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Clinical Research Article

Effects of Metabolic Syndrome on Pregnancy Outcomes in Women Without Polycystic Ovary Syndrome

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Abstract

Context: Metabolic syndrome (MetS) is a cluster of metabolic risk factors that predict cardiovascular disease. Previous studies suggested that MetS impaired clinical outcomes in women with polycystic ovary syndrome (PCOS) undergoing in vitro fertilization (IVF).

Objective: To evaluate the effects of MetS on IVF/intracytoplasmic sperm injection (ICSI) outcomes in women without PCOS.

Methods: This retrospective study collected 8539 eligible women without PCOS who came for their first cycle of IVF/ICSI to the Institute of Women, Children and Reproductive Health, Shandong University, from 2017 to 2020, including 1147 subjects in the MetS group and 7392 in the control group. The primary outcome was live birth. Secondary outcomes included other pregnancy outcomes and the risk of maternal and neonatal complications.

Results: Women in the MetS group had a lower live birth rate (50.6% vs 54.9%, adjusted odds ratio [aOR] 0.87, 95% CI 0.75-1.00, $P = .045$) and higher risks of late miscarriage (5.8% vs 3.3%, aOR 1.52, 95% CI 1.02-2.27, $P = .041$), gestational diabetes mellitus (13.7% vs 7.0%, aOR 1.84, 95% CI 1.30-2.60, $P = .001$), hypertensive disorder of pregnancy (7.8% vs 3.5%, aOR 1.79, 95% CI 1.14-2.83, $P = .012$), and preterm birth (9.0% vs 4.4%, aOR 2.03, 95% CI 1.33-3.08, $P = .001$). Singleton newborns in the MetS group were at higher risk of large for gestational age (33.3% vs 20.5%, aOR 1.66, 95% CI (1.31-2.13), $P < .001$) but at lower risk of small for gestational age (2.7% vs 6.2%, aOR 0.48, 95% CI 0.25-0.90, $P = .023$).

Conclusion: MetS was associated with adverse IVF/ICSI outcomes in women without PCOS.

Key Words: metabolic syndrome, in vitro fertilization-embryo transfer, pregnancy outcomes, maternal and neonatal complications, live birth rate

Abbreviations: AMH, antimüllerian hormone; aOR, adjusted odds ratio; ART, assisted reproductive technology; BMI, body mass index; BP, blood pressure; COH, controlled ovarian hyperstimulation; E2, estradiol; FPG, fasting plasma glucose; FSH, follicle-stimulating hormone; GDM, gestational diabetes mellitus; GnRH, gonadotrophin-releasing hormone; HDL-C, high-density lipoprotein-cholesterol; HDP, hypertensive disorder of pregnancy; HOMA-IR, homeostasis model assessment of insulin resistance; ICSI, intracytoplasmic sperm injection; IR, insulin resistance; IVF-ET, in vitro fertilization and embryo transfer; LDL-C, low-density lipoprotein cholesterol; LGA, large for gestational age; LH, luteinizing hormone; MetS, metabolic syndrome; PCOS, polycystic ovary syndrome; PN, pronuclei; SGA, small for gestational age; TG, triglyceride.

Metabolic syndrome (MetS) is a constellation of metabolic abnormalities that predict cardiovascular disease and type 2 diabetes mellitus [1-3]. These metabolic abnormalities include obesity, elevated plasma glucose, dyslipidemia, and hypertension [1]. Although the prevalence of MetS varies among different regions and ethnic groups and is also influenced by gender and age [4], the global trend of increasing prevalence of MetS has become a public health issue [4]. In China, the prevalence of MetS in residents aged 20 years or older increased from 13.7% in 2001 to 31.1% in 2015-2017 [5]. For Chinese reproductive aged women, the prevalence of MetS is over 10% [6]. Meanwhile, several recent studies showed that MetS was associated with infertility in women [7-9].

In vitro fertilization and embryo transfer (IVF-ET), as the main kind of assisted reproductive technology (ART), has been used for treating infertility for more than 40 years since

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the birth of Louise Brown in the UK in 1978 [10]. Although some risk factors that could affect the outcomes of ART are yet to be illustrated, studies have proved that individual MetS components contribute to poorer ART outcomes [11-17]. A large retrospective study in China suggested that dyslipidemia was negatively associated with live birth rate in patients following IVF/intracytoplasmic sperm injection (ICSI)-ET [11]. A prospective observational cohort study showed that high blood pressure (BP) affected live birth rate negatively in women undergoing fresh embryo transfer [12]. Obesity has been deduced to compromise female fertility [13-16]. Wei et al found that preconception impaired glucose tolerance impaired pregnancy outcomes in ART [17].

Since MetS is more prevalent among women with polycystic ovary syndrome (PCOS) [6], some studies have evaluated the effect of MetS on IVF outcomes in women with PCOS, indicating that MetS impacts ovulation and pregnancy outcomes negatively in women with PCOS [18-21]. Besides, MetS during pregnancy has been reported to aggravate the development of pregnancy-related complications, such as preterm birth, gestational diabetes mellitus (GDM), and preeclampsia [22-24].

Given that the prevalence of MetS in women without PCOS of reproductive age in China is also over 10% [6], to demonstrate whether MetS impairs pregnancy outcomes and increases the risk of maternal and neonatal complications in IVF/ICSI-ET in women without PCOS is also crucial. To the best of our knowledge, no large-scale study has reported the effect of MetS on pregnancy outcomes in women without PCOS who underwent IVF/ICSI. Hence, in this retrospective study, we aimed to explore the effects of MetS on IVF/ICSI-ET outcomes and maternal and neonatal complications in infertile women without PCOS.

Methods and Materials

Study Design and Subjects

This retrospective study included patients who received their first cycle of IVF/ICSI-ET at the Institute of Women, Children and Reproductive Health, Shandong University, from February 2017 to February 2020. The study received ethics approval from the independent ethics committee of the Institute of Women, Children and Reproductive Health, Shandong University. Informed consent was obtained from the subjects.

Requirements for inclusion in this study were infertile women (1) aged 20 to 34 years and (2) weighing more than 40 kg. A woman with any of the following was excluded: (1) history of unilateral oophorectomy; (2) uterine abnormality (eg, abnormal uterine anatomy, adenomyosis, untreated submucous myoma, intrauterine adhesion); (3) recurrent spontaneous abortion or recurrent implantation failure; (4) abnormal parental karyotype; (5) diagnosis of PCOS, according to the modified Rotterdam criteria [25]: menstrual abnormalities combined with hyperandrogenism and (or) polycystic ovaries (defined as either an ovary with 12 or more follicles measuring 2-9 mm in diameter and/or ovarian volume >10 mL on ultrasonography), as validated in Chinese population [26] (medical history including menstrual history and whether hirsutism exists was recorded in detail in the medical records and a transvaginal ultrasonography evaluating the ovaries was performed before the start of IVF/ICSI; women who met the criteria above were excluded); (6) contraindications to IVF procedures or pregnancy (eg, hypertension, diabetes, renal disease, history of thrombosis, severe anemia, undiagnosed liver disease or dysfunction, history of malignant tumor); (7) donor oocyte or spermatozoa; and (8) lack of data for the diagnosis of MetS.

Study Procedures

The subjects were divided into the MetS group and the control group based on the clinical diagnosis of MetS [1], with the exception that body mass index (BMI) was used as a surrogate for waist circumference considering that waist circumference was not measured in clinical practice and that BMI correlates well with MetS and waist circumference [27-29]. BMI was applied to diagnose MetS as a surrogate of waist circumference when subjects were in their second trimester of pregnancy [23] and the waist circumference had not been measured [30, 31] previously. Many studies have found that the cutoffs of BMI for the screening of MetS and abdominal visceral obesity in Chinese people were around 25 kg/m^2 [28, 32, 33], and a BMI ≥25 kg/m^2 predicts cardiometabolic risk well [34, 35]. Therefore, we set BMI ≥25 kg/m^2, which was also recommended as the criterion for obesity in the diagnosis of MetS by Chinese diabetes society in 2004 [36], for the diagnosis of MetS as an appropriate criterion for obesity. MetS was diagnosed with 3 or more of the following criteria: (1) BMI ≥25 kg/m^2, (2) triglyceride (TG) ≥1.7 mmol/L (150 mg/dL) or drug treatment for elevated TG, (3) high-density lipoprotein-cholesterol (HDL-C) ≤1.29 mmol/L (50 mg/dL) or drug treatment for reduced HDL-C, (4) systolic BP ≥130 mmHg and/or diastolic BP ≥85 mmHg, and (5) fasting plasma glucose (FPG) ≥5.6 mmol/L (100 mg/dL) or glucose-lowering drug treatment for diabetes or prediabetes (including impaired fasting glycemia and impaired glucose tolerance).

Height, weight, and BP were measured at the first visit to the hospital. TG, HDL-C, total cholesterol, and low-density lipoprotein cholesterol (LDL-C) were determined by colorimetric assay (TG, Roche catalog # 05171407190; HDL-C, Roche catalog # 07528582190; total cholesterol, Roche catalog # 05168538190; LDL-C, Roche catalog # 07005768190) and FPG was determined by the hexokinase method (Roche catalog # 05168791188) before ovarian stimulation. A transvaginal ultrasonography was performed to record antral follicle count in both ovaries on days 1 to 3 of the menstrual cycle; basal hormones, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), progesterone, and total testosterone were detected by electrochemiluminescence immunoassay (FSH, Roche catalog # 07027346190, RRID: AB_2920600; LH, Roche catalog # 07027575190, RRID: AB_2920601; E2, Roche catalog # 07027249190, RRID: AB_2920599; progesterone, Roche catalog # 07027699190, RRID:AB_2923086; testosterone, Roche catalog # 07027 915190, RRID:AB_3101983) simultaneously. Antimüllerian hormone (AMH) was measured by ultrasensitive enzyme-linked immunosorbent assay (Ansh Labs catalog # AL-124, RRID: AB_2783675) to evaluate the ovary reserve function.

The clinicians chose appropriate ovarian stimulation protocols applied to individuals based on ovarian reserve functions and ages. The protocols included gonadotrophin-releasing hormone (GnRH) agonist long protocol, GnRH antagonist protocol, GnRH agonist short protocol, GnRH agonist

prolonged protocol, and other protocols, which have been described in detail previously [37, 38]. During controlled ovarian hyperstimulation (COH), the patients received recombinant FSH or human menopausal gonadotropin, the dosage of which was determined according to the patient's age, BMI, and ovarian reserve function. The growth of follicles was monitored by ultrasonography and serum sex steroid hormone measurements. Human chorionic gonadotropin or GnRH agonist, or both were administered to trigger final oocyte maturation when at least 2 follicles attained a diameter of 18 mm. Approximately 36 to 38 hours after triggering, oocyte retrieval guided by transvaginal ultrasonography was performed. Fertilization was by IVF, ICSI, or a combination of both.

For fresh embryo transfer, up to 2 embryos were transferred on day 3 to day 5 after oocyte retrieval. Luteal phase supplementation began immediately after oocyte retrieval and was continued until the day when the serum level of human chorionic gonadotropin was measured, 14 days after transfer. For frozen embryo transfer, all the embryos were vitrified. At the appropriate menstrual cycle, up to 2 frozen embryos were thawed and transferred.

Main Outcomes

The outcomes of IVF/ICSI treatment were compared between the MetS group and the control group. The effect of MetS components on the outcomes of IVF/ICSI treatment was also evaluated. The primary outcome was live birth, defined as delivery of any viable infant after 28 weeks of gestation. Secondary outcomes included biochemical pregnancy, clinical pregnancy, early miscarriage, late miscarriage, ectopic pregnancy, and maternal and neonatal complications.

Statistical Analysis

Data analyses were performed using SPSS software (SPSS Inc, version 22.0; Chicago, IL). Normally distributed continuous variables are expressed as mean ± SD with a Student's t test for between-group differences, while non-normally distributed continuous variables are expressed as median (25-75%) with a Kruskal–Wallis nonparametric test for between-group differences. Categorical data are described as a percentage, with a chi-square test to compare between-group differences. Multivariate logistic regression was applied to adjust the effect of confounders. A 2-sided $P < .05$ was considered to be statistically significant.

Results

In this study, a total of 8539 women undergoing their first IVF/ICSI-ET were enrolled, including 1147 women with MetS in the MetS group and 7392 women without MetS in the control group. After oocyte retrieval and IVF/ICSI, 1053 patients in the MetS group and 6705 patients in control group underwent their first embryo transfer cycle, among whom 533 patients with MetS and 3680 patients without MetS ultimately underwent live birth (Fig. 1).

Baseline and Metabolic Characteristics

The baseline characteristics of women in the 2 groups are presented in Table 1. Compared with women without MetS, women with MetS had a longer duration of infertility (3.43, 2.13-5.08, vs 2.97, 1.83-4.51, $P < .001$) and more antral follicles (14.99, 10.92-19.36, vs 13.98, 10.00-18.07, $P < .001$). The husbands of women with MetS were older than the

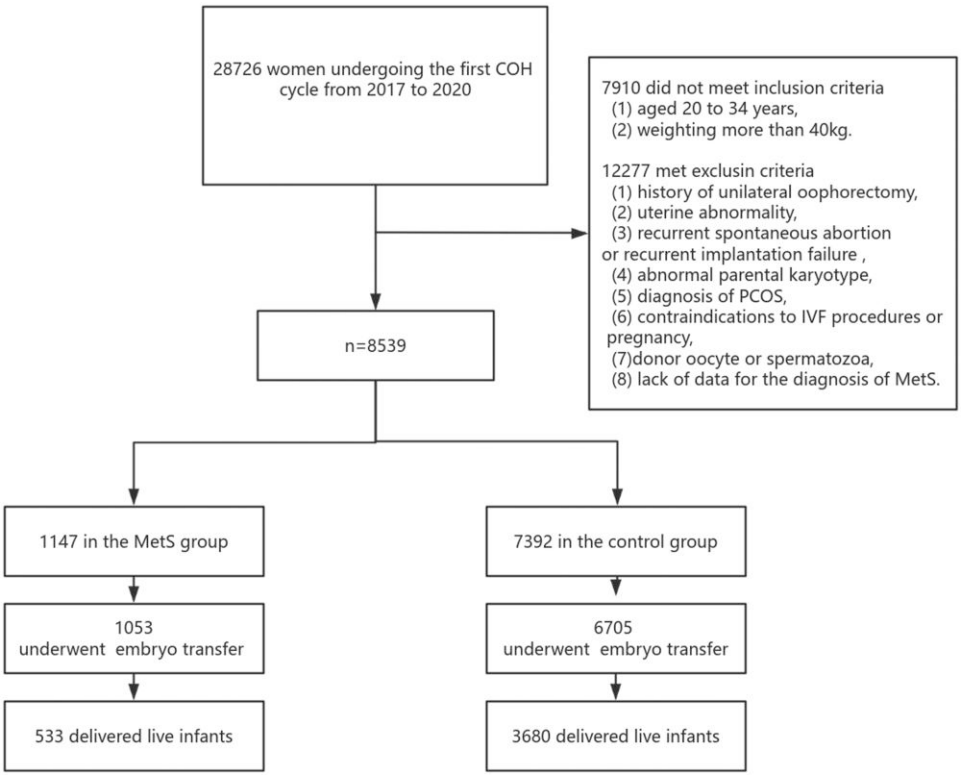

Figure 1. Disposition of subjects (flow diagram).

Abbreviations: COH, controlled ovarian hyperstimulation; MetS, metabolic syndrome; PCOS, polycystic ovary syndrome.

Table 1. Baseline characteristics of patients in MetS group and control group

	MetS group (n = 1147)	Control group (n = 7392)	*P* value
Age (y)	29.08 (27.20-30.57)	28.89 (27.16-30.48)	.143
Age of husband (y)	29.57 (27.61-31.52)	29.33 (27.49-31.22)	.014
Primary infertility (%)	698/1147 (60.9)	4534/7392 (61.3)	.755
Infertility duration (y)	3.43 (2.13-5.08)	2.97 (1.83-4.51)	<.001
Infertility cause (%)			.087
Tubal factors	762/1147 (66.4)	4781/7392 (64.7)	
Male factors	219/1147 (19.1)	1579/7392 (21.4)	
Tubal factors and male factors	89/1147 (7.8)	474/7392 (6.4)	
Others	77/1147 (6.7)	558/7392 (7.5)	
Antral follicle count	14.99 (10.92-19.36)	13.98 (10.00-18.07)	<.001
Parity (%)			.106
≥2	16/1147 (1.4)	73/7392 (1.0)	
1	157/1147 (13.7)	885/7392 (12.0)	
0	974/1147 (84.9)	6434/7392 (87.0)	
AMH level (ng/mL)	2.92 (1.79-4.79)	3.24 (1.87-5.24)	.001
TSH level (mIU/mL)	2.34 (1.66-3.14)	2.21 (1.59-2.97)	<.001
Basal FSH level (IU/L)	5.94 (5.09-6.97)	6.39 (5.49-7.49)	<.001
Basal LH level (IU/L)	4.03 (2.87-5.41)	4.82 (3.63-6.32)	<.001
Basal E2 level (pg/mL)	30.53 (22.9-39.77)	35.10 (26.94-46.04)	<.001
Basal testosterone level (ng/dL)	25.59 (17.75-35.90)	23.77 (16.64-32.29)	<.001

Results are expressed as median (25-75%), or n (%).
Abbreviations: AMH, antimüllerian hormone; E2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; MetS, metabolic syndrome; TSH, thyroid-stimulating hormone.

husbands of those without MetS (29.57, 27.61-31.52, vs 29.33, 27.49-31.22, $P = .014$). No statistically significant differences were noted in terms of age, infertility cause, proportion of primary infertility, and parity between the 2 groups ($P > .05$).

Hormone levels had significant differences between the 2 groups. AMH level (2.92, 1.79-4.79, vs 3.24, 1.87-5.24, $P = .001$), basal FSH level (5.94, 5.09-6.97, vs 6.39, 5.49-7.49, $P < .001$), and basal LH level (4.03, 2.87-5.41, vs 4.82, 3.63-6.32, $P < .001$) were significantly lower while basal testosterone level (25.59, 17.75-35.90, vs 23.77, 16.64-32.29, $P < .001$) and TSH level (2.34, 1.66-3.14, vs 2.21, 1.59-2.97, $P < .001$) were significantly higher in the MetS group.

The frequencies of each diagnostic component of MetS, including HDL ≤ 1.29 mmol/L, BMI ≥ 25 kg/m^2, TG ≥ 1.70 mmol/L, FPG ≥ 5.6 mmol/L, and BP ≥ 130/85 mmHg, were respectively 92.5%, 90.3%, 55.3%, 54.8%, and 38.2% in patients with MetS, significantly higher than in those without MetS, as expected (Table 2). The metabolic characteristics of patients in the 2 groups are compared in Table 2; women with MetS had significantly higher BMI, total cholesterol, TGs, LDL-C, FPG, and systolic and diastolic BP and significantly lower HDL level than those without MetS.

COH Characteristics

Patients' characteristics during COH are presented in Table 3; days of ovarian stimulation (10.35, 9.02-11.95, vs 9.62, 8.41-10.94, $P < .001$), starting dose of Gn (171.75, 145.18-215.04, vs 153.95, 140.33-188.46, $P < .001$) and the consumption of total Gn (2163.64, 1602.68-2926.97, vs 1621.13, 1274.27-2239.75, $P < .001$) were significantly higher in women with MetS. On the trigger day, the LH level was significantly higher in the MetS group (2.26, 1.37-3.53, vs 2.24, 1.55-3.87, $P < .001$), although the E2 level (520.00, 1640.00-3639.75, vs 3001.78, 2099.33-4593.00, $P < .001$) and progesterone level (0.55, 0.36-0.81, vs 0.64, 0.45-0.90, $P < .001$) were significantly lower than in the control group. No differences were observed in terms of COH protocol ($P > .05$).

Embryo Outcomes

Compared with those in the control group, women in the MetS group had significantly less normally fertilized oocytes (6.39, 3.70-9.50, vs 6.79, 4.04-9.64, $P = .014$) and embryos available to transfer (3.23, 1.87-5.13, vs 3.55, 1.98-5.51, $P = .004$). The number of oocytes retrieved and the number of Day-3 good-quality embryos between the 2 groups were similar ($P > .05$) (Table 4).

In the MetS group, the proportion of transferred embryos at the cleavage stage (55.8% vs 52.1%, $P = .014$) and fresh embryo transfer (72.1% vs 65.1%, $P = .004$) were significantly higher. The maximum endometrial thickness before embryo transfer was higher in women with MetS (1.07, 0.94-1.22, vs 1.01, 0.92-1.20, $P = .001$). No significant difference was observed in the number of embryos transferred between the 2 groups ($P > .05$) (Table 4).

Pregnancy Outcomes

In terms of pregnancy outcomes, women in the MetS group had significantly lower live birth rates (50.6% vs 54.9%,

Table 2. Metabolic characteristics of patients in MetS group and control group

	MetS group (n = 1147)	Control group (n = 7392)	*P* value
BMI ≥ 25 kg/m^2 (%)	1036/1147 (90.3)	1453/7392 (19.7)	<.001
TG ≥ 1.70 mmol/L (%)	634/1147 (55.3)	314/7392 (4.2)	<.001
HDL-C ≤ 1.29 mmol/L (%)	1061/1147 (92.5)	2879/7392 (38.9)	<.001
BP ≥ 130/85 mmHg (%)	438/1147 (38.2)	512/7392 (6.9)	<.001
FPG ≥ 5.6 mmol/L (%)	629/1147 (54.8)	950/7392 (12.9)	<.001
BMI (kg/m^2)	27.53 (26.01-29.50)	22.30 (20.49-24.44)	<.001
Blood lipid levels			
Total cholesterol (mmol/L)	4.49 (3.94-5.03)	4.18 (3.72-4.70)	<.001
TG (mmol/L)	1.77 (1.14-2.25)	0.81 (0.62-1.00)	<.001
HDL-C (mmol/L)	1.08 (0.95-1.21)	1.37 (1.19-1.56)	<.001
LDL-C (mmol/L)	2.87 (2.41-3.28)	2.53 (2.17-2.94)	<.001
Blood pressure (mmHg)			
Systolic	122.21 (112.97-131.74)	111.05 (103.44-119.29)	<.001
Diastolic	73.10 (66.67-80.44)	66.01 (60.41-71.87)	<.001
Fasting plasma glucose (mmol/L)	5.63 (5.23-5.83)	5.16 (4.91-5.42)	<.001

Results are expressed as median (25-75%) or n (%).
Abbreviations: BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; TG, triglycerides.

Table 3. COH characteristics of patients in MetS group and control group

	MetS group (n = 1147)	Control group (n = 7392)	*P* value
Days of ovarian stimulation (d)	10.35 (9.02-11.95)	9.62 (8.41-10.94)	<.001
Starting dose of Gn (IU)	171.75 (145.18-215.04)	153.95 (140.33-188.46)	<.001
Total dose of Gn (IU)	2163.64 (1602.68-2926.97)	1621.13 (1274.27-2239.75)	<.001
COH protocol (%)			.193
GnRH agonist long	528/1147 (46.0)	3671/7392 (49.7)	
GnRH agonist short	206/1147 (18.0)	1234/7392 (16.7)	
GnRH agonist ultralong	97/1147 (8.5)	584/7392 (7.9)	
GnRH antagonist	281/1147 (24.5)	1723/7392 (23.3)	
Others	35/1147 (3.1)	180/7392 (2.4)	
LH on trigger day (IU/L)	2.26 (1.37-3.53)	2.24 (1.55-3.87)	<.001
E2 on trigger day (pg/mL)	2520.00 (1640.00-3639.75)	3001.78 (2099.33-4593.00)	<.001
Progesterone on trigger day (ng/mL)	0.55 (0.36-0.81)	0.64 (0.45-0.90)	<.001

Results are expressed as median (25-75%) or n (%).
Abbreviations: COH, controlled ovarian hyperstimulation; E2, estradiol; Gn, gonadotropin; LH, luteinizing hormone; MetS, metabolic syndrome.

$P = .010$) than women in the control group. The risk of early miscarriage (9.8% vs 7.6%, $P = .043$) and late miscarriage (5.8% vs 3.3%, $P = .001$) was also significantly higher in women with MetS than in women without MetS. However, the biochemical pregnancy rate, clinical pregnancy rate, and ectopic pregnancy risk showed no significant difference between the 2 groups ($P > .05$) (Table 4).

A multivariate logistic regression analysis was performed for pregnancy outcomes (Table 5), after adjusting for age, age of husband, infertility duration, antral follicle count, AMH level, TSH level, basal FSH level, basal LH level, basal E2 level, basal testosterone level, days of ovarian stimulation, starting dose of Gn, total dose of Gn, E2 level, LH level, Progesterone on the trigger day, number of 2 pronuclei (PN) fertilized oocytes, number of embryos available to transfer, number of embryos transferred and stage of embryo transferred, maximum endometrial thickness before embryos transferred, and proportion of fresh embryo transferred, MetS was significantly associated with higher risk of late miscarriage (adjusted odds ratio [aOR] 1.52, 95% CI 1.02-2.27, $P = .041$) and lower live birth rate (aOR 0.87, 95% CI 0.75-1.00, $P = .045$). No significant associations were noted between MetS and other pregnancy outcomes ($P > .05$).

After adjusting for confounders, none of the individual MetS components were significantly associated with the rates of

Table 4. Comparison of the clinical outcomes in MetS group and control group

	MetS group (n = 1053)	Control group (n = 6705)	*P* value
Oocytes retrieved	10.56 (6.62-14.78)	10.92 (7.03-14.90)	.128
2PN	6.39 (3.70-9.50)	6.79 (4.04-9.64)	.014
D3 good quality embryos	3.27 (1.42-5.49)	3.46 (1.49-5.81)	.063
Embryos available to transfer	3.23 (1.87-5.13)	3.55 (1.98-5.51)	.004
Stage of embryo transferred (%)			.025
Cleavage stage embryo	588/1053 (55.8)	3496/6705 (52.1)	
Blastocyst	465/1053 (44.2)	3209/6705 (47.9)	
Embryos transferred (%)			.359
One embryo transferred	509/1053 (48.3)	3343/6705 (49.9)	
Two embryos transferred	544/1053 (51.7)	3362/6705 (50.1)	
Fresh embryo transfer	759/1053 (72.1)	4367/6705 (65.1)	<.001
Endometrial thickness before ET (mm)	1.07 (0.94-1.22)	1.01 (0.92-1.20)	.001
Biochemical pregnancy/ET (%)	740/1053 (70.3)	4743/6705 (70.7)	.759
Clinical pregnancy rate/ET (%)	650/1053 (61.7)	4235/4743 (63.2)	.371
Ectopic pregnancy/CP (%)	9/650 (1.4)	82/4235 (1.9)	.333
Early miscarriage/CP (%)	64/650 (9.8)	320/4235 (7.6)	.043
Late miscarriage/CP (%)	38/650 (5.8)	139/4235 (3.3)	.001
Live birth/ET (%)	533/1053 (50.6)	3680/6705 (54.9)	.010

Results expressed as median (25-75%) or n (%).
Abbreviations: CP, clinical pregnancy; D3, day-3; ET, embryo transfer; MetS, metabolic syndrome; PN, pronuclei.

Table 5. Crude and adjusted ORs of MetS for pregnancy outcomes

	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Biochemical pregnancy	0.98 (0.85-1.13)	.759	1.00 (0.86-1.17)	.918
Clinical pregnancy	0.94 (0.82-1.08)	.371	0.96 (0.83-1.10)	.558
Ectopic pregnancy	0.71 (0.36-1.42)	.335	0.81 (0.39-1.69)	.577
Early miscarriage	1.35 (1.01-1.77)	.044	1.32 (0.97-1.78)	.075
Late miscarriage	1.83 (1.27-2.65)	.001	1.52 (1.02-2.27)	.041
Live birth	0.84 (0.74-0.96)	.010	0.87 (0.75-1.00)	.045

Adjusted by age, age of husband, infertility duration, antral follicle count, AMH level, TSH level, basal FSH level, basal LH level, basal E2 level, basal testosterone level, days of ovarian stimulation, starting dose of Gn, total dose of Gn, E2 level, LH level, progesterone on trigger day, number of 2PN, number of embryos available to transfer, number of embryos transferred, stage of embryo transferred, maximum endometrial thickness before embryos transferred, and proportion of fresh embryo transferred.
Abbreviations: E2, estradiol; FSH, follicle-stimulating hormone; Gn, gonadotrophin; LH, luteinizing hormone; MetS, metabolic syndrome; OR, odds ratio; PN, pronuclei; TSH, thyroid-stimulating hormone.

biochemical pregnancy, clinical pregnancy, and ectopic pregnancy (Fig. 2; Tables S1-5 [39]). Risk for early miscarriage was significantly increased with the presence of HDL ≤ 1.29 mmol/L (aOR 1.28, 95% CI 1.03-1.60, $P = .027$), but not with any of the other MetS components (Fig. 2; Table S3 [39]). For late miscarriage, the risk was also significantly increased with the presence of HDL ≤ 1.29 mmol/L (aOR 1.49, 95% CI 1.08-2.05, $P = .015$), but not with any of the other MetS components (Fig. 2; Table S3 [39]). The presence of each individual MetS component is not significantly associated with live birth rate (Fig. 2; Tables S1-5 [39]).

Maternal and Neonatal Complications

For women who had a singleton live birth, the MetS group had increased risk of hypertensive disease of pregnancy (HDP) (7.8% vs 3.5%, $P < .001$), GDM (13.7% vs 7.0%, $P < .001$), and preterm birth (9.0% vs 4.4%, $P < .001$) compared with the control group. Among the singletons born, the risk of large for gestational age (LGA) (33.3% vs 20.5%, $P < 001$) was significantly higher in the MetS group but the risk of small for gestational age (SGA) was significantly lower than in the control group (Table 6).

After adjusting for confounders, the association between MetS and maternal and neonatal complications is still significant (Table 7). Women in the MetS group were at higher risk of HDP (aOR 1.79, 95% CI 1.14-2.83, $P = .012$), GDM (aOR 1.84, 95% CI 1.30-2.60, $P = .001$), and premature birth (aOR 2.03, 95% CI 1.33-3.08, $P = .001$). Singletons born from patients with MetS were at higher risk of LGA (aOR 1.66, 95% CI 1.31-2.13, $P < 001$) but at lower risk of SGA (aOR 0.48, 95% CI 0.25-0.90, $P = .023$).

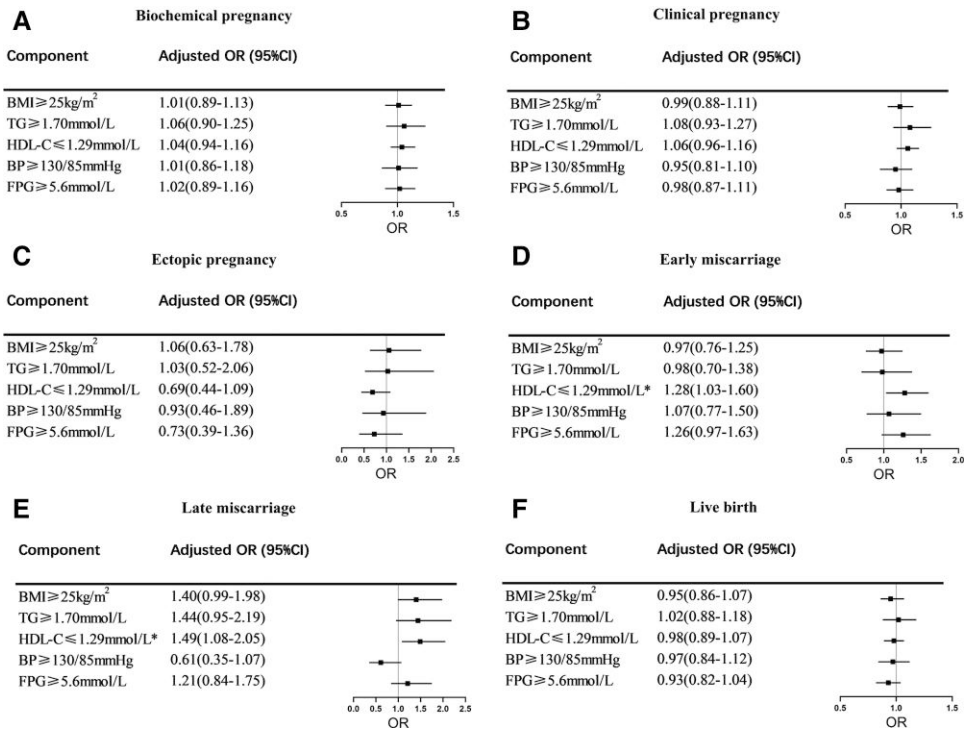

Figure 2. The adjusted OR of individual components of MetS for pregnancy outcomes adjusted by age, age of husband, infertility duration, antral follicle count, AMH level, TSH level, basal FSH level, basal LH level, basal E2 level, basal testosterone level, days of ovarian stimulation, starting dose of Gn, total dose of Gn, E2 level, LH level, progesterone on trigger day, number of 2PN fertilized oocytes, number of embryos available to transfer, number of embryos transferred, and stage of embryo transferred, maximum endometrial thickness before embryos transferred, and proportion of fresh embryo transferred. *$P < .05$; ▪The odds ratio after adjusting for the above factors in the logistic regression model; the horizontal line indicates the 95% CI. Abbreviations: BMI, body mass index; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; BP, blood pressure; OR, odds ratio. (A) The adjusted OR of individual components of MetS for biochemical pregnancy. (B) The adjusted OR of individual components of MetS for clinical pregnancy. (C) The adjusted OR of individual components of MetS for ectopic pregnancy. (D) The adjusted OR of individual components of MetS for early miscarriage. (E) The adjusted OR of individual components of MetS for late miscarriage. (F) The adjusted OR of individual components of MetS for live birth rate.

Table 6. Comparison of the maternal and neonatal complications in MetS group and control group

	MetS group (n = 409)	Control group (n = 2855)	*P* value
HDP (%)	32/409 (7.8)	100/2855 (3.5)	<.001
GDM (%)	56/409 (13.7)	199/2855 (7.0)	<.001
Preterm birth (%)	37/409 (9.0)	125/2855 (4.4)	<.001
LGA (%)	136/409 (33.3)	584/2855 (20.5)	<.001
SGA (%)	11/409 (2.7)	177/2855 (6.2)	.005

Results are expressed as median (25-75%).
Abbreviations: GDM, gestational diabetes mellitus; HDP, hypertensive disease of pregnancy; LGA, large for gestational age; MetS, metabolic syndrome; SGA, small for gestational age.

Table 7. Crude and adjusted ORs of MetS for maternal and neonatal complications

	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
HDP	2.34 (1.55-3.53)	<.001	1.79 (1.14-2.83)	.012
GDM	2.12 (1.54-2.91)	<.001	1.84 (1.30-2.60)	.001
Preterm birth	2.17 (1.48-3.18)	<.001	2.03 (1.33-3.08)	.001
LGA	1.95 (1.56-2.45)	<.001	1.66 (1.31-2.13)	<.001
SGA	0.42 (0.23-0.78)	.006	0.48 (0.25-0.90)	.023

Abbreviations: GDM, gestational diabetes mellitus; HDP, hypertensive disease of pregnancy; LGA, large for gestational age; MetS, metabolic syndrome; OR, odds ratio; SGA, small for gestational age.

In terms of the association between MetS components and maternal and neonatal complications, after adjusting for confounders, individual MetS components that significantly increased the risk for HDP were the presence of HDL ≤ 1.29 mmol/L (aOR 1.69, 95% CI 1.16-2.47, $P = .006$) and BP ≥ 130/85 mmHg (aOR 2.73, 95% CI 1.78-4.18, $P < .001$) (Fig. 3; Tables S8 and 9 [39]). BMI ≥ 25 kg/m^2 (aOR 1.56, 95% CI 1.16-2.09, $P = .003$), HDL-C ≤ 1.29 mmol/L (aOR 1.57, 95% CI 1.20-2.07, $P = .001$) and FPG ≥ 5.6 mmol/L (aOR 1.99, 95% CI 1.48-2.67, $P < .001$) significantly increased risk for GDM, but none of the other individual MetS components increased risk for GDM (Fig. 3; Tables S6, 8, and 10 [39]). BMI ≥ 25 kg/m^2 (aOR 1.55, 95% CI 1.28-1.89, $P < .001$), TG ≥ 1.70 mmol/L (aOR 1.78, 95% CI 1.39-2.28, $P < .001$), HDL-C ≤ 1.29 mmol/L (aOR 1.32, 95% CI 1.10-1.57, $P = .002$), and FPG ≥ 5.6 mmol/L (aOR 1.29, 95% CI 1.04-1.59, $P = .020$) significantly increased the risk for LGA, while the presence of BP ≥ 130/85 mmHg did not significantly affect the risk for LGA (Fig. 3; Tables S6, 7, 8, and 10 [39]). BMI ≥ 25 kg/m^2

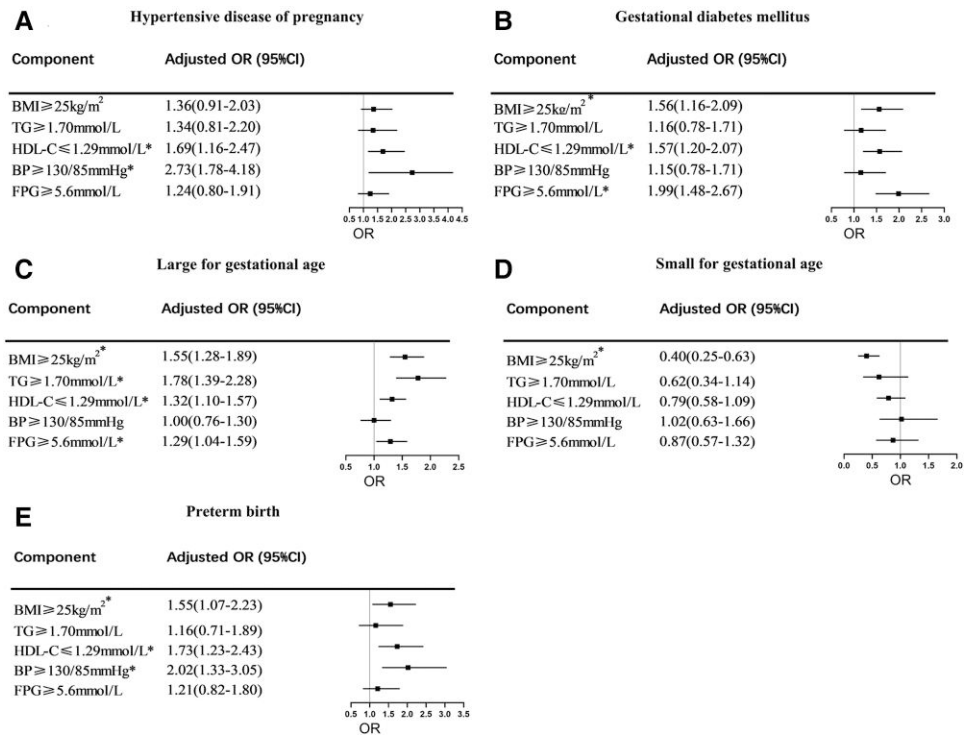

Figure 3. The adjusted OR of individual components of MetS for maternal and neonatal complications adjusted by age, age of husband, infertility duration, antral follicle count, AMH level, TSH level, basal FSH level, basal LH level, basal E2 level, basal testosterone level, days of ovarian stimulation, starting dose of Gn, total dose of Gn, E2 level, LH level, progesterone on trigger day, number of 2PN fertilized oocytes, number of embryos available to transfer, number of embryos transferred, and stage of embryo transferred, maximum endometrial thickness before embryos transferred, and proportion of fresh embryo transferred. Abbreviations: BMI, body mass index; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; BP, blood pressure; OR, odds ratio. *$P < .05$. (A) The adjusted OR of individual components of MetS for hypertensive disease of pregnancy. (B) The adjusted OR of individual components of MetS for gestational diabetes mellitus. (C) The adjusted OR of individual components of MetS for large for gestational age. (D) The adjusted OR of individual components of MetS for small for gestational age. (E) The adjusted OR of individual components of MetS for preterm birth.

significantly decreased the risk for SGA (aOR 0.40, 95% CI 0.25-0.63, $P < .001$) while the other individual MetS components did not significantly affect the risk for SGA (Fig. 3; Table S6 [39]). For preterm birth, risk was significantly increased with the presence of BMI ≥ 25 kg/m^2 (aOR 1.55, 95% CI 1.07-2.23, $P = .019$), HDL-C ≤ 1.29 mmol/L (aOR 1.73, 95% CI 1.23-2.43, $P = .002$) and BP ≥ 130/85 mmHg (aOR 2.02, 95% CI 1.33-3.05, $P = .001$), but not with any of the other MetS components (Fig. 2; Tables S6, 8, and 9 [39]).

Discussion

In this retrospective study of infertile Chinese women without PCOS, we revealed that MetS significantly increased the risk of late miscarriage and reduced the live birth rate of IVF/ICSI-ET. Regarding maternal and neonatal complications, we found MetS was significantly associated with higher risk of GDM, HDP, and preterm birth, and significantly related to higher risk of LGA but lower risk of SGA in singletons.

We also found that the presence of HDL ≤ 1.29 mmol/L significantly increased the risk of early miscarriage and the risk of late miscarriage, but did not significantly affect the live birth rate, while the other individual MetS components had no significant effect on the pregnancy outcomes in women without PCOS who underwent IVF/ICSI-ET. BP ≥ 130/85 mmHg and HDL ≤ 1.29 mmol/L significantly increased the risk of HDP in women who had a singleton live birth in this study. FPG ≥ 5.6 mmol/L and HDL ≤ 1.29 mmol/L significantly increased the risk of GDM. The risk of preterm birth was significantly increased with the presence of BMI ≥ 25 kg/m^2, HDL-C ≤ 1.29 mmol/L, and BP ≥ 130/85 mmHg. As for LGA, BMI ≥ 25 kg/m^2, HDL-C ≤ 1.29 mmol/L, TG ≥ 1.70 mmol/L, and FPG ≥ 5.6 mmol/L significantly increased the risk of LGA, while only BMI ≥ 25 kg/m^2 significantly decreased the risk of SGA.

Few studies have explored the impact of MetS on pregnancy outcomes of IVF/ICSI-ET in women without PCOS. However, because of the similarities between MetS and PCOS, previous studies have focused more on the impact of MetS on ART outcomes in women with PCOS. A secondary analysis of a multicenter randomized trial in 1508 women with PCOS in China has found that MetS increased the miscarriage rate in frozen embryo transfer and decreased the cumulative live birth rate of IVF [18], which is similar to our findings. Moini et al have conducted a prospective study of 194 women with PCOS undergoing IVF in 2022; they reported that MetS in women with PCOS was associated with nonsignificant poor COH and pregnancy outcomes [19]. For women with PCOS who underwent ovulation induction, MetS also decreased the live birth rate [20, 21].

Results of prior studies about MetS and maternal and neonatal complications in IVF/ICSI pregnancies are controversial. He et al reported that the risk of preeclampsia and GDM were comparable between women with MetS and those without MetS undergoing IVF/ICSI-ET, while in frozen cycles, the

birth weight was significant heavier in newborns in the MetS group [18]. Moini et al reported that women in the MetS group had a significantly higher risk of preeclampsia, while no significant difference was observed in the risk of GDM and preterm birth between the 2 groups [19]. As the subjects in the above 2 studies were women with PCOS, these findings could not directly extend to women without PCOS. The existence of PCOS, which was reported to increase the risk of GDM, HDP, preeclampsia, and preterm birth, and is associated with low birth weight in offspring, may mask the influence of MetS on maternal and neonatal complications to some extent.

PCOS and MetS share many similarities in pathophysiology and clinical features, such as obesity and insulin resistance (IR). Although the mechanisms of these 2 syndromes are complex and yet to be totally clarified, differences surely exist between them. IR in PCOS appeared to be intrinsic [40], interacting with adipose tissue abnormalities and hyperandrogenemia [41]. However, in MetS not developed from PCOS, obesity or increased adipose tissue is regarded as a primary driver, provoking IR [42]. Besides, though yet to be further proved in a homogeneous population, the percentage of each individual MetS component may vary in women with PCOS and those without PCOS. For instance, the percentage of FPG $\geq$ 5.6 mmol/L in the MetS group was 62.0% in women with PCOS who underwent IVF/ICSI in the study of He et al [18], and was 54.8% in those without PCOS who underwent IVF/ICSI in our study. Thus, the effect of MetS on IVF/ICSI outcomes in women without PCOS could be different from that in women with PCOS.

MetS in natural conception has been clearly demonstrated related to increased risk of pregnancy complications [22-24, 43, 44]. First and second trimester MetS and its constituents in pregnancy promoted the development of GDM and preeclampsia [23, 24, 43, 44]. Women with MetS were at high risk for preterm birth [22]. These outcomes are mirrored in the association between MetS and the maternal complications in pregnancy via IVF/ICSI-ET in our study.

Individual MetS constituents were reported disadvantageously affecting ART outcomes. Obesity compromises oocyte fertilization, decreases clinical pregnancy rate, and ultimately reduces live birth rate in patients undergoing IVF [13, 14, 45, 46]. Maternal adiposity is also associated with a range of pregnancy complications, such as preeclampsia, GDM, and preterm delivery [47, 48]. Abnormal lipid profile, such as raised TG or LDL-C or reduced HDL-C, has a deleterious impact on live birth rate in patients following IVF/ICSI [11, 49]; dyslipidemia also increased the risk of GDM, preeclampsia, preterm birth, and LGA [50-52]. In addition, IR is associated with adverse pregnancy outcomes in women with PCOS who underwent ART [17]. A prospective observational cohort study has found that even high normal BP affects live birth rate in women undergoing fresh embryo transfer [12]. IR and hypertension also relate to GDM [53]. Examination of effect of MetS as a composite of these components on IVF/ICSI outcomes in our study extends these earlier studies assessing individual components. However, each individual component of MetS was not significantly associated with live birth rate in our study, partly attributed to the slightly changed level of the individual metabolic indexes. This finding also suggested that the entire disordered metabolic status, represented by diagnosis of MetS, rather than individual metabolic abnormality, matters in adversely affecting live birth rate.

MetS might impact the placental through inflammatory settings and oxidative stress, resulting in increased risk of late miscarriage and preterm birth and decreased live birth rate, especially pronounced when maternal complications exist. Individual metabolic risk factors interact with each other and lead to a chronic low-grade inflammatory state and oxidative stress in MetS [42, 54-56]. Turpin et al found that imbalance in angiogenic regulators and oxidative stress biomarkers increased adverse outcomes such as intrauterine fetal death, placental abruption, and stillbirth in women with HDP [57]. Proinflammatory status could affect the pregnancy process, leading to miscarriage, placenta dysfunction, and other pregnancy complications, decreasing the live birth rate [58, 59].

Maternal dyslipidemia and IR in MetS promote excess accretion of adipose tissue, increase protein synthesis in the fetus, and ultimately promote intrauterine fetal growth, especially in GDM [60-62]. Although hypertension is reported to be associated with fetal growth restriction [63], the higher proportions of obesity, dyslipidemia, and hyperglycemia than hypertension in the MetS group of our study could partly explain the manifestation that MetS increased risk of LGA and decreased risk of SGA. The effect of MetS components on the risk of LGA and SGA could also explain the increased risk of LGA and decreased risk of SGA in MetS; hypertension was not found to significantly affect the risk of LGA and SGA, while obesity, dyslipidemia, and hyperglycemia significantly increased the risk of LGA in our study.

One of the strengths of this study is that we explored the effect of MetS on the pregnancy outcomes and maternal and neonatal complications in women without PCOS, which few large studies have investigated before. In clinical practice, clinicians usually pay attention to the metabolic status of women with PCOS and monitor more metabolic indexes in this situation because of common metabolic comorbidities of PCOS, such as obesity and the higher prevalence of MetS in women with PCOS [64]. However, MetS also affects as many as 10% women without PCOS [6], the prevalence of which was also proved in women without PCOS who underwent IVF/ICSI in our study. Therefore, it is crucial to illustrate the effect of MetS on the ART outcomes in women without PCOS. We have found that MetS had a negative impact on IVF/ICSI outcomes in women without PCOS, while individual MetS components were not found to affect the live birth rate in the current study. Moreover, in this study, MetS increased the risk of metabolic-related complications during pregnancy and the risk of preterm birth in women without PCOS, which is different from the results of prior studies focusing on the effect of MetS on IVF/ICSI outcomes in women with PCOS. Our study provides evidence that the metabolic situation of women without PCOS should be noted during the IVF/ICSI-ET cycle, and that clinicians should not only realize the adverse effect of a single metabolic disorder of patients, but also be concerned about their entire metabolic status and identify the subjects with MetS based on the diagnosis of MetS. The large sample size made the results compelling.

We acknowledge that our study has some limitations. As a retrospective study, we could not investigate unknown confounding factors, such as medical interventions and individual behavior. Some indexes reflecting the metabolic status of patients such as waist circumference, hip circumference, and the homeostasis model assessment of insulin resistance (HOMA-IR) were also not measured. Though BMI is correlated with waist circumference, BMI does not directly show the

characteristic visceral obesity of MetS as waist circumference does. IR, common in MetS [56], is also related to adverse pregnancy outcomes [65]; thus, HOMA-IR, not measured in our study, could be an absent potential mediator between MetS and adverse pregnancy outcomes. Besides, the data of metabolic status were only measured before COH, thus the change of metabolic status during IVF/ICSI treatment and the follow-up pregnancy process was unknown.

While our results are convincing, they should be interpreted with caution since only multivariate logistic analysis was used to conclude that MetS has detrimental effects on IVF/ICSI-ET outcomes. Further large prospective studies are required to confirm our results and to explore the mechanism behind these effects.

Conclusion

In summary, our study shows that MetS has a deleterious effect on pregnancy outcomes in women without PCOS undergoing IVF/ICSI-ET. Furthermore, MetS increases the risk of maternal metabolic complications and preterm birth, and LGA in offspring. Therefore, it is crucial for clinicians to pay attention to the metabolic state of patients with infertility undergoing IVF/ICSI-ET, and to focus on pregnancy-related complications during follow-up of patients with MetS during pregnancy. Further prospective studies are required to assess whether medical and behavioral interventions prior to IVF treatment and change of metabolic status have an effect on clinical outcomes.

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Disclosures

The authors declare no conflicts of interest.

Data Availability

The data analyzed during this study are not publicly available but are available from the corresponding author on reasonable request.

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