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Original Research

Overweight might Affect the Live Birth Rate after Frozen Thawed Embryo Transfer Cycles in Chinese Women

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Abstract

Background: Overweight affects about 34.3% of Chinese adults, especially women of childbearing age. The purpose of this study was to investigate whether overweight affect the live birth rate of frozen-thawed embryo transfer (FET) cycles in Chinese mothers. **Methods**: This retrospective case-control study was conducted in all patients undergoing FET cycles from May 2016 to October 2020 at a single center. A total of 969 FET cycles performed in 632 patients were included in the analysis. Patients were divided into the four groups based on the mother's body mass index (BMI): Group 1: BMI <18.5 kg/m^2; Group 2: 18.5 kg/m$^2 \leq$ BMI <24 kg/m^2; Group 3: 24 kg/m$^2 \leq$ BMI <28 kg/m^2; Group 4: BMI ≥ 28 kg/m^2. The main outcome indicator was the live birth rate per FET cycle. The secondary endpoints included rates of biochemical clinical pregnancy, clinical pregnancy, implantation, multiple pregnancy and miscarriage. **Results**: Ovarian reserve parameters were similar among the four groups ($p = 0.382$ for anti-Müllerian hormone and $p = 0.195$ for antral follicle count). Additionally, the rates of chemical pregnancy, clinical pregnancy, implantation and live birth were comparable in the four groups. Pregnancy outcomes were similar among the four groups using logistic regression analysis adjusting for age, anti-Müllerian hormone (AMH), antral follicle count (AFC), endometrial thickness, indication combined with polycystic ovarian syndrome (PCOS), duration of infertility (years), stage of embryos transferred, previous attempts, protocol of endometrial preparation, number of embryos transferred, and BMI. A decreasing tendency in the rates of clinical pregnancy ($p = 0.032$) and live birth ($p = 0.011$) with BMI change was observed through Chi Square for Trend test. **Conclusions**: Overweight might reduce the possibility of live birth after FET cycles in Chinese mothers.

Keywords: overweight; live birth rate; frozen-thawed embryo transfer cycle

1. Introduction

Currently, obesity is an ever-increasing health issue concern in all age groups of people and causes many health related complications. The latest data reports that 34.3% of the adult population is overweight and 16.4% are obese in China [1], particularly women of childbearing age [2]. Obesity is related to numerous chronic and metabolic diseases. Obesity in the elderly can causes hypertension, hyperlipidemia, diabetes and other metabolic diseases; and in women of childbearing age can cause reproductive problems. Obesity negatively affects female fertility because of ovulatory dysfunction, oocyte/embryo quality and endometrial receptivity [3,4]. Regarding assisted reproductive technology (ART), female obesity may reduce the quality of eggs and affect endometrial receptivity, resulting in a reduced chance of pregnancy. Compared with women with a normal body mass index (BMI), female obesity is associated with fewer embryos, lower clinical pregnancy rates and lower live birth rates as reported by Divya *et al*. [5]. In a prospective multicenter cohort study, Ahmed *et al*. [6] found that the rates of implantation, chemical pregnancy and clinical pregnancy were all negatively correlated with rising BMI among patients diagnosed with poor ovarian response. Recent meta-analyses demonstrated that female obesity adversely affects both the live birth and the cumulative live birth rates in *in vitro* fertilization (IVF) cycles [7,8].

Embryo freezing is an important technique that has been increasingly used to lower the risk of developing ovarian hyperstimulation syndrome [9]. However, the association of obesity categorized by BMI and clinical results of frozen-thawed embryo transfer (FET) cycles remains controversial, and few studies have evaluated obesity's influence on FET cycles. Additionally, the effect of overweight on clinical outcomes in overweight individuals is always neglected. A study focusing on the influence of obesity on the clinical results of FET cycles studied in polycystic ovarian syndrome (PCOS) patients found that obesity reduced live birth rates and increased miscarriage rate [10]. Another retrospective cohort study reported that obesity in women did not influence the live birth rate after FET of blastocysts [11].

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Furthermore, a large difference was found in the BMI among different races. In a study exploring ethnic variation in glucose tolerance during pregnancy, the authors found that Chinese women had significantly higher serum glucose levels one hour after ingesting a 50 gm glucose load compared to other ethnic groups, likely because Chinese non obese women with the national standard were fatter in their race [12]. The underlying mechanism may be due to insulin resistance, insulin secretion and clearance and carbohydrate metabolism differences among races [13]. The influence of overweight in Chinese women should not be neglected. Our study aimed to uncover the impact of BMI on the clinical outcomes of Chinese women undergoing frozen embryo transfer cycles.

2. Methods

2.1 Study Population

Patients who had undergone an embryo transfer cycle using frozen thawed embryos from May 2016 to October 2020 at a university-based hospital were the subject of this retrospective analysis. The hospital's database was used to collect all the information anonymously. The patients were separated into the following four groups based on the body mass index (BMI): Group 1: BMI $<$18.5 kg/m^2; Group 2: 18.5 kg/m$^2\leq$ BMI $<$24 kg/m^2; Group 3: 24 kg/m$^2\leq$ BMI $<$28 kg/m^2; Group 4: BMI $\geq$28 kg/m^2 [14].

2.2 Protocols

For these women, there were no definite restrictions on endometrial preparation procedures.

Natural cycle: Patients with regular menstrual cycles underwent a natural cycle. Ultrasonic monitoring was conducted on 10th of the menstruation, luteal support of progesterone capsules (Xianju Pharmaceutical, batch number: H20041902, Taizhou, Zhejiang, China) 150 mg po bid, Progynova (Bayer, batch number: H20160679, Guangzhou, Guangdong, China) 2 mg po tid, Chorionic Gonadotrophin (HCG) (Lizhu, batch number: H44020673, Zhuhai, Guangdong, China) 2000 IU im qod was added when ovulation occurred, and the timing of embryo transfer was planned based on the stage of embryonic developmental on the day of vitrification.

Hormonal replacement cycle: Patients with irregular menstruation underwent hormonal replacement on Days 2–3 of menstruation. Finmatone (Abbott Biologicals B.V., batch number: H20150345, CP Weesp, Holland, Netherlands) 2 mg, tid. Fourteen days later, ultrasound was performed and the hormone levels were checked. When the thickness of the endometrium was more than 8 mm and the E2 level was $>$200 pg/mL, yellow tablets containing 2 mg of estrogen and 10 mg of progesterone and progesterone injection (Xianju Pharmaceutical, batch number: H33020828, Taizhou, Zhejiang, China) were added to initiate transformation and provide luteal support. For cleavage, the transfer took place after 4 days and for blastocysts, it happened after 6 days.

Stimulation cycle: Patients with irregular menstruation could also undergo a stimulation cycle. Letrozole was provided orally 5 mg per day for 5 days on Days 2–3 of menstruation. When a dominant follicle has reached or over 10 mm after 5'days of letrozole (LE) administration, ultrasound monitoring as a natural cycle was conducted. In the case that has no dominant follicle growing, 37.5 IU of HMG (Lizhu, batch number: H10940097, Zhuhai, Guangdong, China) was added to increase follicle growth, with additional doses of 37.5 IU when needed. For embryos in the cleavage stage, the transfer took place after 4 days and for blastocysts, it happened after 6 days. Luteal support matched the natural cycle in many ways.

Down regulation cycle: Patients with endometriosis or adenomyosis underwent a pituitary down regulation protocol. Gonadotropin-releasing hormone agonist (GnRHa) administrated on Day 2–3 of the cycle. Fourteen to 28 days later, ultrasonic monitoring was performed and the hormonal levels were tested; if down regulated successfully, hormone replacement and luteal support were similar to the hormone replacement cycle.

2.3 Outcome Measures

The main measure was the live birth rate, which is defined as the ratio of live births delivered after 28 weeks of gestation to the number of embryo transfer cycles. The rates of chemical pregnancy, clinical pregnancy, implantation and miscarriage were decided to be the secondary outcomes indicator. Serum β-hCG levels $>$50 U/L on Day 12 following blastocyst transplantation or Day 14 following cleavage-stage embryo transplantation were defined as biochemical pregnancy. A gestational sac founded by transvaginal ultrasonography 4 weeks after embryo transfer was considered a clinical pregnancy. The number of gestational sacs divided by the number of embryos transferred equals the implantation rate. Miscarriage was the unintentional loss of a pregnancy before 28 weeks of gestation.

2.4 Statistical Analysis

Means $\pm$ SD (standard deviation) was the form of data presenting. SPSS Version 23.0 (SPSS Inc., Chicago, IL, USA) was used for data analyze. The Kolmogorov–Smirnov test was used to determine whether continuous variables had a normal distribution, and ANOVA was used to compare normally distributed count data with non-normally distributed count data. χ^2 test were used to compare Categorical variables where appropriate. Logistic regression analysis was applied to examine the impact of BMI on the clinical result after confounding factors were adjusted. The relationship between the trend of clinical outcomes based on the normal weight group and increasing BMI was analyzed by Chi Square for Trend test.

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Table 1. Demographic data and cycle characteristics of four groups of patients in frozen-thawed embryo transferred cycles (n = 996 cycles).

	Group 1	Group 2	Group 3	Group 4	*p* value
	(N = 159, 16.0%)	(N = 594, 59.6%)	(N = 184, 18.4%)	(N = 59, 6.0%)	
Age (y)	30.80 ± 4.29	31.37 ± 5.01	33.41 ± 5.32	33.10 ± 5.00	<0.001
BMI (kg/m^2)	17.37 ± 0.71	21.04 ± 1.45	25.59 ± 1.02	29.38 ± 1.40	<0.001
AMH (ng/mL)	4.33 ± 2.90	4.47 ± 3.50	4.01 ± 3.01	4.08 ± 3.60	0.382
AFC (n)	16.39 ± 6.92	16.90 ± 9.62	18.13 ± 10.55	18.61 ± 11.75	0.195
Duration of infertility (years)	2.91 ± 2.31	2.97 ± 2.30	4.05 ± 3.93	4.53 ± 3.84	<0.001
Number of previous embryo transfers	1.61 ± 0.85	1.45 ± 0.73	1.55 ± 0.81	1.54 ± 0.75	0.099
Type of infertility	/	/	/	/	/
Primary infertility	49	195	47	16	0.383
Secondary infertility	43	198	65	19	/
Combined with PCOS	8.8% (14/59)	18.5% (110/594)	26.6% (49/184)	39.0% (23/59)	<0.001
Endometrial thickness (mm)	10.66 ± 2.24	10.56 ± 2.96	9.86 ± 2.94	9.70 ± 3.54	0.005
Day of vitrification	/	/	/	/	0.006
Day 3	98 (61.6%)	441 (74.2%)	124 (67.4%)	46 (78.0%)	/
Day 5/6	61 (38.4%)	153 (25.8%)	60 (32.6%)	13 (22.0%)	/
No. of embryos transferred	1.64 ± 0.54	1.75 ± 0.56	1.71 ± 0.58	1.83 ± 0.56	0.056

Note: All values presented as mean ± SD. $p < 0.05$ is considered statistically significant. BMI, body mass index; AMH, anti-Müllerian hormone; AFC, antral follicle count; PCOS, polycystic ovarian syndrome; SD, standard deviation.

3. Results

A total of 996 cycles of 632 patients were included in our retrospective analysis. The baseline information and cycle parameters of the concluded cycles are presented in Table 1. Among these ART cycles, most women (59.6%) were of normal weight. In 159 (6.0%) studied cycles, women had a low BMI, in another 184 (18.4%) investigated cycles, women were overweight, and in 59 (6.0%) of researched cycles, women are obese. The patients with a low BMI (Group 1) were younger age, had a shorter period of infertility, a smaller proportion with PCOS, and a thicker endometrium. Comparing the patients with obesity (Group 4), to the other groups, demonstrated an older average age, longer period of infertility, a larger proportion of women with PCOS, and a thinner endometrium. There was no significant difference among the four groups regarding ovarian reserve as all groups had equal levels of anti-Müllerian hormone (AMH) ($p = 0.382$) and antral follicle count (AFC) ($p = 0.195$).

Concerning clinical outcomes of the enrolled cycles, the rates of chemical pregnancy, the clinical pregnancy, implantation and live birth were equal across the four groups. There were fewer blastocysts were transferred in Group 4 (the obesity group) than in the other three groups. All four groups received the similar number of embryos transferred. The live birth rate (30.5%) was lower in obese women than in the other three groups. The normal group had a slightly more embryos implanted ($p = 0.133$) and more live births ($p = 0.072$) than the other three groups (Table 2).

Logistic regression analysis of the pregnancy outcomes showed that the rates of biochemical pregnancy, clinical pregnancy, early miscarriage and live delivery were all similar among the four groups adjusted for age, AMH, AFC, endometrium thickness, indication combined with PCOS, duration of infertility (years), stage of embryos transferred, prior attempts, endometrial preparation procedure, number of transplanted embryos, and BMI (Table 3).

As the BMI changed, the percentages of clinical pregnancy ($p = 0.032$) and live delivery ($p = 0.011$) decreased from normal weight, underweight, and overweight to obese, as analyzed by Chi Square for Trend test (Fig. 1 and Table 4).

4. Discussion

4.1 Main Findings

In the present study, a striking finding was that weight increased significantly with age. In line with the finding of Barbara Luke *et al.*'s [15] study that older women were more likely to be obese before having children. Our clinical outcomes were similar in all groups, but showed an inverse tendency with increasing BMI. Interestingly, our results agreed with those of another study conducted in a Chinese group. They found that patients with obesity negatively affected the clinical outcomes compared with the overweight group, likely because they did not use the China classification: obesity was defined as a BMI >27 kg/m^2, overweight was defined as 23–27.4 kg/m^{2}and a normal BMI range was 18.5–22.9 kg/m^2 [16]; additionally, the sample size was large. By contrast, these results may be inconsistent with the limited study conducted by Insogna *et al.* [17] reveal that the BMI in overweight individuals was not associated with a normal BMI range, likely because of racial differences. The proposal of Asians at high risk for chronic dis-

Table 2. Clinical outcomes of four groups of patients in frozen-thawed embryo transferred cycles (n = 996 cycles).

	Group 1	Group 2	Group 3	Group 4	*p* value
	(N = 159)	(N = 594)	(N = 184)	(N = 59)	
Biochemical pregnancy rate (%)	67.3% (107/159)	63.8% (379/594)	59.2% (109/184)	55.9% (33/59)	0.283
Clinical pregnancy rate (%)	49.7% (79/159)	53.2% (316/594)	44.6% (82/184)	45.8% (27/59)	0.180
Miscarriage rate (%)	8.2% (13/159)	8.9% (53/594)	10.3% (19/184)	11.9% (7/59)	0.794
Implantation rate (%)	35.4% (92/260)	38.1% (397/1041)	32.1% (101/315)	30.6% (33/108)	0.133
Multiple-pregnancy rate (%)	8.2% (13/159)	12.8% (76/594)	10.3% (19/184)	10.2% (6/59)	0.382
Ectopic pregnancy rate (%)	1.9% (3/159)	2.2% (13/594)	1.6%% (3/184)	3.4% (2/59)	0.866
Live delivery rate (%)	39.6% (63/159)	42.3% (251/594)	33.2% (61/184)	30.5% (18/59)	0.072

Note: All values presented as mean ± SD. $p < 0.05$ is considered statistically significant. No., Number; SD, standard deviation.

Table 3. Logistic regression on the pregnancy outcomes according to female BMI.

Characteristic		Group 1	Group 2	Group 3	Group 4
		(N = 159)	(N = 594)	(N = 184)	(N = 59)
Biochemical pregnancy rate (%)	aOR	1.228 (0.682–2.210)	reference	1.207 (0.618–2.356)	1.035 (0.551–1.945)
	p value	0.494		0.582	0.915
Clinical pregnancy rate (%)	aOR	1.185 (0.667–2.104)	reference	0.936 (0.490–1.619)	0.874 (0.472–1.619)
	p value	0.562		0.841	0.669
Early miscarriage rate (%)	aOR	0.824 (0.339–2.001)	reference	0.678 (0.240–1.918)	0.781 (0.304–2.009)
	p value	0.668		0.464	0.608
Live delivery rate (%)	aOR	1.613 (0.856–3.039)	reference	1.350 (0.667–2.732)	1.156 (0.586–2.282)
	p value	0.139		0.404	0.676

Note: Analyses were adjusted for age, AMH, AFC, BMI, indication combined with PCOS, duration of infertility (years), previous attempts, protocol of endometrium preparation, endometrium thickness, stage of embryos transferred, and number of embryos transferred. $p < 0.05$ is considered statistically significant.
BMI, body mass index; aOR, adjusted odds ratio.

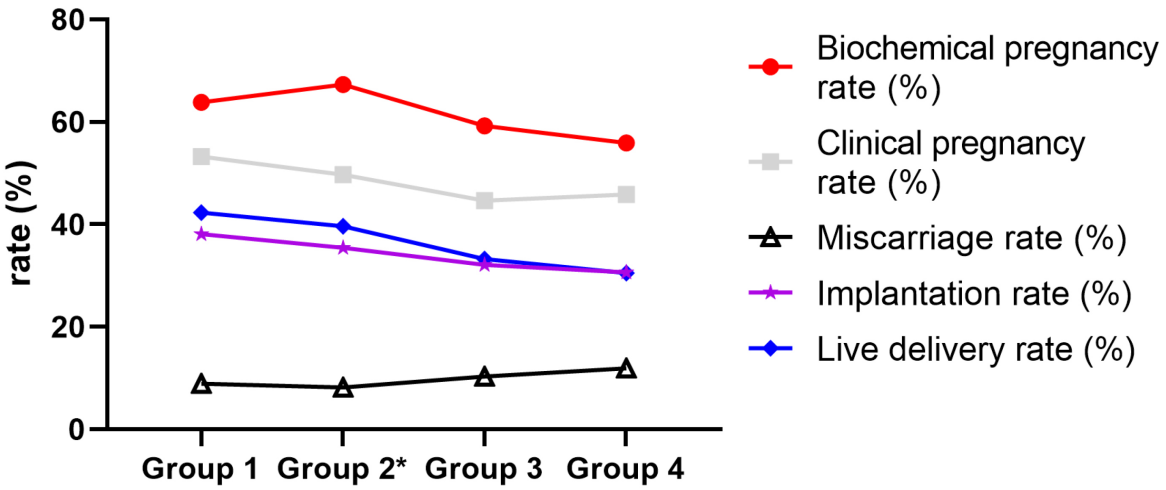

Fig. 1. Chi Square for Trend of clinical outcomes in the 4 groups based on Group 2 (normal weight). "*" means that the results of the trend is based on Group 2.

eases such as type 2 diabetes and cardiovascular disease is considerable at lower BMI cutoffs for overweight individuals [15]. Considering that Asians have a higher percentage of body fat than Caucasians, the Working Group on Obesity in China recommends lower cutoffs for BMI to define overweight and obesity than those used for Caucasians [1,18]. We should not neglect the influence of overweight in female individuals.

Female obesity is associated with a higher proportion of PCOS patients. This finding agrees with the theory that obesity in women contributes to the development of PCOS [8]. A majority of studies have revealed that the

Table 4. Chi Square for Trend test of clinical outcomes in the 4 groups based on Group 2 (normal weight).

Characteristic	Gamma	*p*
No. of Biochemical pregnancy	–0.061	0.292
Clinical pregnancy rate (%)	–0.118	0.032
Implantation	0.065	0.135
Early miscarriage rate (%)	0.061	0.531
Live delivery rate (%)	–0.143	0.011

Note: $p < 0.05$ is considered statistically significant. No., Number.

oocyte quality, maturity, and size decreases with increasing BMI. Also, it has been observed that female obesity is correlated with a reduced number of embryos [5]. Additionally, studies on mice have provided laboratory evidence for embryo development. In a prospective study of mouse embryos, Wenhong Ma *et al*. [19] found that the lipid content and apoptosis rate of fresh embryos from obese mice were significantly higher and the development of embryos was notably delayed, likely caused by endoplasmic reticulum stress, mitochondrial dysfunction, and apoptosis resulting from lipid accumulation. Another study from mice provided laboratory evidence that obesity might impair oocyte maturation and development [20].

Patients who are overweight or obese have reduced implantation rates, which also lead to fewer biochemical pregnancies, clinical pregnancies and live births, suggesting a suboptimal endometrial receptivity in these individuals. According to a recent study, gene expression within the window of implantation in obese women, demonstrated that genes mainly regulating development and biological function such as transcription and biosynthesis were deregulated, particularly in women who are obese with infertility or polycystic ovary syndrome [21]. Other studies on ovum donation have revealed a decrease in endometrium receptivity in obese women [22–24].

Although our study did not explore the mechanism or discuss treatments for patients who were overweight or obese to improve pregnancy outcomes, research has shown that these patients appear to improve pregnancy outcomes significantly from the administration of myo-inositol, vitamin D and alpha-lipoic acid in order to improve insulin sensitivity [25,26]. Administration of myo-inositol can lower the hyper-insulinemic state in obese women with and without PCOS [25,27]. A pilot study has found that adding myo-inositol, alpha-lipoic acid and folic acid to IVF treatment for overweight/obese non-PCOS women improved the quality of their oocytes [27]. Nevertheless, future investigation into the mechanism underlying the improvement in patients' metabolic and psychological status following adjuvant treatments is necessary.

4.2 Strengths and Limitations

The shortcomings of our study were its retrospective nature and small sample size, which reduces its strength of evidence. Prospective studies in population with large sample sizes would strengthen the conclusion that overweight may reduce the rate of live birth in FET cycles. Additionally, too few patients were in the obese cohort (6%), possibly weakening the power to detect differences.

However, we adjusted for confounding factors by logistic analysis to balance the data and make convincing conclusions. We observed a decrease in endometrium receptivity and resulted in a decrease in the implantation rate in patients who were overweight or obese. Large sample studies are needed in the future to make robust conclusions. Furthermore, this study is the first to focus on overweight in Chinese women based on the reasonable cutoff BMI of a Chinese cohort (underweight: BMI <18.5 kg/m^2; normal weight: 18.5 kg/m$^2 \leq$ BMI <24 kg/m^2; overweight: 24 kg/m$^2 \leq$ BMI <28 kg/m^2; obese: BMI ≥ 28 kg/m^2) [14]. Further trend analysis revealed that a decreasing tendency of the rates of clinical pregnancy and live delivery with BMI change. Overweight and obese women's endometrial receptivity should not be neglected.

5. Conclusions

Our findings may encourage women to realize the importance of weight management and pursue a healthy weight regardless of fertility need. Our data reveals that overweight may have a less receptive endometrium to successfully conceive in Chinese women, suggesting that overweight rather than obese women may benefit more from weight control in Chinese women. A prospective study with an expanded sample size and detailed detection of the chemical level of insulin may help to explore the mechanisms involved and make more convincing conclusions.

In summary, overweight might have a reduced possibility of live births after FET cycles in Chinese mothers.

Availability of Data and Materials

The data that support the findings of the study are available from the corresponding author upon reasonable request.

Author Contributions

WX was the major investigator, who conceived and designed the study. MHC and SSJ made substantial contributions to data analysis and interpretation and MHC contributed to drafting the manuscript. XHL, YQZ and YYP completed the data collection. WW made further analysis and interpretation, checked the content and critically revised the manuscript. All authors contributed to revising the manuscript and approved the final manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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