

Risk factors for preeclampsia in infertile Chinese women with polycystic ovary syndrome: A prospective cohort study

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To explore preconception risk factors for preeclampsia (PE) in women with polycystic ovary syndrome (PCOS), a prospective cohort study was conducted in 92 infertile Chinese women with PCOS who had a singleton pregnancy by ovulation induction and were followed up for 6 weeks after delivery. The patients underwent assessment of physical, endocrine, and metabolic features before ovulation induction. Fifteen (16.3%) patients were diagnosed with PE. Logistic regression analysis showed that preconception sex hormone-binding globulin (SHBG), insulin level at 120 minutes, and body mass index were three independent risk factors for PE (odds ratio [OR], 0.981; 95% confidence interval [CI], 0.964–0.998 [$P=.027$]; OR, 1.011; 95% CI, 1.000–1.021 [$P=.048$]; and OR, 1.249; 95% CI, 0.992–1.572 [$P=.059$], respectively). Receiver operator characteristic analysis indicated the risk value of prepregnancy SHBG, insulin level at 120 minutes, and body mass index (area under the curve=.788, .686, and .697, respectively). Preconception low SHBG levels, overweight/obesity, and hyperinsulinism might be correlated with the subsequent development of PE in patients with PCOS.

1 | INTRODUCTION

Polycystic ovary syndrome (PCOS), one of the most common endocrine disturbances, affects 6% to 10% of fertile women¹ and is characterized by irregular menstruation, oligoovulation or anovulation, and hyperandrogenism.² PCOS often presents an increased prevalence of early complications such as fertility and obstetric outcomes, and late complications such as cardiovascular, metabolic, and oncologic diseases. Approaches have been developed to achieve pregnancy and improve the short-term effect of PCOS on women's health; however, its pregnancy complications have received little attention. Meta-analyses have shown that PCOS women can have at least a three-fold increased risk of pregnancy-induced hypertension and preeclampsia (PE),^{3–5} which is a major cause of maternal and fetal morbidity and mortality.

A systematic review reported that features characteristic of PCOS before pregnancy, such as hyperandrogenism, obesity, insulin

resistance (IR), and metabolic abnormalities, might contribute to the increased risk of pregnancy-induced hypertension and PE.⁵ In the current study, we investigated all the possible features, such as weight, body mass index (BMI), waist circumference, waist-hip ratio (WHR), serum sex hormones, sex hormone-binding globulin (SHBG), triglycerides (TGs), glucose, and insulin levels before conception, and identified the possible risk factors for PE in women with PCOS to encourage prompt interventions before pregnancy and improve maternal and neonatal outcomes.

2 | METHODS

2.1 | Patients

The current prospective cohort study ranged from January 2010 to December 2014 and was conducted at the Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China. A total of 92 infertile Chinese women aged 20 to 40 years with PCOS who

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had received singleton pregnancy by ovulation induction with clomiphene, letrozole, or human menopausal gonadotropin were enrolled and followed up for 6 weeks after delivery. The diagnosis of PCOS was made according to the Rotterdam criteria (2003), and at least two of the following three criteria were met: clinical and/or biochemical signs of hyperandrogenism, oligoovulation and/or anovulation, and polycystic ovary on ultrasonography, with the exclusion of any related diseases, such as adrenal congenital hyperplasia, Cushing syndrome, androgen-secreting tumors, Hashimoto's thyroiditis, hyperthyroidism, or hypothyroidism.⁶ Infertility was diagnosed according to the definition of the World Health Organization (WHO) as the inability to conceive despite regular sexual intercourse over 1 year without the use of any contraceptive methods.⁷ PE was diagnosed on the basis of the new onset of hypertension (systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg) and either proteinuria (urine protein ≥ 0.3 g/24 h) or end organ dysfunction or both after 20 weeks of gestation in a previously normotensive woman.⁸ Patients did not take any contraceptives or other drugs in 3 months before ovulation induction. Patients who had diabetes mellitus or hypertension or any other chronic diseases before conception were excluded.

2.2 | Clinical assessment

Prior to ovulation induction, all data of anthropometric measurements were collected, including weight, height, waist and hip circumference, sex hormones such as follicle-stimulating hormone (FSH) (mIU/mL), luteinizing hormone (LH) (mIU/mL), prolactin (PRL) (ng/mL), estradiol (E_2) (pg/mL), progesterone (ng/mL), total testosterone (TT) (ng/mL), dehydroepiandrosterone sulfate (DHEA-S) ($\mu\text{g/dL}$), SHBG (nmol/L), and TGs (mmol/L) obtained in the morning of the third to fifth day of the menstrual cycle, as well as glucose and insulin levels after an oral glucose tolerance test (OGTT) (75-g glucose, 3-hour load).

All blood samples were analyzed at the laboratory of Obstetrics and Gynecology Hospital of Fudan University. SHBG and insulin levels were quantified using a Modular E170 analyzer (Roche Diagnostics, Mannheim, Germany) after calibration with the international standard preparation 95/560, with the within-run coefficient of variation 1.0% (at 21 nmol/L). Glucose and TG levels were measured using a Hitachi 7180 automatic biochemical analyzer (Hitachi, Tokyo, Japan). FSH, LH, PRL, E_2 , progesterone, T, and DHEA-S levels were determined using a Beckman Dxl800 immune analyzer (Beckman, Pasadena, CA).

BMI was calculated by the formula weight/height^2 to estimate body fat; WHR as waist circumference/hip circumference to indicate body fat distribution and estimate central obesity; the homeostasis model assessment (HOMA) to measure IR (formula $\text{HOMA-IR: fasting plasma glucose [FPG] [mmol/L] \times \text{fasting plasma insulin [FPI] [mIU/mL]} / 22.5$);⁹ the area under the curve (AUC) of glucose (GAUC)/insulin (IAUC) according to the formula $0.5 \times (\text{fasting glucose [mmol/L]} / \text{insulin [mIU/mL]} + 3\text{-hour glucose [mmol/L]} / \text{insulin [mIU/mL]} + 1\text{-hour glucose [mmol/L]} / \text{insulin [mIU/mL]} + 2\text{-hour glucose [mmol/L]} / \text{insulin [mIU/mL]})$;¹⁰ IAUC to evaluate IR or hyperinsulinemia (GAUC referring to the level of plasma glucose); and the free

androgen index (FAI), as $\text{TT} \times 100 / \text{SHBG}$, an index of the degree of hyperandrogenism.¹¹

Transvaginal sonography was performed to diagnose PCOS and observe the number and size of the follicles in both ovaries using an Aloka SSD 5500 ultrasonoscope (Aloka Inc, Tokyo, Japan). Optimal follicular growth was monitored in subsequent cycles until ovulation.

2.3 | Ethics statement

The current study was approved by the ethics committee of Obstetrics and Gynecology Hospital, Fudan University. All patients signed written consent giving permission to use their results without mentioning their names in the current study.

2.4 | Statistical analysis

All collected data were analyzed with SPSS software, version 19.0 (IBM Corp, Armonk, NY). The preconception variables were compared between PE and non-PE groups using *t* test with adjustment for BMI when appropriate to eliminate the influence of BMI. Logistic regression analysis was performed using the forward stepwise method (inclusion if $P < .05$) to determine the strength of the associations between the variables with the occurrence of PE. Receiver operator characteristic (ROC) curves were plotted to assess the predictive value of different variables. The area under the ROC curve represented the accuracy of the predictive value for gestational diabetes mellitus.

3 | RESULTS

Of the 92 Chinese infertile patients with PCOS who had singleton pregnancy through ovulation induction, 15 (16.3%) developed PE. Similar features were observed in age (28.2 ± 4.2 vs 27.9 ± 3.7 , $P > .05$), height, waistline, hipline, and WHR between the infertile PCOS women with and without PE (all $P > .05$ after adjustment for BMI). Preconception serum TG and sex hormone levels, such as FSH, LH, PRL, E_2 , DHEA-S, and TT levels were not significantly different in the PE and non-PE groups (all $P > .05$ after adjustment for BMI). Infertile PCOS patients with PE had a lower SHBG level and a higher FAI level (both $P < .05$ after adjustment for BMI). After OGTT, preconception GAUC and plasma insulin level at 120 minutes (INS120) were both higher in the infertile PCOS women with PE (both $P < .05$ after adjustment for BMI), but no significant differences in FPG, FPI, IAUC, glucose level at 120 minutes (G120), and HOMA-IR were seen in the two groups (all $P > .05$ after adjustment for BMI) (Table 1, Figure 1).

It was found that preconception weight, BMI, GAUC, INS120, SHBG, and FAI levels were, without exception, significantly different, as indicated by the univariate logistic regression analysis, with odds ratios (ORs) of 1.085 (95% confidence interval [CI], 1.022–1.153), 1.307 (95% CI, 1.082–1.577), 1.189 (95% CI, 1.035–1.366), 1.009 (95% CI, 1.001–1.018), 1.729 (95% CI, 1.150–2.601), 0.979 (95% CI, 0.964–0.994), and 2.284 (95% CI, 1.342–3.889), respectively (all $P < .05$). The multivariate logistic regression analyses revealed that BMI,

	Non-PE (n=77)	PE (n=15)	P Value	P Value (Adjusted for BMI)
Anthropometric measurements				
Height, m	1.61±0.04	1.62±0.05	.447	–
Weight, kg	60.5±9.8	69.2±10.4	.003	–
BMI, kg/m ²	22.9±4.3	26.3±3.5	.005	–
Waistline, m	0.83±0.09	0.89±0.1	.035	.492
Hipline, m	0.94±0.08	0.98±0.06	.086	.320
WHR	0.88±0.05	0.91±0.05	.153	.874
Sex hormones				
TT, ng/mL	0.58±0.19	0.57±0.18	.871	.546
SHBG, nmol/L	130.0±84.0	47.5±38.8	.000	.011
FAI	1.13±1.14	2.12±1.30	.001	.012
Plasma glucose levels				
FPG, mmol/L	4.9±0.6	5.2±0.5	.168	.394
GLU120, mmol/L	7.0±1.6	7.9±1.5	.071	.263
GAUC, mmol/L	28.7±5.0	32.4±4.6	.012	.031
Plasma insulin levels				
FPI, mmol/L	11.4±4.9	15.3±6.1	.012	.131
INS120, mIU/mL	96.3±57.7	143.5±91.9	.096	.035
IAUC, mIU/mL	302.1±119.5	372.8±225.9	.292	.137
HOMA-IR	2.53±1.22	3.55±1.49	.008	.099
Plasma lipid level				
TGs, mmol/L	1.44±0.76	1.99±0.89	.032	.058

Values are expressed as mean±standard deviation. Analysis by *t* test or paired *t* test. Italicized values indicate significance.

Abbreviations: BMI, body mass index; FAI, free androgen index; FPG, fasting plasma glucose; FPI, fasting plasma insulin; IAUC, area of insulin under the curve; INS120, insulin level at 120 minutes after a 75-g glucose tolerance test; HOMA-IR, homeostasis model of assessment–insulin resistance; GAUC, area of glucose under the curve; GLU120, blood glucose level at 120 minutes after a 75-g glucose tolerance test; PE, preeclampsia; PCOS, polycystic ovary syndrome; SHBG, sex hormone-binding globulin; TGs, triglycerides; TT, total testosterone; WHR, waist–hip ratio.

INS120, and SHBG were included in the regression equation to be the independent risk factor for PE (OR, 1.249; 95% CI, 0.992–1.572 [*P*=.059]; OR, 1.011; 95% CI, 1.000–1.021 [*P*=.048], and OR, 0.981; 95% CI, 0.964–0.998 [*P*=.027]), whereas the predictive value of the other three variables disappeared (both *P*>.05) (Table 2).

As indicated by the ROC curve, the preconception SHBG level exhibited the best predictive accuracy as a risk factor for PE, with an AUC of 0.788 (95% CI, 0.683–0.913; *P*=.002) (Table 3), followed by BMI and INS120, with AUC ROC curves of 0.697 (95% CI, 0.530–0.865; *P*=.033), 0.686 (95% CI, 0.509–0.862; *P*=.044), respectively (Table 3, Figure 2). The optimal cutoff values were not calculated because of the limited group size.

4 | DISCUSSION

The current study showed a strong association of prepregnancy SHBG, BMI, and insulin levels with the development of PE in infertile

TABLE 1 Clinical and Laboratory Data of Women With PCOS Who Did or Did Not Develop PE

patients with PCOS, where preconception SHBG levels seemed to contribute the best predictive value according to both logistic regression analysis and ROC analysis.

As indicated by literature review, we are the first to explore the risk value of preconception SHBG levels for PE in women with PCOS, although it has been reported to be predictive of gestational diabetes mellitus in patients with PCOS.^{11–14} According to a prospective study, the association between the first-trimester SHBG and PE remained significant (per 100-nmol/L increase; OR, 0.66; 95% CI, 0.47–0.92 [*P*=.01]).¹⁵ Moreover, a low preconception SHBG level might also promote the development of PE in patients with PCOS, as reported by another prospective study.¹⁶ The researchers reconstructed associative networks, representing molecular genetic interactions between genes and comorbid disease pairs, including PE, diabetes mellitus, gestational diabetes, and obesity, and found that SHBG was one of the risk gene factors.¹⁶ The pathogenesis, however, remains unknown. In 1998, Sherif and colleagues¹⁷ found a significant negative correlation of SHBG and the sum of insulin during

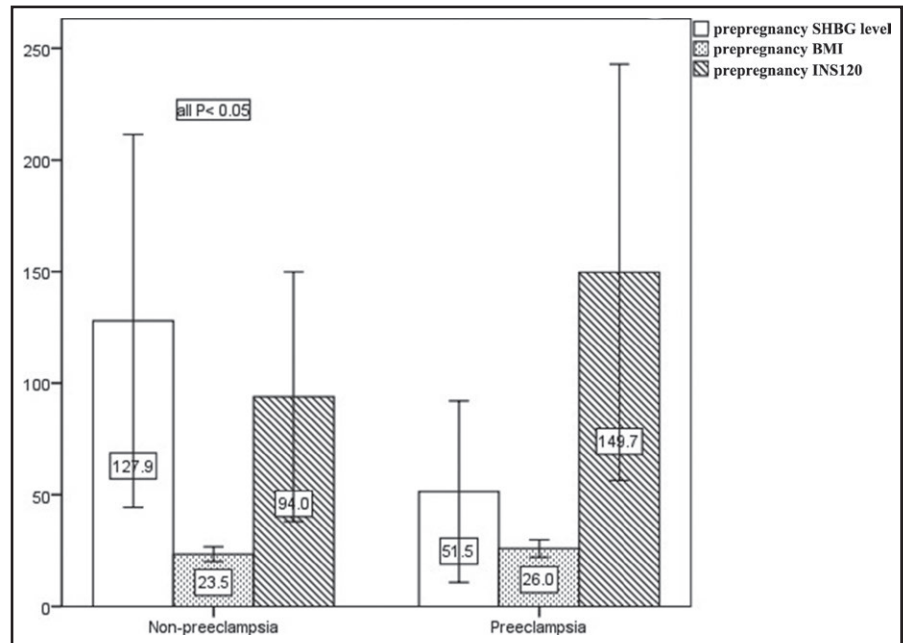


FIGURE 1 Prepregnancy SHBG, BMI, and INS120 levels between women with PCOS who did and did not develop preeclampsia

TABLE 2 Logistic Regression Analyses of Preconception Variables as Risk Factors for Preeclampsia in PCOS Women

Variables	Univariate			Multivariate		
	OR	95% CI	P Value	OR	95% CI	P Value
Weight, kg	1.085	1.022–1.153	.008	–	–	.976
BMI, kg/m ²	1.307	1.082–1.577	.005	1.249	0.992–1.572	.059
GAUC, mmol/L	1.189	1.035–1.366	.014	–	–	.495
INS120, mIU/mL	1.009	1.001–1.018	.027	1.011	1.000–1.021	.048
SHBG, nmol/L	0.979	0.964–0.994	.007	0.981	0.964–0.998	.027
FAI	2.284	1.342–3.889	.002	–	–	.470

Italicized values indicate significance. Abbreviations: BMI, body mass index; CI, confidence interval; FAI, free androgen index; FPG, fasting plasma glucose; FPI, fasting plasma insulin; GAUC, area of glucose under the curve; INS120, insulin level at 120 minutes after a 75-g oral glucose tolerance test; OR, odds ratio; SHBG, sex hormone-binding globulin.

OGTT ($r = -.29$, $P = .039$). A case-control study revealed a significant reverse correlation between SHBG level in blood and a case of PE (adjusted OR, 0.99; 95% CI, 0.98–1.00 [$P = .04$]), independent of IR.¹⁸ SHBG was the major transport protein in plasma for testosterone in women, of which 95% was SHBG-bound.¹⁹ It is well recognized that reduced SHBG levels in the plasma leads to more unbound testosterone and subsequent hyperandrogenism. Carlsen and colleagues²⁰ reported that maternal androgen levels were already elevated in the early second trimester among women who eventually developed PE (OR, 3.7; 95% CI, 1.3–10.4). Naver and colleagues²¹ reported that the overall risk of PE was significantly increased in a hyperandrogenic subsample of women with PCOS (OR, 2.41; 95% CI, 1.26–4.58 [$P < .001$]). Although TT levels before pregnancy are not comparative

between infertile PCOS women with PE and without PE, we indeed found that the value of preconception FAI in women with PCOS was almost two times of that in women without PE, which indicated that a low SHBG level might play an indirect role in the pathogenesis of PE in PCOS. As a result, studies tended to use low SHBG levels as a marker of IR in both cardiovascular disease¹⁷ and in PE.^{15,20} However, it remains unknown whether there is a direct correlation between SHBG and PE in PCOS.

We found that preconception BMI and INS120 also contributed to the development of PE in infertile patients with PCOS (OR, 1.249; 95% CI, 0.992–1.572 and OR, 1.011; 95% CI, 1.000–1.021), meaning that women with PCOS who have a high BMI before pregnancy might have an increased risk for PE; however, we failed to calculate the accurate

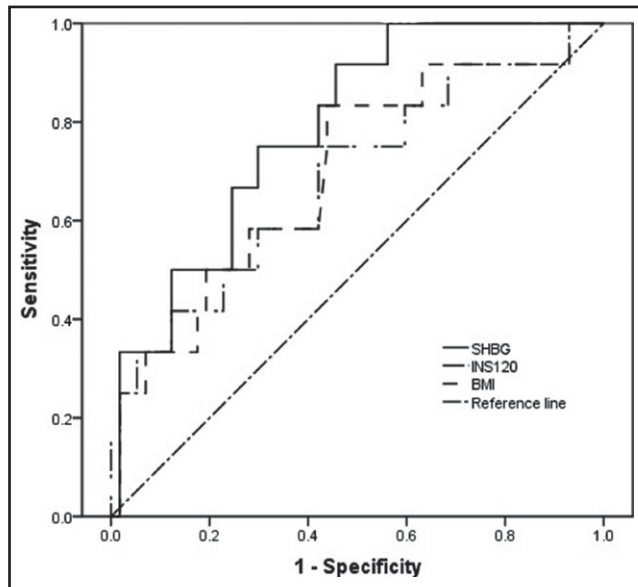


FIGURE 2 Receiver operator characteristic (ROC) curves showing the predictive probabilities of prepregnancy SHBG, body mass index (BMI), and INS120 for preeclampsia in PCOS women

TABLE 3 ROC Curve Analysis of Possible Risk Factors for PE in Women With PCOS

Variable	AUC	95% Confidence Interval		P Value
SHBG, nmol/L	.788	0.663	0.913	.002
BMI, kg/m ²	.697	0.530	0.865	.033
INS120, mIU/mL	.686	0.509	0.862	.044

Italicized values indicate significance.

Abbreviations: AUC, area under the receiver operator characteristic (ROC) curve; BMI, body mass index; INS120, insulin level at 120 minutes after a 75-g glucose tolerance test; PCOS, polycystic ovary syndrome; SHBG, sex hormone-binding globulin.

cutoff value predictive for PE because of the limited group size. It is well recognized that WHO defines the criteria of overweight and obesity for Asians as BMI ≥ 23 kg/m² and ≥ 25 kg/m².²² As concluded by a previously reported meta-analysis that covered a total of 1298 references of 23 studies with 1 387 599 participants, PE was associated with overweight (OR, 1.73; 95% CI, 1.59–1.87; 21 studies [$I^2=62.3\%$]) and obesity (OR, 3.15; 95% CI, 2.96–3.35; 22 studies [$I^2=36.0\%$]).²³ According to a recently reported meta-analysis on whether IR/insulin sensitivity was impaired in obese/nonobese patients with PCOS and obese/nonobese healthy controls, obese patients with PCOS were found statistically to have the highest IR; nonobese and non-PCOS women to have the highest insulin sensitivity; and nonobese PCOS and obese and non-PCOS women to be between this range, with a lower level of IR than obese patients with PCOS and lower insulin sensitivity than nonobese and non-PCOS patients.²⁴ A higher BMI might represent more severe IR and therefore women with PCOS may be more susceptible to PE.

Unfortunately, the prevalence of IR accounts for about 50% to 60% of PCOS cases.²⁵ It was reported that women with prepregnancy IR

were more likely to develop PE (8.4% vs 4.2%, $P<.05$) than controls.²⁶ However, we did not find a statistically significant difference of pre-conception HOMA-IR between PE and non-PE PCOS women after adjusting for BMI in the current study. On the other hand, we found that preconception INS120 was significantly correlated with PE in the infertile women with PCOS, which seemed to be a bigger risk factor when compared with HOMA-IR. Hyperinsulinism, therefore, can also play an important role in the development of PE.

4.1 | Limitations

The prospective study had a limitation of group size and the optimal cutoff values failed to be calculated.

5 | CONCLUSIONS

Low SHBG levels, overweight/obesity, or hyperinsulinism before pregnancy might be preconception risk factors for the subsequent development of PE in infertile women with PCOS. Effective interventions can be performed before pregnancy to avoid PE. Larger prospective cohort studies are still needed to identify a clinically useful prediction model and accurate cutoff value for PE among patients with PCOS.

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DISCLOSURES

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