Association between body mass index and *in vitro* fertilization/intra-cytoplasmic sperm injection outcomes: An analysis of 15,124 normal ovarian responders in China

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Abstract

Background: High body mass index (BMI) results in decreased fecundity, and women with high BMI have reduced rates of clinical pregnancy and live birth in *in vitro* fertilization/intra-cytoplasmic sperm injection (IVF/ICSI). Meanwhile, ovarian responses show great heterogeneity in patients with a high BMI. This study aimed to analyze the effects of a high BMI on IVF/ICSI outcomes in the Chinese female with normal ovarian response.

Methods: We performed a retrospective cohort study comprising 15,124 patients from the medical record system of the Reproductive Center of Peking University Third Hospital, with 3530 (23.3%) in the overweight group and 1380 (9.1%) in the obese group, who had a normal ovarian response (5–15 oocytes retrieved) and underwent fresh embryo transfer (ET) cycles from January 2017 to December 2018, followed by linked frozen-thawed embryo transfer (FET) cycles from January 2017 to December 2020. Cumulative live birth rate (CLBR) was used as the primary outcome. Furthermore, a generalized additive model was applied to visually illustrate the curvilinear relationship between BMI and the outcomes. We used a decision tree to identify the specific population where high BMI had the greatest effect on IVF/ICSI outcomes.

Results: High BMI was associated with poor IVF/ICSI outcomes, both in cumulative cycles and in separate fresh ET or FET cycles. In cumulative cycles, compared with the normal weight group, obesity was correlated with a lower positive pregnancy test rate (adjusted odds ratio [aOR]: 0.809, 95% confidence interval [CI]: 0.682–0.960), lower clinical pregnancy rate (aOR: 0.766, 95% CI: 0.646–0.907), lower live birth rate (aOR: 0.706, 95% CI: 0.595–0.838), higher cesarean section rate (aOR: 2.066, 95% CI: 1.533–2.785), and higher rate of large for gestational age (aOR: 2.273, 95% CI: 1.547–3.341). In the generalized additive model, we found that CLBR declined with increasing BMI, with 24 kg/m^2 as an inflection point. In the decision tree, BMI only made a difference in the population aged ≤34.5 years, with anti-Mullerian hormone >1.395 ng/mL, and the first time for IVF.

Conclusions: High BMI was related to poor IVF/ICSI outcomes in women with a normal ovarian response, and CLBR declined with increasing BMI, partly due to suppressed endometrial receptivity. A high BMI had the most negative effect on young women with anticipated positive prognoses.

Keywords: Obesity; Body mass index; *In vitro* fertilization; Live birth; Decision trees; Normal ovarian response

Introduction

Overweight and obesity are defined as abnormal or excessive fat accumulation, which are frequently evaluated based on body mass index (BMI, weight/height^2, kg/m^2). Worldwide, obesity has nearly tripled since 1975. In China, the prevalence of obesity was 8.1% in 2018, more than twice as high as that in 2004.[1] Overweight and obesity are becoming important public health crises in China, as they have been in developed countries.

Besides cardiometabolic problems, a high BMI has been reported to result in decreased fecundity.[2,3] Excessive body weight negatively affects several processes, including ovulation, oocyte maturation, endometrial receptivity, implantation, and pregnancy continuation.[4] Women with obesity have a high incidence of menstrual irregularity and anovulatory infertility. Even in ovulatory women, obesity is closely associated with a low spontaneous pregnancy rate. Therefore, women with obesity are very likely to require *in vitro* fertilization (IVF) or intra-cytoplasmic sperm injection (ICSI). Studies have shown that women with high BMI have significantly reduced rates of clinical pregnancy and live birth in IVF/ICSI, and the

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rates continually decrease for every one unit increase in BMI.[2,5–7] However, most studies were from Western countries and mainly focused on women of European descent. Evidence regarding the relationship between BMI and IVF/ICSI outcomes in Asian populations is lacking. Asian populations have a high percentage of body fat at a low BMI and a great risk of developing diabetes and cardiovascular disease at a low BMI.[8] With high BMI, Asian women are more likely to fail to achieve a clinical intrauterine gestation (odds ratio [OR] = 1.21 for overweight and 1.73 for obesity) as well as fail to achieve a live birth (OR = 1.56 for overweight and 2.20 for obesity) compared with white women.[9]

Patients undergoing ovarian stimulation have different ovarian responses, and the optimal number of oocytes retrieved is a controversial topic. In randomized controlled and cohort studies, the targeted number of oocytes retrieved ranged from 5 to 14, 8 to 14, or 4 to 15.[10,11] A study in China also pointed out that the optimal number was between 6 and 15.[12] Beyond this range, both poor and hyper-response result in a high cycle cancelation rate, and patients with hyper-response are prone to ovarian hyperstimulation syndrome (OHSS).[10] Although most patients with obesity tend to have a poor ovarian response, some, especially those with polycystic ovary syndrome (PCOS), could have a hyper ovarian response.[6,13]

Therefore, this study aimed to analyze the effects of a high BMI on IVF/ICSI outcomes in the Chinese population. To minimize heterogeneity, the study population was limited to women with a normal ovarian response.

Methods

Ethics approval

This study was approved by the Ethics Committee of Peking University Third Hospital (No. IRB00006761-M2020004). Informed consent was waived because this was a data analysis retrospectively with no personally identifiable information.

Study population

This was a retrospective cohort study of fresh embryo transfer (ET) cycles from January 2017 to December 2018, and subsequent linked frozen-thawed embryo transfer (FET) cycles from January 2017 to December 2020. Data were retrieved from the medical record system of the Reproductive Center of Peking University Third Hospital, and obstetric data were collected by professional recorders via telephone follow-up.

This study included a female population who underwent IVF/ICSI and had a normal ovarian response (5–15 oocytes retrieved). The exclusion criteria were as follows: (1) *in vitro* maturation (IVM) technique; (2) natural cycle protocol or mild ovarian stimulation protocol; (3) couples with chromosomal abnormalities or those undergoing preimplantation genetic testing (PGT); (4) fertility preservation; and (5) missing pregnancy data. According to Chinese BMI criteria, the population was divided into four groups: underweight (BMI <18.5 kg/m^2), normal weight (BMI = 18.5–23.9 kg/m^2), overweight (BMI = 24.0–27.9 kg/m^2), and obese (BMI ≥28.0 kg/m^2).[14]

Treatment protocol

The ovarian stimulation protocol, timing and dose of ovulatory trigger, embryo culture, and transfer process were performed according to the standard protocols of our center. The gonadotropin-releasing hormone agonist (GnRH-a) long protocol, prolonged protocol, short flare protocol, ultrashort flare protocol, and GnRH antagonist protocol were chosen for ovarian stimulation according to different diagnoses and past treatment histories. When two or more follicles reached a diameter of at least 18 mm, 250 μg of recombinant human choriogonadotropin alfa solution for injection (rHCG, Ovidrel, Merck Serono, UK) was administered for triggering. Oocyte retrieval was performed 34–38 h after triggering, and IVF or ICSI was used based on semen analysis results.

The development and quality of embryos were assessed on day 3, considering the percentage of fragmentation and the quality of the cytoplasm. Good-quality embryos on day 3 were defined as embryos that were derived from 2 pronuclear (2PN) embryos and could reach at least six-cell stage with cytoplasmic fragmentation <20%.[15,16] Blastocyst morphology was evaluated on day 5 or Day 6 using the Gardner grading system.[17] Good-quality blastocysts were graded as AA, AB, BA, and BB with expansion grade ≥3.[18,19] One or two embryos were transferred in the fresh ET cycle, as determined by the doctors and embryologists. The surplus embryos were cryopreserved. During FET cycles, frozen embryos were transferred throughout the natural hormone replacement or ovulation induction cycles for endometrial preparation.

For both fresh ET and FET cycles and for both day 3 embryos and blastocysts, serum human chorionic gonadotropin (HCG) was measured 14 days after ET. An ultrasound scan was performed 28 days after ET. In the fresh ET cycle, the luteal phase was supported by a progesterone intravaginal gel (Crinone gel 8%, Merck Serono SA, Geneva, Switzerland) daily. In the natural and ovulation induction cycle of FET, the luteal phase support was 10 mg of oral dydrogesterone (Duphaston, Abbott Biologicals B.V., Weesp, Netherlands) twice daily. In the hormone replacement cycle of FET, luteal phase support was a progesterone intravaginal gel (Crinone gel 8%, Merck Serono SA) daily and 20 mg of oral dydrogesterone twice daily, and the dose was gradually reduced. Luteal phase support was continued until 10 weeks of gestation.

Outcomes

We followed the outcomes until live birth or October 2021. This implied that once patients had live births in fresh ET or any FET cycle, follow-up would be censored. The primary outcome was cumulative live birth rate (CLBR). The secondary outcomes included positive pregnancy test rate, clinical pregnancy rate, live birth

rate, cesarean section rate, preterm delivery rate, neonatal weight type after the fresh ET and FET cycles, and the cumulative outcomes per woman.

A positive pregnancy test was defined as a serum HCG >5 IU/L 14 days after transfer. Clinical pregnancy was defined as the detection of a gestational sac on transvaginal ultrasonography. Ectopic pregnancy was defined as a gestational sac outside the uterine cavity, according to ultrasound or pathological evidence. Twin pregnancy was diagnosed depending on the ultrasound images during the first trimester, whether the patient underwent later multifetal reduction or not. Miscarriage was defined as the loss of a previously documented clinical pregnancy before 28 weeks of gestation. Live birth was defined as delivery at ≥28 weeks of gestational age with the infant(s) born alive. Preterm delivery was defined as delivery before 37 weeks of gestation. For singleton birth weight, small for gestational age (SGA) and large for gestational age (LGA) were defined as the top and bottom 10% of gestational age- and gender-specific birth weights, respectively.[20] CLBR was defined as the live birth rate following a fresh ET cycle and all additional FET cycles in which the transferred embryo was created at the time of fresh IVF stimulation. Once a patient achieved a positive pregnancy test in a fresh cycle or in subsequent frozen cycles, the cumulative positive pregnancy test was positive. The cumulative clinical pregnancy rate was calculated in a similar manner.

Sample size estimation

According to the preliminary statistical results of our center, the CLBR of the obese group was 36.6%, and that of the normal weight group was 42.0%. We set a significance level as 0.05, the statistical power as 80%, and the sample size ratio of the obese group to the normal weight group as 1:4. The sample size required for the obese group was calculated to be 806. The sample size was calculated using the Two Independent Proportions Power Analysis in PASS software (v.11, NCSS, Kaysville, UT, USA).

Statistical analysis

All continuous variables were non-normally distributed and are presented as median (25 quantile, 75 quantile). Categorical variables are presented as proportions in each group. Univariable comparisons among groups were performed using the Kruskal–Wallis *H* test for continuous variables and the Pearson chi-squared test for categorical variables. A two-sided *P*-value <0.05 was considered statistically significant among all four groups, and *P* <0.008 was considered statistically significant for comparisons between any two groups according to Bonferroni-corrected *P*. Logistic regression (enter method) was used to evaluate the correlation between BMI and outcomes, and BMI was used as a continuous and categorical variable, respectively. For outcomes of fresh ET and FET cycles or cumulative outcomes, all models were adjusted for female age, type of infertility, duration of infertility, gravidity, parity, male BMI, male age, basal follicle-stimulating hormone (FSH), antral follicle count (AFC), PCOS, tube factor, endometriosis, uterine factor, number of oocytes retrieved, and number of 2PN zygotes. In the fresh ET cycle model, additional adjusting variables included ovarian stimulation protocol, stimulation duration, total gonadotropin dose, endometrial pattern, estradiol (E_2)/luteinizing hormone (LH)/progesterone (P) on trigger day, number of embryos transferred, and day of ET. In the FET cycle model, additional adjusting variables included the number of transferable embryos, number of frozen embryos, endometrial preparation, and endometrial pattern on the transfer day. In the cumulative outcome model, additional adjusting variables included ovarian stimulation protocol, stimulation duration, total gonadotropin dose, endometrial pattern, E_2/LH/P level on trigger day, number of transferable embryos, number of frozen embryos, number of embryos transferred in the fresh cycle, and day of ET in the fresh cycle. Subgroup analysis was also performed using logistic regression. We did not include basal testosterone and androstenedione in the adjusted calculation because they had clinical cross-correlation with PCOS, and likewise, we did not include basal membrane thickness for the diagnosis of the uterine factor.

Unadjusted and adjusted generalized additive models were conducted using CLBR as the outcome, with the "logit" link function and REML method to find the appropriate degrees of freedom. Adjusting variables included female age, female BMI, type of infertility, PCOS, uterine factor, ovarian stimulation protocol, stimulation duration, total gonadotropin dose, number of oocytes retrieved, number of 2PN zygotes, and day of ET in fresh ET cycles, which were all significant variables after logistic regression of CLBR. In the unadjusted model, a smoothing spline was applied to BMI, and k (the upper limit on the degrees of freedom) was set as 10 according to the Akaike information criterion. In the adjusted model, a smoothing spline was applied to all continuous variables, and the number of knots was determined by default in the mgcv R package (v1.8.40; Wood, S.N., 2011) in R Statistical Software (v4.2.0; R Foundation, Vienna, Austria).

To develop the first-visit characteristics model to predict the CLBR, most of the data were used to generate the decision tree (70%, training dataset) with the growth method CRT, and the remaining data were used to examine the validation of the decision tree (30%, test dataset). The input variables were the baseline characteristics of patients that were statistically or clinically significant, including female age, female BMI, male BMI, type of infertility, duration of infertility, gravidity, parity, basal FSH, anti-Müllerian hormone (AMH), AFC, PCOS, tube factor, endometriosis, uterine factor, male factor, and whether it was the first time for IVF/ICSI. The Gini index was used to split nodes, and the minimum of the Gini gain was set to 0.001. The Gini gain (improvement) of every splitting step [Supplementary Figure 1, http://links.lww.com/CM9/B866]. Growth limits were set so that the tree could not have a depth > five levels. Both parent nodes and child nodes had to have a minimum of 100 cases.

Statistical analyses were performed using SPSS software (v25.0, IBM Corp, Armonk, NY, USA) and R Statistical Software (v4.2.0, R Foundation, Vienna, Austria).

Results

The study included 15,124 patients, with 9120 (60.3%) in the normal weight group, 3530 (23.3%) in the overweight group, 1380 (9.1%) in the obese group, and 1094 (7.2%) in the underweight group. Nearly 70% of the women underwent IVF for the first time, and this proportion was comparable among the groups. The AMH level and proportion of male factor diagnosis were also comparable, of which the AMH level was mainly due to the restriction of normal ovarian responders. All other baseline characteristics, basic evaluations, and diagnoses showed significant differences among the groups. Compared with the normal weight group, women with obesity were younger (32 [29,36] years *vs*. 33 [30,36] years), with more AFC in ultrasound images (12 [8,16] *vs*. 9 [7,12]), but had longer duration of infertility (4 [2,6] years *vs*. 3 [2,5] years), higher serum androgen levels; their spouses were also younger (34 [30,37] years *vs*. 34 [30,38] years) but had higher BMI (25.71 [23.47, 28.34] *vs*. 25.11 [22.86, 27.55]), PCOS was more common (332/1380 [24.1%] *vs*. 599/9120 [6.6%]), and endometriosis was less common (44/1380 [3.2%] *vs*. 709/7.8 [6.6]%) (all P <0.001). The type of infertility, gravidity, parity, basal FSH level, and diagnosis of tube and uterine factors did not show significant differences between the obese and normal weight groups.

For IVF/ICSI treatment, compared with the normal weight group, the obese group required a longer stimulation duration (12 [10,13] days *vs*. 11 [10,13] days, P <0.001). The total dose of gonadotropin increased with the increase of BMI in each group. In particular, although endometrial thickness was comparable among the different BMI groups, endometrial pattern differed significantly. The proportion of patients with pattern A decreased with increasing BMI. The number of oocytes retrieved was lower in women with obesity than that in women with normal weight (9 [7,12] *vs*. 10 [7,12], P = 0.007), even in the interval of 5–15 oocytes retrieved. The insemination method, number of transferable embryos, and number of frozen embryos were not significantly different among the groups [Supplementary Table 1, http://links.lww.com/CM9/B866].

Some planned fresh ETs were canceled (1733/15,124, 11.5%) if fertilization or embryo development failed (146/15,124, 1.0%), if the endometrial thickness was not sufficient (218/15,124, 1.4%), for personal reasons (861/15,124, 5.7%), or if the E_2 levels on trigger day were above 15,000 pmol/L, which implied a high risk of OHSS (508/15,124, 3.4%). After fresh ET cycles, 10,719 women had no live birth, and 6118 (57.1%) of them underwent subsequent FET cycles [Tables 1 and 2]. After logistic regression, compared with the normal weight group, both in fresh ET cycles and FET cycles, the obese group had significantly lower clinical pregnancy rates (aOR = 0.844 [0.717–0.994] in fresh ET cycles, and 0.662 [0.489–0.896] in FET cycles) and lower live birth rates (aOR = 0.753 [0.633–0.897] in fresh ET cycles, and 0.643 [0.465–0.888] in FET cycles) and higher rates of cesarean section (aOR = 2.074 [1.445–2.978] in fresh ET cycles, and 4.158 [1.889–9.151] in FET cycles) and higher rates of LGA (aOR = 2.260 [1.539–3.320] in fresh ET cycles, and 2.661 [1.474–4.804] in FET cycles). The overweight group had comparable effects in fresh ET cycles, but showed no significant effect on outcomes in FET cycles. In fresh ET cycles, compared with the normal weight group, miscarriage (aOR = 1.443 [1.044–1.995]), and preterm delivery rates (aOR = 1.690 [1.174–2.433]) were significantly higher for patients with obesity after regression, and miscarriage occurred at a greater gestational age (P = 0.005).

Notably, the cumulative positive pregnancy test rate, cumulative clinical pregnancy rate, and CLBR significantly decreased with increasing BMI categories in both univariate and logistic regression analyses (all P <0.001 when BMI was calculated in logistic regression as continuous variable) [Tables 2]. At the same time, after regression, the premature delivery rate (P = 0.001), cesarean section rate (P <0.001), and the rate of LGA (P <0.001) significantly increased with increasing BMI. Although the underweight group had seemingly better outcomes in the univariate analysis, they were all non-significant after regression.

The results of the subgroup analysis are listed in Supplementary Table 2, http://links.lww.com/CM9/B866. A total of 1482 patients were diagnosed with PCOS, and except for the cesarean rate, other cumulative outcomes were not significant in overweight or obese women, partly due to the small sample size. For patients without PCOS, the outcomes were similar to those of the whole population. For patients who underwent IVF/ICSI for the first time, the overweight and obesity groups had a comparable trend to the whole study population, although significance was not achieved for cumulative clinical pregnancy and live birth rates in the overweight group.

In the generalized additive model, CLBR tended to decrease when BMI increased from 18.5 kg/m^2 to 24.0 kg/m^2, and after the BMI >24.0 kg/m^2, CLBR decreased more slowly [Figure 1].

In the decision tree, the first-visit characteristics model showed that age was the best discriminator, whereas BMI only made a difference in the population aged ≤34.5 years, with AMH >1.395 ng/mL, and the first time for IVF. For them, CLBR was predicted to be 59.8% when BMI was <23.05 kg/m^2, and 52.0% when BMI was >23.05 kg/m^2. The accuracies of the training and test datasets were 61.1% and 61.2%, respectively [Supplementary Figure 1, http://links.lww.com/CM9/B866]. The BMI cutoff and accuracy fluctuated slightly in different random training datasets, but the whole framework was consistent.

Discussion

In this large observational study, which included the largest number of women with obesity in studies of obesity and assisted reproduction technology (ART) outcomes in China, we found that a high BMI was related to poor IVF/ICSI outcomes in normal ovarian responders. Women with a high BMI had low positive pregnancy test rates, low clinical pregnancy rates, and low live birth rates, both in cumulative cycles and in separate fresh ET cycles. And

Table 1: Characteristics and outcomes of fresh ET cycles and FET cycles and the cumulative outcomes.

Characteristics	Underweight	Normal	Overweight	Obese	H/χ^2 value	*P*-value
Fresh ET cycles	*n* = 936	*n* = 8064	*n* = 3155	*n* = 1236		
No. embryos transferred						
1	109 (11.6)	1017 (12.6)	432 (13.7)	187 (15.1)	8.87†	0.031
2	827 (88.4)	7047 (87.4)	2723 (86.3)	1049 (84.9)		
Day of embryos transferred						
Day 3	856 (92.9)	7421 (93.5)	2896 (93.2)	1112 (91.6)	11.06†	0.087
Day 5	42 (4.6)	275 (3.5)	114 (3.7)	62 (5.1)		
Day 6	23 (2.5)	244 (3.1)	98 (3.2)	40 (3.3)		
No. good-quality embryos transferred						
Zero	101 (11.1)	908 (11.5)	351 (11.4)	134 (11.1)	5.26†	0.949
One day 3	171 (18.8)	1591 (20.2)	595 (19.3)	233 (19.4)		
Two day 3	603 (66.1)	5087 (64.5)	2009 (65.0)	780 (64.8)		
One day 5/6	36 (3.9)	294 (3.7)	129 (4.2)	55 (4.6)		
Two day 5/6	1 (0.1)	11 (0.1)	5 (0.2)	1 (0.1)		
Positive pregnancy test	438 (46.8)	3747 (46.5)	1411 (44.7)	536 (43.4)	6.24†	0.101
Clinical pregnancy	401 (42.8)	3356 (41.6)	1235 (39.1)	468 (37.9)	11.84†	0.008
Ectopic pregnancy	13 (3.2)	90 (2.7)	32 (2.6)	18 (3.8)	2.54†	0.468
Twin pregnancy	110 (27.4)	911 (27.1)	343 (27.8)	138 (29.5)	1.19†	0.757
Miscarriage	61 (15.2)	531 (15.8)	219 (17.7)	91 (19.4)	5.90†	0.117
Miscarriage weeks	8 (7, 10)	8 (7, 9)	8 (7, 8)	8 (7, 20)	9.27*	0.026
Live birth	327 (34.9)	2735 (33.9)	984 (31.2)	359 (29.0)	18.04†	<0.001
Gestational age, weeks	38 (37, 40)	38 (37, 39)	38 (37, 39)	38 (37, 39)	42.84*	<0.001
Premature delivery	49 (15.1)	394 (14.6)	189 (19.5)	75 (21.0)	19.06†	<0.001
Cesarean section	195 (62.1)	1793 (67.6)	762 (79.3)	280 (79.3)	70.46†	<0.001
Neonatal birth weight‡, g	3040 (2650, 3375)	3130 (2725, 3500)	3200 (2700, 3600)	3200 (2750, 3590)	16.95*	<0.001
LGA§	22 (9.3)	336 (16.9)	188 (26.9)	81 (30.8)	80.22†	<0.001
SGA§	28 (11.9)	139 (7.0)	33 (4.7)	10 (3.8)		
FET cycles	*n* = 546	*n* = 4163	*n* = 1659	*n* = 651		
Patients with no live birth in fresh ET cycles having frozen embryos	455/767 (59.3)	3647/6385 (57.1)	1441/2546 (56.6)	575/1021 (56.3)	2.06†	0.560
Patients going through FET cycles	386/455 (84.8)	3091/3647 (84.8)	1240/1441 (86.1)	489/575 (85.0)	1.40†	0.706
No. FET cycles/patients	546/386 (1.41)	4163/3091 (1.35)	1659/1240 (1.34)	651/489 (1.33)	1.92†	0.588
Endometrial preparation						
Natural cycle	303 (55.5)	2280 (54.8)	668 (40.4)	225 (34.7)	174.7†	<0.001
Hormone replacement cycle	209 (38.3)	1546 (37.2)	843 (50.9)	364 (56.2)		
Ovulation induction cycle	34 (6.2)	332 (8.0)	144 (8.7)	59 (9.1)		
Endometrial thickness on transfer day	10 (9, 11)	10 (9, 11)	10 (9, 11)	10 (9, 11)	3.57*	0.312
Endometrial pattern on transfer day						
A	262 (85.6)	1856 (84.2)	692 (83.0)	239 (79.9)	10.96†	0.089
A-B	6 (2.0)	90 (4.1)	42 (5.0)	11 (3.7)		
B	38 (12.4)	257 (11.7)	100 (12.0)	49 (16.4)		
No. embryos transferred						
1	381 (69.8)	2898 (69.6)	1198 (72.2)	457 (70.2)	3.92†	0.270
2	165 (30.2)	1265 (30.4)	461 (27.8)	194 (29.8)		
Day of embryos transferred						
Day 3	117 (21.5)	898 (21.7)	361 (21.8)	132 (20.3)	8.22†	0.220
Day 5	406 (74.8)	3151 (76.1)	1263 (76.3)	496 (76.4)		
Day 6	20 (3.7)	93 (2.2)	32 (1.9)	21 (3.2)		
No. good-quality embryos transferred						
Zero	184 (33.7)	1356 (32.6)	557 (33.6)	220 (33.8)	6.84†	0.868
One day 3	31 (5.7)	198 (4.8)	72 (4.4)	28 (4.3)		
Two day 3	78 (14.3)	635 (15.3)	261 (15.8)	94 (14.5)		
One day 5/6	248 (45.4)	1908 (46.0)	752 (45.4)	298 (45.9)		
Two day 5/6	5 (0.9)	55 (1.3)	13 (0.8)	9 (1.4)		
Positive pregnancy test	290 (53.1)	2000 (48.0)	767 (46.2)	300 (46.1)	8.68†	0.034
Clinical pregnancy	256 (46.9)	1753 (42.1)	682 (41.1)	259 (39.8)	7.22†	0.065
Ectopic pregnancy	1 (0.4)	11 (0.6)	6 (0.9)	1 (0.4)	1.13†	0.771

(*continued*)

Table 1

(Continued)

Characteristics	Underweight	Normal	Overweight	Obese	*H*/χ^2 value	*P*-value
Twin pregnancy	20 (7.8)	145 (8.3)	78 (11.4)	24 (9.3)	6.53†	0.090
Miscarriage	51 (19.9)	339 (19.3)	152 (22.3)	61 (23.6)	4.34†	0.228
Miscarriage weeks	7 (7, 9)	7 (7, 9)	8 (7, 9)	8 (7, 10)	1.13*	0.769
Live birth	203 (37.2)	1399 (33.6)	523 (31.5)	197 (30.3)	8.81†	0.032
Gestational age, weeks	39.00 (38.00, 40.00)	39.00 (38.00, 39.00)	38.00 (37.00, 39.00)	38.00 (37.00, 39.00)	23.53*	<0.001
Premature delivery	21 (10.3)	164 (11.7)	73 (14.0)	36 (18.3)	8.56†	0.037
Cesarean section	119 (59.5)	916 (66.4)	370 (71.8)	160 (81.2)	27.57†	<0.001
Neonatal birth weight‡, g	3217.50 (2910.00, 3500.00)	3300.00 (3000.00, 3600.00)	3315.00 (2990.00, 3700.00)	3400.00 (3000.00, 3690.00)	10.17*	0.022
LGA§	24 (13.3)	319 (23.3)	142 (27.5)	68 (35.1)	32.06†	<0.001
SGA§	12 (6.6)	71 (5.2)	29 (5.6)	15 (7.7)		
Cumulative	*n* = 1094	*n* = 9120	*n* = 3530	*n* = 1380		
Positive pregnancy test	665 (60.8)	5310 (58.2)	2008 (56.9)	768 (55.7)	8.48†	0.037
Clinical pregnancy	622 (56.9)	4872 (53.4)	1818 (51.5)	691 (50.1)	15.06†	0.002
Live birth	531 (48.5)	4134 (45.3)	1507 (42.7)	556 (40.3)	24.34†	<0.001
Gestational age, weeks	39 (37, 40)	38 (37, 39)	38 (37, 39)	38 (37, 39)	65.88*	<0.001
Premature delivery	70 (13.3)	558 (13.6)	261 (17.5)	111 (20.0)	25.89†	<0.001
Cesarean section	314 (61.1)	2709 (67.2)	1132 (76.7)	440 (80.0)	97.75†	<0.001
Neonatal birth weight‡, g	3100 (2750, 3450)	3200 (2800, 3535)	3250 (2775, 3610)	3300 (2850, 3600)	22.38*	<0.001
LGA§	46 (11.0)	655 (19.5)	330 (27.2)	149 (32.6)	96.03†	<0.001
SGA§	40 (9.6)	210 (6.3)	62 (5.1)	25 (5.5)		

Data are presented as *n* (%) or median (Q1, Q3). *Refers to *H* value tested by Kruskal–Wallis *H* test, and †refers to χ^2 value tested by Pearson χ^2 test. ‡Neonatal birth weight: including singleton birth weight and the average of twins. §LGA and SGA: only applicable for singleton. ET: Embryo transfer; FET: Frozen-thawed embryo transfer; LGA: Large for gestational age; SGA: Small for gestational age.

women with a high BMI had high cesarean section and LGA rates. In the generalized additive model, we intuitively presented the decline in CLBR with increasing BMI, and 24 kg/m^2 was an inflection point, indicating the weight-loss goal for improved IVF/ICSI outcomes. Furthermore, in the decision tree, the first-visit characteristics model mimicked the situation in which one patient visited the clinic for the first time, and the doctor had to predict her pregnancy outcome according to baseline characteristics only. We found that high BMI had the most negative effect in young women with anticipated positive prognosis (age ≤34.5 years, AMH >1.395 ng/mL, and first IVF/ICSI). This specific population accounted for approximately 42% of our study population and was the key population for IVF treatment in China.

Previously, the influence of BMI on IVF/ICSI outcomes has been controversial. Although several studies have reported no relationship between fat excess and IVF/ICSI outcomes,[21–23] more clinical studies had conclusions consistent with ours, although they mainly focused on white women.[5–7,24] Many studies have been conducted to determine the underlying mechanisms. Dysregulation of the hypothalamic–pituitary–ovarian axis, insulin resistance, elevated leptin level, increased reactive oxygen species, and chronic low-grade inflammatory state contribute to poor outcomes.[3,25] In our study, we restricted our population to normal ovarian responders, and the number of good embryos transferred was comparable among the groups, which suggests that reduced endometrial receptivity could partly explain the poor outcomes. Some previous studies have included oocyte donation cycles to study the effect of fat excess on the endometrial receptivity. Although one meta-analysis by Jungheim *et al*[26] reported no effect, this analysis only included five studies with 4758 patients, and there was significant heterogeneity and no baseline information about both the donors and recipients. In 2013, Bellver *et al*[27] included 9587 first cycles of ovum donation and found that implantation, clinical pregnancy, and live birth rates were significantly reduced as BMI increased. In 2016, the largest cohort study of BMI in donor cycles with 22,317 donor/recipient oocyte cycles also concluded that pregnancy outcomes worsened as BMI increased.[28] These findings were consistent with those of our study, which demonstrated that excessive female fat may impair endometrial receptivity. Moreover, there was transcriptome evidence that endometrial gene expression in the window of implantation was altered in women with obesity, especially those with PCOS and infertility,[29,30] and endometrial receptivity analysis showed that obesity could delay the window of implantation, and displacement was longer as BMI increased.[31] However, the mechanism has not yet been fully elucidated; metabolic, endocrine, inflammatory, and epigenetic mechanisms may be involved, which is worthy of further exploration.[32]

More attention should be paid to weight loss. Several high-quality randomized clinical trials have performed lifestyle interventions in women with mean BMI ranging from 33 kg/m^2 to 39 kg/m^2, and ultimately reduced BMI by 2.6–3.6 units or reduced weight by 4.4 kg. However, all showed no positive effect on pregnancy outcomes with mild weight loss.[33–35] In our study, considering that the

Table 2: Logistic regression analysis in fresh ET cycles, FET cycles, and cumulative calculation.

			BMI classification						
	BMI*		Underweight		Normal weight	Overweight		Obese	
Outcomes	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)
Fresh ET cycles									
Positive pregnancy test	0.006	0.982 (0.969–0.995)	0.547	0.946 (0.789–1.134)	1	0.076	0.906 (0.813–1.010)	0.115	0.879 (0.749–1.032)
Clinical pregnancy	<0.001	0.976 (0.963–0.989)	0.926	1.009 (0.840–1.211)	1	0.027	0.882 (0.790–0.985)	0.042	0.844 (0.717–0.994)
Ectopic pregnancy	0.671	1.013 (0.954–1.076)	0.829	1.088 (0.505–2.345)	1	0.416	0.799 (0.465–1.373)	0.145	1.631 (0.845–3.149)
Twin pregnancy	0.112	1.019 (0.996–1.043)	0.861	0.973 (0.715–1.324)	1	0.335	1.100 (0.907–1.334)	0.070	1.304 (0.978–1.740)
Miscarriage	0.028	1.031 (1.003–1.060)	0.248	1.244 (0.859–1.799)	1	0.279	1.136 (0.901–1.433)	0.026	1.443 (1.044–1.995)
Live birth	<0.001	0.970 (0.957–0.984)	0.629	0.954 (0.789–1.154)	1	0.039	0.885 (0.788–0.994)	0.002	0.753 (0.633–0.897)
Premature delivery	0.011	1.040 (1.009–1.073)	0.648	1.102 (0.727–1.668)	1	0.021	1.344 (1.045–1.727)	0.005	1.690 (1.174–2.433)
Cesarean section	<0.001	1.095 (1.064–1.127)	0.125	0.781 (0.570–1.071)	1	<0.001	1.979 (1.576–2.485)	<0.001	2.074 (1.445–2.978)
LGA†	<0.001	1.095 (1.059–1.133)	0.200	0.682 (0.380–1.224)	1	0.001	1.581 (1.199–2.085)	<0.001	2.260 (1.539–3.320)
SGA†	0.043	0.937 (0.879–0.998)	0.006	2.188 (1.256–3.809)	1	0.907	0.971 (0.597–1.580)	0.209	0.544 (0.211–1.406)
FET cycles									
Positive pregnancy test	0.014	0.972 (0.950–0.994)	0.940	0.988 (0.729–1.341)	1	0.783	0.972 (0.797–1.186)	0.023	0.710 (0.529–0.953)
Clinical pregnancy	0.010	0.970 (0.948–0.993)	0.572	1.093 (0.803–1.487)	1	0.971	1.004 (0.822–1.226)	0.007	0.662 (0.489–0.896)
Ectopic pregnancy	0.317	0.842 (0.601–1.179)	0.440	2.663 (0.222–31.97)	1	0.696	0.640 (0.068–5.990)	0.997	0 (0–0)
Twin pregnancy	0.420	1.026 (0.964–1.093)	0.246	0.529 (0.180–1.551)	1	0.099	1.536 (0.923–2.555)	0.479	0.698 (0.257–1.892)
Miscarriage	0.353	1.022 (0.977–1.069)	0.526	1.208 (0.674–2.163)	1	0.200	1.277 (0.879–1.856)	0.413	1.278 (0.710–2.301)
Live birth	0.011	0.969 (0.946–0.993)	0.755	0.951 (0.693–1.305)	1	0.460	0.924 (0.750–1.139)	0.007	0.643 (0.465–0.888)
Premature delivery	0.138	1.044 (0.986–1.105)	0.970	0.985 (0.442–2.192)	1	0.274	1.309 (0.808–2.119)	0.226	1.568 (0.757–3.250)
Cesarean section	<0.001	1.092 (1.043–1.143)	0.956	1.015 (0.607–1.696)	1	0.084	1.379 (0.958–1.983)	<0.001	4.158 (1.889–9.151)
LGA†	<0.001	1.114 (1.063–1.167)	0.011	0.344 (0.151–0.781)	1	0.205	1.284 (0.873–1.890)	0.001	2.661 (1.474–4.804)
SGA†	0.505	1.031 (0.942–1.128)	0.547	0.681 (0.195–2.377)	1	0.411	1.348 (0.662–2.746)	0.300	1.844 (0.580–5.860)
Cumulative									
Positive pregnancy test	<0.001	0.972 (0.958–0.986)	0.471	1.075 (0.883–1.309)	1	0.041	0.886 (0.788–0.995)	0.015	0.809 (0.682–0.960)
Clinical pregnancy	<0.001	0.966 (0.952–0.979)	0.176	1.143 (0.942–1.387)	1	0.031	0.881 (0.785–0.989)	0.002	0.766 (0.646–0.907)
Live birth	<0.001	0.962 (0.949–0.976)	0.626	1.048 (0.867–1.268)	1	0.047	0.889 (0.792–0.998)	<0.001	0.706 (0.595–0.838)
Premature delivery	0.001	1.045 (1.017–1.072)	0.870	1.031 (0.716–1.484)	1	0.009	1.337 (1.076–1.662)	0.001	1.677 (1.232–2.283)
Cesarean section	<0.001	1.091 (1.066–1.117)	0.091	0.798 (0.615–1.037)	1	<0.001	1.813 (1.503–2.186)	<0.001	2.066 (1.533–2.785)
LGA†	<0.001	1.095 (1.059–1.133)	0.212	0.689 (0.384–1.237)	1	0.001	1.574 (1.193–2.076)	<0.001	2.273 (1.547–3.341)
SGA†	0.043	0.937 (0.879–0.998)	0.005	2.202 (1.264–3.837)	1	0.923	0.976 (0.600–1.589)	0.216	0.549 (0.212–1.419)

*BMI was calculated in logistic regression as continuous variable. †Rates of LGA and SGA were both calculated with reference of the rate of appropriate for gestational age. BMI: Body mass index; ET: Embryo transfer; FET: Frozen-thawed embryo transfer; LGA: Large for gestational age; SGA: Small for gestational age.

CLBR declined much more slowly when BMI >24 kg/m^2, which is comparable to the cutoff value in the decision tree, we suggest that patients with high BMI should reduce BMI to 24 kg/m^2 or less; otherwise, it would be difficult to eliminate the impact of fat excess on fertility.

However, the results of the first-visit characteristics model indicated that weight loss may not be practicable for everyone. This is probably a waste of valuable time for patients who are relatively older or have poor ovarian response. Several studies have reported similar conclusions. Pinborg *et al*[36] found that BMI had the highest impact on live births in the youngest age group (≤25 years), and the impact continually decreased with increasing age. Goldman *et al*[37] found smaller differences in CLBR across BMI categories in patients older than 38 years. A high BMI seemed more severe in patients undergoing IVF for the first time in our study, but what about patients experiencing recurrent implantation failure (RIF)? Although high BMI has a clear correlation with reduced implantation rate, it is unclear whether weight loss in women with RIF could shorten the time to pregnancy, as RIF could be caused by many other factors, such as immunological factors, chronic endometritis, uterine anatomical abnormalities, and chromosomal abnormalities.[38] Further research is needed in women with RIF.

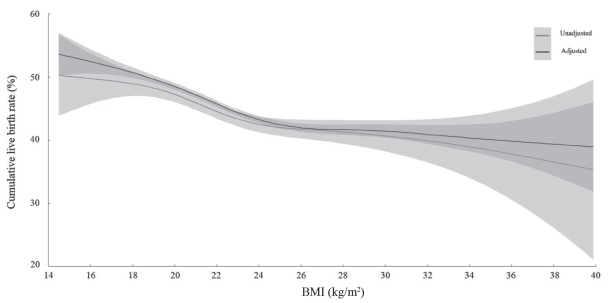

Figure 1: Relationship between BMI and the CLBR. BMI: Body mass index; CLBR: Cumulative live birth rate.

In general, a high BMI indicates poor IVF/ICSI outcomes, but it takes a long time to achieve effective weight loss through either lifestyle intervention or bariatric surgery. Therefore, we recommend that young patients who are overweight or have less severe obesity lose weight, whereas for women with advanced age, poor prognosis, or severe obesity and having difficulty in losing weight in

a short time, undergoing ART as soon as possible would probably be a better choice. It is noteworthy that this recommendation was entirely based on IVF/ICSI outcomes. High BMI not only increases the risk of pregnancy complications[39] but also induces cardiovascular disease, type 2 diabetes, osteoarthritis, and cancer.[2,40] Therefore, the starting time and optimal endpoint of weight loss should be determined by clinicians after a full evaluation.

We acknowledge several limitations in interpreting the findings of this study. First, we only used BMI to evaluate fat excess and did not include other biometric and biochemical variables, such as waist-to-hip ratio, blood pressure, total testosterone, triglycerides, leptin, glycohemoglobin, and C-reactive protein, which could partly explain the relatively low accuracy of the decision tree model. Second, smoking, alcohol consumption, dietary habits, and exercise were not included in this study, and future research should focus on the effects of these lifestyle factors on IVF/ICSI outcomes. Third, this was a retrospective study, although it was based on real-world data. BMI data were collected when patients underwent fresh ET cycles and no changes in BMI during follow-up were included in our study. Prospective interventional studies are needed to evaluate the effects of weight loss on IVF/ICSI outcomes.

In conclusion, high BMI was related to poor IVF/ICSI outcomes in normal ovarian responders in China, both in cumulative cycles and in separate fresh ET or FET cycles, partly because of suppressed endometrial receptivity. A high BMI had the most negative effect on young women with anticipated positive prognoses. We recommend that young patients lose weight, whereas women of advanced age or with poor prognosis should undergo ART as soon as possible. In the future, we expect to study the effects of weight loss in the RIF population. Prospective interventional studies are needed to include more biometric and biochemical variables and to analyze the ways to achieve effective weight loss.

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Conflicts of interest

None.

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