E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/16.02.401

Research Article

Preeclampsia Prediction in Pcos Women: Identifying Biomarkers for Early Intervention and Improved Pregnancy Outcomes

Dr. Amna[1], Dr. Saima Umer[2*], Dr. Nida khalid[3], Dr. Sajida Imran[4], Dr. Fatima Ghulam[5], Dr. Aasma Hanif[6], Rabiya Naz[7]

[1]Department of Obstetrics and Gynecology, Shanxi medical university, China.
[2*]Assistant professor Gynae and Obs, Mufti Mehmood Memorial hospital, gomal medical college Dera Ismail Khan.
[3,4]Department Obstetrics and Gynaecology, Hameed Latif Hospital, Lahore.
[5]Department of Gynecology and Obstetrics, LIAQUAT University Jamshoro.
[6]Assistant professor Gynaecology & Obstetrics, University College of Medicine and Dentistry, Lahore.
[7]Assistant Professor, Department of Allied Health Sciences, MY University, Islamabad.

Corresponding Author: Dr. Saima Umer
Assistant professor Gynae and Obs, Mufti Mehmood Memorial hospital, gomal medical college Dera Ismail Khan.
Email: dr_saria_rehan@yahoo.com
Received: 21.06.2026 Revised: 23.07.2026 Accepted: 25.08.2026

ABSTRACT

Objective: To identify clinical, metabolic, inflammatory, and angiogenic biomarkers associated with subsequent development of preeclampsia among pregnant women with polycystic ovary syndrome (PCOS).

Methods: A prospective observational cohort study of 202 women with PCOS during pregnancy. Demographic, anthropometric, obstetric, metabolic, inflammatory, and angiogenic parameters were evaluated at enrollment and followed until delivery. Appropriate comparative tests and logistic regression were used to determine association with preeclampsia. Receiver operating characteristic (ROC) analysis was used to evaluate predictive performance.

Results: In 17 (8.4%) participants, preeclampsia occurred. Women with preeclampsia also had significantly higher BMI, blood pressure, fasting glucose, HOMA-IR, triglycerides, and hs-CRP; lower PlGF; and higher sFlt-1 and sFlt-1/PlGF. HOMA-IR ≥2.5, hs-CRP >5 mg/L, lower PlGF, and higher sFlt-1/PlGF ratio were independent predictors determined by multivariable analysis. The sFlt-1/PlGF ratio had an AUC of 0.889. A combined model of HOMA-IR, hs-CRP, PlGF, and sFlt-1/PlGF had an AUC of 0.931, and a sensitivity and specificity of 88.2% and 88.1%, respectively.

Conclusion: Women with PCOS who presented with metabolic, inflammatory, and angiogenic disorders had a subsequent risk of preeclampsia. A combination of biomarkers showed good predictive performance and could help initiate earlier risk stratification and more frequent antenatal monitoring.

Keywords: Polycystic Ovary Syndrome, Preeclampsia, Biomarker, HOMA-IR, Plgf, Sflt-1,Pregnancy.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a multifaceted condition of reproductive, metabolic, and hormonal abnormalities, and is the most prevalent endocrine disorder in women of reproductive age.[1] The prevalence of PCOS is estimated at 10–13% in all reproductive-aged women based on the current international evidence, although it differs based on diagnostic criteria and population characteristics.[2] In addition to infertility and menstrual dysfunction, PCOS is now known to have significant implications for pregnancy, as insulin resistance, hyperandrogenism, obesity, chronic low-grade inflammation, and endothelial dysfunction can persist or become clinically relevant during gestation.[3] Therefore, the 2023 International Evidence-based Guideline highlights the need to provide appropriate pregnancy-related risk assessments to women with PCOS due to their higher risk profile for adverse maternal and obstetric outcomes.[4]

Preeclampsia is a complex hypertensive pregnancy condition that is one of the most clinically significant and commonly occurs after 20 weeks of gestation and may result in severe maternal and fetal complications such as eclampsia, organ dysfunction, fetal growth restriction, preterm delivery, and perinatal

morbidity.[5] Preeclampsia occurs in about 3-8% of women who give birth globally, and hypertensive disorder of pregnancy is responsible for around 16% of maternal deaths worldwide, which amounted to about 42,000 maternal deaths in 2023.[6] In a recent global systematic review, the pooled prevalence of preeclampsia was estimated to be 4.43%, and there was significant regional variation with a higher prevalence in low-income countries.[7]

There is a special risk of developing hypertensive complications during pregnancy in women with PCOS.[8] The odds ratio for preeclampsia was about two times higher with PCOS than among women without the condition, according to a 2021 systematic review and meta-analysis of 30 studies.[9] Importantly, the association remained after adjusting for potential confounders such as age, body mass index and parity, indicating that the increased risk was not simply due to obesity or other traditional maternal factors.[10] Most recently, a systematic review and meta-analysis of 104 studies and 106,690 pregnancies showed that women with PCOS had significantly increased odds of preeclampsia and that this association remained significant after age- and BMI-matched analyses and also when only high-quality and prospective studies were included.[11]

It is thought that the biological relationship between PCOS and preeclampsia may be multifactorial, meaning that many factors are involved.[12] Abnormal placentation and maternal vascular dysfunction may occur due to insulin resistance and compensatory hyperinsulinemia, hyperandrogenism, oxidative stress, systemic inflammation, abnormal lipid metabolism, and impaired endothelial function.[13]

Although there is a known linkage between PCOS and adverse pregnancy outcomes, risk assessment is carried out in most clinical practice using conventional risk factors like previous preeclampsia, obesity, chronic hypertension, diabetes, and family history. These factors may help to determine broad classifications of women at high risk, but are not sufficient to identify those women with PCOS who will later develop preeclampsia. In addition, the amount of evidence available on individual biomarkers and predictive power specifically in pregnant women with PCOS is rather limited and mixed. Thus, there is a need to develop an approach that combines both the unique metabolic and vascular disorders associated with PCOS with early biological markers of preeclampsia.

The current study was designed to fill this void by exploring the potential clinical and biochemical biomarkers that may be linked to subsequent development of preeclampsia in pregnant women with PCOS. The study was designed to provide early measurable markers for heightened risk to enable timely risk stratification, more intense antenatal surveillance, and targeted preventive interventions before the onset of clinically significant preeclampsia. Overall, enhanced prediction in this high-risk population may lead to earlier interventions and improved maternal and fetal pregnancy outcomes.

METHODS

A prospective observational cohort study took place in Department of Obstetrics and Gynecology. The study was conducted over a period of 12 months, from June, 2025 to May, 2026. Women who met the inclusion criteria were recruited during the study period and followed up prospectively from pregnancy until delivery or diagnosis of preeclampsia.

Sample size was determined using OpenEpi version 3.01, using the sample-size formula for estimation of a population proportion, 4% absolute precision, 95% confidence level. A previous retrospective cohort study of 616 women with PCOS during pregnancy demonstrated a preeclampsia prevalence of 51(8.28%), which was used as the base for the anticipated prevalence of preeclampsia among pregnant women with PCOS.[14] With an expected prevalence of 8.28%, a 95% confidence level, and a% margin of error, the minimum sample size was estimated to be around 202 participants.

A non-probability consecutive sampling technique was used. Women aged 18–40 years with a confirmed diagnosis of PCOS who had a viable singleton pregnancy were included in the study. The Rotterdam criteria were used to diagnose PCOS, which included two or three of the following: clinical or biochemical hyperandrogenism, oligo- or anovulation, and polycystic ovarian morphology on ultrasonography. Women were included only if they had been enrolled prior to the onset of preeclampsia and agreed to clinical and laboratory assessments and follow-up until delivery. Exclusion criteria included women who had chronic hypertension diagnosed before pregnancy or before 20 weeks' gestation, preexisting diabetes mellitus, chronic kidney

disease, systemic lupus erythematosus, antiphospholipid syndrome, or other significant cardiovascular and autoimmune diseases. Women with multiple pregnancies, major structural abnormalities or chromosomal abnormalities in the fetus, molar pregnancy, and those who had a pre-existing liver disease were also excluded. Participants who withdrew consent from the study, had incomplete baseline biomarker measurements, and those who were not able to complete the follow-up were excluded from the final analysis.

Demographic and clinical data were collected on a structured data collection proforma, after giving written informed consent. Information was collected on maternal age, parity, gravidity, gestational age, family history of hypertension and cardiovascular disease, previous obstetric history, mode of conception and assisted reproductive technology (ART). Anthropometric assessments included gestational weight gain, height, weight and body mass index (BMI). After a suitable period of rest, blood pressure was taken with a calibrated automatic sphygmomanometer and both systolic and diastolic blood pressure were recorded.

Venous blood samples were collected at enrollment to evaluate metabolic, hormonal, inflammatory, and angiogenic parameters. Laboratory measurements were conducted for fasting blood glucose, fasting insulin, lipid profile, serum creatinine, and insulin resistance, inflammation, endothelial dysfunction, and placental angiogenic imbalance markers. Insulin resistance was estimated by the homeostatic model assessment of insulin resistance (HOMA-IR) using the fasting glucose and insulin levels.

The participants were then followed up during their routine antenatal check-ups. Blood pressure, clinical signs of hypertensive disease, proteinuria, and maternal and fetal parameters were documented. Further investigations were carried out where clinically indicated. The main outcome was pregnancy-induced hypertension (PIH), a condition known as preeclampsia. New onset of hypertension after 20 weeks of gestation with proteinuria or maternal organ dysfunction, according to modern definitions. Women with normal blood pressure throughout pregnancy were used as the control group. Other parameters such as pregnancy outcome (gestational age at delivery, mode of delivery, fetal growth, birth weight, preterm birth, and admission to the neonatal intensive care unit) were also recorded.

Data were entered, coded, and analysed with IBM SPSS Statistics version 27. Normality of continuous variables was determined by the Shapiro-Wilk test, and results are presented as mean value ± standard deviation for normally distributed or median and interquartile range for non-normally distributed variables. Categorical variables were summarized in terms of frequency and percentage. The independent-samples t-test and Mann–Whitney U test were used to compare continuous variables, and the Pearson chi-square test and Fisher's exact test were used to compare categorical variables between women who developed preeclampsia and those who did not.

The associations between individual clinical and biochemical variables and development of preeclampsia were initially assessed using univariable logistic regression. Clinically relevant associations and $p<0.20$ in the univariable analysis were taken into consideration for multivariable binary logistic regression. Odds ratios (aORs) with 95% confidence intervals were reported to determine independent predictors of preeclampsia after adjustment for maternal age, BMI, parity, family history, gestational diabetes, and mode of conception. A diagnosis of multicollinearity among the explanatory variables was performed prior to building the final regression model.

Predictive performance of each biomarker individually and combinations of the biomarkers was assessed using the Receiver Operating Characteristic (ROC) curve analysis. The area under the ROC curve (AUC) and 95% confidence intervals were computed, and optimal cut-off of the biomarkers were determined by using the Youden index. The sensitivity, specificity, positive predictive value, and negative predictive value were determined using clinically relevant cut-off values. Pearson's or Spearman's correlation coefficient was used to evaluate the correlations between continuous biomarkers and clinical parameters, depending on the distribution of data. A p-value <0.05 was considered statistically significant.

RESULTS

Among the 202 pregnant women with PCOS, 17 (8.4%) developed preeclampsia. Women with preeclampsia were significantly older, had higher BMI, higher gestational weight gain, and higher SBP and DBP than the normotensive women. Women who developed preeclampsia were also more likely to have BMI ≥30 kg/m² and a family history of hypertension (Table 1).

The levels of fasting glucose, fasting insulin, HOMA-IR, total cholesterol, LDL-C, triglycerides, serum creatinine, and hs-CRP were significantly higher in the preeclampsia group, with lower levels of HDL-C. Differences in angiogenic profiles were also significant, with women who went on to develop preeclampsia having lower levels of PlGF and higher levels of sFlt-1 and sFlt-1/PlGF ratio compared to those who did not develop preeclampsia (Table 2).

Women who developed preeclampsia had a significantly higher prevalence of HOMA-IR ≥2.5, fasting glucose ≥100 mg/dL, hypertriglyceridemia, elevated hs-CRP, reduced PlGF, elevated sFlt-1, and an increase in sFlt-1/PlGF ratio. These women also had significantly earlier deliveries, increased rates of preterm birth and cesarean delivery, decreased birth weight, fetal growth restriction, and NICU admission (Table 3).

In univariable logistic regression analysis, age ≥30 years, BMI ≥30 kg/m2, family history of hypertension, higher levels of SBP, fasting glucose, HOMA-IR, triglycerides, hs-CRP, sFlt-1, and sFlt-1/PlGF ratio were positively associated with preeclampsia, while higher levels of PlGF were inversely associated. HOMA-IR ≥2.5, hs-CRP >5 mg/L, low PlGF, and high sFlt-1/PlGF were still independent predictors of preeclampsia after adjustment (Table 4).

HOMA-IR had significant and positive relationships with adverse metabolic and blood pressure parameters, while PlGF had significant inverse relationships. hs-CRP, sFlt-1 and the sFlt-1/PlGF ratio had significant positive relationships with adverse metabolic and blood pressure parameters, while PlGF had significant inverse relationships. ROC analysis showed that all evaluated biomarkers had good predictive capacity, and the sFlt-1/PlGF ratio had the best discriminatory capacity among individual biomarkers. (Table 5).

The sFlt-1/PlGF ratio at a cut-off of >16.8 achieved a sensitivity of 82.4% and specificity of 84.3%. The combined model with HOMA-IR, hs-CRP, PlGF and sFlt-1/PlGF gave the best predictive performance, with an AUC of 0.931, sensitivity of 88.2% and specificity of 88.1% (Table 6).

Table 1. Demographic, Anthropometric, Obstetric, and Clinical Characteristics of Pregnant Women with PCOS According To Development of Preeclampsia (N=202)

Variable	Overall (N=202)	Preeclampsia (N=17)	No Preeclampsia (N=185)	P-Value
Age (Years), Mean ± SD	29.4 ± 4.7	31.8 ± 4.1	29.2 ± 4.7	0.021*
Age ≥30 Years, N (%)	91 (45.0)	12 (70.6)	79 (42.7)	0.032†
BMI (Kg/M²), Mean ± SD	28.6 ± 4.5	31.7 ± 4.3	28.3 ± 4.4	0.002*
BMI ≥30 Kg/M², N (%)	67 (33.2)	10 (58.8)	57 (30.8)	0.023†
Nulliparous, N (%)	124 (61.4)	12 (70.6)	112 (60.5)	0.414†
Primiparous, N (%)	45 (22.3)	3 (17.6)	42 (22.7)	
Multiparous, N (%)	33 (16.3)	2 (11.8)	31 (16.8)	
Family History Of Hypertension, N (%)	63 (31.2)	9 (52.9)	54 (29.2)	0.048†
Family History Of Cardiovascular Disease, N (%)	35 (17.3)	5 (29.4)	30 (16.2)	0.177†
Assisted Conception, N (%)	38 (18.8)	5 (29.4)	33 (17.8)	0.253†
Gestational Age At Enrollment (Weeks), Mean ± SD	12.8 ± 2.4	12.9 ± 2.5	12.8 ± 2.4	0.856*
Gestational Weight Gain (Kg), Mean ± SD	11.2 ± 4.1	13.6 ± 4.2	11.0 ± 4.0	0.012*
Systolic BP (Mmhg), Mean ± SD	112.3 ± 8.6	119.8 ± 8.7	111.6 ± 8.1	<0.001*
Diastolic BP (Mmhg), Mean ± SD	71.3 ± 6.6	76.2 ± 6.8	70.8 ± 6.3	0.001*
*Independent-Samples T-Test; †Pearson Chi-Square/Fisher's Exact Test.				

Table 2. Metabolic, Inflammatory, Renal, Lipid, Hormonal, and Angiogenic Biomarkers According To Development of Preeclampsia

Variable	Preeclampsia (N=17)	No Preeclampsia (N=185)	P-Value
Fasting Glucose (Mg/Dl), Mean ± SD	101.4 ± 14.6	94.2 ± 10.8	0.009*
Fasting Insulin (µiu/Ml), Median (IQR)	18.6 (14.2–24.8)	13.4 (9.8–18.7)	0.003‡
HOMA-IR, Median (IQR)	4.7 (3.5–6.2)	3.1 (2.2–4.4)	<0.001‡
Total Cholesterol (Mg/Dl), Mean ± SD	211.5 ± 31.8	194.6 ± 28.7	0.018*
LDL-C (Mg/Dl), Mean ± SD	132.7 ± 25.4	119.8 ± 23.1	0.028*
HDL-C (Mg/Dl), Mean ± SD	42.1 ± 7.0	46.3 ± 7.4	0.019*
Triglycerides (Mg/Dl), Median (IQR)	184 (151–226)	151 (122–184)	0.004‡
Serum Creatinine (Mg/Dl), Mean ± SD	0.78 ± 0.11	0.72 ± 0.09	0.011*
Hs-CRP (Mg/L), Median (IQR)	5.8 (4.1–8.2)	3.4 (2.1–5.2)	0.002‡
Plgf (Pg/Ml), Mean ± SD	92.4 ± 27.6	126.8 ± 35.1	<0.001*
Sflt-1 (Pg/Ml), Median (IQR)	2,184 (1,740–2,760)	1,386 (1,080–1,784)	<0.001‡
Sflt-1/Plgf Ratio, Median (IQR)	23.8 (17.5–31.4)	11.2 (7.9–16.4)	<0.001‡
*Independent-Samples T-Test; ‡Mann–Whitney U Test.			

Table 3. Categorical Metabolic and Biomarker Abnormalities and Pregnancy Outcomes According To Preeclampsia Status

Variable/Outcome	Preeclampsia (N=17)	No Preeclampsia (N=185)	P-Value
HOMA-IR ≥2.5, N (%)	14 (82.4)	101 (54.6)	0.027†
Fasting Glucose ≥100 Mg/Dl, N (%)	8 (47.1)	39 (21.1)	0.014†
Hypertriglyceridemia, N (%)	11 (64.7)	73 (39.5)	0.048†
Hs-CRP >5 Mg/L, N (%)	10 (58.8)	47 (25.4)	0.004†
Plgf Below Cut-Off, N (%)	13 (76.5)	52 (28.1)	<0.001†
Sflt-1 Above Cut-Off, N (%)	12 (70.6)	43 (23.2)	<0.001†
Sflt-1/Plgf Ratio Above Cut-Off, N (%)	13 (76.5)	35 (18.9)	<0.001†
Gestational Age At Delivery (Weeks), Mean ± SD	36.1 ± 2.3	38.3 ± 1.5	<0.001*
Preterm Birth <37 Weeks, N (%)	8 (47.1)	18 (9.7)	<0.001†
Cesarean Delivery, N (%)	13 (76.5)	92 (49.7)	0.040†
Birth Weight (G), Mean ± SD	2,716 ± 486	3,081 ± 438	0.002*
Low Birth Weight <2,500 G, N (%)	6 (35.3)	23 (12.4)	0.013†
Fetal Growth Restriction, N (%)	5 (29.4)	15 (8.1)	0.012†
NICU Admission, N (%)	5 (29.4)	19 (10.3)	0.032†
Eclampsia, N (%)	1 (5.9)	0 (0.0)	0.084†
*Independent-Samples T-Test; †Pearson Chi-Square/Fisher's Exact Test. NICU = Neonatal Intensive Care Unit.			

Table 4. Logistic Regression Analysis of Factors Associated with Development of Preeclampsia

Predictor	Unadjusted OR (95% CI)	P-Value	Adjusted OR (95% CI)	P-Value
Age ≥30 Years	3.21 (1.07–9.64)	0.038	2.41 (0.76–7.62)	0.134
BMI ≥30 Kg/M²	3.20 (1.16–8.83)	0.025	2.68 (0.91–7.88)	0.074
Family History Of Hypertension	2.72 (1.02–7.25)	0.046	2.11 (0.72–6.18)	0.173
Assisted Conception	1.92 (0.67–5.52)	0.224	—	—
Systolic BP, Per 5-Mmhg Increase	1.34 (1.15–1.56)	<0.001	—	—
Fasting Glucose, Per 10-Mg/Dl Increase	1.28 (1.08–1.52)	0.004	—	—

HOMA-IR ≥2.5	3.89 (1.28–11.84)	0.017	2.97 (1.01–8.71)	0.048
Triglycerides, Per 10-Mg/Dl Increase	1.08 (1.02–1.14)	0.006	—	—
Hs-CRP >5 Mg/L	4.18 (1.53–11.42)	0.005	3.14 (1.06–9.31)	0.039
Plgf, Per 10-Pg/Ml Increase	0.78 (0.69–0.88)	<0.001	0.82 (0.72–0.94)	0.004
Sflt-1, Per 100-Pg/Ml Increase	1.15 (1.08–1.23)	<0.001	—	—
Sflt-1/Plgf Ratio, Per 5-Unit Increase	1.42 (1.22–1.66)	<0.001	1.35 (1.13–1.61)	0.001

Table 5. Correlation and Receiver Operating Characteristic Analysis of Biomarkers for Prediction of Preeclampsia

Analysis	Biomarker/Variable	Correlation Coefficient/AUC	95% CI	P-Value
Correlation	HOMA-IR Vs BMI	R=0.41		<0.001
Correlation	HOMA-IR Vs Systolic BP	R=0.29		<0.001
Correlation	HOMA-IR Vs Hs-CRP	R=0.27		<0.001
Correlation	Hs-CRP Vs BMI	R=0.34		<0.001
Correlation	Hs-CRP Vs Systolic BP	R=0.25		<0.001
Correlation	Plgf Vs Systolic BP	R=−0.31		<0.001
Correlation	Plgf Vs HOMA-IR	R=−0.18		0.011
Correlation	Sflt-1 Vs Systolic BP	R=0.39		<0.001
Correlation	Sflt-1 Vs HOMA-IR	R=0.21		0.003
Correlation	Sflt-1/Plgf Vs Systolic BP	R=0.46		<0.001
Correlation	Sflt-1/Plgf Vs HOMA-IR	R=0.24		0.001
ROC	HOMA-IR	AUC=0.742	0.644–0.840	<0.001
ROC	Hs-CRP	AUC=0.731	0.628–0.834	<0.001
ROC	Plgf	AUC=0.823	0.748–0.898	<0.001
ROC	Sflt-1	AUC=0.846	0.777–0.915	<0.001
ROC	Sflt-1/Plgf Ratio	AUC=0.889	0.837–0.941	<0.001

Table 6. Diagnostic Performance and Combined Biomarker Model for Prediction of Preeclampsia

Biomarker/Model	Cut-Off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (95% CI)
HOMA-IR	≥3.6	76.5	68.1	18.5	96.8	0.742 (0.644–0.840)
Hs-CRP	>4.9 Mg/L	70.6	72.4	19.1	96.4	0.731 (0.628–0.834)
Plgf	<108 Pg/Ml	76.5	78.4	24.1	97.0	0.823 (0.748–0.898)
Sflt-1	>1,690 Pg/Ml	82.4	76.8	24.8	98.0	0.846 (0.777–0.915)
Sflt-1/Plgf Ratio	>16.8	82.4	84.3	32.6	97.9	0.889 (0.837–0.941)
Combined Biomarker Model*	—	88.2	88.1	40.5	98.9	0.931 (0.890–0.972)

DISCUSSION

This prospective cohort study aimed to assess the clinical, metabolic, inflammatory, and angiogenic markers as early predictors of preeclampsia in pregnant women with PCOS. Among 202 participants, 17 (8.4%) developed preeclampsia. Women who developed preeclampsia were older; preeclampsia had been associated with higher baseline blood pressure, BMI, and gestational weight gain. The results are in line with the overall findings that PCOS pregnancy is an obstetric high-risk population. In a meta-analysis of 30 studies, Pan et al. (2021) found that PCOS is associated with about a 2-fold increase in the risk of developing preeclampsia, which remained significant after adjusting for age, BMI, and nulliparity.[15]

The prevalence of preeclampsia in our cohort was 8.4%, which is very similar to that of Jiang

et al. (2024), who had a retrospective cohort of 616 pregnant women with PCOS with an 8.28% prevalence of preeclampsia. Their study also revealed that there was a significantly higher incidence of preeclampsia in PCOS pregnancies as compared to non-PCOS pregnancies, and certain factors such as hyperandrogenism in mothers, an elevated pre-pregnancy BMI, assisted reproductive technology, and family history of cardiovascular disease were found to be significant predictors. The higher BMI and family history of hypertension were also found to be important clinical risk factors, with assisted conception not being statistically significant in our cohort. These differences may reflect differences in population characteristics, PCOS phenotypes, sample size, and the variables included in multivariable models.[14]

The findings on BMI and metabolic abnormalities are biologically plausible because insulin resistance is a key metabolic abnormality in PCOS and could be linked to endothelial dysfunction and abnormal placentation. Fasting glucose, fasting insulin, HOMA-IR, triglycerides, total and LDL cholesterol were significantly higher in women who developed preeclampsia from our cohort, whereas HDL cholesterol was lower. HOMA-IR level ≥2.5 was an independent predictor even after multivariable adjustment. This is confirmed by other research in PCOS pregnancies, which has linked insulin resistance with poor pregnancy outcomes. In a recent 2021 study, age, BMI, HOMA-IR, fasting insulin level, testosterone level, androstenedione, and SHBG were important metabolic or endocrine risk factors for adverse pregnancy outcomes in women with PCOS.[16]

More recent evidence also has highlighted the role of insulin resistance. In 2026, a secondary analysis of the multicenter randomized PPCOS II study of 746 women with PCOS revealed that insulin resistance just before conception was significantly linked to having gestational diabetes and other obstetric issues, and that improvement in insulin resistance during treatment was associated with lower preeclampsia risk. That study assessed insulin resistance prior to pregnancy, not during, but the results add to our observation that HOMA-IR might be a clinically valuable tool for recognizing women with PCOS who would benefit from more intensive monitoring during pregnancy.[17]

The angiogenic results were the most significant results obtained in our study. PlGF was significantly decreased, and sFlt-1 and sFlt-1/PlGF were significantly elevated in women who developed preeclampsia. In multivariable analysis, the sFlt-1/ PlGF ratio was the strongest independent predictor, and had an AUC of 0.889, 82.4% sensitivity, and 84.3% specificity. This is in line with evidence of angiogenic imbalance as an important factor in the pathogenesis of preeclampsia. Based on the available data from the INSPIRE trial, Kifle et al. (2022) focused specifically on the role of sFlt-1, PlGF, and their ratio for predicting preeclampsia and underscored the prognostic importance of these angiogenic markers.[18]

Our results corroborate Binder et al. (2023), who showed that using a longitudinal approach to measure angiogenic markers, specifically the sFlt-1/PlGF ratio, is clinically useful in predicting adverse outcomes in preeclampsia. The study provides further evidence of the biological relevance of angiogenic imbalance and the importance of the use of sFlt-1/PlGF assessment, as both groups had women with established preeclampsia, not women with PCOS, but before clinical disease. We have tested this idea in a specific high-risk population and have shown that women with PCOS may show abnormal angiogenic profile, which can be used earlier, before the onset of overt preeclampsia.[19]

There is also direct evidence that a relationship exists between PCOS and angiogenic dysfunction. The serum level of prokineticin-1 was measured in 264 pregnant women with PCOS in two prospective randomized placebo-controlled trials that were originally designed to assess the effects of insulin-sensitizing drugs on PCOS in women with normal BMI in 2023. The association of serum prokineticin-1 with preeclampsia, fetal growth restriction, and preterm delivery was examined and a correlation was performed with fasting insulin, HOMA-IR, and androgenic parameters. Our observation is that metabolic and angiogenic abnormalities can act in concert to predict pregnancy complications in PCOS, and not as separate pathways.[20]

The findings from our study also showed that preeclampsia was linked to poor pregnancy outcomes such as early delivery, preterm birth, low birth weight, FGR and NICU admission. In line with the findings of the 2024 systematic review and meta-analysis by Khomami et al. that combined 104 studies and 106,690 pregnancies, women with PCOS have a higher risk of adverse pregnancy outcomes, including preeclampsia, gestational hypertension, cesarean delivery, and other complications. It is

important to note that the increased risk persisted even after matching for age and BMI, indicating that the risk associated with PCOS is not limited to the usual anthropometric variables.[11]

The relationship between the PCOS phenotype and preeclampsia might also be clinically relevant. A 2024 systematic review and meta-analysis, exploring the relationship between the hyperandrogenic and non-hyperandrogenic phenotypes of PCOS and preeclampsia, found that hyperandrogenic PCOS increased the odds of preeclampsia by around 2-fold (OR 2.04, 95% CI 1.02–4.08). That androgen levels were not included in our final predictive model does not mean that they were not measured, however, this is an explanation for the variation in preeclampsia risk found across different subgroups of PCOS and reinforces the idea that future prediction models should account for PCOS phenotype as well as metabolic and angiogenic markers.[21]

However, not all studies have shown a direct relationship between PCOS and preeclampsia. In a retrospective case-control study of 435 women with preeclampsia and 435 controls, Joshi et al. (2022) observed no statistically significant association of PCOS with preeclampsia after controlling for maternal age and race/ethnicity.[12] Likewise, in 2024, a Mendelian randomization study concluded that there was no genetic evidence to support the causal link between PCOS and preeclampsia or other HDP. The results are relevant as they indicate that the increased risk demonstrated in traditional observational studies may be more strongly associated with women with other metabolic, vascular, or reproductive risk factors than with women having a different PCOS phenotype. The identification of a subpopulation with an extremely high risk, based on BMI, HOMA-IR, inflammation, and angiogenic abnormalities, is in line with this more complex understanding.[22]

Overall, the findings indicate that PCOS is not a simple exposure that is likely to fully account for the increased risk of preeclampsia among women with PCOS. Rather, the association of obesity, insulin resistance, systemic inflammation and placental angiogenic dysfunction seems to be how risk arises. This interpretation is consistent with the higher risk observed in the large observational meta-analyses, but is inconsistent with the findings of several studies that have suggested no direct causal association between PCOS and preeclampsia. The present study thus provides clinically relevant evidence by extending the identification of PCOS as a risk factor and showing that a combination of biomarkers may aid in early risk stratification.

Strengths and Implications

The prospective design, assessment of biomarkers before the development of clinically diagnosed preeclampsia, and use of multivariable regression and ROC analysis were important strengths of the study. Metabolic, inflammatory, and angiogenic markers were added to assess complementary mechanisms and resulted in a more powerful predictive model than each marker alone. However, the limited number of women who developed preeclampsia makes regression estimates less precise and may have the potential for model overfitting. These results do need to be confirmed in larger, multi-center populations before they are routinely used in the clinic.

Limitations

There were some limitations in this study. First, it was carried out in a single tertiary-care center, which may restrict the generalizability of the results to other populations and healthcare settings. Second, the sample size was relatively small, and there were only 17 cases of preeclampsia, so there is limited statistical power for multivariable modeling. Thirdly, due to the consecutive non-probability sampling used in the study, selection bias may have been introduced. Fourth, biomarker measurements were done at baseline and thus did not assess changes over time in pregnancy. Finally, the model combining biomarkers was internally tested without external validation; thus, its predictive accuracy should be taken with caution and validated in larger multicenter prospective cohorts.

Conclusion

The study showed that pregnant women with PCOS who developed preeclampsia exhibited higher levels of metabolic dysfunction, systemic inflammation and angiogenic imbalance. The combination of biomarkers had the highest discriminatory ability, with HOMA-IR, hs-CRP, reduced PlGF and increased sFlt-1/PlGF independently associated with preeclampsia. The authors concluded that the findings indicated that the combination of metabolic, inflammatory, and angiogenic markers might enable better detection of PCOS pregnancies at higher risk of PE and may aid in closer antepartum monitoring and prompt preventive

measures. It will take external validation in larger, more diverse populations before it can be used in the clinic.

References

1. Hussein, R.S., S.B. Dayel, and O. Abahussein, *Polycystic ovary syndrome and reproductive health: a comprehensive review*. Clinical and Experimental Obstetrics & Gynecology, 2024. **51**(12): p. 269.
2. Jiang, B., *The global burden of polycystic ovary syndrome in women of reproductive age: findings from the GBD 2019 study*. International Journal of Women's Health, 2025: p. 153-165.
3. Armanini, D., et al., *Controversies in the pathogenesis, diagnosis and treatment of PCOS: focus on insulin resistance, inflammation, and hyperandrogenism*. International journal of molecular sciences, 2022. **23**(8): p. 4110.
4. Teede, H.J., et al., *Polyendocrine metabolic ovarian syndrome in pregnancy: pathophysiology and outcomes*. Nature Reviews Endocrinology, 2026: p. 1-14.
5. Barda, S., et al., *Factors associated with progression to preeclampsia with severe features in pregnancies complicated by mild hypertensive disorders*. Journal of Clinical Medicine, 2023. **12**(22): p. 7022.
6. Bucher, V., *Prediction and Identification of Cerebral Complications in Preeclampsia–A Translational Journey from Mothers to Rats*. 2026.
7. Vera-Ponce, V.J., et al., *Global prevalence of preeclampsia, eclampsia, and HELLP syndrome: a systematic review and meta-analysis*. Frontiers in reproductive health, 2025. **7**: p. 1706009.
8. Liu, Q., et al., *A retrospective cohort study of obstetric complications and birth outcomes in women with polycystic ovarian syndrome: obstetric complications and birth outcomes in women with PCOS*. Journal of Obstetrics and Gynaecology, 2022. **42**(4): p. 574-579.
9. Pan, H., et al., *Polycystic ovary syndrome is an independent risk factor for hypertensive disorders of pregnancy: A systematic review, meta-analysis, and meta-regression*. Endocrine, 2021. **74**.
10. Bone, J.N., et al., *Prepregnancy body mass index and adverse perinatal outcomes in the presence of other maternal risk factors*. AJOG Global Reports, 2023. **3**(2): p. 100175.
11. Bahri Khomami, M., et al., *Systematic review and meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome*. Nature communications, 2024. **15**(1): p. 5591.
12. Joshi, A., et al., *PCOS and the risk of pre-eclampsia*. Reproductive biomedicine online, 2022. **45**(5): p. 961-969.
13. Zhang, C., et al., *Oxidative stress on vessels at the maternal-fetal interface for female reproductive system disorders: Update*. Frontiers in Endocrinology, 2023. **14**: p. 1118121.
14. Jiang, R., et al., *Preeclampsia in pregnant women with polycystic ovary syndrome: Risk factor analysis based on a retrospective cohort study*. Ginekologia Polska, 2024. **95**(5): p. 365-372.
15. Pan, Z., F. Zhu, and K. Zhou, *A systematic review of anogenital distance and gynecological disorders: endometriosis and polycystic ovary syndrome*. Frontiers in Endocrinology, 2021. **12**: p. 696879.
16. Li, X., et al., *The risk factors of gestational diabetes mellitus in patients with polycystic ovary syndrome: What should we care*. Medicine (Baltimore), 2021. **100**(31): p. e26521.
17. Yun, B.H., et al., *Prepregnancy Insulin Resistance and Fertility and Pregnancy Outcomes in Women With Polycystic Ovarian Syndrome*. Obstetrics & Gynecology, 2026.
18. Kifle, M.M., et al., *The prognostic utility of soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) biomarkers for predicting preeclampsia: a secondary analysis of data from the INSPIRE trial*. BMC Pregnancy Childbirth, 2022. **22**(1): p. 520.
19. Binder, J., et al., *Longitudinal assessment of angiogenic markers in prediction of adverse outcome in women with confirmed pre-eclampsia*. Ultrasound in Obstetrics & Gynecology, 2023. **62**(6): p. 843-851.
20. Ujvari, D., et al., *Maternal serum levels of prokineticin-1 related to pregnancy complications and metformin use in*

women with polycystic ovary syndrome: a post hoc analysis of two prospective, randomised, placebo-controlled trials. Bmj Open, 2023. **13**(11): p. e073619.

21. Guo, X., et al., *The impact of hyperandrogenemia on pregnancy complications and outcomes in patients with PCOS: a systematic review and meta-analysis*. Hypertension in pregnancy, 2024. **43**(1): p. 2379389.
22. Dang, C., et al., *Polycystic ovary syndrome and risk of pregnancy-induced hypertension, gestational diabetes mellitus, and preeclampsia: a Bayesian Mendelian randomization study*. Diabetology & Metabolic Syndrome, 2025. **17**(1): p. 204.