Effect of male body mass index on live-birth sex ratio of singletons after assisted reproduction technology

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Objective: To determine the effect of male body mass index (BMI) on the probability of achieving a live birth and the sex ratio of singletons at birth after IVF and intracytoplasmic sperm injection (ICSI) treatment.
Design: A retrospective cohort study.
Setting: University-affiliated infertility center.
Patient(s): Patients seeking infertility treatment who received IVF or ICSI treatment with autologous oocytes from January 2009 to December 2013.
Intervention(s): None.
Main Outcome Measure(s): Live-birth sex ratio of singletons at birth stratified by male BMI and adjusted by parental age, parental BMI, type of infertility, parity, embryo culture media, and cause of infertility.
Result(s): A total of 8,490 couples undergoing IVF or ICSI treatment resulted in 39.12% live births and gave birth to 2,377 live birth singletons and 943 twins. There was no significant difference in the live birth rate between groups stratified by BMI. The probability of live births for overweight and obese groups were not decreased compared with the normal-weight group; similar null findings existed in the IVF and ICSI subgroups. Of note, the sex ratio of offspring in the overweight and obese male groups was significantly higher than in the normal-weight group (1.27 vs. 1.07). Male BMI was significantly associated with sex ratio of singletons after adjusting for confounders. In twins, incidences of twins with male-male infants in the overweight/obese group were not different from the normal-weight group.
Conclusion(s): Increased male BMI has no effect on live birth success, but has an increased probability of giving birth to male singletons. (Fertil Steril® 2015;104:1406–10. ©2015 by American Society for Reproductive Medicine.)
Key Words: Body mass index, sex ratio, live birth, in vitro fertilization, intracytoplasmic sperm injection

The proportion of overweight and obese adults has increased over the past 30 years, and this trend is also evident in adolescents (1). Because of the increase in prevalence, obesity has become a major health challenge worldwide. In China, the proportion of overweight and obese adults approached 30% in 2004; overweight and obese adults increased 39% and 97%, respectively, compared with 1992 data (Survey for Chinese Nutrition and Health status, published by the National Health Administration). Overweight and obese status are known to be associated with the incidence of chronic diseases, including type II diabetes, cancer, and cardiovascular diseases (2). In recent decades, attention has been directed toward the effect of elevated body mass index (BMI) on reproductive outcome, especially among couples seeking infertility treatment.

There is general agreement that a high female BMI negatively influences the probability of achieving a successful live birth (3); however, evidence on the

Received May 12, 2015; revised and accepted August 12, 2015; published online September 8, 2015.
J.Z. has nothing to disclose. W.T. has nothing to disclose. J.M. has nothing to disclose. J.L. has nothing to disclose. X.Z. has nothing to disclose. P.L. has nothing to disclose. J.Q. has nothing to disclose.
Supported by the National Natural Science Foundation of China for Young Scholars (81300483).
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Fertility and Sterility® Vol. 104, No. 6, December 2015 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.08.017

effect of excess male weight on live births is limited and contradictory (4–6). The impact of male obesity on sperm parameters has been studied (7, 8) and systematically reviewed (9). A higher semen concentration and total motile sperm count significantly increases the odds of having a Y chromosome–bearing sperm (10). In turn, this may lead to sex imbalance at birth in infertile males. However, it is unexpected that association between male infertility and a female-biased offspring sex ratio was not found (11). Moreover, many factors are sometimes associated with the sex ratio at birth, including paternal age >40 years of age (12, 13), maternal age >40 years of age (14) multiparity (14, 15), parental smoking (16, 17), and assisted reproduction technology (intracytoplasmic sperm injection [18, 19], blastocyst culture [20], and embryo culture media [21]). Until now, no evidence has shown an association between male BMI and the sex ratio at birth after assisted reproduction, but a large number of studies have suggested that there is an association between an elevated paternal BMI around conception with a higher BMI of offspring (22, 23), and there is a potential association between the paternal health status and health of the offspring (24–26).

Given that there is no information regarding the effect of male BMI on the live-birth sex ratio of singletons and conflicting evidence on association between male BMI and live birth success, the objective of the present study was to investigate whether or not elevated male BMI has an influence on the live-birth sex ratio of singletons based on a large single-center database. It is hypothesized that elevated male BMI does not influence live birth success but may be associated with sex ratio imbalance at birth.

MATERIALS AND METHODS

Population Selection

This retrospective cohort study was approved by the Ethics Committee of Peking University Third Hospital. Patients who underwent IVF–day 3 embryo transfer fresh cycles with autologous oocytes from January 2009 to December 2013 at the Reproductive Medical Centre of Peking University Third Hospital were analyzed. Only the first infertility treatment was eligible for this study; all couples were present in the database with only one cycle. Women <40 years of age were included. Moreover, all included transfer cycles involved double embryos because double-embryo transfer is the routine practice in our clinic. All patients included in this study were diagnosed with tubal or male factor alone. Physicians recorded infertility reasons as follows: tubal factors, male factors, endometriosis, diminished ovarian reserve, uterine disorders, ovulation disorders, and PCOS. More than one infertility diagnosis could be recorded for each couple. Patients were excluded if preimplantation genetic diagnosis, in vitro maturation, and donor sperm were used. In analyzing the sex ratio of singletons and twins, only data from singletons and twins born alive after the 22nd week of gestation were included.

BMI Assessment

Nurses recorded the weights and heights of all patients after the initial consultation. The BMI was calculated as kg/m^2. All 8,490 men were separated into three groups based on the classification and evaluation criteria of the World Health Organization, as follows: normal-weight group: 18.50 kg/m^2 $\leq$ BMI $<$ 25.00 kg/m^2; overweight group: 25.00 kg/m^2 $\leq$ BMI $<$ 30.00 kg/m^2; and obese group: BMI $\geq$30 kg/m^2.

IVF Outcomes Assessment

Patients underwent IVF or ICSI treatment as clinically indicated. IVF and ICSI were performed according to the routine laboratory insemination procedures on the day of oocyte retrieval. The presence of two pronuclei and two polar bodies was observed 17–19 hours after insemination or injection. Embryo morphology was evaluated 68–72 hours after insemination in terms of cell number, cell size, and cell fragmentation. Live birth was defined as the birth in which at least one fetus was live born.

Statistical Analysis

All statistical analyses were performed with the use of the Statistical Package for the Social Sciences software (SPSS version 17.0) and Statistical Analysis System (SAS version 9.4). In SPSS, continuous variables, including female/male age and parental BMI, were compared by means of analysis of variance, and categoric variables, including semen concentration, sperm motility, parity, and type of infertility were evaluated by means of χ^2 tests. The adjusted risk ratio (aRR) was used to estimate the incidence of live births in the male overweight/obesity category compared with the normal-weight male category after adjusting for parental age, female BMI, type of infertility, and parity with the use of a Poisson model with a robust error variance in SAS. The RR was used to estimate the incidence of the male singletons in the overweight and obese male categories compared with the normal-weight male category. Similarly, a Poisson model with a robust error variance was used to evaluate the possible association of male BMI with incidences of male infants after adjusting for confounders, including female/male age, female BMI, parity, type of infertility, embryo culture media, and cause of infertility.

RESULTS

The 8,490 transfer cycles resulted in 39.12% live births. As presented in Table 1, the average male BMIs were 22.48 kg/m^2, 27.10 kg/m^2, and 32.14 kg/m^2 in the normal-weight, overweight, and obese categories, respectively; the female BMIs were positively correlated with the male categories ($P<.001$). There was a significant difference in female ($P<.001$) and male age ($P<.001$) across the male BMI categories. The proportions of men with abnormal sperm parameters (semen concentration <15 million/mL [$P=.001$] and sperm motility <32% [$P=.006$]) were significantly different across the male BMI categories. No statistical differences existed regarding type of infertility and women's parity across the male categories ($P>.05$).

As presented in Table 2, male BMI was not significantly associated with live births (overweight: $P=.282$; obese: $P=.944$) after adjusting for female BMI, female/male age,

TABLE 1

Characteristics of the study population stratified by male BMI.

Characteristic	Normal weight (n = 4,241)	Overweight (n = 3,470)	Obesity (n = 779)	*P* value
Male age (y)	32.10 ± 4.76	32.68 ± 4.85	31.72 ± 4.59	< .001
Male BMI (kg/m^2)	22.48 ± 1.68	27.1 ± 1.35	32.14 ± 1.98	< .001
Semen concentration <15 million/mL (%)	29.43	27.73	34.06	.001
Sperm motility (a+b) <32%	53.58	53.58	59.39	.006
Female age (y)	30.28 ± 3.60	30.71 ± 3.52	30.36 ± 3.42	< .001
Female BMI (kg/m^2)	22.43 ± 2.84	22.83 ± 3.01	22.98 ± 3.04	< .001
Multipara (%)	5.19	5.27	5.13	.980
Secondary infertility (%)	44.73	45.99	45.70	.528

Note: BMI = body mass index.

Zhu. Male BMI and live-birth sex ratio of singletons. Fertil Steril 2015.

type of infertility, and parity. The probabilities of live birth for the overweight (1.031, 95% confidence interval [CI] 0.975–1.090) and obese (1.003, 95% CI 0.912–1.104) male groups were not decreased. In the IVF subgroup, a similar aRR suggested no apparent reduction in live births in the overweight (1.064, 95% CI 0.989–1.146) and obese (0.997, 95% CI 0.867–1.147) groups; null findings were also observed in the ICSI subgroup in the overweight (0.987, 95% CI 0.906–1.075) and obese (0.994, 95% CI 0.871–1.135) groups.

The 8,490 transfer cycles resulted in 2,377 live born singletons. The normal-weight group gave birth to 611 male and 569 female infants, and the overweight and obese groups gave birth to 670 male and 527 female infants. There was a clear sex bias across the male BMI categories; the sex ratio of overweight and obese men was significantly higher than the normal-weight group (1.27 vs. 1.07; P=.044). The RR suggested an 8.1% increase in male singletons at birth compared with the normal-weight group (RR 1.081; Table 3). A Poisson model with a robust error variance was used to adjust for confounders, including female/male age, female BMI, type of infertility, parity, embryo culture media, and cause of infertility; male BMI alone was significantly associated with incidences of male singletons (P=.042; RR 1.081, 95% CI 1.003–1.164; Table 4).

The 8,490 transfer cycles resulted in 943 live born twins. The normal-weight group gave birth to 487 male and 445 female infants, and the overweight and obese groups gave birth to 477 male and 477 female infants. Although the sex ratio of the overweight/obese group is lower than the normal-weight group, the difference did not reach statistical significance (1.00 vs. 1.09; P=.334; Supplemental Table 1, available online at www.fertstert.org). Likewise, the incidences of male/male infants (RR 0.922, 95% CI 0.778–1.091) and male/female infants (RR 0.931, 95% CI 0.834–1.040) in overweight/obesity were not different from the normal-weight group after male/female age, paternal BMI, parity and type of infertility were adjusted with the use of a Poisson model with a robust error variance (Supplemental Table 2, available online at www.fertstert.org).

DISCUSSION

It is well known that assisted reproductive technologies (ART) are associated with sex bias of IVF babies; however, no evidence has shown an association between patient factors, such as male BMI, and sex bias at birth following IVF or ICSI treatment. The present study, using a large single center database, is the first to report that overweight and obese men lead to a higher sex ratio at birth compared with normal-weight men.

The mechanism of sex bias associated with male BMI is unclear. There is general agreement in a rodent model regarding the negative effect of overweight and obese males on sperm motility and sperm count (27, 28); however, in

TABLE 2

Analysis of probability of achieving live birth according to male BMI stratification following IVF or ICSI treatment: results with the use of a Poisson model with a robust error variance.

Insemination method	Male BMI	Live birth rate (%)	aRR (95% CI)	*P* value
IVF	Normal weight	37.06	1.000	
IVF	Overweight	39.35	1.064 (0.989–1.146)	.097
IVF	Obesity	36.86	0.997 (0.867–1.147)	.970
ICSI	Normal weight	41.34	1.000	
ICSI	Overweight	39.96	0.987 (0.906–1.075)	.769
ICSI	Obesity	40.41	0.994 (0.871–1.135)	.932
IVF+ICSI	Normal weight	38.81	1.000	
IVF+ICSI	Overweight	39.60	1.031 (0.975–1.090)	.282
IVF+ICSI	Obesity	38.64	1.003 (0.912–1.104)	.944

Note: aRR = adjusted risk ratio (female/male age, female BMI, type of infertility, and parity); BMI = body mass index; CI = confidence interval; ICSI = intracytoplasmic sperm injection.

Zhu. Male BMI and live-birth sex ratio of singletons. Fertil Steril 2015.

TABLE 3

Sex ratio following IVF or ICSI treatment, stratified by male BMI.

Variable	Normal weight (n = 1,180)	Overweight/obesity (n = 1,197)	*P* value
Sex ratio (M/F)	1.07 (611/569)	1.27 (670/527)	.044
RR	1.000	1.081	

Note: RR = risk ratio; other abbreviations as in Table 2.

Zhu. Male BMI and live-birth sex ratio of singletons. Fertil Steril 2015.

humans controversy still exists regarding the impact of overweight and obese males on sperm parameters. In the present study, abnormal sperm parameters were more frequently observed in the obese group. No statistical difference in sperm parameters was found between the normal and overweight groups. Interestingly, severe male infertility is predicted to give birth to more female offspring owing to sperm sex bias (10); however, association between male infertility and a female-biased offspring sex ratio was not confirmed with 25,738 children of men who attended a sperm analysis laboratory in Denmark (11). Likewise, the present study suggests no association of male infertility with sex ratio according to poisson regression. A recent comprehensive study found that the human sex ratio is 0.5 at conception, which contradicts the common claim of male bias at conception (29). It is speculated that the sex bias observed in the overweight/obesity male group occurred after fertilization, which represents a compromised function of X- or Y-bearing sperm on embryogenesis. Tesarik et al. (28) suggested that paternal effects play an important role in the first cell cycle of embryogenesis. Therefore, the sex difference at birth may be due to preferential female embryo loss of the overweight and obese male groups in early embryo development. Given the scarce biologic evidence supporting this association, any conclusions around the association with sex ratio are preliminary. It is controversial whether maternal age, paternal age, and multiple births affect the sex ratio at birth (12–15, 30, 31). ART is reported to influence the sex ratio of singletons; ICSI significantly reduces the sex ratio at birth (18, 19). Blastocyst culture leads to male sex bias at birth because male embryos develop faster than female embryos (20). Our previous study suggested that embryo culture media could alter the sex ratio of singletons resulting from ICSI treatment. Cycles with blastocyst transfer were excluded from the present study, and some of the confounders were built into and adjusted in a statistical model. After correction, male BMI was significantly and independently associated with the sex ratio of singletons at birth; the odds of male singletons in overweight/obesity was higher than in normal weight. When the multiple births were identified as a separate group, it was unexpected that we did not find a higher percentage of males in the twins group with overweight and obesity. The incidences of male-male infants in overweight/obesity were not different from the normal-weight group after confounders were controlled. This might be partially explained by multiple births per se associated with sex ratio at birth (12). However, Bu et al. reported that multiple gestations were not associated with sex ratio in a Chinese ART population (31). The evidence around sex ratio of multiple births is conflicting. A limitation of the present study was that not all confounders were included in the poisson regression model. Smoking status, which has been reported to skew the human sex ratio at birth, was not available in our database (16, 17). Other lifestyle factors and the social environment have an impact on the human sex ratio at birth, but they were not registered in the database.

The secondary finding was that overweight and obese men are not associated with the probability of achieving live birth success. The effect of female BMI on pregnancy and live birth has been extensively studied, but studies of the male BMI effect are limited and contradictory; earlier studies suggested a negative effect of increased male BMI on pregnancy and live birth (4, 32), but those two studies were limited by a small sample size (n = 305 and 290 for ART treatment). Petersen et al. (6) reported a decreased probability of live births in overweight and obese groups in a large sample size (n = 25,191 for ART treatment), but no statistical difference was reported. Our study is in agreement with a recently published prospective cohort study (5), that increased male BMI does not influence live births among couples undergoing infertility treatment. The selected population in the study design made this study unique; exclusion of factors associated with extremely poor live birth outcome is a prerequisite for an analysis of the independent male BMI effect, such as IVF repeated failure, maternal age >40 years (33, 34), diminished ovarian reserve (35), and endometrisis (36, 37).

In conclusion, we found no association of male BMI with probability of achieving live birth success, after taking into account several confounders, such as female/male age, female BMI, type of infertility, and parity. Nevertheless, increased male BMI may be associated with an increase in the likelihood of giving birth to male babies after adjustment for relevant confounders.

TABLE 4

Analysis of factors associated with the sex of 2,377 singletons: Poisson model with a robust error variance.

Factor	*P* value	RR	95% CI for RR
Male overweight/obesity[a]	.042	1.081	1.003–1.164
Female age	.391	0.994	0.980–1.008
Male age	.342	1.005	0.995–1.015
Type of infertility	.112	1.069	0.985–1.160
Parity	.271	0.905	0.759–1.080
Female overweight/obesity[b]	.763	0.985	0.894–1.086
G5 series		1.000	
Global	.365	0.958	0.873–1.051
G5 series PLUS	.933	1.004	0.913–1.105
Quinns'	.927	0.993	0.860–1.147
Female factor		1.000	
Male factor	.110	0.924	0.838–1.018
Male and female factor	.923	0.995	0.907–1.092
Unexplained factor	.362	0.891	0.694–1.143

Note: The outcome was probability of male singletons. Abbreviations as in Table 2 and 3.
[a,b] The corresponding normal-weight group was defined as reference.

Zhu. Male BMI and live-birth sex ratio of singletons. Fertil Steril 2015.

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SUPPLEMENTAL TABLE 1

Sex ratio of multiple births following IVF or ICSI treatments, stratified by male BMI.

Variable	Normal weight	Overweight/obesity	*P* value
Sex ratio (M/F)	1.09 (487/445)	1.00 (477/477)	.334

Note: BMI = body mass index; ICSI = intracytoplasmic sperm injection.

Zhu. Male BMI and live-birth sex ratio of singletons. Fertil Steril 2015.

SUPPLEMENTAL TABLE 2

Analysis of factors associated with the sex ratio of 943 twins: Poisson model with a robust error variance.

Sex ratio	Factor	*P* value	RR	95% CI for RR
1 female/1 male	Female age	.354	1.011	0.988–1.034
	Male age	.074	0.984	0.967–1.002
	Male BMI	.206	0.931	0.834–1.040
	Female BMI	.847	1.014	0.878–1.172
	Parity	.793	1.032	0.817–1.303
	Type of infertility	.124	1.094	0.976–1.226
2 male	Female age	.203	1.022	0.988–1.057
	Male age	.354	0.988	0.964–1.013
	Male BMI	.344	0.922	0.778–1.091
	Female BMI	.674	0.951	0.751–1.203
	Parity	.820	1.044	0.720–1.514
	Type of infertility	.725	1.033	0.862–1.239

Note: Twins with two female infants was defined as the reference group. BMI = body mass index; CI = confidence interval; RR = risk ratio.

Zhu. Male BMI and live-birth sex ratio of singletons. Fertil Steril 2015.