN <35 AND ≥35 YEAR OLD PATIENTS: RESULTS FROM A SINGLE CENTER. T. H. Taylor, a J. L. Patrick, a W. Hewitt, a J. G. Whelan, a L. N. Johnson, a S. Katz, a Reproductive Endocrinology Associates of Charlotte, Charlotte, NC; Embryology, REACH, Cornelius, NC; REACH, Charlotte, NC; Reproductive Endocrinology / Infertility, REACH, Charlotte, NC.

OBJECTIVE: To compare the initial day 5 PGT findings with that of the re-biopsy on day 5 as well as a biopsy from the same blastocyst on day 6.

DESIGN: Observational, double blinded

MATERIALS AND METHODS: Previously diagnosed aneuploid day 5 blastocysts designated for research were used in this study. Aneuploid day 5 blastocysts were warmed and allowed 2-3 hours to re-expand. After re-expansion and still on day 5, the blastocysts underwent an additional biopsy. After the additional day 5 biopsy, the blastocysts were allowed to culture for another 24 hours until day 6. On day 6 the blastocysts were biopsied again. The embryologists and the genetics lab were both blinded to the original biopsy results and the re-biopsy samples. To summarize, each blastocyst underwent a total of 3 biopsies, one from the initial PGT report (day 5), one from the additional day 5 biopsy, and one from the day 6 biopsy.

RESULTS: A total of 15 blastocysts from 10 patients (30.9±6.8 years) were warmed. All 15 (100%) blastocysts survived the warming and re-biopsy. Of these blastocysts, 3 (20%) showed some concordance between the day 5 biopsies, 9 (60%) showed complete concordance between the day 5 biopsies, and 3 (20%) were deemed euploid after the second day 5 biopsy. The same blastocysts were cultured to day 6 and biopsied. Of the day 6 biopsies, 14 (93.3%) showed some concordance with either of the day 5 biopsies and 7 (46.6%) showed complete concordance across all three biopsy results. Five (33.3%) of the 15 blastocysts were diagnosed as euploid mosaic as the initial day 5 diagnosis. Upon re-biopsy on day 5, 3 (60.0%) were diagnosed as euploid and 2 (40.0%) were fully concordant with the day 5 mosaic aneuploidy diagnosis. When cultured to day 6, all 15 (100%) of mosaic blastocysts were diagnosed as euploid.

CONCLUSIONS: Initial readings of aneuploid blastocysts remained congruent between day 5 and day 6 biopsies with the exception of mosaic embryos which were euploid upon re-biopsy on day 6.

Supported by: Invitae

P-749 Wednesday, October 10, 2018 6:30 AM


OBJECTIVE: To evaluate the effect of age on euploid embryo and clinical pregnancy rates in oocyte donors and determine if there is a difference in euploid embryo rates when accounting for embryologic mosaicism using two different techniques of pre-implantation genetic testing for aneuploidy (PIT-A): array comparative genomic hybridization (aCGH) and next generation sequencing (NGS).

DESIGN: Retrospective cohort study

MATERIALS AND METHODS: All donor IVF/PAT-A cycles from January 2012 to March 2018 were reviewed. From 2012-2015 both aCGH and NGS were used. From 2016-2018 only aCGH was used. The comparison was performed between donors aged ≤35 years old undergoing PGT with either hrNGS or lrNGS. In patients ≤35 years old, both hrNGS and lrNGS improved ongoing pregnancy rates and significantly lowered miscarriage rates.

Supported by: Invitae
and NGS without mosaicism reporting (woM) were used. NGS with mosaicism reporting (wM) began in 2016. Euploid embryo rates and clinical pregnancy rates within the two groups, woM and wM, were stratified by age of the donor (21-29 years) at the time of retrieval. Clinical pregnancy was defined by the number of fetal heartbeats at 6-7 weeks gestation by the total number of embryos transferred. Descriptive data was analyzed as percentages and means with standard deviations. Statistical differences between groups were determined using Fisher’s exact and/or chi-square with a p-value <0.05 considered significant.

RESULTS: 925 donor oocyte IVF/PGT-A cycles were performed, resulting in 9325 trophectoderm biopsies, 3414 in the woM group and 5911 in the wM group. The euploidy rate in the woM group was a bell curve with lowest euploidy rate in the extreme age groups (ages 21 and 29, 69% & 73%). In the wM group, the euploidy rate remained similar across age groups (mean 63%) and was 10% lower than the woM group. Despite this difference, the percentage of cycles without a euploid embryo for transfer was the same between groups (0.09%). There was no significant difference in clinical pregnancy rate per embryo transferred between the PGT-A technologies.

CONCLUSIONS: This large donor oocyte/PGT-A cohort verifies previous data regarding the effect of age on the euploid rate when utilizing techniques that do not report mosaicism. In contrast, when mosaicism is reported, there is a similar euploidy rate across age groups. Despite a lower number of euploid embryos in the wM group, there was no difference in the percentage of cycles that had no embryos available for transfer or clinical pregnancy rate. This study supports utilizing donors (age 21-29) including the ends of the standard age range with new PGT-A technology with mosaicism reporting.

P-750 Wednesday, October 10, 2018 6:30 AM

EMBRYO GENDER AFFECTS PREGNANCY RATES AS BIOPSY DAY INCREASES AND EMBRYO QUALITY DECREASES. T. Zore,a Z. Al-Safi,a A. L. Akopians,b H. Danzer, b M. Surrey,c S. Ghadir,c J. Barrittd Obsterics and Gynecology, UCLA REI Division, Los Angeles, CA;Obsterics and Gynecology, UCLA, Los Angeles, CA; Southern California Reproductive Center, Beverly Hills, CA; ART Reproductive Center, Beverly Hills, CA.

OBJECTIVE: To determine if gender, in combination with embryo biopsy day and embryo quality, has an impact on pregnancy rates after transfer of embryos that have undergone pre-implantation genetic testing for aneuploidy (PGT-A) using next-generation sequencing (NGS).

DESIGN: Retrospective data analysis of laboratory and clinical outcomes following PGT-A.

MATERIALS AND METHODS: Patients who underwent a frozen euploid single embryo transfer between January 2016 and December 2017 at a single laboratory were assessed. Embryos were cultured to the hatching blastocyst stage (HB) and assigned an overall grade of good, fair or poor. Only HB embryos that were of good or fair quality underwent trophectoderm biopsy on day 5 or 6 with subsequent PGT-A using NGS for genetic results. Chi-square was used to compare differences between groups and a multivariate logistic regression was used to adjust for embryo biopsy day, embryo grade as well as oocyte age. P < 0.05 was considered statistically significant.

RESULTS: 514 women underwent a total of 581 frozen single euploid embryo transfers. The mean oocyte age was 34.6 years and the overall pregnancy rate was 62.3%. 71% of embryos were biopsied on day 5 and 68% percent of all of the embryos were of good quality at biopsy. The highest pregnancy rate in both male and female embryos occurred in the group that had a transfer of a day 5 good quality embryo (67% and 67.5% respectively; Table 1). At biopsy day increased and embryo quality decreased, the odds ratio that an embryo would result in a pregnancy decreased significantly for male embryos (Day 5-Good = 1.0, Day 5-Fair = 0.82, Day 6-Good = 0.63 and Day 6-Fair = 0.5; p = 0.016) and more dramatically for female embryos (Day 5-Good = 1.0, Day 5-Fair = 0.63, Day 6-Good = 0.61 and Day 6-Fair = 0.38; p = 0.019).

CONCLUSIONS: Compared to male embryos, female embryos have a significantly decreased odds ratio for pregnancy as the day of biopsy increases and embryo quality decreases. These data may provide useful information when counseling patients on which embryo to transfer if gender is not preferred.

P-751 Wednesday, October 10, 2018 6:30 AM

PREGNANCY RATES SIGNIFICANTLY DECREASE WITH BIOPSY AFTER DAY 5 AND A DECREASE IN EMBRYO GRADE. T. Zore,a Z. Al-Safi,a A. L. Akopians,b H. Danzer, b M. Surrey,c S. Ghadir,c J. Barritti Obsterics and Gynecology, UCLA, Los Angeles, CA; Southern California Reproductive Center, Beverly Hills, CA; ART Reproductive Center, Beverly Hills, CA.

OBJECTIVE: To compare whether trophectoderm biopsy day or embryo quality have an effect on pregnancy rates after transfer of embryos which underwent pre-implantation genetic testing for aneuploidy (PGT-A) using next-generation sequencing (NGS).

DESIGN: Retrospective data analysis of laboratory and clinical outcomes following PGT-A and frozen embryo transfer.

MATERIALS AND METHODS: Patients who underwent a frozen euploid single embryo transfer between January 2016 and December 2017 at a single laboratory were assessed. Embryos were cultured to the hatching blastocyst stage (HB) and assigned an overall grade of good, fair or poor. Only HB embryos that were of good or fair quality underwent trophectoderm biopsy on day 5 or 6 with subsequent PGT-A using NGS for genetic results. Chi-square was used to compare differences between groups and a multivariate logistic regression was used to adjust for embryo biopsy day, embryo grade as well as oocyte age. P < 0.05 was considered statistically significant.

RESULTS: 514 women underwent a total of 581 frozen single euploid embryo transfers. The mean oocyte age was 34.6 years and the overall pregnancy rate was 62.3%. 71% of embryos were biopsied on day 5 and 68% percent of all of the embryos were of good quality at biopsy. A significant overall reduction in pregnancy rates was seen (67.3% down to 50.9%) as the day of biopsy increased and the quality of the embryo declined (p = 0.013; Table 1). Although, there was a 6.6% decline in pregnancy rate between day 5/fair and day 6/good embryos, no significant difference was able to be determined due to limited samples in each transfer group (p = 0.43). Additionally, while there was a 9.7% decline in pregnancy rates between days 5/fair and day 6 embryos of good or fair quality, this was also not significantly different (p = 0.16).

CONCLUSIONS: These findings demonstrate that as embryos require longer to grow to a biopsy stage or are of less quality, the overall pregnancy rates significantly decline. Although each step down in embryo quality and advancing day of biopsy results in at least a 5% decrease in pregnancy, a much larger sample size will be required to detect these differences significantly. Additionally, our data suggest that delaying biopsy to potentially improve embryo quality does not result in a significant increased pregnancy rate. Overall, our data can be of use in deciding which embryos to biopsy, on which day of development, as well as guiding patients in setting expectations for transfer outcomes from euploid embryos.

Embryo development characteristics and pregnancy outcomes by embryo gender

<table>
<thead>
<tr>
<th>Day of Biopsy</th>
<th>Grade at Biopsy</th>
<th>Male Embryo Pregnancy (Rate)</th>
<th>Mean Male Oocyte Age (SD)</th>
<th>Female Embryo Pregnancy (Rate)</th>
<th>Mean Female Oocyte Age (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>HB-Good</td>
<td>118/176 (67%)</td>
<td>33.7 (4.8)</td>
<td>106/157 (67.5%)</td>
<td>34.4 (5)</td>
</tr>
<tr>
<td>5</td>
<td>HB-Fair</td>
<td>27/41 (65.9%)</td>
<td>33.8 (5)</td>
<td>21/36 (58.3%)</td>
<td>35.6 (5.6)</td>
</tr>
<tr>
<td>6</td>
<td>HB-Good</td>
<td>15/27 (55.6%)</td>
<td>34.7 (4.9)</td>
<td>19/34 (55.9%)</td>
<td>33.9 (5.6)</td>
</tr>
<tr>
<td>6</td>
<td>HB-Fair</td>
<td>31/53 (58.5%)</td>
<td>34.1 (5.8)</td>
<td>25/57 (43.9%)</td>
<td>35.6 (4.8)</td>
</tr>
</tbody>
</table>

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Embryo biopsy day and grading characteristics associated with pregnancy outcomes

<table>
<thead>
<tr>
<th>Day of embryo biopsy</th>
<th>Grade of embryo biopsy</th>
<th>Pregnancy (Rate)</th>
<th>Mean oocyte age, years (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>HB-Good</td>
<td>224/333 (67.3%)</td>
<td>34.1 (4.9)</td>
</tr>
<tr>
<td>5</td>
<td>HB-Fair</td>
<td>48/77 (62.3%)</td>
<td>34.6 (5.3)</td>
</tr>
<tr>
<td>6</td>
<td>HB-Good</td>
<td>34/61 (55.7%)</td>
<td>34.2 (5.3)</td>
</tr>
<tr>
<td>6</td>
<td>HB-Fair</td>
<td>56/110 (50.9%)</td>
<td>34.9 (5.3)</td>
</tr>
</tbody>
</table>

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OBJECTIVE: CoQ10 is a necessary component in the electron transport chain and its role in the generation of ATP is well documented in human oocytes. ATP is needed during embryonic development specifically for chromosome segregation. Thus, the oral supplementation of CoQ10 prior to an IVF cycle can possibly decrease chromosomal aneuploidy in AMA patients.

DESIGN: Double blinded, randomized control trial, pilot study.

MATERIALS AND METHODS: Inclusion criteria consisted of patients that were 36-42 years old, AMH ≤ 2.0 ng/mL, 1st cycle of IVF treatment, and an antral follicle count (AFC) between ≥ 6 and ≤ 19. A total of 21 patients were randomized between placebo (twice daily; Group 1) or oral supplement with CoQ10 (125 mg/twice daily; Group 2) for 3 months prior to IVF. Patients had plasma drawn three months prior to oocyte retrieval for baseline CoQ10 levels, at start of stimulation, and at retrieval. A total of 9 and 12 patients were randomized to Group 1 and 2, respectively. Both groups underwent a microdose GnRH agonist stimulation (high dose Bravelle and Menopur) with retrieval. Due to the low number of embryos from this patient population, all usable, non-usable and arrested embryos were biopsied and analyzed for chromosome copy number with SNP array. Patient, doctor, embryologist, and PGS lab were all blinded to which supplement the patient received.

RESULTS: There was no difference in maternal age, Day 3 FSH, AMH, and AFC between Group 1 and Group 2. Baseline CoQ10 levels were significantly lower in Group 1 (0.7±0.5 μg/mL) compared to Group 2 (0.9±0.2 μg/mL; P<0.05). After three months of oral supplementation, Group 1 had a significantly lower plasma CoQ10 level compared to Group 2, 0.9±0.6 μg/mL and 2.6±0.9 μg/mL, respectively (P<0.05). The CoQ10 levels were also significantly lower at retrieval between Group 1 and Group 2, 0.8±0.3 μg/mL and 2.2±1.2 μg/mL, respectively (P<0.05). The average number of eggs retrieved, maturity, and fertilization was not significant between Groups 1 and 2. In terms of ploidy, 10/17 (58.8%) and 11/34 (32.4%) embryos were euploid from Group 1 and Group 2, respectively (NS).

CONCLUSIONS: Our data suggest that oral supplementation of CoQ10 can increase plasma levels of CoQ10; however, CoQ10 did not affect chromosomal aneuploidy.

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OBJECTIVE: The Practice Committee for the American Society for Reproductive Medicine (ASRM) has stated that more data are needed to determine the effectiveness, safety, and appropriate applications of preimplantation genetic testing for aneuploidy (PGT-A). Nevertheless, PGT-A is increasingly being adopted into routine practice. We aimed to explore how patients make decisions regarding the use of preimplantation genetic testing for aneuploidy (PGT-A) and its associated risks.

DESIGN: Cross-sectional survey at an academic medical center

MATERIALS AND METHODS: Three-hundred subjects initiating an IVF treatment cycle over an eight-week period were asked to complete a validated survey regarding their level of knowledge of and how they decided whether or not to pursue PGT-A. All patients were previously counseled in a physician-led seminar and in individual consultation with their physician that the primary goal of PGT-A is to maximize pregnancy rates per embryo transfer. Survey responses were compared between those who elected PGT-A and those who did not with a chi-squared or t-test, where appropriate.

RESULTS: Of 191 subjects who completed the survey, 117 (61%) planned PGT-A, while 74 (39%) did not. Among those who decided to undergo PGT-A, 56% stated their primary reason was to have a healthy baby, while 18% chose PGT-A to reduce the incidence of birth defects, and 16% aimed to decrease the risk of miscarriage. Patients who decided not to pursue PGT-A stated they prioritized avoiding the scenario in which they might have no embryos to transfer (36%) or reducing cost (31%). Patients who elected to undergo PGT-A rated themselves more knowledgeable surrounding the technology when compared with those who did not (58 vs 47 on scale 0 to 100, p<0.02). Both groups rated physicians as the single most important source of information in their decision-making surrounding the use of PGT-A (56% vs 68% p=NS).

CONCLUSIONS: Patients who chose to undergo PGT-A have different priorities from those who do not. Many patients planning PGT-A do so for reasons that are not evidence-based. While patients cite physicians as their primary source of information in the decision-making process, rationales for selecting PGT-A are inconsistent with physician counseling.

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OBJECTIVE: The Preimplantation Genetic Diagnosis International Society (PGDIS) recommend the use of the high resolution next-generation sequencing (hr-NGS) that can detect mosaicism in excess of 20%. Therefore, embryos with less than 20% aneuploidy in the TE sample are considered euploid and routinely transferred. Those over 80% as aneuploid and subsequently discarded. The 20-80% range as mosaic and transferred with caution, only in absence of euploid embryos. These cutoffs are currently debated. We recently reported the birth of 17 healthy babies from the transfer of 33 low grade (<50%) mosaic embryos with an overall live birth rate (LB) and abortion rate (AR) similar to the LB and AR obtained with euploid embryos (Rubino et al., 2018). The current study reports a greater number of cases.

DESIGN: Retrospective analysis of the pregnancy outcome of replaced low rate mosaic embryos (20%-50% abnormal cells in the trophectoderm biopsy) as diagnosed with the use of hr-NGS.

MATERIALS AND METHODS: This study included only patients that received a single embryo transfer of low rate mosaic embryos and for which the delivery of a newborn could be confirmed. NGS was performed by Nexgenomics, LLC, Pasadena by means of platform Veryseq NGS (Illunina). Nexgenomics position is to use an artificial cutoff of 50% to classify all the mosaicisms events as normal or abnormal. Mosaicism ≤20% is considered euploid embryos.
TABLE 1. Comparison of the pregnancy outcomes of low rate mosaic and control embryos

<table>
<thead>
<tr>
<th>Type of mosaicism</th>
<th>Segmental*</th>
<th>Single-Double 1-12**</th>
<th>Single-Double 13-22**</th>
<th>X-Y</th>
<th>Complex</th>
<th>Total</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>38.8±6.4</td>
<td>40.8±6.9</td>
<td>36.3±5.0</td>
<td>49.1</td>
<td>36.2±4.0</td>
<td>39.1±6.4</td>
<td>39.3±6.3</td>
</tr>
<tr>
<td>N of transfer cycles</td>
<td>22</td>
<td>15</td>
<td>12</td>
<td>1</td>
<td>5</td>
<td>55</td>
<td>110</td>
</tr>
<tr>
<td>Embryos transferred</td>
<td>22</td>
<td>15</td>
<td>12</td>
<td>1</td>
<td>5</td>
<td>55</td>
<td>110</td>
</tr>
<tr>
<td>Embryos Implanted</td>
<td>16</td>
<td>10</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>37</td>
<td>73</td>
</tr>
<tr>
<td>Implantation rate (IR)</td>
<td>72.3%</td>
<td>66.7%</td>
<td>75.0%</td>
<td>-</td>
<td>0</td>
<td>67.3%</td>
<td>66.4%</td>
</tr>
<tr>
<td>Abortions</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Abortion rate (AR)</td>
<td>6.3%</td>
<td>10.0%</td>
<td>11.1%</td>
<td>-</td>
<td>-</td>
<td>10.8%</td>
<td>13.7%</td>
</tr>
<tr>
<td>Deliveries</td>
<td>15</td>
<td>9</td>
<td>8</td>
<td>1</td>
<td>0</td>
<td>33</td>
<td>63</td>
</tr>
<tr>
<td>Live birth rate(LBR)</td>
<td>68.2%</td>
<td>60.0%</td>
<td>66.7%</td>
<td>-</td>
<td>-</td>
<td>60.0%</td>
<td>57.3%</td>
</tr>
</tbody>
</table>

*Segmental: regarding a piece of chromosome; **Single-double 1-12: regarding one of two entire chromosomes from number 1 to number 12; ***Single-double 13-22: regarding one or two entire chromosomes from number 13 to number 22.

suggested that low grade mosaic embryos (<50%) can have the same potential to give healthy newborn as euploid embryos and the PGDIS guidelines needs to be reconsidered. As far as we know this is the second study that provides data about the LBR of mosaic embryos (Greco et al., 2015). No deliveries were obtained from the transfer of complex mosaic embryos.

References:
1. P. Rubino, X. Li, R. Ruiz De Assin Alonso, K. Mazmanian, et al. Embryos classified as low grade mosaic (<50%) after preimplantation genetic screening (PGS) by means of high resolution next-generation sequencing (hr-NGS), can have the same competence of producing healthy newborns as euploid embryos. Fertility and Sterility, Vol. 109, Issue 3, e46-e47

P-755 Wednesday, October 10, 2018 6:30 AM

MOSAIC EMBRYO TRANSFER: A SURVEY OF CURRENT U.S. ART CLINIC PRACTICES. T. Kim,* M. F. Neblett,* L. M. Shandley,* K. Omurtag,* H. S. Hipp,* J. F. Kawwass.* Emory Reproductive Center, Emory University School of Medicine, Atlanta, GA; Reproductive Endocrinology and Infertility, Washington University School of Medicine in St. Louis, St Louis, MO.

OBJECTIVE: To characterize national mosaic embryo transfer practices. More specifically, to determine the percentage of assisted reproductive technology (ART) clinics in the United States that perform preimplantation testing for aneuploidy (PGT-A) and that transfer mosaic embryos. We also describe mosaicism cut-offs, the percentage mosaicism in an embryo that is considered for transfer.

DESIGN: Cross-sectional survey

MATERIALS AND METHODS: An anonymous 14-question survey was emailed to medical directors at 417 U.S. ART clinics with unique identification codes. Main outcomes measured were use of PGT-A, willingness to transfer mosaic embryos, and mosaicism cut-offs. Descriptive statistics were used to analyze survey responses including demographic information. Logistic regression was performed to identify clinic factors associated with reporting having ever transferred a mosaic embryo.

RESULTS: Of the 417 U.S. ART clinics contacted, 269 (64.5%) completed a survey, including 170 (63.2%) private, 56 (20.8%) academic, and 43 (16.0%) hybrid clinics. Clinics were well represented across regions in the U.S. Most clinics reported conducting PGT-A on less than 50% of all IVF cycles. The most common type of PGT-A technology used was next generation sequencing (NGS) at 90.7%. Ninety-six (35.7%) clinics receive mosaicism data on their PGT-A report; of those 96 clinics, the most common threshold for determining an embryo aneuploid by clinics’ primary genetics labs was <20% normal (35.4%) and euploid as >80% normal (44.8%). 40 (41.7%) have transferred a mosaic embryo, and 60 (62.5%) would transfer a mosaic embryo based on a global clinic policy or individual provider preference. Nearly 40% of clinics were unsure about their thresholds for mosaic transfer while about one-fourth of clinics reported they had no threshold for which they would or would not transfer a mosaic embryo. Private (odds ratio [OR] 1.1, 95% confidence interval [CI] 0.6, 2.0) and hybrid (OR 1.0, 95% CI 0.5, 2.4) clinics were just as likely as academic clinics to report having transferred a mosaic or aneuploid embryo. Clinics in the northeastern U.S. were more likely to have transferred a mosaic embryo than clinics in other regions (OR 1.7, 95% CI 1.0, 2.9). Most clinics (72.9%) report they do not have a unique consent for transfer of mosaic embryos.

CONCLUSIONS: There is variability in classification and transfer practices of mosaic embryos among U.S. ART clinics. These findings provide an opportunity to establish mosaicism thresholds and create standardized guidelines for transferring mosaic embryos.

Supported by: Emory University School of Medicine - Department of Obstetrics and Gynecology

P-756 Wednesday, October 10, 2018 6:30 AM

DISCREPANCY IN PGT-A RESULTS AMONG DIFFERENT GENETIC REFERENCE LABORATORIES: HOW ACCURATE ARE THE RESULTS AND ARE WE DISCARDING EUPLOID EMBRYOS?. F. Sharara, M. Goodwin, G. A. Abd. Virginia Center for Reproductive Medicine, Reston, VA.

OBJECTIVE: The use of pre-implantation genetic testing for aneuploidy (PGT-A) has been increasing steadily for the past few years. The policy of most programs is to discard aneuploid embryos unless they are mosaic. Most IVF centers use one preferred genetics reference laboratory to send their biopsied samples. However, there are no direct comparative data among these labs, which may use different platforms. Specifically, there is minimal data on whether the results are concordant when the same aneuploid embryo is re-biopsied and sent to a different genetic reference laboratory. This has substantial importance for counseling and clinical management.

DESIGN: Embryos donated for research after being declared as aneuploid by PGT-A testing in lab A were re-biopsied and sent to a different genetic reference laboratory (lab B). Lab B was blinded to the initial results.

MATERIALS AND METHODS: A total of 34 aneuploid embryos tested at lab A were re-biopsied, yielding 44 samples (8 were biopsied twice or three times from different areas) and sent to reference laboratory B. Of these, 30 were tested by a-CGH and 14 by NGS in lab A. All 44 samples were retested

Lab A Lab B (all NGS)

| Sample #5 | 44XX, monosomy 10 & 13 (a-CGH) | 49 XY, +11, +19, +21 |
| Sample #10 | 46XY, monosomy 2, trisomy 9 (a-CGH) | 47 XXX |
| Sample #11 | 45 XX, monosomy 17 (a-CGH) | 46 XX |
| Sample #13 | 45 XX, monosomy 11 (a-CGH) | 45 XX, monosomy 22 |
| Sample #14 | 45XX, monosomy 20 (a-CGH) | 47 XY, trisomy 19 |
| Sample #16 | 45 XY, monosomy 22 (NGS) | 45 XX, monosomy 9 |
| Sample #19 | 45XX, monosomy 22(a-CGH) | 45XX, monosomy 20 |
| Sample #23 | Complex abnormal(a-CGH) | 46XX |
| Sample #24 | Complex abnormal(a-CGH) | 46XX |
| Sample #30 | 48 XY trisomy 4, trisomy 5(a-CGH) | 46XY |
| Sample #38 | 46XX, trisomy 19, long arm deletion CMS 1 (NGS) | 46XX |

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by NGS in lab B. All biopsied samples were from the trophoectoderm and no inner cell mass biopsies were performed.

RESULTS: Of the 44 total samples, there were 16 with discrepancies between labs A and B, a 36% difference: 4 had gender differences, 7 had chromosomal differences, and most importantly, 5 were euploid (11.4%). Of the 14 NGS aneuploid samples from lab A, 12 concurred in lab B but 2 were euploid (one was reported as trisomy 4 and trisomy 5, and the other was trisomy 19 with long arm duplication on chromosome 1). We had no mosaicism data from lab A as it did not report mosaicism at the time.

CONCLUSIONS: We have found significant differences between the two reference laboratories in a small number of samples. There were gender and chromosomal differences and, most worrisome, 11.4% of the discarded embryos were euploid on repeat testing in a different laboratory. While most of the samples were a-CGH tested, discrepancies were also noted in the more robust NGS platform. This could be due to mosaicism, specifically when biopsying another area of the trophoectoderm. Our results add to the criticism of indiscriminate PGT-A testing regardless of age or, as some have suggested, whether it needs to be done at all. Our results need to be interpreted with extreme caution as it is unknown which of the two reference laboratories has the correct diagnosis (there is concern that both also could be wrong since we did not test the inner cell mass). More studies with larger numbers and comparing more than 2 reference laboratories need to be performed.

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CLINICAL OUTCOME OF PREIMPLANTATION GENETIC DIAGNOSIS(PGD) USING FISH FOR COUPLES OF RECIPROCAL AND ROBERTSONIAN TRANSLOCATIONS BETWEEN MALE AND FEMALE CARRIERS. M. Choo, H. Kim, I. Song. Reproductive Endocrinology and Infertility, Cheil General Hospital and Women’s Healthcare Center, Seoul, Korea, Republic of.

OBJECTIVE: Carriers of reciprocal and Robertsonian translocation are phenotypically normal, but they are known to be at an increased risk of chromosomally abnormal pregnancy. FISH (fluorescent in situ hybridization) has been an useful diagnostic technique for translocation carriers wishing to have babies. Using FISH, the frequency of each segregation mode differs depending on the gender of carriers. However, according to most studies, the rate of embryos with normal FISH results is not different between male and female carriers both in reciprocal and Robertsonian translocation. In PGD using FISH for carriers of reciprocal and Robertsonian translocation, is there any difference according to gender of carriers?

DESIGN: Retrospective. PGD using FISH was performed in 864 cycles of 857 couples (male carrier: 341, female carrier: 516) with reciprocal translocation, and 252 cycles of 134 couples (male carrier: 42, female carrier: 92) with Robertsonian translocation from December 1997 to July 2017.

MATERIALS AND METHODS: Patients confirmed as translocation carriers who carried ICSI cycles with PGD-FISH. We compared transferrable embryo rate (per diagnosed embryos), CPR (clinical pregnancy rate) and LBR (live birth rate) between male and female carrier in reciprocal and Robertsonian translocation, respectively.

RESULTS: In reciprocal translocation, there were no significant differences between male and female carriers with respect to transferrable embryo rate (male: 22.2% vs female: 20.3%, p=0.359), CPR (male: 24.3% vs female: 24.7%, p=0.882) and LBR (male: 18.7% vs female: 19.7%, p=0.711). In Robertsonian translocation, transferrable embryo rate was significantly higher in male than female carriers (male: 30.2% vs female: 24.9%, p=0.012). CPR (male: 20.6% vs female: 27.2%, p=0.286) and LBR (male: 16.2% vs female: 18.5%, p=0.672) did not differ between genders.

CONCLUSIONS: This data indicates the possibility of normal or balanced embryos could be decreased in female than male carrier especially with Robertsonian translocation, nevertheless the live birth rate is not different. Our data may be useful to counsel with translocation carriers for PGD.

ANALYSIS OF CHROMOSOME-SPECIFIC RESULTS FOR NEXT GENERATION SEQUENCING (NGS) OF TROPHECTODERM (TE) BIOSPIES HINTS AT MECHANISMS OF OCCURRENCE FOR SEGMENTAL ANEUPLOIDIES. D. H. McCulloh, " A. G. Besser, " C. McCaffrey, J. A. Grifo." NYU Langone Fertility Center, New York, NY; "New York University Langone Fertility Center, New York, NY; "Ob/Gyn, NYU Langone Medical Center, NY, NY.

OBJECTIVE: NGS data collected during Preimplantation Genetic Testing for Aneuploidy (PGT-A) has a lot of fluctuations (noise). The noise is smoothed by averaging the counts of many loci throughout each chromosome. The total amount of noise reduction per chromosome is inversely related to the number of loci averaged and varies with chromosome length. Therefore, it is possible that longer chromosomes could experience a higher rate of errors that SAs of the longer q arm are more common than SAs of the shorter p arm. Further analyses based on the sizes and chromosome length suggests that small chromosomal segments are susceptible to aberrant detection due to NGS noise, potentially leading to false positive PGT-A results.

MATERIALS AND METHODS: The incidences of SAs were determined for each chromosome, and compared to the known length of each chromosome. Embryos tested for single gene mutations and translocations were excluded as were embryos with nullisomies, tetrasomies. Only embryos with 1 or 2 SAs were included in the analysis.

RESULTS: 1383 embryos (13%) had SAs. There were 612 partial monosomies, 317 partial trisomies, 41 with two partial monosomies, 18 with two partial trisomies, and 76 with both a partial monosomy and a partial trisomy. Others SAs occurred with whole chromosome aneuploidies (183) or as higher order SAs (partial nulli-, tetra-, penta-, hexasomies) (136). Seventy-five percent of the SAs were reported as mosaic. The incidence of SAs for each chromosome was between 0.3 and 9.2% of the total SAs and was positively correlated with chromosome length (R=0.97, R² = 0.95, p < 0.01). SAs of the q arm were nearly twice as common as SAs of the p arm. Between 5 and 15% of the SAs spanned the centromere, including both the p and q arms.

CONCLUSIONS: The positive association between the incidence of SAs and chromosome length suggests that small chromosomal segments are susceptible to aberrant detection due to NGS noise, potentially leading to false positive PGT-A results. The high incidence of mosaicism and the observation that SAs of the longer q arm are more common than SAs of the shorter p arm and both consistent with aberrant detection due to NGS noise. Alternatively, it is possible that longer chromosomes could experience a higher rate of errors in replication leading to more actual SAs. Further analyses based on the sizes of SAs may provide some additional information.

EVALUATION OF BLASTOCOEelial FLUID, TROPHECTODERM AND INNER CELL MASS FOR CHROMOSOME ANALYSIS USING NEXT-GENERATION SEQUENCING. R. Matsunaga, 1 S. Watanabe, 2 K. Isobe, Y. Ohbuki, 3 M. Miura, 4 Y. Kobayashi, 5 M. Kamihata, 6 T. Maeda, 7 H. Makino, 8 M. Ochi, 9 T. Horiih, 8 Ochi Yume Clinic Nagoya, Nagoya, Japan; 1Department of Life Sciences, Prefectural University of Hiroshima, Hiroshima, Japan.

OBJECTIVE: The utility of BF as a source of DNA for non-invasive PGS has been previously studied. It has been reported that BF ploidy analyzed by array-comparative genomic hybridization (aCGH) corresponds with the ploidy measured in TE and the whole embryo. However, there is little positive evidence indicating that BF is useful for PGS. We evaluate blastocoelic fluid, trophectoderm and inner cell mass for chromosome analysis using next-generation sequencing.

DESIGN: Twenty, vitrified-warmed blastocysts donated for research (donor age: 26-42 years) were used for the present study. BF, TE and ICM were biopsied from each blastocyst and DNA analyzed by Next Generation Sequencing (NGS). The results from BF samples were compared with the corresponding TE and ICM samples.

MATERIALS AND METHODS: Warmw day 5/6 blastocysts were cultured and a BF biopsy collected when blastocysts had expanded to more than 160um in diameter. After BF biopsy and blastocysts re-expansion, ICM was separated from TE by laser pulses. NGS was used to determine concordance rates for whole chromosome copy number between these three samples.

RESULTS: The amplification rate of BF samples after whole genome amplification (WGA) was 60% (12/20). Fifteen of 20 (75.0%) of the ICM samples were 100% concordant and two samples were partially concordant with (cases where the ploidy condition was confirmed, but not all single chromosomes corresponded) TE samples from the same embryos. Three blastocysts were discordant between ICM and TE. The full concordance rate between BF and ICM was 25.0% (3/12) and between BF and TE was 8.3% (1/12). The partial concordance rate between BF and ICM was 16.7% (2/12) and between BF and TE was 25% (3/12). The discordance rates were 58.3% (7/12) and 66.7% (8/12) respectively. Five out of 6 BF samples (83%) from blastocysts were aneuploid or mosaic whereas corresponding ICM and TE were characterized as euploid.

CONCLUSIONS: The chromosomal status of BF samples shows low concordance with ICM and TE samples from the same blastocysts. BF is not a valid source of DNA for chromosomal testing.
STRATEGIES TO ACHIEVE COMBINED NON-INVASIVE PGT-M AND PGT-A ON SPENT CULTURE MEDIA USING TARGET SEQUENCE ENRICHMENT. C. Robinson M. J. Jasper. RHS Ltd, Thebarton, Australia.

OBJECTIVE: Challenges to the clinical use of non-invasive preimplantation genetic testing for aneuploidy (PGT-A) include achieving high concordance between the spent embryo culture media and embryo biopsy results and also the ability to distinguish contaminating maternal DNA from the embryonic DNA. Combining Whole Genome Amplification (WGA) along with specific primers in a single PCR reaction allows both aneuploidy detection (PGT-A) and targeted higher resolution Next Generation Sequencing (NGS). Using DOPify and RHS’ Target Sequence Enrichment (TSE) protocol provides a strategy to combine monogenic disease detection (PGT-M) with PGT-A.

DESIGN: The aim of this study was to demonstrate the development of a multiplexed PCR primer panel for novel sequence enrichment of DNA contained in spent embryo culture media for combined PGT-M and PGT-A.

MATERIALS AND METHODS: Spent embryo culture media was collected by clinics under their ethics approval from single embryo culture droplets and stored at -20°C. To accommodate the biochemical composition of culture media and the presence of known PCR inhibitors, samples were amplified using a re-formulated version of DOPify. Furthermore, the TSE protocol (RHS Ltd) was added with the inclusion of sequence specific PCR primers for BRCA1 (PCR products 192-286bp) and Haemoglobin subunit beta (HBB) for β-Thalassemia mutation detection (PCR products 454-554bp). Enrichment of the target sequence during WGA was confirmed using multiplex PCR and the specific PCR products generated were pooled (~1:10) back in with the original WGA with TSE DNA prior to sequencing using a single index. Sequencing was performed according to the standard PG-Seq 48 sample protocol on a MiSeq sequencer (Illumina) and data was bioinformatically aligned to hg19, analysed using PG-Seq software and viewed using Integrative Genomics Viewer (Broad Institute).

RESULTS: The re-formulated DOPify improved DNA yield and also amplified mitochondrial DNA from spent culture media with output measures becoming comparable to biopsy results. Enrichment of the target BRCA1 and HBB sequences was confirmed by semi-quantitative sequence specific PCR and NGS and results compared to the control spent culture media sample (WGA only). Coverage and read depth of BRCA1 and HBB sequences was optimised through the dilution of multiplex PCR products pooled with the WGA with TSE DNA prior to sequencing.

CONCLUSIONS: The targeted and concurrent enrichment of multiple clinically relevant sequences using PCR panels during DOPify WGA for non-invasive PGT from spent embryo culture media provided a mechanism to generate PGT-M results while also providing aneuploidy information. Further incorporation of primers targeting the amplification of single nucleotide polymorphisms would provide a mechanism to detect maternal DNA within a spent culture media sample.
ACCURATE COMBINED PREIMPLANTATION GENETIC TESTING WITH DOPIFY AND TARGET SEQUENCE ENRICHMENT: S. Protopsaltis, K. A. Warren, M. J. Jasper. RHS Ltd, Thebarton, Australia.

OBJECTIVE: Allele Drop Out (ADO), or failed PCR amplification of one or both alleles, presents a significant risk of misdiagnosis or the return of a “no result” for preimplantation genetic testing of monogenic diseases (PGT-M). Although a PGT-M result may indicate that an embryo is unaffected by a monogenic disease, standard PGT-M methods are unable to assess aneuploidy and up to 50% of these transferred embryos may be aneuploid1. Combining Whole Genome Amplification (WGA) along with gene-specific primers in a single reaction to allow both aneuploidy detection (PGT-A) and monogenic disease detection (PGT-M) is an advantage of DOPify and RHS’ Target Sequence Enrichment (TSE) protocol.

DESIGN: This study aims to compare ADO rates across three different approaches; Gene Specific PCR only, DOPify WGA only and DOPify WGA with TSE.

MATERIALS AND METHODS: Thirty 5-cell aliquots were manually sorted from cell line GM14090 containing a 2bp heterozygous BRCA1 mutation on chromosome 17 and aneuploid cell line GM04965, 48,XXY,+21 (Coriell Institute). For the Gene Specific PCR only approach, cells were subjected to a round of sequence specific PCR using multiplex PCR (Qiagen) and three sets of BRCA1 primers. One BRCA1 primer set amplifies the region containing the 2bp deletion and the other two primer sets amplify linked markers. For the DOPify WGA only approach, cells were amplified according to standard protocol with no BRCA1 primers added. For the DOPify WGA with TSE approach, cells were amplified with the inclusion of the three BRCA1 primer sets according to the DOPify TSE protocol. PCR products from the three approaches were then diluted 1/10 and seeded into a second sequence specific multiplex PCR using the three sets of BRCA1 primers to generate sufficient DNA for sequencing. Presence, allele frequency and read depth of the 2bp heterozygous deletion and the linked markers were measured to assess ADO.

RESULTS: The allele frequency and read depth for the three PCR approaches for GM14090 are listed in the table below. The linked marker primer sets were less efficient in the multiplex PCR, as evidenced by their lower read depth. These results may be improved with further multiplex optimisation and deeper sequencing. Correct aneuploidy results were obtained for all cells processed with the DOPify TSE protocol which passed sequencing quality control.

CONCLUSIONS: DOPify with TSE enables a sensitive and reliable PGT-M result; showing no ADO in any of the three regions amplified by the sequence specific primers and linked markers, while also providing accurate PGT-A information from a single embryo biopsy.

References: Goldman et al. J Genet Couns 2017;25:1327-37

<table>
<thead>
<tr>
<th>Allele Frequency and Read Depth</th>
<th>Gene Specific PCR Only (PGT-M)</th>
<th>DOPify Only (PGT-A)</th>
<th>DOPify with TSE (PGT-M and PGT-A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of both alleles/number passed</td>
<td>BRCAl 2bp Deletion</td>
<td>10/10</td>
<td>7/9</td>
</tr>
<tr>
<td>QC (read depth &gt;10)</td>
<td>D17S855</td>
<td>9/9</td>
<td>9/9</td>
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<td>Allele frequency (%)</td>
<td>D17S1185</td>
<td>8/8</td>
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<td>BRCAl 2bp Deletion</td>
<td>47.1</td>
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<td>Read Depth</td>
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OBJECTIVE: When an embryo biopsy is performed prior to Preimplantation Genetic Testing for Aneuploidy (PGT-A), the biopsy is washed in PBS or similar buffer to remove residual culture media before being placed in a tube for Whole Genome Amplification (WGA). The amount of buffer transferred to the tube can vary from the recommended amount (<2 µL) to a larger volume. It is unknown what effect increased volumes of transfer buffer have on the WGA and subsequent PGT-A test result.

DESIGN: This study aimed to determine the maximum volume of PBS that can be transferred into a tube with an embryo biopsy without compromising WGA using DOPify.

MATERIALS AND METHODS: To replicate the effect of transferring different volumes of buffer with an embryo biopsy, a 5-cell equivalent amount of human genomic DNA (30pg, Promega) had incremental volumes of PBS (0-10 µL) added before standard DOPify WGA (RHS Ltd). This was then repeated with 5-cell aliquots manually sorted from a 48,XXY,+21 cell line (GM04965, Coriell Institute) to determine the effect on cells representing a trisomy/dysmorphic embryo. Larger volume 40µL DOPify reactions were also performed on 5-cell aliquots with an additional 0-20 µL of PBS added. WGA DNA was processed for PGT-A using the standard PG-Seq 48 sample protocol for MiSeq sequencing. Intensity of the WGA PCR product smear, DNA yield and karyotype after sequencing were analysed.

RESULTS: A DNA smear was visualised for all genomic DNA 25 µL DOPify amplifications with yields decreasing significantly (P <0.05) when 5 µL or more of PBS was added prior to the WGA reaction. A similar result was observed with the 5-cell aliquots, with the DNA yield decreasing as the volume of additional PBS increased; from 47 ng/µL with no PBS added to 8 ng/µL after 10µL of PBS was added. A significant decrease in yield (P<0.05) compared to the standard was observed after the addition of 6 µL of PBS. The correct karyotype results were obtained following the addition of 6 µL and 7 µL PBS, suggesting a reduction in WGA yield does not necessarily compromise the PGT-A test result. Expected PCR yields and correct karyotypes were obtained for the 40 µL master mix amplifications for all additional PBS volumes up to and including 8 µL however WGA yields dropped considerably for volumes higher than this.

CONCLUSIONS: The efficiency of the WGA PCR is impacted by the volume of transfer buffer accompanying the embryo biopsy. Transfer buffer volumes of up to 5µL can be transferred into a tube with an embryo biopsy with no decrease in yield or adverse result after standard 25 µL DOPify WGA. However, for transfer buffer volumes greater than 5 µL it is recommended that the WGA reaction volume is increased to 40 µL.

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SIMULTANEOUS DETECTION OF CHROMOSOMAL ANEUPLOIDY AND A MONOGENIC DISEASE BY NEXT-GENERATION SEQUENCING WITH LINKAGE ANALYSIS. M. Cetinkaya, M. Tufekci, B. Umay Kara, Y. Kumtepe Colakoglu, S. Kahraman. Assisted Reproductive Technologies and Reproductive Genetics Center, Istanbul Memorial Hospital, Istanbul, Turkey.

OBJECTIVE: The current approaches for PGT-M generally uses standard panels pre-designed for each disease. The present study applied whole genome amplification (WGA) of biopsied trisomy/dysmorphic cells and concurrent next-generation sequencing (NGS)-based single nucleotide polymorphism (SNP) haplotyping on an Ion Torrent Personal Genome Machine (PGM) with the aim of customized testing for each family.

DESIGN: Exome sequencing data of a consanguineous family applying for ART (mother, father and child), who gave their informed consent, was used to establish the haplotype of the thalassemia gene locus-based on informative SNPs by using the VcTools and R software.

<table>
<thead>
<tr>
<th>Gene Specific PCR Only (PGT-M)</th>
<th>DOPify Only (PGT-A)</th>
<th>DOPify with TSE (PGT-M and PGT-A)</th>
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</tr>
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<td>Read Depth</td>
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<td></td>
<td>77±49</td>
<td>14±36</td>
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OBJECTIVE: It has been established that embryos diagnosed as chromosomally mosaic can result in healthy babies. Our aim was to assess whether embryos mosaic for a segmental aneuploidy (MS; including both deletions and duplications) and whole chromosome aneuploidy (MWC) may have different reproductive potential. We compared the reproductive potential of MS embryos to MWC embryos to determine whether the type of mosaicism impacts risks for potential offsprings.

MATERIALS AND METHODS: A total of 88 loci containing 116 SNPs located 2 Mb upstream and 2 Mb downstream of the beta globin gene locus (HBB) were selected for NGS-based SNP haplotyping. These loci were then submitted to a primer design website (www.amplicseq.com); Thermo Fisher Scientific. The WGA products of three embryos generated during the IVF cycle of the couple and which were diagnosed as aneuploid were used for the Amplicon Library Preparation in addition to the genomic DNA of the child (using Ion AmpliSeq™ Library kits) for PGT-M and in parallel for PGT-A. To validate the SNP-based haplotype, a STR markers-based haplotype was also established.

RESULTS: The SNP-based haplotypes of the tested embryos and of the child were successfully constructed by NGS with linkage analysis, using GeneHunter v2.15 software. Out of the three embryos tested with family customized PGT-M panel, the first embryo was found to be haploidogenous with the child for the HBB locus. The second embryo shared only the paternal allele, whereas the third embryo was carrying the other parental alleles when compared to the child’s alleles. These haplotypes were also verified by classical STR marker-based haplotyping. Read depth of amplicons ranged between 70 and 6800. The parallel PGS diagnoses of the three embryos were identical with the original diagnoses of the respective embryos. The variations of SNP call rates and read depths of the trophectoderm samples were correlated with library concentrations.

CONCLUSIONS: In conclusion, this approach allows for a successful simultaneous detection of chromosomal aneuploidy and a monogenic disease by NGS with linkage analysis. Especially in but not limited to consanguineous families, establishing family-specific gene panels for PGT-M maximizes allelic information with a minimum number of SNPs without the need for direct mutation testing thus lowering the cost of testing per embryo.

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ORIGIN OF FALSE POSITIVES AND FALSE NEGATIVES IN NON-INVASIVE PREIMPLANTATION GENETIC TESTING FOR ANEUPLOIDIES. C. Rubio Lluesa,a L. F. Rienzi, L. Navarro Sanchez,a D. Chimadomo, C. M. Garcia-Pascual,a D. Soscia,b L. Martinez-Merino,a A. Capalbo,a F. Ubaldi,d C. Simon,b PGT Research, Igenomix, Paterna, Spain; aIVF Laboratory, Genera, Rome, Italy; bPGT Research, Igenomix, Marostica, Italy; cIVF Clinician, Genera, Rome, Italy; dValencia University, Igenomix, Paterna, Spain.

OBJECTIVE: Recent studies have reported the existence of embryonic cell-free DNA in the spent culture media, with results that vary widely among different groups, opening a new era of possibilities for non-invasive preimplantation genetic testing of aneuploidies (niPGT-A). Our objective was to analyse false positive and false negative rates according to the number and type of aneuploidies found in the embryonic DNA of the spent culture media versus the results of the trophectoderm biopsy.

DESIGN: Prospective study performed from November 2017 to March 2018, analysing paired samples of trophoderm biopsies and spent culture media from 112 blastocysts. Analysis of both types of samples from each blastocyst was performed blindly.

MATERIALS AND METHODS: Blastocyst biopsies were performed on days 5 (33 blastocysts), day 6 (69 blastocysts), or day 7 (10 blastocysts). Spent culture media was collected individually from each blastocyst just before biopsy, without any prior embryo manipulation. Both spent culture media and trophectoderm biopsies were analysed by Next Generation Sequencing using the Ion ReproSeq PGS Kit (ThermoFisher Scientific) with a modified protocol to improve amplification efficiency.

RESULTS: Informative results were obtained in 106 out of 112 spent culture media (94.6% overall successful amplification); 81.8% successful amplification in spent culture media from day 5 blastocysts and 100% amplification from day 6/7 blastocysts. Overall concordance rate between trophectoderm biopsies and spent culture media in terms of aneuploidy or euploidy diagnosis was 78.3%: 63.0% for day 5 and 83.5% for day 6/7 blastocysts. Regarding the discrepancies, only 3 false negatives were observed in the spent culture media compared to the trophectoderm biopsy (3.7% false negative rate for day 5 and 2.5% for day 6/7 blastocysts). Two of them were clearly the result of contamination with maternal DNA, and the third one corresponded to a mosaic trophectoderm biopsy. In all three cases, only one aneuploid chromosome was observed. There were 15 false positives: 29.6% for day 5 and 8.9% for day 6/7 embryos. Interestingly, more than half of them showed chaotic profiles with 6 or more aneuploid chromosomes (50.0% and 51.7% of the day 5 and day 6/7 false positives, respectively). The chromosomes showing the higher false positive rates were 8, 12, 17 and 20.

CONCLUSIONS: High concordance rates were achieved with niPGT-A, mostly in day 6/7 embryos. The higher incidence of amplification failures and false positives at day 5, suggest that low embryonic DNA concentration on the media account for the poorer results obtained. The niPGT-A approach would help patient’s access to aneuploidy testing by avoiding the need of invasive biopsy techniques and by reducing the cost of the procedure.

Supported by: This study has been funded by Igenomix and GENERA Centres for Reproductive Medicine
THE INCREASE IN THE ANEUPLOIDY RATE IN EMBRYOS IS MOSTLY DUE TO AN ABSOLUTE DECREASE IN THE NUMBER OF EUPLOID EMBRYOS. T. Escudero S. Munne. Research, CooperGenomics, Livingston, NJ.

OBJECTIVE: This increase on the aneuploidy rate could with the advance of the maternal age could be cause by either an increase of aneuploid embryos per cycle or by a reduction on the absolute number of euploid embryos per cycle. The objective of this study is to ascertain if the source of increase in the rate of aneuploid embryos with advancing maternal age is due to one or the other.

DESIGN: Retrospective study

MATERIALS AND METHODS: Retrospective study of 55,403 embryos from 10,497 cycles from 2013 to 2017, from 126 IVF centers analyzed by Next Generation Sequencing (NGS). Embryos were classified by their diagnosis into: euploid, mosaic, complex mosaic, aneuploid, complex aneuploid, “mosaic and aneuploid”, and mixed complex. Cycles were distributed in age groups (<35, 35-37, 38-40, 41-42, >42) plus an egg donor group. For each age group, the average and standard deviation of each type of embryo per cycle were obtained. ANOVA analysis was applied to compare the difference “between” age groups and “inside” age groups for the different types of embryos, Pearson C values were obtained to study the degree of correlation of average number of the different types of embryos with age.

RESULTS: The results are summarized in table 1. Euploid and “mosaics with a euploid” line showed strong negative correlations with maternal age but aneuploid and “aneuploid and mosaic” only showed a mild increase with the bulk of the increase in aneuploidy rates being caused by a decrease in euploid embryos, not an increase in aneuploid ones.

CONCLUSIONS: The dramatic decrease in aneuploidy rates is mostly cause by a decrease in euploid embryos, not an increase in aneuploid ones. That is, there are no more aneuploid eggs made or recruited with age but fewer euploid ones, with euploid ones almost exhausted after age 42. The observation that aneuploid embryos are almost constant with age suggest a different causative mechanism than one in which aneuploid embryos would increase with age and euploid ones remain constant or decrease. Mosaics, being post-meiotic are just a fraction of euploid or aneuploid ones, and thus increase or decrease with them.

Supported by: N/A

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OBJECTIVE: Methods for preimplantation genetic screening of embryos have evolved from FISH to microarrays and most recently to next-generation sequencing (NGS). Here we report the first application of nanopore-based sequencing for preimplantation genetic screening (PGS) on trophoderm biopsy samples using a rapid multiplex short-read MinION sequencing library preparation. The objective of this study is to determine if a handheld, nanopore-based, third-generation DNA sequencer can be used for rapid preimplantation genetic screening (PGS).

DESIGN: In vitro study

MATERIALS AND METHODS: Using a self-developed short-read DNA library preparation and data analysis protocol, we performed nanopore-based sequencing using a hand-held MinION DNA sequencer. Briefly, the novel library preparation method consisted of whole-genome amplification, end preparation with subsequent purification, and 1-step barcode and sequencing adapter ligation, also with subsequent purification. Genomic DNA from trophoderm biopsy samples (n=9) was also subjected to SurePlex whole genome amplification (WGA) and tested using traditional next-generation sequencing (NGS) at a reference laboratory. Samples included 3 normal samples (two normal males and one normal female); 2 samples with aneuploidy of a single chromosome (one female Monosomy 22, one female Trisomy 19), and 4 samples with aneuploidy on more than one chromosome (a female with Trisomy 22 and Monosomy X, a female with Trisomy 13 and Monosomy 14, a male with XXY and Trisomy 15, and a female with Mosaic Trisomy 6, Monosomy 15 and Monosomy 18). We then compared the predicted karyotype results from NGS and nanopore-based sequencing and the time required for library preparation and sequencing.

RESULTS: Bar-coded, multiplexed, short-read DNA library preparation was completed in 45 minutes. Sequencing times varied from 1 to 2 hours. Whole-chromosome aneuploidy screening results obtained from nanopore-based sequencing were identical to those obtained using NGS.

CONCLUSIONS: Aneuploidy screening could be performed on 5 samples in one nanopore flow cell with 1 to 2-hour sequencing times. These times compare favorably with NGS library preparation (>3.5 hours) and sequencing (>12 hours) times. Overall, MinION nanopore sequencing is a promising tool to perform rapid PGS assay onsite with a rapid turnover time, enabling same-day testing and embryo transfer thus obviating the need for complex, large and expensive DNA sequencers or frozen embryos.

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OBJECTIVE: Assess relationships, if any, between embryo ploidy and the mean diameter of the follicle from which the oocyte originated.

DESIGN: IRB-approved prospective observational cohort study

MATERIALS AND METHODS: Patients underwent routine ovarian stimulation with exogenous gonadotropins. During oocyte collection, follicle diameters were sonographically measured on two perpendicular axes, and the mean was calculated for each follicle. Embryos were group cultured to the blastocyst stage according to mean follicle diameter (≤9.5, 10-12.5, 13-15.5, 16-18.5, 19-21.5, 22-24.5, 25-27.5, and ≥28mm). Next-generation sequencing (NGS) followed trophectoderm biopsy. Chi-square analysis compared aneuploidy rates among follicle diameter groups. Stepwise logistic regression was used to identify significant predictors of aneuploidy. P<0.05 was considered significant.

RESULTS: There were 318 blastocysts derived from measured follicles that had definitive NGS results (normal or abnormal), while 4 embryos with no test result were excluded. Of the 318 included blastocysts, 169 had normal (euploid) copy numbers and 149 had abnormal (aneuploid) copy numbers. Chi-square analysis found no relationship between aneuploidy and follicle size group (P=0.46). Among variables available for logistic regression, only patient age was retained in the logistic model (P=0.0020), while mean follicle diameter and blastocyst morphology parameters (blastocyst expansion, ICM, and trophectoderm quality) were not significant.

CONCLUSIONS: Among blastocysts selected for biopsy, the diameter of the originating follicle was not a significant predictor of embryo ploidy.

<table>
<thead>
<tr>
<th>Mean follicle diameter</th>
<th>Blastocysts</th>
<th>Euploid blastocysts</th>
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<tbody>
<tr>
<td>≤9.5mm</td>
<td>12</td>
<td>5 (41.7%)</td>
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<tr>
<td>10-12.5mm</td>
<td>32</td>
<td>17 (53.1%)</td>
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<td>13-15.5mm</td>
<td>51</td>
<td>29 (56.9%)</td>
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<td>16-18.5mm</td>
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<td>22-24.5mm</td>
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<td>25-27.5mm</td>
<td>15</td>
<td>10 (66.7%)</td>
</tr>
<tr>
<td>≥28mm</td>
<td>10</td>
<td>6 (60.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>318</td>
<td>169 (53.1%)</td>
</tr>
</tbody>
</table>

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CHROMOSOMAL ABNORMALITIES DEMONSTRATED BY IN-VIVO CONCEIVED & CULTURED HUMAN EMBRYOS. S. B. Munne, S. T. Nakajima, S. Najimbadi, M. V. Sauer, J. Rivas, J. Robins, L. P. Shulman, T. Escudero, A. Nadal, T. M. Macaso, J. E. Baster, CooperGenomics, Livingston, NJ; Ob/Gyn, Stanford Medical Center, Sunnyvale, CA; Center For Reproductive Health & Gynecology, Beverly Hills,
OBJECTIVE: In vitro conceived embryos have a high rate of chromosome abnormalities, increasing with advancing maternal age, but also influenced by iatrogenic factors including the assisted reproductive technology (ART) process itself. However, the rate of chromosome abnormalities of in vitro conceived & cultured blastocysts is unknown.

DESIGN: We performed a prospective study of women (n=64) to determine the frequency of chromosome abnormalities of in-vivo conceived embryos using a new uterine lavage system (Previvo Genetics, Inc). All lavages were performed in Punta Mita, Mexico during August 2017 to March 2018.

MATERIALS AND METHODS: Subjects were pretreated with oral contraceptives & stimulated with gonadotropins for 104 treatment cycles. The 64 were performed in Punta Mita, Mexico during August 2017 to March 2018.

RESULTS: A total of 104 uterine lavage cycles yielded 111 embryos. Of those, 77 (69%) were blastocysts & the other 34 (31%) were multi-cell. A majority of multi-cell embryos did not yield PGT-A results & were excluded from the study, while 95% (73/77) of blastocysts were analyzed. Of those 39% (24/73) were euploid, 16% (12/73) were low-mosaic (20-40% abnormal), 7% (5/73) were high-mosaics (>40% abnormal), & the remaining 41% (30/73) were aneuploid.

CONCLUSIONS: Work on the range of chromosome abnormalities in in-vitro conceived & cultured egg donors across ART centers was performed with aCGH which would classify low mosaics as normal. Grouping euploid & low-mosaic in-vivo embryos, the rate of "aCGH-normal" embryos would be 51% (38/73), compared to 40-80% for ART embryos. However, one must consider that after the lavage procedure, residual hCG production was detected despite GnRH antagonist administration and uterine curettage, suggesting some euploid embryos may not have been included in the study. We conclude that the rate of chromosome abnormalities in in-vitro conceived embryos is within range of in-vitro conceived ones.

Supported by: Previvo Genetics Inc. San Carlos, California, USA

P-774 Wednesday, October 10, 2018 6:30 AM

BLASTOCYST ACCUMULATION FOR PREIMPLANTATION GENETIC TESTING: EFFECTIVE APPROACH IN ADVANCED REPRODUCTIVE AGED WOMEN. M. Deyeza, A. N. P. Polyzos, B. Coroleu, J. Rodriguez-Purata, L. Coll, I. Rodriguez, P. Barri, Obstetrics, Gynecology and Reproduction, Hospital Universitario Dexeus, Barcelona, Spain; Obstetrics, Gynecology and Reproduction. Hospital Universitario Dexeus, Barcelona, Spain; Dexeus University Hospital, Barcelona, Spain.

OBJECTIVE: One of the main limiting factors in preimplantation genetic testing for aneuploidies (PGT-A) for advanced maternal age is not having enough available embryos for biopsy in order to find at least 1 euploid blastocyst.

This study aims to analyse, for the first time, the potential benefit of blastocyst accumulation in PGT-A in women of advanced reproductive age.

DESIGN: Retrospective study performed in a University-affiliated fertility clinic. 284 women aged ≥38 years undergoing PGT-A were included. According to our policy of blastocyst accumulation and to the expected age-related aneuploidy rate, patients with >4 blastocysts in the first cycle didn’t undergo further stimulations (group "≥4 no acc"), whereas women with ≤4 blastocysts in the first stimulation were recommended to accumulate: 45% accumulated (group "≤4 acc"), 55% didn’t (group "≤4 no acc").

MATERIALS AND METHODS: Group "≥4 no acc": n=107. Group "≤4 acc": n=19. Group "≤4 no acc": n=98. Trophoectoderm biopsy was performed at blastocyst stage, blastocysts were vitrified and comprehensive chromosome testing was done with aCGH. Patients with >1 euploid blastocyst might have done >1 embryo transfer; therefore main outcome is expressed as CPR/patient. Categorical variables were compared with Chi-Square test, continuous variables with ANOVA, in case of a significant test, Bonferroni multiple comparisons adjustment was performed.

RESULTS: Age, antral follicle count (AFC) and AMH, did not differ significantly between groups "≤4 acc" and "≤4 no acc". Mean age of patients of group "≥4 no acc" was significantly lower compared to "≤4 acc" and "≤4 no acc" (40 vs. 40.9 vs. 40.7, respectively). AFC and AMH were significantly higher in patients of group "≥4 no acc" compared to the other groups (AFC: 15.9 vs. 12.2 vs. 12; AMH: 3 vs. 1.8 vs. 1.8, respectively). Mean number of biopsied embryos was similar in "≥4 no acc" and "≤4 acc" (7.1 and 6.7, respectively) but significantly lower in "≤4 no acc" (2.4). Mean number of euploid embryos was 2.2 in group "≥4 no acc", 1.5 in "≤4 acc" and 0.6 in "≤4 no acc" (p=0.001). The probability of having ≥1 euploid embryo was 84% for "≥4 no acc", 71% for "≤4 acc" and 44% for "≤4 no acc". Out of the patients that accumulated, 29% didn’t have any euploid embryo, 28% had it not in the first but in subsequent stimulations. CPR/patient was 68% in "≥4 no acc", 48% in "≤4 acc" and 26% in "≤4 no acc" (OR between groups "≥4 acc" and "≤4 no acc"=2.5, 95% CI [1.3-4.8]).

CONCLUSIONS: According to our results, PGT-A should be offered to advanced reproductive aged women with a good profile of ovarian reserve markers or willing to undergo several stimulation cycles. If not so, PGT-A should be proposed with caution as, if ≤4 blastocysts are obtained, CPR/patient do not reach 30%.

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EMBRYO QUALITY AND RATE OF DEVELOPMENT AS PREDICTIVE TOOLS FOR EMBRYO SELECTION. C. R. MacDonough, R. Halverson, N. A. Klein, G. D. Ball. Seattle Reproductive Medicine, Seattle, WA.

OBJECTIVE: This study was designed to examine the relationship between embryo quality, day of biopsy, and ploidy; with the goal of improving embryo selection criteria for frozen embryo transfer (FET).

DESIGN: In this retrospective study, data were collected from 696 patients who underwent 904 autologous preimplantation genetic testing - aneuploidy (PGT-A) cycles between 2015 and 2017. Variables included for analysis were patient age, embryo morphology and day of trophoderm biopsy. Only good and fair embryos based on SART criteria were considered for biopsy. A total of 3,502 embryos were biopsied and analyzed.

MATERIALS AND METHODS: Blastocysts from autologous oocytes were assessed for morphology prior to undergoing trophoderm biopsy on day 5 or day 6. All embryos were then vitrified and ploidy assessed by a third party testing laboratory using array comparative genetic

### Statistical Comparisons Within Age Groups (*p<.01)

<table>
<thead>
<tr>
<th>Patient Age</th>
<th>Day 5 GOOD</th>
<th>Day 6 GOOD</th>
<th>Day 5 FAIR</th>
<th>Day 6 FAIR</th>
<th>Total Embryos Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>75% (322/429)*</td>
<td>72% (248/345)*</td>
<td>58% (70/119)*</td>
<td>58% (115/197)*</td>
<td>1090</td>
</tr>
<tr>
<td>35-37</td>
<td>66% (287/437)*</td>
<td>60% (180/300)*</td>
<td>53% (59/111)*</td>
<td>41% (75/181)*</td>
<td>1029</td>
</tr>
<tr>
<td>38-40</td>
<td>55% (190/346)*</td>
<td>44% (129/294)*</td>
<td>41% (48/116)*</td>
<td>31% (65/211)*</td>
<td>967</td>
</tr>
<tr>
<td>&gt;40</td>
<td>37% (58/158)*</td>
<td>28% (31/109)*</td>
<td>21% (10/47)*</td>
<td>16% (16/102)*</td>
<td>416</td>
</tr>
<tr>
<td>Overall</td>
<td>63% (857/1370)*</td>
<td>56% (588/1048)*</td>
<td>48% (187/393)*</td>
<td>39% (271/691)*</td>
<td>3502</td>
</tr>
</tbody>
</table>
hybridization, next-generation sequencing, or single-nucleotide polymorphism microarray. Patients who utilized monogenic preimplantation genetic testing were not included in this study. Mosaic (0.14%) and inconclusive (1.04%) results were excluded from the data set. Statistical comparisons were made by Chi-Square analysis. RESULTS: The average age of autologous patients was 36.7. An average of 3.9 embryos were biopsied per cycle. Good quality embryos that were biopsied on day 5 showed the highest euploid rate of 63% (857/1370). Good quality embryos biopsied on day 6 had a euploid rate of 56% (388/1048). Fair quality embryos were significantly less likely to yield euploid results, with embryos biopsied on day 5 returning a euploid rate of 48% (187/393) and embryos biopsied on day 6 returning a euploid rate of 39% (271/691). When stratified by age, this trend held significance (p < 0.01).

CONCLUSIONS: Establishing a hierarchy of embryo quality and rate of development can help guide embryo selection for frozen embryo transfers for patients who did not utilize PGT. These data suggest that in the absence of PGT, embryo quality is the single most important factor in selecting a euploid embryo for transfer, while rate of development to the blastocyst stage should be considered secondarily. Further studies will be necessary to identify other laboratory and clinical factors that contribute to the success of an FET cycle.

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COMPARISON OF IMPLANTATION RATES OF EUPLOID EMBRYOS BASED ON DAY OF BIOPSY AND PATIENT AGE. C. Hibray, C. R. MacDonough, R. Halverson, N. A. Klein, G. Ball. Seattle Reproductive Medicine, Seattle, WA.

OBJECTIVE: To compare implantation rates between frozen embryo transfer (FET) cycles when transferring a single euploid blastocyst biopsied on day 5 or day 6 across different age groups.

DESIGN: Retrospective cohort study.

MATERIALS AND METHODS: Between January 2015 and December 2017, implantation rates for preimplantation genetic testing for aneuploidy (PGT-A) screened embryos were evaluated for 699 FET cycles. The selected FET cycles had one embryo transferred that had been biopsied and frozen on day 5 (D5) or day 6 (D6). The average patient age at time of cryopreservation for the autologous embryos frozen on D5 was 35.9 years and on D6 was 36.0 years. Only good or fair grade blastocysts using the SART embryo grading system were biopsied and vitrified. Ploidy was determined by either array comparative genomic hybridization, next-generation sequencing, or single-nucleotide polymorphism microarray. Implantation was defined as presence of an intrauterine gestational sac after 6 weeks gestation. Group comparisons were made using Chi-Square analysis.

RESULTS: A total of 699 warmed euploid blastocysts were transferred individually on day 5 (n=425) or day 6 (n=274). Overall, euploid FET implantation rates were significantly higher for embryos biopsied on D5 compared to those biopsied on D6 (66% vs. 55%, p < 0.01). Implantation rates for patients age <35 years were not significantly different (p>0.05) between the embryos biopsied on D5 with rates of 60% (n=121) and rates of 57% on D6 (n=90). Implantation rates for patients age 35-37 years were significantly different (p<0.05) with rates of 68% on D5 (n=121) and 54% on D6 (n=84). Similarly, patients age 38-40 years also showed a significant difference (p<0.01) with rates of 74% on D5 (n=112) and 54% on D6 (n=74). There was no difference in implantation rates for patients >40 years (p>0.5) with rates of 57% on D5 (n=47) and 58% on D6 (n=26).

CONCLUSIONS: Overall implantation rates were higher for embryos biopsied and vitrified on day 5 versus day 6. When the data were stratified by age, there was a clear trend of higher implantation for all age groups except >40 for day 5 embryos versus day 6 embryos. However, statistical significance was reached only in the 35-37 and 38-40 age groups. Day of embryo biopsy should be considered when selecting embryos for FET. Further study will be needed to determine if this trend holds true for all age groups and if embryo quality plays a role in implantation.

Table 1

<table>
<thead>
<tr>
<th>ANALYZED FACTOR</th>
<th>EUPLOID</th>
<th>ANEUPLOID</th>
<th>MOSAICISM</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age &lt;30</td>
<td>108 (57.8%)</td>
<td>26 (13.9%)</td>
<td>53 (28.3%)</td>
<td>NS (0.124)</td>
</tr>
<tr>
<td>Maternal age 30-34</td>
<td>47 (55.3%)</td>
<td>18 (21.2%)</td>
<td>20 (23.5%)</td>
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</tr>
<tr>
<td>Maternal age 35-39</td>
<td>71 (32.3%)</td>
<td>82 (37.3%)</td>
<td>67 (30.4%)</td>
<td></td>
</tr>
<tr>
<td>Maternal age &gt;40</td>
<td>23 (14.1%)</td>
<td>107 (65.6%)</td>
<td>33 (20.3%)</td>
<td></td>
</tr>
<tr>
<td>PGT-A indication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced maternal age (≥ 38 y/o)</td>
<td>42 (19.2%)</td>
<td>129 (58.9%)</td>
<td>48 (21.9%)</td>
<td>NS (0.325)</td>
</tr>
<tr>
<td>Recurrent pregnancy loss (≥ 2 miscarriages)</td>
<td>16 (36.4%)</td>
<td>16 (36.3%)</td>
<td>12 (27.3%)</td>
<td></td>
</tr>
<tr>
<td>Repeated implantation failure</td>
<td>27 (39.1%)</td>
<td>21 (30.5%)</td>
<td>21 (30.4%)</td>
<td></td>
</tr>
<tr>
<td>Time to pregnancy</td>
<td>155 (54.4%)</td>
<td>49 (17.2%)</td>
<td>81 (28.4%)</td>
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<tr>
<td>Presence of male factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male factor</td>
<td>63 (34.3%)</td>
<td>72 (39.1%)</td>
<td>49 (26.6%)</td>
<td>NS (0.799)</td>
</tr>
<tr>
<td>No male factor</td>
<td>165 (41.4%)</td>
<td>130 (33.0%)</td>
<td>101 (25.6%)</td>
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<tr>
<td>Day of biopsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 5 biopsy</td>
<td>47 (44.7%)</td>
<td>28 (26.7%)</td>
<td>30 (28.6%)</td>
<td>NS (0.939)</td>
</tr>
<tr>
<td>Day 6 biopsy</td>
<td>130 (38.6%)</td>
<td>112 (33.2%)</td>
<td>95 (28.2%)</td>
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</tr>
<tr>
<td>Type of OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Low-dose of gonadotropins</td>
<td>149 (45.7%)</td>
<td>84 (25.8%)</td>
<td>93 (28.5%)</td>
<td>NS (0.246)</td>
</tr>
<tr>
<td>High-dose of gonadotropins</td>
<td>96 (32.5%)</td>
<td>127 (41.3%)</td>
<td>72 (24.4%)</td>
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</tr>
<tr>
<td>OS length</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10 days of OS</td>
<td>179 (42.2%)</td>
<td>131 (30.9%)</td>
<td>114 (26.9%)</td>
<td>NS (0.793)</td>
</tr>
<tr>
<td>&gt; 10 days of OS</td>
<td>66 (33.5%)</td>
<td>80 (40.6%)</td>
<td>51 (25.9%)</td>
<td></td>
</tr>
</tbody>
</table>

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ANALYSIS OF DIFFERENT FACTORS THAT COULD INFLUENCE ON THE RESULTS OF MOSAIC EMBRYOS IN PGT-A CYCLES. D. Lorenzi, M. Bilinski, P. R. Nicotra Perassi, S. Gonzalez Klikailo, F. Noblia, F. Nodar, S. Payer, Novagen, Buenos Aires, Argentina; CEGYR, Buenos Aires, Argentina.

OBJECTIVE: It has been reported that several factors may affect euploidy rates during assisted reproduction treatments. The aim of the present study...
that should be analyzed in the future. Therefore, we can conclude that mosaic embryo rate may be related to ovarian stimulation conditions had also no influence on the quantity of mosaic embryos. This result permitted the study of female age, PGT-A indication, day of biopsy (day 5 or 6), male factor (oligospermia, asthenospermia and teratospermia), OS (low-dose of gonadotropins: <300 IU, or high-dose of gonadotropins: ≥300 IU of gonadotropins), and finally ovarian stimulation length (<10 days or >10 days). Chi-square test was applied for the statistical analysis.

RESULTS: Currently, the level of mosaicism in our center is 26%. The results are shown in table 1. The amount of mosaic embryos was no statistical different among the different age groups. This result permitted the analysis of the other factors. No significant differences were observed according to PGT-A indication. Male factor had no impact on mosaicism results. Ovarian stimulation conditions had also no influence on the quantity of mosaic embryos. The day of blastocyst biopsy was no relevant according to the number of embryos with a mosaic result.

CONCLUSIONS: From these results, we concluded that all these analyzed factors have no significant impact on the results of mosaic embryos formation. Therefore, we can conclude that mosaic embryo rate may be related to other factors like laboratory conditions or technical issues during biopsy, that should be analyzed in the future.


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OBJECTIVE: Preimplantation HLA genotyping is an important test for IVF patients who need to select a potential matching donor progeny to save a sibling with life-threatening disease. To select HLA matching embryo, preimplantation HLA genotyping test usually need to be done combined with regular PGS. High-resolution HLA genotyping by NGS has been recently developed and become more widely used in conventional HLA genotyping lab, in replacement of the traditional way of sequencing each HLA loci individually. Here we studied the feasibility, accuracy and reproducibility of NGS HLA genotyping in the same blastocyst biopsy collected for regular PGS.

DESIGN: Feasibility and validation study.

MATERIALS AND METHODS: Genomic DNA (gDNA) of known HLA genotype were tested for the feasibility and accuracy. Low amount of genomic DNA was amplified by multiple displacement amplification (MDA) and then, 8 HLA loci (HLA-A, -B2, -C, -DPAl, -DPB1, DQA1, DRB2, DQB1) specific amplification were done on the MDA amplified product. HLA loci amplification product NGS library were generated and sequenced. Regular blastocyst biopsy whole genome amplification product (for regular PGS) were used for HLA loci library generation and sequenced to evaluate the method’s reproducibility.

RESULTS: gDNA MDA product can be used for high resolution NGS HLA genotyping. We tested 26 gDNA MDA product and all sample’s typing result matches to the known 8 HLA loci genotype. 5 samples were repeated more than twice, and the same result was obtained every time. 12 blastocyst biopsy samples that had whole genome amplification for regular PGS were also used to test the reproducibility. With the WGA product, we were able to make the same definitive HLA typing result.

CONCLUSIONS: The high resolution NGS HLA genotyping test newly used in conventional HLA genotyping lab can potentially be used in preimplantation HLA genotyping. This will allow IVF patients with HLA need to have both regular PGS and high-quality HLA genotype test performed with the same blastocyst biopsy sample.

Supported by: PacGenomics

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OBJECTIVE: Whole genome next generation sequencing (NGS) for pre-implantation genetic screen (PGS) has higher sensitivity and accuracy in detecting unbalanced translocation and partial aneuploid than targeted NGS. Whole genome NGS also detect some triploid, the most common polyploidy, of the sex chromosomes are unbalanced (69, XXY, and 69, XXY). Unlike targeted NGS, whole genome NGS unusually does not detect triploid 69, XXX, neither does it provide additional data to confirm triploid 69, XXY and 69, XYY identified in PGS. Here we tested using DNA fingerprinting in combination with whole genome NGS to identify and confirm sex chromosome balanced and unbalanced triploid in PGS.

DESIGN: Feasibility and validation study.

MATERIALS AND METHODS: The feasibility is tested on of 5 known triploid cell lines and 5 known diploid cell lines. 24 fingerprinting loci were tested. Further validation and accuracy were tested on 16 blastocyst biopsy samples whole genome amplification product. All 16 samples had whole genome NGS for PGS and were potential triploid samples. 15 of them were identified by unbalanced sex chromosomes for PGS. 1 of them showed 46, XX for PGS but is suspected to be 69, XXX triploid because of the enlarged nuclei observed by the embryologist. DNA fingerprinting was performed on the 16 PGS samples to identify and confirm the triploid embryos. FISH was performed to confirm the DNA fingerprinting result.

RESULTS: Homozygous or heterozygous loci (24 of 24) in DNA fingerprinting were detected for all 5 known diploid cell lines, confirming diploid. For the 5 known triploid cell lines, 5 to 10 out of the 24 DNA fingerprinting loci has 3 genotypes, confirming triploid. Among the 15 potential triploid samples identified by PGS, 13 showed triploid in DNA fingerprinting, with 3 to 11 loci having 3 genotypes; 2 showed diploid in DNA fingerprinting. The enlarged nuclei sample with 46, XX for PGS also showed triploid in DNA fingerprinting, with 7 out of 24 loci having 3 genotypes. The 16 embryos FISH result confirmed the DNA fingerprinting result, demonstrating DNA fingerprinting is accurate in identifying and confirming triploid in PGS sample.

CONCLUSIONS: DNA fingerprinting test on whole genome amplified PGS samples is a simple and accurate method to examine triploid status of embryos. It can confirm triploid indicated by embryo morphology. Triploid identification in PGS based on unbalanced sex chromosomes can be difficult and not reliable, especially when embryo DNA quality is compromised. In this situation DNA fingerprinting can identify and confirm the real triploid embryos. Used in combination with whole genome NGS, DNA fingerprinting allows patients to benefit from the advantages of the whole genome NGS, and at the same time, identifying the triploid embryos to reduce pregnancy loss.

Supported by: PACGENOMICS

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IVF OUTCOMES FOR TRANSLLOCATION CARRIERS COMPARING FLUORESCENCE IN-SITU HYBRIDIZATION, MICROARRAY, COMPARATIVE GENOMIC HYBRIDIZATION, AND NEXT-GENERATION SEQUENCING. C. Bartels, J. Nulsen, D. R. Grow, A. Bartolucci, C. A. Benadiva, University of Connecticut School of Medicine, Farmington, CT; OB/GYN, Center for Advanced Reproductive Services, Farmington, CT.

OBJECTIVE: Preimplantation genetic diagnosis (PGD) is used to diagnose unbalanced embryos in translocation carriers. This study aimed to compare IVF outcomes of patients who underwent PGD for either reciprocal translocation carriers.
or Robertsonian translocations using one of three methods: fluorescence in-situ hybridization (FISH), microarray comparative genomic hybridization (aCGH), and next-generation sequencing (NGS).

**RESULTS:** 40 translocation carriers receiving care at a large university-affiliated center underwent a total of 73 PGD cycles, including 31 FISH cycles, 24 aCGH cycles, and 18 NGS cycles. 8 carriers had Robertsonian translocations, and 32 had reciprocal translocations.

**CONCLUSIONS:** Results reflect the progression of technological advances in PGD. Although we would expect higher aneuploidy rates from day 3 embryos, less aneuploidy was detected with FISH likely due to limited number of chromosomes tested. Although not statistically significant, there was a reduction of losses in the NGS group, which may reflect an improved capability for detecting aneuploidy. There was a higher number of unbalanced embryos detected by FISH testing. One potential theory to explain this finding is the loss of unbalanced embryos from the day 3 embryo stage to blastocyst stage. This is the first report of outcomes for translocation carriers after PGD with NGS, and although not statistically significant, our findings suggest an improvement in pregnancy outcomes parallel to the advancement in technology.

**REFERENCES:**

FERTILITY & STERILITY

PGD Testing Method and Outcomes

<table>
<thead>
<tr>
<th>FISH</th>
<th>aCGH</th>
<th>NGS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age</td>
<td>34.1 ± 3.7</td>
<td>33.8 ± 3.4</td>
<td>32.7 ± 3.3</td>
</tr>
<tr>
<td>Number of oocytes retrieved</td>
<td>18.2 ± 8.6</td>
<td>18.6 ± 9.6</td>
<td>16.4 ± 8.4</td>
</tr>
<tr>
<td>Number of embryos biopsied per cycle</td>
<td>8.6 ± 4.5</td>
<td>8.1 ± 3.2</td>
<td>5.9 ± 4.0</td>
</tr>
<tr>
<td>Number of normal or balanced embryos per cycle</td>
<td>1.1 ± 1.4</td>
<td>1.9 ± 1.8</td>
<td>1.2 ± 1.1</td>
</tr>
<tr>
<td>Number of unbalanced embryos per cycle</td>
<td>6.6 ± 3.8</td>
<td>3.8 ± 2.6</td>
<td>3.2 ± 2.4</td>
</tr>
<tr>
<td>Number of aneuploid embryos per cycle</td>
<td>0.43 ± 1.2</td>
<td>1.6 ± 1.4</td>
<td>1.3 ± 2.6</td>
</tr>
<tr>
<td>Number of unbalanced embryos</td>
<td>0.43 ± 0.68</td>
<td>0.75 ± 1.0</td>
<td>0.22 ± 0.43</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>44.0% (11/25)</td>
<td>53.3% (16/30)</td>
<td>80.0% (8/10)</td>
</tr>
<tr>
<td>Ongoing pregnancy rate</td>
<td>44.4% (8/18)</td>
<td>50.0% (10/20)</td>
<td>77.8% (7/9)</td>
</tr>
<tr>
<td>Clinical pregnancy loss</td>
<td>18.2% (2/11)</td>
<td>18.8% (3/16)</td>
<td>0.0% (0/8)</td>
</tr>
</tbody>
</table>

| OBJECTIVE: To evaluate whether the use of multiple displacement amplification (MDA) as the first step could increase the diagnosis efficiency of preimplantation genetic diagnosis (PGD) for \( \alpha \)-thalassemia. Y. Fu, X. Shen, C. Zhou. First Affiliated Hospital of SunYat-sen University, Center for Reproductive Medicine, Guang Zhou, China. |

**RESULTS:** Statistically significant differences in some demographic factors, notably age and previous pregnancy/IVF history were apparent in PGD cycles. Our primary outcome was an ongoing and delivered pregnancy, with secondary outcomes of clinical pregnancy, twin delivery, gestation at delivery and birthweight. Adjustment regression models utilised almost all demographic and stimulation variables (except gravidity, parity and number of embryos biopsied). PGS had a statistically significant superior rate of ongoing and delivered pregnancies compared to non-PGS cases (OR 1.86, 95% CI 1.36-2.04, P < 0.01). Furthermore, misdiagnosis rate was lower in the MDA+PCR group than in the PCR group, but it was not statistically significant (0% versus 1.84%, P = 0.317). Besides, the implantation rate was significantly higher in the MDA+PCR group than in the PCR group (50.36% versus 40.23%, P < 0.01). Clinical pregnancy rate, miscarriage rate, ectopic pregnancy rate, and live birth rate were similar in both groups.

**CONCLUSIONS:** When MDA is used as the first step, diagnosis efficiency may be increased. It is highly effective for PGD for \( \alpha \)-thalassemia and deserve wide usage.
rates, in spite of the increased age of the PGS cohort. Furthermore, no statistically significant difference in twin delivery rates, gestation at delivery and birthweight occurred. These results are in line with both expectations and other previous studies. This study provides an Australian perspective on the evidence for the use of PGS and should facilitate confidence amongst clinicians and patients that PGS produces superior pregnancy outcomes, especially for older women.

P-783 Wednesday, October 10, 2018 6:30 AM

VARIANT DETECTION BY NGS FROM EMBRYO BIOSIES. S. S. Sawarkar, a A. Shankugam, a P. Patrizio, a S. B. Munne. b Research, CooperGenomics, Livingston, NJ; aCooper Genomics, Livingston, NJ; bYale University Fertility Center, New Haven, CT; cLaboratory Professional, CooperGenomics, Livingston, NJ;

OBJECTIVE: To reliably detect single nucleotide polymorphisms and small variants at genome scale from human embryo using NGS.

DESIGN: Study was performed prospectively. The study was primarily performed on samples of 3-5 lymphocytes (n=2) isolated from human blood. Bulk DNA from the same blood was used as positive control. Single cells (n=10) were obtained from one single human blastocyst. Blastocyst biopsy from multiple blastocysts was also used in the study for performance comparisons.

MATERIALS AND METHODS: Samples were amplified using a modified MDA method. Whole genome sequencing (WGS) was performed on amplified samples. Variant calling was performed using a GATK based bioinformatics pipeline with custom scripts for downstream analysis. Comparison with variants calls from positive control (bulk sample) yielded sensitivity and positive predictive values. Single cells and blastocyst biopsy were also processed and analyzed similarly.

RESULTS: Variant calls were generated from low DNA-input lymphocyte samples’ sequencing data after alignment and post-processing. Comparison with variant calls from positive control (bulk sample) yielded sensitivity and positive predictive values. Two independent replicates of low DNA-input samples had variant calls with an average sensitivity of ~95% (0.9403, 0.9958) and a positive predictive value of ~95% (0.9501, 0.9558). Variant calling was also performed on five embryo biopsies (3-5 cells each). Comparison with low DNA-input lymphocyte samples (since positive controls were unavailable) showed similar coverage and variant patterns, suggesting that similar sensitivity and positive predictive values may be expected. Finally, eight single cell samples, obtained by disaggregating a single embryo were analyzed. Variant calls from these samples were compared within each other and the dbSNP database as proxy positive controls. It was observed that 40-50% of variants identified in a single sample were observed in 6 or more other samples (mean value of 46%), but among these 94.9% of variants were found in dbSNP, suggesting that high specificity is possible, with appropriate stringent filtering.

CONCLUSIONS: Currently, SNP based panels are used for PGD (Karyo-Mapping). The increased resolution from a NGS based approach could potentially obviate the requirements of additional family members for performing PGD. Additionally the possibility of detecting de novo mutations accurately opens up an entire area of previously unexplored territory within human fertility. Low “n” due to high cost of Whole Genome Sequencing was a limiting factor. Findings will need to be replicated on more embryo biopsies with suitable positive controls.

P-784 Wednesday, October 10, 2018 6:30 AM

HOW INDICATIVE IS THE TROPHECTODERM BIOSPY OF THE ICM IN HUMAN EMBRYOS?. S. S. Sawarkar,a L. Ribustello,a D. Griffin,b S. Wang,c S. B. Munne. aResearch, CooperGenomics, Livingston, NJ; bUniversity of Kent, Canterbury, United Kingdom; cLaboratory Professional, CooperGenomics, Livingston, NJ;

OBJECTIVE: To determine how indicative the trophectoderm biopsy is of the ICM in human embryos

DESIGN: The study was performed in a prospective fashion on a total of (n=47) preimplantation genetic diagnosis blastocysts that were donated by 17 couples who were undergoing IVF treatment. All embryos used in the study were donated for research purposes. The ages of the female patients in the study ranged from 21 to 44.

MATERIALS AND METHODS: Embryos were thawed and biopsied multiple times, including the ICM. PGS analysis was performed on the NGS platform for the individual biopsies. Data analysis was performed on the BlueFuse software. Concordance of PGS was measured by looking at PGS result (ploidy concordance). Samples (n=4) with at least one of the biopsies resulting in a chaotic profile/no result outcome were excluded from the study.

RESULTS: Ploidy concordance was observed in 90.70% (39/43) of the embryos between ICM and TE biopsies. 90.62% (29/32) of the euploid ICMs were concordant with their respective TE biopsies. 100% aneuploid ICMs (9/9) were found to be concordant with respective TE biopsies. Only 2 embryos were observed to be mosaic. While 1 mosaic ICM was concordant, other was discordant. All discordant euploid ICMs (n=3) had a mosaic/complex mosaic corresponding trophectoderm biopsy.

CONCLUSIONS: Despite the limited number of embryos (n=47) this study presents evidence in support of the TE biopsy being a good representation of the ploidy of the ICM, except in mosaic cases, as expected. Euploidy and aneuploidy between the ICM and the TE biopsy were highly concordant. These results can be used to further counsel patient expectations while undergoing PGS during IVF, especially when the patient has no euploid embryos for transfer.

P-785 Wednesday, October 10, 2018 6:30 AM

THE DISTRIBUTION OF CHROMOSOME ERRORS INVOLVED IN ANEUPLOIDY, MOSAICISM OR SEGMENTAL DELETIONS IS UNIQUE TO THE PGT-A RESULT. S. McReynolds, L. Henry, K. de Klerk, J. B. Schipper, T. Jarvis, W. B. Schoolcraft, M. Katz-Jaffe. Colorado Center for Reproductive Medicine, Lone Tree, CO.

OBJECTIVE: With the introduction of next generation sequencing (NGS) for preimplantation genetic testing for aneuploidy (PGT-A) the presence of chromosomal mosaicism and segmental imbalances are more clearly determined in trophectoderm (TE) biopsies. The aim of this study was to investigate the clinical association of chromosomal mosaicism and segmental deletions in TE biopsied human blastocysts.

MATERIALS AND METHODS: Diagnosis of chromosome number from TE biopsies was performed using VeriSeq™ NGS (Illumina) at a single genetics laboratory. Six IVF clinics across North America were included with their own unique population demographic and patient clinical management. Embryos in the six IVF laboratories were cultured under similar optimized conditions utilizing the same consumables, reagents, equipment and comparable biopsy techniques. Chromosome mosaicism and segmental deletion TE biopsy results were evaluated in association with clinical and IVF parameters. Statistical analysis included Student’s t-test, Fisher’s Exact and ANOVA where appropriate, significance at P<0.05.

RESULTS: Across the six IVF clinics, following TE biopsy of 27,775 human blastocysts, chromosomal mosaicism and segmental deletions were observed at only 2.3% and 1.9% respectively, with no significant variability between clinics. Reproductive age (mean maternal age = 35.6 ± 3.7 years; mean paternal age = 38.4 ± 5.9 years), infertility diagnosis, ovarian reserve, fertilization, embryo development, blastocyst morphology and the day of biopsy, were not associated with the incidence of chromosomal mosaicism or segmental deletions in TE biopsies (P≥0.05; ns). The distribution of chromosome errors was significantly unique to the PGT-A result (P<0.05). Complete aneuploidy most frequently included the smaller size chromosomes (16, 21, and 22) that typically result in miscarriage. In contrast, errors identified in mosaic TE biopsies were completely random across the 23 pairs of chromosomes, while the larger size chromosomes (1-11) were significantly associated with a segmental deletion TE biopsy result (P<0.05). Further examination of segmental deletion blastocysts (n=40) confirmed the original diagnosis within the corresponding inner cell mass (ICM) with high reliability (87.5%). Examples include clinically recognizable genetic disorders like, 1p36 deletion syndrome and Wolf-Hirschhorn syndrome, among others.

CONCLUSIONS: This large dataset of human blastocysts has revealed the distribution of chromosome errors to be significantly unique to the PGT-A result. Understanding the clinical association of mosaicism and segmental deletions in TE biopsies is critical to the overall efficiency of PGT-A. Furthermore, reliable identification of clinically recognizable deletion syndromes in the corresponding ICM supports the concern for the transfer of blastocysts identified with segmental deletions.
ANALYSIS OF THE EMBRYONIC MEDIA DROP AS A NON-INVASIVE ALTERNATIVE TO BLASTOCYST BIOPSY IN PREIMPLANTATION GENETIC TESTING FOR ANEUPLOIDY. M. Katz-Jaffe, B. McCallie, S. Reynolds, L. Henry, S. McCormick, W. B. Schoolcraft. Colorado Center for Reproductive Medicine, Lone Tree, CO.

OBJECTIVE: Current methods for preimplantation genetic testing of aneuploidy (PGT-A) require the biopsy of cells from the developing embryo. Improvements in clinical outcomes with PGT-A have been reported worldwide. Nevertheless, biopsy procedures are invasive with the potential to impact embryonic developmental competence, are costly to the patient and time consuming for the embryology laboratory. The aim of this study was to blindly analyze the embryonic media drop as a non-invasive alternative to blastocyst biopsy for PGT-A.

DESIGN: Prospective cohort blinded study.

MATERIALS AND METHODS: Infertility patients planning in vitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI) and PGT-A between January-March 2018 (n=14) were consented with IRB approval to media drop analysis following blastocyst development. Blastocysts were biopsied on either day 5 or day 6 of development upon identification of an inner cell mass. Media drops (20 µl) were collected at two different development timepoints, from day 3 to day 5 of embryo culture, as well as day 5 to day 6 of blastocyst culture. Trophoderm (TE) biopsies and media drops were collected separately and blindly analyzed for chromosome constitution using the next generation sequencing, VeriSeq® platform (Illumina). Chromosome numeration from these two embryonic DNA sources were decoded and compared to evaluate the clinical efficiency of media drop analysis for PGT-A.

RESULTS: DNA amplification was observed in 100% of the media drop samples (n=9), with 80 (87.9%) resulting in sufficient quantities of DNA for a reliable PGT-A result. Concordance with TE biopsy was confirmed in 72 (90%) of the media drop samples for embryo sex and 64 (80%) of the media drop samples for the overall PGT-A result. The 10% sex discordance represented euploid males diagnosed as euploid females due to the presence of maternal DNA contamination in the media drop from fallen cumulus cells following zona pellucida expansion. Interestingly, this sex discordance was only observed in day 3 to day 5 media drop samples, and not in any of the day 5 to day 6 media drop samples. The remaining 10% discordance represented media drop samples that were misrepresented with a mixture of different autosomal aneuploidy, including a few media drop samples with the reverse aneuploidy, which would be the expected result following mitotic cell division errors.

CONCLUSIONS: Our clinical data suggests that embryonic DNA is present and can be utilized for PGT-A in media drops at later stages of blastocyst development. Overall, the accuracy and reliability of blastocyst DNA in media drops was observed to be lower than intact nucleated TE biopsied cells. However, ongoing improvements in both the embryology and genetic laboratories are focused on closing this gap in order to offer infertility patients an option of non-invasive PGT-A.

P-786 Wednesday, October 10, 2018 6:30 AM

THE FIRST REPORT OF COMPREHENSIVE PREIMPLANTATION GENETIC TESTING FOR CHROMOSOMAL STRUCTURAL REARRANGEMENTS (PGT-SR) USING LONG READ SEQUENCING. S. Madjunkova, R. Antes, R. Abramov, Y. Yin, S. Chen, P. Puzarte, L. Jorgensen, S. Sundaravadanan, J. Simpson, G. Duckett, S. Madjunkova, R. Abramov, Y. Yin. Reproductive Genetics, CReAte Fertility Centre, Toronto, ON, Canada; Reproductive Genetics, CReAte Fertility Centre, Toronto, ON, Canada; Department of OBGYN and Gynecology, University of Toronto, Toronto, ON, Canada; Centre for Cancer Research, Toronto, ON, Canada; Reproductive Genetics, CReAte Fertility Centre, Toronto, ON, Canada; Departments of Obstetrics and Gynecology and Physiology, University of Toronto, Toronto, ON, Canada.

OBJECTIVE: The current diagnostic approach for carriers of balanced chromosomal rearrangements (BCR), at higher risk for reproductive failure, recurrent miscarriages or offspring with unbalanced CR, involves PGT-SR to select apparently balanced euploid embryos for transfer, to achieve higher implantation rates and lower miscarriage rates. Detection of carrier BCR status of embryos and possible cryptic microdeletions/duplications at breakpoint sites is difficult with standard NGS. The main limitation is production of short DNA reads, making detection of breakpoints challenging, even with extensive high depth sequencing and complicated bioinformatics analysis. Here we utilized, a novel sequencing technology for long single-molecule reads, Nanopore MinIon™ sequencing, to overcome the above mentioned limitations, allowing for detection and mapping of CRs.

DESIGN: Prospective cohort study

MATERIALS AND METHODS: This study had institutional REB approval. Six couples undergoing PGT-SR for BCR [46 XX, t(8;22)(q24.3;q11.2), 46 XX, (t1.2;p34.1;p13), 46XX,t(16;14)(p25;q23.3), 46XX,t(11.22)(23.2;q11.2), 46XX, inv(16;3.4), 46 XX, inv(8)(q13q24.3)] and their embryos (n=29) were included. Standard PGT-SR was performed on the embryonic DNA from D5/D6 TE biopsies using VeriSeq kits and BlueFuse software. We applied whole genome long read sequencing using the MinIon™ for detection of CR on parental genomic DNA (both partners) and embryonic DNA using 1D-igation kit and Nanopore MinIon™ sequencing.

RESULTS: Deep sequencing of human blastocyst mt-DNA detected a high frequency of SNPs (≈11.2±3.8/embryo), with 30% heteroplasmic and deleterious mutation enrichment in embryos with poor outcomes. Our findings suggest that mtDNA analysis could potentially be adapted as a novel marker to prioritize euploid embryos for uterine transfer.

Supported by: Create Fertility Centre
RESULTS: Using NGS, embryos were categorized as euploid/balanced, mosaic and/or aneuploid/unbalanced. We established a protocol for comprehensive PGT-SR using the handheld MinION™ sequencer and developed a bioinformatics pipeline to successfully define and map the CR break-points from the long-read data. The mean genome coverage was 3.5x, with an average read length of 4kb. Custom breakpoint PCR amplification systems were designed for each CR breakpoint, allowing high sensitivity testing. Sanger sequencing confirmed the full sequence of the breakpoints and we achieved base pair resolution sensitivity to detect embryos that were balanced CR carriers vs. non-carriers. Our comprehensive PGT-SR showed that out of 12 euploid/balanced embryos, 4 were carriers of balanced CRs. Aneuploidy detection with the MinION is also possible as well as phasing of the chromosomes involved in the CR.

CONCLUSIONS: We have demonstrated, for the first time ever, application of long-read Nanopore™ sequencing as a novel solution for high resolution comprehensive clinical PGT-SR.

Supported by: CReATe Fertility Centre

P-789 Wednesday, October 10, 2018 6:30 AM

DETECTION OF EXACT FRAGILE X CGG REPEAT SIZE OF EMBRYONIC TROPHOECTODERM BIOPSIES. J. L. Bedard,a C. Jalas,a X. Tao,a R. Scott.a,b

1Foundation for Embryonic Competence, Basking Ridge, NJ; 2IVI RMA, Basking Ridge, NJ.

OBJECTIVE: A premutation Fragile X Mental Retardation 1 (FMR1) gene allele exhibits the presence of 55-200 repeats and is paired with an increased risk for other Fragile X (FX) associated disorders. Premature ovarian insufficiency (POI) affects about 20% of female premutation carriers and results in hindering the outcomes of in-vitro fertilization (IVF). Additionally, there is an increased risk of expansion of the unstable CGG repeat sequence when the allele reaches the premutation range. Current pre-implantation genetic diagnosis (PGD) for FXS, involves tracking the affected X chromosome using linked markers, without observation of the size of the CGG repeats. This study sought to establish a method to determine CGG repeat sizes within the FMR1 gene of trophectoderm (TE) biopsies.

DESIGN: Experimentally, blind study

MATERIALS AND METHODS: Phase I genomic DNA (gDNA) validation: gDNA was isolated from 17 patients with known CGG repeat sizes to validate Ampliseq PCR/CE FMR1 Reagent Kit (Asuragen). Capillary electrophoresis (CE) was conducted using the 3730xl DNA Analyzer (Thermo Fisher Scientific). Phase II 6-cell samples validation: 84 samples of 6 cells were collected from cell lines with known FX repeat sizes (23-477 CGG repeats) (Coriell Repository) to mimic a TE biopsy. These samples were amplified with the REPLI-g Single Cell Kit (Qiagen), then subjected to the Ampliseq PCR and CE. Phase III TE biopsies validation: TE biopsies from five discarded aneuploid whole embryos (expected CGG repeats sizes from 29 to >200 CGG based on parental genotypes and linked markers) were blinded, then amplified and underwent the Ampliseq PCR and CE.

RESULTS: Phase I: All gDNA samples exhibited the expected CGG repeat size compared to the results from two reference laboratories. Phase II: The 6-cell samples showed CGG repeat sizes as expected. Phase III: The results of TE biopsies were consistent to the parental CGG repeats sizes.

CONCLUSIONS: CGG repeat sizes and expansion can be observed using this new methodology on TE biopsies. This methodology has the potential application to assess the amount of expansion for patients with limited numbers of usable embryos. A validation with a larger sample size will be needed before clinical use. Transferring embryos with FMR1 premutation alleles will encompass more diligent genetic counseling and detailed consents.

P-790 Wednesday, October 10, 2018 6:30 AM

88 MOSAIC EMBRYO TRANSFERS IN A SINGLE CLINIC: WHAT WE HAVE LEARNED. M. Viotti,a A. Victor,a A. D. Griffin,a J. Jaundall,a A. Brake,a L. Lepkowski,a C. Zouves,a F. Barnes,b,c Zouves Foundation for Reproductive Medicine, Foster City, CA; Zouves Fertility Center, Foster City, CA; 1University of Kent, Canterbury, United Kingdom.

OBJECTIVE: IVF clinics are transferring embryos classified as euploid-aneuploid mosaic by preimplantation genetic testing (PGT-A) with greater frequency to patients who lack available euploid embryos. Nevertheless, there is a lack of evidence-based guidelines that establish which characteristics and genetic abnormalities affect a mosaic embryo’s clinical predictive outcome.

DESIGN: Embryos were tested by PGT-A and samples classified as mosaic were transferred in a prospective manner into IVF patients. Success rates were analyzed by sorting type of mosaicism.

MATERIALS AND METHODS: 88 mosaic blastocysts were transferred at a single IVF program from August of 2015 through March of 2018. All embryos were tested in-house by Next Generation Sequencing (NGS) on trophectoderm biopsies obtained from blastocysts at 5-7 days of development.

RESULTS: Of the 88 transferred mosaic embryos, 52 (59.1%) established a chemical pregnancy, 33 (37.5%) developed an embryonic sac (implantation), and 26 (29.5%) developed a fetal heartbeat (FHB). Of these 26, 10 resulted in a live birth and at the time of analysis 16 were ongoing pregnancies, meaning that no post-FHB miscarriages had occurred. Mosaic embryos derived from oocytes younger than 35 years old had a significantly higher implantation rate than embryos from oocytes 35 years or older (50.0% to 21.2%, n = 28 and 52 respectively) as well as comparable implantation rates to euploid embryos from across all age groups (younger than 35 years, n=141: 51.1%; greater than 35 years, n=341: 48.4%). For mosaic embryos displaying only a single segmental chromosomal abnormality (n=26) the chances of implanting (42.5%) and developing a FHB (42.3%) were significantly higher than embryos with monosomy in whole chromosome(s) or multiple segmentals (on average 32.8% implantation and 26.5% FHB, n=49). In our data set, the percentage of aneuploid cells present in the mosaic population did not affect chances of success, as we found that embryos with mosaicism levels in the 20%-50% range (n=63) had similar rates of implantation and FHB (36.5% and 30.2%) compared to those in the 50%-80% range (38.9% and 33.3%, n=18). Lastly, embryos diagnosed with mosaic trisomies did not have a significant difference in implantation or FHB development (n=30, 33.3%, 30.0%) from those with monosomies (n=28, 32.1%, 25.9%).

CONCLUSIONS: Embryos classified as mosaic are capable of producing healthy babies and should be considered for transfer when a euploid embryo is not available. When there are multiple mosaic embryos to select from for any given patient, our data suggests embryos diagnosed with a single segmental abnormality should be preferred.

Supported by: This study was funded by the Zouves Foundation for Reproductive Medicine and Zouves Fertility Center.

P-791 Wednesday, October 10, 2018 6:30 AM

EXTENDED CULTURE TO DAY 7 CONTRIBUTES TO PREGNANCY OUTCOME IN PGT-A CYCLES. D. W. Matt,a,b D. Graff,a J. Collier,a B. Willkerson,a,* Virginia IFV and Andrology Center, Richmond, VA; bVirginia Fertility Associates, Richmond, VA.

OBJECTIVE: To evaluate the blastocyst quality, euploid, and pregnancy rates of Day 7 blastocysts compared to Day 5 and Day 6 blastocysts in PGT-A cycles.

DESIGN: Our ART program routinely biopsies blastocysts on Day 5, Day 6, and Day 7 of culture. In this retrospective study, we compared the blastocyst quality, euploid rate, and pregnancy outcome from PGT-A cycles from 2016 and 2017.

MATERIALS AND METHODS: We analyzed 315 PGT-A cycles (mean patient age = 36.3 yrs) resulting in 2088 biopsied blastocysts. Laser assisted trophectoderm biopsies were performed on Day 5 (approx. 114 hr post ICSI), Day 6 (138 hr), or Day 7 (162 hr). Each blastocyst was graded using Gardner grading, as GOOD (3,4,5; AA, AB, BA), FAIR (3,4,5; BB), or POOR (3,4,5; AC, CA, CB, CC). All biopsied blastocysts were vitrified, and all biopsies were subjected to NGS testing. In order to compare blastocyst quality and age, only single euploid blastocyst FETs were analyzed in this study. Differences in blastocyst quality and euploidy between Day 5, 6 and 7 were compared by chi-square analysis with p-values < 0.05 considered significant.

RESULTS: Of the 2088 biopsied blastocysts, 41% were Day 5, 48% Day 6, and 11% Day 7. GOOD quality blastocysts on Day 5, 6, and 7 were 52%, 30%, 7%, respectively. FAIR quality blastocysts on Day 5, 6, and 7 were 33%, 48%, 26%, respectively. POOR quality blastocysts on Day 5, 6, and 7 were 9%, 30%, 67%, respectively. Blastocyst quality was significantly different (p<0.001) between all blastocyst days. Euploid rates on Day 5
(5%) were greater (p<0.001) than Day 6 (35%) and 7 (33%), but Day 6 euploid rates were not different from Day 7. Failed amplification rates were similar at 2%, 2%, and 3% on Day 5, 6, and 7, respectively. Euploid rates correlated with blastocyst quality on Day 5 (GOOD = 55%; FAIR = 47%; POOR = 35%) and Day 6 (GOOD = 49%; FAIR = 32%; POOR = 25%), but not on Day 7 (GOOD = 25%; FAIR = 43%; POOR = 30%). Single euploid blastocyst FET pregnancy rates as detailed in Table 1 on Day 5, 6, and 7 were 75%, 63%, 35%, respectively (p<0.01). Furthermore, pregnancy rates were positively correlated to blastocyst quality.

CONCLUSIONS: Although Day 7 blastocysts represented only 11% of all the blastocysts biopsied in these PGT-A cycles, the euploid ratio was similar to those seen in Day 6 blastocysts, but markedly lower than Day 5 blastocysts. Furthermore, although the blastocyst quality is low in Day 7 biopsied blastocysts with only 7% GOOD quality, 35% of our patients achieved pregnancy from Day 7 single euploid FETs. These results support the continued practice of extended blastocyst culture to Day 7 to increase PGT-A pregnancy rates per retrieval cycle.

<table>
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<td>51/71 (72%)</td>
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P-792 Wednesday, October 10, 2018 6:30 AM

IS MITOCHONDRIAL DNA (mtDNA) QUANTIFICATION A POTENTIAL BIOMARKER FOR SELECTION AMONG EUPLOID EMBRYOS? M. Bilinski,a D. Lorenzi,a M. Fabbro,a V. Rovera,a S. M. Gonzalez Klukai-lo,a M. Galain,a F. Noblia,b S. Papier,a,b F. Nodar,a,b aNovagen, Buenos Aires, Argentina; bCEGYR, Buenos Aires, Argentina.

OBJECTIVE: Recently, there have been controversial publications about the clinical relevance of mtDNA quantification in human blastocysts. Previous studies have not found an association between this parameter and ploidy, maternal age or pregnancy outcome. However, some laboratories, based on their evidence, apply this quantification as an implantation potential biomarker. Thus, the aim of this study was to evaluate if there was a potential relationship between human blastocyst mtDNA content and female age, embryo ploidy and clinical pregnancy outcome.

DESIGN: Retrospective cohort study. MATERIALS AND METHODS: A cohort of 447 blastocysts obtained from 202 couples, with an average female age of 33.8 years (21–46), undergoing preimplantation genetic testing for aneuploidies (PGT-A) were included. Data was collected between April 2016 and March 2018 from a single center. Mosaical embryos (between 20%-80%) were excluded from this analysis. Trophoderm biopsies were assessed by NGS (Veriseq-ILLUMINA). For each sample, reads were aligned to the human reference genome (hg19) and the mtDNA genome separately. The number of reads that mapped to the mtDNA were divided by the number of reads that mapped to the nuclear DNA in order to normalize technical variability. The resulting values were mathematically adjusted by correction factors for embryo ploidy (complete monosomals or trisomies) and gender previously reported. T-test was performed for statistical analysis in order to analyze mtDNA scores regarding embryo aneuploidy, maternal age and clinical pregnancy.

RESULTS: Regarding all blastocysts analyzed, 236 (53%) were euploid and 210 (47%) aneuploid. The amount of mtDNA was significantly higher in euploid embryos (P= 0.0002). However, the amount of mtDNA was not different between euploid embryos from younger (<38 years, n=187) and older women (≥38 years, n=49) (P=0.6870). During the period covered, 65 single embryo transfer were performed after thawing, resulting in 37 (57%) HCG-beta subunit positive and 26 (40%) ongoing pregnancies. The mtDNA score from euploid blastocysts that achieved a clinical pregnancy was not significantly different from those that did not result in an ongoing pregnancy (P=0.7589).

CONCLUSIONS: This study contributes evidence that mtDNA quantification in euploid embryos have no clinical impact in pregnancy outcome. mtDNA score was only statistically associated with chromosomal aneuploidy suggesting that high levels of mtDNA may have a negative impact resulting in an inadequate chromosome segregation.

DESIGN: This is a retrospective study. We analyzed our center’s IVF outcome data from January 1-2016 to October 31-2017. We had a total case number of 303 IVF cases with PGS and AMH data.

MATERIALS AND METHODS: We collected the PGS analysis data with a patient with an AMH level. Then we statistically analyzed its co-relation with PGS data and age, AMH level and the number of oocytes. We compared clinical data between all abnormal PGS cases and normal cases. All data were analyzed through SPSS statistics.

RESULTS: We In the case of age, the low AMH group and 35 ~ 39 age group had a significantly high aneuploidy ratio, compared to the group with high AMH levels. Based on the number oocytes, the age group of those over 40 years old (≥40) had more than ten oocytes that showed a significantly high normal PGS outcome, compared to those with a low number of oocytes. Even a patient(s) in the young age group with low AMH (35-39, AMH ≤ 2.33) could need a recommendation in PGS to select a normal embryo. Therefore, the old age group with a high number of oocytes (age ≥35, the number of oocytes ≥10) wouldn’t be as recommended for PGS than those patients who harvested a low number of oocytes.

CONCLUSIONS: Some specific factors have a certain effect to aneuploidy ratios of embryos depending on its age, the AMH level and the number of collected oocytes. PGS is a good tool for selecting an embryo with a normal chromosome. However, we need a critical recommendation guideline for patients. Our study may help in setting up the criteria guideline of PGS.

P-795 Wednesday, October 10, 2018 8:30 AM

PREIMPLANTATION GENETIC TESTING FOR ANEUPLOIDY (PGT-A) FOLLOWED BY PGT- FOR NON-DOMINANT/GENOMIC/SINGLE GENE DISORDERS (PGT-M) IS THE SEQUENCE OF CHOICE IN PRECONCEPTION GENETIC TESTING WITH NON-DOMINANT DISORDERS. B. Abitana, T. Singerb, C. Mullinc, S. L. Bristowd, A. Hershlagd. aDepartment of Obstetrics and Gynecology, North Shore University Hospital, Manhasset, NY; bOb/Gyn, Lenx Hill Hospital, Roslyn, NY; cNorthwell Fertility, Manhasset, NY; dNorthwell Health Fertility, Manhasset, NY.

OBJECTIVE: The increased utilization of PGT-A and its inclusion in many if not most in vitro fertilization (IVF) cycles requiring PGT-M is associated with increased cost to patients, as well as an overload to the embryo-genetic lab. Some genetic labs currently offer sequential testing options, as opposed to concurrent PGT-A and PGT-M, for patients undergoing both analyses. We investigated when sequential PGT-A should precede PGT-M.

DESIGN: Retrospective cohort review.

MATERIALS AND METHODS: We conducted an analysis of PGT-M/PGT-A cases at a single academic fertility center between September 2014 and March 2017. All embryo biopsies were analyzed by a single reference lab (CooperGenomics, Inc, NJ). Patients were stratified by mode of inheritance of single-gene disorder tested for PGT-M and were divided according to the Society for Assisted Reproductive Technology (SART) age groups (<35, 35-37, 38-40, 41-42, >42 years of age).

RESULTS: The study population included 62 IVF-PGT-M/PGT-A cycles from 45 patients, including 383 embryos. 34 cases with 210 embryos were Autosomal recessive (AR), 14 cases with 89 embryos were Autosomal Dominant (AD), and 12 cases with 82 embryos were X-linked recessive (XLR). The mean patient age was 35, with a total aneuploidy rate of 44% (169/383). Embryos in all groups and across all age ranges were abnormal by PGT-A more often than by PGT-M except for the <35 year old age group for AD diseases (Table 1).

CONCLUSIONS: 1. Sequential genetic studies of embryos should replace concomitant PGT-A and PGT-M on all embryos.2. For autosomal recessive and x-linked genes, PGT-A preceding PGT-M is the most cost-efficient approach for the patient, and can eliminate unnecessary, labor-intensive testing by genetic labs.3. Future, larger scale studies are needed to corroborate this approach.

Table 1

<table>
<thead>
<tr>
<th>PGS Outcome</th>
<th>≤34</th>
<th>35-39</th>
<th>≥40</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL ABNORMAL</td>
<td>6.07±2.9</td>
<td>2.33±1.6*</td>
<td>2.00±1.5</td>
<td>0.942</td>
</tr>
<tr>
<td>NORMAL</td>
<td>6.23±5.7</td>
<td>3.51±2.3*</td>
<td>2.51±1.7</td>
<td>0.027</td>
</tr>
</tbody>
</table>
| CONCLUSIONS: 1. Sequential genetic studies of embryos should replace concomitant PGT-A and PGT-M on all embryos.2. For autosomal recessive and x-linked genes, PGT-A preceding PGT-M is the most cost-efficient approach for the patient, and can eliminate unnecessary, labor-intensive testing by genetic labs.3. Future, larger scale studies are needed to corroborate this approach.

P-796 Wednesday, October 10, 2018 8:30 AM


OBJECTIVE: Preimplantation genetic testing for aneuploidy (PGT-A) has been increasingly used to identify euploid embryos. The present study evaluates clinical outcomes of euploid frozen embryo transfers (FET) in 2016-2017, following trophectoderm (TE) biopsy (BX) on day 5 (D5), day 6 (D6), or day 7 (D7).

DESIGN: Retrospective study.

MATERIALS AND METHODS: Trophectoderm biopsy was performed on embryos once they reached blastocyst (BL) stage on D5, D6, or D7, where the day of biopsy indicates the rate of development. We analyzed a total of 1889 FETs following D5, D6, or D7 TE BX. Comparative genomic hybridization array, SNP microarray, or Next-generation sequencing was used for PGT-A. Transfer was performed following vitrification and warming. Clinical outcomes of implantation rate (IR), ongoing pregnancy/delivered (OGD), and spontaneous abortion (SAb) were compared among different BX days per patient age groups, using Kruskal-Wallis testing for IR and Chi-squared analysis for OGD and SAb. Statistical significance was defined as P < 0.05.

RESULTS: For patients of all ages, all clinical outcomes (IR, OGD, and SAb) showed statistical significance correlated to the rate of embryo development. In patients under 35 years of age, OGD was significantly higher in D5 euploid embryos compared to D6 or D7. For patients 38 years of age and older, IR and OGD were statistically higher in D5 euploid embryos.

CONCLUSIONS: Overall, D5 euploid BL showed improved clinical outcomes compared to D6 or D7, suggesting that delayed embryo development may have an adverse effect on clinical outcomes, despite the proven euploid status. Interestingly, for younger patients (<35), D5 euploid BL improved continuation of pregnancy (OGD), while other clinical outcomes were not significantly different among D5, D6, or D7. However, for older patients...
FERTILITY & STERILITY®

Clinical Outcomes Post TE BX/FET

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<thead>
<tr>
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<tbody>
<tr>
<td>IR</td>
<td>72.5%**</td>
<td>68.2%</td>
<td>74.4%</td>
<td>77.0%**</td>
<td>71.2%*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>OGD*</td>
<td>429 (63%)*</td>
<td>128 (60%)*</td>
<td>113 (65%)*</td>
<td>113 (68%)*</td>
<td>75 (59%)*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SAb (losses/CP;%)</td>
<td>65 (10%)*</td>
<td>20 (9%)</td>
<td>13 (7%)</td>
<td>17 (10%)</td>
<td>15 (12%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IR</td>
<td>60.9%**</td>
<td>60.8%</td>
<td>64.1%</td>
<td>61.1%**</td>
<td>57.5%*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>OGD*</td>
<td>540 (49%)*</td>
<td>155 (49%)*</td>
<td>131 (53%)*</td>
<td>149 (47%)*</td>
<td>105 (45%)*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SAb (losses/CP;%)</td>
<td>129 (12%)*</td>
<td>38 (12%)</td>
<td>25 (10%)</td>
<td>38 (12%)</td>
<td>28 (12%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IR</td>
<td>43.2%**</td>
<td>45.5%</td>
<td>68.8%</td>
<td>31.7%**</td>
<td>43.8%*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>OGD*</td>
<td>32 (35%)*</td>
<td>8 (40%)*</td>
<td>8 (53%)*</td>
<td>11 (27%)*</td>
<td>5 (31%)*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SAb (losses/CP;%)</td>
<td>8 (9%)*</td>
<td>2 (10%)</td>
<td>2 (13%)</td>
<td>2 (5%)</td>
<td>2 (13%)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*: P < 0.05 ; **: P < 0.01 ; *: Ongoing pregnancies were defined as those with fetal cardiac activity at or beyond 8 weeks of gestational age.

RESULTS: 97% (106/109) of the samples with known CCG repeats and mosaicism were successfully identified. Of the 17 embryonic DNA samples analyzed, 6 affected males with > 200 CCG repeats, 9 normal females and 2 males embryos with premutation alleles were diagnosed.

CONCLUSIONS: We demonstrate the validation of using a PCR based and capillary electrophoresis experimental protocol to identify CCG repeats within adult and embryonic DNA samples. We can identify premutation CCG male carrier embryos from maternal premutation carriers within an in vitro fertilization setting.
RESULTS: Three carrier patients participated in this ongoing study. The attached table details results. Using SNP analysis, parental origin from the carrier and sperm source were confirmed. Quantification of mitochondrial heteroplasmy using Taqman PCR detected no mutation load in embryos. NGS data will be presented.

CONCLUSIONS: MRT is an effective procedure for patients carrying disease causing mitochondrial mutations. We demonstrate the feasibility of MRT to remove disease causing mtDNA from pre-implantation embryos in an academic IVF center and have created high quality embryos. Our results are a step towards embryo transfer and establishing MRT as an option for women who carry disease causing mtDNA mutations.


Supported by: Supported by a grant from the American Society for Reproductive Medicine.

P-799 Friday, October 10, 2018 6:30 AM

WHO ARE THE PATIENTS THAT CAN REALLY BENEFIT FROM PREIMPLANTATION GENETIC TESTING FOR ANEUPLOIDY? AN AGE-ADJUSTED ANALYSIS TO CALCULATE THE NUMBER OF OO- CYTES TO HAVE ONE EUPLOID EMBRYO. N. P. Polyzos,a I. Rodriguez,a M. Devesa,a P. Drakopoulos,a M. Parriego,a J. Rodriguez-Purata,a A. Veiga,a P. Barri,a B. Coroleua aObstetrics, Gynecology and Reproduction, Hospital Universitario Dexeus, Barcelona, Spain; b Vrije Universiteit Brussel, Brussels, Belgium.

OBJECTIVE: To estimate the exact number of oocytes needed to have at least one euploid embryo according to age.

DESIGN: This is a retrospective analysis carried out in a University-affiliated tertiary centre between January 2015 and June 2017.

MATERIALS AND METHODS: Overall 385 infertile women who underwent 510 controlled ovarian stimulation cycles for PG-T-A were included. In total 2097 embryos were biopsied and comprehensive chromosome testing (CCS) was done by using a-CGH. Following ovarian stimulation and ICSI, total 2097 embryos were biopsied and comprehensive chromosome testing for aneuploidy? An age-adjusted analysis to calculate the number of oocytes to have one euploid embryo. This probability was used to calculate the number of oocytes needed to have at least one euploid embryo according to age and the number of oocytes, and a second to estimate the probability per patient to obtain one euploid embryo, according to age.

RESULTS: Three carrier patients participated in this ongoing study. The attached table details results. Using SNP analysis, parental origin from the carrier and sperm source were confirmed. Quantification of mitochondrial heteroplasmy using Taqman PCR detected no mutation load in embryos. NGS data will be presented.

CONCLUSIONS: MRT is an effective procedure for patients carrying disease causing mitochondrial mutations. We demonstrate the feasibility of MRT to remove disease causing mtDNA from pre-implantation embryos in an academic IVF center and have created high quality embryos. Our results are a step towards embryo transfer and establishing MRT as an option for women who carry disease causing mtDNA mutations.


Supported by: Supported by a grant from the American Society for Reproductive Medicine.

P-800 Wednesday, October 10, 2018 6:30 AM


OBJECTIVE: EB is increasingly common as more couples delay childbearing. Moreover, performing PG-T-A before EB provides confidence that stored embryos are genetically competent and have a high chance of live birth (LB). We aimed to assess the specifics of blastocyst (BL) morphology in determining LB after euploid embryo (EE) transfer and develop counseling tools for patients electing EB+PG-T-A.

DESIGN: Retrospective cohort at a large university-based program.

MATERIALS AND METHODS: We reviewed all IVF cycles from 1/2014 - 2/2018 where fresh oocytes served as the female gamete and a single cryopreserved EE was transferred. We assessed age at retrieval, BL expansion (BE), inner cell mass (ICM) and trophectoderm (TE). EE, ICM and TE grades were based on Gardner’s criteria. Outcomes were ongoing pregnancy (≥12 wks gestation) / live birth rate (LBR), implantation rate (IR) and spontaneous abortion rate (SABR). Fisher’s exact test was used.

RESULTS: See Table. We reviewed 1641 transfers (142 donor+1499 autologous; median age at retrieval 37y, IQR 33-40y, range 21-46y). Overall IR was 66%, SABR was 12%, and LBR was 57%. There were 12 pregnancy terminations (TOP) and 7 ectopics. When stratified by BE, no differences in IR, SABR, or LBR were noted. When stratified by ICM grade, EE with ICM-C had a lower IR than with ICM-A and B (35% vs. 71% and 68%, p<0.01) and EE with ICM-A had a lower SABR than with ICM-B (6% vs. 13%, p=0.02); notably, EE with ICM-A had a higher LBR than with ICM-B and C (66% vs. 58% and 34%, p<0.03) and EE with ICM-B had a higher LBR than with ICM-C (58% vs. 34%, p<0.01). When stratified by TE grade, EE with TE-C had a lower IR than with TE-A and B (51% vs. 80% and 69%, p<0.01) and EE with TE-A had a lower SABR than with TE-C (3% vs. 18%, p<0.03); notably, EE with TE-C had a lower LBR than with TE- A and B (41% vs. 73% and 60%, p<0.01). Outcome differences re: ICM and TE were maternal-age dependent. When comparing LBrs re: ICM+TE grade combinations, ICM-A+TE-A= 19/26 (73%), ICM-A+TE-B= 125/195 (64%), ICM-B+TE-A= 13/19 (68%), ICM-B+TE-B= 658/1101 (60%), ICM-B+TE-C= 91/205 (44%), ICM-C+TE-B= 23/57 (40%), and ICM C+TE-C= 8/36 (22%). Only one EE had ICM+A+TE-C and one ICM+ C+TE-A (both LBs).

CONCLUSIONS: Euploidy is not the sole determinant when selecting embryos. Our data suggest that ICM and TE each play individual and critical roles related to IR, SABR and LBR - even with EE. In our study, EE with the best morphology had a LBR of 73% while EE with the worst had a LBR of 22%. These data add to realistic counseling for patients using EB+PG-T-A for future pregnancy. Further, they help elucidate the biology of implantation and pregnancy, suggesting TE (placenta precursor) is as important as ICM (future fetus).

Embryo morphologic parameters and outcome data

<table>
<thead>
<tr>
<th>Embryo Parameter</th>
<th>IR</th>
<th>SABR</th>
<th>LBR</th>
<th>TOP + Ectopic Pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>BE: &lt; 2 (n=110)</td>
<td>73/110 (66%)</td>
<td>14/73 (19%)</td>
<td>58/110 (53%)</td>
<td>1+0/110 (1%)</td>
</tr>
<tr>
<td>BE: 3 (n=1389)</td>
<td>928/1389 (67%)</td>
<td>104/928 (11%)</td>
<td>808/1389 (58%)</td>
<td>9+7/1389 (1%)</td>
</tr>
<tr>
<td>BE:4 (n=63)</td>
<td>40/63 (63%)</td>
<td>6/40 (15%)</td>
<td>32/63 (51%)</td>
<td>2+/63 (3%)</td>
</tr>
<tr>
<td>BE: ≥ 5 (n=79)</td>
<td>47/79 (59%)</td>
<td>6/47 (13%)</td>
<td>41/79 (52%)</td>
<td>0+/79 (0%)</td>
</tr>
<tr>
<td>ICM: A (n=221)</td>
<td>157/221 (71%)</td>
<td>10/157 (6%)</td>
<td>145/221 (66%)</td>
<td>1+1/221 (1%)</td>
</tr>
<tr>
<td>ICM: B (n=1325)</td>
<td>898/1325 (68%)</td>
<td>119/898 (13%)</td>
<td>762/1325 (58%)</td>
<td>11+/6/1325 (1%)</td>
</tr>
<tr>
<td>ICM: C (n=95)</td>
<td>33/95 (35%)</td>
<td>1/33 (3%)</td>
<td>32/95 (34%)</td>
<td>0+/95 (0%)</td>
</tr>
<tr>
<td>TE: A (n=45)</td>
<td>36/45 (80%)</td>
<td>1+/36 (3%)</td>
<td>33/45 (73%)</td>
<td>0+/45 (0%)</td>
</tr>
<tr>
<td>TE: B (n=1335)</td>
<td>928/1335 (69%)</td>
<td>107/928 (12%)</td>
<td>806/1335 (60%)</td>
<td>10+/5/1335 (1%)</td>
</tr>
<tr>
<td>TE: C (n=243)</td>
<td>124/243 (51%)</td>
<td>22/124 (18%)</td>
<td>100/243 (41%)</td>
<td>2+/0/243 (1%)</td>
</tr>
</tbody>
</table>
VIDEO SESSION 1
VIDEO PROGRAM PRIZE SESSION

V-1 Monday, October 8, 2018 4:30 PM
UGMENTATION: FROM BACK TABLE TO EMBRYO TRANSFER. E. G. Richards,a R. Flyckt,a A. Tzakis,a C. Quintini,a K. Hashimoto,a T. Falcone.a aCleveland Clinic, Cleveland, OH; bCleveland Clinic, Weston, FL.

OBJECTIVE: To demonstrate our technique of uterus transplantation into a living recipient using a deceased donor model.

METHODOLOGY: We report the case of a recent successful uterus transplant from a deceased multi-organ donor. This video uses live action footage from surgery and detailed diagrams to review the process of enrollment into our research trial and the techniques used in the re-implantation procedure. Main outcome measures include long-term survival and cold ischemia time, onset of menstrual cycling, ultrasound and MRI imaging, and history from cervical biopsies.

CONCLUSIONS: Uterine transplantation is a rapidly evolving surgical treatment for uterine factor infertility. Extensive coordination and planning is required for a successful outcome. In addition to the many live births already reported following uterus transplant, many more are anticipated in the coming months, as research efforts accelerate worldwide.

V-2 Monday, October 8, 2018 4:42 PM
ROBOT-ASSISTED ORTHOTOPIC AND HETEROTOPIC OVARIAN TISSUE TRANSPLANTATION TECHNIQUES. K. Oktay,a T. Kawahara,b E. Taylan,a K. Hiraoka,a T. Ishikawa,b K. Kawai,a G. Cillo,a G. n. shah,d R. Ramasamy,a Urbology, University of Miami, Miami, FL; cUrology, University of Miami Miller School of Medicine, Miami, FL; dUrology, University of Miami, Miami, FL.

OBJECTIVE: To illustrate three major techniques of ovarian auto-transplantation that have been developed by us.

METHODOLOGY: A step-by-step video demonstration of three surgical techniques of ovarian auto-transplantation (OTT) in an academic center. Three patients who previously underwent ovarian tissue harvesting and cryopreservation for fertility preservation before gonadotoxic cancer treatments or radical cancer surgery are presented to illustrate three different surgical approaches to OTT. In general, all OTTs consist of three steps: 1) Microsurgical construction of the ovarian tissue graft, 2) Preparation of the recipient site, and 3) Transplantation of the reconstructed ovarian graft to the recipient site. The illustrated techniques include robot-assisted orthotopic (technique 1) and heterotopic (technique 2) approaches utilizing the da Vinci Xi (Intuitive Surgical Inc., CA, USA) robotic system and a decellularized human extracellular tissue matrix (Alloderm; LifeCell Corp., Branchburg, NJ, USA) as a tissue scaffold, as well as a percutaneous auto-transplantation approach (technique 3).

CONCLUSIONS: We illustrated three main techniques of OTT resulting in the restoration of ovarian function in all cases. Robotic ovarian transplanation may have several advantages, which include precision, more delicate graft handling and reduced time from tissue thawing to transplantation. The utility of the extracellular tissue matrix may enhance this technique by serving as a niche for ovarian reconstruction and potentially improving neo-vascularization. Percutaneous ovarian auto-transplantation is a simple approach which can be used in surgically high risk patients.

V-3 Monday, October 8, 2018 4:55 PM
ONCOFERTILITY PATIENT ADVOCACY: SPEAK UP, MAKE CHANGE. M. Thompson. Department of Quality and Safety - Patient and Family Advisory Council, Memorial Sloan Kettering Cancer Center, Stamford, CT.

Oncofertility patients are a unique population that come to fertility clinics emotionally devastated and without time to spare. These young adults are grappling with fears of mortality while deciding whether or not they have the ability, desire, time and access, to preserve their fertility and along with the hope of future family-building options. Patients desire care beyond treatment - and this starts with access. As financial barriers are often the limiting factor to patients access, the need for fertility preservation insurance coverage is increasingly recognized in public policy. In 2017 we saw the first state enact a law change to require fertility preservation coverage - a success attributed to patient-led advocacy - a citizen activist and a legislator, both with cancer. Part of healing for oncofertility patients can be making access to care easier for future patients. This video highlights an example of the importance of patient advocacy and showcases what success can mean if patients speak up for change.

V-4 Monday, October 8, 2018 5:05 PM
TRANSURETHRAL ABLATION OF PROSTATIC UTRICLE CYST USING HOLMIUM LASER. R. J. Carrasquillo,a L. F. Savio,b J. M. Dubin,c h. n. shah,d R. Ramasamy,a Urbology, University of Miami, Miami, FL; cUrology, University of Miami Miller School of Medicine, Miami, FL; dUrology, University of Miami, Miami, FL.

OBJECTIVE: The purpose of this video is to demonstrate a safe and effective approach to the treatment of obstructing midline prostate utricle cyst using holmium laser.

METHODOLOGY: A 33-year-old man presented with chronic pelvic pain, pain with ejaculation, and infertility. Semen analysis demonstrated oligo-asthenoteratozoospermia with the poor viability and CT scan identified the presence of a midline 2-3 cm prostatic cyst with dilated seminal vesicles bilaterally. Transrectal ultrasound in the office confirmed the diagnosis of midline obstructing prostatic utricle cyst and estimate distance from the urethra. Patient signed informed consent for surgery as well as the use of his medical records and creation of an instructional surgical video. The patient was then taken to the OR for transurethral ablation using holmium laser to un-roof the cyst. Retrograde vesiculography was performed to confirm patency of the ejaculatory ducts. Outpatient surgery was tolerated well and the patient discharged. Postoperatively at 4 weeks his symptoms had abated and semen analysis revealed normozoospermia.

CONCLUSIONS: We demonstrate safe and effective transurethral resection of a midline prostate utricle cyst with holmium laser. Preoperative transrectal ultrasound or cross-sectional imaging can be useful for operative planning. When the orifices of the ejaculatory ducts can be identified, vesiculography can be performed to confirm patency of the ducts and seminal vesicles after relief of the obstructing cyst.

V-5 Monday, October 8, 2018 5:17 PM
PIEZO-ICSI. K. Hiraoka,a T. Ishikawa,b K. Kawai,a T. Harada,a Kameda Medical and Dental University, Kamogawa, Japan; bUrology, University of Tokyo Medical and Dental University, Tokyo, Japan; cKameda IVF Clinic Makuhari, Chiba, Japan.

The Piezo-ICSI could perform the membrane breakage by applying a Piezo pulse which produced ultra-fast submicron forward momentum using flat-tipped micropettes with no-bevel or spike. Before performing the Piezo-ICSI, operation liquid was placed in the middle of the micropipette about 10-15 mm. Then the micropipette was inserted and clamped into the micropipette holder. The Piezo-micromanipulator drive unit was attached to the micropipette holder. After operation liquid was pushed to the tip of the micropipette, 7% PVP was aspirated into the micropipette. The sperm was then immobilized by applying a few Piezo pulses during the sperm’s tail was attached to the edge of the micropipette and aspirated into the micropipette. Without oocyte deformation, the micropipette was gently placed against the zona pellucida while Piezo pulses were applied, to allow the pipette to break through the zona pellucida and not the membrane. The sperm was advanced until the sperm head was near the tip of the micropipette, and the micropipette was advanced forward (to ~60 % of the oocyte diameter) to stretch the membrane. The breakage of the membrane was performed by applying one Piezo pulse without aspirating the cytoplasm. From the Piezo pulse, the sperm was injected into the oocyte. In our previous analysis, the calculated mean volume of cytoplasm aspirated into the micropipette with Conventional-ICSI (2746 ± 940 μm3) was significantly higher than with Piezo-ICSI (0 ± 0 μm3) (P < 0.05). In addition, significantly higher rates for survival (99% vs. 90%), fertilization (89% vs. 68%), good quality Day-3 embryo (55% vs. 37%), pregnancy (51% vs. 19%), implantation (31% vs. 19%), and live births (25% vs. 15%) were obtained when using the Piezo-ICSI.
VIDEO SESSION 2

**V-6 Tuesday, October 9, 2018 4:15 PM**

**HYSTEROSCOPIC RECOGNITION AND SUBSEQUENT MANAGEMENT OF UTERINE ARTERIOVENOUS MALFORMATION.** J. A. Gingold, L. D. Bradley.

**OBJECTIVE:** Uterine arteriovenous malformation (AVM) is a rare finding often associated with prior pregnancy or uterine surgery. Accurate recognition is mandatory prior to any uterine instrumentation, as biopsy or curettage can lead to unanticipated massive hemorrhage.

**METHODOLOGY:** This video describes the clinical history, workup and treatment of a 22 year old woman who presented with vaginal bleeding 9 weeks following a first-trimester termination of pregnancy. Her ultrasound demonstrated a heterogeneous vascular mass that was initially concerning for retained products of conception. Hysterectomy revealed a large pulsating bluish vascular mass that was recognized as a uterine AVM. Subsequent MRI and MRA confirmed the diagnosis and she underwent bilateral uterine artery embolization. Follow-up office hysteroscopy confirmed resolution of the AVM.

**CONCLUSIONS:** Uterine AVM is a rare but cannot-miss diagnosis. This video demonstrates its key characteristics on ultrasound, hysteroscopy, MRI/CT and angiogram.

**V-7 Tuesday, October 9, 2018 4:21 PM**

**SHAVING TECHNIQUES FOR PERITONEAL AND DEEPLY INFILTRATIVE ENDOMETRIOSIS.** J. L. Hudgens, H. Ramadan, L. Vignali.

**OBJECTIVE:** The purpose of this video is to present shaving techniques for patient with peritoneal and deeply infiltrative endometriosis.

**METHODOLOGY:** Patients with infertility and pelvic pain often present with findings of endometriosis. Some patients present with multifocal peritoneal lesions that may overlie the ureter, bladder, or rectum. In some patients, a shaving technique for excision of endometriosis may be a viable approach. In our video we will present shaving techniques for the excision of these lesions. Our video will highlight the fundamentals of the dissection including tissue traction, avascular dissection, and safe use of electrosurgery.

**CONCLUSIONS:** For some patient with superficial or deeply infiltrative endometriosis, a shaving excisional technique is a safe and effective treatment option.

**V-8 Tuesday, October 9, 2018 4:29 PM**

**OVARIAN TISSUE VITRIFICATION USING OPEN AND CLOSED DEVICES, AND THAWING PROCEDURE.** Y. Sugishita, T. Kawahara, E. Taylan, K. Oktay, N. Suzuki. Department of Obstetrics and Gynecology, Center for Reproductive Medicine, St. Marianna University, School of Medicine., Kawasaki, Kanagawa, Japan.

**OBJECTIVE:** To demonstrate ovarian tissue vitrification technique using open (Cryo Device Type M, Kitazato, Japan) and closed (Cryo-Sheet, Kitazato, Japan) devices, and thawing procedure for fertility preservation.

**METHODOLOGY:** A step by step video demonstration of ovarian tissue vitrification and thawing procedure. Following oophorectomy, ovary was placed in saline and brought to the laboratory on an ice pack for cryopreservation. Cryopreservation procedure was performed under sterile conditions. Initially, the ovary was transferred to tissue culture media (modified HTF), examined for visible antral follicles and then the observed follicles were aspirated using an 18-gauge syringe. The collected follicular fluid was transferred to a petri dish and examined under an optical microscope for healthy oocytes. The identified mature oocytes were directly cryopreserved, while immature oocytes were primarily subjected to in vitro maturation process and matured oocytes were frozen. Subsequently, the ovary was cut into two halves, and the medulla was removed from the ovarian cortex by gentle dissection using a curved scissors until the cortical thickness reaches to approximately 1-mm. Ovarian cortex was cut into 10x10 mm small pieces, and then cortical pieces were transferred sequentially to cryoprotectant solutions which were composed of different concentrations of ethylene glycol and sucrose (Ova Cryo Kit Type M, Kitazato, Japan). At the final step of the cryopreservation, the cortical samples were loaded on to the open and closed devices, inserted directly into the liquid nitrogen, and were stored for future use. For thawing procedure, both open and closed devices loaded with cortical samples were initially placed in step 1 thawing media warmed at 37 °C, and then cortical pieces were sequentially subjected to thawing solutions (Ova Thawing Kit Type M, Kitazato, Japan).

**CONCLUSIONS:** Ovarian tissue cryopreservation is an essential procedure for fertility preservation, and it can be successfully performed via vitrification method using either open or closed devices. We have previously shown that histological evaluation of thawed samples from vitrified ovarian tissues provided similar follicular viability features to slow-frozen ovarian tissues.
hemostatic resection. Following this, the patient underwent frozen embryo transfer resulting in an intrauterine pregnancy.

CONCLUSIONS: Although methotrexate administration is often first line therapy of cervical ectopic pregnancy, surgical management can be indicated when there is methotrexate treatment failure or contraindications to administration. In this video we have emphasized a unique technique for resolution of a cervical ectopic pregnancy as a consequence of ART with focus on uterine preservation. We urge you to carefully consider introduction of this technique for use in your patients with similar complications following ART.

References:

V-10 Tuesday, October 9, 2018 4:50 PM

2-PORT MYOMECTOMY TECHNIQUE FOR A TYPE 2-5 LEIOMYOMA
J. L. Hudgens, B. Deyeler, M. Thomas, M. Smith, Eastern Virginia Medical School, Norfolk, VA; University of MS Medical Center, Madison, MS; OBGYN, Eastern Virginia Medical School, Norfolk, VA.

OBJECTIVE: The purpose of this video is to present a two port myomectomy technique for a type 2 through 5 leiomyoma with significant distortion of the endometrial cavity.

METHODOLOGY: The approach to minimally invasive myomectomy has been revisited since the F.D.A warning placed on electromechanical morcellation. The introduction of new technologies has given the opportunity for technological advancements and improvement in surgical outcomes. In this video we will present a novel technique to minimally invasive myomectomy that requires the use of only two laparoscopic ports. The utilization of a gel port at the umbilicus allows the use of both a laparoscope and an instrument at the umbilicus. This allows the procedure to be performed with the addition of a single 5mm trocar in the right lower quadrant. The use of a 45 degree bariatric laparoscope at the umbilicus allows for adequate triangulation of the instruments and the target anatomy.

In this video we will present a 27 year old nulliparous patient that presented with menorrhagia and infertility. Transvaginal ultrasound revealed a 6cm type 2-5 leiomyoma with significant distortion of the endometrial cavity. We will demonstrate a technique for enucleation of the submucous component of the leiomyoma including repair of an endometrial defect. Our video will also highlight the advantages of the 2 port technique which include improved traction of the leiomyoma, ideal ergonomics for suturing, and a cosmetic tissue extraction site.

CONCLUSIONS: Our 2 port laparoscopic techniques offers a minimally invasive approach to myomectomy that is safe, cosmetic and offers some ergonomic advantages over traditional laparoscopic techniques.

V-11 Tuesday, October 9, 2018 4:58 PM

GENTLE HYSTEROSCOPIC INTRAUTERINE INSEMINATION FOR EXTREME VAGINISMUS
J. P. Parry, M. C. Thomas, S. J. Estes, L. Dormann, V. L. Butler, S. R. Lindheim, Positive Steps Fertility, Madison, MS; Obsetrics & Gynecology, University of Mississippi Medical Center, Jackson, MS; Penn State Health, Hummelstowm, PA; Wright State Integrated OB, GYN Residency Program, Dayton, OH.

OBJECTIVE: The purpose of this video is to teach viewers how to perform vaginoscopy and hysteroscopic insemination for patients with high risk for false passages or extremes of pelvic discomfort.

METHODOLOGY: We present a case report for a 29 year old G0 with one year of subfertility associated with diminished ovarian reserve (AFC = 4), ulcerative colitis and extreme vaginismus previously unalleviated by dilators, SSRIs, and vaginal diazepam. Her first attempt at insemination with a pedi- atric speculum led to such discomfort and pelvic tension that post-procedural pelvic relaxation led to marked focal incontinence and meaningful embarrassment. Vaginoscopy and hysteroscopy are performed with a 2.9 mm flex- ible hysteroscope with saline as vaginal distention media and sperm wash media for distention media started after reaching the cervical os. Insemina- tion is performed through sperm introduction via the inflow channel.

CONCLUSIONS: The patient described the vaginoscopy with hystero- scopic intrauterine insemination as markedly decreasing discomfort when compared with her prior classic insemination with speculum use. The patient also conceived twins with the procedure. Much of the literature on hystero- scopic insemination is in equine models or predates ICSI for humans. Small caliber flexible endoscopes with high resolution allow gentle, effective, and efficient therapy in patients with high risk for false tracts or extreme vagi- nismus. The demonstrated technique combines two core REI skills in a way that facilitates dignity and safety in patients with exceptional discomfort or difficult anatomy.

V-12 Tuesday, October 9, 2018 5:05 PM

ENDOSCOPIC LASER LITHOTRIPSY FOR SEMINAL VESICLE CALCULI
F. Tenorio Lira Neto, J. Borges Cabral Junior, M. P. Correia, R. Prado Lyra, R. J. Lisboa Lyra, Andros Recife, Recife, Brazil; Universidade de Pernambuco, Recife, Brazil; facultade de medicina de olinda, Olinda, Brazil.

Seemal vesicle stones were first reported by White in 1926. Two hundred fourteen cases have been described so far. In this video, we review some basic aspects of seminal vesicle calculi and report a case performed in our institu- tion. Haematospermia is the most common symptom, present in 70% of the cases. Ejaculatory pain is also common and may be felt in the perineum or scrotum. Patients may also present with hypo- spermia, infertility, and urinary tract infections, such as seminal vesiculitis and prostatitis. The physical exam of these patients is usually unremarkable, with normal testes, epididymides and vasa. If the seminal vesicles are enlarged, they can be sometimes palpable during digital rectal examination. Semen analysis often reveals low volume, pH and fructose levels due to absence of seminal vesicle fluid. Increased red blood cells count and decreased sperm count can also be found. Transrectal ultrasonography is a safe, effective and inexpensive imaging mo- dality. It has detected 50% of the reported cases of seminal vesicle calculi and is considered the first line exam. Magnetic resonance imaging is more sen- sitive than transrectal ultrasonography because seminal vesicle calculi have a high protein and low calcium content. In addition, it provides more detailed anatomic information and better calculi measurement, and it has the potential to detect hemorrhage site. It can be used as first line imaging modality in patients with high risk for false tracts or extreme vaginismus. Transrectal ultrasonography is a safe, effective and inexpensive imaging modality. It has detected 50% of the reported cases of seminal vesicle calculi and is considered the first line exam. Magnetic resonance imaging is more sensitive than transrectal ultrasonography because seminal vesicle calculi have a high protein and low calcium content. In addition, it provides more detailed anatomic information and better calculi measurement, and it has the potential to detect hemorrhage site. It can be used as first line imaging modality or if transrectal ultrasound is unable to provide adequate information. The first treatment modalities used were open surgery to extract calculi. These were followed by laparoscopic procedures. With the introduction of the resecto- scope, resection of the ejaculatory ducts became the gold-standard treat- ment. Recently, more sophisticated endoscopic equipment allowed the development of even less invasive techniques, and the seminal vesiculotomy couple with laser lithotripsy has been performed. The patient was a twenty- one years old healthy male. He had a history of right orchiepididymitis with painful ejaculations, which was treated with antibiotics and resolved within one week. One month later he observed decreased semen volume that pro- gressed to aspermia. He didn’t complain of hematospermia, and his semen analysis revealed aspermia. An MRI was performed and showed bilaterally dilated ejaculatory ducts, and thickening of both seminal vesicles walls. Several calculi were found in both ejaculatory ducts and in the right seminal vesicle, the largest measuring 1 centimeter. In conclusion, seminal vesicle calculi should be remembered in patients with some ejaculatory symptoms. Seminal vesiculotomy coupled with laser lithotripsy is an effective treat- ment.

V-13 Tuesday, October 9, 2018 5:12 PM

ROBOT ASSISTED LAPAROSCOPIC MYOMECTOMY FOR SUBMUCOSAL MYOMA
M. Kim, Y. Chung, H. Hwang, J. Namkung, Y. Han, Department of Obstetrics and Gynecology, Seoul St. Mary’s Hospital, College of
OBJECTIVE: To review the surgical method for submucosal myoma as robot-assisted laparoscopic myomectomy.

METHODOLOGY: 35 year old woman with heavy menstrual bleeding and history of three times of IVF failure visited Seoul St. Mary's hospital. She was married, and have no cause of infertility except myomas. Submucosal myoma was diagnosed by pelvic ultrasonography. Pelvic MRI was performed for detecting exact location and sized of the lesion. Multiple myomas including 3.2cm sized submucosal myoma were noted. The robot-assisted laparoscopic myomectomy was performed under general anesthesia. We navigate submucosal myoma with real time hysterosonography. During enucleation, endometrial cavity was distinguished by carmin fluid filling. Exact border between myoma and endometrium was noted, so myoma could be removed without endometrial injury. Remaining myometrium was sutured layer by layer with PDS. Measurements and Main Results Heavy menstrual bleeding was nearly disappeared after surgery. Three months after surgery, patient had pelvic ultrasonography for evaluating status of uterus. There was no remaining myomas in pelvic ultrasonography.

CONCLUSIONS: Myoma is one of common gynecologic disease. Especially submucosal myoma causes severe menstrual bleeding and subfertility. Traditionally submucosal myoma is removed thorough hysteroscopy. However, if the myoma is big, hysteroscopic resection could be difficult and injured endometrium too large area. Robot assisted laparoscopic myomectomy can be one of choice for submucosal myoma patients who want to fertility preservation.

SUCCESSFUL CASE REPORT.

VIDEO SESSION 3

V-14 Wednesday, October 10, 2018 3:45 PM

LAPAROSCOPIC OVARIAN TRANSPOSITION- A REVIEW OF INDICATIONS, TECHNIQUES AND EXPECTED OUTCOMES, HIGHLIGHTED BY A SUCCESSFUL CASE REPORT. J. Friedman, S. Butler, M. Milad. Obstetrics and Gynecology, Northwestern University, Chicago, IL.

OBJECTIVE: To review the indications, approaches and expected outcomes of ovarian transposition as highlighted by a specific case report.

METHODOLOGY: Ovarian transposition involves preserving ovarian function by repositioning the ovaries out of the field of radiation. Candidates include reproductive age women who will be undergoing pelvic radiation who wish to preserve their fertility or prevent premature menopause. Research suggests that many of the appropriate candidates do not receive adequate information regarding this procedure. The two approaches to ovarian transposition are the medial and lateral approach, wherein the ovaries are transposed to the uterosacral ligaments or the anterolateral side walls, respectively. The lateral approach is used when more extensive radiation is planned, and it has also been associated with better outcomes. A review of the literature demonstrates success rates between 70-90% after ovarian transposition. When used to prevent premature ovarian failure, success is measured by lack of menopausal symptoms with or without serum FSH and E2 levels post-radiation. Higher success is seen in younger patients who do not undergo any concurrent chemotherapy and whose total radiation dose is less than 4 Gray. Our patient is a 36 year-old female undergoing bilateral ovarian cystectomy for dermoid cysts.

CONCLUSIONS: The success of ovarian transposition is dependent upon the surgical technique used. When performed properly, ovarian transposition can be successful in preventing premature menopause. Further research is needed to determine the optimal surgical technique for ovarian transposition.

V-15 Wednesday, October 10, 2018 3:52 PM

INTRAOPERATIVE MANAGEMENT OF DERMOID CYST RUPTURE. C. Fortin, C. Hur, T. Falcone. Obstetrics & Gynecology, Cleveland Clinic, Cleveland, OH.

OBJECTIVE: The objective of this video is to review operative techniques for managing intraoperative rupture of a dermoid cyst. We describe the case of a 36 year old female undergoing bilateral ovarian cystectomy for dermoid cysts.

METHODOLOGY: The following tips can be helpful in managing intraoperative dermoid cyst rupture: 1) Fill the pelvic preemptively with irrigation so that when rupture occurs, fatty components will float on the surface, 2) Reverse Trendelenburg position to keep cyst contents within the pelvis, 3) Use a 10 mm suction-irrigator for more rapid irrigation and suction of larger cyst contents, and 4) Irrigate copiously with several liters of warmed fluid, until aspirated fluid is clear.

CONCLUSIONS: Intraoperative rupture of a dermoid cyst can be difficult to manage with consequent morbidity such as chemical peritonitis. The use of appropriate surgical technique can improve efficiency and minimize this risk.

V-17 Wednesday, October 10, 2018 4:00 PM

PREDICTIVE VALUE OF DYNAMIC TRANSVAGINAL ULTRASOUND FOR EVALUATING PELVIC ORGAN MOBILITY: SURGICAL AND REPRODUCTIVE IMPLICATIONS. J. Tan, A. H. Yosef, C. Allaire, P. Yong, M. A. Bedaiwy. Obstetrics & Gynecology, University of British Columbia, Vancouver, BC, Canada; Clinical Professor, UBC department of OB/Gyn, Vancouver, BC, Canada; BC Women’s Hospital, Vancouver, BC, Canada; Obstetrics and Gynecology, University of British Columbia, Vancouver, BC, Canada.

OBJECTIVE: To review the techniques of dynamic transvaginal ultrasound (TV-US) for evaluating pelvic organ mobility and demonstrate the components of a positive and negative ‘sliding sign’ with respect to deep infiltrating endometriosis (DIE) involving the pouch of Douglas (POD).

CONCLUSIONS: The predictive value of TV-US for evaluating POD obliteration and summarize the surgical and reproductive implications of a negative sliding sign with regards to endometriosis-associated infertility and management of deep infiltrating endometriosis involving the posterior compartment of the pelvis.

METHODOLOGY: Animated diagrams, laparoscopic video, and pelvic ultrasonography will be employed to review the anatomic components and procedural techniques involved in dynamic TV-US, specifically in regard to evaluating POD obliteration in the retro-cervical space and at the level of the upper uterus and fundus. Based on an analysis of clinical data from a prospective data registry at a tertiary care clinic in Vancouver, BC, we will also present data in support of dynamic TV-US compared to standard bimanual examination for diagnosing POD obliteration in patients with suspected endometriosis.

CONCLUSIONS: Evaluating pelvic organ mobility is important for both surgical and reproductive treatment planning. In this regard, non-invasive point-of-care evaluation of the sliding sign by TV-US in patients with suspected endometriosis has superior sensitivity, and similar specificity as pelvic examination for the prediction of pouch of Douglas obliteration. Ultimately, dynamic TV-US may also have the potential to challenge traditional laparoscopy as the ‘gold standard’ modality for evaluating posterior compartment DIE. However, further research is required to assess the benefits of dynamic TV-US for predicting the endometriosis fertility index without resorting to invasive laparoscopy.
LAPAROSCOPIC APPROACH TO CORNITAL ECTOPIC: A STEP-BY-STEP DEMONSTRATION. R. M. Wynnott, E. Mikhail. Obstetrics and Gynecology, University of South Florida, Tampa, FL.

OBJECTIVE: A step-by-step demonstration of the resection of a large cornual ectopic pregnancy, highlighting laparoscopic techniques.

METHODOLOGY: A 31 year old G2P1001 at 9 weeks 0 days by transvaginal ultrasound and a beta hCG of 13,099 presented to the emergency department for vaginal bleeding and cramping left lower quadrant pain. Her ultrasound was suspicious for cornual ectopic pregnancy, which was confirmed by MRI. She was taken to the operating room for resection. Patient underwent laparoscopic resection of a large cornual ectopic pregnancy. Her pathology was confirmatory and her beta hCG decreased as expected. She had a normal post-operative course.

CONCLUSIONS: Laparoscopic cornual resection is a safe and effective method for management of large cornual ectopic pregnancy.

EXCISION OF ADENOMYSOSIS IN THE SETTING OF RECURRENT IVF FAILURE. R. M. Wynnott,* E. New,* A. Imudia. *Obstetrics and Gynecology, University of South Florida, Tampa, FL; †University of South Florida, Tampa, FL.

OBJECTIVE: To demonstrate robotic assisted laparoscopic excision of adenomyosis to improve success of in vitro fertilization in select patients.

METHODOLOGY: 37-year-old female presenting to infertility clinic after one spontaneous pregnancy that resulted in spontaneous abortion. She was initially referred for workup of possible male factor infertility. Following comprehensive fertility testing, she underwent a cycle of in vitro fertilization (IVF), conceived, and had a biochemical pregnancy. This occurred with her second cycle of IVF as well. She then underwent a workup for recurrent pregnancy loss, including antiphospholipid antibody syndrome testing, which was essentially negative. She subsequently underwent 2 additional cycles of IVF, with positive pregnancy tests followed by declining beta hCG both times. Patient was highly suspected to have adenomyosis given sonographic appearance of the uterus during follicular monitoring and early pregnancy assessments. Given this suspicin, pelvic MRI with and without contrast was recommended. Her MRI revealed a focal adenomyoma in the posterior uterus. The patient was counseled that the extent and severity of her adenomyosis may be inducing inflammation that could be interfering with successful implantation of the embryos. Given that most of the disease was on the posterior wall and was focal, an attempt could be made at resection to reduce the inflammatory burden on the uterus and future pregnancy. The patient opted for robotic assisted laparoscopic excision of adenomyoma. Her pathology was confirmatory and she had a normal post-operative course. She underwent hysteroscopy three months later and had a normal endometrial cavity. She then underwent an IVF cycle.

CONCLUSIONS: The patient is currently pregnant with appropriately rising beta hCGs. Robotic assisted laparoscopic excision of adenomyosis may be a useful procedure in patients with recurrent pregnancy loss and otherwise negative recurrent pregnancy loss testing and suspicion for focal adenomyosis on imaging.

STRATEGIES FOR MINIMIZING OVARIAN INJURY DURING THE SURGICAL TREATMENT OF OVARIAN ENDOMETRIOSIS. N. C. Llarena, T. Falcone. Cleveland Clinic, Cleveland, OH.

OBJECTIVE: Surgical treatment of ovarian endometriosis has the potential to compromise ovarian reserve. Here we demonstrate surgical strategies to minimize ovarian injury and highlight the utility of a helium plasma device during ovarian cystectomy.

METHODOLOGY: This video demonstrates the surgical treatment of an endometrioma in a 25-year-old nulliparous patient with chronic pelvic pain. Preoperative MRI revealed a L endometrioma and hydrosalpinx, and the patient was consented for ovarian cystectomy and salpingectomy. The ovarian cortex overlying the endometrioma is incised using a helium plasma device, and the endometrioma is dissected away from the ovarian parenchyma. Hydrodissection assists in separating the cyst wall from the ovarian stroma, and plasma energy is used to separate fibrinous adhesions between the endometrioma and ovarian tissue. Bipolar electrocautery is used sparingly to achieve hemostasis.

CONCLUSIONS: Meticulous surgical technique and judicious use of electrocautery may help minimize damage to the ovary. Endometriomas should be enucleated rather than coagulated or vaporized to reduce recurrence rates and optimize fertility.
O-265 Wednesday, October 10, 2018 10:45 AM

ARTIFICIAL INTELLIGENCE AS A NOVEL APPROACH FOR EMBRYO SELECTION. A. Tran,1 S. Cooke,2 P. J. Illingworth,3 D. K. Gardner.4 Harrison AI, Willoughby, Australia; 3IVF Australia, Greenwich, Australia; 2Melbourne IVF, East Melbourne, Australia.

Abstract:

OBJECTIVE: To develop and validate an artificial intelligence (AI) system that directly predicts the probability that an embryo can lead to a pregnancy with a fetal heart (FH) following embryo transfer (ET), through the automated analysis of raw time-lapse (TL) video sequences.

DESIGN: The authors used AI to analyse TL videos. All embryos were included regardless of their development stage, grade, ploidy, fertilization status, culture method and duration. IVF and ICSI cycles were both included. The TL cycles were collected from 8 laboratories in 4 countries between 2014 and early 2018. All patients were included with a mean age of 35.6 years (age range: 22-50 years). The primary outcome measure was the presence of a FH. The two possible outcomes were defined as: (a) YES (FH detected at 6-8 weeks of gestation), or (b) NO (ET with a negative FH or discarded embryos due to cleavage arrest, abnormal fertilization, aneuploidy or very poor morphology; single ET and double ET with either a negative FH or two FHs were included.

MATERIALS AND METHODS: The AI is a deep neural network trained with a large multicentre, multinational dataset of TL videos to perform binary classification tasks. From training, it empirically derived spatial-temporal features from the TL videos that are effective in predicting FH outcome independent of maternal age and specific culture method. Once trained, the neural network took a raw TL video as the input and produced a continuous probabilistic score (range 0-100%) as the output. This score was calibrated to the probability that the given embryo would develop into a FH. A total of 10,208 embryos from 1,603 patients were extracted. 2000 embryos were transferred, 73% of which were single ET, 14% double ET resulting in only one FH and 4.6% recovery in the other two groups combined (p = 0.034, F = 4.89). For uniformity, the data were reanalyzed after restriction to the single largest chemotherapy group (AC-T: Doxorubicin+Cyclophosphamide followed by Paclitaxel; n = 85). The geometric mean AMH recoveries for these new groups (n = 25, 46 and 16, respectively) were 3.2%, 4.7% and 1.3%. When the BRCA mutation positive group was compared with other two groups, the former had significantly worse recovery of serum AMH levels (ANOVA, p = 0.04, F = 4.2). In mouse oocytes exposed to chemotherapy, BRCA gene suppression resulted in significantly lower survival compared to controls (40.5% vs. 58.95% p = 0.03).

CONCLUSIONS: These data show that DNA DSB repair function is critical in oocyte survival against gonadotoxic CT and women with breast cancer and pathogenic BRCA mutations have increased liability to CT-induced ovarian reserve loss. These findings increase our understanding of the mechanism of chemotherapy-induced ovarian damage as well as pointing to the need to preferentially counsel BRCA mutation carriers for fertility preservation before CT.

References: None.

Financial Support: Virtus Health Ltd

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O-266 Wednesday, October 10, 2018 11:00 AM

INCREASED CHEMOTHERAPY-INDUCED OVARIAN RESERVE LOSS IN WOMEN WITH BRCA MUTATIONS: A PROSPECTIVE LONGITUDINAL STUDY WITH MECHANISTIC CONFIRMATION. K. Oktay,1 G. Bedoschi,4 S. Goldfarb,6 S. Titus,7 G. Palomaki,2 M. Dickler.3 1OB/GYN, Yale School of Medicine, New Haven, CT; 2MSKCC, New York, NY; 3Women & Infants Hospital, Providence, RI.

Abstract:

OBJECTIVE: BRCA1 and 2 are the members of ATM-mediated double strand break (DSB) repair pathway, critical in maintaining the human genome integrity against genotoxic insult. DNA repair efficiency appears to play a key role in oocyte aging and women with BRCA mutations may have accelerated ovarian aging due to deficient DNA DSB repair in their oocytes.1-8 Further, more, gonadotoxic chemotherapy (CT) causes DSBs in oocytes, which trigger apoptotic death of human primordial follicles.9 Hence, we hypothesized that because the oocytes of women with BRCA mutations are DNA DSB repair deficient, they may be more likely to lose their ovarian reserve after CT.

METHODS AND METHODS: Women with early stage breast cancer were enrolled before CT between 2009 and 2017. Sera were obtained at baseline and 18 to 24 months after CT. Stored sera were assayed for AMH and the values were age adjusted. Of the 235 enrolled, 117 evaluable women were stratified into three groups: those never tested (n = 38), those negative (n = 65) or positive (n = 14) for a pathogenic BRCA mutation. Ovarian recovery was defined as the geometric mean of the post CT-age adjusted AMH levels compared to baseline. Additionally, to confirm the biological basis, BRCA gene function was suppressed in mouse oocytes via microinjection of interfering RNA (siRNA), which were then in vitro cultured with doxorubicin (n = 128 oocytes) and sham injected sibling oocytes (n = 69) served as controls.

RESULTS: Compared to the lower risk (BRCA-untested) control group, base-line AMH levels averaged 76% and 66% in those negative or positive for BRCA mutations (p = 0.0178). The geometric mean recoveries for the not tested, BRCA negative and BRCA positive groups were 3.7%, 5.2% and 1.6%, respectively. The mean recovery in the BRCA mutation positive group was about one-third the 4.6% recovery in the other two groups combined (p = 0.034, F = 4.89). For uniformity, the data were reanalyzed after restriction to the single largest chemotherapy group (AC-T: Doxorubicin+Cyclophosphamide followed by Paclitaxel; n = 85). The geometric mean AMH recoveries for these new groups (n = 25, 46 and 16, respectively) were 3.2%, 4.7% and 1.3%. When the BRCA mutation positive group was compared with other two groups, the former had significantly worse recovery of serum AMH levels (ANOVA, p = 0.04, F = 4.2). In mouse oocytes exposed to chemotherapy, BRCA gene suppression resulted in significantly lower survival compared to controls (40.5% vs. 58.95% p = 0.03).

CONCLUSIONS: These data show that DNA DSB repair function is critical in oocyte survival against gonadotoxic CT and women with breast cancer and pathogenic BRCA mutations have increased liability to CT-induced ovarian reserve loss. These findings increase our understanding of the mechanism of chemotherapy-induced ovarian damage as well as pointing to the need to preferentially counsel BRCA mutation carriers for fertility preservation before CT.

References: None.

Financial Support: NIH RO1 HD053112

O-267 Wednesday, October 10, 2018 11:15 AM

EFFECTIVENESS OF THE NATURAL CYCLES FERTILITY AWARENESS BASED APPLICATION AS A METHOD OF PREGNANCY PREVENTION. J. Bull,4 S. Rowland,4 E. McIlwaine,4 K. GemzellDanielsson,5 J. Trussell,6 E. Berglund Scherwitzl,7 R. Scherwitzl.8 4NaturalCycles NordicAB, Stockholm, Sweden; 5Department of Clinical Sciences at Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden; 6Office of Population Research, Princeton University, Princeton, NJ.

Abstract:

METHOD OF PREGNANCY PREVENTION.

FERTILITY AWARENESS BASED APPLICATION AS A EFFECTIVENESS OF THE NATURAL CYCLES

LAT-BREAKING ABSTRACTS
Abstract:

O-268 Wednesday, October 10, 2018 11:30 AM

CHROMOSOME MOSAICISM IS IMPACTED BY COMPROMISED EMBRYO CULTURE CONDITIONS.

M. Katz-Iaffe, a J. Parks, b S. McReynolds, c L. Henry, a W. B. Schoolcraft, a Colorado Center for Reproductive Medicine, Lone Tree, CO; Fertility Genetics, Colorado Center for Reproductive Medicine, Lone tree, CO; Fertility Genetics, Colorado Center For Reproductive Medicine, Lone Tree, CO.

Abstract:

OBJECTIVE: Chromosome mis-segregation during embryonic mitotic cell division is responsible for the generation of mosaicism. Estimates of embryonic chromosomal mosaicism in the literature have been inconsistent with potentially high rates influenced by clinical IVF laboratory procedures. The aim of this study was to evaluate the impact of compromised embryo culture conditions on the incidence of chromosomal mosaicism.

DESIGN: Research Design

MATERIALS AND METHODS: Infertile patients (n=434) with vitrified zygotes underwent warming for culture to the blastocyst stage utilizing standard optimized culture conditions at 5% O₂ and appropriate CO₂ in a commercial sequential media (Control). Tubal trophoderm biopsies were performed upon observation of the inner cell mass, and analyzed for aneuploidy using the VeriSeq® NGS platform (Illumina). The test group included surpluses frozen and cryopreserved, normally fertilized zygotes with unknown chromosome numberation were donated with patient and IRB consent. After warming, zygotes were cultured in the same commercial sequential media at compromised 20% O₂ and reduced CO₂. Individual blastocysts were dissected into 4 segments (n=60), followed by blinded analysis for aneuploidy at the same genetics laboratory. Results for all 4 segments were compiled together for a comprehensive chromosomal picture of each individual blastocyst. Mosaicism rates were calculated and statistical analysis included Fisher’s exact test, significance at P<0.05.

RESULTS: The overall incidence of chromosome mosaicism, following TE biopsy of 2,997 blastocysts generated from vitrified zygotes and cultured under optimized culture conditions was observed at 2.3%. In contrast, there was a significant increase in the incidence of mosaicism for human blastocysts cultured under compromised laboratory conditions (Test=20% vs. Control=2.3%; P=0.0003). The majority of the embryonic mitotic errors (67%) observed in these mosaic blastocysts cultured under compromised conditions were anaphase lag. This resulted in the presence of two populations, one euploid and one monosomy for a single chromosome, which typically included a smaller size chromosome. Of the remaining blastocysts cultured under compromised laboratory conditions, 60% were uniformly euploid and 20% were uniformly aneuploid.

CONCLUSIONS: This novel study revealed an impact of compromised embryo culture conditions on mitotic cell division and chromosome segregation resulting in post-zygotic errors and thereby elevating the expected biological representation of chromosomal mosaicism. Additionally, this study affirms that chromosomal mosaicism in blastocysts cultured under optimized laboratory conditions more closely resembles the low incidence of mosaicism in human clinical pregnancies (1%-2%).

Abstract:

O-269 Wednesday, October 10, 2018 11:45 AM

STEM CELLS INJECTION IN THE OVARY INCREASED THE OOCYTE AND EMBRYO PRODUCTION IN BOVINE FEMALES. J. G. Soares, a G. F. Rossi, a B. M. Bayeux, c R. C. Rochetti, b G. F. Maoraz, a F. M. Elliff, f Y. F. Watanabe, b F. M. Monteiro, e N. N. Rodrigues, i J. S. Sales, b M. F. Nogueira, a P. S. Barusselli, a E. G. Lo Turco, a UNIFESP, Sao Paulo, Brazil; b UNIFESP, São Paulo, Brazil; c UNIFESP, Jaboticabal, Brazil; d USP, Sao Paulo, Brazil; e UNIFESP, Sao Paulo, Brazil; f Vitrogen – YVF Biotech, Cravinhos, Brazil; g IZ-APTA, Sertãozinho, Brazil; h UPLA, Lavras, Brazil; i UNESP, Assis, Brazil.

Abstract:

OBJECTIVE: The aim of this study was to evaluate the follicular population, oocytes recovery rate per OPU and embryo production after the injection of allogeneic mesenchymal stem cells (MSCs) in the ovarian cortical layer.

DESIGN: 27 Nelore (Bos indicus) cows were synchronized for follicular growth wave [D-65: injection of an intravaginal P4 device (1.0 g) and administrations of EB (2.0 mg im) and PGF2α (0.53 mg im)]. On D-60 the P4 device was removed and the animals submitted to ultrasonographic evaluations and ovum pick up (OPU) followed by in vitro embryo production (IVEP) at 30-day intervals (D-30 and D0). On D1, cows were distributed to one of three experimental groups: CONT (no stem cells application; n=7), MSC1 (MSCs application in one ovary - 5x10⁶ cells per ovary - n=10) and MSC2 (MSCs application in two ovaries - 5x10⁶ cells per ovary - n=10).

MATERIALS AND METHODS: Allogeneic MSCs from adipogenic origin were isolated and cultivated in IMDM medium with 20% FBS and 1% P/S, at 37 °C in 5% of CO₂ for cellular expansion from third passage. MSCs were characterized by Flow Cytometry, with the CD44 and CD29 as positive markers, presenting 93.2% and 98.4% positivity and the CD18 and CD45 negative markers, that showed 96% and 99.4%. After MSCs application, the cows of all groups were again submitted to follicular synchronizations, ultrasonographic evaluations and OPU-IVEP procedures (n=30, 60, 90, 120, 150 and 180 days). The data were analyzed as time-repeated measures using the GLIMMIX procedure of SAS.

RESULTS: After the MSCs treatment was observed interaction between treatment and time for the numeric variables: total follicles aspirated (P=0.001) total oocytes retrieved (P=0.01), viable (P=0.03) and cleaved (P=0.02), total embryos per OPU session (P=0.01) and hatched blastocysts (P=0.05). In cows receiving MSCs, the production curve of numeric variables presented less reduction in time in relation to CONT group. Interaction between treatment and time was not observed for the rates evaluated. It was
verified that cows receiving MSCs had an increase in the oocytes recovery rate (CONT = 62.6%, MSC1 = 62.8% and MSC2 = 67.8%; P = 0.01), viable oocytes rate (CONT = 63.0%, MSC1 = 64.3% and MSC2 = 67.8%; P = 0.01); cleaved rate (CONT = 63.8%, MSC1 = 67.9% and MSC2 = 64.5%; P = 0.03), blastocyst rate (CONT = 34.7%, MSC1 = 39.0% and MSC2 = 33.3%; P = 0.001) and hatched blastocysts rate (CONT = 26.8%, MSC1 = 31.5% and MSC2 = 26.2%; P = 0.0003).

CONCLUSIONS: We concluded that MSCs application increased the OPU-IVEP efficiency in bovine female models.

REFERENCES: None.

FINANCIAL SUPPORT: Fapesp 2012/50533-2 (GIFT)

O-270 Wednesday, October 10, 2018 12:00 PM

AUTOMATED SPERM MORPHOLOGY TESTING USING ARTIFICIAL INTELLIGENCE. P. Thirumalaraju, C. L. Bormann, M. Kanakasabapathy, F. Doshi, I. Souter, I. Dimitriadis, H. Shafiee. Brigham and Women’s Hospital, Harvard Medical School, Cambridge, MA; Massachusetts General Hospital-Harvard Medical School, Boston, MA.

Abstract: The standard methods for analyzing sperm morphology using Krueger strict grading criteria is time-consuming and is the main reason most semen analyses take >1 day to finalize. All proposed alternative technologies have either been too expensive or inaccurate for clinical cost-effectiveness. Thus, manual image-based sperm morphology assessment continues to be the gold standard modality in clinical semen analysis. A reliable, inexpensive, automated technology for sperm morphology testing can significantly improve clinical workflow for semen analysis.

DESIGN: We developed an artificial neural network, trained and validated with over 3,500 images of sperm acquired using clinical benchtop microscopes. To evaluate the developed artificial intelligence, we allowed the network to evaluate stained slide images that were available to us through the American Association of Bioanalysts (AAB) Proficiency Testing Service (PTS). The developed algorithm assessed a total of 9 semen samples on our system, evaluating at least 350 sperm images per sample.

RESULTS: When our network was tested with 415 individual sperm images, our network was able to correctly identify 371 sperm (~89%) based on annotations obtained from technicians. We then evaluated our network’s performance in assessing semen samples for sperm morphology testing. The network performed with an accuracy of 100% in identifying all abnormal and normal samples (n = 9) in comparison to the national average reported by the AAB. The sensitivity and specificity of the network was 100% with a positive and negative predictive values of 100%.

CONCLUSIONS: The reported artificial intelligence technology is inexpensive and can work with optical imaging systems currently used in most fertility clinics. Thus, the technology can be integrated into fertility clinics with very minimal principal and operational costs. Also, since our results suggest that this technology can perform with high accuracy reliably and rapidly, the reported technology in a clinical setting may significantly improve the clinical workflow for semen analysis.


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AUTHOR AND SPOUSE/PARTNER DISCLOSURES INDEX: ORAL AND POSTER SESSIONS

All speakers at the 2018 ASRM Annual Meeting and Postgraduate Courses were required to complete a disclosure form. These disclosures were reviewed and potential conflicts of interest resolved by the Subcommittee on Standards of Commercial Support of the Continuing Medical Education Committee. Each abstract or video author is listed below along with any relationships their partners/spouses disclosed.

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I may undertake paid consultancy for Myovant Sciences Inc in future during development of their kisspeptin analogue. The findings of this research have not been edited or censored by anyone from Myovant Sciences, Paid consultant (Myself)

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Glass, K. N/A, Dr. Gleicher is listed as co-inventor on a number of pending patent applications claiming diagnostic and therapeutic benefits from determination of CGG repeat numbers and ovarian FMRI genotypes and sub-genotypes. (Myself); Neureuticals, LLC, Dr. Gleicher is co-inventor of awarded U.S. patents, claiming therapeutic benefits for supplementation of DHEA in women with diminished ovarian reserve, a topic discussed in this talk. Other patent applications in regards to DHEA and other fertility-related claims, with no relationship to this talk, are pending. Dr. Gleicher receives royalties from, and owns shares in Fertility Neureuticals, LLC, a distributor of a DHEA product. (Myself)

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<td>Endpoint Outcomes, sponsorship by Allergan, Paid consultant (Myself)</td>
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<td>Rhoton-Vlasak, A. S.</td>
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<td>Robinson, K.</td>
<td>Invitae, Full-time company employee (Myself); Invitae, Direct stockholder (Myself)</td>
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<td>Rodriguez-Ginorio, D.</td>
<td>AbbVie, Investigator and served on advisory boards (Myself)</td>
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<td>Rohde, B.</td>
<td>Bayer AG, Pharmaceuticals, R&amp;D, Dept. of Clinical Sciences, Full-time company employee (Myself)</td>
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<td>Rosen, M.</td>
<td>DxNow, Clinical Advisory Board (Myself); OvaScience, Clinical Advisory Board (Myself); Ferring, Clinical Advisory Panel (Myself)</td>
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Ruiz-Alonso, M. Igenomix S.L., Full-time company employee (Myself & Spouse/Partner)

Sadruddin, S. Reproductive Biology Associates, Full-time company employee (Myself)

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<td>Velumani, A.</td>
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<td>Verhoeve, H.</td>
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<td>Vireque, A. A.</td>
<td>Invitra - Tecnologia da Reproducao Assistida LTDA, I’m co-founder of a startup focused in R&amp;D and research</td>
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<td>Abbvie, Honoraria (Myself); Allergan, Honoraria (Myself)</td>
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