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Original Research Article

Integrated First-Trimester Assessment of Maternal Factors, Placental Growth Factor, and Placental Volume for Prediction of Preeclampsia

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Abstract:

Background: Preeclampsia is a major hypertensive disorder of pregnancy associated with significant maternal and perinatal morbidity and mortality. Early identification of high-risk women during the first trimester may allow timely preventive interventions and improved outcomes.

Aim: To evaluate the predictive performance of first-trimester maternal characteristics, serum placental growth factor (PlGF), and estimated placental volume for the development of preeclampsia.

Methodology: This prospective observational study included 80 singleton pregnancies between 11 and 13+6 weeks of gestation. Maternal clinical data were recorded, serum PlGF levels were measured using ELISA, and placental volume was assessed by three-dimensional ultrasonography. Participants were followed until delivery for the development of preeclampsia. Diagnostic performance was evaluated using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Results: Preeclampsia developed in 17.5% of participants. Women who developed preeclampsia had significantly lower first-trimester PlGF levels and placental volumes, and higher body mass index ($p < 0.05$). PlGF alone showed a sensitivity of 71.4% and specificity of 81.8%, while reduced placental volume demonstrated moderate predictive accuracy. The combined model incorporating maternal characteristics, PlGF, and placental volume achieved the highest sensitivity (85.7%) and specificity (89.4%), with a negative predictive value of 96.7%.

Conclusion: Integration of maternal characteristics with first-trimester PlGF and placental volume significantly improves early prediction of preeclampsia. An integrated screening approach may facilitate early risk stratification and targeted preventive care.

Keywords: Preeclampsia, First-trimester screening, Placental growth factor, Placental volume, Prediction, Maternal risk factors.

Introduction

Preeclampsia is a pregnancy-specific hypertensive disorder characterized by new-onset hypertension after 20 weeks of gestation, accompanied by proteinuria or evidence of maternal end-organ dysfunction. It remains one of the leading causes of maternal and perinatal morbidity and mortality worldwide [1]. Globally, preeclampsia affects approximately 2–8% of pregnancies and contributes substantially to adverse maternal and neonatal outcomes. Despite advances in obstetric care, preeclampsia continues to pose significant clinical challenges due to its complex pathophysiology, variable clinical presentation, and the absence of a definitive cure other than delivery. The underlying mechanisms are not completely understood, although abnormal placentation and subsequent endothelial dysfunction are considered central to disease development. Early identification of women at increased risk is essential, as it enables timely implementation of preventive strategies and closer antenatal surveillance. First-trimester risk assessment has therefore gained increasing importance in contemporary obstetric practice, with the aim of improving maternal and perinatal outcomes through targeted intervention and monitoring [2].

The pathophysiology of preeclampsia develops through multiple pathways because the condition requires multiple processes to function, yet abnormal placentation operates as the primary mechanism which drives the disease forward [3]. During normal pregnancy, trophoblastic invasion of the maternal spiral arteries leads to their remodeling into low-

resistance vessels that can supply the increasing needs, which the developing fetus requires for growth. Preeclampsia interferes with this process because it prevents proper uteroplacental blood flow, which results in placental tissue death and the subsequent release of antiangiogenic substances into the bloodstream of the mother. These changes ultimately create a situation of widespread endothelial dysfunction, which shows clinical symptoms through hypertension and proteinuria and various other body system issues [4]. The onset of placental abnormalities occurs during the early stages of pregnancy, which happens before preeclampsia shows its first clinical signs, thus emphasizing the usefulness of first-trimester tests.

Maternal characteristics and clinical history have long been used to identify women at increased risk of preeclampsia [5]. The established risk indicators for this condition include advanced maternal age nulliparity and obesity together with chronic hypertension and diabetes mellitus and renal disease and autoimmune disorders and prior preeclampsia. The screening method which uses only maternal characteristics shows poor results because many women who develop preeclampsia lack known risk factors and many high-risk women remain disease-free. Researchers have started investigating the use of biochemical and biophysical markers to detect early-stage placental dysfunction because of this research limitation.

Placental growth factor (PlGF), a proangiogenic protein belonging to the vascular endothelial growth factor family, has emerged as a promising biomarker for preeclampsia prediction [6]. The body produces higher levels of PlGF during early pregnancy because it functions as a vital component for developing placental blood vessels and for creating new blood vessels in the placenta. Maternal serum PlGF concentrations demonstrate a significant decrease during the first trimester for pregnancies that progress to early-onset preeclampsia [7]. The placenta undergoes developmental impairment because of this reduction which creates a situation where proangiogenic factors and antiangiogenic factors do not exist in balance. The first-trimester PlGF measurement enables clinicians to assess early placental health which enhances risk evaluation when combined with maternal clinical information.

Besides biochemical markers, the development of imaging technologies has allowed measuring the morphology of the placenta in early pregnancy [8]. Estimated placental volume (EPV), which is normally determined by three-dimensional ultrasound, is used as a measure of placental growth and development. Reduced placental volume at the first trimester has been linked to poor placentation as well as high chances of poor pregnancy outcomes such as preeclampsia, fetal growth retardation, and preterm birth [9]. However, as compared to the conventional two-dimensional measurements, three-dimensional ultrasound can be used to measure placental size in a more comprehensive and comprehensive fashion, which provides an effective and non-invasive and reproducible approach to early risk detection.

Combining maternal features, biochemical (PlGF) and biophysical (estimated placenta volume) parameters can be considered a multifactorial strategy of prediction of preeclampsia in the first trimester [10]. Such a combined screening approach is consistent with the realization that preeclampsia is a heterogeneous disease that has different etiologies and clinical manifestations. With the addition of the markers of maternal risk factors as well as early placental development, predictive models may have a higher sensitivity and specificity than single-parameter screening approaches.

Clinical implications of early detection of women with high risks of developing preeclampsia are significant. In evidence, it has been alleged that preventive measures like taking low doses of aspirin before gestation period of 16 weeks can greatly help in reducing the rate of preeclampsia, especially an early onset. What is more, individualized antenatal care, such as more frequent observation, referral to specialized centers in time, and better preparedness to possible complications, is possible with risk stratification during the first trimester. In this regard, the first-trimester prediction models with maternal characteristics, placental growth factor, and estimated placental volume have a significant potential of enhancing maternal and perinatal outcomes.

This attempt to predict preeclampsia in the first trimester with a combination of maternal, PlGF and estimated placenta volume indicates a paradigm change of pre-early screening to pathophysiology screening. The method is not only more accurate in predictive outcomes, but also contributes to the general aim of preventive obstetric care, through facilitating early intervention and specific management decisions in women with the potential of this potentially fatal condition.

Methodology

Study Design: This was a prospective observational study designed to evaluate the effectiveness of first-trimester screening for the prediction of preeclampsia using maternal characteristics, serum placental growth factor (PlGF) levels, and estimated placental volume assessed by three-dimensional ultrasonography. Pregnant women were enrolled during their first trimester and followed prospectively to assess outcomes related to preeclampsia.

Study Area: The study was conducted in the Department of Obstetrics and Gynaecology, Nalanda Medical College and Hospital, Patna, Bihar, India.

Study Duration: The duration of the study was one year from September 2023 to August 2024

Study Participants: A total of 80 pregnant women with singleton pregnancies between 11 and 13+6 weeks of gestation, confirmed by ultrasonography, were enrolled consecutively after obtaining written informed consent.

Inclusion Criteria

- Pregnant women aged 18–34 years
- Singleton pregnancy
- Gestational age between 11 and 13+6 weeks, confirmed by ultrasonography
- Willingness to participate and provide written informed consent

Exclusion Criteria

- Chronic hypertension
- Diabetes mellitus
- Renal disease
- Autoimmune disorders
- Multiple pregnancy
- Structural or chromosomal fetal abnormalities
- Use of aspirin or antihypertensive therapy in early pregnancy

Sample Size: The sample size was calculated based on the expected incidence of preeclampsia and anticipated sensitivity of the combined screening model.

Assuming:

- Expected incidence of preeclampsia = 10% (based on previous literature)
- Expected sensitivity of combined screening model = 85%
- Confidence level = 95%
- Allowable error = 10%

Using the standard formula for diagnostic test evaluation, the minimum required sample size was estimated to be 73 participants. Considering possible dropouts and incomplete follow-up, a total of 80 participants were enrolled.

Procedure: At enrollment, detailed maternal history was recorded including age, parity, BMI, previous obstetric history, and family history of hypertension. General and obstetric examinations were performed.

Venous blood samples were collected under aseptic precautions. Serum was separated and stored at –70°C until analysis. Serum PlGF concentration was measured using a commercially available ELISA kit according to manufacturer instructions. Measurements were performed in duplicate, and results were expressed in pg/mL.

Three-dimensional transabdominal ultrasonography was performed using a 4–8 MHz transducer. Placental volume was calculated using VOCAL™ software with an 85° rotational sweep and six rotational planes at 30° intervals. Manual tracing of placental contours was performed excluding the uterine wall.

Participants were followed throughout pregnancy. The primary outcome was the development of preeclampsia.

Preeclampsia: Preeclampsia was diagnosed according to the criteria established by the American College of Obstetricians and Gynecologists (ACOG). It was defined as new-onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on two occasions at least 4 hours apart) occurring after 20 weeks of gestation, accompanied by proteinuria (≥300 mg in a 24-hour urine collection or urine protein/creatinine ratio ≥0.3). In the absence of proteinuria, preeclampsia was diagnosed if hypertension was associated with evidence of maternal end-organ dysfunction, including thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, or new-onset cerebral or visual disturbances.

Statistical Analysis: Data were analyzed using SPSS version 27.0. Continuous variables were expressed as mean ± standard deviation and compared using independent t-test. Categorical variables were expressed as frequencies and percentages and analyzed using chi-square test. Receiver Operating Characteristic (ROC) curve analysis was performed to determine optimal cut-off values and calculate sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Result

The study examined 80 participants to establish baseline maternal characteristics which showed that mothers had an average age of 26.4 ± 4.2 years and they entered the study at 12.1 ± 0.8 weeks of pregnancy. Most study participants showed body mass index results of 24.8 ± 3.1 kg/m² which indicated that they maintained body weight between normal and slightly overweight. The obstetric profile of the study group showed a balanced distribution between first-time mothers who made up 52.5% and women who had given birth before who accounted for 47.5%. The study population contained substantial risk factors for hypertensive disorders in pregnancy because 22.5% of participants reported family history of hypertension and 7.5% had previous cases of preeclampsia.

Table 1: Baseline Maternal Characteristics of Study Participants (n = 80)	
Variable	**Mean ± SD / n (%)**
Maternal age (years)	26.4 ± 4.2
Gestational age at enrolment (weeks)	12.1 ± 0.8
Body mass index (kg/m²)	24.8 ± 3.1
Primigravida	42 (52.5%)
Multigravida	38 (47.5%)
Family history of hypertension	18 (22.5%)
Previous history of preeclampsia	6 (7.5%)

Table 2 presents the laboratory and ultrasonographic findings from the first trimester of the study. The mean serum placental growth factor (PlGF) level showed 86.3 ± 28.7 pg/mL which demonstrated early placental angiogenic activity with moderate inter-individual variability. The average placental volume measured 63.5 ± 14.9 cm³, indicating adequate placental development during the first trimester. The hemoglobin levels showed an average value of 11.2 ± 1.1 g/dL, which indicated that most participants kept their hemoglobin levels between normal and the lower limit of the normal range for pregnancy. The mean platelet count showed 2.48 ± 0.52 × 10^5/μL which fell within the normal physiological range and demonstrated that the participant maintained normal blood cell levels during early pregnancy.

Table 2: First Trimester Laboratory and Ultrasonographic Parameters	
Parameter	**Mean ± SD**
Serum PlGF (pg/mL)	86.3 ± 28.7
Placental volume (cm³)	63.5 ± 14.9
Hemoglobin (g/dL)	11.2 ± 1.1
Platelet count (×10^5/μL)	2.48 ± 0.52

Table 3 shows that preeclampsia developed in 14 out of the study participants, accounting for 17.5%, while the majority, 66 participants (82.5%), did not develop preeclampsia during the study period. Among those who developed preeclampsia, early-onset preeclampsia occurring before 34 weeks of gestation was observed in 5 participants (6.3%), whereas late-onset preeclampsia occurring at or after 34 weeks was more common, affecting 9 participants (11.2%). The distribution shows that preeclampsia occurred at a low rate among participants, yet the late-onset form of the condition affected a greater number of cases than the early-onset type.

Table 3: Incidence of Preeclampsia Among Study Participants	
Outcome	**n (%)**
Developed preeclampsia	14 (17.5%)
Did not develop preeclampsia	66 (82.5%)
Early-onset preeclampsia (<34 weeks)	5 (6.3%)
Late-onset preeclampsia (≥34 weeks)	9 (11.2%)

Table 4 compares first-trimester parameters between women who developed preeclampsia and those who did not. Women with preeclampsia showed both lower average serum PlGF levels and reduced placental volume when compared to the non-preeclampsia group, which demonstrated they developed placentas improperly during early pregnancy ($p < 0.001$ for both). The women with preeclampsia obtained higher average BMI values, which demonstrates a connection between elevated maternal body fat and increased risk of the condition ($p = 0.003$). The preeclampsia group showed delivery at an earlier gestational age because they had a greater chance of delivering their babies before reaching term ($p < 0.001$). The findings demonstrate early biochemical differences together with placental and maternal distinctions that appear in pregnancies complicated by preeclampsia.

Table 4: Comparison of First Trimester Parameters Between Women with and Without Preeclampsia			
Parameter	**Preeclampsia (n=14) Mean ± SD**	**No Preeclampsia (n=66) Mean ± SD**	**p-value**
Serum PlGF (pg/mL)	52.6 ± 18.4	94.1 ± 24.3	<0.001
Placental volume (cm³)	48.3 ± 10.2	67.1 ± 13.6	<0.001
BMI (kg/m²)	27.1 ± 3.4	24.2 ± 2.8	0.003
Gestational age at delivery (weeks)	35.6 ± 2.8	38.4 ± 1.6	<0.001

Table 5 presents data that shows how different first-trimester markers predict preeclampsia, which demonstrates that each individual measurement shows distinct results when compared to the combined testing method. The test showed good results because it achieved 71.4% sensitivity and 81.8% specificity through PlGF testing, which produced a 93.1% negative predictive value that doctors can use to confirm patient diagnosis. The combination of placental volume and maternal characteristics demonstrated diminished predictive capacity because their individual testing showed reduced sensitivity and lesser ability to identify actual cases. The combined model which included maternal data and PlGF and placental volume achieved its best performance through 85.7% sensitivity and 89.4% specificity and 66.7% PPV and 96.7% NPV. The study results demonstrate that using multiple biochemical and biophysical and maternal assessment methods enables better early preeclampsia detection than single assessment tests.

Table 5: Predictive Performance of First Trimester Markers for Preeclampsia

Parameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Low PlGF alone	71.4	81.8	45.5	93.1
Reduced placental volume alone	64.3	78.8	39.1	90.7
Maternal characteristics alone	57.1	74.2	33.3	88.4
Combined model (maternal + PlGF + placental volume)	85.7	89.4	66.7	96.7

Discussion

The current research shows that first-trimester preeclampsia prediction improves when maternal characteristics get combined with serum placental growth factor (PlGF) levels and estimated placental volume (EPV) measurements. The assessment at around 12 weeks of gestation allows evaluation of biomarkers during the critical phase of placental development when abnormal placentation begins to manifest. The preeclampsia rate in this group reached 17.5%, which demonstrates the prevalence of hypertensive disorders in tertiary healthcare facilities while showing the need for early risk assessment.

The current research shows that women who developed preeclampsia had lower first-trimester serum PlGF levels than the normotensive control group. The results demonstrate that low PlGF levels provided a sensitivity of 71.4% and a specificity of 81.8% while achieving a high negative predictive value of 93.1% and a low positive predictive value of 45.5%. PlGF serves as a useful tool for preeclampsia prediction because it accurately identifies women who will not develop the condition. Akolekar et al. (2008) [11] reported that low first-trimester PlGF levels were associated with increased risk of preeclampsia with detection rates of 55% for early-onset and 33% for late-onset disease at a 10% false-positive rate. Negm et al. (2022) [12] found that women who developed preeclampsia showed significantly lower maternal PlGF levels. Sonek et al. (2018) [13] found that PlGF levels decreased in affected pregnancies although different study designs and sample sizes produced varying statistical significance results. The research results confirm that PlGF acts as an early marker for placental dysfunction.

The study found that estimated placental volume showed decreased measurement as an important result. Women who developed preeclampsia showed lower EPV measurements during their first trimester compared to the control group. The assessment showed that reduced placental volume produced a test result which had 64.3% accuracy and 78.8% accuracy, showing it could make predictions about outcomes but at an average level. The research by Kim et al. (2021) [14] showed that first-trimester placental volumes in women who later developed preeclampsia showed lower values than normal, which indicates that the insufficient growth of the placenta shows that the trophoblastic cells did not enter the body properly. Sonek et al. (2018) [13] also observed reduced EPV in preeclampsia cases, though variability in statistical significance may be attributed to methodological differences. The research by Soongsatitanon and Phupong (2019) [15] shows that early assessment of placental volume delivers predictive value because it helps doctors discover which pregnancies face high risks of hypertensive disorders and fetal growth restriction.

Maternal body mass index (BMI) was significantly higher in the preeclampsia group in our study, reinforcing the established association between maternal obesity and hypertensive disorders of pregnancy. Elevated BMI contributes to systemic inflammation, endothelial dysfunction, and metabolic imbalance, which may exacerbate abnormal placentation. Kholin et al. (2018) [16] similarly identified maternal factors, including BMI, as important contributors to early prediction models for preeclampsia.

Parity did not show a statistically significant association with preeclampsia in the present study, consistent with the findings of Negm et al. (2022) [12]. Although Kashanian et al. (2011) [17] reported a protective effect of multiparity, variations across

studies may be influenced by demographic, genetic, and environmental factors.

Importantly, the combined predictive model incorporating maternal characteristics, serum PlGF, and placental volume demonstrated superior diagnostic performance compared to individual parameters. The combined model achieved a sensitivity of 85.7% and specificity of 89.4%, with a high negative predictive value of 96.7%. This supports the concept that preeclampsia is a multifactorial disorder and that integrated screening approaches provide better risk stratification than single-marker strategies. Similar multifactorial models have been recommended in previous literature for improving early detection and enabling timely preventive interventions.

Agrawal et al. (2019) [18] reported that the predictive accuracy of PlGF improves with advancing gestation; however, our findings demonstrate that meaningful predictive performance can already be achieved during the early first trimester when combined with maternal and ultrasonographic parameters. Early identification is clinically relevant, as it allows consideration of preventive strategies such as low-dose aspirin and closer antenatal surveillance.

The study has certain limitations, including a relatively small sample size and a limited number of preeclampsia cases, which may influence the precision of predictive estimates. Larger multicentric studies are required to validate optimal cut-off values and assess generalizability across different populations. Nevertheless, the present study provides evidence that first-trimester integration of maternal characteristics, PlGF, and placental volume enhances early prediction of preeclampsia and may facilitate improved maternal and perinatal outcomes through targeted monitoring and preventive care.

Conclusion

The present study demonstrates that first-trimester integration of maternal characteristics, serum placental growth factor (PlGF), and estimated placental volume significantly enhances the early prediction of preeclampsia. Women who subsequently developed preeclampsia showed significantly lower PlGF levels and reduced placental volume, along with higher maternal body mass index, compared to normotensive pregnancies. While individual markers demonstrated moderate predictive performance, the combined model achieved superior sensitivity and specificity, highlighting the multifactorial nature of preeclampsia. Early identification of high-risk pregnancies during the first trimester allows timely implementation of preventive strategies, including closer antenatal surveillance and consideration of low-dose aspirin therapy. Therefore, an integrated screening approach may improve risk stratification and contribute to better maternal and perinatal outcomes. Further large-scale studies are recommended to validate these findings and establish standardized cut-off values for routine clinical use.

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