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Low concordance between first-trimester ophthalmic artery Doppler and uterine artery–based algorithms for preeclampsia risk assessment: cross-sectional agreement study

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ABSTRACT

Background: Preeclampsia is a complex multisystem syndrome that remains one of the leading causes of maternal and neonatal morbidity and mortality. The first-trimester screening integrates maternal factors, mean arterial pressure, biochemical markers, and uterine artery Doppler indices. Ophthalmic artery (OA) Doppler has been proposed as a complementary marker reflecting maternal systemic and cerebral hemodynamic adaptation. The concordance between –based assessment and established uterine artery–based models remains insufficiently characterized.

Objective: To evaluate the agreement between a first-trimester ophthalmic artery Doppler–based algorithm and the conventional uterine artery–based algorithm for preeclampsia risk classification.

Methods: This cross-sectional agreement study included 116 pregnancies evaluated between 11+0 and 13+6 weeks of gestation. Risk was calculated using two Fetal Medicine Foundation algorithms: Algorithm 1 (A1), incorporating uterine artery pulsatility index and Algorithm 2 (A2), incorporating OA peak systolic velocity PSV ratio. Agreement was assessed using crude agreement, Cohen's kappa with 95% confidence interval, prevalence-adjusted bias-adjusted kappa (PABAK), McNemar's test for paired proportions, and odds ratio with 95% confidence interval. Statistical significance was set at $p < 0.05$.

Results: Algorithm 1 classified 23.3% of women as high risk, whereas Algorithm 2 classified 15.5% as high risk. Only 1.7% were classified as high risk by both methods. Crude agreement was 64.7%. Cohen's kappa indicated poor agreement beyond chance ($\kappa = -0.12$; 95% CI −0.40 to 0.16). McNemar's test was not statistically significant ($p = 0.21$). The odds ratio for concordant high-risk classification was 0.36 (95% CI 0.08–1.70). PABAK indicated fair agreement after prevalence adjustment.

Conclusion: First-trimester ophthalmic artery–based and uterine artery–based risk algorithms demonstrated limited concordance. Prospective outcome-based studies are required to determine the clinical relevance of these findings.

Key Words: Preeclampsia, Doppler ultrasonography, ophthalmic artery, uterine artery, first trimester pregnancy, risk assessment

Abbreviations

PE	preeclampsia
CRL	crown-rump length
OA	ophthalmic artery
UTA-PI	uterine artery pulsatility index
OA PSV ratio	maternal ophthalmic artery Doppler PSV ratio
A1/Algorithm 1	the preeclampsia assessment risk developed by the Fetal Medicine Foundation that uses UTA-PI, which is, the traditional screening approach
A2/Algorithm 2	the preeclampsia assessment risk developed by the Fetal Medicine Foundation that uses the ophthalmic artery PSV

Introduction

Preeclampsia (PE) remains one of the leading causes of maternal and perinatal morbidity and mortality worldwide and represents a complex multisystem disorder with significant consequences for the maternal–fetal dyad. Early identification of pregnant women at high risk is crucial for the implementation of prophylactic interventions and optimized antenatal care.

Established first-trimester screening is based on algorithms integrating maternal characteristics, mean arterial pressure, serum biomarkers, and uterine artery pulsatility index (UTA-PI). While uterine artery Doppler primarily reflects placental development and trophoblastic invasion, maternal ophthalmic artery (OA) Doppler peak systolic velocity (PSV) ratio has emerged as a promising approach for assessing maternal systemic and cerebral hemodynamic adaptation to pregnancy.

As the first branch of the internal carotid artery, the OA shares hemodynamic properties with the intracranial circulation. Ophthalmic artery Doppler provides a noninvasive assessment of cerebral perfusion and vascular tone, alterations that frequently precede the clinical manifestation of preeclampsia. Among Doppler indices, the ratio between the second and first systolic velocity peaks (PSV ratio) has demonstrated superior diagnostic performance, with increased values reported in women who subsequently develop the disease.

The objective of this study was to evaluate agreement between these two first-trimester screening approaches.

Methods

Study Design and Population: This was a cross-sectional agreement study conducted in a private fetal medicine clinic in Brazil. Singleton pregnancies between 11+0 and 13+6 weeks of gestation (CRL between 45–84 mm) were consecutively included. Exclusion criteria were multiple pregnancy and incomplete Doppler assessment.

Risk Assessment: All participants underwent first-trimester ultrasound using a GE Healthcare Voluson Expert 22 system, between September 29, 2025, and December 26, 2025. Risk calculation used two independent Fetal Medicine Foundation software platforms: Algorithm 1 (A1) employed the ASTRAIA/NEXUS software (version 29.2.1; Copyright 2000–2026 NEXUS/ASTRAIA GmbH, www.nexus-astraia.com) which included maternal characteristics, mean arterial pressure, biochemical markers, and UTA-PI. Algorithm 2 (A2) used the FMF risk calculator (The Fetal Medicine Foundation software Shell 1.0.3, UI 1.0.19, API 1.0.0, Models main/0.0.1) that included maternal characteristics, mean arterial pressure, biochemical markers, and OA peak systolic velocity ratio.

Statistical Analysis: Agreement between the first-trimester preeclampsia screening A1 and A2 was evaluated using Cohen's kappa coefficient. To address the potential impact of imbalance in the

prevalence of high-risk classifications, the prevalence-adjusted bias-adjusted kappa (PABAK) was also calculated. The 95% confidence interval for Cohen's kappa was derived using the asymptotic variance method. Additionally, McNemar's test was performed to assess whether there was a systematic difference between the two methods in the classification of high-risk cases. An odds ratio with 95% CI was calculated to quantify the association between classifications. Statistical significance was defined as $p < 0.05$. Analyses were exploratory; no formal sample size calculation was performed.

Ethical Considerations: All data were anonymized prior to analysis. The study followed principles of the Declaration of Helsinki.

Results

A total of 116 pregnant women were included in the agreement analysis. The overall observed agreement between the FMF-based algorithm and the OA Doppler model was 64.7%. Table 1 shows the cross-classification of risk categories between the FMF-based algorithm (A1) and the OA Doppler model (A2).

Table 1

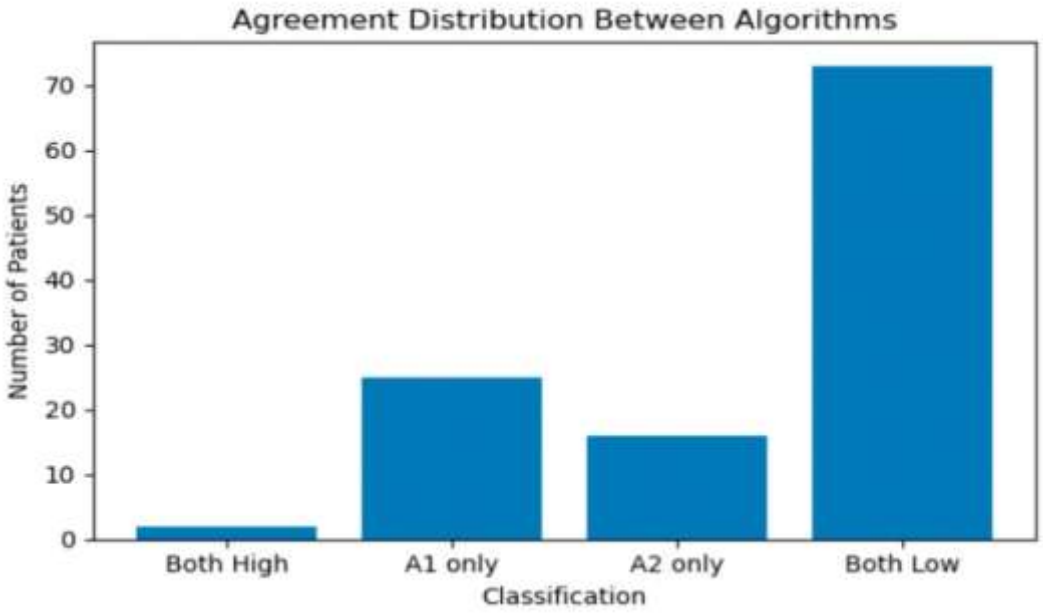
	A2 High Risk	A2 Low Risk
A1 High Risk	2	25
A1 Low Risk	16	73

Cohen's kappa coefficient demonstrated poor agreement beyond chance ($\kappa = -0.12$; 95% CI −0.40 to 0.16). However, due to the low prevalence of high-risk classifications and the resulting imbalance between categories, kappa values may underestimate agreement in scenarios of asymmetric marginal distributions.

The prevalence-adjusted bias-adjusted kappa (PABAK) was therefore calculated and yielded a value of 0.293, also indicating fair agreement after adjustment for prevalence and potential classification bias.

The proportion of patients classified as high risk differed between the two methods: 23.3% according to the FMF-based algorithm and 15.5% according to the OA Doppler model. Despite differences in classification frequency, McNemar's test did not demonstrate a statistically significant asymmetry in discordant classifications ($p = 0.21$), indicating that neither method consistently classified more patients as high risk than the other. Figure 1 illustrates the distribution of agreement and disagreement between the two screening algorithms.

Figure 1



The modest level of agreement suggests that maternal OA Doppler assessment may capture different pathophysiological aspects of preeclampsia risk compared to the FMF-based screening algorithm.

Three key considerations:

1.Cohen's kappa alone indicated agreement worse than chance (κ = −0.12), probably due to the low prevalence of high-risk cases.

2.PABAK corrects for this effect and shows that the true agreement is fair, although still insufficient to consider the methods interchangeable.

3.The difference between kappa and PABAK reinforces that a low prevalence of positive events can underestimate true agreement.

Discussion

Prediction of preeclampsia remains a central objective of contemporary obstetrics research. Among validated predictive models, uterine artery Doppler represents the most frequently applied parameter because of its relative contribution and clinical relevance compared with other predictive markers.

This study demonstrated limited agreement beyond chance between the two screening approaches. Although the overall observed agreement exceeded 60%, traditional Cohen's kappa suggested limited concordance, highlighting the influence of low event prevalence on agreement statistics.

The negative or low kappa values observed emphasize a well-recognized limitation of Cohen's kappa in scenarios where positive outcomes are infrequent. In this context, the application of PABAK provided a more reliable estimate of agreement by adjusting for prevalence imbalance and potential classification bias. Even after adjustment, agreement remained fair, suggesting that the two screening strategies are not interchangeable.

The modest level of agreement suggests that maternal OA Doppler may capture distinct vascular phenomena not fully represented in traditional FMF-based screening. Whereas the FMF algorithm integrates maternal characteristics, uterine artery Doppler, and biochemical markers to assess placental development and perfusion, OA Doppler primarily reflects maternal central and cerebral hemodynamic adaptation. This difference in physiological domains may explain the discordance observed between methods and indicates that the two approaches should not be considered interchangeable.

Gana et al. found that the OA PSV ratio is significantly increased in pregnancies that later develop preeclampsia, particularly early-onset cases. This effect varies with gestational age at delivery, and the small number of cases (especially preterm PE) introduces uncertainty in the estimates.

By contrast, previous modeling analyses showed that screening based on combined mean arterial pressure, UTA-PI and biomarkers performed consistently with previous large-scale studies. The OA PSV ratio improved the prediction of preterm PE beyond maternal risk factors and standard biomarkers combinations, but it did not enhance the prediction of term PE. This study cannot perform these analyses because the pregnancies are still ongoing, and it is not yet known which of the patients classified as high risk for PE will actually develop the disease.

Sarno et al. reported that the OA PSV ratio measured at 35–37 weeks' gestation is associated with the prediction of a subsequent preeclamptic delivery, particularly when onset occurs within three weeks after evaluation; however its predictive value seems to be limited to the third trimester rather than the first trimester.

According to Lau et al, integration of ophthalmic artery Doppler with maternal risk factors and blood pressure parameters has the potential to substitute biomarker testing in the prediction of imminent PE at 35–37 weeks' gestation.

In the study of Saikumar et al, the OA PSV ratio showed greater predictive performance than UTA-PI for preeclampsia screening at 18–24 weeks of gestation, indicating possible applicability in routine ultrasound practice pending validation in larger cohorts

De Mello et al, demonstrated through meta-analytic evidence that OA Doppler constitutes a valuable adjunctive tool for the diagnosis of general and severe preeclampsia, however, in the second and third trimesters.

Meta-analyses by Kalafat et al. have shown that ophthalmic artery Doppler in the first or second trimester has standalone predictive value for the development of early-onset PE, which is equivalent to that of the uterine artery Doppler evaluation.

Conclusion

First-trimester preeclampsia risk assessment based on maternal ophthalmic artery Doppler demonstrated limited concordance with uterine artery–based FMF screening. These findings suggest that the two approaches may identify different high-risk populations and that OA Doppler may reflect maternal hemodynamic mechanisms not fully captured by traditional screening models. Outcome-based prospective studies are required to determine whether ophthalmic artery Doppler provides independent prognostic value before clinical integration.

Conflict of Interest:

The authors have no conflicts of interest to declare.

Funding Statement:

None.

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