Preovulation body mass index and pregnancy after first frozen embryo transfer in patients with polycystic ovary syndrome and insulin resistance

Hao Liang, M.D., Ning Li, M.D., and Rong Li, M.D.

The Second Nanning People's Hospital, Nanning City, People's Republic of China

Objective: To examine the association between preovulation body mass index and pregnancy outcomes after frozen embryo transfer in patients with polycystic ovary syndrome with insulin resistance.
Design: This was a single-center, retrospective cohort study.
Patient(s): Women with infertility, diagnosed with polycystic ovary syndrome and insulin resistance, and treated at the Reproductive Medicine Center, Second People's Hospital of Nanning, China, between January 2020 and August 2023, were included.
Exposure: Patients were divided into four groups according to their body mass index (BMI): slim (<18.5 kg/m^2), normal ($18.5\leq$ BMI <24 kg/m^2), overweight ($24\leq$ BMI <28 kg/m^2), or obese (≥ 28 kg/m^2).
Main Outcome Measure(s): The main pregnancy outcomes included rates of embryo implantation, biochemical pregnancy, clinical pregnancy, and ongoing pregnancy.
Result(s): In total, 282 eligible patients were included. A linear association was observed between the BMI and clinical pregnancy outcomes of the first frozen embryo transfer. After accounting for all potential variables, each 1 kg/m^2 increase in BMI was linked to a 2% decrease in the embryo implantation rate, 11% decrease in the frequency of biochemical pregnancy, and 9% decrease in the both clinical and ongoing pregnancy rates.
Conclusion(s): In patients with polycystic ovary syndrome and insulin resistance, a higher BMI was associated with lower rates of embryo implantation, biochemical pregnancy, clinical pregnancy, and ongoing pregnancy. (Fertil Steril® 2025;123:105–14. ©2024 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Body mass index, polycystic ovary syndrome, insulin resistance, frozen-thawed embryo transfer, pregnancy outcome

Polycystic ovary syndrome (PCOS) is a frequent cause of infertility in females, affecting 5%–10% of the population. This syndrome is characterized by menstrual irregularities, obesity, and high levels of androgens. More prevalent during reproductive years, PCOS (1) is a metabolic disorder characterized by endocrine disruption. Its causative factors are complex, and its exact pathogenesis remains unknown (2). Insulin resistance (IR) is a key pathophysiological aspect of PCOS and is strongly associated with its development. Approximately half of the patients with PCOS also exhibit IR, making its treatment a focal point in reproductive research (3, 4). Guo et al. (5) demonstrated that body mass index (BMI) and IR are separate factors that contribute to early miscarriage in young patients with PCOS during their initial embryo transfer cycle. A meta-analysis by Cassar et al. (6) revealed that a high

Received April 4, 2024; revised and accepted August 12, 2024; published online August 16, 2024.
Supported by a research grant (No. Guike AA22096032) from Guangxi Science and Technology Major Project; Supported by research grant (No. Z-A20221165, No. Z20210397, and No. Z-A20221144) from Guangxi Zhuang Autonomous Region Health Department; and Nanning Scientific and Technology Base project (No. 20223050).
Availability of data and materials: Data and materials were sourced from the Center for Reproductive Medicine of the Second People's Hospital of Nanning City, after ethical review and approval for data usage.
Correspondence: Rong Li, M.D., The Second Nanning People's Hospital, Nanning City, People's Republic of China (E-mail: LiRong@sr.gxmu.edu.cn).

Fertil Steril® Vol. 123, No. 1, January 2025 0015-0282

https://doi.org/10.1016/j.fertnstert.2024.08.328

BMI worsens IR in individuals with PCOS. Furthermore, Zhang et al. (7) found that IR tends to increase as BMI increases, suggesting a connection between obesity and IR. Insulin resistance and hyperinsulinemia are frequently observed in women with PCOS and are often associated with obesity. This association between obesity and IR can exacerbate the prevalence of IR in individuals with obesity, creating a mutually reinforcing cycle. Therefore, PCOS and comorbid IR may be associated with poor pregnancy outcomes.

Body mass index is a key factor influencing pregnancy outcomes. Recently, the effect of BMI on assisted reproductive outcomes has received increasing attention. Increased BMI in individuals with PCOS is correlated with a need for high drug doses to induce ovulation during assisted reproductive therapy (8). Additionally, the number of mature oocytes and viable embryos decreases, implying that an elevated BMI negatively affects the success of in vitro fertilization (IVF) procedures (8). Abnormally high BMI in patients with PCOS may reduce embryo quality, causing higher miscarriage rates. Consequently, weight control in patients with PCOS before IVF can improve pregnancy outcomes (9). Zhang et al. (10) found that patients with obesity had lower rates of embryo implantation, clinical pregnancy, and live births than those with normal weight. Patients with obesity also have high rates of early- and mid-term miscarriages.

This study investigated the correlation between BMI and the success of initial frozen-thawed embryo transfer (FET) in women with infertility and PCOS with comorbid IR. This study aimed to explore the relationship between BMI and FET pregnancy outcomes in patients with PCOS and IR.

MATERIALS AND METHODS

Study population

This single-center retrospective cohort study was approved by the Ethics Committee of the Second Nanning People's Hospital (approval number, Y2024215). This study analyzed the data of patients with PCOS who underwent initial FET at the Reproductive Medicine Center of the Second Nanning People's Hospital from January 2020 to August 2023. The inclusion criteria applied to eligible women were: a diagnosis of IR and participation in their first FET-assisted conception cycle. The exclusion criteria were abnormal uterine development (including uni- or bicornuate uterus, uterus didelphys, and mediastinal uterus), a history of recurrent abortion, chromosomal abnormalities in either partner, intimal thickness of <7 mm before transfer, and patient age >40 years. Each pair participating in the study agreed to undergo assisted reproduction treatment therapy by signing a consent form. The study adhered to the principles of the Declaration of Helsinki.

Diagnostic criteria and formulas

Polycystic ovary syndrome was diagnosed using the 2003 Rotterdam criteria, which mandates that two of the following criteria are met: irregular periods and or lack of ovulation, signs of high androgen levels determined either clinically or through laboratory tests, and the presence of ovarian cysts on ultrasound (11).

Insulin resistance was evaluated by calculating the Homeostasis Model Assessment IR (HOMA-IR) index using the formula of HOMA-IR equals fasting blood glucose (mmol/L) multiplied by fasting insulin (mU/mL) divided by 22.5. An HOMA-IR value ≥ 2.69 was classified as IR (12). The Chinese Working Group on Obesity categorized individuals based on their BMI (kg/m^2) as follows: slim, <18.5; normal, $18.5 \leq$ BMI <24; overweight, $24 \leq$ BMI <28; and obese, ≤ 28.

Using the PETER scoring system, cleavage-stage embryos were scored by assessing their morphology, fragmentation, and size (I/II8 or I/II7/9, good; I/II/4/5/6/$\geq$10, fair). The degrees of blastocyst expansion and endocytosis, and the levels of trophectoderm, were scored using the Gardner scoring system (3/4/5AA/AB/BA or 3/4/5BB, good and 3/4/5AC/BC/CA/CB, fair). Embryos rated as good were considered as high-quality. The rate of high-quality embryos was determined by dividing the number of high-quality embryos transferred by the total number of embryos transferred.

Uterus intimal morphology on the day of transfer was classified as follows: For type A, the functional layer of the endometrium appears dark on B-mode ultrasound, whereas the uterine cavity and anterior and posterior basal lines appear as light-colored echoes, thus forming the triple line sign. For type B, the endometrium is homogeneous and moderately echogenic on B-mode ultrasound, with intermittent strong echoes from the uterine cavity line. For type C, the endometrium is homogeneous and hyperechoic on B-mode ultrasound, with the uterine cavity line no longer visible. Endometrium types A–B and B–C exhibit transitional patterns.

Endometrial preparation for the first FET and luteal support after embryo freezing

Natural cycle program. This program involved initiating ultrasound monitoring of follicles on days 10–12 of the menstrual cycle. After ovulation, oral dydrogesterone or vaginal progesterone gel was administered for luteal support. This support facilitates the endometrial transition from the proliferative phase to the secretory phase. All patients underwent FET; therefore, the day of transfer was determined by the patient's embryo type. Cleavage-stage embryos were transferred on the third day after ovulation and blastocysts on the fifth or sixth day after ovulation.

Modified natural cycle program. This program involved administering oral letrozole from the fourth to the fifth days of the menstrual cycle to promote ovulation. Follicular development was monitored for 5 days, and urogonovine was injected if the dominant follicle was <12 mm in diameter. When the dominant follicle reached a diameter of ≥ 18 mm, chorionic gonadotropin was administered intramuscularly. Luteal support was provided from the day of ovulation (see hormone replacement treatment [HRT] section), from which point the endometrium changed from a proliferative to a secretory phase. The type of embryo cultured in vitro

determined the timing of embryo transfer. Cleavage-stage embryos were transferred on day 3 after the phase change and blastocysts on day 5 or 6.

Hormone replacement treatment. Hormone replacement treatment was administered from day 2–3 of natural menstruation or withdrawal bleeding. Estrogen (estradiol valerate) was administered (2 mg twice a day) for 5 days and then increased (3 mg twice a day). Because estrogen use can increase the risk of thrombosis, oral aspirin (50–100 mg once a day) was administered to prevent thrombosis after contraindications to aspirin use were ruled out. After 10–15 days of continuous medication, the condition of the endometrium was monitored using ultrasound, and serum estradiol (E_2) and progesterone levels were measured. When the endometrial thickness was approximately exceeding 7–8 mm and the E_2 level was >200 pg/mL, progesterone conversion was performed using two commonly used methods to move the endometrium from the proliferative to the secretory phase. The first method involved intramuscular injection of progesterone (60 mg/d) combined with oral dydrogesterone tablets (20 mg/d). The second method involved using a sustained-release vaginal progesterone gel (90 mg/d) combined with dydrogesterone tablets (20 mg/d). Both luteal support regimens required oral dydrogesterone, but the choice between intramuscular progesterone or progesterone vaginal gel was made according to the patient's preference, after considering economic and comfort points of view. Depending on the type of embryo cultured in vitro, cleavage-stage embryos were transferred on day 3 after transformation and blastocysts on day 5 or 6 after transformation.

Gonadotropin-releasing hormone agonist combined with HRT. This protocol is often used clinically in patients with PCOS who have a combination of elevated luteinizing hormone to improve the pelvic microenvironment, increase endometrial tolerance, and reduce luteinizing hormone levels. The treatment involved a hormone replacement cycle after leuprolide acetate downregulation. Leuprolide acetate was subcutaneously administered at a full (3.75 mg) or half dose on day 2 of menstruation or 7 days after ovulation was detected on transvaginal ultrasound. On days 20–28, hormone levels and ultrasound were monitored. The downregulation criteria included E_2 levels <50 ng/L, follicle-stimulating hormone (FSH) levels <5 IU/L, luteinizing hormone levels <5 IU/L, and an endometrial thickness <5 mm. When the downregulation criteria were met, estrogen (estradiol valerate) was administered. The remaining procedures were performed as described in the HRT protocol.

Pregnancy outcomes

The pregnancy outcomes examined were the rates of embryo implantation, biochemical pregnancy, clinical pregnancy, and ongoing pregnancy. A biochemical pregnancy (chorionic gonadotropin-positive result) was defined as a peripheral blood chorionic gonadotropin level >25 mIU/mL at 14 days after the embryo transfer. The embryo implantation rate was calculated by dividing the total number of gestational sacs by the total number of embryos transferred and multiplying it by 100%. Clinical pregnancy was defined as the presence of at least one intrauterine gestational sac within 4–5 weeks of transfer. Ectopic pregnancies were excluded from the study. Ongoing pregnancy was defined as pregnancy lasting ≥12 weeks. Miscarriages were categorized as spontaneous abortions before 28 weeks of gestation, including biochemical pregnancies and early or late miscarriages. Luteal support medications were discontinued after 8–10 weeks of pregnancy.

Statistical analysis

Histogram distributions, Q–Q plots, and the Kolmogorov–Smirnov test were used to assess the normality of variables. Normally distributed continuous variables are reported as mean ± standard deviation and skewed continuous variables are reported as medians with interquartile ranges. Categorical variables are presented as frequencies and percentages. Statistical analysis included the χ^2 or Fisher's exact test for categorical variables, one-way analysis of variance for normally distributed variables, and the Kruskal–Wallis H test for skewed variables to examine differences among the four distinct groups.

Linear regression analysis was used to explore the relationship between the BMI and embryo implantation rate. To investigate the association between BMI and biochemical, clinical, and ongoing pregnancies, a multivariate analysis (binary logistic regression) was performed. BMI was entered as a continuous variable (per kg/m^2). Confounding variables were selected based on expert judgment and included all covariates that were significant in the univariate analysis. Potential multicollinearity was assessed using the variance inflation factor, with values ≥5 indicating multicollinearity.

We developed five models for the analysis: model 1 was the crude model; model 2 was adjusted for basal endocrine factors (baseline FSH [bFSH], baseline prolactin [bPRL], baseline progesterone [bProg], baseline E_2 [bE_2], and baseline antimüllerian hormone [bAMH] levels); model 3 was further adjusted for age; model 4 was adjusted for intimal thickness and morphology; and model 5, the primary model, was additionally controlled for the rate of high-quality embryos.

We categorized the BMI into quartiles, tertiles, and quintiles, calculating the *P* for trends to validate the results obtained with BMI treated as a continuous variable and to explore potential nonlinearity. We used a generalized additive model with natural splines (four knots) to examine the nonlinear association between BMI and the embryo implantation rate. To explore the potential nonlinear dose–response relationships between BMI and biochemical, clinical, and ongoing pregnancies, restricted cubic spline models were used to generate smooth curves. Specifically, the BMI was treated as a continuous variable with four knots (5th, 35th, 65th, and 95th percentiles), as recommended by Harrell et al. (13). Nonlinearity was assessed by introducing a quadratic term into the regression models. To observe a nonlinear relationship, a two-piecewise regression model was employed to determine the threshold effect of BMI on the rates of embryo implantation and biochemical, clinical, and ongoing pregnancies using a smoothing plot. Subgroup analyses were performed based on the subgroup variables,

and interactions across subgroups were assessed using the likelihood ratio test.

Missing data for noncore variables were processed using the K-Nearest Neighbor single-weighted interpolation method. A series of sensitivity analyses were performed to assess the robustness of our findings and evaluate how different association inference models impacted our conclusions. The effect sizes and *P*-values from all models were compared. Two-sided *P*-values of $<.05$ were considered statistically significant.

All statistical analyses were conducted using R Statistical Software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org) and the Free Statistics Analysis Platform (version 1.9; Beijing, China, http://www.clinicalscientists.cn/freestatistics).

RESULTS

Baseline characteristics of participants

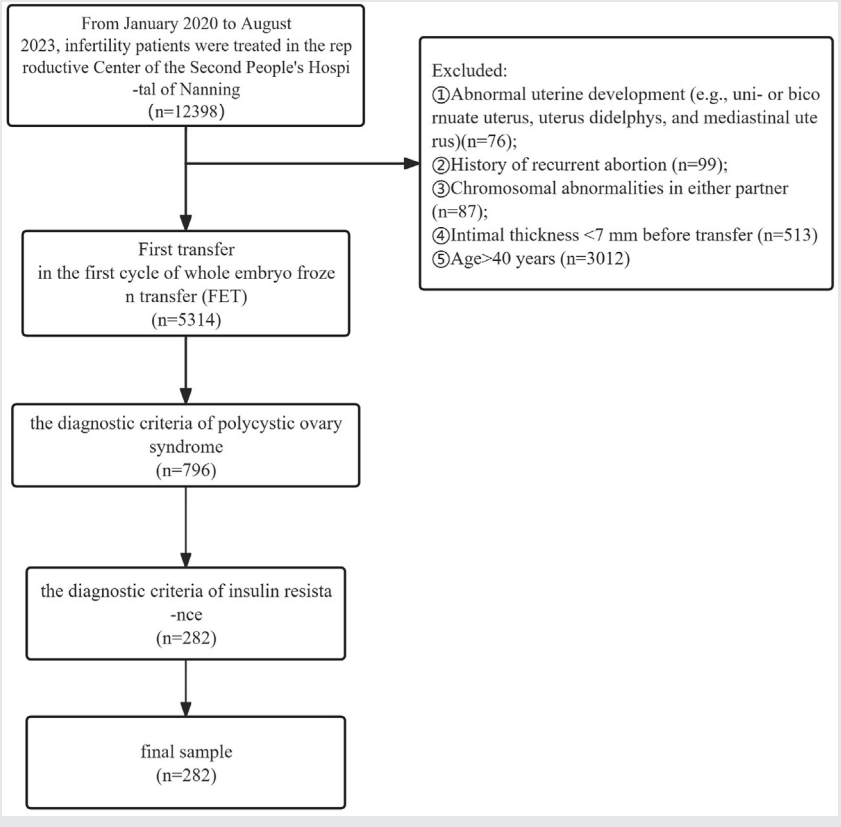
A total of 282 patients met the inclusion criteria, as shown in Figure 1. Table 1 shows the demographic characteristics of the four patient groups. Of these patients with PCOS and IR, 5.3% were slim, 50.4% had a normal BMI, 34.4% were overweight, and 9.9% were obese.

Significant differences were observed in bFSH, bProg, and bPRL levels among patients in the different weight groups. The HRT regimen was used more frequently than the other three endometrial preparation regimens, with an overall usage rate of 66.7%, and a specific usage rate of 86.7% in the slim group, 63.4% in the normal group, 63.3% in the overweight group, and 85.2% in the obese group. Intergroup differences were significant ($P<.05$). The dominant pretransfer endometrial morphology in the four groups was type A, with occurrence rates of 40.4% overall, 60% in the slim group, 44.4% in the normal group, 32.7% in the overweight group, and 37% in the obese group; intergroup differences were significant ($P<.05$). No significant differences were found for age, type of infertility, bE_2 level, bAMH level, endothelial thickness, number of embryos transferred, high-quality embryo rate, embryo implantation rate, number of gestational sacs, number of fetal heartbeats, type of pregnancy, or number of live births (all $P>.05$). Supplemental Table 1 (available online) shows the pregnancy outcomes for each BMI group.

Association between BMI and pregnancy outcomes

Table 2 shows the outcomes of the multivariate linear analysis and logistic correlation analysis regression models, which demonstrate the association between BMI and each clinical pregnancy outcome. On the basis of the univariate and

FIGURE 1



Flow chart of the study cohort.

Liang. BMI's impact on FET in PCOS with IR. Fertil Steril 2025.

TABLE 1

Baseline characteristics of the study population.

Variables	Total (n = 282)	Slim (n = 15)	Normal (n = 142)	Overweight (n = 98)	Obese (n = 27)	P
Age (y), mean ± SD	30.9 ± 3.9	29.4 ± 5.2	30.5 ± 3.7	31.5 ± 4.0	31.7 ± 3.4	.069
Infertility kind, n (%)						.848
Primary	151 (53.5)	9 (60)	73 (51.4)	55 (56.1)	14 (51.9)	—
Secondary	131 (46.5)	6 (40)	69 (48.6)	43 (43.9)	13 (48.1)	—
bFSH, mIU/mL, mean ± SD	4.9 ± 1.9	6.1 ± 1.3	5.1 ± 2.2	4.6 ± 1.6	4.8 ± 0.9	.03
bT, ng/dL, mean ± SD	42.3 ± 16.2	42.3 ± 11.0	41.5 ± 14.5	42.3 ± 15.5	46.4 ± 26.4	.563
bE_2, pg/mL, median (IQR)	30.4 (21.2–39.0)	25.0 (22.5–33.5)	29.0 (21.0–37.0)	31.0 (22.0–41.0)	34.0 (24.5–39.5)	.317
bProg, ng/mL, median (IQR)	0.2 (0.2–0.3)	0.4 (0.3–0.5)	0.2 (0.2–0.4)	0.2 (0.2–0.3)	0.2 (0.1–0.2)	.002
bLH, mIU/mL, median (IQR)	5.0 (3.3–7.3)	7.2 (5.1–9.6)	4.9 (3.3–7.2)	4.7 (3.1–6.8)	5.4 (3.3–7.3)	.068
bPRL, ng/mL, median (IQR)	16.3 (11.4–21.0)	20.4 (15.8–23.8)	17.4 (12.1–23.2)	15.3 (11.6–19.7)	11.1 (8.8–14.8)	< .001
bAMH, ng/mL, median (IQR)	6.4 (5.0–8.8)	6.2 (5.3–8.6)	6.5 (4.9–9.1)	6.9 (5.2–9.0)	5.4 (4.3–6.6)	.061
Superovulation protocol, n (%)						.788
Antagonist regimen	259 (91.8)	15 (100)	133 (93.7)	87 (88.8)	24 (88.9)	—
Luteal phase long program	14 (5.0)	0 (0)	6 (4.2)	6 (6.1)	2 (7.4)	—
Microstimulus	4 (1.4)	0 (0)	2 (1.4)	2 (2)	0 (0)	—
Superlong protocol	3 (1.1)	0 (0)	1 (0.7)	1 (1)	1 (3.7)	—
PPOS	1 (0.4)	0 (0)	0 (0)	1 (1)	0 (0)	—
Luteal phase ovarian stimulation	1 (0.4)	0 (0)	0 (0)	1 (1)	0 (0)	—
Endometrial preparation regimen, n (%)						< .001
HRT	188 (66.7)	13 (86.7)	90 (63.4)	62 (63.3)	23 (85.2)	—
GnRHa+HRT	67 (23.8)	1 (6.7)	46 (32.4)	17 (17.3)	3 (11.1)	—
Modified natural cycle	17 (6.0)	1 (6.7)	3 (2.1)	13 (13.3)	0 (0)	—
Natural cycle	10 (3.5)	0 (0)	3 (2.1)	6 (6.1)	1 (3.7)	—
Intimal thickness (mm), mean ± SD	9.4 ± 1.6	9.5 ± 1.1	9.4 ± 1.3	9.3 ± 1.9	9.8 ± 1.9	.563
Intimal morphology, n (%)						.004
A	114 (40.4)	9 (60)	63 (44.4)	32 (32.7)	10 (37)	—
A–B	83 (29.4)	5 (33.3)	46 (32.4)	28 (28.6)	4 (14.8)	—
B	50 (17.7)	0 (0)	25 (17.6)	21 (21.4)	4 (14.8)	—
B–C	16 (5.7)	0 (0)	3 (2.1)	8 (8.2)	5 (18.5)	—
C	19 (6.7)	1 (6.7)	5 (3.5)	9 (9.2)	4 (14.8)	—
Embryo kind, n (%)						.233
Cleavage embryo	57 (20.2)	2 (13.3)	23 (16.2)	26 (26.5)	6 (22.2)	—
Blastocyst	225 (79.8)	13 (86.7)	119 (83.8)	72 (73.5)	21 (77.8)	—
No. of embryos transferred, mean ± SD	1.3 ± 0.5	1.2 ± 0.4	1.3 ± 0.5	1.3 ± 0.5	1.2 ± 0.4	.484
No. of High-quality embryos, median (IQR)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	0.0 (0.0–1.0)	.002
High-quality embryo rate, median (IQR)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	0.0 (0.0–1.0)	.011

Note: bAMH = baseline antimüllerian hormone; bE_2 = baseline estradiol; bFSH = baseline follicle-stimulating hormone; bLH = baseline luteinizing hormone; BMI = body mass index; bPRL = baseline prolactin; bProg = progesterone; bT = baseline testosterone; HRT = hormone replacement treatment; IQR = interquartile range; PPOS = progestin primed ovarian stimulation.

Liang. BMI's impact on FET in PCOS with IR. Fertil Steril 2025.

clinical experience analyses, five models (models 1–5) were established.

In model 1, the BMI was negatively associated with the rates of embryo implantation (β, −0.02; 95% confidence interval [CI], −0.04 to 0), biochemical pregnancy (odds ratio [OR], 0.92; 95% CI, 0.86–0.99), clinical pregnancy (OR, 0.92; 95% CI, 0.86–0.99), and ongoing pregnancy (OR, 0.91; 95% CI, 084–0.98). A multivariable regression model was used to correct for other possible confounders, including basal endocrine (bFSH, bPRL, bProg, bE_2, and bAMH) levels, age, preimplantation intimal thickness, morphology, high-quality embryo rates, and BMI; the negative correlations with the rates of embryo implantation (β, −0.02; 95% CI, −0.04 to 0), biochemical pregnancy (OR, 0.89; 95% CI, 0.82–0.97), clinical pregnancy (OR, 0.91; 95% CI, 0.84–0.99), and ongoing pregnancy (OR, 0.91; 95% CI, 083–1) remained significant. After adjusting for all factors that may have affected pregnancy outcomes (model 5), each unit increase in BMI was associated with a 2% decrease in the embryo implantation rate ($P < .05$), an 11% decrease in the biochemical pregnancy rate ($P < .05$), and a 9% decrease in both the clinical ($P < .05$) and ongoing ($P > .05$) pregnancy rates (Table 2).

The results of model 5 demonstrated an association between the BMI and the rates of embryo implantation (Fig. 2A), biochemical pregnancy (Fig. 2B), clinical pregnancy (Fig. 2C), and ongoing pregnancy (Fig. 2D); all had negative

TABLE 2

Logistic or linear multivariate analysis of pregnancy outcomes and body mass index (n = 282).

		Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	n.event %	95% CI	*P*	95% CI	*P*	95% CI	*P*	95% CI	*P*	95% CI	*P*
Embryo implantation rate	—	−0.02 (−0.04 to 0)	.037	−0.02 (−0.04 to 0)	.045	−0.02 (−0.04 to 0)	.037	−0.02 (−0.04 to 0)	.034	−0.02 (−0.04 to 0)	.045
Biochemical pregnancy	152 (53.9)	0.92 (0.86–0.99)	.022	0.89 (0.82–0.97)	.005	0.89 (0.82–0.96)	.004	0.89 (0.82–0.97)	.008	0.89 (0.82–0.97)	.009
Clinical pregnancy	128 (45.4)	0.92 (0.86–0.99)	.031	0.92 (0.86–1)	.04	0.92 (0.85–0.99)	.036	0.91 (0.84–0.99)	.032	0.91 (0.84–0.99)	.033
Ongoing pregnancy	95 (33.7)	0.91 (0.84–0.98)	.013	0.9 (0.82–0.98)	.017	0.9 (0.82–0.98)	.017	0.91 (0.83–1)	.043	0.91 (0.83–1)	.062

Note: Model 1: crude model. Model 2: adjusted for basal endocrine (bFSH, bPRL, bProg, bE_2, and bAMH). Model 3: adjusted for Model 2 + age. Model 4: adjusted for Model 3 + intimal thickness + intimal morphology. Model 5: adjusted for Model 4 + high-quality embryos rate. Linear multivariate analysis was used for embryo implantation rates in the table, and the effect value was *β*. Biochemical pregnancy, clinical pregnancy, and ongoing pregnancy were analyzed using logical multivariate analysis, and the effect value was OR. bAMH = baseline antimüllerian hormone; bE_2 = baseline estradiol; bFSH = baseline follicle-stimulating hormone; bPRL = baseline prolactin; bProg = progesterone; CI = confidence interval; OR = odds ratio.

linear associations (*P* for nonlinearity >.05). Supplemental Tables 2–5 present the results of the multivariable analysis of the association between categorical BMI and individual pregnancy outcomes, from which the trends in the parameter estimates for categorical BMI were generally consistent with the linear test of curve fitting.

Subgroups analyses

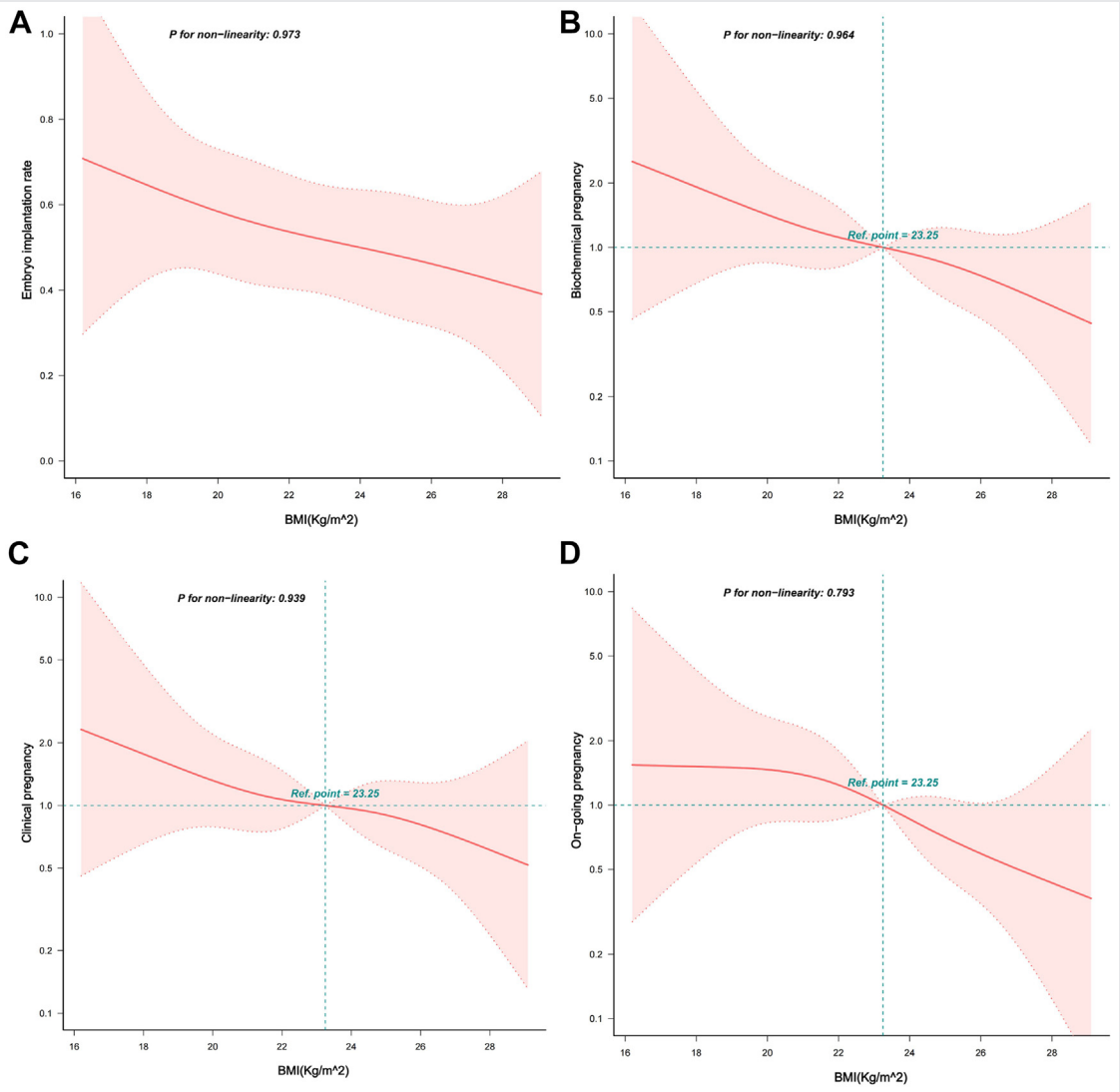
On the basis of model 5, Supplemental Figures 1A–D (available online) show the forest plots of the subgroup analysis of the associations between BMI and the rates of embryo implantation, biochemical pregnancy, clinical pregnancy, and ongoing pregnancy. These associations were stable across subgroups defined by age, infertility type, and embryo type (all *P*>.05).

DISCUSSION

This study investigated the association between BMI and pregnancy outcomes after FET. This retrospective study analyzed the pregnancy outcomes in 282 women with PCOS and comorbid IR who were infertile and underwent FET. The results showed that BMI was negatively correlated with the rates of embryo implantation, biochemical pregnancy, clinical pregnancy, and ongoing pregnancy, and all rates decreased as BMI increased. On the basis of clinical experience and univariate analysis, this study considered the confounding factors that may affect the pregnancy outcomes of FET and used a five-model multivariate analysis, gradually adding each confounding factor to the analysis to elucidate the effect of each confounding factor on the correlation between the BMI and each pregnancy outcome. According to our findings, the effect values did not vary appreciably between models, indicating that the relationship between the BMI and each pregnancy outcome was not significantly affected by the confounders, that is, the BMI independently affected each of the four pregnancy outcomes. Moreover, the interaction between subgroups was also assessed to explore any differences in the effect values between the three subgroups of age, infertility type, and embryo type; no differences were observed (*P*>.05). This indicates that the relationship between the BMI and each pregnancy outcome is not affected by these subgroups, further supporting the stability of the findings.

Patients with PCOS and high BMIs require high doses of medications to induce ovulation during treatment, resulting in fewer mature oocytes and euploid embryos. Therefore, a high BMI can be detrimental to IVF success rates (8). A meta-analysis by Cassar et al. (6) showed that an increase in BMI can directly aggravate the degree of IR in patients with PCOS. An increase in visceral fat can lead to high insulin levels and IR, indicating a correlation between obesity and IR in individuals with PCOS (14). According to Zhang et al. (7), IR gradually increases as the BMI increases, suggesting a potential link between obesity and IR. Patients with PCOS show a strong association between IR levels and success rates of IVF and embryo transfer treatment, including fertilization, miscarriage, and continuation rates (15). Body mass index plays a crucial role in determining pregnancy outcomes,

FIGURE 2



(**A**) Curve fitting BMI in relation to embryo implantation rate (*P* for nonlinearity >.05). (**B**) Curve fitting BMI in relation to biochemical pregnancy (*P* for nonlinearity >.05). (**C**) Curve fitting BMI in relation to clinical pregnancy (*P* for nonlinearity >.05). (**D**) Curve fitting BMI in relation to ongoing pregnancy (*P* for nonlinearity >.05). It presents spline plots illustrating the relationship between BMI levels and embryo implantation rate, restricted cubic spline plots illustrating the relationship between BMI levels and biochemical pregnancy, clinical pregnancy, and ongoing pregnancy, after adjustment for covariates (bFSH, bPRL, bProg, bE_2, bAMH, age, Intimal thickness, intimal morphology, high-quality embryos rate). The prominent central lines represent the estimated adjusted ORs, accompanied by shaded ribbons indicating the 95% CIs. The horizontal dotted lines represent an OR of 1.0 (reference point). The reference point was established at the median BMI level (23.25 kg/m^2). Notably, there is considerable variation in the 95% CIs at the extremes due to limited patient numbers and the cubic fit. Only 95% of the data were shown. bAMH = antimüllerian hormone; bE_2 = baseline estradiol; bFSH = baseline follicle-stimulating hormone; BMI = body mass index; bPRL = baseline prolactin; bProg = progesterone; CI = confidence interval; OR = odds ratio.

Liang. BMI's impact on FET in PCOS with IR. Fertil Steril 2025.

and obesity is linked to higher rates of pregnancy issues such as preterm labor, cesarean delivery, and neonatal asphyxia (16, 17). Zhang et al. (10) found that patients who were obese had lower rates of embryo implantation, clinical pregnancy, and live births than patients who had a normal weight; the rates of early- and mid-term miscarriage were higher. Obesity-related metabolic disorders, such as abnormal glucose metabolism and IR, may affect endometrial tolerance, resulting in implantation failure and recurrent miscarriages. Nevertheless, being overweight or obese does not reduce the chances of successful implantation and live birth during single blastocyst transfer FET cycles nor does it increase the likelihood of miscarriage (18). Xiaoqing et al. (19) discovered that patients with PCOS who were overweight and or obese had

notably higher rates of preterm labor, cesarean section, and miscarriage, whereas the embryo implantation, clinical pregnancy, live birth, and neonatal birth weight rates were not significantly different.

Progesterone dose is another factor that might be associated with the reduced pregnancy outcomes observed with increasing weight. If progesterone levels are low in individuals living with obesity and or overweight (20, 21), the pregnancy rates – including those for pregnancies from FET – are reduced (22). Women with higher BMIs have lower progesterone levels (23), which may be due to the distribution volume (24). Patients with obesity who receive injections have lower progesterone levels because of failure to deliver the medication into the muscle (25). The possibility of lower progesterone levels in the luteal phase is indirectly supported by the lower ongoing pregnancy rate observed in the unadjusted data ($P=.053$), which approached statistical significance. Thus, based on the data presented, the possibility of lower progesterone levels in the luteal phase appears to be a limitation of the present study.

The pathomechanism of PCOS-related infertility may be the progressive arrest of most follicles at any stage during the follicular development cycle in PCOS. The disrupted development of hair follicles is caused by high levels of androgens, insulin, IR, reactive oxygen species, and inflammatory cytokines found in individuals with obesity (26). Insulin promotes PCOS through the phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) signaling pathways. The presence of strongly bound insulin receptors on human follicular membranes indicates that insulin may play a direct role in important physiological processes in follicular membrane cells (26). Reduced glucose transporter-4 (GLUT-4) levels (27) can lead to defects in downstream signaling pathways, potentially causing IR. Insulin resistance affects endometrial growth by causing abnormal protein expression linked to cell growth in the endometrial tissue (15). Transcriptomic analysis has revealed notable changes in gene activity in the endometrium during the implantation period in women with infertility who are obese compared with those in women with infertility who are of normal weight. These changes can adversely affect pregnancy outcomes in patients with obesity (28). Women who are overweight have a higher likelihood of stromal metaplasia in the endometrium, which can lead to issues with embryo implantation and affect placental development (29). Gateva et al. (30) found that patients with PCOS but without obesity tended to have lower levels of peroxiredoxin 4 than those with PCOS and obesity; however, patients with obesity have significantly higher levels of abdominal peroxiredoxin 4. Obesity is characterized by widespread and specific fat cell formation, elevated cholesterol levels, and fat buildup, resulting in inflammation, oxidative stress, and ovarian dysfunction (31). Diminished fertility is partially due to low-quality oocytes. Central obesity results in fewer recycled oocytes than noncentral obesity (32). Obesity significantly impacts the expression of SIRT7 (Sirtuins7) in oocytes, leading to changes in the developmental potential of early embryos through the regulation of meiosis and oxidative stress (33). Individuals who are obese show decreased levels of TP53-induced glycolysis and apoptosis regulator, leading to negative effects on meiotic progression. This is possibly due to reactive oxygen species (34).

This study had limitations. First, the sample size was small; future studies should consider expanding the sample size to obtain more conclusive results. Second, this study was retrospective, and the results should be confirmed in randomized controlled trials. Endometrial preparation varied greatly among the participants ($P<.001$), which might have contributed to the outcomes observed. Insulin resistance is significant at HbA1c (glycated hemoglobin A1c) levels of 6.5%–10.0%, a level related to decreased glucose availability, decreased glycogen synthesis, and insulin defects (35). However, this study did not examine HbA1c levels in patients with PCOS and IR; future studies should focus on HbA1c levels in this patient population.

CONCLUSION

This study examined the association between BMI and FET outcomes in women with PCOS and IR who were infertile. The results showed that a higher BMI in these patients was associated with reduced rates of embryo implantation, biochemical pregnancy, and clinical pregnancy. The BMI was also negatively correlated with ongoing pregnancy but was influenced by the high-quality embryo rate. The findings of the present study could help clinicians provide targeted clinical pregnancy programs for this patient population.

Acknowledgments

The authors gratefully thank Jie Liu, M.D., of the Department of Vascular and Endovascular Surgery at the General Hospital of the Chinese People's Liberation Army for providing statistical data and study design consultation. The authors would also like to thank Haibo Li, M.D., for the statistical methods consultation. The authors also thank Yihua Yang, M.D., from the Reproductive Center of the First Affiliated Hospital of Guangxi Medical University for providing advice on refining the details.

CRediT Authorship Contribution Statement

Hao Liang: Conceptualization, Data curation, Formal analysis, Investigation. Ning Li: Writing – original draft, Writing – review & editing. Rong Li: Writing – review & editing.

Declaration of Interests

H.L. has nothing to disclose. N.L. has nothing to disclose. R.L. has nothing to disclose.

REFERENCES

1. Behboudi-Gandevani S, Amiri M, Cheraghi L, Amanollahi Soudmand S, Azizi F, Ramezani Tehrani F. The risk of chronic kidney disease among women with polycystic ovary syndrome: a long-term population-based cohort study. Clin Endocrinol (Oxf) 2020;93:590–7.
2. Shi S, Hong T, Jiang F, Zhuang Y, Chen L, Huang X. Letrozole and human menopausal gonadotropin for ovulation induction in clomiphene resistance polycystic ovary syndrome patients: a randomized controlled study. Medicine 2020;99:e18383.
3. Abuelezz NZ, Shabana ME, Abdel-Mageed HM, Rashed L, Morcos GNB. Nanocurcumin alleviates insulin resistance and pancreatic deficits in

polycystic ovary syndrome rats: insights on PI3K/AkT/mTOR and TNF-α modulations. Life Sci 2020;256:118003.
4. Ying L, Peihong L, Ling G, Ning T, Jing S, Yi C. Effect of pre-pregnancy body mass index on hypertensive disorders in pregnancy in patients with polycystic ovary syndrome. China Fam Plan Obstet Gynaecol 2020;12:41–4.
5. Guo J, Chen Y, Jiang Y, Zhang C. Effects of body mass index and insulin resistance on first-time assisted conception and perinatal outcomes in young polycystic ovary syndrome patients. Front Endocrinol 2023;14:1170816.
6. Cassar S, Misso ML, Hopkins WG, Shaw CS, Teede HJ, Stepto NK. Insulin resistance in polycystic ovary syndrome: a systematic review and meta-analysis of euglycaemic–hyperinsulinaemic clamp studies. Hum Reprod 2016;31:2619–31.
7. Zhang JD, Liu ZH. Effect of body mass index on the outcome of ovulation-promoting pregnancy in patients with polycystic ovary syndrome. Hebei Med 2022;44:249–52.
8. Shalom-Paz E, Marzal A, Wiser A, Almog B, Reinblatt S, Tulandi T, et al. Effects of different body mass indices on in vitro maturation in women with polycystic ovaries. Fertil Steril 2011;96:336–9.
9. Haixia J, Aixiang L, Wenyan S, Gang L, Shanjun D, Yingpu S. Impact of body mass index on clinical outcomes in fresh and first frozen-thawed embryo transfer cycles. Chin J Reprod Contracept 2019;39:357–64.
10. Zhang J, Liu H, Mao X, Chen Q, Fan Y, Xiao Y, et al. Effect of body mass index on pregnancy outcomes in a freeze-all policy: an analysis of 22,043 first autologous frozen-thawed embryo transfer cycles in China. BMC Med 2019;17:114.
11. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81:19–25.
12. Yiyuan M, Qingzhen X. Inflammatory mechanisms of polycystic ovary syndrome combined with metabolic disorders. China Fam Plan Obstet Gynaecol 2021;13:20–3.
13. Harrell FE, Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modelling strategies for improved prognostic prediction. Stat Med 1984;3:143–52.
14. Carmina E, Bucchieri S, Esposito A, Del Puente A, Mansueto P, Orio F, et al. Abdominal fat quantity and distribution in women with polycystic ovary syndrome and extent of its relation to insulin resistance. J Clin Endocrinol Metab 2007;92:2500–5.
15. Ling XU, Rui X, Zhi-Hong N, Qin-Fen Z, Qin SHI. Analysis of clinical outcomes of in vitro fertilisation-embryo transfer in patients with polycystic ovary syndrome with different levels of insulin resistance. Chin J Eugen Genet 2018;26:111–4.
16. Zhu AH, Ye Q. Clinical analysis of pregnancy complications and pregnancy outcomes in obese pregnant women. J Pract Gynaecol Endocrinol (Electron Ed) 2016;3:66–7.
17. Rich-Edwards JW, Spiegelman D, Garland M, Hertzmark E, Hunter DJ, Colditz GA, et al. physical activity, body mass index, and ovulatory disorder infertility. Epidemiology 2002;13:184–90.
18. Ma L, Dong J, Xia M, Meng H, Ma X, Diao F, et al. Effect of female body mass index on pregnancy outcomes in frozen-thawed embryo transfer cycles during IVF cycles. J Reprod Med 2020;29:803–7.
19. Xiaoqing L, Yongmei Z, Chenning L, Li T, Yan S. Influence of body mass index on pregnancy outcome of first freeze-thawed embryo transfer in patients with polycystic ovary syndrome. Gynaecol Genet (Electron Version) 2022;12:20–4.
20. Thomsen LH, Kesmodel US, Erb K, Bungum L, Pedersen D, Hauge B, et al. The impact of luteal serum progesterone levels on live birth rates-a prospective study of 602 IVF/ICSI cycles. Hum Reprod 2018;33:1506–16.
21. Yovich JL, Conceicao JL, Stanger JD, Hinchliffe PM, Keane KN. Mid-luteal serum progesterone concentrations govern implantation rates for cryopreserved embryo transfers conducted under hormone replacement. Reprod BioMed Online 2015;31:180–91.
22. Whynott RM, Summers KM, Jakubiak M, Van Voorhis BJ, Mejia RB. The effect of weight and body mass index on serum progesterone values and live birth rate in cryopreserved in vitro fertilization cycles. F S Rep 2021;2:195–200.
23. Shen Z, Luo X, Xu J, Jiang Y, Chen W, Yang Q, et al. Effect of BMI on the value of serum progesterone to predict clinical pregnancy outcome in IVF/ICSI cycles: a retrospective cohort study. Front Endocrinol 2023;14:1162302.
24. Brady PC, Kaser DJ, Ginsburg ES, Ashby RK, Missmer SA, Correia KF, et al. Serum progesterone concentration on day of embryo transfer in donor oocyte cycles. J Assist Reprod Genet 2014;31:569–75.
25. Shah DK, Missmer SA, Correia KFB, Ginsburg ES. Pharmacokinetics of human chorionic gonadotropin injection in obese and normal-weight women. J Clin Endocrinol Metab 2014;99:1314–21.
26. Zeng X, Xie Y, Liu Y, Long S, Mo Z. Polycystic ovarian syndrome: correlation between hyperandrogenism, insulin resistance and obesity. Clin Chim Acta 2020;502:214–21.
27. Ciaraldi TP, Morales AJ, Hickman MG, Odom-Ford R, Olefsky JM, Yen SSC. Cellular insulin resistance in adipocytes from obese polycystic ovary syndrome subjects involves adenosine modulation of insulin sensitivity. J Clin Endocrinol Metab 1997;82:1421–5.
28. Comstock IA, Diaz-Gimeno P, Cabanillas S, Bellver J, Sebastian-Leon P, Shah M, et al. Does an increased body mass index affect endometrial gene expression patterns in infertile patients? A functional genomics analysis. Fertil Steril 2017;107:740–8.e2.
29. Rhee JS, Saben JL, Mayer AL, Schulte MB, Asghar Z, Stephens C, et al. Diet-induced obesity impairs endometrial stromal cell decidualization: a potential role for impaired autophagy. Hum Reprod 2016;31:1315–26.
30. Gateva AT, Velikova TV, Kamenov ZA. Peroxiredoxin 4 levels in patients with PCOS and/or obesity. J Gynecol Obstet Hum Reprod 2019;48:739–43.
31. De Araújo JFP, Podratz PL, Sena GC, Merlo E, Freitas-Lima LC, Ayub JGM, et al. The obesogen tributyltin induces abnormal ovarian adipogenesis in adult female rats. Toxicol Lett 2018;295:99–114.
32. Li Y, Lin H, Pan P, Yang D, Zhang Q. Impact of central obesity on women with polycystic ovary syndrome undergoing in vitro fertilization. BioResearch Open Access 2018;7:116–22.
33. Gao M, Li X, He Y, Han L, Qiu D, Ling L, et al. SIRT7 functions in redox homeostasis and cytoskeletal organization during oocyte maturation. FASEB J 2018;32:6228–38.
34. Wang H, Cheng Q, Li X, Hu F, Han L, Zhang H, et al. Loss of TIGAR induces oxidative stress and meiotic defects in oocytes from obese mice. Mol Cell Proteomics 2018;17:1354–64.
35. Xijian L, Fulian W, Ze Congji Z, Bam LY, Tongjun T. Glycosylated haemoglobin and islet function level changes in diabetes mellitus. Int J Lab Med 2019;40:2546–50.

Indice de masa corporal preovulatorio y embarazo tras la primera transferencia transferencia de embriones congelados ovario poliquístico y resistencia a la insulina

Objetivo: Examinar la asociación entre el índice de masa corporal preovulatorio y los resultados del embarazo tras la transferencia de embriones congelados en pacientes con síndrome de ovario poliquístico con resistencia a la insulina.

Diseño: Se trata de un estudio de cohortes retrospectivo de un solo centro.

Entorno: No aplicable.

Paciente(s): Mujeres con infertilidad, diagnosticadas con síndrome de ovario poliquístico y resistencia a la insulina, y tratadas en el Centro de Medicina Reproductiva del Segundo Hospital Popular de Nanning, China, entre enero de 2020 y agosto de 2023.

Intervención(es): Las pacientes se dividieron en cuatro grupos según su índice de masa corporal (IMC): delgada (<18,5 kg/m2), normal (18,5IMC <24 kg/m2), sobrepeso (24% IMC <28 kg/m2), u obesidad (R28 kg/m2).

Medida(s) principal(es) de desenlace: Los principales desenlaces de embarazo incluyeron tasas de implantación embrionaria, embarazo bioquímico, embarazo clínico y embarazo en curso.

Resultados: En total, se incluyeron 282 pacientes elegibles. Se observó una asociación lineal entre el IMC y los resultados clínicos del embarazo de la primera transferencia de embriones congelados. Tras tener en cuenta todas las variables potenciales, cada aumento de 1 kg/m2 en el IMC se relacionó con una disminución del 2% en la implantación embrionaria., una disminución del 11% en la tasa de fecundación in vitro y una reducción del 10% en la tasa de embarazo, un 11% en la frecuencia de embarazo bioquímico y un 9% en las tasas de embarazo clínico y embarazo en curso.

Conclusiones: En pacientes con síndrome de ovario poliquístico y resistencia a la insulina, un mayor IMC se asoció con menores tasas de implantación embrionaria, embarazo bioquímico, embarazo clínico y embarazo en curso.