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The PPOS protocol mitigates the detrimental effects of high BMI on embryo and clinical pregnancy outcomes

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Abstract

Background The impact of high body mass index (BMI) on embryo and pregnancy outcomes in women using the PPOS (progestin-primed ovarian stimulation) protocol during their first frozen embryo transfer (FET) cycles is not clear. This study is to investigate the impact of BMI on oocyte, embryo, and pregnancy outcomes in patients who underwent the PPOS protocol.

Methods This retrospective study included the first FET cycle of 22,392 patients following the PPOS protocol. The impact of BMI on oocyte and pregnancy outcomes was assessed across different BMI groups, using direct acyclic graph to determine covariates, followed by the application of multiple linear and logistic regressions to further validate this influence.

Results The high BMI groups exhibited a higher number of oocytes; however, no significant differences were observed in good-quality embryos, clinical pregnancy rate, and implantation rate. Nevertheless, the high BMI groups demonstrated a significantly elevated miscarriage rate (9.9% vs. 12.2% vs. 15.7% vs. 18.3%, $P<0.001$), particularly in late miscarriages, resulting in lower live birth rates (LBR, 41.1% vs. 40.2% vs. 37.3% vs. 36.2%, $P=0.001$). These findings were further confirmed through multiple liner and logistic regression analyses. Additionally, several maternal factors showed significant associations with adjusted odds ratios for early miscarriage. However, women with a BMI ≥ 24 who underwent hormone replacement cycle or hMG late stimulation protocol for endometrial preparation experienced an increased risk of late miscarriage.

Conclusions By utilizing the PPOS protocol, women with a high BMI exhibit comparable outcomes in terms of embryo and clinical pregnancies. However, an elevated BMI is associated with an increased risk of miscarriage,

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leading to a lower LBR. Adopting appropriate endometrial preparation protocols such as natural cycles and letrozole stimulation cycles may potentially offer benefits in reducing miscarriages.

Keywords High BMI, PPOS protocol, Clinical outcomes, Affecting factor, Endometrial preparation

Background

There is abundant evidence showing that women with high BMI experience a wide spectrum of reproductive complications, such as infertility [1–3] and miscarriage [4, 5] by changing the endocrine status [6], oocyte quality [7, 8] and endometrial receptivity [9, 10]. Therefore, more and more infertile women with high BMI resort to assisted reproductive technology (ART). A majority of research found that women with high BMI had more inferior pregnancy outcomes than the non-obese women based on fresh and frozen embryo transfer [11–13].

In overweight/obese patients, the hypothalamic-pituitary-ovarian axis function exhibits distinct patterns that deviate from those observed in individuals with normal reproductive states; specifically, obese women demonstrate reduced pulsatile luteinizing hormone amplitude and progesterone metabolite excretion [14]. Therefore, it is imperative to implement appropriate controlled ovarian hyperstimulation (COH) protocols for these patients. For instance, a higher dosage of gonadotropin and an extended stimulation period are deemed necessary [15]. The efficacy of the luteal long agonist protocol was demonstrated to be superior to that of the flexible antagonist protocol [16], while another study showed that potential benefits of GnRH-a long protocol for obese women [17]. Additionally, for high BMI PCOS (polycystic ovary syndrome) patients, an ultra-long protocol was found to result in a higher live birth rate compared to a standard long protocol [18].

The concept of progestin-primed ovarian stimulation (PPOS) was internationally proposed as a new ovulation induction technique, following the success of endogenous progesterone (luteal phase stimulation) [19] and exogenous progesterone follicular phase controlled ovulation techniques [20]. PPOS represents a significant milestone in the development of human controlled ovarian hyperstimulation techniques [21, 22], and was acknowledged by the American Board of Reproductive Medicine in 2018 as an innovative research contribution to "Forty Years of IVF" [23].

The impact of high BMI on embryo and pregnancy outcomes remains unclear when patients adopt this novel COH protocol - PPOS. Our and previous researches [24–26] with contradictory findings prompted us to conduct this retrospective analysis involving a large cohort of women with high BMI, aiming to explore the impact of high BMI on embryo and pregnancy outcomes in women adopting the PPOS protocol.

Methods

Study population

This retrospective study was approved by the ethics committee of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (SH9H-2022-T155-1). This study was in accordance with the Declaration of Helsinki. The data of this study was obtained from the database in assisted reproduction department of the Ninth People's Hospital, Shanghai JiaoTong University School of Medicine from 2010 to 2022. There is no patient and public involvement in this research. A total of 22,392 women using the PPOS protocol and undergoing their first FET cycle were enrolled. They are divided into four subgroups according to Asian BMI categories [27]: BMI < 18.5 kg/m^2 (n=2264), 18.5–23.99 kg/m^2 (n=15110), 24–27.99 kg/m^2 (n=3996), and ≥28 kg/m^2 (n=1022). To further explore embryo and pregnancy outcomes among the women's BMI ≥ 28 kg/m^2, WHO BMI classification were used to divided these patients into three additional group : 28–29.99 kg/m^2 (n=563), 30–34.99 kg/m^2 (n=383), and ≥35 kg/m^2 (n=76) [28].

We also investigate the ART outcomes associated with target organ injuries related to obesity, including high blood pressure (HBP), diabetes mellitus (DM) and hyperlipidemia. The metabolism syndrome in China was defined according to 2016 Chinese guidelines for the management of dyslipidemia in adults [29], which should meet three or more of the following abnormalities: (a) central obesity (Waist Circumference ≥ 85 cm for women); (b) elevated triglyceride level ≥ 1.7mmol/L or receipt of treatment; (c) reduced HDL-C level (< 1.0mmol/L) or receipt of treatment; (d) systolic blood pressure ≥ 130mmHg or diastolic blood pressure ≥ 85mmHg or current treatment for hypertension or previously diagnosed hypertension; (e) elevated fasting plasma glucose level (FPG ≥ 6.1mmol/L or 2 h postprandial PG ≥ 7.8mmol/L) or previously diagnosed diabetes mellitus. For definition (a), we did not record waist circumference for patients. For definition (b) and (c), they are belonged to blood lipid test. Although the liver and kidney function tests are compulsory, the blood lipid test is not mandatory in our IVF center.The missing data of waist circumference and blood lipid level would bring some inaccuracies to our diagnosis to metabolism syndrome. Therefore, we employed the following strategies to identify subgroups for analyzing target organ damage related to metabolism in obese patients (BMI ≥ 28 kg/m^2). Firstly, we thoroughly reviewed the complete medical

histories of all patients and identified those with a documented diagnosis of high blood pressure (HBP) and/or diabetes mellitus (DM) by physician internist, who were receiving relevant medication treatment. These patients were classified into group 1 ($n=27$). Additionally, upon examining their paper-based medical records, we discovered that three patients had provided their blood lipid level results. Secondly, we extracted all blood pressure data from our electronic database, the HBP was defined as (d) in definition. Based on this information, we categorized the patients into group 2 ($n=116$; comprising individuals with at least two HBP recordings in our database), group 3 ($n=319$; consisting of patients with only one HBP recording in our database), and group 4 ($n=361$; including individuals without any HBP recordings in our database). It is worth noting that there were also 199 patients without any recorded blood pressure measurements in our database, who were subsequently excluded from this particular sub-analysis.

Controlled ovarian hyperstimulation (COH), oocyte retrieval and in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI)

All study participants underwent a COH protocol to retrieve oocytes, and we only enrolled those who followed the PPOS protocol [20, 30–37]. The final stage of oocyte maturation was triggered when there were more than 3 dominant follicles reaching a diameter of 18 mm. This was achieved by using triptorelin (0.1–0.2 mg; decapeptyl, Ferring Pharmaceuticals, China) or intramuscular injections of hCG (1,000–5000 IU; Lizhu Pharmaceutical Trading Co., China), or through co-triggering via subcutaneous injections of triptorelin (0.1–0.2 mg) and intramuscular injections of hCG (1,000–5000 IU). Transvaginal ultrasound–guided oocyte retrieval was performed 32–40 h after trigger. After IVF (in-vitro fertilization) or ICSI (intracytoplasmic sperm injection), embryos on Day 3 were examined and graded based on the number of blastomeres, regularity and degree of embryonic fragmentation according to the Cummins criteria [30]. All top-quality embryos included grades I and II 8-cell blastomere embryos were vitrified on the Day 3. Embryos of grade III and IV were vitrified after extendedly cultured in 10%-SSS supplemented Continuous Single Culture medium (CSC; Irvine Scientific, CA, USA) to blastocyst stage.

Frozen embryo transfer (FET) and endometrial preparation

Before embryo transplantation, patients usually choose one of four endometrial preparations: (a) Natural cycle: If patients have a normal dominate follicle size and endometrium thickness monitored on cycle day 12 by the ultrasound test, they will not receive any medicine until trigger day. (b) Hormone replacement cycle: If patients have a history of thin endometrium, a short length of menstrual cycle less than 23 days, or abnormal uterine bleeding (menostaxis or ovulation bleeding), they will take oral ethinyl estradiol (25 μg twice per day, Xinyi Pharmaceutical Co., China) from cycle day 3 onward for at least 14 days. (c) hMG late stimulation cycle: If patients have a regular menstrual cycle and the diameter of dominate follicles is less than 10 mm on cycle day 12, they will receive small doses of hMG. (d) Letrozole mild stimulation cycle: If patients have a prolonged menstrual cycle, letrozole (2.5 mg/d, Jiangsu Hengrui Co., China) will be used for the initial 3–5 days according to their length of menstrual cycle before using hMG. The drugs were used for luteal support until a gestation of 10 weeks, and the detailed regimen was described in our previous study [20]. Miscarriages are classified as early miscarriages (with 12 weeks) or late miscarriages (from 13 to 28 weeks' gestation) [38].

Statistical analysis

Statistical analyses were carried out by SPSS 24.0 (SPSS Inc., Chicago, IL, USA), GraphPad Prism 6 (GraphPad software Inc., La Jolla, CA 92037 USA) and R software (R for windows, 3.5.3versions). Our data are presented as the means ± Standard Deviation (SD), or if the distribution is non-normal, as median with inter quartile range. The one-way ANOVA analysis was used to compare data among the four groups assuming normality; otherwise, a nonparametric test was applied. Proportions were analyzed using Fisher's exact test or $\chi 2$ test when appropriate.

The potential confounding factors of oocytes and embryos were determined using a direct acyclic graph (DAG) [39] based on the variables presented in Table 1. The potential confounding factors of pregnancy outcomes were determined using a direct acyclic graph (DAG) based on the variables presented in Tables 1 and 2. The DAG was drawn using DAGitty browser-based software (available at: http://www.dagitty.net/dags.html). If there were multiple minimal sufficient adjustment sets, the better fit model would be chosen. Therefore, the final minimal sufficient adjustment sets for estimating the total effect of BMI were AFC and age on oocytes and embryo outcomes; and AFC, age, and endometrial preparation method for pregnancy outcomes. Regarding Table 3, multinomial logistics regression was conducted using live birth as a reference to compare the influence of different factors on early miscarriage and late miscarriage separately. $P<0.05$ was considered statistically significant and shown it bold in table.

Table 1 Baseline characteristics, clinical variables and IVF/ICSI outcomes of women with PPOS by BMI category (kg/m^2)

BMI groups (kg/m2)	< 18.5	18.5-23.99	24-27.99	≥ 28	*P*-value
Patients (n)	2264	15,110	3996	1022	
Age (y)	31.20 ± 4.27 [a]	32.51 ± 4.72 [b]	32.92 ± 4.97 [c]	31.92 ± 4.73 [d]	**< 0.001**
Duration of infertility(y)	3.00 ± 2.54 [a]	3.14 ± 2.93 [b]	3.47 ± 3.18 [c]	3.81 ± 3.33 [d]	**< 0.001**
Primary infertility, n(%)	1423 (62.9%) [a]	8138 (53.9%) [b]	2044 (51.2%) [c]	609 (59.6%) [a]	**< 0.001**
Cause of infertility, n(%)					**< 0.001**
Tubal factor	1163 (51.4) [a]	7890 (52.2) [a]	2049 (51.3) [a]	467 (45.7) [b]	
Male factor	339 (15.0) [a]	2169 (14.4) [a]	554 (13.9) [a]	167 (16.3) [a]	
Combination of tubal and male factors	174 (7.7) [a]	1329 (8.8) [a]	302 (7.6) [a]	72 (7.0) [a]	
Other factors	588 (26.0) [ab]	3722 (24.6) [b]	1091 (27.3) [ac]	316 (30.9) [c]	
Patients with uterine malformation, Asherman Syndrome or PCSD (%)	14 (0.62%)	157 (1.04%)	37 (0.93%)	7 (0.68%)	0.201
Day3 AFC	7.56 ± 7.33 [a]	7.66 ± 7.65 [a]	8.75 ± 8.49 [b]	10.33 ± 9.21 [c]	**< 0.001**
HMG doses (IU)	1792.52 ± 409.90 [a]	1869.65 ± 448.45 [b]	2097.92 ± 602.96 [c]	2395.79 ± 874.15 [d]	**< 0.001**
PCOS (%)	128 (5.7) [a]	1093 (7.2) [b]	671 (16.8) [c]	332 (32.5) [d]	**< 0.001**
Oocytes retrieved (n)	12.37 ± 7.42 [a]	11.74 ± 7.61 [b]	11.67 ± 7.93 [b]	12.01 ± 8.37 [ab]	**0.002**
Mature oocytes (n)	10.60 ± 6.29 [a]	10.04 ± 6.39 [b]	10.01 ± 6.69 [b]	10.28 ± 7.15 [ab]	**0.001**
Method of fertilization					**< 0.001**
IVF	1294 (57.2%) [ab]	8643 (57.2%) [b]	2249 (56.3%) [ab]	534 (52.3%) [a]	
ICSI	595 (26.3%) [a]	4222 (27.9%) [a]	1106 (27.7%) [a]	270 (26.4%) [a]	
IVF + ICSI	375 (16.6%) [a]	2245 (14.9%) [a]	641 (16.0%) [a]	218 (21.3%) [b]	
Fertilized oocytes (n)	8.81 ± 5.38 [a]	8.40 ± 5.47 [b]	8.31 ± 5.66 [b]	8.55 ± 6.04 [ab]	**0.004**
Top-quality embryos (n)	4.18 ± 3.32	4.11 ± 3.23	4.18 ± 3.38	4.32 ± 3.58	0.162
Viable embryos (n)	4.70 ± 2.95	4.60 ± 2.96	4.57 ± 3.02	4.67 ± 3.14	0.351

For continuous data, one-way ANOVA analysis was performed; for proportions, the chi-square test was utilized. Different superscript letters indicate significant differences between groups. Abbreviations: PPOS - progestin-primed ovarian stimulation; IVF - in vitro fertilization; ICSI - intracytoplasmic sperm injection; BMI - body mass index; AFC - antral follicle count; PCOS - polycystic ovary syndrome; HMG - human menopausal gonodotrophin; PCSD - previous cesarean scar defect. $P < 0.05$ was considered statistically significant and shown it bold in table

Table 2 Pregnancy outcomes of women with PPOS by BMI category (kg/m^2)

BMI groups (kg/m2)	< 18.5	18.5-23.99	24-27.99	≥ 28	*P*-value
Patients (n)	2264	15,110	3996	1022	
Endometrial preparation					**< 0.001**
Natural cycle	504 (22.3) [a]	2983 (19.7) [b]	546 (13.7) [c]	90 (8.8) [d]	
Hormone replacement cycle	608 (26.9) [a]	4432 (29.3) [a]	1334 (33.4) [b]	367 (35.9) [b]	
Letrozole stimulation protocol	645 (28.5) [ab]	4247 (28.1) [b]	1237 (31.0) [a]	390 (38.2) [c]	
hMG late stimulation cycle	507 (22.4) [a]	3448 (22.8) [a]	879 (22.0) [a]	175 (17.1) [b]	
Endometrium thickness (mm)	10.47 ± 2.21 [a]	10.55 ± 2.26 [a]	10.65 ± 2.31 [b]	10.72 ± 2.40 [b]	**0.002**
Transferred embryos (n)	1.71 ± 0.45 [a]	1.71 ± 0.45 [a]	1.68 ± 0.47 [b]	1.60 ± 0.49 [c]	**< 0.001**
Embryo stage					**0.001**
Cleavage embryo	1902 (84.0) [a]	12,787 (84.6) [a]	3345 (83.7) [a]	816(79.8) [b]	
Blastocyst embryo	362 (16.0) [a]	2323 (15.4) [a]	651 (16.3) [a]	206 (20.2) [b]	
Clinical pregnancy rate (n, %)	1133 (50.0)	7518 (49.8)	1959 (49.0)	507 (49.6)	0.841
Implantation rate (n, %)	1414/3879 (36.5)	9286/25,891 (35.9)	2402/6710 (35.8)	617/1636 (37.7)	0.431
Ectopic pregnancy (n, %)	100/1133 (8.8%) [ab]	604/7518 (8.0%) [b]	189/1959 (9.6%) [a]	54/507 (10.7%) [a]	**0.036**
Miscarriage rate (miscarriage/intrauterine pregnancy) (n, %)	102/1033 (9.9) [a]	845/6914 (12.2) [a]	278 /1770 (15.7) [b]	83/453 (18.3) [b]	**< 0.001**
Miscarriage period					**< 0.001**
Early miscarriage	87 (85.3%) [ab]	721 (85.3%) [b]	206 (74.1%) [a]	58 (69.9%) [a]	
Late miscarriage	15 (14.7%) [ab]	124 (14.7%) [b]	72 (25.9%) [a]	25 (30.1%) [a]	
Live birth rate per patient (n, %)	931 (41.1) [a]	6069 (40.2) [ab]	1492 (37.3) [c]	370 (36.2) [bc]	**0.001**

For continuous data, one-way ANOVA analysis was performed; for proportions, the chi-square test was utilized. Different superscript letters indicate significant differences between groups. Abbreviation: PPOS: progestin-primed ovarian stimulation; BMI: body mass index. $P < 0.05$ was considered statistically significant and shown it bold in table

Table 3 The influence of different BMI on oocytes, embryos, and pregnancy outcomes

	Normal Weight (BMI 18.5-23.99)	Underweight (BMI < 18.5)		Overweight (BMI 24-27.99)		Obese (BMI ≥ 28)	
Liner regression	**Reference**	**Coefficient(95%CI)**	***P* value**	**Coefficient(95%CI)**	***P* value**	**Coefficient(95%CI)**	***P* value**
Retrieved Oocytes							
Unadjusted	1	0.63 (0.29,0.97)	**< 0.001**	-0.07 (-0.34,0.20)	0.616	0.27 (-0.22,0.76)	0.275
Adjusted	1	0.03 (-0.28,0.33)	0.850	-0.16 (-0.40, 0.08)	0.197	-0.72 (-1.16, -0.29)	**0.001**
Good-quality embryos							
Unadjusted	1	0.07 (-0.08, 0.21)	0.353	0.07 (-0.04, 0.18)	0.233	0.21 (0.00, 0.42)	0.051
Adjusted	1	-0.10 (-0.24, 0.04)	0.152	0.05 (-0.06, 0.16)	0.347	-0.05 (-0.25, 0.15)	0.600
Viable embryos							
Unadjusted	1	0.10 (-0.03, 0.23)	0.132	-0.03 (-0.13, 0.08)	0.608	0.07 (-0.12, 0.26)	0.489
Adjusted	1	-0.09 (-0.22, 0.03)	0.150	-0.04 (-0.14, 0.06)	0.459	-0.20 (-0.38, -0.03)	**0.025**
Logistics regression	**Reference**	**Odds ratio(95%CI)**	**P value**	**Odds ratio(95%CI)**	**P value**	**Odds ratio(95%CI)**	**P value**
Clinical pregnancy rate							
Unadjusted	1	1.01 (0.93, 1.11)	0.798	0.97 (0.91, 1.04)	0.411	0.99 (0.88, 1.13)	0.928
Adjusted	1	0.91 (0.83, 1.00)	**0.047**	1.00 (0.93, 1.08)	0.910	0.95 (0.84, 1.09)	0.484
Miscarriage rate							
Unadjusted	1	0.79 (0.63, 0.98)	**0.030**	1.34 (1.16, 1.55)	**< 0.001**	1.61 (1.26, 2.07)	**< 0.001**
Adjusted	1	0.86 (0.69, 1.08)	0.191	1.28 (1.10, 1.48)	**0.001**	1.64 (1.27, 2.11)	**< 0.001**
Live birth rate							
Unadjusted	1	1.04 (0.95, 1.14)	0.387	0.89 (0.83, 0.95)	**0.001**	0.85 (0.74, 0.96)	**0.012**
Adjusted	1	0.93 (0.85, 1.02)	0.107	0.92 (0.86, 0.99)	**0.034**	0.81 (0.71, 0.93)	**0.003**

The potential confounding factors of oocytes and embryos were determined using a direct acyclic graph (DAG) based on the variables presented in Table 1. The potential confounding factors of pregnancy outcomes were determined using a direct acyclic graph (DAG) based on the variables presented in Tables 1 and 2. The final minimal sufficient adjustment sets for estimating the total effect of BMI included AFC and age for oocyte and embryo outcomes, as well as AFC, age, and endometrial preparation method for pregnancy outcomes. Abbreviations: BMI - body mass index; CI - confidence interval. $P<0.05$ was considered statistically significant and shown it bold in table

Table 4 Crude and adjusted ORs of miscarriage in women using PPOS under different clinical characters

	Early miscarriage (live birth as ref.)				Late miscarriage (live birth as ref.)			
Variable	**Crude OR (95% CI)**	***P*-value**	**Adjusted OR (95% CI)**	***P*-value**	**Crude OR (95% CI)**	***P*-value**	**Adjusted OR(95% CI)**	***P*-value**
Women's age	1.12 (1.10–1.13)	**< 0.001**	1.12 (1.10–1.13)	**< 0.001**	1.02 (0.99–1.05)	0.216	1.02 (0.99–1.06)	0.157
Women's BMI (18.5-23.99 as ref.)								
< 18.5	0.79 (0.62–0.99)	**0.043**	0.87 (0.69–1.11)	0.266	0.79 (0.46–1.35)	0.389	0.82 (0.48–1.41)	0.475
24-27.99	1.16 (0.99–1.37)	0.074	1.11 (0.94–1.31)	0.230	2.36 (1.76–3.18)	**< 0.001**	2.24 (1.66–3.01)	**< 0.001**
≥ 28	1.32 (0.99–1.76)	0.059	1.37 (1.02–1.83)	**0.036**	3.31 (2.13–5.15)	**< 0.001**	3.06 (1.95–4.78)	**< 0.001**
AFC	0.99 (0.99-1.00)	0.112	1.01 (0.99–1.01)	0.279	1.02(1.00-1.03)	**0.027**	1.01 (0.99–1.03)	0.091
Endometrial preparation (Natural cycle as ref.)								
Hormone replacement cycle Letrozole stimulation cycle	1.45 (1.20–1.75)	**< 0.001**	1.44 (1.18–1.75)	**< 0.001**	2.86 (1.80–4.54)	**< 0.001**	2.43 (1.52–3.88)	**< 0.001**
Letrozole stimulation protocol	0.99 (0.81–1.21)	0.928	1.03 (0.83–1.27)	0.793	1.77 (1.10–2.87)	**0.020**	1.45 (0.88–2.39)	0.144
hMG late stimulation cycle	1.27 (1.04–1.55)	**0.018**	1.28 (1.04–1.57)	**0.019**	2.25 (1.39–3.66)	**< 0.001**	2.05 (1.26–3.33)	**0.004**

Multinomial logistic regression was employed to examine the significant factors associated with 1st and 2nd /3rd trimester miscarriage, using live birth as the reference category. The confoundings were identified through the use of a Directed Acyclic Graph (DAG). Abbreviations: PPOS (progestin-primed ovarian stimulation), BMI (body mass index), AFC (antral follicle count), OR (odds ratio), CI (confidence interval). Ref (reference). $P<0.05$ was considered statistically significant and shown it bold in table

Results

Characteristics and embryo outcomes of women with normal and high BMI undergoing the PPOS protocol

The characteristics and outcomes of patients in their first FET cycles were presented in Table 1. Women with a BMI of 18.5-23.99 and 24-27.99 exhibited higher age and lower primary infertility rates compared to those in the <18.5-23.99 and ≥28 BMI groups. The women with higher BMI exhibited a prolonged duration of infertility, a higher rate of PCOS, and an increased number of AFC (antral follicle count). Significant higher HMG doses were using in overweight and obesity patients (1792.52±409.90 vs. 1869.65±448.45 vs. 2097.92±602.96 vs. 2395.79±874.15, $P<0.001$). However, there was no significant difference in the number of oocytes and

mature oocytes between women with normal BMI and those with high BMI. After fertilization, the fertilized oocytes also showed the same tendency with oocytes. Furthermore, these four groups achieved similar top-quality embryos and viable embryos across four BMI groups. The subgroup analysis among ≥28 BMI groups also showed no difference in oocyte retrieved (Fig. 1A1), good-quality embryos (Fig. 1B1) and viable embryos (Fig. 1C1) with normal BMI patients.

Pregnancy outcomes of women with normal and high BMI undergoing the PPOS protocol

In Table 2, the high BMI groups showed a higher application rate of hormone replacement cycle and letrozole stimulation protocol. The BMI≥28 group transferred fewer embryos with a higher proportion of blastocyst embryos, but no significant differences were observed in the stage of transferred embryos among other BMI groups. As for pregnancy outcomes, the clinical pregnancy rate and implantation rate were similar across the four women's BMI groups. However, there was a significant increasing trend in the miscarriage rate among BMI groups, and there was also an increase in second/third trimester miscarriages. Therefore, the live birth rates decreased significantly among four BMI groups. The subgroup analysis among individuals with a BMI of ≥28 also revealed no significant difference in the clinical pregnancy rate (Fig. 1D1). However, there was an elevated incidence of miscarriage (Fig. 1E1) and a lower rate of live births (Fig. 1F1) observed specifically among patients with normal BMI.

We also analyzed the clinical outcomes associated target organ damage related to obesity in obese patients (BMI≥28 kg/m^2) in Supplementary Table 1. Compared with group 3 (patients with only one HBP recording in the database) and group 4 (patients with no HBP recordings in the database), patients in group 2 (patients with at least two HBP recordings in the database) had an older age (group 2–4: 33.97 vs. 31.48 vs. 31.58) and thus a lower Day3 AFC (group 2–4: 8.12 vs.11.56 vs.10.93). Regarding oocyte and embryo outcomes, group 2 had fewer retrieved oocytes, mature oocytes, good-quality embryos, and viable embryos; therefore, group 2 had the lowest clinical pregnancy rate (31.9% vs. 52.8% vs. 45.7%) and live birth rate (19.8% vs. 39.2% vs. 31.0%) compared to groups 3 and 4.

The impact of BMI on oocyte, embryo and pregnancy outcomes in women undergoing the PPOS protocol

As shown in Table 3, after adjusting for other confounders using DAG, women with a BMI≥28 showed a negative correction in the number of retrieved oocytes and viable embryos. The negative diversity mainly focuses in 30-34.99 BMI groups (Fig. 1A2-A3, B2-B3, C2-C3). However, the BMI did not have an impact on the number of top-quality embryos. Regarding pregnancy outcomes, the clinical pregnancy rate was not found to be associated with higher BMI after adjustment. However, a high BMI significantly increased the miscarriage rate, mainly in BMI 28-29.99 and BMI 30-34.99 group (Fig. 1E1-E3), and subsequently decreased the live birth rate, mainly in BMI 30-34.99 group (Fig. 1F1-F3). These data suggest that a high BMI may lead to a higher miscarriage rate, particularly in late miscarriage rate; therefore, we further used DAG to determine related covariates and conducted multivariable logistic regression on miscarriage rates.

The potential confounding factors of early and late miscarriage in women during their first FET cycles

Table 4 showed the crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) between miscarriage and potential confounding factors from minimal sufficient adjustment sets using DAG (Supplementary Fig. 1). After conducting univariable and multivariable regression analyses, it was found that the rate of early miscarriage significantly increased with the older age. However, no significant association was observed between the rate of late miscarriage and age, and AFC.

As far as BMI is concerned, the adjusted ORs for BMI≥28 was found to increase the rate of early trimester miscarriage. However, both women with a BMI of 24-27.99 and those with a BMI≥28 both significantly contributed to an increased late abortion rate. Women with a high BMI who receive hormone replacement and hMG late stimulation as endometrial preparation had significantly higher adjusted ORs for both early and late miscarriage rate in their first FET cycles.

Discussion

Our study firstly found the impact of the PPOS protocol on mitigating adverse oocyte outcomes and endometrial receptivity associated with high BMI. We observed no significant differences in good-quality embryos among different BMI groups when utilizing the PPOS protocol. Additionally, there were no difference in clinical pregnancy rate during their first FET cycle. However, a higher BMI was found to increase the risk of miscarriage, particularly in late miscarriage, consequently reducing live birth rates. Implementing appropriate endometrial preparation methods such as natural cycles and letrozole stimulation cycles may prove beneficial in decreasing the incidence of late miscarriages.

Although the oocyte quality or endometrial receptivity has been recognized as the primary factor contributing to impaired fertility in obese individuals for several decades in ART studies [32, 33], there is limited research focusing on the impact of different COH protocols in ameliorating the deleterious oocyte outcomes or endometrial

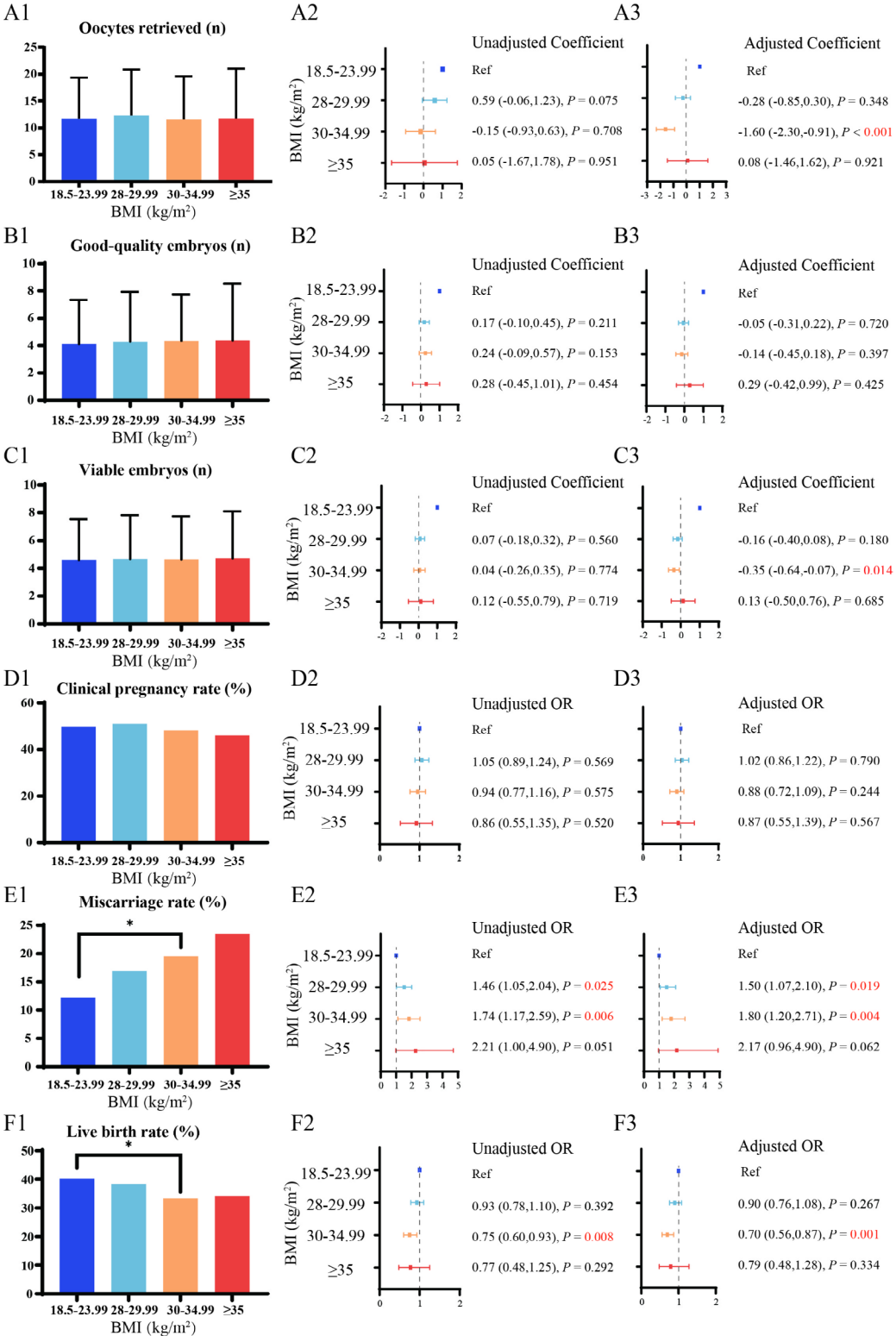

Fig. 1 A sub-analysis of oocytes, embryos, and pregnancy outcomes among obese patients (BMI ≥ 28). It shows the number of oocytes retrieved (**A**1), good-quality embryos (**B**1), and viable embryos (**C**1) for both normal weight patients and different subgroups of obese patients based on BMI ranges of 28-29.99, 30-34.99, and ≥ 35. A2-3, B2-3, and C2-3 present unadjusted coefficients (95% CI) as well as adjusted coefficients (95% CI) for A1, B1, and C1 respectively. The clinical pregnancy rate (**D**1), miscarriage rate (**E**1), and live birth rate (**F**1) among normal weight patients, as well as subgroups of obese patients, are presented. D2-3, E2-3, and F2-3 represent unadjusted coefficients (95% CI) and adjusted coefficients (95% CI) for D1, E1, and F1 respectively

receptivity associated with high BMI. Compared with GnRH (gonadotropin releasing hormone) antagonist protocol, long agonist protocol would benefit in obtaining more oocytes [40]. For high BMI PCOS patients, an ultra-long protocol showed a thicker endometrium and a higher live birth rate compared to a standard long protocol [18].

In this study, we investigate novel findings that indicate an absence of adverse effects on high-quality embryos and the clinical pregnancy rate during the first FET cycles when utilizing the PPOS protocol, even with an increase in female BMI. These results suggest that the PPOS protocol only mitigate the adverse impact of high BMI on embryo outcomes, which is consistent with previous research [25] indicating that BMI does not affect ovarian stimulation outcome in the PPOS protocol. We further investigated the outcomes of patients with metabolic-related diseases resulting from obesity. On one hand, patients with hypertension exhibited advanced age, which could be attributed to the positive correlation between hypertension and aging [41]. This may lead to a decline in subsequent embryonic and pregnancy outcomes due to their lower antral follicle counts (AFCs), although no difference was observed in terms of miscarriage rate. On the other side, previous literature has also demonstrated that even slightly elevated blood pressure levels can result in adverse IVF outcome [42]. Another study showed that an inverse association between prepregnancy hypertension and live birth rate [43]. Our study yielded similar findings; however, a more rigorous assessment would require conducting a prospective study using comprehensive evaluation indicators.However, it is important to note that the PPOS protocol may not mitigate the adverse impact of high BMI on endometrial receptivity. Women with high BMI levels demonstrate significantly higher rates of miscarriage, leading to a decreased live birth rate. Nevertheless, there is potential for ameliorating the negative influence of high BMI on endometrial receptivity through the adoption of a natural cycle or letrozole stimulation protocol for endometrial preparation. Consequently, our findings suggest that incorporating the PPOS protocol during COH and implementing a natural cycle or letrozole stimulation protocol for endometrial preparation could present as a more favorable option for patients with high BMI.

The potential reasons for the elimination of the diverse effect of high BMI on embryos by PPOS may be elucidated as follows. In comparison to down-regulation protocols (such as 2672.8IU in long protocol and 2027.9IU in PPOS [44], 2661.34IU in GnRH-a long protocol and 1944.49IU in PPOS [45], 2700.0IU in ultra-long protocol and 2662.5IU in PPOS [46]), patients utilizing the PPOS protocol do not require a substantial amount of gonadotropin consumption. High BMI patients typically necessitate higher doses of gonadotropin during controlled ovarian stimulation to achieve adequate ovarian response (also shown in Table 1), owing to their larger body surface area [47]. Consequently, high BMI patients using the PPOS protocol could reduce their gonadotropin usage to some extent compared to those using down-regulation protocols. Another plausible explanation is that while down-regulation medications induce robust LH (luteinizing hormone) suppression and significantly lower LH levels in both long and short protocols, the PPOS protocol maintains a certain level of LH (approximately 1.8 IU/L on trigger day [20]) that is higher than that achieved with down-regulation protocols, while simultaneously inhibiting premature LH surges. Due to its minimal impact on suppressing circulating LH levels compared to down-regulation protocols and reduced gonadotropin dosage requirements, obese patients utilizing PPOS-related protocols demonstrate enhanced sensitivity towards gonadotropin stimulation and can achieve comparable embryo quality as normal weight patients.

Even among patients following the PPOS protocol, a higher BMI was still observed to be associated with an increased risk of miscarriage, particularly late miscarriages, which aligns with previous research findings. Bellver et al. [10] demonstrated that obese women exhibited dysregulated genes related to crucial biological processes such as development, morphogenesis, and immune system function in their endometrium. Additionally, Jungheim et al. [34] reviewed that the heightened risk of miscarriage and abnormal intrauterine environment further contributed to impaired reproductive function in individuals with obesity. Given the elevated progesterone levels associated with the PPOS protocol, frozen embryo transfer is adopted allowing patients to choose an optimal time window for transfer; this not only facilitates recovery from ovarian hyperstimulation but also enables adjustment of endometrial thickness to minimize pregnancy loss risks. Consequently, while the role of the PPOS protocol in improving endometrial status is limited in scope.

Importantly, our findings suggest that in comparison to endometrial preparation using natural cycles, women with high BMI who underwent hormone replacement therapy (HRT) protocol and hMG late stimulation protocol exhibited an elevated risk of miscarriage and a reduced live birth rate, whereas the letrozole stimulation protocol did not demonstrate such associations. These results are consistent with a large cohort study where HRT cycle (n=8139) showed significantly lower birth rates than natural cycle (n=3156) and stimulated cycle (n=3156) in frozen embryo transfer [48]. The use of HRT did not promote normal dominant follicle growth, necessitating additional exogenous progesterone due to the lack of corpus luteum formation [49]. Despite the

supplementation of exogenous progesterone, almost one-third of patients in the HRT cycle still displayed inadequate serum progesterone levels [50]. This insufficient progesterone level in the HRT cycle was found to significantly decrease the live birth rate [51], which has been observed in both PCOS patients [52] and non-PCOS patients [53]. Both the letrozole stimulation protocol and hMG late stimulation protocol are categorized as endometrium preparation through stimulation cycles. HMG administration is usually added when follicle growth is slower than in a natural cycle, which may result in subsequent endogenic luteal function defects and an increased risk of miscarriage. However, in the case of letrozole stimulation protocol, letrozole is applied from the early follicular phase, leading to varying effects on miscarriage rates. One potential mechanism for improving reproductive outcomes through the letrozole stimulation protocol is its ability to enhance endometrial receptivity by upregulating uterine receptivity markers such as integrin, leukemia inhibitory factor, and L-selectin [54]. On one hand, the gene expression pattern of endometrium in obese patients differs from that of normal weight patients [55]. On the other hand, obese is associated with irregular menstruation, polycystic disease, increased antral follicle count (AFC), and drug insensitivity, necessitating different methods for endometrial preparation. However, there have been limited studies investigating the impact of various endometrial preparation approaches on obese patients. Therefore, future research should focus on conducting more precise clinical and mechanistic investigations to explore these potential mechanisms.

This study investigates the impact of BMI on embryo and pregnancy outcomes in women using the PPOS protocol. Our findings demonstrate that patients with high BMI achieve comparable numbers of embryos and clinical pregnancies to those with normal BMI when utilizing the PPOS protocol, but exhibit a higher rate of miscarriage in their first FET cycles. Adopting appropriate endometrial preparation methods, such as natural cycles and letrozole stimulation cycles, may effectively reduce the incidence of miscarriages. Overall, our results suggest that combining the PPOS protocol with natural cycles and letrozole stimulation cycles for endometrial preparation could be a more favorable option for patients with high BMI.

However, this is a retrospective study without randomization for analyzing the oocyte and pregnancy outcomes of women adopting PPOS protocol in their first FET. The WHO BMI classification was employed for subanalysis among individuals with high BMI (≥28). However, it is worth noting that there were limited patients in the BMI ≥ 35 group, which may introduce some potential bias. Except for the live birth rate, other perinatal outcomes of women with high BMI in FET need to be explored in the future research, because BMI itself is an independent factor affecting perinatal outcomes [5, 36, 37, 56], such as being overweight or obese was associated with an increased risk of still birth, large for gestational age, macrosomia, admission to the neonatal intensive care unit and low birth weight [36]. In our sub-analysis of ART outcomes associated metabolic-related diseases in obesity, a significant proportion of patients lacked blood lipid level data, which hindered us from making definitive diagnoses of metabolic syndrome. Consequently, we relied solely on reviewing patients' blood pressure information available in our database for analysis purposes. Moving forward in future clinical processes, we aim to conduct comprehensive assessments encompassing these patients. At the same time, this study did not have a control group using other protocols. However, according to previous reports [57], high BMI did have adverse effects on embryo outcomes and clinical pregnancies, especially fresh embryo transfer protocols. Our study showed that this bad effect would be ameliorated by adopting PPOS protocol combined with frozen embryo transfer.

Conclusions

In conclusion, for women adopting PPOS-related protocols, the increasing BMI did not have a detrimental influence on embryo outcomes and clinical pregnancy rate in their first FET cycles; whereas high BMI would lead to higher miscarriage rate (especially late-term) and lower live birth rate. After the logistic regression analyses, proper endometrial preparation (natural cycle and letrozole stimulation cycle) would be beneficial to lower the miscarriage rate. These findings provide the valuable reference for women with high BMI in ART treatment.

Abbreviations

BMI	Body Mass Index
FET	Frozen Embryo Transfer
PPOS	Progestin-Primed Ovarian Stimulation
ART	Assisted Reproductive Technology
COH	Controlled Ovarian Hyperstimulation
PCOS	Polycystic Ovary Syndrome
IVF	In-Vitro Fertilization
ICSI	Intracytoplasmic Sperm Injection
AFC	Antral Follicle Count
ORs	Odds Ratios
CIs	Confidence Intervals
GnRH	Gonadotropin Releasing Hormone
LH	Luteinizing Hormone
HRT	Hormone Replacement Therapy

Supplementary Information

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Supplementary Material 1: **Supplementary Figure 1**. The potential confounding factors of pregnancy outcomes were determined using a direct acyclic graph (DAG).

Supplementary Material 2: **Supplementary Table 1**. Baseline characteristics, IVF/ICSI and pregnancy outcomes of obese.

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Author contributions
Data gathering and analysis were done by XS, ML and YN. Article drafting was done by XS. XS helped to prepare the study and analyze the data. The following individuals participated in ovarian stimulation protocols, oocyte retrieval, IVF/ICSI, embryo transfer, and data collection: YL, TW, JS, KL and HG. The whole study, including its idea, design, execution, and methods was under the supervision of KL and LW. All authors reviewed this paper.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This retrospective study was approved by the ethics committee of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (SH9H-2022-T155-1). This study was in accordance with the Declaration of Helsinki. This is a retrospective and non-interventional study, written informed consent was waived by the Ethics Committee of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine.

Clinical trial number
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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