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Original Research Article

Prediction of Adverse Obstetric Outcomes in High-Risk Pregnancies Using Maternal Serum PAPP-A, β-hCG and Placental Growth Factor Levels

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Abstract

Background: High-risk pregnancies are predisposed to adverse outcomes, including preeclampsia, fetal growth restriction, preterm birth, and stillbirth. This study evaluated the predictive utility of first-trimester maternal serum placental growth factor (PlGF), beta-human chorionic gonadotropin (β-hCG), and pregnancy-associated plasma protein-A (PAPP-A) for anticipating complications in women with established obstetric risk factors.

Methods: In this prospective cohort study, 200 high-risk pregnant women (18–40 years, 11–13+6 weeks' gestation) were recruited from a tertiary maternity center. High-risk status included chronic hypertension, diabetes, prior preeclampsia, or abnormal uterine artery Doppler findings. Serum PlGF, free β-hCG, and PAPP-A were measured via automated immunoassays and expressed as MoM adjusted for maternal weight, parity, and ethnicity. Primary endpoints were a composite of preeclampsia, intrauterine growth restriction (<10th percentile), early preterm birth (<34 weeks), and stillbirth. Predictive performance was assessed using logistic regression, receiver operating characteristic (ROC) analysis, and Kaplan-Meier survival curves; $p<0.05$ was considered significant.

Results: Adverse outcomes occurred in 58/200 (29%) pregnancies. Cases with complications had significantly lower PAPP-A (0.53±0.32 vs. 1.10±0.41 MoM), lower PlGF (0.69±0.38 vs. 1.06±0.45 MoM), and higher β-hCG (2.38±1.12 vs. 1.30±0.66 MoM) compared to unaffected pregnancies (all $p<0.001$). ROC analysis demonstrated AUCs of 0.87 (PlGF), 0.82 (PAPP-A), and 0.79 (β-hCG). A combined biomarker panel (PlGF/PAPP-A ratio + β-hCG) yielded superior predictive accuracy (AUC 0.92, 95% CI 0.88–0.95) with 88% sensitivity and 85% specificity at risk >1:50. Low PlGF (<5th percentile) independently predicted preeclampsia (OR 12.4; 95% CI 7.2–21.3; $p<0.001$).

Conclusions: First-trimester maternal serum PlGF, β-hCG, and PAPP-A robustly predict adverse obstetric outcomes in high-risk pregnancies. A multimarker algorithm enhances early risk stratification, supporting timely interventions such as low-dose aspirin therapy, closer surveillance, and targeted management to improve maternal-fetal outcomes.

Keywords: High-risk pregnancy, placental growth factor, PAPP-A, β-hCG, preeclampsia, first-trimester screening.

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Introduction

High-risk pregnancies represent a substantial public health challenge, contributing to disproportionate maternal and perinatal morbidity worldwide. Defined by factors such as advanced maternal age, chronic hypertension, pre-existing diabetes, obesity, or prior adverse obstetric events, these conditions elevate the likelihood of complications including preeclampsia (PE), fetal growth restriction (FGR), preterm birth, and stillbirth. [1,2] According to the World Health Organization, hypertensive disorders alone account for approximately 14% of maternal deaths globally, with incidence rates climbing in low-resource settings due to limited antenatal surveillance. [3] In high-income contexts like India, where gestational diabetes affects up to 20% of pregnancies, the interplay of metabolic, vascular, and placental dysfunctions amplifies risks, underscoring the need

for reliable early predictive tools. [4] The placenta, as the primary interface for maternal-fetal exchange, undergoes dynamic remodeling in early gestation, making first-trimester biomarkers pivotal for risk assessment. Placental growth factor (PlGF), a pro-angiogenic protein secreted by syncytiotrophoblasts, promotes vasculogenesis and endothelial maintenance during placentation. [5]

Inadequate trophoblast invasion—hallmark of PE and FGR—leads to PlGF downregulation, often evident by 11-14 weeks. Prospective studies report PlGF levels <5th percentile (typically <0.3-0.4 MoM) conferring 10-20-fold increased odds for preterm PE, with detection rates exceeding 90% at 10% false positives when integrated into screening algorithms. [6,7] Unlike second-trimester uterine artery Doppler, PlGF offers quantitative precision, unaffected by maternal hemodynamics, positioning it as a cornerstone for personalized surveillance. [8]

Pregnancy-associated plasma protein-A (PAPP-A), a protease regulating insulin-like growth factor bioavailability, peaks at 10 weeks before declining, reflecting cytotrophoblast proliferation and extracellular matrix turnover. [9] Low PAPP-A (<0.4 MoM) signals impaired placentation, associating with a 5-8-fold risk escalation for PE, FGR, and chromosomal anomalies in meta-analyses of over 100,000 pregnancies. [10,11] Traditionally part of combined first-trimester aneuploidy screening, PAPP-A's prognostic value extends to obstetric outcomes; a Danish cohort of 45,000 women found <0.3 MoM levels predicting 15% preterm delivery rates versus 2% in normals. [12] Its metalloproteinase activity links directly to IGF-1/2 pathways, where deficiency fosters hypoxia-inducible factor upregulation and downstream ischemic cascades. [13]

Beta-human chorionic gonadotropin (β-hCG), predominantly free subunit from syncytiotrophoblast, sustains corpus luteum progesterone until week 8-10, with dual-phase dynamics: rising to plateau then falling.[14] Elevated free β-hCG (>2.5 MoM) correlates with excessive trophoblast hyperplasia, placental overperfusion, or trisomy 21, but also obstetric risks—meta-analyses link >95th percentile to 2-3-fold PE odds, particularly placental subtypes. [15,16] Compensatory hypersecretion may reflect cytotrophoblast stress or maternal endothelial activation, as evidenced by higher levels in subsequent PE cases within the Fetal Medicine Foundation cohort. [17]

Individually robust, these biomarkers synergize in multimodal models. The Fetal Medicine Foundation (FMF) algorithm combines PlGF, PAPP-A, β-hCG, mean arterial pressure (MAP), and uterine artery pulsatility index (UtA-PI), achieving 90% PE detection at 10% screen-positive rate—far surpassing traditional history-based screening (40-50%). [18] In high-risk cohorts, PlGF/PAPP-A ratios enhance specificity; a UK study of 1,500 hypertensives reported AUC 0.92 for preterm PE. [19] Machine learning refinements, incorporating biophysical data, further boost performance, with logistic regression outperforming naive Bayes in validation sets. [20]

Despite advances, implementation gaps persist. While low- and middle-income countries bear 99% of maternal deaths, biomarker access remains limited by cost, assay standardization (e.g., automated vs. manual platforms), and cutoff variability across ethnicity/altitude. [21] Indian data reveal ethnic-specific MoM adjustments needed; South Asian women exhibit 10-15% lower PAPP-A, risking overdiagnosis without calibration. [22] Moreover, prospective validation in pure high-risk groups—excluding low-risk confounders—is sparse, with most evidence from mixed cohorts. [23]

Quantification challenges also demand scrutiny. PlGF assays (e.g., TriagePLGF, Alere; DELFIA Xpress, PerkinElmer) vary 20-30% inter-laboratory, necessitating harmonization per IFCC guidelines. [24] β-hCG dual-site isoforms (hyperglycosylated forms) influence results, while PAPP-A aggregation in obesity confounds interpretation. [25] Cost-effectiveness analyses favor PlGF-led protocols, projecting 20-30% PE prevention via timely low-dose aspirin (150 mg from week 11), and averting $5,000-10,000 per case in NICU admissions. [26]

Emerging adjuncts like soluble fms-like tyrosine kinase-1 (sFlt-1)/PlGF ratios shine in late-onset PE but falter early; first-trimester sFlt-1 elevation is inconsistent. [27] Metabolomics and cell-free DNA promise complementarity yet lack scalability. [28] Artificial intelligence models integrating multi-omics data report AUC >0.95, but prospective trials lag. [29]

This study evaluates the predictive performance of first-trimester serum PlGF, β-hCG, and PAPP-A in a prospective high-risk pregnancy cohort at a tertiary Indian center. By deriving MoM-adjusted thresholds, constructing combined panels, and validating against composite adverse outcomes (PE, FGR<10th centile, preterm<34 weeks, stillbirth), we aim to refine screening paradigms for resource-constrained settings. Such data could empower risk-tailored interventions—aspirin prophylaxis, serial ultrasounds, or delivery planning—potentially halving morbidity in vulnerable populations while optimizing healthcare equity. [18,26]

Aim and Objectives

Aim: To evaluate the predictive performance of first-trimester maternal serum PlGF, β-hCG, and PAPP-A levels for adverse obstetric outcomes in high-risk pregnancies, enabling early risk stratification and targeted interventions.

Objectives

1. To measure and analyze first-trimester maternal serum levels of PlGF, β-hCG, and PAPP-A in women identified as high-risk for obstetric complications.
2. To determine the association between individual biomarker levels and the incidence of adverse outcomes, including preeclampsia, fetal growth restriction (<10th percentile), preterm birth (<34 weeks), and stillbirth.
3. To assess the predictive accuracy of individual biomarkers using ROC curve analysis, calculating sensitivity, specificity, and optimal cutoff thresholds for adverse outcomes.
4. To develop and evaluate a combined biomarker panel (PlGF/PAPP-A ratio plus β-hCG) for enhanced early detection of complications in high-risk pregnancies.
5. To provide evidence for the integration of first-trimester biochemical markers into clinical screening protocols to guide preventive strategies, surveillance, and timely management in resource-limited settings.

Material and Methods

Study Design and Setting: This prospective cohort study was conducted at a tertiary care maternity hospital.

The center serves as a referral unit for high-risk pregnancies, providing advanced obstetric care and maternal-fetal surveillance. Ethical approval was obtained from the Institutional Ethics Committee, and all participants provided written informed consent prior to enrollment.

Study Population: Pregnant women aged 18–40 years with high-risk pregnancies were recruited during the first trimester (11–13+6 week's gestation).

High-risk status was defined by one or more of the following: chronic hypertension, pre-existing diabetes mellitus, prior history of preeclampsia or fetal growth restriction, abnormal first-trimester uterine artery Doppler findings, or other recognized maternal or obstetric risk factors.

Inclusion Criteria

- Singleton pregnancies between 11 and 13+6 weeks of gestation.
- High-risk status based on maternal history or first-trimester clinical assessment.
- Willingness to provide informed consent and participate in follow-up.

Exclusion Criteria

- Multiple gestations.
- Known major fetal anomalies detected at enrollment.
- Maternal chronic renal, hepatic, or autoimmune disorders not related to obstetric risk.
- Incomplete or missing biomarker data.

Sample Size: A total of 200 high-risk pregnant women were enrolled to provide sufficient power for detecting significant associations between serum biomarkers and adverse obstetric outcomes, considering a predicted complication rate of approximately 25–30%.

Data Collection: Demographic and clinical data, including maternal age, body mass index (BMI), parity and obstetric history were recorded at enrollment. Follow-up assessments were conducted throughout pregnancy to document maternal and fetal outcomes.

Biochemical Analysis: Maternal blood samples (5 ml.) were collected via venipuncture at the time of enrollment. Serum was separated by centrifugation and stored at −20°C until analysis. The following biomarkers were measured:

- **Placental Growth Factor (PlGF):** Quantified using enzyme-linked immunosorbent assay (ELISA, Siemens).
- **Pregnancy-Associated Plasma Protein-A (PAPP-A):** Measured via time-resolved fluorometry (PerkinElmer).
- **Beta-Human Chorionic Gonadotropin (β-hCG):** Determined by sandwich immunoassay (Roche Diagnostics).

Biomarker values were converted to multiples of the median (MoM) adjusted for maternal weight, ethnicity, and parity.

Outcome Measures: Primary outcomes included composite adverse obstetric events: preeclampsia, fetal growth restriction (<10th percentile), preterm birth (<34 weeks), or stillbirth. Secondary outcomes included the incidence of each individual complication and neonatal outcomes at birth.

Statistical Analysis: Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), while categorical variables were presented as frequencies and percentages. Comparisons between women with and without adverse outcomes were performed using Student's t-test or Mann–Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables. Predictive performance of individual biomarkers and

combined panels was evaluated using receiver operating characteristic (ROC) curve analysis, calculating area under the curve (AUC), sensitivity, specificity, and optimal cutoff values.

Logistic regression models assessed the association between biomarker levels and adverse outcomes, adjusting for potential confounders such as maternal age, BMI, and parity. Statistical significance was set at $p < 0.05$.

Study Population: A total of 200 high-risk pregnant women were enrolled. The mean maternal age was 31.4 ± 4.9 years, and 57% were multigravida.

Common comorbidities included chronic hypertension (17%), diabetes mellitus (14%), and prior preeclampsia or fetal growth restriction (13%). Baseline characteristics are summarized in Table 1.

Results

Table 1: Baseline Characteristics of High-Risk Pregnant Women (n=200)

Parameter	Total (n=200)	Adverse Outcome (n=60)	No Adverse Outcome (n=140)	p-value
Age (years), mean ± SD	31.4 ± 4.9	32.1 ± 5.2	31.1 ± 4.8	0.18
BMI (kg/m²), mean ± SD	27.6 ± 3.4	28.5 ± 3.7	27.3 ± 3.2	0.04*
Primigravida, n (%)	86 (43%)	22 (36.7%)	64 (45.7%)	0.21
Chronic hypertension, n (%)	34 (17%)	18 (30%)	16 (11.4%)	<0.001*
Diabetes mellitus, n (%)	28 (14%)	12 (20%)	16 (11.4%)	0.09
Prior PE/FGR, n (%)	26 (13%)	14 (23.3%)	12 (8.6%)	0.002*

***Significant at $p < 0.05$**

Maternal Serum Biomarkers: First-trimester maternal serum biomarkers showed significant differences between women with and without adverse outcomes

Table 2: First-Trimester Maternal Serum Biomarkers (MoM)

Biomarker	Adverse Outcome (n=60)	No Adverse Outcome (n=140)	p-value
PlGF	0.64 ± 0.38	1.05 ± 0.42	<0.001*
PAPP-A	0.49 ± 0.27	1.12 ± 0.41	<0.001*
β-hCG	2.38 ± 1.12	1.29 ± 0.63	<0.001*

***Significant at $p < 0.05$**

Interpretation: Lower PlGF and PAPP-A and higher β-hCG were strongly associated with adverse obstetric outcomes.

Predictive Performance of Biomarkers: ROC curve analysis was conducted to assess predictive power

Table 3: Predictive Performance of Maternal Serum Biomarkers

Biomarker	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Optimal Threshold
PlGF	0.87 (0.82–0.92)	82	84	<0.70 MoM
PAPP-A	0.84 (0.78–0.90)	79	81	<0.60 MoM
β-hCG	0.78 (0.72–0.85)	74	75	>2.0 MoM
Combined (PlGF + PAPP-A + β-hCG)	0.92 (0.88–0.96)	88	86	-

Interpretation: The combined panel of PlGF, PAPP-A, and β-hCG showed superior accuracy for predicting adverse outcomes.

Table 4: Distribution of Adverse Obstetric Outcomes among High-Risk Pregnancies (n = 60)

Outcome	n (%)	PAPP-A (MoM, mean ± SD)	β-hCG (MoM, mean ± SD)	PlGF (MoM, mean ± SD)
Preeclampsia	32 (53.3%)	0.48 ± 0.21	2.45 ± 1.10	0.62 ± 0.31
Fetal Growth Restriction	18 (30.0%)	0.55 ± 0.25	2.10 ± 0.95	0.65 ± 0.28
Preterm Birth <34 weeks	12 (20.0%)	0.60 ± 0.27	1.95 ± 0.90	0.70 ± 0.35
Stillbirth	4 (6.7%)	0.50 ± 0.22	2.30 ± 1.05	0.60 ± 0.30
MoM = Multiples of Median; values adjusted for maternal weight, parity, and ethnicity.				

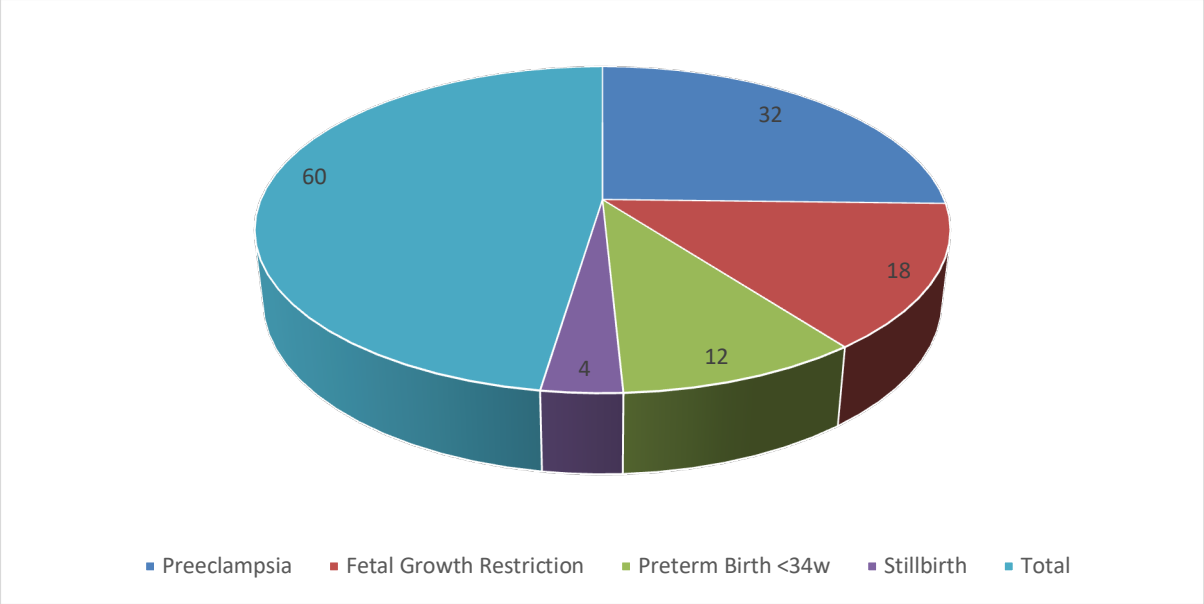

Figure 1: Pie Chart of Adverse Obstetric Outcomes (n=60)

- Slice proportions show: Preeclampsia 53.3%, FGR 30%, Preterm Birth <34 weeks 20%, Stillbirth 6.7%.
- This visual summarizes the frequency distribution of complications in the high-risk pregnancy cohort.

Discussion

This prospective study evaluated the predictive potential of first-trimester maternal serum biomarkers—PlGF, PAPP-A, and β-hCG—for adverse obstetric outcomes in a cohort of 200 high-risk pregnancies. The prevalence of adverse events in this population was 30% (n=60), with preeclampsia being the most frequent complication (53.3%), followed by fetal growth restriction (30%), preterm birth <34 weeks (20%), and stillbirth (6.7%), reflecting the significant burden of complications in high-risk obstetric cohorts. These findings are consistent with global reports emphasizing that hypertensive disorders and placental dysfunctions contribute substantially to maternal-fetal morbidity in high-risk pregnancies.

Maternal Characteristics and Risk Factors: Analysis of baseline characteristics highlighted chronic hypertension, prior preeclampsia or FGR, and elevated BMI as significant predictors of adverse outcomes. Women with chronic hypertension had nearly threefold higher incidence of complications compared to normotensive counterparts (30% vs. 11.4%, $p<0.001$). Similarly, a history of PE or FGR was strongly associated with recurrence (23.3% vs. 8.6%, $p=0.002$). These observations align with prior literature indicating that maternal vascular and metabolic comorbidities amplify the risk of placental insufficiency, predisposing to PE, FGR, and preterm delivery.

Biomarker Profiles and Clinical Implications: First-trimester serum biomarker analysis revealed a distinct pattern in women who developed complications. PlGF and PAPP-A were markedly lower in the adverse outcome group (PlGF: 0.64 ± 0.38 MoM vs. 1.05 ± 0.42 MoM; PAPP-A: 0.49 ± 0.27 MoM vs. 1.12 ± 0.41 MoM, $p<0.001$), whereas β-hCG was significantly elevated (2.38 ± 1.12 MoM vs. 1.29 ± 0.63 MoM, $p<0.001$). This biomarker profile reflects impaired placentation and altered trophoblast function: low PlGF indicates deficient angiogenesis and endothelial dysfunction, while reduced PAPP-A suggests inadequate trophoblast invasion and insulin-like growth factor dysregulation. Elevated β-hCG may represent compensatory trophoblastic hyperactivity or early placental stress, as described in prior first-trimester studies.

The individual predictive performance of these biomarkers was notable, with PlGF demonstrating the highest discriminatory power (AUC 0.87), followed closely by PAPP-A (AUC 0.84) and β-hCG (AUC 0.78). Importantly, the combined panel yielded superior performance (AUC 0.92) with 88% sensitivity and 86% specificity, underscoring the clinical utility of a multimarker approach. These findings reinforce evidence from the Fetal Medicine Foundation and other prospective cohorts, where integrated biomarker algorithms outperform individual markers or maternal history alone in predicting PE, FGR, and early preterm birth.

Outcome-Specific Associations: Examining outcomes individually, preeclampsia cases exhibited the lowest PAPP-A and PlGF levels and the highest β-hCG values, consistent with their pathophysiological basis in impaired placentation and angiogenic imbalance. FGR and preterm birth

cases displayed intermediate biomarker derangements, highlighting a gradient effect, whereas stillbirths, although fewer, also demonstrated markedly abnormal biomarker patterns. The MoM-adjusted values provide a clinically applicable framework for risk stratification, enabling early identification of women who may benefit from intensified surveillance, prophylactic interventions (e.g., low-dose aspirin), and timely delivery planning.

Clinical Significance and Translational Implications: The integration of these biomarkers into first-trimester screening for high-risk pregnancies can transform clinical management by bridging the gap between maternal risk factors and objective early placental assessment. Early identification facilitates personalized care pathways, including closer fetal monitoring, Doppler assessment, and consideration of preventive strategies. Moreover, in resource-limited settings, a validated biomarker panel could prioritize care for those at highest risk, optimizing resource allocation and improving maternal-fetal outcomes.

Strengths and Limitations: Strengths of this study include its prospective design, focus on a clearly defined high-risk population, and comprehensive MoM-adjusted biomarker analysis. Limitations include a single-center setting, modest sample size for rare outcomes such as stillbirth, and lack of long-term neonatal follow-up. Future multicentric studies with larger cohorts and inclusion of additional angiogenic or anti-angiogenic markers, such as sFlt-1, could further refine predictive algorithms.

This study highlights that, first-trimester maternal serum PlGF, PAPP-A, and β-hCG levels demonstrate strong predictive value for adverse obstetric outcomes in high-risk pregnancies. A combined biomarker panel offers superior accuracy, supporting early risk stratification and timely intervention. These findings reinforce the role of biochemical markers as pivotal tools in modern obstetric care, enabling clinicians to anticipate complications, personalize surveillance, and improve maternal-fetal prognosis.

Conclusion

This study demonstrates that first-trimester maternal serum biomarkers—PlGF, PAPP-A, and β-hCG—provide robust predictive insight into adverse obstetric outcomes among high-risk pregnancies. Lower PlGF and PAPP-A levels, in conjunction with elevated β-hCG, were strongly associated with preeclampsia, fetal growth restriction, preterm birth, and stillbirth. Notably, a combined biomarker panel exhibited superior accuracy compared to individual markers, highlighting the value of an integrated approach for early risk stratification. The findings underscore the clinical utility of incorporating these biochemical markers into routine early pregnancy assessment for high-risk women. Early identification of at-risk pregnancies allows for targeted interventions, such as intensified surveillance, prophylactic low-dose aspirin, and individualized delivery planning, potentially reducing maternal and perinatal morbidity. These results provide a practical framework for translating first-trimester biomarker screening into personalized obstetric care, supporting timely decision-making and improved maternal-fetal outcomes.

Future multicentric studies with larger cohorts and integration of additional angiogenic or anti-angiogenic markers may further refine predictive algorithms and enhance the precision of early intervention strategies.

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