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® 2017;107:422–9. ©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

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nationwide survey in the United States suggested that success rates in 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, because it is highly correlated with both the starting dose of stimulation and the GnRH analogue used. Basal E_2 and T were considered to be less important predictors for outcome, although they differed significantly across BMI categories. AFC, hydrosalpinx, endometrial thickness on the day of hCG, number of embryos transferred, development stage of transferred embryos (cleavage/blastocyst), and presence of at least one good-quality embryo transferred were also included in the model, because of their clinical importance.

Because including patients contributing to multiple cycles might go against the independent assumption of logistic regression, we analyzed our data with the use of the generalized estimating equations (GEE) model and logistic regression. Both methods yielded reasonably similar findings (Supplemental Table 1, available online at www.fertstert.org). Because logistic models are easier to interpret, we used a multivariable logistic regression to develop a model.

A Stata program was used to quantify the contribution of each of the potential confounding factors to the changes in the effect size of underweight for live birth rates in the final model (16). The program evaluated the effects of potential confounding factors in a stepwise manner. Initially, with the use of the forward strategy, the variable causing the largest change in the effect measurement was included, and in the next step, the variable that caused the largest change among the remaining variables was included. This process continued until all of the variables were added to the model.

In addition, we explored the age stratum–specific odds ratios (ORs) of underweight for live birth. The interaction between BMI and patient age was also investigated in a multivariate model.

All calculations were performed with the use of SPSS (version 19; IBM) and Stata (version 12; Statacorp). In all analyses, $P<.05$ was considered to be significant.

RESULTS

A total of 4,798 fresh transfer cycles performed on 4,401 women were reviewed. The mean age of the population was 31.35 ± 4.29 years, with a range of 20–46 years and a mean BMI of 21.13 ± 2.81 kg/m^2. A total of 886 cycles were performed on underweight women (BMI <18.5 kg/m^2), and 670 cycles were performed on overweight women (BMI ≥25 kg/m^2). Categorized according to BMI, detailed patient baseline characteristics and cycle outcomes are presented in Tables 1 and 2. Compared with normal-weight patients, underweight patients were characterized by younger age and shorter duration of infertility, whereas the overweight patient demographics were biased toward advanced age (Tables 1 and 2). The mean baseline FSH and LH decreased with increasing BMI from 8.02 ± 3.02 mIU/mL and 5.18 ± 2.76 mIU/mL, respectively, in underweight patients to 6.99 ± 2.06 mIU/mL and 4.31 ± 2.80 mIU/mL in the overweight patients. The proportion of cycles with PCOS increased with increasing BMI (P value for trend <.001). The underweight group had significantly fewer cycles with a PCOS diagnosis (2.6%) but significantly more cycles with endometriosis (16.7%) compared with the normal-weight and overweight groups. During stimulation, the starting and total dose also increased with increasing BMI, ranging from 206.2 ± 35.7 IU and 2,304.59 ± 592.54 IU, respectively, in the underweight group to 215.8 ± 32.6 IU and 2,443.59 ± 681.45 IU in the overweight group. Following the stimulation, however, more oocytes were retrieved in the underweight group than in the normal-weight ($P=.043$) and overweight groups ($P<.001$). The cleavage rates, numbers of cleavages, and proportions of good-quality embryos on day 3 were similar among the groups. For fresh embryo transfers, no significant difference was detected in embryo parameters (number of embryos transferred, development stage of transferred embryos, and proportion of the presence of at least one top-quality embryo transferred). Across all groups, a mean of 1.85 embryos were transferred per cycle, and the proportion of cycles with at least one top-quality embryo transferred was 29.6%.

The overall pregnancy rate, miscarriage rate, and live birth rate were 58.9%, 11.5%, and 51.4%, respectively. Bivariate analyses showed that pregnancy rates, miscarriage rates per pregnancy, and live birth rates were similar among BMI categories, with the exception of an increase of marginal significance ($P=.049$) in miscarriage rates that was observed in underweight women (13.8%) compared with normal-weight women (10.7%). When adjusted for potential confounding factors, however, underweight was associated with reduced live birth rates (OR 0.80, 95% confidence interval [CI] 0.68–0.94), whereas the association between overweight and live birth rates was insignificant (OR 0.90. 95% CI 0.75–1.10; Table 3).

The OR for miscarriage per pregnancy also was adjusted for the same set of confounding factors (Table 2). It was found that underweight increased the miscarriage rates 1.51-fold (95% CI 1.13–2.07) compared with the normal-weight group, and overweight had no significant effect on miscarriage rates (OR 1.17, 95% CI 0.83–1.64).

The contribution of each of the aforementioned potential confounding factors to the change in the effect size of the association of underweight with live birth rates was quantified (Supplemental Fig. 1, available online at www.fertstert.org). In the multivariate model, patient age was the most potent confounder, causing a 10.5% reduction in the OR for live births compared with the underweight and normal-weight groups. Subsequently, the addition of AFC resulted in a 2.8% increase in the OR of underweight subjects, whereas the addition of GnRH agonist/antagonist resulted in a 2.5% decrease. The addition of other confounding factors, including starting dose of gonadotropin (−1.25%), basal FSH (+0.90%), number of oocytes retrieved (−1.21%), presence of at least one good-quality embryo transferred (+0.75%), progesterone elevation (+0.76%), diagnosis of PCOS (−0.41%), number of embryos transferred (−0.60%), basal LH (−0.44%), type of infertility (−0.42%), developmental stage of the embryos (−0.37%), duration of infertility (−0.25%), endometrial thickness (+0.22%), diagnosis of hydrosalpinx (−0.22%), diagnosis of endometriosis (−0.1%), previous embryo transfer attempts (−0.09%), insemination protocol (−0.05%), and diagnosis of male infertility (−0.14%), caused only minor changes in the OR for live birth in underweight women (Supplemental Fig. 1).

To investigate the interaction between age and BMI in the multivariate regression model, the total sample was divided

TABLE 1

Baseline characteristics and ovarian stimulation parameters.

Variable	Underweight (< 18.5 kg/m^2; n = 886)	Normal weight (18.5–24.9 kg/m^2; n = 3,642)	Overweight (≥25 kg/m^2; n = 670)	Underweight vs. normal weight	Overweight vs. normal weight	Overweight vs. underweight
Age, y	30.31 ± 3.88	31.55 ± 4.34	32.01 ± 4.26	< .001	.086	< .001
Age category, y				< .001	< .001	< .001
<28	547/886 (61.7)	1,840/3,242 (56.8)	345/670 (51.5)			
28–34	209/886 (23.6)	607/3,242 (18.7)	109/670 (16.3)			
≥35	130/886 (14.7)	795/3,242 (24.5)	216/670 (32.2)			
Previous attempts of embryo transfer	0.247 ± 0.66	0.335 ± 0.82	0.307 ± 0.82	.004	.245	.012
Primary infertility/secondary infertility (%)	499/387 (56.3/43.7)	1,525/17,17 (47.0/53.0)	300/370 (44.8/55.2)	< .001	.285	< .001
Duration of infertility, y	4.40 ± 2.83	4.76 ± 3.37	5.07 ± 3.65	.004	.131	.003
BMI, kg/m^2	17.48 ± 3.02	21.63 ± 1.60	26.18 ± 1.72	< .001	< .001	< .001
Additional etiologies						
PCOS (%)	23/886 (2.6)	182/3,242 (5.6)	71/670 (10.6)	< .001	< .001	< .001
Endometriosis (%)	148/886 (16.7)	394/3,242 (12.2)	49/670 (7.3)	< .001	< .001	< .001
Hydrosalpinx (%)	33/886 (3.7)	136/3,242 (4.2)	34/670 (5.1)	.531	.309	.194
Male factor (%)	156/886 (17.6)	447/3,242 (13.8)	93/670 (13.9)	.004	.049	.047
Basal FSH, mIU/mL	8.02 ± 3.02	7.48 ± 2.41	6.99 ± 2.06	< .001	.002	< .001
Basal LH, mIU/mL	5.18 ± 2.76	4.59 ± 2.71	4.31 ± 2.80	< .001	.111	< .001
Basal E_2, pg/mL	46.36 ± 26.8	42.33 ± 27.8	37.97 ± 23.3	< .001	.012	< .001
Basal T, ng/mL	0.63 ± 3.65	0.57 ± 2.62	0.41 ± 0.48	.584	.378	.274
Basal AFC	7.88 ± 4.02	8.17 ± 4.24	8.32 ± 4.41	.063	.571	.13
Agonist/antagonist (%)	780/106 (88.0/12.0)	2,683/559 (82.8/17.2)	518/152 (77.3/22.7)	< .001	< .001	< .001
Total gonadotropin dose, IU	2,304.59 ± 592.54	2,312.62 ± 597.71	2,443.59 ± 681.45	.722	.001	.001
Starting dose of stimulation, IU	206.2 ± 35.7	210.1 ± 32.3	215.8 ± 32.6	.017	.374	.002
Endometrial thickness on day of hCG, mm	10.81 ± 4.49	10.78 ± 2.89	11.06 ± 2.43	.798	.179	.279
Progesterone elevation (>1.5 ng/mL) on day of hCG (%)	224/886 (25.3)	587/3,242 (18.1)	85/670 (12.7)	< .001	.001	< .001

Note: Unless otherwise specified, results are presented as mean ± SD. AFC = antral follicle count; BMI = body mass index; PCOS = polycystic ovarian syndrome.

Cai. Low BMI compromises live birth rate. Fertil Steril 2016.

TABLE 2

Outcome of ovarian stimulation, fertilization, and embryo transfer.

Variable	Underweight (< 18.5 kg/m^2; n = 886)	Normal weight (18.5–24.9 kg/m^2; n = 3,642)	Overweight (≥25 kg/m^2; n = 670)	Underweight vs. normal weight	Overweight vs. normal weight	Overweight vs. underweight
No. of oocytes retrieved	9.61 ± 4.87	9.23 ± 5.11	8.35 ± 5.01	.043	.006	< .001
Mature oocyte rate, %	88.10 ± 13.85	88.92 ± 14.34	88.89 ± 14.37	.124	.966	.429
ICSI/IVF (%)	246/640 (27.8/72.2)	847/2,395 (26.1/73.9)	176/494 (26.3/73.7)	.327	.939	.511
Fertilization rate, %	79.15 ± 18.83	80.92 ± 18.98	80.88 ± 18.51	.012	.972	.188
Cleavage rate, %	86.83 ± 15.76	86.45 ± 16.52	87.83 ± 15.92	.541	.18	.375
Good embryo proportion, %	74.79 ± 30.20	74.92 ± 29.69	79.01 ± 28.48	.911	.029	.041
Number of cleavage	5.49 ± 3.27	5.42 ± 3.47	4.83 ± 3.25	.584	.006	.005
No. of embryos transferred (%)				.157	.415	.883
One	165/886 (18.6)	604/3,242 (18.6)	121/670 (18.1)			
Two	699/886 (78.9)	2,514/3,242 (77.5)	530/670 (79.1)			
Three	22/886 (2.5)	124/3,242 (3.8)	19/670 (2.8)			
At least one top-quality embryo transferred (%)	251/886 (28.3)	977/3,242 (30.1)	192/670 (28.7)	.297	.446	.887
Cleavage-stage transfer/blastocyst transfer (%)	806/80 (91/9)	2,979/263 (91.9/8.1)	625/45 (93.3/6.7)	.381	.222	.947
Clinical pregnancy (%)	523/886 (59)	1,928/3,242 (59.5)	376/670 (56.1)	.813	.109	.25
Abortion/pregnancy (%)	72/523 (13.8)	206/1,928 (10.7)	49/376 (13)	.049	.184	.75
Live birth (%)	443/886 (50)	1,700/3,242 (52.4)	324/670 (48.4)	.198	.054	.521

Note: Unless otherwise specified, results are presented as mean ± SD. ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization.

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TABLE 3

Logistic regression analysis of live birth per transfer and miscarriage per pregnancy.

Variable	Category	OR (95% CI) Live birth per transfer	OR (95% CI) Miscarriage per pregnancy
Body mass index	Underweight vs. normal	0.80 (0.68–0.94)	1.53 (1.13–2.07)
	Overweight vs. normal	0.92 (0.77–1.10)	1.15 (0.82–1.63)
Age	Per year increased	0.96 (0.95–0.98)	1.08 (1.04–1.12)
Duration of infertility	Per year increased	0.97 (0.95–0.99)	1.02 (0.99–1.07)
Type of infertility	Primary vs. secondary	1.06 (0.93–1.21)	0.86 (0.67–1.11)
Previous embryo transfer attempts	Per transfer increased	1.00 (0.92–1.09)	0.912 (0.77–1.08)
PCOS	With vs. without	0.94 (0.70–1.27)	1.42 (0.83–2.45)
Endometriosis	With vs. without	1.02 (0.85–1.24)	1.22 (0.87–1.72)
Hydrosalpinix	With vs. without	0.67 (0.49–0.90)	0.75 (0.35–1.58)
Male infertility	With vs. without	1.11 (0.88–1.41)	0.80 (0.50–1.29)
Basal FSH	Per mIU increased	0.99 (0.97–1.02)	1.01 (0.96–1.06)
Basal LH	Per mIU increased	1.02 (0.99–1.04)	0.97 (0.92–1.02)
AFC	Per AFC increased	0.99 (0.98–1.02)	1.00 (0.97–1.04)
GnRH analogue	Antagonist vs. agonist	0.49 (0.41–0.59)	1.46 (1.01–2.12)
Starting dose of stimulation	Per 75 IU increased	0.78 (0.65–0.93)	1.01 (0.71–1.45)
No. of oocytes retrieved	Per oocyte increased	1.02 (1.01–1.04)	1.01 (0.98–1.04)
Insemination protocol	IVF vs. ICSI	0.93 (0.77–1.13)	1.10 (0.76–1.58)
Development stage of transferred embryos	Cleavage vs. blastocyst	0.42 (0.32–0.57)	0.88 (0.68–1.14)
No. of embryos transferred	Two vs. one	3.06 (2.47–3.78)	0.60 (0.39–0.92)
	Three vs. one	3.17 (2.15–4.67)	0.52 (0.24–1.13)
At least one top-quality embryo transferred	Yes vs. no	1.38 (1.20–1.58)	1.23 (0.70–2.17)
Progesterone elevation	Yes vs. no	0.89 (0.76–1.04)	1.04 (0.77–1.42)
Endometrial thickness	Per mm increased	1.02 (0.99–1.05)	1.01 (0.99–1.04)

Note: AFC = antral follicle count; CI = confidence interval; OR = odds ratio; PCOS = polycystic ovary syndrome.

Cai. Low BMI compromises live birth rate. Fertil Steril 2016.

into subgroups according to age categories (Table 1). The crude live birth rates did not differ significantly through BMI categories in cycles performed in women aged <28 years (54.1%, 56.3%, and 53.6% for low, normal, and high BMI categories, respectively; $P=.497$) and 28–34 years (55%, 59.5%, and 56.9% for low, normal, and high BMI categories, respectively; $P=.510$). However, the live birth rate in low-BMI cycles (24.6%) was significantly lower than in normal-BMI cycles (38.1%; $P=.003$) and high-BMI cycles (35.6%; $P=.032$) in cycles of women aged ≥35 years. When the multivariate logistic regression was performed in different age categories, the adjusted ORs for live birth comparing underweight and normal-weight groups were 0.91 (95% CI 0.73–1.13) in women aged <28 years, 0.80 (95% CI 0.61–1.05) in women aged 28–34 years, and 0.43 (95% CI 0.27–0.68) in women aged ≥35 years. An interaction term (age category × BMI category) was introduced in the multivariate logistic regression models (Table 4). When an interaction analysis was performed, the OR for live birth was dramatically decreased in women aged ≥35 years compared with those aged 28–34 years, whereas younger women (<28 years) did not present significant differences compared with women aged 28–34 years. On the other hand, the difference was found to not be significantly different in any of the age categories in overweight women.

DISCUSSION

In Chinese women undergoing IVF-ET in fresh transfer cycles, this study demonstrated decreased live birth rates and increased miscarriage rates in patients with low BMI, after multivariate logistic regression analysis, suggesting that underweight is a negative predictor for IVF outcomes. Although obesity has been clearly associated with unfavorable IVF outcomes, the present study adds to the existing knowledge by highlighting the potential detrimental effect of being underweight.

The "inverted U shape" associations between body weight and IVF outcome have been shown in several studies (6, 7, 11, 17). Those studies suggested that both high BMI and low BMI may have a detrimental effect on IVF outcomes. However, many of the results did not reach statistical significance in terms of live birth rate reduction in low-BMI

TABLE 4

Interaction between age category and the effect of BMI on live birth rates, derived from a multivariate logistic regression model.

Age categories	OR (95% CI) Underweight vs. normal weight	OR (95% CI) Overweight vs. normal weight
<28 y vs. 28–34 y	0.94 (0.65–1.38)	1.00 (0.62–1.64)
≥35 y vs. 28–34 y	0.53 (0.33–0.86)	1.04 (0.69–1.56)

Note: Live birth was the dependent variable, BMI and age categories the interaction terms (BMI category × age category), and duration of infertility, type of infertility, previous attempts of embryo transfer, basal FSH, LH, and AFC, GnRH analogue, diagnoses of PCOS, endometriosis, hydrosalpinx, and male infertility, starting dose of stimulation, number of oocytes, insemination protocols, number and developmental stage of embryos transferred, presence of top-quality embryo, endometrial thickness, and progesterone elevation independent variables. Abbreviations as in Table 3.

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women. Veleva et al. demonstrated a quadratic relationship between BMI and the risk of miscarriage, indicating that the risk of miscarriage increases in both underweight and obese women (11). Our data echoed that study by showing a significant association between low BMI and both miscarriage rates and live birth rates and thus further supports the idea that both extremes of body weight are detrimental to IVF outcomes.

A large retrospective study based on the 2008–2010 Society for Assisted Reproductive Technology registry (SART) data also showed a subtle decrease in live birth rates in fresh cycles of those reporting low BMI compared with the cycles of those of normal weight (2). However, the difference was relatively small and diminished in subgroup analysis. In addition, the pregnancy loss per clinical pregnancy was similar between the cycles of underweight and normal-weight subjects. Because the large study was unable to adjust for patient race among BMI categories, the association between BMI and IVF outcomes might have been affected by the heterogeneous ethnicity of the participants (2). The work of Luke et al. suggested an interaction between race and BMI effect, in which Asian women were more likely to suffer reduced IVF outcomes associated with increased BMI (18). However, they did not analyze the data from underweight women owing to small numbers of conforming subjects within the group. It is still not known whether the distribution of patient race contributes to the diverse impact of low BMI.

A previous study based on the Chinese population also showed a lower clinical pregnancy rate in underweight women compared with normal-weight women (10). However, after adjusting for differences in age and infertility diagnoses, the data showed that the OR for clinical pregnancy was 0.718 (95% CI 0.49–1.042) in the underweight group compared with the normal-weight group. The authors stated that it remained to be examined whether this was caused by the low sample size of the underweight women. In our study, a larger cohort was investigated, and the negative effect of low BMI was confirmed in a multivariate model.

Low BMI may disrupt the IVF outcome in several ways. The female reproductive system is sensitive to energy imbalances (19), and a low BMI may suggest inadequate energy intake and status, leading to a negative energy balance. In other animals, it is known that low energy intakes are associated with gonadotropin concentrations, follicle growth, and oocyte quality. The same may also be true in humans, because an inverted U-shaped relationship between BMI and the number of developed embryos was also observed in women undergoing IVF (17). The energy-regulating hormones that are differentially regulated in obese women are also a response to energy restriction (20). The roles of energy-regulating hormones as paracrine and endocrine factors in regulating follicle growth and endometrial receptivity have been explored in earlier literature (21), and they may underlie additional mechanisms by which energy restriction affects fecundity. For example, leptin, a well known regulator of food intake and energy balance, positively correlates with BMI (22). Leptin also plays a role in the embryo-maternal cross-talk at the time of implantation. Low endometrial leptin expressions are associated with implantation failure (23), and abnormally low leptin concentrations are observed in some pregnancy-associated pathologies, such as recurrent spontaneous abortion in the first trimester of pregnancy (24). Therefore, the reduced fecundity of underweight women may be partially mediated by decreased leptin levels (11). Interestingly, advanced age also contributes to decreased leptin levels independently from adiposity (25). The fact that the leptin system could be controlled by independent factors such as BMI and age, may imply a potential biologic interaction between these factors and the leptin-mediated effects.

Among the confounding factors that were adjusted for in the multivariate analysis, age of the patient was the most potent, causing a 10.5% reduction in the OR for live birth when comparing underweight patients with normal-weight patients. This result suggested that considerable bias may originate from the unbalanced distribution of age between study groups when investigating the effect of BMI on IVF outcomes. Moreover, the stratum-specific effects suggested that low BMI had a more profound effect on live birth rates in patients older than 35 years, whereas the effect in younger patients was insignificant. This finding suggests that the negative association between low BMI and live birth is less likely to be observed in younger women, even if age is adjusted for as a confounding factor. The analysis may also partially explain why many other studies did not find a significant effect in underweight women (5, 9, 12), because the age distribution among underweight women may be quite different among different populations. Although investigating a small population of younger age is less likely to detect the association between underweight and live birth, the SART data revealed a subtle decrease in live births in a large cohort of underweight women with a mean age of 34.7 years (2). Nevertheless, women of advanced age are associated with more profound negative predictors for live birth, such as diminished ovarian reserves and poor quality of embryos transferred, which should also be taken into consideration in relevant studies.

Unlike many studies regarding the effect of BMI on IVF outcomes, our study failed to show a significant association between overweight and live birth rates. This may be due to the lack of patients conforming to the WHO class I or higher obesity classes (BMI >30 kg/m^2) in our study, or it may be because we excluded diabetic/glucose intolerant patients. Moreover, obesity disturbs the IVF process in part by disrupting ovarian response. Even in the PCOS patients, among whom a high response would be expected, obese women are at an increased risk of cycle cancellation due to insufficient response. However, their live birth rates are similar to those of nonobese women once oocyte retrieval is achieved (26). Because the present study took only fresh transfer cycles into account, and was adjusted for the parameters of embryo transfer, the differences due to a decline in ovarian response associated with obesity may have been diminished.

Our conclusions are limited by the retrospective nature of the study, and the single-center design also weakens the universality of our observations. However, given that the dataset was obtained within a relatively short period, it may also reduce the potential confounding effects of technique shift over time and regions. The results of the study should also be interpreted with caution for the reason that the cause of

the underweight status of the subjects in our population was not investigated, although we did exclude known diagnoses such as thyroid abnormalities. Underweight status is often associated with insufficient food intake, but it may also imply the presence of chronic disease. This may emphasize the importance of counseling underweight women on adequate food intake. Other factors, such as lower leptin levels, increased insulin sensitivity, and the changes in the action of skeletal muscle adenosine monophosphate–activated protein kinase may also be considered (11). An epidemiologic study also suggested an association between BMI and socioeconomic status (27); the latter may also affect the patients' decision making as well as their performance in IVF cycles.

In conclusion, our study suggests that underweight is associated with negative outcomes in fresh transfer cycles, especially for women of advanced age. Weight counseling may therefore be helpful not only for obese patients but also for underweight patients, before initiating IVF cycles.

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SUPPLEMENTAL TABLE 1

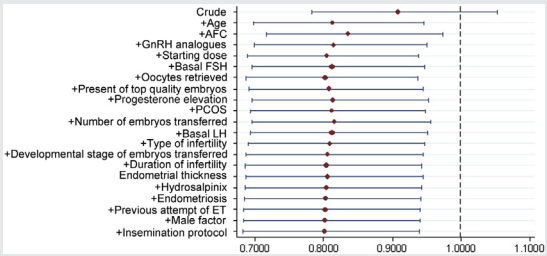
Comparison of the results of logistic regression analysis and generalized estimating equations (GEE) analysis of live birth per transfer.

		OR (95% CI)	
Variable	**Category**	**GEE**	**Basic logistic**
BMI	Underweight vs. normal	0.80 (0.68–0.94)	0.80 (0.68–0.94)
	Overweight vs. normal	0.92 (0.77–1.103)	0.92 (0.77–1.10)
Age	Per year increased	0.96 (0.95–0.98)	0.96 (0.95–0.98)
Duration of infertility	Per year increased	0.98 (0.96–1.00)	0.97 (0.95–0.99)
Type of infertility	Primary vs. secondary	1.06 (0.93–1.21)	1.06 (0.93–1.21)
Previous embryo transfer attempts	Per transfer increased	1.00 (0.92–1.08)	1.00 (0.92–1.09)
PCOS	With vs. without	0.95 (0.70–1.28)	0.94 (0.70–1.27)
Endometriosis	With vs. without	1.04 (0.86–1.25)	1.02 (0.85–1.24)
Hydrosalpinix	With vs. without	0.66 (0.49–0.90)	0.67 (0.49–0.90)
Male infertility	With vs. without	1.13 (0.89–1.43)	1.11 (0.88–1.41)
Basal FSH	Per mIU increased	1.00 (0.97–1.02)	0.99 (0.97–1.02)
Basal LH	Per mIU increased	1.02 (1.00–1.04)	1.02 (0.99–1.04)
AFC	Per AFC increased	1.00 (0.98–1.02)	0.99 (0.98–1.02)
GnRH analogue	Antagonist vs. agonist	0.49 (0.41–0.60)	0.49 (0.41–0.59)
Starting dose of stimulation	Per 75 IU increased	0.78 (0.65–0.93)	0.78 (0.65–0.93)
No. of oocytes retrieved	Per oocyte increased	1.02 (1.01–1.04)	1.02 (1.01–1.04)
Insemination protocol	IVF vs. ICSI	0.94 (0.78–1.13)	0.93 (0.77–1.13)
Development stage of transferred embryos	Cleavage vs. blastocyst	0.42 (0.31–0.57)	0.42 (0.32–0.57)
No. of embryos transferred	Two vs. one	3.18 (2.12–4.76)	3.06 (2.47–3.78)
	Three vs. one	3.05 (2.46–3.78)	3.17 (2.15–4.67)
At least one top-quality embryo transferred	Yes vs. no	1.38 (1.20–1.58)	1.38 (1.20–1.58)
Progesterone elevation	Yes vs. no	0.89 (0.76–1.04)	0.89 (0.76–1.04)
Endometrial thickness	Per mm increased	1.02 (0.99–1.06)	1.02 (0.99–1.05)

Note: AFC = antral follicle count; CI = confidence interval; OR = odds ratio; PCOS = polycystic ovary syndrome.

Cai. Low BMI compromises live birth rate. Fertil Steril 2016.

SUPPLEMENTAL FIGURE 1



The change in the estimate of the effect of underweight (body mass index <18.5 kg/m^2) on live birth rates with each variable added to the multivariable logistic regression model. AFC = antral follicle count; ET = embryo transfer; PCOS = polycystic ovary syndrome.

Cai. Low BMI compromises live birth rate. Fertil Steril 2016.