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RESEARCH

Effect of BMI on cumulative live birth rates in patients that completed IVF treatment: a retrospective cohort study of 16,126 patients

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Abstract

Although several studies have reported that high maternal BMI could influence the cumulative live birth rate (CLBR) in fresh embryo transfer cycles, the association of BMI with CLBR remains unclear in patients that completed IVF treatment. In this study, we examined the association of maternal BMI with CLBR, including repetitive one oocyte pick-up (OPU) and all fresh and frozen embryo transfer until live birth or embryos were run out. A total of 16,126 patients' data were included in the analysis and were divided into four groups based on BMI. We found that patients' characteristics, embryo parameters, and pregnancy outcomes differed among different BMI groups. Multivariate logistic regression showed that being underweight was associated with a higher possibility of having live birth than the reference group (OR (95% CI) 1.40 (1.22–1.59), $P < 0.001$), whereas being overweight and obese were associated with a lower possibility of having live birth than the reference group ((OR (95% CI) 0.81 (0.74–0.90), $P < 0.001$) and (OR (95% CI) 0.68 (0.55–0.85), $P < 0.001$)). After adjustment for confounding factors, the reference group was associated with a higher possibility of having live birth, with a significant difference found between the obese and reference groups (OR (95% CI) 0.55 (0.43–0.70), $P < 0.001$). An association was found between CLBR and BMI, indicating that an increase in BMI results in a decline in CLBR. Moreover, the CLBR of patients with different characteristics differed in the various BMI groups. Taken together, our data show that maternal BMI has a significant impact on CLBR.

Keywords: body mass index; cumulative live birth rate; *in vitro* fertilization; overweight; obesity

Introduction

Being obese or overweight could have several consequences on an individual's health status (1). Globally, obesity is approaching pandemic levels (2), given that obesity is associated with many health conditions, such as hyperlipidemia (3), diabetes (3), hypertension (4), vascular disease (5), bone and joint abnormalities (6), and abnormal hormone secretion (7). In women of childbearing age, obesity is a common disease, which when present during pregnancy could pose short- and long-term consequences on both mother and child (8). Besides, obesity can lead to infertility, while in early pregnancy, it could result in spontaneous abortion and congenital malformations (9).

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Infertility is a disease of the male or female reproductive system that results in failure to conceive after 12 months or longer of natural fertilization (10). According to estimates by the World Health Organization, about one in six couples of reproductive age worldwide may need assisted reproductive technology (ART) due to fertility problems (10, 11). ART, including *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI), has been widely used among infertility patients (12).

Substantial evidence shows that overweight or obese women tend to have lower success rates of IVF/ICSI, embryo transfer (ET), or frozen–thawed embryo transfer (FET) (13, 14). The reasons for these include, obesity induces ovarian inflammation and reduces oocyte quality (15), and also affects endometrial receptivity by displacing the window of implantation (16). Similarly, obesity can affect the oocyte and the preimplantation embryo, with disrupted meiotic spindle formation and mitochondrial dynamics (17). Moreover, in obese women, endometrial implantation and other reproductive functions are affected by complications, including delayed conceptions, and increased miscarriage rate, thereby affecting the live birth rate (LBR) (18).

For assisted reproduction in female patients, the cumulative live birth rate (CLBR) takes into account pregnancy outcomes and treatment duration, based on which an appropriate and comprehensive analysis of the impact of BMI (body mass index) on ART outcomes can be made using CLBR (including all fresh and frozen embryo transfers at the time of reporting). In this study, data from 16,126 patients undergoing IVF/FET between January 1, 2015, and March 15, 2021 (Follow-up deadline: March 15, 2022), were analyzed using chi-square test, Kruskal–Wallis test, and logistic regression analysis to determine the effect of maternal overweight/obesity on CLBR after IVF/FET. The purpose of this research is to gather data that can be instrumental as a counseling aid, offering invaluable insights for women who have a high BMI and are facing fertility challenges.

Materials and methods

Participants

This retrospective study collected data from female patients who underwent assisted reproduction (i.e. IVF/ICSI treatment using fresh/frozen embryo transfer strategy) at the Department of Reproductive Medicine, Luohu People's Hospital, Shenzhen, China, from January 2015 to March 2021. This study was approved by the Reproductive Medicine Ethics Committee of Shenzhen Luohu People's Hospital (no. 2021-LHRMYY-SZLL-003).

All patients (n=16,126) who presented at the Department of Reproductive Medicine were used for the analysis. The following patients were excluded: (i) egg cryopreservation ($n=39$); (ii) these patients retain cryopreserved embryos that have not undergone transplantation; despite the absence of a successful live birth, surplus embryos remain available ($n=2634$); (3) maternal death caused by gestational hypertension ($n=1$). The data of 13,452 patients were included in the final analysis and were divided into four groups based on BMI calculated from weight and height information obtained at the initial consultation. Following the BMI guidelines and Chinese characteristics (19, 20), the patients were divided into four groups, i.e. (i) underweight (BMI < 18.5 kg/m^2), (ii) reference (BMI ≥ 18.5 kg/m^2 and BMI < 24 kg/m^2), (iii) overweight (BMI ≥ 24 kg/m^2 and BMI < 28 kg/m^2), and (iv) obese (BMI ≥ 28 kg/m^2). Flowchart and data processing are displayed in Fig. 1.

IVF protocols

The protocol for ovarian stimulation (OS) was determined individually according to standard practice

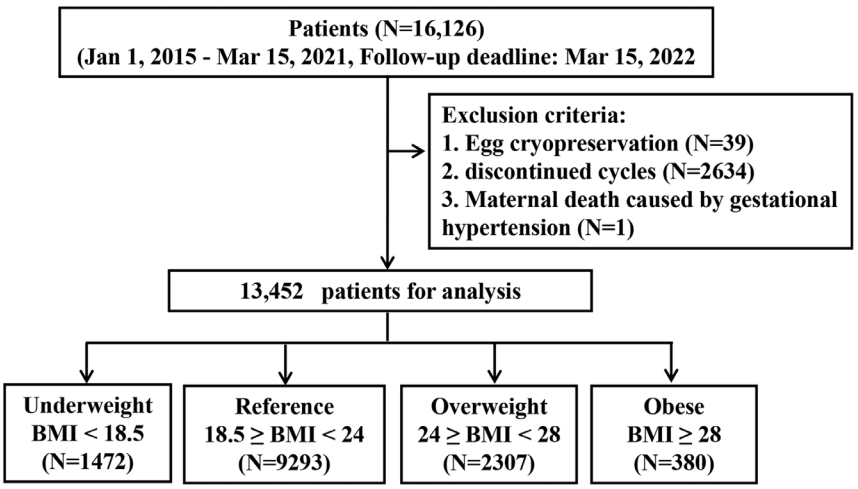

Figure 1

Flowchart of data collection and processing (BMI, kg/m^2).

and the patient's characteristics, including age, BMI, basal follicle-stimulating hormone (FSH), and antral follicle count (AFC), anti-Müllerian hormone (AMH), basal luteinizing hormone (LH), and basal estradiol (E2). Most patients were treated with a long gonadotropin-releasing hormone (GnRH) agonist or a GnRH antagonist protocol (21). For women with diminished ovarian reserves, the mild ovulation protocol (22) or luteal phase ovarian (23) stimulation was attempted. In these protocols, 4000–10,000 IU human chorionic gonadotropin (hCG) was administered when more than 60% of follicles were >16 mm in diameter. Transvaginal ultrasound-guided oocyte retrieval was performed 36–37 h after hCG injection, followed by IVF or ICSI based on sperm parameters. Embryos were scored according to the morphology assessment described by the Istanbul Consensus (24). Next, the patient underwent embryo transfer (day 3 cleavage-stage embryos or day-5/6 blastocysts). The maximum number of embryos transferred was two. For luteal phase support, progesterone injection (20–60 mg/day) was started after oocyte retrieval and maintained until a negative serum beta-hCG or the eighth to tenth week of pregnancy.

The primary outcome measure was the CLBR, defined as at least one live birth at the fresh and all subsequent frozen embryo transfers of the IVF/ICSI cycles.

Statistical analysis

Data were analyzed using SPSS (Statistical Package for the Social Sciences, IBM Corporation) version 26.0. $P < 0.05$ was used to indicate a significant statistical difference.

Continuous variables are presented as the mean ± s.d. or median (IQR), and categorical variables are shown as numbers (%). Normality was checked through Kolmogorov–Smirnov test. Kruskal–Wallis test was used for continuous variables and the chi-square test was used for categorical variables. Multivariate logistic regression was performed to compare the live birth rates between the four protocols. The results are presented as the adjusted odds ratio (OR) and 95% confidence interval (CI). A logistic regression model was used to evaluate the association of CLBR with continuous BMI using Stata (Stata Statistical software, StataCorp LP, College Station, TX, USA) version 17.0. Confounders that were included for adjustment are maternal age, AMH, OS protocol, infertility factor, AFC, basal FSH, basal LH, and basal E2. The predicted probability of CLBR was calculated and modeled with continuous BMI as restricted cubic splines (RCS) with four knots set at default positions.

Many studies have shown that maternal age, AMH levels, OS protocol, factors of potential inferiority, and AFC significantly impact CLBR in ART (25, 26, 27, 28). Consequently, we employed multiple logistic regression analysis to conduct subgroup analyses based on BMI grouping. Additional analyses were performed after stratification of the participants by maternal age (age <30 years vs age ≥30 years) (28) and AMH levels (AMH ≤ 3 ng/mL vs 3 ng/mL < AMH < 6 ng/mL vs AMH ≥ 6 ng/mL) (28), as well as combined stratification of these parameters.

Results

Patient characteristics, embryo parameters, and pregnancy outcomes

After excluding data that did not meet the inclusion criteria from the 16,126 IVF patients, data from 13,452 patients were analyzed (Fig. 1) and categorized into four groups based on BMI, i.e. underweight ($n = 1472$), normal weight or reference ($n = 9293$), overweight ($n = 2307$), and obese ($n = 380$). Table 1 shows the demographics and baseline characteristics of patients in the different subgroups. Chi-square test and Kruskal–Wallis test analysis of the baseline characteristics revealed significant differences between the underweight and reference groups in maternal age, BMI, type of infertility, infertility factor, basal FSH, basal LH, basal E2, AMH, OS protocol, and total Gn dose IU (Table 1). In contrast, no significant differences were observed in the length of infertility and AFC (Table 1). When comparing the overweight with reference groups, significant differences were observed in maternal age, BMI, length of infertility, type of infertility, infertility factor, basal FSH, basal LH, basal E2, AFC, and total Gn dose IU, whereas no significant differences were found in AMH, and OS protocol (Table 1). A comparison between the obese and reference groups revealed significant differences in BMI, length of infertility, infertility factor, basal FSH, basal LH, basal E2, AMH, AFC, and total Gn dose IU, while no significant differences were found in maternal age, type of infertility, and OS protocol (Table 1).

Embryonic developmental indices, i.e. the number of oocytes, embryo parameters, and cumulative live birth rates for the different groups are shown in Table 2. Analysis of these data revealed significant differences in the number of oocytes, number of cleavage, no. 2 pronucleus (2PN), number of day 3 useable embryos, number of day 3 good-quality embryos, oocyte output rate (number of oocytes/AFC), and CLBR between underweight, reference, and overweight groups (Table 2). However, no significant differences were observed in all parameters when comparing the obese group with overweight group (Table 2). A significant difference in oocyte output rate and CLBR was found between the other groups and reference group (Table 2). These results indicate that maternal BMI affects the baseline characteristics, such as embryo parameters and CLBR, especially the oocyte output rate and CLBR, which decreases with an increase in BMI.

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Table 1 Clinical characteristics of the study population.

Variables	Underweight	Reference	Overweight	Obese	*P*
Patients (*n*)	1472	9293	2307	380	
Age at start of first cycle (years)	31 (28–34)[a]	33 (29–36)[b]	34 (30–38)[c]	33 (29–36)[b]	<0.001
1: <30	592, 40.22%	2435, 26.20%	489, 21.20%	102, 26.84%	
2: ≥30 and <40	829, 56.32%	5941, 63.93%	1450, 62.85%	234, 61.58%	
3: ≥40	51, 3.46%	917, 9.87%	368, 15.95%	44, 11.58%	
Body mass index (kg/m^2)	17.80 (17.22–18.22)[a]	21.09 (19.92–22.27)[b]	25.10 (24.46–26.10)[c]	29.44 (28.52–31.11)[d]	<0.001
Length of infertility (years)	3 (2–5)[a]	3 (2–5)[a]	3 (2–6)[c]	4 (2–7)[d]	<0.001
1: ≤2	516, 35.05%	3433, 36.94%	776, 33.64%	111, 29.21%	
2: >2 and ≤5	657, 44.63%	3758, 40.44%	894, 38.75%	139, 36.58%	
3: >5	299, 20.31%	2102, 22.62%	637, 27.61%	130, 34.21%	
Type of infertility	[a]	[b]	[c]	[bc]	<0.001
1: Primary	715, 48.57%	5587, 60.12%	1469, 63.68%	220, 57.89%	
2: Secondary	757, 51.43%	3706, 39.88%	838, 36.32%	160, 42.11%	
Infertility factor (*n*, %)	[a]	[b]	[c]	[d]	<0.001
1: Endometriosis	97, 6.59%	372, 4.00%	56, 2.43%	8, 2.11%	
2: Ovarian factor	98, 6.66%	760, 8.18%	187, 8.11%	26, 6.84%	
3: Tubal factor	936, 63.59%	6102, 65.66%	1534, 66.49%	246, 66.49%	
4: PCOS	51, 3.46%	369, 3.97%	148, 6.42%	53, 6.42%	
5: Male factor	177, 12.02%	931, 10.02%	213, 9.23%	21, 9.23%	
6: Uterine	70, 4.76%	584, 6.28%	135, 5.85%	18, 5.85%	
7: Other reasons	43, 2.92%	175, 1.88%	34, 1.47%	8, 1.47%	
Basal FSH (IU/L)	7.74 (6.55–9.26)[a]	7.41 (6.29–8.88)[b]	7.01 (5.92–8.27)[c]	6.59 (5.58–8.02)[d]	<0.001
Basal LH (IU/L)	4.93 (3.59–6.51)[a]	4.22 (3.18–5.67)[b]	3.77 (2.73–5.33)[c]	3.68 (2.55–6.07)[c]	<0.001
Basal E2 (IU/L)	49 (38–65)[a]	45 (33–58) [b]	41 (31–55)[c]	41 (30–56)[c]	<0.001
AMH	3.42 (2.06–5.50)[a]	3.11 (1.70–5.13) [b]	3.08 (1.64–5.11)[b]	3.54 (2.03–6.26)[a]	<0.001
AFC	13 (8–18)[ab]	12 (8–18)[a]	13 (8–20)[b]	16 (10–24)[c]	<0.001
OS Protocol	[a]	[b]	[b]	[ab]	<0.001
1: GnRH agonist	997, 67.73%	5856, 63.02%	1393, 60.38%	251, 66.05%	
2: GnRH antagonist	219, 14.88%	1471, 15.83%	399, 17.30%	63, 16.58%	
3: Other	256, 17.39%	1966, 21.16%	515, 22.32%	66, 17.37%	
Total Gn dose IU	2025 (1575–2625)[a]	2100 (1612.5–2700)[b]	2250 (1800–2800)[c]	2400 (1912.5–3000)[d]	<0.001

Different lowercase letters (a, b, c, d) represent significant differences between groups.

Table 2 Oocytes, embryo parameters, and cumulative live birth rates of the study population.

Variables	Underweight	Reference	Overweight	Obese	*P*
Patients (*n*)	1472	9293	2307	380	
No. of oocytes	12 (8–18)[a]	12 (6–17)[b]	11 (6–16)[c]	12 (7–17)[abc]	<0.001
No. of cleavage	8 (5–12)[a]	7 (4–11)[b]	7 (4–11)[c]	7 (4–11)[bc]	<0.001
No. 2PN	8 (5–12)[a]	8 (4–12)[b]	7 (4–11)[c]	7 (4–11)[bc]	<0.001
No. of day 3 useable embryos	6 (4–10)[a]	6 (3–10)[b]	5 (3–9)[c]	6 (3–9)[abc]	<0.001
No. of day 3 good-quality embryos	4 (2–7)[a]	4 (2–7)[a]	4 (2–6)[b]	4 (2–7)[ab]	<0.001
No. of oocytes/AFC	100 (68.75–130)[a]	91.67 (64.71–125)[b]	80 (54.55–110.53)[c]	73.68 (50–105)[c]	<0.001
Cumulative live birth rate (%)	1157 (78.60%)[a]	6733 (72.45%)[b]	1571 (68.10%)[c]	244 (64.21%)[c]	<0.001

Different lowercase letters (a, b, c, d) represent significant differences between groups.

Table 3 Logistic regression analysis for cumulative live birth rates in BMI groups.

Group	**Nonadjusted OR** (95% CI)	***P***	**Adjusted I OR** (95% CI)	***P***	**Adjusted II OR** (95% CI)	***P***
Reference	1.00 (ref)	–	1.00 (ref)	–	1.00 (ref)	–
Underweight	1.40 (1.22–1.59)	<0.001	1.00 (0.87–1.16)	0.996	1.03 (0.89–1.20)	0.647
Overweight	0.81 (0.74–0.90)	<0.001	0.94 (0.84–1.05)	0.288	0.90 (0.80–1.01)	0.062
Obese	0.68 (0.55–0.85)	<0.001	0.60 (0.47–0.76)	<0.001	0.55 (0.43–0.70)	<0.001

Adjusted I for maternal age, AMH, OS protocol.
Adjusted II for maternal age, AMH, OS protocol, Infertility factor, AFC, basal FSH, basal LH, basal E2

The cumulative live birth rate of different BMI groups

To compare the live birth rates of the different BMI groups, multivariate logistic regression was performed. When considering only the effect of BMI on CLBR without including other confounding factors, the multivariate logistic regression analysis showed that the underweight was associated with a higher possibility of having live birth compared to the reference group (OR (95% CI) 1.40 (1.22–1.59), $P < 0.001$), while the overweight and obese were associated with a lower possibility of having live birth than the reference group ((OR (95% CI) 0.81 (0.74–0.90), $P < 0.001$) and (OR (95% CI) 0.68 (0.55–0.85), $P < 0.001$)), as CLBR decreased with increasing maternal BMI (Table 3). Due to the importance of patient age, ovarian reserve, and OS protocol on CLBR (28, 29, 30), the above conditions were included in the adjustment factors in model I. In the adjusted model I, it was found that the BMI of obese patients significantly decreased the CLBR compared to the normal weight group (OR (95% CI) 0.60 (0.47–0.76), $P < 0.001$) (Table 3). Similarly, when adjusted for maternal age, AMH, OS protocol, infertility factor, AFC, basal FSH, basal LH, and basal E2 (adjusted model II), CLBR decreased in the overweight and obese groups, with a significant difference observed between the obese and reference groups (OR (95% CI) 0.55 (0.43–0.70), $P < 0.001$) (Table 3). We explored the dose–response association between maternal BMI and CLBR using restrictive cubic spline models, as depicted in Fig. 2. We found no nonlinear association between CLBR and maternal BMI (linear trend Wald test, $P = 0.422$), although we found that the predicted probability of CLBR scarcely changes when BMI was below 23.0 but decreased above this cutoff. These findings contribute to a more nuanced understanding of the intricate dynamics characterizing the relationship between BMI and cumulative live birth rates in our study. These results indicate that the maternal BMI has a significant impact on CLBR, especially in overweight/obese patients.

Combined maternal BMI with various parameters to analyze their impact on CLBR

To analyze the CLBR of patients with different characteristics and BMI, multivariate logistic regression was performed with maternal age, AMH, OS protocol, infertility factor, and AFC levels included as the

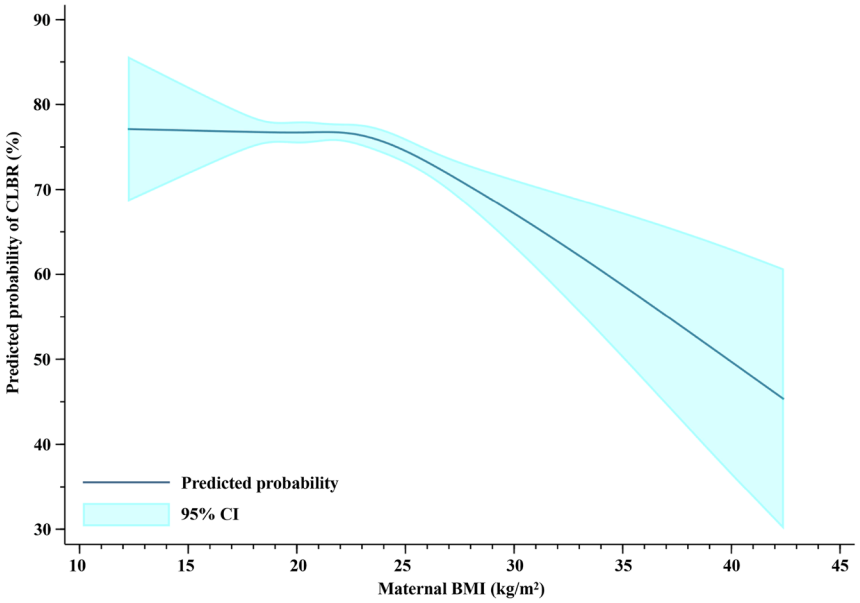

Figure 2

Cumulative live birth curves for patients based on maternal BMI groups. Data were adjusted for confounders, including maternal age, anti-Müllerian hormone (AMH), ovarian stimulation (OS) protocol, infertility factor, antral follicle count (AFC), basal follicle-stimulating hormone (FSH), basal luteinizing hormone (LH), and basal estradiol (E2).

confounders (Table 4). The analysis was stratified according to maternal age. When maternal age <30 years, the CLBR was significantly lower in both the overweight and obese groups compared to the reference group ((OR (95% CI) 0.70 (0.53–0.93), P = 0.012) and (OR (95% CI) 0.46 (0.28–0.75), P = 0.002)). Among those with age ≥30 and age ≤39, the possibility of live births in the obese group was lower than the reference group (OR (95% CI) 0.50 (0.37–0.67), P < 0.001). Although there was no significant difference in the age ≥ 40 subgroup, we found that the CLBR decreased with increasing age, i.e. the CLBR ranged from 86.66–25.49% in the underweight group, 86.69–24.43% in the reference group, 83.84–27.17% in the overweight group, and 77.45–29.55% in the obese group (Table 4). The multivariate logistic regression analysis was stratified according to AMH. When AMH ≤3, the CLBR was significantly lower in both the overweight and obese groups compared to the reference group (OR (95% CI) 0.85 (0.74–0.99), P = 0.039) and (OR (95% CI) 0.60 (0.42–0.86), P = 0.005), respectively. Among patients with AMH >3 and AMH <6, the possibility of live births in the underweight group was higher than in the reference groups (OR (95% CI) 1.36 (1.03–1.81), P = 0.030) and the CLBR was significantly lower in obese groups compared to the reference group (OR (95% CI) 0.58 (0.37–0.90), P = 0.015). When AMH ≥6, the CLBR was significantly lower in obese groups compared to the reference group (OR (95% CI) 0.44 (0.27–0.71), P = 0.001) (Table 4). Among women who used GnRH agonist, the obese group had a lower possibility of live births than the reference group (OR (95% CI) 0.45 (0.33–0.60), P < 0.001), whereas among women who used GnRH antagonist or other protocol, no significant differences were observed (Table 4). Similarly, the analysis was done according to the infertility factor. When the patient's infertility diagnosis was tubal factor, the CLBR was significantly lower in both the overweight and obese groups compared to the reference group (OR (95% CI) 0.85 (0.74–0.98), P = 0.024) and (OR (95% CI) 0.61 (0.45–0.83), P = 0.001), respectively. In the meanwhile, when the patient's infertility factors were endometriosis, PCOS or uterine, the obese group had a lower possibility of live births than the reference group (OR (95% CI) 0.15 (0.03–0.74), P = 0.019), (OR (95% CI) 0.30 (0.15–0.60), P = 0.001), and (OR (95% CI) 0.14 (0.04–0.45), P = 0.001), respectively (Table 4). On the other hand, when the analysis was done according to AFC, among women with AFC > 15, the possibility of live births was lower in the obese group compared to the reference group (OR (95% CI) 0.41 (0.29–0.57), P < 0.001), as the CLBR increased with increasing AFC in all groups (Table 4).

When the different BMI groups were further subdivided based on age and ovarian reserve before carrying out the multiple logistic regression analysis, for younger patients (age <30), the lower CLBR was in the overweight group with inadequate ovarian reserve (AMH ≤3), which was significantly different compared to the reference group (OR (95% CI) 0.46 (0.29–0.73), P = 0.001) (Table 5). The CLBR was also lower in the obese group with normal ovarian reserve (AMH >3 and AMH <6) compared to the reference group (OR (95% CI) 0.39 (0.18-0.85), P = 0.018) (Table 5). For maternal age ≥ 30 with inadequate ovarian reserve (AMH ≤3), the possibility of live births was higher in the underweight group than in the reference group (OR (95% CI) 1.34 (1.09–1.65), P = 0.006), and the overweight and obese groups had a lower possibility of live births than the reference group ((OR (95% CI) 0.75 (0.65–0.87), P < 0.001) or (OR (95% CI) 0.55 (0.38–0.80), P = 0.002)) (Table 5). For maternal age ≥ 30 with normal ovarian reserve (AMH >3 and AMH <6), the possibility of live births was higher in the underweight group than the reference group (OR (95% CI) 1.72 (1.22–2.41), P = 0.002), and the possibility of live births was lower in the obese group than the reference group (OR (95% CI) 0.59 (0.36–0.98), P = 0.041) (Table 5). Whereas, for those age ≥30 with adequate ovarian reserve patients (AMH ≥6), the obese group had a lower possibility of live births than the reference group (OR (95% CI) 0.36 (0.20–0.63), P < 0.001) (Table 5). These data further show that maternal BMI, age, and ovarian reserve affect CLBR.

Discussion

In reproductive medicine, individualized IVF-ET protocol provided based on each individual's characteristics to maximize pregnancy rates and live birth rates, while reducing ovarian hyperstimulation syndrome (OHSS) and adverse pregnancy outcomes, remains a great challenge (31). The advancements in endocrinology in recent years makes BMI determination vital in developing IVF-ET protocols. In this retrospective single-center study, analysis of patients' data without any confounders revealed that CLBR increased among underweight women but decreased in overweight and obese women when compared with standard-weight women. Moreover, among women of different BMI, the embryonic development indicators, such as oocyte output rate, no. 2PN, and number of day 3 usable embryos were similar to those of CLBR (Table 2).

The negative effect of high maternal BMI has been shown in fresh embryo transfer cycles (32). On the other hand, the results of frozen–thawed embryo transfer cycles are controversial (33, 34) because these studies are cycle-based and only used few embryos that resulted from OPU cycle, which may represent only part of the embryonic development potential. For example, Fedorcsak *et al.* first reported the association between BMI and CLBR in female patients undergoing one OPU cycle (35). Unlike these previous studies, our calculation of CLBR was based on the patients' outcome measures, ensuring that patients had completed IVF treatment, including repetitive OPU and all fresh and frozen embryos were transferred until live birth or embryos were run out. When the association between

Table 4 Subgroup analysis of CLBR according to maternal age, AMH, OS protocol, infertility factor, and AFC.

		Reference		Underweight		Overweight		Obese	
	n	**CLBR (*n*, %)**	**Ref.**	**CLBR (*n*, %)**	**OR (95% CI) *P***	**CLBR (*n*, %)**	**OR (95% CI) *P***	**CLBR (*n*, %)**	**OR (95% CI) *P***
Age									
<30	3618	2111, 86.69%	1	513, 86.66%	1.02 (0.78–1.34) 0.873	410, 83.84%	0.70 (0.53–0.93) 0.012	79, 77.45%	0.46 (0.28–0.75) 0.002
≥30 and ≤39	8454	4398, 74.03%	1	631, 76.12%	1.18 (0.99–1.40) 0.066	1061, 73.17%	0.89 (0.78–1.02) 0.087	152, 64.96%	0.50 (0.37–0.67) <0.001
≥40	1380	224, 24.43%	1	13, 25.49%	1.23 (0.63–2.41) 0.550	100, 27.17%	0.99 (0.74–1.33) 0.949	13, 29.55%	1.05 (0.52–2.12) 0.889
AMH									
≤3	6442	2788, 61.64%	1	430, 67.82%	0.93 (0.77–1.14) 0.490	609, 53.94%	0.85 (0.74–0.99) 0.039	80, 51.28%	0.60 (0.42–0.86) 0.005
>3 and <6	4439	2443, 80.31%	1	459, 87.10%	1.36 (1.03–1.81) 0.030	588, 78.61%	0.95 (0.78–1.17) 0.654	89, 72.95%	0.58 (0.37–0.90) 0.015
≥6	2571	1502, 86.92%	1	268, 86.17%	0.81 (0.56–1.15) 0.238	374, 86.98%	1.09 (0.79–1.50) 0.602	75, 73.53%	0.44 (0.27–0.71) 0.001
OS protocol									
GnRH agonist	8497	4793, 81.85%	1	860, 86.26%	1.15 (0.94–1.40) 0.168	1098, 78.82%	0.88 (0.75–1.02) 0.094	176, 70.12%	0.45 (0.33–0.60) <0.001
GnRH antagonist	2152	1030, 70.02%	1	155, 70.78%	0.74 (0.53–1.03) 0.076	262, 65.66%	0.87 (0.67–1.13) 0.299	40, 63.49%	0.75 (0.42–1.33) 0.326
Other	2803	910, 46.29%	1	142, 55.47%	1.02 (0.76–1.37) 0.890	211, 40.97%	0.98 (0.79–1.22) 0.887	28, 42.42%	0.84 (0.49–1.44) 0.521
Infertility factor									
Endometriosis	533	255, 68.55%	1	79, 81.44%	1.53 (0.84–2.80) 0.164	42, 75.00%	1.11 (0.55–2.25) 0.765	3, 37.50%	0.15 (0.03–0.74) 0.019
Ovarian factor	1071	299, 39.34%	1	69, 70.41%	0.55 (0.30–1.01) 0.053	67, 35.83%	1.24 (0.86–1.80) 0.252	19, 73.08%	1.31 (0.48–3.59) 0.600
Tubal factor	8818	4596, 75.32%	1	740, 79.06%	0.99 (0.83–1.19) 0.935	1084, 70.66%	0.85 (0.74–0.98) 0.024	164, 66.67%	0.61 (0.45–0.83) 0.001
PCOS	621	322, 87.26%	1	40, 78.43%	0.91 (0.39–2.12) 0.832	120, 81.08%	0.72 (0.42–1.24) 0.236	31, 58.49%	0.30 (0.15–0.60) 0.001
Male factor	1342	730, 78.41%	1	143, 80.79%	1.13 (0.73–1.76) 0.580	154, 72.30%	0.95 (0.65–1.39) 0.805	14, 66.67%	0.55 (0.19–1.63) 0.283
Uterine	807	399, 68.32%	1	53, 75.71%	0.85 (0.43–1.68) 0.641	79, 58.52%	1.04 (0.66–1.66) 0.854	8, 44.44%	0.14 (0.04–0.45) 0.001
Other	260	132, 75.43%	1	33, 76.74%	1.20 (0.44–3.27) 0.721	25, 73.53%	1.23 (0.45–3.36) 0.683	5, 62.50%	0.53 (0.08–3.42) 0.506
AFC									
≤4	1353	358, 36.87%	1	50, 43.75%	0.91 (0.58–1.42) 0.674	81, 34.91%	1.26 (0.90–1.76) 0.171	11, 29.73%	0.72 (0.33–1.59) 0.415
>4 and ≤9	3138	1359, 62.48%	1	251, 69.64%	0.95 (0.73–1.23) 0.677	293, 53.27%	0.85 (0.69–1.05) 0.130	29, 55.77%	0.91 (0.50–1.65) 0.753
>9 and ≤15	4187	2308, 76.60%	1	400, 83.30%	1.15 (0.88–1.50) 0.299	434, 72.33%	1.00 (0.81–1.23) 0.974	64, 68.82%	0.78 (0.48–1.25) 0.296
>15	4774	2708, 86.41%	1	456, 88.01%	0.96 (0.72–1.28) 0.783	763, 82.58%	0.82 (0.67–1.01) 0.059	140, 70.71%	0.41 (0.29–0.57) <0.001

Adjusted for maternal age, AMH, OS protocol, Infertility factor, AFC, basal FSH, basal LH, and basal E2.

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Table 5 Multivariate logistic regression of CLBR according to BMI combined with age and ovarian reserve.

			Reference		Underweight		Overweight		Obese	
		n	CLBR (*n*, %)	Ref	CLBR (*n*, %)	OR (95% CI) *P*	CLBR (*n*, %)	OR (95% CI) *P*	CLBR (*n*, %)	OR (95% CI) *P*
Age <30	AMH ≤ 3	1041	597, 81.89%	1	129, 78.18%	0.80 (0.51–1.24) 0.314	88, 72.13%	0.46 (0.29–0.73) 0.001	18, 72.00%	0.51 (0.20–1.30) 0.156
	3 < AMH < 6	1448	854, 88.68%	1	230, 90.91%	1.33 (0.83–2.15) 0.240	166, 85.13%	0.72 (0.46–1.14) 0.159	28, 75.68%	0.39 (0.18–0.85) 0.018
	AMH ≥6	1129	660, 88.83%	1	154, 88.51%	0.89 (0.52–1.51) 0.657	156, 90.70%	1.29 (0.72–2.30) 0.390	33, 82.50%	0.59 (0.25–1.39) 0.229
Age ≥30	AMH ≤3	5401	2191, 57.75%	1	301, 64.18%	1.34 (1.09–1.65) 0.006	521, 51.74%	0.75 (0.65–0.87) <0.001	62, 47.33%	0.55 (0.38–0.80) 0.002
	3 < AMH < 6	2991	1589,76.43%	1	229, 83.58%	1.72 (1.22–2.41) 0.002	422, 76.31%	0.93 (0.74–1.16) 0.515	61, 71.76%	0.59 (0.36–0.98) 0.041
	AMH ≥6	1442	842, 85.48%	1	114, 83.21%	0.81 (0.50–1.33) 0.407	218, 84.50%	0.92 (0.62–1.35) 0.668	42, 67.74%	0.36 (0.20–0.63) <0.001

Adjusted for maternal age, AMH, OS protocol, Infertility factor, AFC, basal FSH, basal LH, and basal E2.

BMI and IVF outcome in female patients receiving IVF was examined, both had an 'inverted U shape' (Fig. 2), consistent with previous studies (32). Most previous studies focused on the effects of maternal underweight (<18.5 kg/m^2) and overweight (24–28 kg/m^2) on pregnancy outcomes (36, 37), while some studies combined obese and overweight patients in their analysis (38, 39). Here, obese and overweight patients were separated, in which case embryonic development-related indicators and CLBR were found to increase in underweight group but decreased in the overweight (Table 2), as reported in the 2008–2013 United States Society for Assisted Reproductive Technology registry (40, 41). Besides, the CLBR of obese women was significantly decreased with increased BMI after adjusting for potential confounders (i.e. age, AMH, OS protocol, Infertility factor, AFC, basal FSH, basal LH, basal E2) (Table 3).

Obesity negatively impacts female reproductive potential through its effect on the hypothalamic–pituitary–ovarian axis, resulting in causing ovulation and menstrual disorders, and consequently on female reproductive function (42). Pathophysiological studies indicate that the incidence of impaired glucose tolerance increases in obese women, both in and out of pregnancy (43). Similarly, high insulin levels can increase free androgens by inhibiting the synthesis of hepatic sex hormone-binding proteins or by binding to the insulin-like growth factor 1 (IGF-1) receptor, resulting in hyperandrogenemia (44). Given that elevated androgens in serum or ovary can inhibit follicular growth and maturation to cause follicular atresia (45), this could explain why in the present study a compromised oocyte output rate (oocyte count/AFC) was observed with an increase in BMI (Table 2). Moreover, white adipocytes secrete leptin, while obese patients are prone to leptin resistance (46). Given that leptin and its receptors are most commonly found in adipose tissues, and also expressed in human ovarian granulosa cells, endometrial glands, stromal cells, and fallopian tube epithelium (46), which are closely related to the female reproductive system, high levels of leptin in the follicular fluid can directly affect granulosa cell differentiation to induce tumor necrosis factor alpha (TNFα) and interleukin 6 (IL-6) secretion by mononuclear macrophages, which interferes with the development of dominant follicles and therefore reduces oocyte quality (47). Besides its effect on oocyte quality, obesity affects endometrial tolerance. In obese patients, impaired glucose metabolism and disturbed adipokine expression has adverse effects on endometrial methylation, resulting in decreased endometrial tolerance and therefore increased incidence of infertility and miscarriages (48).

In addition, a combination of age and ovarian reserve index should be taken into account when exploring the relationship between BMI and CLBR in IVF. A 2015 committee opinion from the American Society for Reproductive Medicine states that the benefits of weight loss must be balanced with the decline in fertility that

accompanies advancing age (49). To our knowledge, this is the first study that considers the combined impact of age and BMI on cumulative live birth rates. The results of our study found that when normal ovarian reserve BMI has a greater influence on live birth at younger ages as compared to older ages (Table 5). Therefore, taking time to achieve a lower BMI prior to IVF in young patients with normal ovarian reserve may be beneficial. On the other hand, overweight or obese older women even if they have normal ovarian reserve, may actually do very little to help improve live births if they delay attempting conception to lose weight. Although maternal BMI can significantly affect CLBR, the need for weight control should be fully evaluated prior to assisted reproduction. Longer weight control regimens can potentially increase the maternal age that could result in a rapid decline in AFC, which has a greater influence on CLBR (50). Some studies have found that weight loss did not shorten the time to live birth or increase LBR (51, 52). In terms of overall health status, weight loss may still be the healthier option, especially for younger patients.

Although 13,452 patients were analyzed in this study, there are still limitations in our findings given that single center data was used, which cannot be generalized to the entire population. Moreover, the BMI was calculated from data collected only at the beginning of the IVF treatment, which would differ from the BMI during IVF treatment and pregnancy. Besides, given the vast differences among the global populations, with Asians generally known to have lower BMI compared with non-Asians of the same age (19), the study results should be interpreted with caution when considering other populations and regions.

Conclusion

Collectively, the findings here revealed an association between maternal BMI and CLBR, with the CLBR found to decrease obese women. Since the effect of BMI on live birth rates also depends on factors such as age and ovarian reserve, clinicians should evaluate the need for weight loss to improve live birth rates before patients undergo IVF treatment. Therefore, a combination of these indicators and a discussion with patients on the overall health benefits of weight loss, fertility, and pregnancy is essential.

Declaration of interest

There are no relevant financial or nonfinancial competing interests to report.

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Author contribution statement

ZZ and SJL conceived and designed the study; XMZ, MQZ, and SJL acquired funding; ZZ and HZL performed the analysis; SJL, HZ, and FGW contributed analytic tools; SJL supervised the work; ZZ and SJL wrote the original draft, reviewed and edited the paper. All authors have read and agreed to the published version of the manuscript.

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