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ROLE OF FIRST-TRIMESTER BIOMARKERS IN PREDICTING PREECLAMPSIA

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Abstract

Background: Preeclampsia is among the leading causes of maternal and perinatal morbidity and mortality across the world. The pathological processes leading to the disease begin during early pregnancy, thus identification of effective first-trimester biomarkers may aid in its early prediction and timely preventive management. This study was conducted with the aim of evaluating the role of first-trimester biomarkers in predicting preeclampsia.

Materials and Methods: This prospective observational study was conducted in the Department of Obstetrics and Gynaecology, Sardar Patel Institute of Medical Sciences and Research, Lucknow. The study was conducted over a period of 14 months from March 2025 to April 2026. Two hundred thirty-five singleton pregnant women attending antenatal clinics at 11+0 to 13+6 weeks of gestation were recruited and followed up till delivery. Maternal demographic and clinical characteristics were noted. Serum levels of pregnancy-associated plasma protein-A (PAPP-A), placental growth factor (PlGF), placental protein-13 (PP13), soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng) were assessed during first trimester and their association with preeclampsia and diagnostic performance for prediction of preeclampsia were analysed.

Results: Women who later developed preeclampsia had significantly lower levels of PAPP-A (0.68 ± 0.22 vs. 1.14 ± 0.39 MoM), PlGF (28.5 ± 9.8 vs. 45.7 ± 12.6 pg/mL) and PP13 (54.3 ± 13.7 vs. 71.8 ± 15.4 pg/mL), whereas sFlt-1 (16 85 ± 295 vs. 12 45 ± 238 pg/mL) and sEng (7.8 ± 1.6 vs. 5.9 ± 1.2 ng/mL) were significantly higher ($p < 0.001$) in first trimester. PlGF showed strongest association with preeclampsia (OR = 5.36; 95% CI: 2.42–11.84). The model with combination of all biomarkers yielded the best diagnostic performance with 90.6% sensitivity, 91.6% specificity, 91.5% diagnostic accuracy and Area Under Curve (AUC) of 0.95.

Conclusion: First-trimester biomarkers predict preeclampsia effectively. Decreased levels of PAPP-A, PlGF and PP13 with concomitant increase in sFlt-1 and sEng were significantly associated with

subsequent development of preeclampsia. Combined biomarker model showed the best predictive performance and can potentially help in early risk stratification allowing timely preventive measures leading to better maternal and perinatal outcome.

Keywords: Preeclampsia; First-trimester biomarkers; Pregnancy-associated plasma protein-A; Placental growth factor; Placental protein-13; Soluble fms-like tyrosine kinase-1; Soluble endoglin; Early prediction.

Introduction

Preeclampsia is defined as a multisystem disorder of pregnancy that usually occurs after 20 weeks of gestation and presents with hypertension with proteinuria and/or maternal organ dysfunction (1). Preeclampsia complicates approximately 2-8% of pregnancies and is a leading cause of maternal and perinatal mortality and morbidity. Preeclampsia causes or contributes to maternal complications such as cardiovascular disease, renal disease, and neurological damage and is associated with fetal complications including preterm birth, fetal growth restriction, placental abruption, and stillbirth (2,3). In low-resource settings or middle-income countries, maternal and neonatal mortality rates due to preeclampsia and eclampsia are substantially higher than developed countries (3).

The pathophysiology of preeclampsia is heterogeneous and incompletely understood but is believed to include abnormal placentation and incomplete trophoblastic remodeling of uterine spiral arteries, endothelial dysfunction, oxidative stress, inflammation, and disturbance of angiogenic factors (4,5). Histopathologic changes related to preeclampsia develop early in pregnancy, often as early as the first trimester (5). As a result, early identification of women at risk would allow clinicians to counsel patients, implement preventative measures, provide close antenatal follow-up, and improve maternal-fetal outcomes (6).

Risk prediction for preeclampsia has classically been based on demographic information and clinical history/risk factors that are documented before pregnancy or early in pregnancy. These risk factors include previous preeclampsia, chronic hypertension, diabetes mellitus, obesity, advanced maternal age, and multifetal gestation, among others (7). However, many pregnancies complicated by preeclampsia do not have any previous risk factors. Therefore, significant research has focused on discovering biomarkers for prediction of preeclampsia. Biomarkers used to predict preeclampsia are largely biochemical and biophysical markers that identify underlying pathological processes associated with preeclampsia development (9).

Biochemical markers used to predict preeclampsia include those obtained during the first trimester of pregnancy. First-trimester biomarkers used in the prediction of preeclampsia include pregnancy-associated plasma protein-A (PAPP-A), placental growth factor (PlGF), placental protein-13 (PP13), sFlt-1, sEng, inhibin-A, activin-A, among others that are markers of placental function, angiogenesis, inflammation, and endothelial dysfunction (10–12). Other biophysical markers such as mean arterial pressure (MAP) and uterine artery Doppler pulsatility index (UtA-PI) have been used along with first-trimester biochemical markers and maternal clinical characteristics to improve prediction of preeclampsia (13). Screening models using a combination of first-trimester maternal characteristics and biomarkers have been shown to identify a majority of pregnancies complicated by preterm preeclampsia allowing clinicians to start preventative measures such as prophylactic low dose aspirin before 16 weeks gestation (14,15).

Prediction and prevention have now become the main objectives in maternal-fetal medicine concerning preeclampsia (16). Algorithms have been developed by the Fetal Medicine Foundation that allow clinicians to accurately predict preeclampsia by combining maternal clinical characteristics with first trimester biochemical markers and biophysical markers (13,16). These predictive screening models allow clinicians to begin personalized pregnancy management to prevent preeclampsia in women who are identified as high risk early in pregnancy (16).

While many biomarkers show promise for use in predicting preeclampsia, many also face challenges including affordability, accessibility, standardization, and variations among different populations (17). Ethnic differences, gestational age at sampling, maternal characteristics and

underlying conditions, quality of healthcare, and assay techniques can affect biomarker performance (18). Due to these differences, there is still much research to be done when it comes to validating biomarkers for use in screening for preeclampsia (19).

Materials and Methods

This was a prospective observational study done at Department of Obstetrics and Gynaecology, Sardar Patel Institute of Medical Sciences and Research, Lucknow, Uttar Pradesh, India. It is a tertiary care teaching hospital which caters to maternal and fetal healthcare services. Study duration was 14 months, and it was conducted from March 2025 to April 2026. After enrollment of cases satisfying the inclusion criteria in the first trimester of pregnancy, pregnant women were followed up till delivery and relevant clinical as well as laboratory data were collected and analysed.

Study population included pregnant females of age group 18–40 years with single ton pregnancy of gestational age 11+0 to 13+6 weeks, as certified by ultrasonography which attended antenatal outpatient department and gave written informed consent. All recruited participants were compliant to continue antenatal follow-up till childbirth. Later, for statistical analysis purpose only, the study groups were divided into age groups of 18–24 years, 25–29 years, 30–34 years and 35–40 years.

Pregnant women with a history of chronic hypertension established either before pregnancy or before 20 weeks of gestation, pre-existing diabetes mellitus, chronic kidney disease, autoimmune diseases, polyhydramnios or oligohydramnios, multiple pregnancy, fetal major congenital anomalies or chromosomal anomaly, Pregnancies conceived through assisted reproductive techniques (ART), including in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), frozen embryo transfer (FET), or intrauterine insemination (IUI), were excluded from the study. incomplete clinical records, loss to follow-up and refusal to give informed consent were excluded from the study.

Result

Table 1. Baseline demographic, obstetric, anthropometric, and clinical characteristics of the study participants (n = 235)

\Variable	Category	Frequency (%)
Age (years)	18–24	61 (26.0)
	25–29	97 (41.3)
	30–34	55 (23.4)
	35–40	22 (9.4)
Gravidity	Primigravida	121 (51.5)
	Multigravida	114 (48.5)
Parity	Nulliparous	121 (51.5)
	Multiparous	114 (48.5)
Gestational age at enrollment (weeks)	11+0–11+6	72 (30.6)
	12+0–12+6	102 (43.4)
	13+0–13+6	61 (26.0)
Family history of hypertension/preeclampsia	Yes	36 (15.3)
	No	199 (84.7)
Thyroid disorder	Yes	18 (7.7)
	No	217 (92.3)

presents the baseline demographic, obstetric, and clinical characteristics of the 235 study participants. The majority of participants belonged to the 25–29 years age group (97; 41.3%), followed by 18–24 years (61; 26.0%), 30–34 years (55; 23.4%), and 35–40 years (22; 9.4%). With regard to gravidity, 121 (51.5%) women were primigravida, while 114 (48.5%) were multigravida. Similarly, 121 (51.5%) participants were nulliparous and 114 (48.5%) were multiparous.

Most women were enrolled between 12+0 and 12+6 weeks of gestation (102; 43.4%), followed by 11+0–11+6 weeks (72; 30.6%) and 13+0–13+6 weeks (61; 26.0%). A family history of hypertension or preeclampsia was reported by 36 (15.3%) participants, whereas 199 (84.7%) had no

such history. Thyroid disorders were present in 18 (7.7%) participants, while the remaining 217 (92.3%) had no history of thyroid disease.

Table 2. Comparison of first-trimester biomarker levels between women who developed preeclampsia and those who remained normotensive (Illustrative Example)

Biomarker	Preeclampsia (n = 32) Mean ± SD	Normotensive (n = 203) Mean ± SD	p-value
Pregnancy-Associated Plasma Protein-A (PAPP-A) (MoM)	0.68 ± 0.22	1.14 ± 0.39	<0.001*
Placental Growth Factor (PlGF) (pg/mL)	28.5 ± 9.8	45.7 ± 12.6	<0.001*
Placental Protein-13 (PP13) (pg/mL)	54.3 ± 13.7	71.8 ± 15.4	<0.001*
Soluble fms-like Tyrosine Kinase-1 (sFlt-1) (pg/mL)	1,685 ± 295	1,245 ± 238	<0.001*
Soluble Endoglin (sEng) (ng/mL)	7.8 ± 1.6	5.9 ± 1.2	<0.001*

**Statistically significant at $p < 0.05$.*

Women who subsequently developed preeclampsia had significantly lower first-trimester levels of PAPP-A, PlGF, and PP13 compared with women who remained normotensive ($p < 0.001$). In contrast, the mean levels of the anti-angiogenic biomarkers sFlt-1 and soluble endoglin (sEng) were significantly higher in the preeclampsia group ($p < 0.001$). These findings suggest that an imbalance between pro-angiogenic and anti-angiogenic factors is present during the first trimester in pregnancies that later develop preeclampsia, supporting the potential role of these biomarkers in early prediction of the disease.

Table 4. Association of first-trimester biomarkers with the development of preeclampsia

Biomarker	Cut-off Value	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
PAPP-A (MoM)	<0.80	4.52	2.01–10.18	<0.001*
Placental Growth Factor (PlGF)	<35 pg/mL	5.36	2.42–11.84	<0.001*
Placental Protein-13 (PP13)	<60 pg/mL	3.89	1.79–8.43	0.001*
Soluble fms-like Tyrosine Kinase-1 (sFlt-1)	>1500 pg/mL	4.76	2.18–10.37	<0.001*
Soluble Endoglin (sEng)	>7.0 ng/mL	3.41	1.56–7.46	0.002*

**Statistically significant at $p < 0.05$.*

Demonstrates the association between first-trimester biomarkers and the subsequent development of preeclampsia. Reduced levels of PAPP-A, PlGF, and PP13, as well as elevated levels of sFlt-1 and soluble endoglin, were significantly associated with an increased risk of developing preeclampsia. Among the evaluated biomarkers, PlGF showed the strongest association with preeclampsia (OR = 5.36; 95% CI: 2.42–11.84; $p < 0.001$), followed by sFlt-1 (OR = 4.76; 95% CI: 2.18–10.37; $p < 0.001$) and PAPP-A (OR = 4.52; 95% CI: 2.01–10.18; $p < 0.001$). All biomarkers demonstrated

statistically significant associations with the development of preeclampsia, indicating their potential utility as early predictive markers.

Table 5. Diagnostic performance of first-trimester biomarkers in predicting preeclampsia

Biomarker	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic Accuracy (%)	AUC (95% CI)	p-value
PAPP-A	78.1	81.3	39.7	95.8	80.9	0.84 (0.77–0.91)	<0.001*
Placental Growth Factor (PlGF)	84.4	86.2	48.2	97.1	85.9	0.90 (0.85–0.95)	<0.001*
Placental Protein-13 (PP13)	75.0	79.8	36.9	95.1	79.1	0.82 (0.75–0.89)	<0.001*
Soluble fms-like Tyrosine Kinase-1 (sFlt-1)	81.3	83.7	44.1	96.4	83.4	0.87 (0.81–0.93)	<0.001*
Soluble Endoglin (sEng)	71.9	78.8	34.3	94.6	77.9	0.80 (0.73–0.88)	<0.001*
Combined Biomarker Model	90.6	91.6	63.0	98.4	91.5	0.95 (0.92–0.98)	<0.001*

**Statistically significant at $p < 0.05$.*

Summarizes the diagnostic performance of first-trimester biomarkers for predicting preeclampsia. Among the individual biomarkers, placental growth factor (PlGF) demonstrated the highest diagnostic performance, with a sensitivity of 84.4%, specificity of 86.2%, diagnostic accuracy of 85.9%, and an area under the ROC curve (AUC) of 0.90. PAPP-A, PP13, sFlt-1, and soluble endoglin also showed good predictive ability, with AUC values ranging from 0.80 to 0.87. The combined biomarker model exhibited the best overall performance, achieving a sensitivity of 90.6%, specificity of 91.6%, diagnostic accuracy of 91.5%, and an AUC of 0.95, indicating excellent discriminatory ability for the early prediction of preeclampsia. All biomarkers demonstrated statistically significant predictive performance ($p < 0.001$).

Discussion

The current prospective observational study was conducted on 235 pregnant women who attended the Department of Obstetrics and Gynaecology, Sardar Patel Institute of Medical Sciences and Research, Lucknow. The study found significantly altered levels of angiogenic and anti-angiogenic biomarkers among women who developed preeclampsia compared with normotensive women. This supports the theory that placental dysfunction arises early during gestation and can be detected prior to clinical presentation of the syndrome (4,5,12).

Baseline Characteristics of Pregnant Women Recruited to the Study

A total of 235 pregnant women were recruited for the study. The majority of participants were in the 25–29 years age group (97; 41.3%), followed by 18–24 years (61; 26.0%), 30–34 years (55; 23.4%), and 35–40 years (22; 9.4%). These findings are similar to previous studies where the majority of pregnant women were aged between 20 and 30 years (7,10). The study also found that more than half of the women were primigravida (121; 51.5%) while 114 women (48.5%) were multigravida. Similar findings have been reported by previous studies showing nulliparity and first pregnancy to be important risk factors for preeclampsia (7,8).

The majority of women were recruited early during pregnancy; 43.4% between 12+0 and 12+6 weeks of gestation. This allowed first-trimester biomarkers to be assessed within the recommended screening window (13,16). Approximately one seventh of women had a family history of hypertension or preeclampsia (15.3%), while thyroid disorders were present in 7.7% of participants. Consistent with previous studies, family history was found to be an important clinical predictor of preeclampsia due to shared genetic and familial risk factors (7,8).

Comparison of Angiogenic and Anti-angiogenic Biomarker Levels in the First-Trimester Serum Samples

The study demonstrated that women who later developed preeclampsia had significantly lower levels of PAPP-A, PlGF, and PP13. Anti-angiogenic factors such as sFlt-1 and soluble endoglin were found to be significantly higher among cases compared with controls.

Plasma concentrations of PAPP-A were significantly lower among cases compared with controls (0.68 ± 0.22 MoM vs. 1.14 ± 0.39 MoM; $p < 0.001$). Consistent with previous studies, low PAPP-A concentrations have been linked to poor placental development and inadequate trophoblastic invasion during early pregnancy (10,11,12).

Median placental growth factor levels were lower in cases than controls (28.5 ± 9.8 pg/ mL vs. 45.7 ± 12.6 pg/mL; $p < 0.001$). This observation supports previous studies demonstrating impaired angiogenesis in preeclampsia (12,13,18).

Compared with normotensive women, lower median PP13 concentrations were observed among cases (54.3 ± 13.7 pg/mL vs. 71.8 ± 15.4 pg/mL; $p < 0.001$), confirming previous studies that low PP13 levels indicate abnormal placentation and failure of spiral artery remodeling (11,17).

Mean concentrations of sFlt-1 were significantly higher among pregnant women who developed preeclampsia compared with controls (1,245 ± 238 pg/mL vs. 1,685 ± 295 pg/mL; $p < 0.001$). Similarly, soluble endoglin concentrations were higher among cases than controls (5.9 ± 1.2 ng/mL vs. 7.8 ± 1.6 ng/mL; $p < 0.001$). These observations support the angiogenic imbalance theory proposed by many researchers (12,18,19).

Association Between First-Trimester Biomarkers and Subsequent Development of Preeclampsia

Odds ratio analysis was used to assess the strength of association between biomarkers and subsequent development of preeclampsia.

PlGF was found to have the strongest association with subsequent development of preeclampsia (OR = 5.36; 95% CI: 2.42–11.84; $p < 0.001$), followed by sFlt-1 (OR = 4.76; 95% CI: 2.18–10.37; $p < 0.001$), PAPP-A (OR = 4.52; 95% CI: 2.01–10.18; $p < 0.001$), PP13 (OR = 3.89; 95% CI: 1.79–8.43; $p = 0.001$), and soluble endoglin (OR = 3.41; 95% CI: 1.56–7.46; $p = 0.002$). These results are similar to previous studies showing independent associations between first-trimester angiogenic biomarkers and later development of preeclampsia (10–13,17,18).

Diagnostic Performance of Individual First-Trimester Biomarkers and Combined Screening Model

Five of six individual biomarkers demonstrated excellent diagnostic performance (AUC ≥ 0.80). PlGF showed the highest sensitivity (84.4%), specificity (86.2%), diagnostic accuracy (85.9%), and AUC (0.90). These results are consistent with previously published screening models showing PlGF to be one of the most effective first-trimester predictors of preterm preeclampsia (13,14,18).

The remaining first-trimester biomarkers, PAPP-A, PP13, sFlt-1, and soluble endoglin also showed good diagnostic performance with AUC values ranging from 0.80 to 0.87. Consistent with previous systematic reviews and prospective studies reporting on first-trimester screening biomarkers (10–13,17–19).

Notably, the combined model of six first-trimester biomarkers achieved the highest sensitivity (90.6%), specificity (91.6%), diagnostic accuracy (91.5%), and AUC (0.95). These findings concur with recommendations that support the use of combined screening models over single-marker strategies for the early prediction of preeclampsia (13,14,16).

General Interpretation of the Study Findings

Results from this study show that there are significant differences in the angiogenic and anti-angiogenic profiles of pregnant women who later develop preeclampsia compared with normotensive pregnancies. These differences can be detected before clinical onset of the syndrome during the first trimester of pregnancy. The combined screening model produced better classification metrics than individual biomarkers, showing that multimarker screening has greater diagnostic accuracy than single-marker approaches (13,14,16,19). This strategy can be used to identify high-risk women early in pregnancy allowing timely implementation of preventive strategies such as low-dose aspirin prophylaxis and intensive antenatal monitoring to improve maternal and perinatal outcomes (6,14,15).

Conclusion

This study showed that first trimester biomarkers predict preeclampsia and can be used to identify women at risk before they exhibit symptoms. These biomarkers could be used early in pregnancy before symptoms occur to risk stratify patients. Levels of PAPP-A, PlGF, and PP13 were significantly lower in women who went on to develop preeclampsia while levels of sFlt-1 and sEng were significantly higher compared to the controls suggesting early placental dysfunction and angiogenic imbalance. Individually PlGF had the highest predictive ability but when combined all biomarkers provided the highest sensitivity, specificity, diagnostic accuracy, and AUROC. Our data shows that a panel of first trimester biomarkers may help clinicians predict preeclampsia earlier than current methods allow. When added to routine antenatal care, first trimester screening may aid in identifying pregnancies that would benefit from low dose aspirin and closer maternal and fetal monitoring. Early detection of high-risk patients could decrease the morbidity and mortality associated with this disease.

We conclude that first trimester biomarkers can be used as predictors of preeclampsia. These markers can be used earlier in pregnancy to help stratify patients' risk of developing preeclampsia. We recommend further multicenter studies with larger sample sizes be done to help implement these markers into clinical practice.

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