Age is a better predictor of pregnancy potential than basal follicle-stimulating hormone levels in women undergoing in vitro fertilization

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Objective: To analyze to what extent the parameters of ovarian functional reserve including female age and basal FSH levels will affect the results of ovarian hyperstimulation and IVF outcome.

Design: Retrospective cohort study.

Setting: University hospital infertility center.

Patient(s): One thousand forty-five women undergoing their first cycle of IVF with ovarian stimulation after pituitary desensitization.

Intervention(s): None.

Main Outcome Measure(s): Cycle parameters, cancellation rate, implantation rate, and pregnancy rate.

Result(s): Both increasing age and basal FSH were associated significantly with reduced numbers of oocytes collected, oocytes fertilized, and embryos transferred. The combined use of age and basal FSH significantly improves the predictive power for these parameters. Increasing age, but not basal FSH, was associated significantly with reduced implantation rate and pregnancy rate. Logistic regression analysis revealed that age, but not basal FSH, was an independent predictor of pregnancy rate. Neither age nor basal FSH had significant association with fertilization rate, miscarriage rate, or ectopic pregnancy rate.

Conclusion(s): Both basal FSH and age contributed to the prediction of the quantitative ovarian reserve as reflected by the number of oocytes collected. However, age is a better predictor of pregnancy potential for women undergoing IVF. (Fertil Steril® 2003;79:63–8. ©2003 by American Society for Reproductive Medicine.)

Key Words: Basal FSH, female age, IVF, pregnancy, ovarian reserve

One of the factors that infertile couples take into consideration before deciding to embark on IVF treatment is the expected chance of achieving a pregnancy. For appropriate counseling of patients before IVF, a number of factors closely related to pregnancy outcome have to be considered. Age of the female partner (1, 2), basal (day 2 or 3 of menstrual cycle) serum FSH level (3), and infertility diagnosis (4) are commonly accepted as pretreatment characteristics among the factors that influence IVF success rates.

The value of patient’s age in predicting performances in assisted reproductive technologies (ART) is well established. Fecundity in both natural and stimulated ovarian cycles declines with maternal age, beginning in the late 20s and becoming more abrupt in the late 30s. This decline has been observed in population-based studies (5), ovulation induction, and in IVF (6). In addition, the experience in IVF programs reveals that women of the same age are heterogeneous with regard to their ovarian response, probably because of a significant variation in follicle reserve. Thus, age alone has limited predictive value, and it would be helpful for both patient counseling and clinical management to have another independent prognostic factor that can predict the true reproductive potential of each woman. The Norfolk group has addressed this issue, and found
that the serum FSH concentration at the start of the treatment cycle was more predictive of outcome (7).

The increase in FSH levels as a consequence of follicle depletion can start very early during reproductive age and tends to accelerate after age 37 years (8, 9). One study has reported that women may begin to have a subtle increase in their serum FSH concentrations in their middle 30s, coinciding with the time at which fertility begins to decline (10). The use of early follicular phase (basal) serum FSH concentration was described by Scott et al. (11) as a predictor of IVF outcome and was found to be more predictive than age in recent studies (7, 12, 13). Basal FSH can be used to identify women who are very likely to perform poorly in IVF, probably because of diminished ovarian reserve. Measuring basal FSH should, therefore, be regarded as a prognostic test for IVF treatment failure.

Female age and basal FSH level are independently associated with IVF outcome. They are both related to the same phenomenon, namely ovarian reserve, which can be defined as the quality and the quantity of the remaining follicle pool. The development of diminished ovarian reserve generally reflects the processes of follicular depletion and decline in oocyte quality (7, 10, 11). Diminished ovarian reserve is a natural physiologic occurrence noted in most women during their mid to late 30s and occasionally earlier (14).

Outcomes in ovulation induction and IVF are strongly dependent on ovarian responsiveness to exogenous stimulation. Predictors of this responsiveness provide the physician with valuable information when counseling patients. In 1996, Magarelli et al. (15) demonstrated that a combination of basal (day 2 or 3) FSH level and chronological age are useful predictors of fertility potential in women aged ≥35 years undergoing ovulation induction therapy.

The aim of this retrospective study is to analyze to what extent the parameters of ovarian functional reserve including female age and basal FSH levels will affect the results of ovarian stimulation and IVF outcome.

**MATERIALS AND METHODS**

**Study Subjects**

This study was a retrospective, single-center study on the results of ovarian stimulation and IVF outcomes based on the data reviewed in the medical records of the patients undergoing IVF treatments at National Taiwan University Hospital between July 1995 and June 2000. Only patients using the combination of GnRH analogue (GnRH-a) and gonadotropins for controlled ovarian stimulation were included in this study. A total of 1,045 women undergoing IVF treatment cycles either by IVF-ET or tubal embryo transfer were enrolled in this retrospective cohort study. Only the first IVF treatment cycle was selected in those women with multiple IVF treatment cycles.

The etiologies of infertility included tubal factor (387 cycles, 37.0%), male factor (369 cycles, 35.3%), ovarian factor (143 cycles, 13.7%), endometriosis (187 cycles, 17.9%), unexplained infertility (143 cycles, 13.7%), and uterine factor (70 cycles, 6.7%).

Age was calculated as completed years on the day of starting ovarian stimulation. Serum FSH levels on day 2 or 3 of menstrual cycle obtained 1–3 months before an IVF attempt were used as basal FSH. We used a chemiluminescent immunoassay (Immulite; Diagnostic Products Corporation, Los Angeles, CA) for quantitative measurement of FSH in serum. The intraassay coefficient of variation (CV) was 5.4% at an FSH level of 7.8 mIU/mL. The interassay CV was 8.1% at an FSH level of 8.3 mIU/mL.

Institutional review board approval was not required because our IVF unit is licensed and regulated by the Human and Fertilization Authority and there were no interventions other than those for standard IVF.

**Ovarian Stimulation Protocols**

Six hundred nineteen cycles were stimulated using the long GnRH-a protocol with intranasal buserelin (Supremon; Hoechst Laboratory, Frankfurt, Germany), 800 μg, daily starting during the midluteal phase of the previous cycle. Satisfactory suppression was proven by serum E2 level <50 pg/mL (conversion factor to international system of units [SI] unit, 3.671) on the second day of the treatment cycle. The dosage of buserelin was reduced to 400 μg daily on the third day, and ovarian stimulation with gonadotropins was initiated on the same day. The dosage of gonadotropins was 150 IU of FSH (Metrodin; Serono, Rome, Italy) in the morning and 150 IU of hMG (Pergonal; Serono) in the evening for 4 days consecutively (days 3–6). Afterward, we halved FSH, but continued hMG (150–300 IU) until the day before administering 10,000 IU of hCG (Profasi; Serono). The GnRH-a was curtailed on the day of hCG administration. Oocyte retrieval was performed 34–36 hours after the hCG injection. All patients received luteal support, using P in oil, 25 mg IM daily, for 14 days, and hCG, 1,500 IU IM, on the third, sixth and ninth days after oocyte retrieval.

Four hundred twenty-six cycles were stimulated with the short GnRH-a protocol, and the procedures were similar to those of the long GnRH-a protocol except that GnRH-a, 800 μg daily, was initiated on the second day of treatment cycle until the day of hCG administration. Follicle-stimulating hormone, 150 IU in the morning, and hMG 150 IU in the evening, were administered for 2 days (days 5 and 6), and then only hMG was continued at an adjustable dosage (150–300 IU) until the day of hCG administration.

Cutoff values of the woman’s age (<35, 35–39, ≥40 years) and basal FSH level (<10, ≥10 mIU/mL) were empirically selected to divide the IVF cycles into six groups, including group 1 (age: <35; basal FSH: <10), group 2 (age: <35; basal FSH: ≥10), group 3 (age: 35–39; basal
In vitro fertilization performance and pregnancy outcomes in 1,045 cycles of women according to age and basal FSH levels.

| TABLE 1 |

<table>
<thead>
<tr>
<th>FSH &lt;10/mIU/mL</th>
<th>FSH ≥10mIU/mL</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>&lt;35</td>
</tr>
<tr>
<td>hMG/FSH used (ampoules)</td>
<td>26.9 ± 7.4</td>
</tr>
<tr>
<td>Peak E2 level (pg/mL)</td>
<td>2,071 ± 1,389</td>
</tr>
<tr>
<td>No. of follicles ≥10 mm</td>
<td>13.1 ± 7.1</td>
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<tr>
<td>No. of oocytes retrieved</td>
<td>13.3 ± 8.3</td>
</tr>
<tr>
<td>No. of oocytes fertilized</td>
<td>8.3 ± 5.3</td>
</tr>
<tr>
<td>No. of embryos transferred</td>
<td>4.9 ± 1.6</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>65.6 ± 22.6</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>17.6</td>
</tr>
<tr>
<td>Cancellation rate (%)</td>
<td>5.3</td>
</tr>
<tr>
<td>Clinical pregnancy rate (%)</td>
<td>47.5</td>
</tr>
<tr>
<td>Ongoing pregnancy rate (%)</td>
<td>38.6</td>
</tr>
<tr>
<td>Miscarriage rate (%)</td>
<td>7.0</td>
</tr>
<tr>
<td>Ectopic pregnancy rate (%)</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Note: Values are means ± SD unless otherwise indicated. NS = not significant.

a P values by one-way ANOVA and χ² test where appropriate.
b P<.001 compared with the same age group in category of FSH <10 mIU/mL.
c P<.01 compared with the same age group in category of FSH <10 mIU/mL.
d P<.05 compared with the same age group in category of FSH <10 mIU/mL.
e P<.05 compared between group 4 and 5.


FSH: <10), group 4 (age: 35–39; basal FSH ≥10), group 5 (age: ≥40; basal FSH: <10), and group 6 (age: ≥40; basal FSH: ≥10). We divided the covariates into categories to make their effects more interpretable.

Number of ampules of gonadotropins used, serum E₂ levels on the day of hCG administration, numbers of follicles >10 mm in diameter on the day of hCG administration, number of oocytes retrieved, number of oocytes fertilized, number of embryos transferred, fertilization rates, implantation rates, cancellation rates, clinical pregnancy rates, and pregnancy outcomes were compared between these groups.

Pregnancies were established by elevated serum levels of β-subunit of hCG (β-hCG) >10 mIU/mL 14 days after embryos transferred. A clinical pregnancy was defined as identification of gestational sac ultrasonographically 3 weeks after embryos transferred. Ongoing pregnancy rate referred to the percentage of pregnancies continuing after 20 weeks of gestation. Miscarriage rate referred to the percentage of pregnancies ending before 20 weeks of gestation. Implantation rate was defined as the number of gestational sacs documented divided by the number of embryos transferred. Cancellation rate was defined as the number of the cycles canceled divided by the number of treatment cycles initiated.

Statistical Analysis

The data were analyzed with Student’s t-test, Fisher’s exact test, χ² test, and one-way analysis of variance (ANOVA), as appropriate by using the Statistical Package for the Social Sciences (version 9.0; SPSS Inc., Chicago, IL). In cases in which ANOVA detected significant change, the least-significant difference test was used for subsequent post hoc multiple comparisons. Statistical significance was defined as a value of P<.05.

Receiver operating characteristic curve analysis was used to estimate the predictive power of the measured variables. The relative ability of age and basal FSH to predict the IVF outcome was compared by calculating the areas under the receiver operating-characteristic curve (AUCs) and their 95% confidence intervals (95% CIs). MedCalc software was used to compare the areas under two receiver operating characteristic curves (version 6.14; MedCalc, Broekstraat, Belgium). Logistic regression was performed to determine the independent effect of individual variables.

RESULTS

Table 1 details the data on IVF outcomes, implantation rates, cancellation rates, and pregnancy rates among the six groups. As shown in Table 1, increased age was significantly associated with less follicles ≥10 mm on the day of hCG administration, less number of oocytes retrieved, less number of oocytes fertilized, less number of embryos transferred, lower implantation rates, lower clinical pregnancy rates, and lower ongoing pregnancy rates. These trends were observed...
both in those groups with FSH < 10 mIU/mL and groups with FSH ≥ 10 mIU/mL. Higher cancellation rates and lower peaked E2 levels were significantly associated with increased age in those groups with FSH < 10 mIU/mL, but not in groups with FSH ≥ 10 mIU/mL.

When compared, the effects of FSH on cycle parameters and pregnancy outcome between the various same age groups (group 2 vs. 1, group 4 vs. 3, group 6 vs. 5), the data showed that women with higher FSH levels were significantly associated with lower peak E2 levels and less number of follicles ≥ 10 mm on the day of hCG administration, less number of oocytes retrieved, less number of oocytes fertilized, and less number of embryos transferred. On the other hand, significantly lower clinical pregnancy rates, higher cancellation rates, and less total gonadotropin doses required were only observed between the age groups of <35-year-old (group 2 vs. 1), but not in the age groups of ≥35-year-old (group 4 vs. 3, group 6 vs. 5).

Neither the woman’s age nor the basal FSH concentration was significantly correlated with the fertilization rate, miscarriage rate, or ectopic pregnancy rate.

Table 2 compares the predictive power of age and basal FSH in selected end points of IVF performances. Age alone is a better predictor of pregnancy potential than basal FSH (AUCs 0.617 and 0.542, respectively; P = .002). The predictive power improved slightly when both age and basal FSH were taken into account (AUCs 0.617 and 0.627, respectively; P = .002). Logistic regression analysis also showed that age (odds ratio = 0.532, 95% CI 0.423 to 0.671, P<.001), but not basal FSH, was an independent predictor of pregnancy rate.

The predictive power of the number of oocytes collected did not differ significantly between the age and basal FSH (AUCs 0.668 and 0.703, respectively, P = .106). However, the combined use of age and basal FSH significantly improves the predictive accuracy.

The diagnostic accuracy of cancellation risk did not differ significantly between the age and basal FSH (AUCs 0.599 and 0.601, respectively, P = .781). The combined use of age and basal FSH did not improve the predictive accuracy.

**DISCUSSION**

In our study, women <35 years old experienced different IVF performances, closely related to their basal FSH levels. Those with basal FSH < 10 mIU/mL (group 1) had the best IVF performance among all groups. Those with basal FSH ≥ 10 mIU/mL (group 2) had poorer IVF performances compared with group 1, reflected by lower peak serum E2 level and a lesser number of follicles ≥ 10 mm on the day of hCG administration, a lesser number of oocytes retrieved, a lesser number of oocytes fertilized, a lesser number of embryos transferred, a higher cancellation rate, and a lesser clinical pregnancy rate. However, there were no significant differences in implantation rate and ongoing pregnancy rate between these two groups.

According to the present data, younger women (<35 years old) with elevated basal FSH can still have a favorable IVF outcome reflected by a good ongoing pregnancy rate despite poorer IVF performances. The possible explanation might be that patients <35 years old with elevated basal FSH (≥ 10 mIU/mL) have a decreased remaining follicle pool, but the quality of their remaining follicles is not diminished. That is to say that basal FSH is a good predictor of the size of the remaining follicle pool (i.e., the quantity of ovarian reserve rather than the quality of it).

Elevated basal FSH levels are indicative of diminished quantitative ovarian reserve, as women with increased basal FSH levels frequently have decreased oocyte yields in IVF programs (1). In the present study, elevated basal FSH (≥ 10 mIU/mL) (in groups 2, 4, and 6) was associated with lower peak serum E2 levels, less number of follicles, less number of oocytes retrieved and fertilized, less number of embryos

<table>
<thead>
<tr>
<th>End point</th>
<th>Age alone</th>
<th>FSH alone</th>
<th>Age and FSH combined</th>
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</thead>
<tbody>
<tr>
<td>No. of oocyte retrieved ≥ 10</td>
<td>0.688 (0.637–0.697)</td>
<td>0.703 (0.674–0.732)</td>
<td>0.718 (0.688–0.746)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>0.617 (0.578–0.647)</td>
<td>0.545 (0.514–0.575)</td>
<td>0.627 (0.597–0.657)</td>
</tr>
<tr>
<td>Cancellation</td>
<td>0.599 (0.569–0.697)</td>
<td>0.601 (0.571–0.631)</td>
<td>0.610 (0.579–0.639)</td>
</tr>
</tbody>
</table>

Note: Values in parentheses are 95% confidence interval. ROC = receiver-operating characteristic.

* P<.001 compared with FSH alone.

* P = .014 compared with age alone.

* P = .002 between age and FSH.
transferred, less clinical pregnancy rates, but with higher cancellation rates (group 2 vs. 1, group 4 vs. 3, group 6 vs. 5).

In comparison, between group 4 and group 5, there are significantly lower implantation and clinical pregnancy rates as noted in group 5 despite slightly more oocytes retrieved in this group. It demonstrates that women with advanced age, despite having low basal FSH (group 5), had a limited chance of achieving pregnancies in IVF cycles. Thus, according to the present study, age alone is a better predictor of pregnancy potential than basal FSH. This observation agrees with the report by Seibel et al. (16), which showed that age is the most useful predictive factor of success in IVF.

The importance of basal FSH concentrations to predict pregnancies in women aged 40 years or more undergoing ovulation induction therapy has been demonstrated previously (12). The probability of a clinical pregnancy per treatment cycle decreased sharply as a function of patient age and increasing FSH concentrations in these infertile patients (12). In the present study, women aged 40 years or more with elevated basal FSH (≥10 mIU/mL) (group 6) had very dismal IVF performances. The clinical pregnancy rate and the ongoing pregnancy rate were as low as 11.4% and 4.5%, respectively. The reasons for such poor results are related to an aging population of oocytes of poor quality (17) and a gradual depletion of the follicle pool. Therefore, this group of patients should be carefully counseled on their low chances of conception with their own gametes, even when undergoing IVF treatments. An oocyte donation program will be a more reasonable alternative, if applicable.

With increasing age, ovarian reserve diminishes and spontaneous fecundity rate as well as success rates in IVF programs decline. The age-related decrease in fertility is due primarily to oocyte senescence rather than to poor endometrial receptivity, as suggested by the observation of high pregnancy outcome in oocyte donation programs (18). In IVF programs, older women produce less oocytes (19) and have lower implantation rates (20), thus reflecting both the smaller size and the impaired quality of their follicle pool. Similar trends were observed in our study. The results of women >40 years of age in our study are not encouraging, although they are very similar to those found in the literature (12, 19). In the women >40 years of age (groups 5 and 6), the number of oocytes retrieved, the number of embryos obtained, the implantation rates, and the pregnancy rates were significantly decreased, but the cancellation rate was significantly increased.

Concomitantly with a quantitative decrease in the total number of primordial follicles in the ovary, the aging process results in a qualitative alteration in the oocytes, with an increase in the frequency of trisomy 21 and an increase in aneuploidy discovered after analyzing the conceptus in spontaneous abortion (21). The miscarriage rates in our study showed no significant differences among the other groups compared with group 1. However, when we compared the percentages of clinical pregnancies resulting in miscarriages, it showed that clinically pregnant women aged 40 years or more (groups 5 and 6) had a higher miscarriage rate (6/19 = 31.6%) than that (39/268 = 14.6%) of clinically pregnant women aged <35 years (groups 1 and 2) (P = .049). This might be the result of diminished qualitative ovarian reserve due to the aging process.

The total number of gonadotropins (hMG/FSH) used were significantly lower in groups 2, 4, 5, and 6 compared with group 1. This is because higher percentages of long protocol were used in these groups and patients with long protocol treatments tend to consume more ampules of gonadotropins than those with short protocol treatments, as reported previously (22). In our study, there were significantly higher cancellation rates in groups 2, 4, 5, and 6. It means that elevated basal FSH level (≥10 mIU/mL) and old age (≥40 years old) are associated with higher cancellation rates due to higher proportions of poor response to ovarian hyperstimulation. There were no obvious differences in fertilization rate among all groups. It is believed that the fertilization rate is predominantly determined by the male factor rather than the ovarian factor, as reflected by age and basal FSH.

In conclusion, the present study demonstrates that both basal FSH and age contributed to the prediction of the quantitative ovarian reserve as reflected by the number of oocytes collected. However, age is a better predictor of the pregnancy potential for women undergoing IVF. In light of the low success rate, women >40 years old, especially those with elevated basal FSH levels, should be informed of the low chance of pregnancy (and a high chance of pregnancy loss) with their own gametes before embarking on expensive IVF treatments.

References


