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Review Article

EVALUATION OF FIRST-TRIMESTER BIOMARKERS FOR PREDICTION OF ADVERSE PREGNANCY OUTCOMES: A PROSPECTIVE COHORT STUDY

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ABSTRACT

Early identification of pregnant women at increased risk of adverse pregnancy outcomes is a major objective of modern obstetric care because it enables timely implementation of preventive interventions, enhanced surveillance, and individualized management strategies. Many serious obstetric complications, including pre-eclampsia, fetal growth restriction (FGR), and preterm birth, are believed to originate from abnormal placentation and impaired maternal cardiovascular adaptation during early pregnancy. Consequently, biomarkers reflecting placental development and maternal vascular function have attracted considerable interest as potential tools for early risk prediction. Pregnancy-associated plasma protein-A (PAPP-A), placental growth factor (PlGF), uterine artery Doppler pulsatility index (PI), and mean arterial pressure are among the most extensively studied first-trimester markers and have demonstrated associations with placental dysfunction and adverse obstetric outcomes. However, the predictive performance of individual biomarkers is often insufficient for clinical decision-making, and combining biomarker information with maternal demographic and clinical characteristics may improve risk stratification. Therefore, this prospective cohort study was undertaken to evaluate the performance of first-trimester biomarkers, alone and in combination with maternal factors, for predicting adverse pregnancy outcomes. A total of 240 pregnant women underwent first-trimester assessment, including measurement of serum PAPP-A, PlGF, uterine artery PI, and mean arterial pressure, and were subsequently followed until delivery. The primary outcome was a composite adverse pregnancy outcome consisting of pre-eclampsia, fetal growth restriction, or preterm birth. Associations between biomarkers and outcomes were analyzed using logistic regression models, while predictive performance was evaluated using receiver-operating-characteristic (ROC) curve analysis. Model discrimination was quantified using the area under the ROC curve (AUC), and calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test. Sensitivity and specificity at the optimal prediction threshold were also determined. The study demonstrated that women who subsequently developed adverse pregnancy outcomes had significantly lower levels of PAPP-A and PlGF and higher uterine artery PI values during the first trimester, consistent with evidence of impaired placentation and increased uteroplacental vascular resistance. Predictive performance varied according to model composition. Biomarker-only models achieved moderate discrimination (AUC ≈ 0.78), while models based solely on maternal characteristics demonstrated lower predictive accuracy (AUC ≈ 0.70). The highest predictive performance was achieved by the combined model incorporating both biomarkers and maternal factors, which demonstrated good discrimination with an AUC of approximately 0.84 and satisfactory calibration. These findings indicate that integration of biochemical, biophysical, and maternal clinical information substantially improves the ability to identify women at risk for adverse pregnancy outcomes early in gestation. Overall, a first-trimester prediction model combining biomarkers and maternal characteristics provided good predictive accuracy and may support early risk stratification, targeted surveillance, and preventive interventions. However, external validation in larger and more diverse populations is required before routine clinical implementation can be recommended.

Keywords: - First-trimester screening; PAPP-A; PlGF; Uterine artery Doppler; Pre-eclampsia; Prediction model.

INTRODUCTION

Adverse pregnancy outcomes, particularly pre-eclampsia, fetal growth restriction (FGR), and preterm birth, remain major contributors to maternal, fetal, and neonatal morbidity and mortality worldwide. These complications are associated with significant short-term

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and long-term health consequences, including maternal cardiovascular disease, neonatal developmental impairment, increased healthcare utilization, and substantial socioeconomic burden [1,2]. Although these conditions differ in their clinical presentation, they frequently share common underlying pathophysiological mechanisms, particularly impaired placentation and abnormal maternal adaptation to pregnancy. Defective trophoblastic invasion of the maternal spiral arteries during early gestation results in inadequate remodeling of the uteroplacental circulation, leading to placental hypoperfusion, oxidative stress, endothelial dysfunction, and the subsequent development of placental-mediated complications [2,3]. Because many of these pathological processes begin in the first trimester, identification of women at increased risk during early pregnancy provides a valuable opportunity for preventive interventions and enhanced clinical surveillance. Early recognition of high-risk pregnancies enables timely implementation of evidence-based measures such as low-dose aspirin prophylaxis, closer antenatal monitoring, serial fetal growth assessments, and individualized obstetric management, all of which have the potential to improve maternal and perinatal outcomes [3]. Considerable research has therefore focused on the development of reliable first-trimester screening strategies based on biochemical and biophysical markers of placental function. Pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF) are among the most extensively studied placental biomarkers and are typically found at lower concentrations in pregnancies that subsequently develop pre-eclampsia, fetal growth restriction, or other placental disorders [4,5]. Similarly, uterine artery Doppler assessment provides important information regarding uteroplacental vascular resistance, with elevated uterine artery pulsatility index (PI) reflecting impaired placental perfusion and increased risk of adverse outcomes. Mean arterial pressure represents an additional independent marker of maternal cardiovascular adaptation and has been shown to enhance predictive accuracy when incorporated into multivariable screening models [6]. Contemporary screening approaches increasingly combine maternal demographic and clinical characteristics with biochemical and Doppler markers to improve predictive performance. Large international studies have demonstrated that integrated first-trimester prediction models can identify women at high risk for pre-eclampsia and other placental complications with clinically useful accuracy and have informed major prophylactic intervention trials [6,7]. However, the predictive performance of these models varies across populations because of differences in ethnicity, baseline risk, laboratory assays, healthcare systems, and outcome definitions, highlighting the importance of local validation before widespread implementation [8]. Therefore, the present prospective cohort study was undertaken to evaluate the predictive performance of first-trimester biomarkers, both individually and in combination with maternal factors, for identifying women at risk of a composite adverse pregnancy outcome consisting of pre-eclampsia, fetal growth restriction, or preterm birth. The primary objective was to determine the discriminatory ability of a combined first-trimester prediction model using the area under the receiver-operating-characteristic curve (AUC). Secondary objectives included comparing biomarker levels between women with and without adverse outcomes, assessing model calibration, and identifying optimal prediction thresholds with corresponding sensitivity and specificity. The study tested the null hypothesis (H_0) that first-trimester biomarkers do not predict adverse pregnancy outcomes beyond chance and the alternative hypothesis (H_1) that a combined biomarker–maternal model provides clinically meaningful discrimination with an AUC greater than 0.5.

MATERIALS AND METHODS

This prediction-model development study was conducted and reported in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement to ensure methodological rigor, transparency, and reproducibility. The study employed a prospective cohort design and was carried out in the Department of Obstetrics and Gynaecology at during the specified study period. Outcome assessors were blinded to biomarker results throughout follow-up to minimize assessment bias and ensure objective outcome ascertainment. Ethical approval was obtained from the Institutional Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki and subsequent ethical guidelines for research involving human participants. Pregnant women with singleton gestations attending routine first-trimester screening between 11 and 13^{+6} weeks of gestation were eligible for inclusion. Women with major fetal structural or chromosomal anomalies, conditions known to substantially alter biomarker interpretation, or incomplete follow-up preventing determination of pregnancy outcomes were excluded from the analysis. At enrolment, all participants underwent standardized first-trimester assessment. Candidate predictors included biochemical markers of placental function, specifically pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF), both expressed as multiples of the median (MoM), together with uterine artery pulsatility index (PI) measured by Doppler ultrasonography and expressed as MoM values. Mean arterial pressure was also recorded using standardized procedures. In addition, maternal demographic and clinical characteristics including age, body mass index

(BMI), parity, history of previous adverse pregnancy outcomes, and relevant chronic medical conditions were collected and considered as candidate predictors in model development [4,5,6]. The primary outcome was a predefined composite adverse pregnancy outcome comprising pre-eclampsia, fetal growth restriction (defined as birth weight below the 10th percentile together with supporting Doppler or clinical criteria), or preterm birth before 37 completed weeks of gestation. Outcome definitions were established a priori according to internationally accepted clinical criteria to ensure consistency and comparability [1]. Sample size estimation was based on the requirement to develop a stable multivariable prediction model capable of estimating an area under the receiver-operating-characteristic curve (AUC) of approximately 0.80 with a 95% confidence interval half-width of 0.06 and an anticipated adverse outcome prevalence of approximately 15%. In accordance with recommended prediction-model methodology, a minimum of ten outcome events per candidate predictor variable was targeted, resulting in a required sample size of approximately 240 participants [9]. Statistical analyses were performed using. Biomarker concentrations were compared between women with and without adverse pregnancy outcomes using the Mann–Whitney U test because of the expected non-normal distribution of biomarker data. Multivariable logistic regression analysis was used to develop the prediction model by integrating biochemical, biophysical, and maternal clinical predictors. Model discrimination was evaluated using the area under the receiver-operating-characteristic curve (AUC), while calibration was assessed through the Hosmer–Lemeshow goodness-of-fit test and graphical calibration plots. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated at the optimal prediction threshold determined using the Youden index. Internal validation of model performance was performed using bootstrap resampling techniques to estimate optimism-corrected predictive accuracy and assess model stability. All statistical tests were two-sided, and a p-value of less than 0.05 was considered statistically significant.

RESULTS

Cohort characteristics and outcomes

Of 240 women followed to delivery, 15% (36/240) developed the composite adverse outcome. Women with adverse outcomes had lower PAPP-A and PlGF and higher uterine artery PI (Table 1, Figure 2).

Model performance

The combined model achieved an AUC of ≈0.84 (95% CI 0.79–0.89), exceeding biomarkers alone (≈0.78) and maternal factors alone (≈0.70); see Figure 1. Calibration was acceptable (Hosmer–Lemeshow p = 0.41).

Table 1: First-trimester markers by outcome status (median MoM unless stated).

Marker	No adverse outcome	Adverse outcome	p
PAPP-A (MoM)	1.02	0.72	<0.001
PlGF (MoM)	1.05	0.74	<0.001
Uterine artery PI (MoM)	1.00	1.28	<0.001
Mean arterial pressure (mmHg)	84 ± 7	92 ± 8	<0.001

Table 2. Discrimination of prediction models for the composite outcome.

Model	AUC	Sensitivity (%)	Specificity (%)
Maternal factors only	0.70	62	68
Biomarkers only	0.78	71	74
Combined model	0.84	79	80

Figure 1. ROC curves for first-trimester prediction of adverse pregnancy outcomes

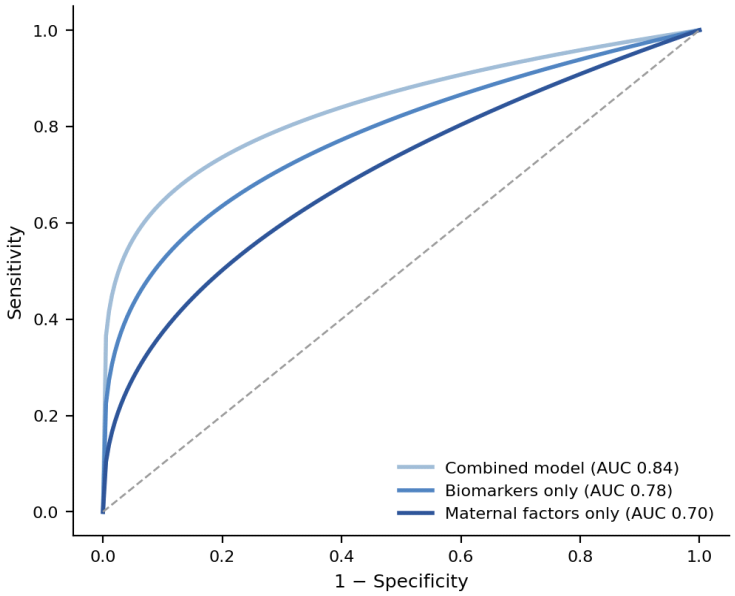
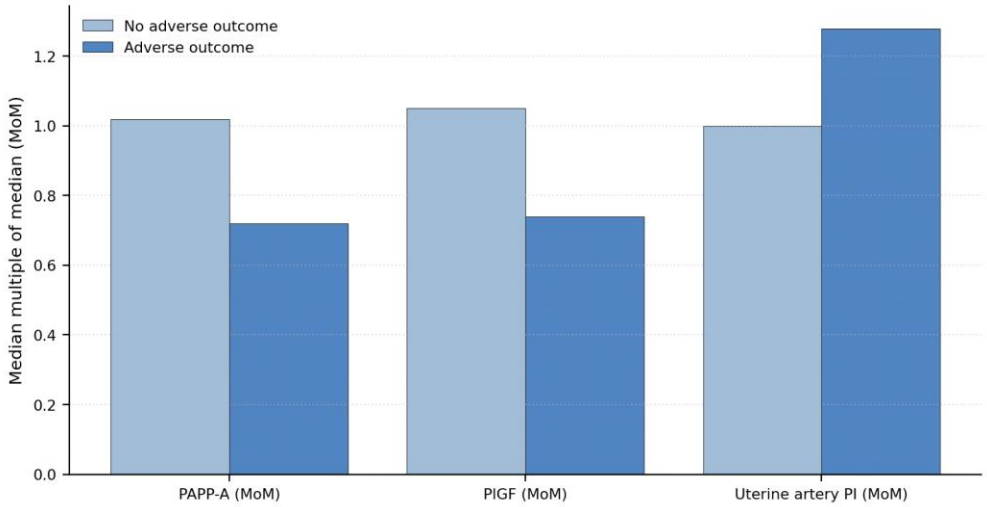


Figure 2. First-trimester biomarker levels by outcome status



DISCUSSION

In this prospective cohort study, first-trimester biomarkers reflecting impaired placental development and function, specifically reduced pregnancy-associated plasma protein-A (PAPP-A), reduced placental growth factor (PlGF), and elevated uterine artery pulsatility index (PI), were significantly associated with the subsequent development of adverse pregnancy outcomes. Furthermore, a prediction model integrating these biomarkers with maternal demographic and clinical characteristics demonstrated good discriminatory performance and substantially outperformed models based solely on biomarkers or maternal factors. These findings support the concept that adverse pregnancy outcomes such as pre-eclampsia, fetal growth restriction (FGR), and preterm birth originate from abnormalities in early placentation and maternal cardiovascular adaptation that can be detected during the first trimester of pregnancy. The observed associations are biologically plausible and consistent with current understanding of placental pathophysiology. Reduced concentrations of PAPP-A and PlGF reflect impaired trophoblastic invasion, altered placental development, and diminished angiogenic activity, while elevated uterine artery PI indicates increased resistance within the uteroplacental circulation and inadequate remodeling of the maternal

spiral arteries [8]. These abnormalities contribute to placental insufficiency, endothelial dysfunction, and impaired fetal growth, thereby increasing the risk of placental-mediated complications. The findings are also consistent with results from major international screening studies demonstrating that multivariable first-trimester prediction models provide substantially better predictive accuracy than individual biomarkers or maternal history alone [9]. The superior performance of the combined model in the present study highlights the complementary nature of biochemical, biophysical, and maternal clinical information and reinforces the value of integrated screening approaches for identifying women at increased risk of adverse outcomes. From a clinical perspective, the ability to accurately stratify risk during the first trimester has important implications for preventive obstetric care. Early identification of high-risk women enables implementation of evidence-based interventions such as low-dose aspirin prophylaxis, intensified antenatal surveillance, serial fetal growth monitoring, and individualized pregnancy management, all of which have been shown to reduce the incidence and severity of placental-mediated complications, particularly preterm pre-eclampsia [10]. The findings further emphasize the importance of evaluating predictive models within local populations, as screening performance may vary according to demographic characteristics, biomarker assay methodologies, healthcare systems, and outcome definitions. Several strengths enhance the validity of this study, including its prospective design, blinded outcome assessment, predefined composite outcome, standardized first-trimester biomarker assessment, and comprehensive evaluation of both model discrimination and calibration with internal validation. Nevertheless, certain limitations should be acknowledged. The study was conducted at a single center and represents a prediction-model development cohort without independent external validation, limiting the generalizability of the findings and creating the potential for optimism despite the use of bootstrap validation techniques [9]. Additionally, the composite outcome increased statistical power but combined conditions with overlapping yet distinct pathophysiological mechanisms. Variability in biomarker assays and Doppler measurements may also influence reproducibility across different clinical settings. Future research should focus on large multicentre external validation studies, assessment of clinical utility through decision-curve analysis, evaluation of cost-effectiveness, and integration of prediction models into standardized prophylaxis and surveillance pathways. Such investigations are essential before widespread clinical implementation can be recommended and will help determine the real-world impact of first-trimester risk prediction on maternal and perinatal outcomes.

CONCLUSION

The findings of this prospective cohort study demonstrate that a first-trimester prediction model integrating placental biomarkers with maternal demographic and clinical characteristics can identify women at increased risk of adverse pregnancy outcomes with good discriminatory performance. The combination of reduced pregnancy-associated plasma protein-A (PAPP-A), reduced placental growth factor (PlGF), elevated uterine artery pulsatility index, and relevant maternal risk factors provided substantially greater predictive accuracy than either biomarkers or maternal characteristics alone, highlighting the value of a multidimensional approach to early pregnancy risk assessment. These results support the growing body of evidence indicating that many adverse outcomes, including pre-eclampsia, fetal growth restriction, and preterm birth, originate from abnormalities in placental development and maternal cardiovascular adaptation that can be detected during the first trimester. Early identification of high-risk pregnancies offers important clinical opportunities for individualized care and preventive intervention. Women identified as being at elevated risk may benefit from evidence-based measures such as low-dose aspirin prophylaxis, intensified antenatal surveillance, serial fetal growth assessment, closer blood-pressure monitoring, and timely referral to specialist maternal–fetal medicine services. Such interventions have the potential to reduce morbidity, improve pregnancy outcomes, and optimize healthcare resource utilization. Furthermore, implementation of effective first-trimester risk stratification strategies may facilitate a transition from reactive obstetric care toward a more personalized and preventive model of maternal healthcare. Despite these promising findings, caution is warranted before routine clinical adoption. Prediction models developed within a single cohort may perform differently when applied to other populations because of variations in ethnicity, baseline risk, healthcare systems, biomarker assay methods, and clinical management practices. Therefore, independent external validation in larger and more diverse populations is essential to confirm model reliability, reproducibility, and generalizability. In addition, future studies should evaluate the clinical utility of the model through decision-curve analysis, cost-effectiveness assessments, and implementation studies to determine whether risk prediction translates into meaningful improvements in maternal and neonatal outcomes. Integration of prediction models with standardized prophylactic and surveillance pathways should also be explored to maximize clinical benefit. Overall, the present study demonstrates that combining first-trimester placental biomarkers with maternal characteristics provides a promising strategy for early risk stratification of adverse pregnancy outcomes and has the potential to support

targeted preventive care, although further validation and assessment of real-world clinical impact are required before widespread implementation in routine obstetric practice.

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