GYNECOLOGY

Influence of metabolic syndrome on female fertility and in vitro fertilization outcomes in PCOS women

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OBJECTIVE: With a high incidence of insulin resistance, central obesity and dyslipidemia, women with polycystic ovary syndrome are susceptible to metabolic syndrome (MetS). Our objective was to explore whether metabolic syndrome had an effect on overall female fertility and in vitro fertilization outcomes in infertile women with polycystic ovary syndrome.

STUDY DESIGN: This was a secondary analysis of a multicenter randomized trial in 1508 women with polycystic ovary syndrome, which was originally designed to compare the live birth rate after fresh-embryo transfer vs frozen embryo transfer (Frefro-PCOS). At baseline, metabolic parameters, including body mass index, waist and hip circumference, blood pressure, lipid profile, fasting, and 2 hour glucose and insulin levels after a 75 g oral glucose tolerance test were measured. All subjects were divided into a metabolic syndrome group (metabolic syndrome) and absence of metabolic syndrome group (nonmetabolic syndrome) according to diagnostic criteria. Descriptive statistics and logistic regression models tested the association between metabolic syndrome and overall fertility and in vitro fertilization cycle stimulation characteristics and clinical outcomes.

RESULTS: Metabolic syndrome was identified in 410 of 1508 infertile women with polycystic ovary syndrome (27.2%). Patients with metabolic syndrome had longer infertility duration (4.0 ± 2.2 vs 3.7 ± 2.2, $P = .004$) compared with those without metabolic syndrome. During ovarian stimulation, those with metabolic syndrome required significantly higher and longer doses of gonadotropin and had lower peak estradiol level, fewer retrieved oocytes, available embryos, a lower oocyte utilization rate, and ovarian hyperstimulation syndrome than those with nonmetabolic syndrome. The cumulative live birth rate did not show a significant between-group difference (57.8% vs 62.2%, $P = .119$). Multivariate logistic regression analysis adjusted for age, duration of infertility, body mass index, thyroid-stimulating hormone, metabolic syndrome group, homeostatic model assessment of insulin resistance, metformin utilization, number of available embryos, and embryos transferred showed that the number of embryos transferred and the number of available embryos were positively but metabolic syndrome negatively associated with the cumulative live birth rate (odds ratio, 2.18, 1.10, and 0.70, respectively, $P < .05$).

CONCLUSION: Women with polycystic ovary syndrome with metabolic syndrome have a negative impact from female fecundity, and this suggests an adverse effect on in vitro fertilization cycle stimulation characteristics and clinical outcomes.

Key words: cumulative live birth, female fertility, in vitro fertilization, metabolic syndrome, polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is recognized as the most common endocrine disorder affecting up to 6−21% of reproductive-age women.[1−3] The common features of PCOS include oligomenorrhea, hyperandrogenism, infertility, obesity, insulin resistance, and dyslipidemia.[4,5]

PCOS shares many similarities with metabolic syndrome (MetS) in pathophysiology and clinical features, including abdominal obesity, insulin resistance, and dyslipidemia. Studies showed that the prevalence of MetS in PCOS vary in different populations and is nearly 2-fold higher than age-matched women in the general population.[6]

MetS is defined as a constellation of metabolic disorders including abdominal obesity, glucose intolerance or insulin resistance, dyslipidemia, and hypertension.[7−9] As in obesity in general, insulin resistance and dyslipidemia, typical characteristics of MetS, have been deduced to have negative effects on fertility and pregnancy with compromised embryo development, impaired endometrial receptivity, and poor reproductive outcomes.[10] However, few studies have focused on the metabolic disorders in MetS, and to our knowledge, there is no large-scale study illustrating associations between MetS and female fertility and in vitro fertilization (IVF) outcomes.

We recently completed a large, multicenter, randomized controlled trial of fresh-embryo transfer compared with elective frozen embryo transfer among women with PCOS (Frefro-PCOS),[11] concluding that frozen-embryo transfer was associated with a higher live birth rate, lower risk of ovarian hyperstimulation syndrome (OHSS), and a higher risk of preeclampsia compared with fresh-embryo transfers. In that study, physical and biochemical parameters were prospectively documented. In the present study, a secondary analysis was performed to explore the influences of MetS on female fertility and IVF outcomes including cumulative live birth rates.

Materials and Methods

Study subjects

Frefro-PCOS was conducted during June 2013 and July 2015 across 14 centers in China. The original study was approved by the ethics committees of the Reproductive Medical Center of Renji Hospital and other study sites. All patients

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AJOG at a Glance

Why was this study conducted?

With a high incidence of insulin resistance, central obesity, and dyslipidemia, women with polycystic ovary syndrome (PCOS) are susceptible to metabolic syndrome. Whether metabolic syndrome had an effect on female fertility and in vitro fertilization outcomes in women with PCOS is unclear.

Key findings

Women with PCOS and metabolic syndrome had a longer duration of infertility and were negatively associated with a cumulative in vitro fertilization live birth rate.

What does this add to what is known?

Metabolic disorders are associated with impaired fertility in women with PCOS and awareness in screening may have an impact on outcomes.

previously provided written informed consent before participation.

Previously, 1508 infertile women with PCOS undergoing their first IVF cycle who were enrolled were included in this secondary analysis. The rationale, design, and conduct of that trial and primary outcomes have been reported earlier.[11,12]

Briefly, inclusion criteria were as follows: (1) women with infertility aged ≥20 and <35 years old and weight ≥40 kg; (2) diagnosed with PCOS by modified Rotterdam criteria,[13] which included menstrual abnormalities (irregular uterine bleeding, oligomenorrhea, or amenorrhea) combined with either hyperandrogenism or polycystic ovaries, as validated in our Chinese population[13]; (3) indications for IVF/intracytoplasmic sperm injection had been met.

Subjects with any of the following were excluded: (1) history of unilateral oophorectomy; (2) uterine abnormality; (3) abnormal karyotype (chromosome polymorphisms were not excluded); (4) recurrent spontaneous miscarriage (including biochemical pregnancies); and (5) other medical conditions that contraindicated assisted reproductive technology and/or pregnancy.

Study procedures

This retrospective study evaluated subjects assigned to 2 groups: the MetS group and the non-MetS group. MetS was diagnosed by the global definition with waist circumference (WC) for Asians with 3 or more of the following criteria[14]: (1) WC ≥80 cm; (2) triglyceride (TG) ≥1.7 mmol/L (150 mg/dL) or specific medication to treat; (3) high-density lipoprotein-cholesterol (HDL-C) ≤1.29 mmol/L (50 mg/dL) or specific medication to treat; (4) blood pressure ≥130/85 mm Hg or specific medication to treat; and (5) fasting plasma glucose ≥5.6 mmol/L (100 mg/dL) or specific medication to treat.

Demographic and clinical characteristics were compared between the MetS group and the non-MetS group. We also analyzed the association of the number of metabolic abnormalities (1 and 2 indices and those fulfilling the diagnostic criteria for MetS) with female fertility and IVF outcomes.

The ovarian stimulation regimen, oocytes retrieval, and fertilization were performed under standardized protocol as previously described followed by a planned transfer of up to 2 day 3 embryos, as recommended by the American Society of Reproductive Medicine and Chinese guidelines.[12,13]

In brief, recombinant follicle-stimulating hormone (FSH; Gonal-F, Merck Serono, Darmstadt, Switzerland) at a daily dose of 112.5 IU for patients weighing 60 kg or less and 150 IU for those weighing more than 60 kg was started on day 2 or 3 of the menstrual cycle and adjusted according to ovarian response. Human menopausal gonadotropin (Menopur; Ferring, Switzerland) was added at the discretion of local investigators. Gonadotropin-releasing hormone antagonist (Cetrorelix 250 μg; Merck Serono) was started when the lead follicle exceeded 12 mm. Urinary human chorionic gonadotropin (4000−8000 IU) was administered when 2 or more follicles measured 18 mm or more. Oocyte retrieval was performed 34−36 hours later.

Physical examination

In both study groups, blood pressure (BP) was measured in a sitting position after a 10 minute rest using an electronic BP monitor with an inflatable cuff size appropriate for the upper arm circumference. A second measurement was taken after 1 minute with the average of both measurements in cases in which the reading was abnormal.

Anthropometric variables including body height (centimeters), weight (kiliograms), WC (centimetersl halfway between the lower ribs and the superior anterior iliac spine of the pelvis) and hip circumferences (centimeters; at the level of the pubic symphysis) were measured.

Laboratory assessment

Hormone level and metabolic examinations

FSH, luteinizing hormone, estradiol (E2), progesterone, and total testosterone were measured by chemiluminescence (Beckman Access Health Company, Miami, FL). Total cholesterol, HDL-C, low-density lipoprotein cholesterol, and TGs were determined by the precipitation and enzymatic method (Ft-7060; Beckman Coulter Inc, Galway, Ireland). A 75 g oral glucose tolerance test was given and insulin levels were measured before ovarian stimulation. Plasma glucose and insulin were measured by the hexokinase method (Beckman Access Health Company, Chaska, MN).

Statistical analysis

Our primary outcome measured was cumulative live birth rate, which was defined as all fresh and frozen embryo transfers performed within 12 months after the initial transfer in those with and without MetS. Secondary outcomes included the impact of MetS on cycle stimulation characteristics and the association of these and anthropometric baseline demographics on live birth and cumulative live birth rates.

TABLE 1
Demographics and baseline profiles of women with PCOS and with and without MetS

Variables	MetS	non-MetS	*P* value
n	410	1098	—
Age, y	28.3 ± 3.0	28.1 ± 3.0	.169
WC ≥80 cm	97.8% (401/410)	49.7% (546/1098)	< .001
HDL ≤1.29 mmol/L	92% (377/410)	33.1% (363/1098)	< .001
On medical therapy[a]	0% (0)	0% (0)	—
FPG ≥5.6 mmol/L	62.0% (254/410)	15.8% (173/1098)	< .001
On medical therapy[b]	4.3% (11/254)	2.9% (5/173)	.605
TG ≥1.7mmol/L	60.5% (248/410)	8.7% (96/1098)	< .001
On medical therapy[a]	0% (0)	0% (0)	—
BP ≥130/85 mm Hg	23.7% (97/410)	2.5% (27/1098)	< .001
On medical therapy[b]	8.2% (8/97)	0% (0)	—
Infertility duration, y	4.0 ± 2.2	3.7 ± 2.2	.004
Infertility cause, %, n			
Ovulation dysfunction alone	19.8 (81)	18.0 (198)	.456
Ovulation dysfunction and tubal factor	60.5 (248)	52.5 (576)	.005
Ovulation dysfunction and male factor	15.6 (64)	22.9 (251)	.002
Ovulation dysfunction and tubal and male factor	4.1 (17)	6.6 (73)	.086
Basal FSH level, IU/L	5.7 ± 1.4	6.3 ± 1.5	< .001
Basal LH level, IU/L	8.9 ± 5.3	9.1 ± 5.9	.596
LH/FSH	1.6 ± 0.9	1.5 ± 1.0	.321
Basal E2 level, pg/mL	42.1 ± 29.8	43.5 ± 24	.355
Basal testosterone level, ng/dL	44.1 ± 19.9	41.3 ± 18.1	.011
TSH, IU/L	2.8 ± 1.7	2.3 ± 1.4	< .001
Blood lipid levels			
TC, mmol/L	4.7 ± 0.9	4.6 ± 1.0	.035
TG, mmol/L	1.9 ± 1.1	1.1 ± 0.5	< .001
HDL, mmol/L	1.1 ± 0.3	1.5 ± 0.4	< .001
HOMA-IR	4.8 ± 2.9	2.6 ± 1.7	< .001
Antral follicle counts, n	30.5 ± 9.3	28.7 ± 7.6	< .001
BMI, kg/m^2	26.6 ± 3.3	22.8 ± 3.3	< .001
Blood pressure, mm Hg			
Systolic	124.9 ± 12.9	116.5 ± 11.1	< .001
Diastolic	79.4 ± 9.2	74.0 ± 7.9	< .001
Metformin treatment[c]	27.1 (111/410)	13.9 (153/1098)	< .001

Data are presented as either means ± SD or % (number).

BMI, body mass index; *HDL*, high-density lipoprotein; *HOMA-IR*, homeostasis model assessment for insulin resistance; *TC*, total cholesterol; *TG*, triglycerides; *TSH*, thyroid stimulating hormone.

[a] Treatment for high TG and low HDL cholesterol levels for Chinese women of reproductive age includes low-fat diet and exercise, unless the TG level is >5.7 mmol/L or other risk factors for cardiovascular diseases are present; [b] Treatment for blood pressure and fasting plasma glucose is recommended when blood pressure is ≥140/90 mm Hg and fasting plasma glucose is ≥7.0 mmol/L; [c] Used at least during oocyte retrieval cycle and fresh embryo transfer.

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TABLE 2
Cycle stimulation characteristics and cumulative live birth rates in women with PCOS and with and without MetS

Variables	MetS group	non-MetS group	*P* value
n	410	1098	—
rFSH initiating dose, IU	144.05 ± 16.9	128.28 ± 19.33	< .001
Duration of ovarian stimulation, d	10.8 ± 2.47	10.1 ± 1.94	< .001
Total Gn dose, IU	1906.97 ± 829.59	1458.06 ± 560.83	< .001
Peak estradiol, pg/mL	3892.04 ± 2125.48	4336.31 ± 2195.3	< .001
LH on day of hCG day, IU/L	3.18 ± 3.22	2.57 ± 2.81	< .001
Peak progesterone level, ng/mL	1.03 ± 0.6	1.03 ± 0.53	.888
Endometrial thickness, mm	10.7 ± 2.0	10.4 ± 2.1	.005
Number of oocytes retrieved	13.75 ± 5.7	14.46 ± 5.96	.036
Number available embryos	5.37 ± 3.35	6.07 ± 3.35	< .001
Oocyte utilization rate (×100%)	0.41 ± 0.2	0.44 ± 0.2	.004
Cumulative live birth rate	57.8 (237)	62.2 (683)	.119

Data are presented as either means ± SD or % (number).

Gn, gonadotropin; *hCG*, human chorionic gonadotropin; *LH*, luteinizing hormone; *rFSH*, recombinanat follicle-stimulating hormone.

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Data were analyzed using SPSS software (SPSS Inc, version 21.0; Chicago, IL). Continuous data were expressed as mean ± SD, with a Student *t* test if data were normally distributed or Kruskal-Wallis nonparametric method if needed for between-group differences. Categorical data are presented as the number of cases and frequency (percentage), with a χ^2 analysis to assess between-group differences. A statistical trend test was used to assess the association of ordered correlated variables. Multivariate logistic regression was used to adjust the effect of baseline characteristics and groups. A 2-sided alpha level of 0.05 was considered statistically significant without correction for multiple comparisons.

Results

Baseline characteristics

In total, 55% of patients (n = 829) had a body mass index (BMI) <24 kg/m^2 (healthy weight); 30% (n = 453) had a BMI of 24−27.9 kg/m^2 (overweight); and 15% (n = 226) had a BMI >28 kg/m^2 (obese). MetS was present in 27.2% of subjects (410 of 1508; 10.5%, 87 in healthy weight; 42.2%, 191 in overweight; and 58.4%, 132 obese subjects).

Baseline clinical and biochemical characteristics based on the presence or absence of MetS are presented in Table 1. Those with MetS had significantly greater BMI (26.6 ± 3.3 kg/m^2 vs 22.8 ± 3.3 kg/m^2, $P < .001$) and longer duration of infertility (4.0 ± 2.2 years vs 3.7 ± 2.2 years, $P = .004$) compared with women without MetS. Those with MetS had significantly more subjects with ovulation dysfunction and tubal factor infertility (60.5 vs 52.5%, $P = .005$) but fewer subjects with ovulation dysfunction and male factor infertility (15.6% vs 22.9%, $P = .002$) than those without MetS.

While both groups were similar with respect to age, the basal serum FSH level was significantly lower, and the total antral follicle count and total testosterone were significantly higher in the MetS group. As expected, those with MetS had significantly higher systolic and diastolic blood pressure, thyroid-stimulating hormone (TSH), total cholesterol, TGs, and homeostatic model assessment of insulin resistance (HOMA-IR) and a significantly lower HDL level compared with those without MetS.

Significantly more women with MetS were on Metformin than those without MetS (27.1% vs 13.9%, $P < 0.001$). Significantly more women with MetS had a WC ≥80 cm, HDL-C ≤1.29 mmol/L, fasting plasma glucose ≥5.6 mmol/L, TGs ≥1.7 mmol/L, and BP ≥130/85 mm Hg than those without MetS. No differences were noted in those taking medical therapy (Table 1).

Cycle stimulation characteristics and cumulative live birth

During ovarian stimulation, recombinant FSH initiating dose, days of stimulation, total dose of gonadotropin (Gn) used were significantly higher in those with MetS. At the time of human chorionic gonadotropin, serum luteinizing hormone level and endometrial thickness were significantly higher in the MetS group, although peak E2 and number of oocytes retrieved were significantly lower than in the non-MetS group. Those without MetS had a higher rate of oocyte utilization and more available embryos. The cumulative live birth rate was higher in non-MetS group but without significant between-group difference ($P = .12$; Table 2).

Clinical outcomes in fresh and frozen cycles

Given that the original trial demonstrated significantly higher live birth rates in those randomized to frozen embryo transfers,[11] group analysis in

TABLE 3
Clinical, live birth, miscarriage, and OHSS rates and obstetrical complications following first embryo transfer cycle

Variables	Fresh-embryo transfer			Frozen-embryo transfer		
	MetS (n = 212)	non-MetS (n = 522)	*P* value	MetS (n = 190)	non-MetS (n = 550)	*P* value
Clinical pregnancy rate	57.1 (121)	54.6 (285)	0.54	64.7 (123)	61.3 (337)	.39
Miscarriage rate	28.9 (35)	22.8 (65)	0.19	21.1 (26)	13.4 (45)	.04
Live birth rate	40.6 (86)	42.03 (219)	0.72	49.7 (94)	52.8 (289)	.46
Cumulative live birth rate	55.7 (118)	60.7 (317)	0.21	62.6 (119)	66.5 (366)	.33
OHSS[a]	3.9 (8/207)	8.3 (46/555)	0.03	2.0 (4/203)	1.1 (6/54)	.47
Pregnancy complications						
Gestational diabetes	8.26 (10)	5.63 (16)	0.32	4.92 (6)	5.99 (20)	.66
Preeclampsia	0 (0)	1.06 (3)	0.26	4.92 (6)	4.79 (16)	.96
Birthweight, g	2924.4 ± 717.41	2871.4 ± 677.4	0.48	3114.64 ± 891.7	2953.4 ± 764.9	.08

Data are presented as either means ± SD or % (number).

OHSS, ovarian hyper-stimulation syndrome.

[a] Calculated based on intent to treat.

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this study was similarly done comparing fresh and frozen cycle outcomes separately in those with and without MetS (as shown in Table 3). Clinical, live birth, and cumulative live birth rates were similar in both groups, although miscarriage rates were significantly higher only in those with MetS in frozen cycles (21.1% vs 13.4%, $P = .04$).

In fresh-embryo transfer cycles, those subjects without MetS had significantly higher rates of OHSS compared with those with MetS (8.3% vs 3.9%, $P = .03$). No differences in pregnancy-related complications including gestational diabetes, preeclampsia, and birthweights were noted.

Association with metabolic abnormalities

To further explore the association with the number of metabolic abnormalities, subjects were grouped according to the absence and presence of any 1, 2, or ≥3 indices as required for the diagnosis of MetS. Duration of infertility, BMI, WC and hip circumference; waist to hip ratio, TSH, TGs, HOMA-IR, days of stimulation, and total Gn dose were greater when the number of metabolic abnormalities increased. Alternatively, peak E2, number of oocytes retrieved, available embryos, oocyte utilization rates, and incidence of OHSS were lower the greater the number of metabolic abnormalities (see Supplemental Tables 1−3).

Using a statistical trend test adjusting for BMI, basal FSH, waist to hip ratio, TSH, TGs, HDL, HOMA-IR, total Gn dose, and OHSS rate in fresh transfers showed significant association with an increasing number of abnormal metabolic indices (Supplemental Table 4 and Figure).

Multivariate logistic regression analysis

A binary logistic regression model was performed for cumulative live birth. Univariate logistic regression was performed to identify potential confounders, and variables with a value of $P < .1$ and those known and important potential confounders were included in the multivariable logistic regression analysis. Age, duration of infertility, BMI, TSH, presence or absence of MetS, HOMA-IR Metformin utilization, number of available embryos, and embryos transferred were included in the final model (see Supplemental Table 5).

The number of available embryos and embryos transferred were positively associated (odds ratio [OR], 1.10, 95% confidence interva [CI], 1.05−1.16, $P < .01$; OR, 2.18, 95% CI, 1.13−4.19, $P = .02$), and MetS was negatively associated with cumulative live birth rate (OR, 0.70, 95% CI, 0.51−0.96, $P = .03$; Table 4).

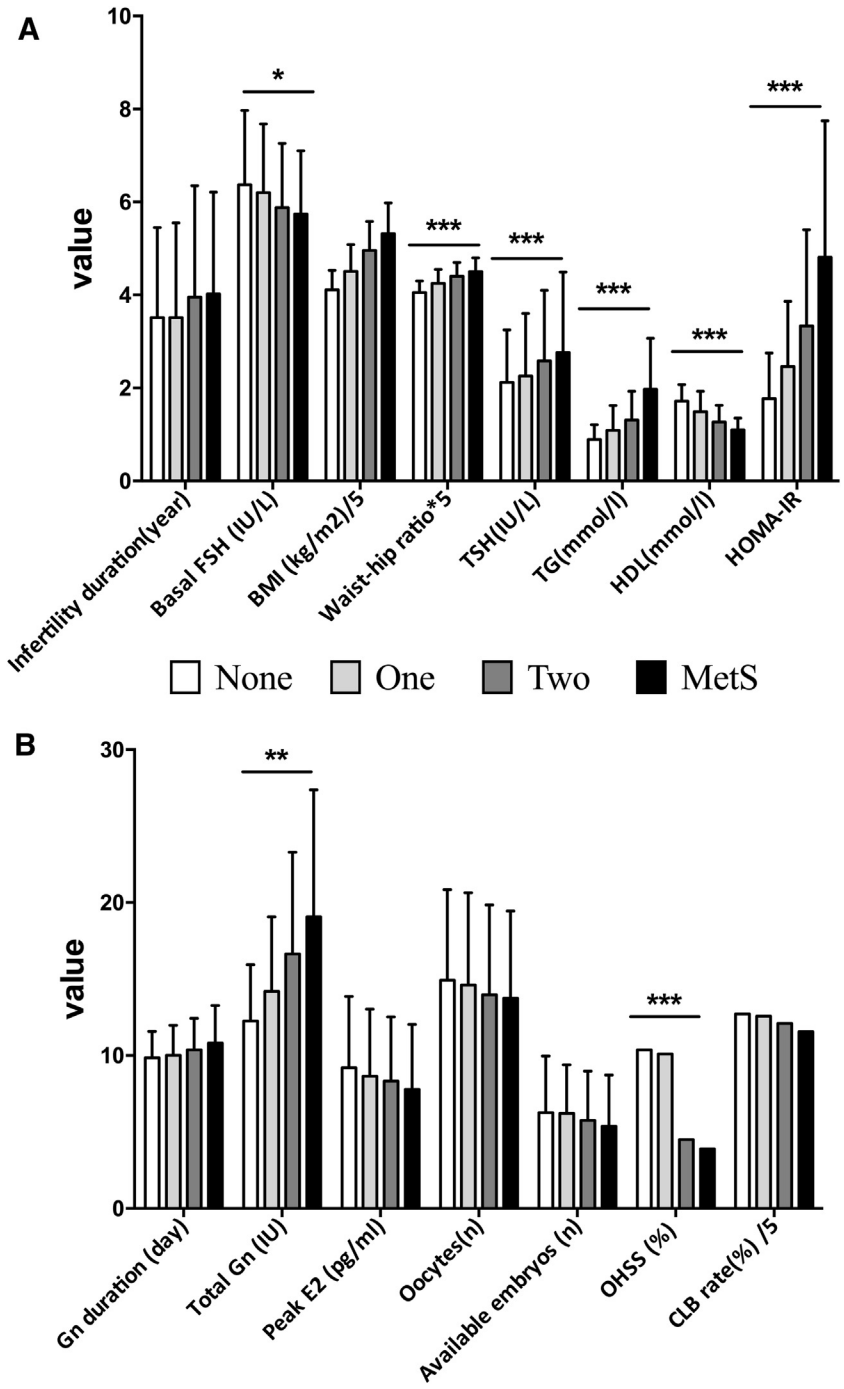
Comment

In this secondary analysis of our previous randomized controlled trial of 1508 infertile Chinese PCOS women, the prevalence of MetS was 27.2%, and our findings revealed that those with MetS had increased length of infertility and poorer IVF cycle stimulation characteristics including higher Gn requirements, fewer number of retrieved oocytes, and fewer available embryos for transfer.

In the regression model, cumulative live birth rates were significantly lower in those with MetS. This suggests that MetS alone has a deleterious impact on ovarian response, oocyte competence, and IVF live birth rates in PCOS women.

Interestingly, the prevalence of MetS in our study (27.2%) was higher than previously reported epidemiological data of age-matched reproductive-age Chinese PCOS women (19.1%).[15] Given the same population type, matched age

FIGURE
Chaging trend of parameters associated with severity of metabolism abnormalities



A, Clinical and biochemical characteristics at baseline. **B,** Cycle stimulation characteristics and cumulative live birth. *Asterisks* represent significant difference of statistical trend test with adjustment of BMI. *Singel asterisk* indicates $P < .05$; *double asterisks* indicate $P < 0.001$; *triple asterisks* indicate $P < .0001$.

BMI, body mass index; *CLB*, cumulative live birth; *Gn*, gonadotropin; *HDL*, high-density lipoprotein; *HOMA-IR*, homeostasis model assessment for insulin resistance; *OHSS*, ovarian hyperstimulation syndrome; *TG*, triglyceroids; *TSH*, thyroid stimulating hormone.

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of subjects, and the same diagnostic criteria used for MetS and the higher prevalence in our infertile PCOS, we further investigated the influence of MetS on fertility.

It is well established the detrimental effects of obesity have also been reported in assisted reproduction, including suboptimal responses to ovarian stimulation and pregnancy outcomes in patients undergoing ovulation induction, IVF, and ovum donation.[16,17]

Maternal adiposity is associated with a range of adverse pregnancy outcomes, regardless of the mode of conception. These outcomes include gestational diabetes; preeclampsia; preterm birth; neonatal morbidity, such as fetal macrosomia; and childhood obesity with its host of metabolic disorders, including type 2 diabetes and cardiovascular disease.[18]

These adverse effects may be especially pronounced in women with a BMI (>30 kg/m^2, central adiposity, and polycystic ovarian syndrome.[16,19] Data also suggest that even modest increases in maternal BMI are associated with an increased risk of fetal death, stillbirth, and infant death.[20]

To our knowledge, few studies have assessed the impact of MetS on fertility in PCOS women. Insulin resistance and dyslipidemia, typical characteristics of MetS, appear to play a critical pathophysiologic role in human health, including female fertility.[10] MetS is a state of chronic inflammation, which, along with dyslipidemia, may contribute to known adverse reproductive outcomes.[21,22]

Abnormal lipid metabolism induces endothelial damage, which may reduce placental perfusion and lead to preeclampsia or spontaneous preterm birth.[22] Alterations in carbohydrate metabolism related to insulin resistance and greater carbohydrate intake may also impair ovulation and have deleterious effects on endometrial development and implantation.[16,23]

Recently Banuls et al demonstrated that patients with PCOS and with MetS had elevated lipolysis in follicular fluid, with higher total cholesterol and TGs and lower high-density lipoprotein

TABLE 4
Results of multivariate analysis with forward approach regression

Variables		*P* value	OR	95% CI
Variables in equation	MetS group	.03	0.70	0.51 ~ 0.96
	Embryos transferred, n	.02	2.18	1.13 ~ 4.19
	Available embryos, n	< .01	1.10	1.05 ~ 1.16
Variables not in equation	Age, y	.99		
	Infertility duration, y	.63		
	BMI, kg/m^2	.19		
	TSH, IU/L	.58		
	HOMA-IR	.59		
	Metformin treatment	.99		

CI, confidence interval; *OR*, odds ratio.

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concentrations. It has been suggested that this may play a role in altered embryo development in patients with PCOS and MetS.[24] The altered maternal metabolic environment might contribute to altered glucose and lipid metabolism leading to steroidogenic dysfunction, oocyte development, and potential endometrial receptivity.

Our data further suggest not only is steroidogenic dysfunction present as peak E2 levels are reduced with MetS and with increasing metabolic indices, but also oocyte competence (even in the face of normal basal FSH and antral follicle counts) and endometrial receptivity have an adverse impact as depicted by the increased Gn requirements, longer days of stimulation, reduced oocyte utilization, and available embryos.

We acknowledge that our study has several limitations. As in any secondary analysis, selection bias cannot be excluded. The original Frefro-PCOS trial was also not designed to study the association between MetS and IVF outcome, and in this secondary analysis study, subjects were retrospectively grouped into MetS and non-MetS.

There was also not any limit to adjunctive therapies including diet, exercise, or medication before or during IVF treatment. Physicians encouraged dieting, exercising, and prescribed adjuvant medications including metformin as was deemed necessary; however, because information regarding dosage and duration were not fully recorded, it was not possible to rule the possible effect as confounding variables.

While MetS was found to be associated with lower cumulative live birth rates after multivariable adjusted analysis, lack of potential confounders including number of transfer cycles, day of embryo transfer, and endometrium preparation in frozen embryo transfer cycles tested in the model may have compromised the reliability of our results.

Lastly, as an observational study, it was not possible to determine whether medical and/or behavioral interventions to improve underlying metabolic abnormalities had an impact on the IVF outcomes.

While our results are compelling, they should be interpreted with caution because the deleterious impact on cumulative live birth rates was concluded only with multiple regression. Further studies are needed to confirm and expand on our observations and to determine how MetS influences female fertility and the impact of intervention on IVF outcomes.

In summary, this secondary analysis of our previous randomized controlled trial shows for the first time that women with PCOS and MetS have a negative impact on female fecundity and suggests a negative association of MetS and IVF cycle stimulation characteristics and clinical outcomes. Furthermore, the prevalence may be higher in infertile PCOS women than age-matched reproductive women and highlights the importance of metabolic profile screening prior to assisted reproduction therapy. Further work is necessary to assess the impact of medical and behavioral interventions prior to IVF treatment and clinical outcomes. ■

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SUPPLEMENTAL TABLE 1
Grouped metabolic abnormalities and basal hormone-anthropometric profiles

Variables	None	One[a]	Two[a]	MetS[b]	*P* value (k-w)
n	280	431	387	410	NA
Age, y	27.9 ± 3.0	28.1 ± 3.0	28.3 ± 3.1	28.3 ± 3.0	.298
Duration of infertility, y	3.5 ± 1.9	3.5 ± 2.0	4.0 ± 2.4	4.0 ± 2.2	.0005
Antral follicle count, n	29.0 ± 7.3	28.3 ± 7.7	29.1 ± 7.8	30.5 ± 9.3	.003
BMI, kg/m^2	20.6 ± 2.1	22.5 ± 2.9	24.8 ± 3.1	26.6 ± 3.3	< .0001
Waistline, cm	72.9 ± 4.5	80.0 ± 8.4	86.2 ± 8.2	90.5 ± 8.0	< .0001
Hip circumferenc, cm	90.1 ± 5.0	94.2 ± 7.3	97.8 ± 7.9	100.9 ± 8.2	< .0001
Blood pressure, mm Hg					
Systolic	113.9 ± 10.8	115.6 ± 10.3	119.3 ± 11.5	124.9 ± 12.9	< .0001
Diastolic	72.0 ± 7.1	73.8 ± 7.4	75.8 ± 8.5	79.4 ± 9.2	< .0001
TSH, IU/L	2.1 ± 1.1	2.3 ± 1.3	2.6 ± 1.5	2.76 ± 1.73	< .0001
Blood lipid levels					
TC, mmol/L	4.8 ± 0.7	4.5 ± 1.1	4.54 ± 1.1	4.7 ± 0.9	< .0001
TG, mmol/L	0.9 ± 0.3	1.1 ± 0.5	1.3 ± 0.6	2.0 ± 1.1	< .0001
HDL, mmol/L	1.7 ± 0.4	1.5 ± 0.4	1.3 ± 0.4	1.1 ± 0.3	< .0001
HOMA-IR	1.8 ± 1.0	2.5 ± 1.4	3.3 ± 2.1	4.8 ± 2.9	< .0001

BMI, body mass index; *HDL*, high-density lipoprotein; *HOMA-IR*, and homeostatic model assessment of insulin resistance; *TC*, total cholesterol; *TG*, triglyceride; *TSH*, thyroid-stimulating hormone.

[a] Metabolic abnormality; [b] Three or more criteria for MetS.

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SUPPLEMENTAL TABLE 2
Grouped metabolic abnormalities and IVF cycle stimulation and cumulative live birth rates

Variables	None	One[a]	Two[a]	MetS[b]	*P* value
n	280	431	387	410	NA
Gn duration, d	9.9 ± 1.7	10.0 ± 2.0	10.4 ± 2.1	10.8 ± 2.5	< .0001
Total Gn dose, IU	1224.8 ± 370.0	1419.3 ± 486.6	1663.8 ± 665.4	1907.0 ± 829.6	< .0001
Peak E2, pg/mL	4598.9 ± 2329.9	4323.8 ± 2190.9	4168.7 ± 2090.3	3892.0 ± 2125.5	< .0001
Peak P4 level, ng/mL	1.1 ± 0.5	1.0 ± 0.5	1.0 ± 0.6	1.0 ± 0.6	.710
Number of retrieved oocytes	14.9 ± 5.9	14.6 ± 6.0	14.0 ± 5.9	13.8 ± 5.7	.048
Number of available embryos	6.3 ± 3.7	6.2 ± 3.2	5.8 ± 3.2	5.4 ± 3.4	< .0001
Utilization of oocytes (×100%)	0.4 ± 0.2	0.5 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	.010
Cumulative live birth rate	63.6 (178)	62.9 (271)	60.5 (234)	57.8 (237)	.360

E2, estradiol; *Gn*, gonadotropin.

[a] Metabolic abnormality; [b] Three or more criteria for MetS.

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SUPPLEMENTAL TABLE 3
Grouped metabolic abnormalities and clinical outcomes after first embryo transfer cycle

Variables	Fresh-embryo transfer group				*P* value	Frozen-embryo transfer group				*P* value
	None	One[a]	Two[a]	MetS[b]		None	One[a]	Two[a]	MetS[b]	
Clinical pregnancy rate	53.3 (72)	55.3 (109)	54.7 (104)	57.1 (121)	.92	59.4 (82)	64.7 (145)	58.5 (110)	64.7 (123)	.45
Miscarriage rate	20.8 (15/72)	25.7 (28/109)	21.2 (22/10)	28.9 (35/121)	.48	14.6 (12/82)	13.1 (19/145)	12.7 (14/110)	21.1 (26/123)	.23
Live birth rate	42.2 (57)	40.8 (80)	43.2 (82)	40.6 (86)	.95	50.7 (70)	55.7 (123)	51.1 (96)	49.7 (94)	.63
Premature birth rate	16.7 (12/72)	12.8 (14/109)	14.4 (15/104)	19.0 (23/121)	.57	20.7 (17/82)	18.6 (27/145)	19.1 (21/110)	16.3 (20/123)	.87
OHSS[c]	10.8 (16/148)	10.1 (21/207)	4.5 (9/200)	3.9 (8/207)	.01	0.8 (1/132)	0.4 (1/224)	2.1 (4/187)	2.0 (4/203)	.36
Pregnancy complications										
Gestational diabetes	4.2 (3)	1.9 (2)	10.6 (11)	8.3 (10)	.045	6.1 (5)	4.2 (6)	8.2 (9)	4.9 (6)	.57
Preeclampsia	0	0	2.9 (3)	0	.03	3.7 (3)	3.5 (5)	7.3 (8)	4.9 (6)	.53
Cumulative live birth rate	61.5 (83)	59.9 (118)	61.1 (116)	55.7 (118)	.64	68.8 (95)	68.3 (153)	62.8 (118)	62.6 (119)	.43
Birth weight, g	2884.1 ± 618.8	2852.1 ± 645.5	2881.1 ± 744.7	2924.4 ± 717.4	.89	2881.8 ± 756.2	2984.8 ± 796.3	2966.9 ± 733.2	3114.6 ± 891.7	.19

OHSS, ovarian hyperstimulation syndrome.

[a] Metabolic abnormality; [b] Three or more criteria for MetS; [c] OHSS calculated based on intent to treat.

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SUPPLEMENTAL TABLE 4
Statistical trend test

Items	*P* value
Infertility duration	.21
Basal FSH	.01
Waist to hip ratio	< .0001
TSH	< .0001
TG	< .0001
HDL	< .0001
HOMA-IR	< .0001
Duration of ovarian stimulation	.13
Total Gn dose	.003
Estradiol level on hCG day	.32
Number of oocytes retrieved	.57
Number of available embryos	.72
OHSS	.0005
CLB	.08

CLB, cumulative live birth; *FSH*, follicle-stimulating hormone; *Gn*, gonadotropin; *hCG*, human chorionic gonadotropin; *HDL*, high-density lipoprotein; *HOMA-IR*, and homeostatic model assessment of insulin resistance; *OHSS*, ovarian hyperstimulation syndrome; *TG*, triglyceride; *TSH*, thyroid-stimulating hormone.

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SUPPLEMENTAL TABLE 5
Results of univariate analysis

Variables	*P* value	OR	95% CI
Age, y	.830	1.01	0.96 ~ 1.01
Infertility duration, y	.410	0.97	0.91 ~ 1.04
Basal FSH level, IU/L	.760	0.98	0.88 ~ 1.10
Basal LH level, IU/L	.540	1.01	0.97 ~ 1.04
Basal E2 level, pg/mL	.870	1.00	1.00 ~ 1.01
Basal testosterone level, ng/dL	.530	0.97	0.88 ~ 1.07
Antral follicle count, n	.460	0.99	0.98 ~ 1.01
Infertility cause	.980	1.00	0.79 ~ 1.27
BMI, kg/m^2	.020	0.96	0.92 ~ 0.99
TSH, IU/L	.090	0.99	0.98 ~ 1.04
MetS group	.030	0.71	0.52 ~ 0.96
HOMA-IR	.080	0.95	0.89 ~ 1.01
Insemination method	.700	0.94	0.64 ~ 1.35
Fresh vs frozen	.680	0.94	0.69 ~ 1.27
Metformin treatment	.940	1.01	0.70 ~ 1.47
Total Gn dose	.420	1.00	1.00 ~ 1.00
E2 of HCG day	.500	1.00	1.00 ~ 1.00
Number of embryos transferred	.001	2.77	1.48 ~ 5.18
Number of available embryos	.000	1.12	1.06 ~ 1.18

BMI, body mass index; *CI*, confidence interval; *E2*, estradiol; *FSH*, follicle-stimulating hormone; *Gn*, gonadotropin; *HCG*, human chorionic godadotropin; *HOMA-IR*, and homeostatic model assessment of insulin resistance; *LH*, luteinizing hormone; *MetS*, metabolic syndrome; *TG*, triglyceride; *TSH*, thyroid-stimulating hormone; *E2*, estradiol; *Gn*, gonadotropin.

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