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Low body mass index compromises live birth rate in fresh transfer in vitro fertilization cycles: a retrospective study in a Chinese population

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Objective: To evaluate the effects of low body mass index (BMI) on in vitro fertilization (IVF) outcomes in fresh transfer cycles.
Design: Retrospective cohort study.
Setting: University-affiliated hospital.
Patient(s): A total of 4,798 cycles with conventional stimulation and fresh transfer in a single IVF center during the period 2013–2014. Low BMI (<18.5 kg/m^2) was defined according to World Health Organization guidelines, and cycles within a normal weight range (18.5–24.9 kg/m^2) were used as reference.
Intervention(s): None.
Main Outcome Measure(s): Live birth rate per fresh embryo transfer.
Result(s): Low BMI was associated with reduced live birth rates and increased miscarriage rates compared with normal weight, controlling for important covariates known to influence IVF outcomes. Patient age was the most potent confounder, causing a 10.5% reduction in the odds ratio (OR) for live birth between the groups compared. When an interaction term (age $\times$ BMI) was introduced, the OR for live birth was reduced in cycles of those aged ≥ 35 years compared with cycles of those aged 28–34 years, whereas the change in OR between cycles in those aged <28 and cycles in those aged 28–34 years was insignificant.
Conclusion(s): Low BMI is associated with negative outcomes in fresh transfer cycles, especially for women of advanced age. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: In vitro fertilization, body mass index, underweight, fresh embryo transfer, live birth

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Body mass index (BMI) is an important clinical characteristic for both planning the stimulation regimen and counseling on the chances of success after in vitro fertilization (IVF). A number of studies have associated increased BMI with higher doses of gonadotropins, longer durations of ovarian stimulation, and poorer IVF success rates (1–4), leading to increasing concerns regarding obese or overweight women receiving IVF treatment.

At the other extreme of body weight, women with low BMI are also known to risk unfavorable pregnancy outcomes and infertility problems. However, evidence regarding the effects of low BMI on IVF outcomes is conflicting (5–11). Early studies suggested a lack of association between low BMI and impaired IVF outcomes (5, 7–9, 12). However, they were based on relatively small sample size. For instance, Fedorcsak et al. reviewed 5,019 IVF or intracytoplasmic sperm injection (ICSI) treatments in 2,660 couples, but only 76 underweight women were included (9). On the other hand, Veleva et al. established a positive association between underweight and miscarriage in a cohort containing 3,330 pregnancies derived from IVF/ICSI (11), suggesting that underweight women are less likely to achieve a live birth even after pregnancy has been established. The most recent nationwide survey in the United States suggested that success rates in

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fresh autologous cycles are highest in those with low and normal BMIs compared with those with high BMIs, but it also showed a subtle decrease in live birth rates in cycles with low BMI compared with cycles with normal BMI. The heterogeneity among studies may be explained by statistical phenomena, such as the infrequency of underweight subjects (9), and/or biologic differences among patient populations, such as basal clinical characteristics and ethnicity.

Most of the studies were performed in white populations, and the information regarding IVF outcomes in underweight Asian populations is still limited. The Asian population in general has a lower BMI than that observed for non-Asian populations, and therefore the BMI distribution is shifted to the left (13). The desire for thinness and social pressure among young women may also contribute to this trend (14). A negative effect of low BMI on IVF outcomes, if there is any, may therefore be more profound in Asian women in their reproductive age. In the present study, we sought to evaluate the impact of low BMI on the live birth rates among women undergoing IVF-ET in fresh autologous cycles in a retrospective Chinese population.

MATERIALS AND METHODS

Study Subjects

A retrospective analysis was performed of patients who underwent IVF/ICSI treatment and fresh autologous embryo transfer in the affiliated Chenggong Hospital of Xiamen University in the period from January 2013 to December 2014. Institutional Review Board approval for this retrospective study was obtained from the Ethics Committee of the Medical College Xiamen University. Informed consents were not necessary, because the research was based on nonidentifiable records as approved by the Ethics Committee.

Only patients undergoing conventional ovarian stimulation (agonist or antagonist) were reviewed. Patients on mild stimulation cycles, natural cycles, and luteal-phase stimulation cycles were excluded from the study (n = 157). We also excluded patients with diagnoses of diabetes, glucose intolerance, and thyroid abnormality (n = 137). The criteria for BMI categories were consistent with the international classifications of the World Health Organization (WHO) (13). Patients with a BMI <18.5 kg/m^2 were considered to be underweight and those with a BMI ≥ 25 kg/m^2 were considered to be overweight. Because the purpose of the study was to investigate the effects of low BMI, and owing to the fact that there was only a small number of patients conforming to the WHO class I or higher obesity classes (BMI >30 kg/m^2) in our population (n = 30), we did not analyze the data from patients with a BMI >30 kg/m^2.

Treatment Protocol

In all stimulation cycles, patients received one to three ampules (75–225 IU) of gonadotropin per day during the gonadotropin stimulation. The initial and ongoing dosage was adjusted according to the patient's age, antral follicle count (AFC), BMI, and follicular growth response. Recombinant FSH (Gonal-F; Merck-Serono) or domestic urinary hMG (urofollitropin for injection; Livzon Pharma) was used for the gonadotropin stimulation. During the treatment, the ovarian response was monitored by means of transvaginal ultrasound measurements of follicular growth and serum E_2 level every 1–3 days. Gonadotropin stimulation continued until ultrasonography revealed at least one follicle measuring ≥ 18 mm in mean diameter. Then 5,000–10,000 IU hCG (human chorionic gonadotrophin for injection; Livzon Pharma) was injected intramuscularly. Oocyte retrieval was scheduled for 34–36 hours after hCG administration. Oocyte retrieval was carried out under transvaginal ultrasound guidance.

Oocytes were inseminated using either conventional IVF or ICSI. The pronuclei were identified 17–18 hours later. On day 3, the embryos were assigned quality grades, and embryos that reached the 8-cell stage with even cleavage and $<20\%$ fragmentation were classified as good quality. For patients receiving blastocyst transfer, the Gardner scale (15) was used to evaluate the embryo quality. Top-quality embryos for transfer were defined as those with $<10\%$ fragmentation, on-time cell size on day 3, and with good inner cell mass and good trophectoderm on day 5.

Fresh embryo transfers were performed on either day 3 or day 5. The number of embryos transferred ranged from one to three according to national regulations. Transferring three embryos was considered only in women of advanced age or repeated failure, and no patients had more than two blastocysts transferred. The luteal phase support was sustained with natural progesterone in oil (Progesterone Injection; XianJu Pharma, China), 60 mg intramuscularly daily from the oocyte retrieval day. Clinical pregnancy was defined as the presence of one or more gestational sacs detected by means of an ultrasound scan performed 4 weeks after embryo transfer. Miscarriage was defined as an intrauterine pregnancy failing to reach 22 weeks of gestation. Live birth was defined as the delivery of a live infant after 24 weeks of gestation.

Statistical Analysis

The distribution of continuous variables wass described with the use of the mean and standard deviation (SD). Categoric variables were presented as proportion and percentage of the total. For continuous variables, normality plots and a Shapiro-Wilk test were used for normality testing, and a *t* test or Mann-Whitney *U* test was used for comparison. Dichotomous variables were analyzed by means of a chi-square test or Fisher exact test as appropriate.

Multivariate logistic regression analyses were performed to evaluate the association between BMI and the probability of live birth, with adjustments made for important covariates and potential confounding factors. Variables including patient age, duration of infertility, type of infertility (primary/secondary), basal endocrine parameters (FSH, LH), previous embryo transfer attempts, additional etiologies (polycystic ovary syndrome [PCOS], endometriosis, and male factor infertility), type of GnRH analogue (agonist/antagonist), starting dose of stimulation, number of oocytes retrieved, and progesterone elevation on the day of hCG (>1.5 ng/mL) were included as potential confounding factors, because they are all associated with BMI distribution and known to influence outcomes. Total dose of stimulation was not included,