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First-trimester ophthalmic artery Doppler for prediction of early-onset and preterm preeclampsia: a systematic review and critical appraisal

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ABSTRACT

Background: First-trimester screening for preterm preeclampsia (PE) is often performed using the Fetal Medicine Foundation (FMF) Bayes' theorem-based competing-risks model, which combines maternal factors with mean arterial pressure, uterine artery pulsatility index and placental growth factor, with pregnancy-associated plasma protein-A included in some models. Ophthalmic artery (OA) Doppler has been proposed as an additional marker of maternal vascular adaptation, but its clinical contribution remains uncertain. This review critically evaluates the predictive performance of first-trimester OA Doppler for early-onset and preterm PE, and assesses its incremental value beyond established screening models.

Methods: A PRISMA-guided systematic review was conducted. Studies assessing first-trimester OA Doppler in singleton pregnancies for the prediction of early-onset or preterm PE were included. Risk of bias was assessed using PROBAST. Given heterogeneity in population risk, Doppler indices, outcome definitions, and model structure, results were synthesized narratively.

Results: Five prospective cohort reports, representing four unique cohorts, met the inclusion criteria. In large unselected cohorts, OA Doppler showed limited standalone predictive value. Its contribution within multivariable models was modest, with detection rates for preterm PE of approximately 56–59% at a 10% false-positive rate. Smaller selected or mixed-risk cohorts reported substantially higher discrimination, including AUROC values up to 0.98. However, these estimates were based on few outcome events, lacked validation, and were most consistent with overfitting. All reports had high risk of bias in the analysis domain; therefore, reported AUROC and detection-rate estimates should be interpreted as exploratory.

Conclusions: Reported performance of first-trimester OA Doppler is strongly influenced by population risk and model structure. Current evidence suggests limited standalone value and

uncertain incremental benefit beyond established screening. Future studies should use standardised acquisition and reporting, consistent PE definitions and prespecified validation to enable data pooling and determine whether OA Doppler has clinically meaningful incremental value.

Systematic review registration: PROSPERO CRD420261289728.

Keywords: ophthalmic artery Doppler; preeclampsia; first-trimester screening; prediction model.

Background

Preeclampsia (PE) is a multisystem hypertensive disorder of pregnancy arising after 20 weeks' gestation and remains a leading cause of maternal and perinatal morbidity and mortality worldwide. It is commonly subclassified by gestational timing into early-onset (<34 weeks) and late-onset (≥ 34 weeks), or alternatively into preterm (<37 weeks) and term (≥ 37 weeks) disease (1-3). Early-onset PE carries a high burden of severe complications, including eclampsia, placental abruption, and HELLP syndrome, contributing substantially to maternal and perinatal morbidity and mortality. It also increases long-term cardiovascular and metabolic sequelae (4, 5). Globally, PE affects 3-8% of pregnancies and remains a leading contributor to maternal deaths (6). Early identification of high-risk pregnancies enables the initiation of preventive interventions, most notably low-dose aspirin before 16 weeks' gestation, which has been shown to significantly reduce the incidence of early and preterm PE (7). Contemporary first-trimester screening models integrating maternal risk factors, mean arterial pressure (MAP), uterine artery (UtA) Doppler, and placental biomarkers such as placental growth factor (PlGF) achieve high detection rates (DR) for early disease, although false-positive rates and implementation challenges remain (8-12).

Ophthalmic artery (OA) Doppler has emerged as a potential adjunctive marker, reflecting maternal systemic and cerebral vascular adaptation. Doppler-derived indices - including pulsatility index

(PI), resistive index (RI), peak systolic velocity (PSV), and the PSV ratio (PSV2/PSV1) have been reported to differ in pregnancies that subsequently develop PE (13) (Figure 1). Unlike placental markers, OA Doppler may provide insight into maternal hemodynamic response, offering a theoretically complementary dimension to prediction models.

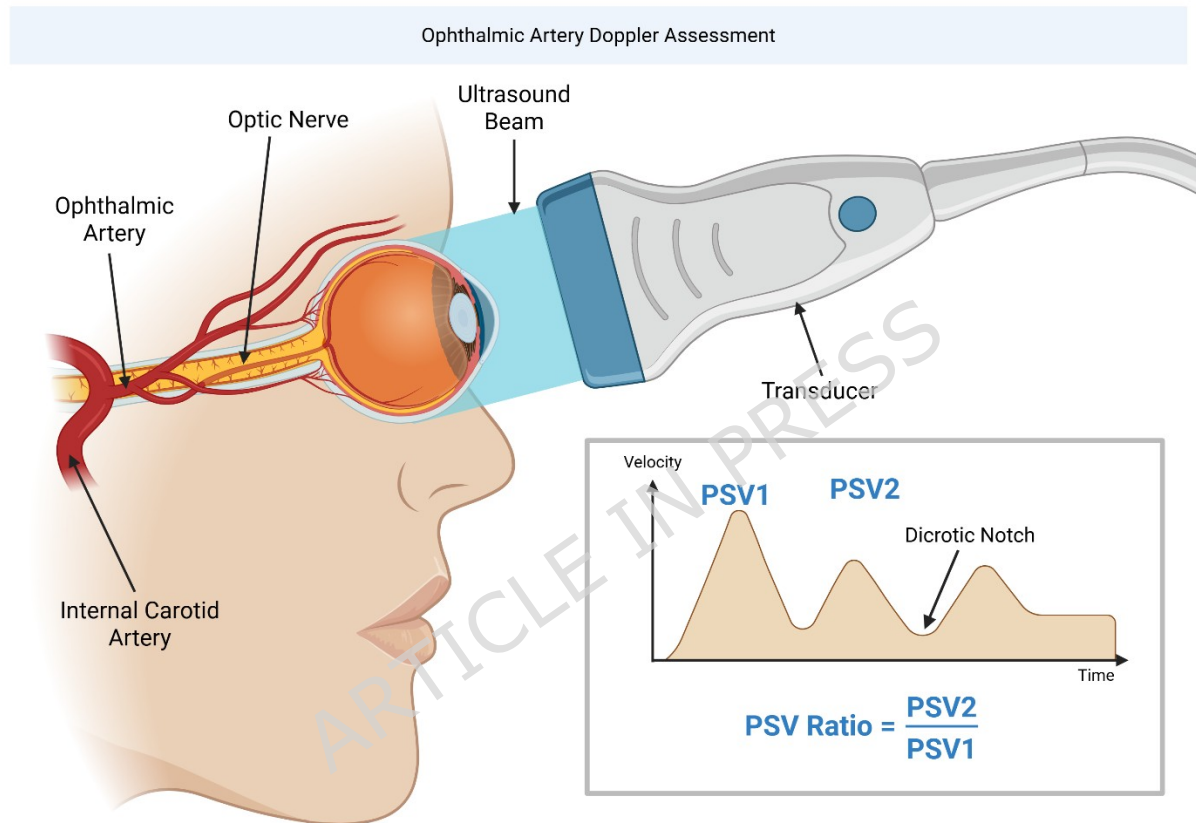


Figure 1. Schematic representation of ophthalmic artery Doppler assessment demonstrating the transorbital ultrasound approach and the derivation of peak systolic velocity. Created in BioRender. Blackwell, J. (2026) <https://BioRender.com/zj5xsbw>

However, the clinical relevance of OA Doppler remains uncertain. Existing studies report variable predictive performance, and prior reviews have largely focused on descriptive summaries without critically evaluating methodological limitations and confounding. It is unclear whether OA

Doppler meaningfully enhances prediction beyond established multiparametric screening approaches (14-17).

Given the publication of recent reviews and the growing interest in OA Doppler as a maternal vascular marker, a focused appraisal of the first-trimester evidence is timely. This review evaluates first-trimester ophthalmic artery Doppler for prediction of early-onset and preterm PE, distinguishes standalone performance from added value within established screening models, and examines the methodological limitations that may inflate reported performance estimates.

Methods

Information Source and Search Strategy

A comprehensive literature search across PubMed, Embase, Scopus, Web of Science, the Cochrane Library including supplementary searches of Google Scholar was done to identify studies evaluating first-trimester OA Doppler for prediction of PE. MeSH terms and keywords included combinations of “ophthalmic artery,” “Doppler,” “first trimester,” and “preeclampsia” and other synonyms combined as appropriate using the Boolean operators "AND" and "OR". Searches covered database inception to January 2026, followed PRISMA guidelines, and were PROSPERO-registered (CRD420261289728). The complete database search strings are provided in Appendix A.

Eligibility Criteria

Eligible studies were peer-reviewed observational or prospective cohorts assessing first-trimester OA Doppler (<14 weeks) in singleton pregnancies. Studies of non-OA Doppler, multifetal pregnancies, post-diagnosis PE, term-only PE, or non-PE outcomes were excluded. Outcomes focused on early and preterm PE with predictive metrics, compared against maternal factors, MAP, UtA Doppler, and biochemical markers, see Table 1.

Table 1 Eligibility criteria for study inclusion and exclusion

	INCLUSION	EXCLUSION
Population	Pregnant women in the first trimester (≤ 14 weeks gestation), singleton pregnancies	Second- or third-trimester populations, non-pregnant populations, multifetal pregnancies, post-diagnosis or established PE cohorts
Intervention/Exposure	Maternal OA Doppler ultrasound, first-trimester Doppler indices (e.g. PSV ratio, PR, PI, RI)	UtA Doppler only, other vascular imaging without OA assessment, non-Doppler imaging (e.g. MRI, CT)
Comparator/Context	Prediction models with or without incremental value; comparisons against maternal risk factors, MAP, UtA Doppler, biochemical markers (e.g. PlGF, Pregnancy-Associated Plasma Protein A (PAPP-A))	Studies with no predictive context, descriptive physiology studies without comparison, purely methodological or technical papers
Outcome	Preterm PE (< 37 weeks), early-onset PE (where reported), prediction performance metrics (AUROC, DR, sensitivity/specificity)	Term PE only; outcomes without PE prediction (SGA, GDM, neurological complications); studies reporting Doppler changes after PE diagnosis
Study Characteristics	Prospective or retrospective primary research; observational cohort studies; first-trimester screening studies; peer-reviewed full-text articles; human studies	Systematic/narrative reviews, meta-analyses, conference abstracts, protocols or methods-only papers, case reports/case series, animal studies, reference-range/normative studies without outcomes
Others	English language; sufficient methodological detail for risk-of-bias assessment; clear gestational age and outcome definition	Abstract-only publications; insufficient data for screening/extraction; duplicate publications without distinct relevant analyses

Study Selection and Data Extraction

All records were imported into Covidence and screened by four reviewers (18). Two reviewers independently extracted data using a pilot-tested form covering study design, population, OA

Doppler indices, comparator variables, outcomes, and predictive metrics. Disagreements were resolved by consensus.

Note on terminology: Some studies reported predictive performance as area under the curve (AUC), others as area under the receiver operating characteristic curve (AUROC). For narrative synthesis, all measures are referred to as AUROC for consistency, while original terms are retained in tables and direct quotes.

Risk of Bias Assessment

Risk of bias and applicability were assessed using the Prediction model Risk Of Bias ASsessment Tool (PROBAST) across four domains: participants, predictors, outcomes, and analysis. Each domain was rated as low, high, or unclear risk of bias. Assessments were performed independently by two reviewers, with disagreements resolved by consensus (19).

Data Synthesis

Clinical and methodological heterogeneity across study populations, OA Doppler indices, outcome definitions, and model structures precluded quantitative meta-analysis. Studies using different first-trimester OA Doppler indices, including Gurgel-Alves et al., were retained. Findings were therefore synthesised narratively, stratified by Doppler index, outcome (early-onset and preterm PE), gestational age at assessment, and model context. Reports from overlapping cohorts were treated as non-independent and not counted as independent validation or replication.

Results

Study Selection

A total of 1,212 records were identified, 354 duplicates were removed, leaving 858 for title/abstract screening. After excluding 843, 15 full texts were assessed, and 10 were excluded for design, population, or intervention issues. Five reports were included, representing four unique cohorts because Gana (2022) and Gana (2025) were confirmed by author correspondence to derive from the same cohort, see Figure 2.

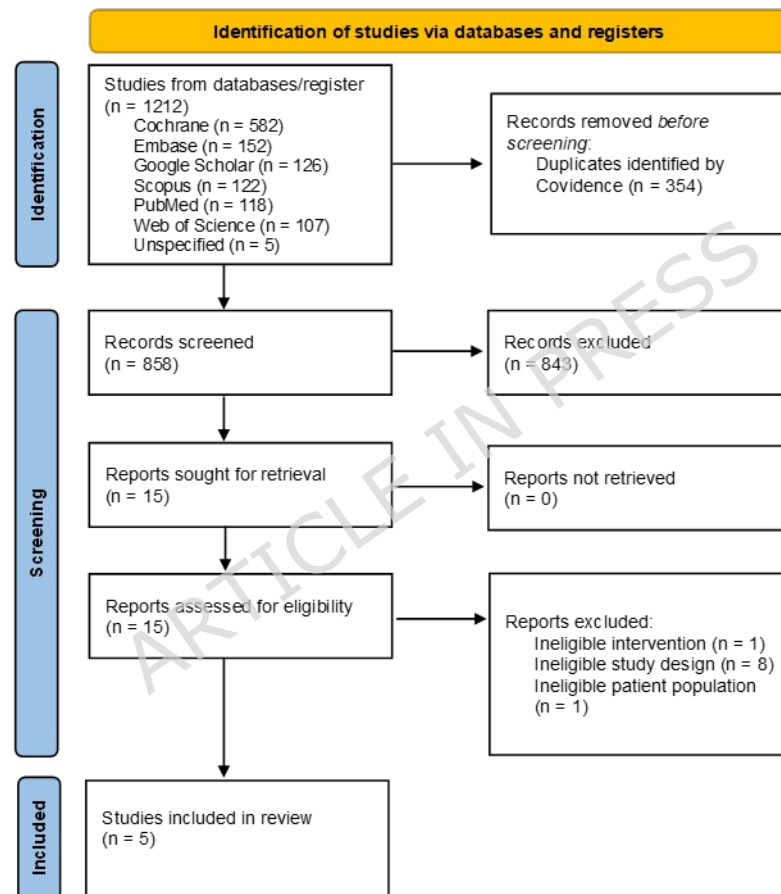


Figure 2. PRISMA 2020 flow diagram reporting selection of studies, adapted from Page et al (20).

Study Characteristics

Five prospective observational cohort reports were included, conducted in tertiary referral centers across Europe, South America, and Asia. These represented four unique cohorts because Gana

(2022) and Gana (2025) derived from the same Harris Birthright cohort and were treated as non-independent reports. Sample sizes ranged from 311 to 4,066 participants. All studies performed OA Doppler assessment predominantly in the first trimester. The Doppler indices assessed varied across studies; however, PSV based indices, particularly PSV ratios, were most consistently reported. Predictive performance was evaluated using the AUROC and DR at specified false-positive rates (Table 2).

Table 2. Study characteristics of papers included in the systematic review

Author (year)	Study center	Study design	Population size	Screening period	OA Doppler indices measured	Prevalence of PE (%)
Gurgel-Alves (2014) (22)	Department of Public Health State University of Ceará, Fortaleza, Ceará, Brazil	Prospective observational cohort	440	August 2009 - February 2011	PI, RI, PD1, PSV, PR	7
Gana (2022) (14)‡	Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK	Prospective observational cohort	4066	June 2019 - February 2021	PSV1, PSV2, PSV ratio	2.8
Kusuma (2023) (17)	Harapan Kita National Women and Children Hospital, West Jakarta, Indonesia	Prospective observational cohort	946	August 2019 - October 2020	PSV1, PSV2, PSV ratio (reported as PR)	7.5
Gana (2025) (15)‡	Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK	Prospective observational cohort	4054	June 2019 - February 2022	PSV1, PSV2, PI, PSV ratio	2.8
Redishetty (2025) (21)	Department of Obstetrics Medicine & Fetal Medicine, Fernandez Foundation, Hyderabad, India	Prospective observational cohort	311	Not reported	PSV1, PSV2, PSV ratio	1.6

Abbreviations: FMF, Fetal Medicine Foundation; OA, ophthalmic artery; PD1, first peak diastolic velocity; PE, preeclampsia; PI, pulsatility index; PR, peak ratio; PSV, peak systolic velocity; PSV1, first peak systolic velocity; PSV2, second peak systolic velocity; RI, resistive index. ‡ Gana (2022) and Gana (2025) were confirmed by author correspondence to derive from the same cohort and were treated as non-independent reports.

Risk of Bias Assessment

Risk of bias was assessed using the PROBAST tool, see Figure 3. Across all included studies, risk of bias was judged to be low in the domains of participants, predictors, and outcomes. All studies were considered to have a high risk of bias in the analysis domain. Studies had small event numbers and lacked validation. Consequently, the overall risk of bias was rated as high for all included studies. Applicability concerns were considered low across domains.

	Risk of Bias				
	D1	D2	D3	D4	Overall
Gurgel-Alves (2014)					
Gana (2022)					
Kusuma (2023)					
Gana (2025)					
Redishetty (2025)					

D1 - Participants

D2 - Predictor

D3 - Outcome

D4 - Analysis

Judgement

 High

 Unclear

 Low

Figure 3. Risk of Bias assessment of Included studies (14, 15, 17, 21, 22)

Gurgel-Alves et al. and Gana et al. evaluated OA Doppler in the context of multivariable prediction models and compared its performance with established first-trimester screening approaches (14, 22). Author correspondence confirmed that Gana (2022) and Gana (2025) derived from the same cohort; these reports were therefore treated as non-independent evidence. Kusuma et al. assessed the contribution of the PSV ratio within a comprehensive model incorporating maternal factors, MAP, UtA-PI, and PlGF (17). Redishetty et al. evaluated HDP as a composite outcome, of which only a small proportion represented PE (of 311 women, 32

developed HDP, including 5 with PE alone). This inclusion of heterogeneous hypertensive disorders rather than isolated PE limits interpretability and comparability with other studies (21). Across the included studies, see Table 3, the PSV ratio was the most frequently evaluated OA Doppler index, while PD1 and PI were assessed less consistently. Reported predictive performance varied widely across studies. OA Doppler generally demonstrated higher predictive performance for early-onset and preterm PE compared to term disease. Larger, population-based cohorts reported DR of approximately 56-59% at a 10% false-positive rate for preterm PE, with multivariable models achieving AUROC values ranging from 0.75 to 0.86. Smaller or selected cohorts reported higher DR, reaching up to 100% (17, 21, 22). Because all reports were at high risk of bias in the analysis domain, these values should be interpreted as exploratory rather than reliable estimates of clinical performance.

Table 3. Summary of OA Doppler indices and predictive performance for PE

Author (year)	Study Population	Model Type	Main OA index used	Outcome assessed	Gestational definition	AUROC (95% CI)	DR (At 10% FPR)	Incremental value of OA Doppler
Gurgel-Alves (2014) (22)	High-risk / selected cohort	Multivariable (maternal + Doppler)	PD1	PE	Early PE (<34 w), Late PE (≥34 w)	OA alone: Early PE: ~0.56 Late PE: ~0.53	OA alone: 16-19% Early PE: ~11% Late PE: ~22%	Improved performance only when combined with maternal factors; no significant advantage over UtA-PI models
Gana (2022) (14)‡	General population (FMF cohort)	Competing risk models	PSV ratio	PE	Preterm PE (<37 w), Term PE (≥37 w)	Model: Early PE: ~0.865 Late PE: ~0.696	Early PE: ~56% Late PE: ~23.6% (preterm)	Modest incremental improvement for preterm PE; no benefit for term PE
Kusuma (2023) (17)	Smaller / selected cohort	Bayesian multivariable model	PSV ratio (PR)	PE	Early PE (<34 w), Preterm PE (<37 w)	Early PE: 0.981 Preterm PE: 0.919	Early PE: 100% Preterm PE: 71%	Apparent improvement likely due to overfitting; no validation
Gana (2025) (15)‡	General population	Logistic + ROC analysis	PSV ratio & PI	PE	Early PE (<37 w), Late PE (≥37 w)	PSV ratio: Early PE: ~0.758	Not reported	PSV ratio outperformed OA PI but required combination with other

							Late PE: ~0.627		markers
Redishetty (2025) (21)	Mixed risk cohort	Multivariable model	PSV ratio	HDP (incl. PE)	All gestations	Model: ~0.833 [†]	59.4% [‡]	Improved performance in combined models; outcome heterogeneity limits interpretation	

Definitions of early, preterm, and late pre-eclampsia vary across studies and are reported as per original publications.

[†] AUROC and DR in Redishetty (2025) reflect combined model performance, not OA Doppler alone. [‡] Gana (2022) and Gana (2025) were confirmed by author correspondence to derive from the same cohort and were treated as non-independent reports. Abbreviations: AUROC, area under the receiver operating characteristic curve; DR, detection rate; FMF, Fetal Medicine Foundation; FPR, false-positive rate; HDP, hypertensive disorders of pregnancy; OA, ophthalmic artery; PD1, first peak diastolic velocity; PE, preeclampsia; PI, pulsatility index; PR, peak ratio; PSV, peak systolic velocity; UtA-PI, uterine artery pulsatility index.

Discussion

Five prospective cohort reports representing four unique cohorts evaluated first-trimester OA Doppler for prediction of PE. Overall, predictive performance was inconsistent and was more favourable in small or selected cohorts than in larger, unselected populations. Standalone OA measures performed poorly. Any apparent benefit was generally observed only when OA Doppler was incorporated into multivariable models that already included established screening variables. Where OA Doppler was evaluated independently, discriminatory ability was low, with AUROC values of approximately 0.53-0.61 and DR of approximately 16-19% at a 10% false-positive rate. Higher performance was reported only in multivariable models incorporating maternal factors, MAP, UtA-PI, and PlGF. In larger cohorts, these models achieved AUROC values of approximately 0.75-0.86 and DR for preterm PE of approximately 56-59%.

A clear difference was observed between large population-based cohorts and smaller studies with few outcome events. The most striking estimates were reported in cohorts with limited event numbers and no external validation, making overfitting a major concern. This was most evident in the study by Kusuma et al., in which AUROC values of 0.981 for early-onset PE and 0.919 for

preterm PE, together with a 100% DR for early disease, were reported despite only nine early-onset cases (17). Taken together, these findings suggest that the apparent promise of OA Doppler may have been inflated in some studies and that its reproducibility in routine clinical practice remains uncertain.

Pathophysiology and Clinical Significance

The observed variation in predictive performance across PE subtypes is biologically plausible. Early-onset PE is primarily a placental disorder characterised by impaired trophoblast invasion and inadequate spiral artery remodelling, leading to placental ischemia and systemic endothelial dysfunction. In contrast, late-onset PE is more strongly influenced by maternal cardiovascular and metabolic factors (2, 23, 24).

OA Doppler reflects maternal systemic and cerebral vascular adaptation rather than placental pathology. This likely explains its relatively better performance in predicting early-onset and preterm PE compared with term disease. For example, AUROC values for preterm or early PE reached approximately 0.88 in multivariable models, compared with 0.76 for term PE (13, 15, 25).

Incremental value of OA Doppler

The extent to which OA Doppler adds to established first-trimester screening remains uncertain. Several reports described better performance when OA Doppler was added to multivariable models, but the gains were generally small, and model structures differed across reports. In larger cohorts, improvements in DR were modest and were not seen consistently across PE phenotypes. This weakens the case for OA Doppler as a clinically useful addition to established first-trimester screening. For example, in Gurgel-Alves et al., models combining maternal factors with OA

Doppler achieved DR of 48%, compared with 58% when combined with UtA Doppler, with no statistically significant difference in AUC between models. In Gana et al. (2022), addition of the PSV ratio improved detection of preterm PE from 46.3% to 58.4% when added to maternal factors alone, and from 65.9% to 70.6% in models already including maternal factors, MAP, and UtA-PI, representing only modest incremental gains (14). The later Gana et al. (2025) report is from the same cohort and was therefore not interpreted as independent validation of this finding. In Redishetty et al., inclusion of OA Doppler (PSV ratio) improved DR for hypertensive disorders of pregnancy from 56.3% to 59.4-62.5%, with corresponding AUROC values rising to ~0.83. However, only 5 cases of PE were included, limiting conclusions on the specific predictive value of OA Doppler for preterm PE; exclusion of this composite-outcome study did not alter the overall conclusion that incremental value remains uncertain (21).

However, these improvements were inconsistently reported and primarily assessed using AUROC. None of the included studies evaluated calibration, net reclassification improvement, or decision-curve analysis (16). Second-trimester data also support improved detection when OA Doppler is included (26). Conversely, third-trimester studies and late/term PE show little added value, suggesting its utility is greatest in early and preterm disease, where maternal vascular adaptation is critical (16). As a result, it remains unclear whether these modest statistical improvements translate into meaningful clinical benefit. Current evidence therefore does not support a consistent or clinically significant incremental value of OA Doppler beyond established first-trimester screening models.

Methodological Considerations and Sources of Bias

All included studies were judged to be at high risk of bias in the analysis domain using PROBAST. This was primarily driven by small numbers of outcome events (e.g., 9 early PE cases in Kusuma et al.; 31 PE cases in Gurgel-Alves et al.; 32 HDP cases in Redishetty et al.), inadequate handling of missing data, absence of internal or external validation, non-independence of the two Gana reports, and the use of a composite HDP outcome in Redishetty et al. (17, 21, 22). These limitations substantially increase the risk of overfitting and inflation of predictive performance. As a result, no reliable estimate of the predictive performance of first-trimester OA Doppler can be derived from the current evidence base.

Confounding represents an additional limitation. Adjustment for low-dose aspirin use was inconsistent, despite its known effect in reducing early-onset and preterm PE. Aspirin exposure was reported in the Gana cohort at low frequency, but it was not clearly incorporated as a covariate, treatment variable, or time-dependent factor in the final predictive models; the remaining reports either did not report aspirin exposure or did not describe adjustment for it. Variation in population characteristics, including baseline risk, comorbidities, and ethnicity, further contributes to heterogeneity (27, 28).

Differences in outcome definitions and methodological approaches limit comparability across studies. Early-onset PE was variably defined (e.g., <34 vs <37 weeks), and predictive approaches included multivariable logistic/ROC models, FMF Bayes theorem-based competing-risk models, and a Bayesian survival-time model. Additional heterogeneity arose from sample size, missing data, Doppler acquisition protocols, gestational timing of assessment, and the use of different OA indices or multiparametric combinations. Infection status was not reported in any included study; therefore, potential confounding by COVID-19 could not be assessed. Collectively, these factors

contribute to variability in reported outcomes and should be considered when interpreting the generalisability of findings.

Clinical Implications

Current evidence does not support the routine use of OA Doppler as a stand-alone screening tool for PE. While OA Doppler provides insight into maternal vascular adaptation, its predictive performance is insufficient when used in isolation and provides limited additional predictive benefit.

However, OA Doppler may still have a role as part of a multimarker approach, particularly for early-onset and preterm PE. Integration with maternal risk factors, MAP, UtA Doppler, and biochemical markers may improve early risk stratification, but this requires validation in large, representative cohorts using standardised methodologies. Implementation in clinical practice would require clear demonstration of clinical utility, cost-effectiveness, and reproducibility, none of which have been adequately addressed to date (29, 30).

Future Directions

Future research should prioritise large, multicentre studies with sufficient event numbers to ensure statistical robustness and generalisability. Standardisation of OA Doppler acquisition protocols, gestational timing, and outcome definitions is essential to reduce heterogeneity. Recent efforts to establish gestational age-specific reference ranges for OA Doppler indices may improve interpretation and facilitate integration into predictive models (31).

In addition, future studies should incorporate rigorous statistical methodologies, including internal and external validation, calibration assessment, and evaluation of clinical utility using decision-curve analysis and net reclassification improvement. Longitudinal assessment of OA Doppler

indices and maternal hemodynamics alongside established screening indices across early pregnancy may provide further insight into dynamic maternal vascular adaptation and improve prediction beyond single timepoint measurements.

Crucially, adjustment for key confounders must be systematically incorporated into future models. Without addressing these methodological limitations, the true clinical value of OA Doppler will remain uncertain. Collectively, these steps are necessary to determine whether OA Doppler can evolve from an observational biomarker into a clinically meaningful component of first-trimester PE screening.

Strengths and Limitations

This review has several strengths. It used a prespecified protocol, clear eligibility criteria, duplicate screening and extraction, and structured risk-of-bias assessment with PROBAST. It also focused on a clinically relevant question: whether first-trimester OA Doppler adds to established screening for early-onset and preterm PE.

The review also has important limitations. Only five reports, representing four unique cohorts, met the inclusion criteria; several had few outcome events, and all were at high risk of bias in the analysis domain. None included robust external validation. The Gana (2022) and Gana (2025) reports were confirmed to derive from the same cohort and were therefore not treated as independent evidence. Redishetty et al. reported a composite HDP outcome rather than isolated preterm or early-onset PE, with only five PE cases, and was retained only as contextual evidence; excluding it did not change the overall conclusion. Differences in OA indices, study populations, outcome definitions, model structures, and reported metrics limited comparability and precluded meta-analysis. Restriction to English-language studies and the predominance of single-centre cohorts may also limit generalisability.

Conclusions

Current evidence does not support the routine use of first-trimester OA Doppler for PE screening. Although OA Doppler, particularly the PSV ratio, may provide limited additional information within multivariable models, its standalone performance is weak. Available estimates are undermined by small event numbers, heterogeneous outcome definitions, inconsistent model structures, limited validation and high risk of bias in the analysis domain. Consequently, no reliable pooled estimate of predictive performance or incremental clinical value can currently be derived from the available evidence.

Future studies should adopt a standardised minimum framework to improve comparability and enable eventual data pooling. At a minimum, studies should recruit clearly defined singleton first-trimester populations, assess OA Doppler within a prespecified gestational window, and report PSV1, PSV2 and the PSV ratio using consistent acquisition methods. They should also use internationally accepted definitions of early-onset and preterm PE, report aspirin exposure and

other key confounders, and compare OA Doppler against established first-trimester screening models incorporating maternal factors, MAP, UtA-PI and PlGF. Model development and validation strategies should be prespecified, with calibration and clinical utility assessed before implementation is considered. This standardisation is essential to determine whether OA Doppler has clinically meaningful incremental value in first-trimester screening for PE.

Abbreviations

The following abbreviations are used in this manuscript:

AUC Area under the curve
 AUROC Area under the receiver operating characteristic curve
 DR Detection rate
 FMF Fetal Medicine Foundation
 FPR False-positive rate
 HDP Hypertensive disorders of pregnancy
 MAP Mean arterial pressure
 OA Ophthalmic artery
 PD1 First peak diastolic velocity
 PAPP-A Pregnancy-associated plasma protein A
 PE Preeclampsia
 PI Pulsatility index
 PlGF Placental growth factor
 PR Peak ratio
 PROBAST Prediction model Risk Of Bias ASsessment Tool
 PSV Peak systolic velocity
 PSV1 First peak systolic velocity
 PSV2 Second peak systolic velocity
 RI Resistive index
 UtA Uterine artery

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Competing interests: The authors declare no competing interests.

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Data availability

All data and materials necessary to support the findings of this study are included in the manuscript.

Author Contributions: Conceptualization, J.B.; methodology, S.A., Z.M., H.J., R.K., S.D. and J.B.; study design, U.T. and J.B.; literature search strategy, S.D.; screening and data extraction, S.A., Z.M., H.J. and R.K.; formal analysis and interpretation, S.A., Z.M., H.J., R.K. and J.B.; writing—original draft preparation, S.A., Z.M., H.J., R.K. and J.B.; writing—review and editing, S.A., Z.M., H.J., R.K., S.D., U.T. and J.B.; supervision, J.B.; project administration, J.B. All authors have read and agreed to the published version of the manuscript.

References

1. Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Karumanchi SA, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens.* 2022;27:148-69.
2. Kariori M, Katsi V, Tsioufis C. Late vs. Early Preeclampsia. *Int J Mol Sci.* 2025;26(22).
3. Han L, Holland OJ, Da Silva Costa F, Perkins AV. Potential biomarkers for late-onset and term preeclampsia: A scoping review. *Front Physiol.* 2023;14:1143543.
4. Lisonkova S, Sabr Y, Mayer C, Young C, Skoll A, Joseph KS. Maternal morbidity associated with early-onset and late-onset preeclampsia. *Obstet Gynecol.* 2014;124(4):771-81.
5. Dall'Asta A, D'Antonio F, Saccone G, Buca D, Mastantuoni E, Liberati M, et al. Cardiovascular events following pregnancy complicated by pre-eclampsia with emphasis on comparison between early- and late-onset forms: systematic review and meta-analysis. *Ultrasound Obstet Gynecol.* 2021;57(5):698-709.
6. Organization WH. Pre-eclampsia [Web page]. Geneva: World Health Organization; 2025 [updated 10 December 2025; cited 2026 12 February]. WHO fact sheet summarising epidemiology, risk factors, diagnosis, prevention and management of pre-eclampsia.]. Available from: <https://www.who.int/news-room/fact-sheets/detail/pre-eclampsia>.
7. Cui Y, Zhu B, Zheng F. Low-dose aspirin at ≤ 16 weeks of gestation for preventing preeclampsia and its maternal and neonatal adverse outcomes: A systematic review and meta-analysis. *Exp Ther Med.* 2018;15(5):4361-9.
8. Tan MY, Syngelaki A, Poon LC, Rolnik DL, O'Gorman N, Delgado JL, et al. Screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. *Ultrasound Obstet Gynecol.* 2018;52(2):186-95.
9. Liu J, Chen Y, Tai ST, Nguyen-Hoang L, Li K, Lin J, et al. First Trimester Preeclampsia Screening and Prevention: Perspective in Chinese Mainland. *Maternal-Fetal Medicine.* 2024;6(2):84-91.
10. First-Trimester Screening Program for the Risk of Pre-eclampsia Using a Multiple-Marker Algorithm: A Health Technology Assessment. *Ont Health Technol Assess Ser.* 2023;22(5):1-118.

11. Dhaifalah I, Magalova E, Studnykova D, Havalova J, Slintakova E, Cuckle H. Quality assessment of first-trimester screening for preterm pre-eclampsia. *Ultrasound Obstet Gynecol.* 2022;60(6):746-50.
12. Kane SC. First trimester screening for pre-eclampsia. *Obstet Med.* 2016;9(3):106-12.
13. Kalafat E, Laoreti A, Khalil A, Da Silva Costa F, Thilaganathan B. Ophthalmic artery Doppler for prediction of pre-eclampsia: systematic review and meta-analysis. *Ultrasound Obstet Gynecol.* 2018;51(6):731-7.
14. Gana N, Sarno M, Vieira N, Wright A, Charakida M, Nicolaides KH. Ophthalmic artery Doppler at 11-13 weeks' gestation in prediction of pre-eclampsia. *Ultrasound Obstet Gynecol.* 2022;59(6):731-6.
15. Gana N, Pittokopitou S, Solonos F, Perdeica A, Fitiri M, Nicolaides KH. Ophthalmic Artery Doppler Indices at 11-13 Weeks of Gestation in Relation to Early and Late Preeclampsia. *J Clin Med.* 2025;14(13).
16. Arkorful J, Browne JL, Adu-Bonsaffoh K, Ali S, Srofenyoh E, Bloemenkamp KMW. Predictive accuracy of ophthalmic artery Doppler for pre-eclampsia: a systematic review. *BMJ Open.* 2025;15(6):e094348.
17. Kusuma RA, Nurdianti DS, Al Fattah AN, Danukusumo D, Abdullah S, Sini I. Ophthalmic artery Doppler for pre-eclampsia prediction at the first trimester: a Bayesian survival-time model. *J Ultrasound.* 2023;26(1):155-62.
18. Covidence systematic review software. Melbourne, Australia: Veritas Health Innovation; 2024.
19. Wolff RF, Moons KGM, Riley RD, Whiting PF, Westwood M, Collins GS, et al. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. *Ann Intern Med.* 2019;170(1):51-8.
20. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71.
21. Redishetty S, More G, Tarakeshwari S, Suseela V, Geeta K, Swapna S. Prediction of Pre-Eclampsia Based on Maternal Clinical Characteristics, Placental Growth Factor, Mean Arterial Pressure, First-Trimester Uterine and Ophthalmic Artery Doppler: A Prospective Observational Cohort Study. *The Journal of Obstetrics and Gynecology of India.* 2025.
22. Gurgel Alves JA, Praciano de Sousa PC, Bezerra Maia EHMS, Kane SC, da Silva Costa F. First-trimester maternal ophthalmic artery Doppler analysis for prediction of pre-eclampsia. *Ultrasound Obstet Gynecol.* 2014;44(4):411-8.
23. Santulli G, Kansakar U, Varzideh F. Epidemiology and Pathophysiology of Preeclampsia: New Mechanistic Insights. *Hypertension.* 2025;82(5):800-3.
24. Uzan J, Carbonnel M, Piconne O, Asmar R, Ayoubi JM. Pre-eclampsia: pathophysiology, diagnosis, and management. *Vasc Health Risk Manag.* 2011;7:467-74.
25. Sapantzoglou I, Antsaklis P, Pergialiotis V, Chatziioannou MI, Fasoulakis Z, Daskalaki MA, et al. Added value of ophthalmic artery Doppler in prediction of pre-eclampsia: systematic review and meta-analysis. *Ultrasound Obstet Gynecol.* 2025;66(6):716-23.
26. Sapantzoglou I, Wright A, Arozena MG, Campos RV, Charakida M, Nicolaides KH. Ophthalmic artery Doppler in combination with other biomarkers in prediction of pre-eclampsia at 19-23 weeks' gestation. *Ultrasound Obstet Gynecol.* 2021;57(1):75-83.

27. Horgan R, Hage Diab Y, Waller J, Abuhamad A, Saade G. Low-dose aspirin therapy for the prevention of preeclampsia: time to reconsider our recommendations? *Am J Obstet Gynecol.* 2023;229(4):410-8.
28. Rolnik DL, Nicolaides KH, Poon LC. Prevention of preeclampsia with aspirin. *Am J Obstet Gynecol.* 2022;226(2s):S1108-s19.
29. American College of O, Gynecologists. Low-dose aspirin use during pregnancy. *Obstet Gynecol.* 2018;132(1):e44-e52.
30. Lourenço I, Gomes H, Ribeiro J, Caeiro F, Rocha P, Francisco C. Screening for Preeclampsia in the First Trimester and Aspirin Prophylaxis: Our First Year. *Rev Bras Ginecol Obstet.* 2020;42(7):390-6.
31. Kusuma RA, Rachman IT, Setyawan A, Welly A, Al Fattah AN, Nurdianti DS. Reference ranges for peak systolic velocity ratio of ophthalmic artery Doppler from first to third trimester based on serial Doppler measurements. *Arch Gynecol Obstet.* 2025;312(5):1661-5.

APPENDICES

Full Database Search Strategies

The complete electronic search strategies used for each database are provided below.

PubMed:

```
(("Pre-Eclampsia"[Mesh] OR preeclampsia[tiab] OR pre-eclampsia[tiab] OR
"preterm preeclampsia"[tiab] OR "Hypertension, Pregnancy-Induced"[Mesh] OR
"hypertensive disorders of pregnancy"[tiab])
AND ("Ophthalmic Artery"[Mesh] OR "ophthalmic artery"[tiab] OR "ophthalmic
doppler"[tiab] OR "ophthalmic artery doppler"[tiab])
AND ("Ultrasonography, Doppler"[Mesh] OR doppler[tiab] OR
ultrasonograph*[tiab] OR ultrasound[tiab])
AND ("Pregnancy Trimester, First"[Mesh] OR "first trimester"[tiab] OR first-
trimester[tiab] OR "early pregnancy"[tiab]
OR (( "10 weeks"[tiab] OR "11 weeks"[tiab] OR "12 weeks"[tiab] OR "13
weeks"[tiab] OR "14 weeks"[tiab]
OR "10 wk"[tiab] OR "11 wk"[tiab] OR "12 wk"[tiab] OR "13 wk"[tiab] OR "14
wk"[tiab]
OR "10 wks"[tiab] OR "11 wks"[tiab] OR "12 wks"[tiab] OR "13 wks"[tiab] OR
"14 wks"[tiab]))
AND (gestation*[tiab] OR pregnan*[tiab]))))
```

Embase:

('preeclampsia'/exp OR 'preeclampsia':ti,ab,kw OR 'pre-eclampsia':ti,ab,kw OR 'hypertensive disorders of pregnancy':ti,ab,kw OR 'pregnancy-induced hypertension':ti,ab,kw)

AND ('ophthalmic artery'/exp OR 'ophthalmic artery':ti,ab,kw OR 'ophthalmic doppler':ti,ab,kw OR 'ophthalmic artery doppler':ti,ab,kw OR 'ocular artery':ti,ab,kw OR 'transorbital':ti,ab,kw OR 'transorbital doppler':ti,ab,kw OR 'ophthalmic artery pulsatility index':ti,ab,kw OR 'ophthalmic artery resistance index':ti,ab,kw OR 'ophthalmic artery pi':ti,ab,kw OR 'ophthalmic artery ri':ti,ab,kw OR 'oa doppler':ti,ab,kw)

AND ('doppler ultrasonography'/exp OR 'doppler':ti,ab,kw OR 'ultrasonograph*':ti,ab,kw OR 'ultrasound':ti,ab,kw)

AND ('pregnancy'/exp OR 'first trimester pregnancy'/exp OR 'first trimester':ti,ab,kw OR 'first-trimester':ti,ab,kw OR 'early pregnancy':ti,ab,kw OR 'first trimester screening':ti,ab,kw OR '11-14 weeks':ti,ab,kw OR '11-14 weeks':ti,ab,kw OR 'gestation*':ti,ab,kw OR 'pregnan*':ti,ab,kw)

Scopus:

TITLE-ABS-KEY(("pre-eclampsia" OR preeclampsia OR "hypertensive disorders of pregnancy" OR "pregnancy induced hypertension"))

AND TITLE-ABS-KEY(("ophthalmic artery" OR "ophthalmic artery doppler" OR "ophthalmic doppler" OR "ocular artery" OR transorbital OR "transorbital doppler" OR "ophthalmic artery pulsatility index" OR "ophthalmic artery resistance index" OR "ophthalmic artery PI" OR "ophthalmic artery RI" OR "OA doppler"))

AND TITLE-ABS-KEY((doppler OR ultrasonograph* OR ultrasound))

AND TITLE-ABS-KEY(("first trimester" OR first-trimester OR "early pregnancy" OR "first trimester screening" OR "11-14 weeks" OR "11 14 weeks" OR gestation* OR pregnan*))

Web of Science:

```

TS= (("pre-eclampsia" OR preeclampsia OR "hypertensive disorders of pregnancy"
OR "pregnancy induced hypertension"))
AND TS= (("ophthalmic artery" OR "ophthalmic artery doppler" OR "ophthalmic
doppler" OR "ocular artery" OR transorbital OR "transorbital doppler" OR
"ophthalmic artery pulsatility index" OR "ophthalmic artery resistance index"
OR "ophthalmic artery PI" OR "ophthalmic artery RI" OR "OA doppler"))
AND TS= ((doppler OR ultrasonograph* OR ultrasound))
AND TS= (("first trimester" OR first-trimester OR "early pregnancy" OR "first
trimester screening" OR "11-14 weeks" OR "11 14 weeks" OR gestation* OR
pregnan*))

```

Cochrane Library:

```

#1 MeSH descriptor: [Pre-Eclampsia] explode all trees
#2 (preeclampsia OR pre-eclampsia OR "hypertensive disorders of pregnancy" OR
"pregnancy induced hypertension")
#3 #1 OR #2
#4 MeSH descriptor: [Ophthalmic Artery] explode all trees
#5 ("ophthalmic artery" OR "ophthalmic doppler")
#6 #4 OR #5
#7 MeSH descriptor: [Ultrasonography, Doppler] explode all trees
#8 (doppler OR ultrasonograph* OR ultrasound)
#9 #7 OR #8
#10 MeSH descriptor: [Pregnancy] explode all trees
#11 MeSH descriptor: [Pregnancy Trimester, First] explode all trees
#12 "first trimester" OR first-trimester OR "early pregnancy" OR "first
trimester screening" OR "11-14 weeks" OR "11 14 weeks" OR gestation* OR
pregnan*
#13 #10 OR #11 OR #12

```

#14 #3 AND #6 AND #9 AND #13

#15 #9 AND #13

#16 #2 #15

#17 #6 AND #16

#18 #3 AND #9

#19 #18 AND #13

Google Scholar:

("pre-eclampsia" OR preeclampsia) AND ("ophthalmic artery" OR "ophthalmic artery Doppler") AND (Doppler OR ultrasound) AND ("first trimester" OR "early pregnancy" OR "11-14 weeks")

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