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The Value of Ophthalmic Artery Doppler Parameters as a Predictive Tool in Preeclamptic Patients: A Systematic Review and Meta-analysis of Diagnostic Test Accuracy

I Wayan Agus Surya Pradnyana[1*], Endang Sri Widiyanti[2], I Gde Arie Kusuma Wijaya[3], Made Favian Budi Gunawan[1], I Gusti Ayu Cintya Paramyta[1], Ni Nengah Devianti Wulan Pradnyani[1]

Abstract

Objectives: Early detection of preeclampsia (PE) is crucial to prevent severe maternal and fetal complications. Ophthalmic artery Doppler (OAD) presents a viable and non-invasive placenta-independent approach, especially in low-resource settings. This study aims to evaluate the diagnostic accuracy of OAD parameters and address the lack of standardized protocols and comparative analyses with other biomarkers.

Methods: This study followed PRISMA guidelines. Data on peak ratio (PR), resistance index (RI), and pulsatility index (PI) were extracted from studies comparing PE and normotensive pregnancies. Bivariate models were used for summary ROC curves to estimate pooled sensitivity, specificity, diagnostic odds ratio (DOR), and area under the curve (AUC). All analyses were performed using R Studio.

Results: Seventeen studies involving 2699 pregnant women were included. The PR showed a pooled sensitivity of 0.80 (95% CI 0.66–0.89, $I^2 = 0.0\%$), specificity of 0.92 (95% CI 0.80–0.97, $I^2 = 91.0\%$), DOR of 48.85 (95% CI 12.79–186.53, $I^2 = 50.5\%$, $P < 0.001$), and AUC of 0.911. The RI showed a pooled sensitivity of 0.76 (95% CI 0.68–0.82, $I^2 = 0\%$), specificity of 0.76 (95% CI 0.57–0.88, $I^2 = 93.2\%$), DOR of 11.14 (95% CI 6.01–20.64, $I^2 = 35.6\%$, $P < 0.001$), and AUC of 0.774. The PI showed a pooled sensitivity of 0.69 (95% CI 0.58–0.78, $I^2 = 75.2\%$), specificity of 0.86 (95% CI 0.64–0.96, $I^2 = 88.2\%$), DOR of 12.89 (95% CI 5.40–30.78, $I^2 = 85.2\%$, $P< 0.001$), and AUC of 0.768. The pooled analysis of PR, PI, and RI showed that the PE group had MDs of -0.21 (95% CI -0.21; -0.02), -0.36 (95% CI -0.56; -0.15), and -0.06 (95% CI -0.08; -0.03), respectively.

Conclusions: The OAD, particularly the PR parameter, demonstrates high diagnostic accuracy, strong sensitivity, and specificity for identifying PE.

Keywords: Ophthalmic artery, Diagnosis, Doppler, Preeclampsia, Accuracy

Introduction

Preeclampsia (PE) is a complex, pregnancy-specific disorder involving multiple organ systems, primarily characterized by an abnormal vascular response during placentation. This abnormality occurs in expanded systemic vascular resistance, a prothrombotic environment, and endothelial dysfunction. Clinically, PE is distinguished by consistently elevated blood pressure readings surpassing 140/90 mm Hg on two occasions at least six hours apart, with proteinuria, occurring after 20 weeks of incubation in ladies who were previously normotensive and non-proteinuric, and typically resolves within six weeks after delivery (1). Affecting approximately 2%–8% of pregnancies, PE remains a leading cause of maternal and perinatal morbidity and mortality, with a higher incidence noted among primigravidae, occurring in about 5–10% of pregnancies (1,2).

Hypertensive disorders constitute the most frequently encountered medical complications during pregnancy, impacting up to 10% of all gestations (3). The ability to accurately predict the onset of PE holds significant clinical value, as it would facilitate enhanced monitoring and timely management of at-risk individuals (4). One widely accepted theory suggests that severe hypertension raises cerebral autoregulatory thresholds, leading to vasodilation and resultant cerebral edema (5). Maternal cerebral circulation can be assessed non-invasively using Doppler ultrasound of the ophthalmic artery, as the hemodynamic parameters obtained are thought to mirror cerebral perfusion (6). Several studies have proposed a relationship between PE and heightened orbital vascular resistance, which is evident through alterations in maternal ophthalmic artery flow velocity patterns (7). Screening for PE includes several biomarkers, such as the soluble fms-like tyrosine kinase-1 (sFlt-1) to placental growth factor (PlGF) ratio, which has demonstrated substantial predictive value, particularly in early-onset cases. However, these methods can be limited by high

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[1]Faculty of Medicine, Udayana University, Prof. dr. I.G.N.G Ngoerah General Hospital, Denpasar, Bali, Indonesia. [2]Maternal Fetal Medicine Division, Department of Obstetrics and Gynecology, Udayana University, Prof. dr. I.G.N.G Ngoerah General Hospital, Denpasar, Bali, Indonesia. [3]Faculty of Medicine, Ganesha University, Buleleng General Hospital, Singaraja, Bali, Indonesia.

***Corresponding Author:** I Wayan Agus Surya Pradnyana, Email: suryapradnyana@student.unud.ac.id

costs, technical requirements, and reduced availability in low-resource settings (7).

Ophthalmic artery Doppler (OAD) ultrasonography is a non-invasive technique for assessing central vascular hemodynamics in pregnant individuals. It has garnered substantial scientific attention as a potential screening modality, particularly for hypertensive disorders of pregnancy. Prior research has demonstrated that OAD can independently predict early-onset PE, with predictive accuracy comparable to uterine artery Doppler assessments (8). It has been demonstrated that OAD independently predicts early-onset PE, exhibiting predictive capabilities comparable to uterine artery Doppler assessments (9). Notably, this technique possesses several advantages: it is easily integrated into routine obstetric practice using standard ultrasound devices, remains unaffected by maternal obesity, and provides consistent reference ranges across all trimesters (2). These properties position the ophthalmic supply route Doppler as an exceptionally profitable prescient device in resource-limited settings. Subsequently, this study and meta-analysis aimed to assess the demonstrative execution of OAD to back its potential clinical application.

Methods

Protocol and Registration

This systematic review and meta-analysis adhered to the PRISMA guidelines, ensuring transparency, methodological rigor, and reproducibility in evaluating and synthesizing the relevant studies.

Literature Search and Study Selection

A systematic and thorough search was undertaken across various online databases, including PubMed, MEDLINE, Web of Science, EMBASE, ScienceDirect, and the Cochrane Library, from their establishment to March 1, 2024. The Population–Intervention–Comparison–Outcome (PICO) framework was used to define a clinical question, structure the article research clearly, and help ensure clarity, relevance, and comprehensiveness in determining the scope of the review. The study PICO framework is as follows, Population (P): Pregnant women with PE, Intervention (I): OAD parameters (peak systolic velocity [PSV], end-diastolic velocity [EDV], second systolic velocity peak (P2), resistance index (RI), pulsatility index (PI) and peak ratio (PR). Comparison (C): Pregnant women without PE. Outcome (O): Diagnostic accuracy (false positive, false negative, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC)

Keywords and Medical Subject Headings (MeSH) phrases pertaining to "ophthalmic artery," "Doppler," "ultrasound," "preeclampsia", "pregnancy", "diagnosis", and "predict" were included in the search strategy. The titles and abstracts of retrieved records were checked to eliminate duplicate entries and irrelevant research. The remaining records' full-text articles were then appraised for eligibility using preset inclusion criteria. In addition, a manual check of reference lists from included studies and pertinent review articles was conducted to identify any possibly eligible studies that were missed during the original database search. Gray Literature, such as conference proceedings and unpublished studies, was not included in this search to avoid incomplete data and results while focusing on peer-reviewed, high-quality evidence. This decision might limit comprehensiveness, but it enhances the reliability and reproducibility of the findings in these studies. The inclusion criteria included: (a) design of randomized controlled trials, prospective or retrospective cohort studies, case-control studies, and cross-sectional research; (b) study populations consisting of women diagnosed with PE and normotensive pregnant women as controls; and (c) studies mentioned at least one Doppler parameter of the ophthalmic artery, including PSV, EDV, second systolic velocity peak (P2), RI, PI, and PR. The exclusion criteria include conference summaries, review articles, cases or cases where cases, animal research, and non-detected publications. Two authors (I.W.A.S.P. and N.N.D.W.P.) are dedicated to the articles' titles, summaries, and complete documents. Any differences were settled after consulting a third author (E.S.W.). These exclusion criteria were designed to help ensure methodological integrity and proper evidence synthesis. Case reports and case series were excluded since those studies have no comparative control group and statistical power, which diminishes their ability to offer objective case appraisals. Case reports and series are uncontrolled descriptive studies, and animal experiments involve non-human subjects. These designs usually fall outside the PICO (Population–Intervention–Comparison–Outcome) scope of human-health intervention reviews. Accordingly, they are routinely excluded to ensure that included studies are methodologically comparable and directly relevant to the clinical question While such reports may provide early insight into atypical presentations of PE, their anecdotal nature risks draw attention elsewhere instead of generalizable diagnostic trends which negate the purpose of this review where this review was made to identify consistent, population-level patterns. Abstracts from conferences and review articles were avoided for their incomplete or duplicative data, where abstracts frequently lack peer-reviewed methodological detail. Exclusion of non-English publications allows data to be interpreted appropriately when extracted, but is a choice that, unintentionally, limits geographic diversity. The reasons for eliminating each full-text publication were noted, and reference lists from selected papers were examined for other investigations. The reviewers re-evaluated any anomalies to ensure that the database was accurate.

Data Extraction and Quality Assessment

All data used in this overview have been extracted

directly from the main text or the included studies' tables. Data extraction is made independently by two authors (I.W.A.S.P. and N.N.D.W.P.) to minimize errors and ensure accuracy. For each eligible research, the following variables have been systematically collected: Names of the first author, year of publication, research design, total sample size and detailed information on OAD parameters, including PSV, EDV, second systolic velocity peak (P2), RI, PI, and PR. The data of diagnostic efficiency - positive, false negative, sensitivity, specificity, and PPV - have also been extracted when available.

Two reviewers (M.F.B.G., I.G.A.K.W.) independently assessed the risk of bias and methodological quality of all included studies using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool, which is specifically designed to evaluate the quality of diagnostic accuracy studies. QUADAS-2 reviews four main areas: patient selection, checking indicators, reference standards, and flow and calendar of participants through research. Each area has been evaluated for the risk of misleading and is concerned about its applicability. Studies have been classified as low, high, or unclear risks in each field according to the criteria described in the QUADAS-2 frame. The Newcastle-Ottawa Scale (NOS) tool has been used for non-diagnostic test studies.

Statistical Analysis

To compare the mean values of OAD parameters between PE cases and normal pregnancies during the antenatal period (serving as the control group), we conducted meta-analyses using random-effects models if heterogeneity is >60% and fixed models if heterogeneity <60%, using the DerSimonian and Laird method for inverse variance estimation (10). In this case, a 60% threshold for heterogeneity cut-off was used based on the commonly accepted guidelines in meta-analysis literature. If the I^2 value is above 50-60%, it indicates substantial heterogeneity that ensures the random effect approach while considering the variability between studies (11). The Cochrane Handbook suggests that in estimating heterogeneity, both I^2 and the clinical and methodological diversity of the included studies should be considered. It also recommends using a random-effects model when there is moderate to substantial heterogeneity because this model assumes that the underlying effects in different studies are more likely to vary. It is less optimistic than fixed-effects models (12).

To evaluate publication bias, an essential aspect of meta-analysis, we employed funnel plot analysis to assess symmetry when a sufficient number of studies met the inclusion criteria. This approach strengthens the reliability of the meta-analytic findings by detecting small-study effects or selective outcome reporting, thereby improving confidence in the validity of the results.

When possible, subgroup meta-analyses were performed to differentiate moderate or late-onset PE cases from severe or early-onset PE cases. The I^2 statistic was used to quantify statistical heterogeneity. Later, univariate analysis of sensitivity and specificity was performed, then the diagnostic and uniform assessment of the summary characteristics of the receptor operating characteristic (ROC), derived from the Bivariate models adjusted by data to estimate global sensitivity and specificity. We also analyze the positive likelihood ratio (PLR), negative likelihood ratio (NLR), PPV, NPV, and AUC. Statistical analyses were conducted using R Studio software.

Quality of Evidence Assessment

This article has used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) of evaluating, developing, and evaluating to assess the quality of evidence for clinical application across the included studies. This shows sensitivity and specificity, with the overall level of evidence shown in four types (high, moderate, low, very low).

Results

Study Selection and Data Extractions

Among the 1586 articles initially identified, 729 were identified as duplicates, while 786 were excluded after assessing their titles and abstracts. Any disagreements regarding selection were resolved through mutual consensus between the two researchers involved. A total of 71 articles remained for the assessment of eligibility via full-text review, of which 54 were subsequently excluded based on specific criteria: 31 did not meet the inclusion criteria, and 23 were deemed irrelevant to the research question. Ultimately, seventeen studies (1,2,5-8,13-23) were selected for qualitative and quantitative synthesis, encompassing 2699 patients (Figure 1).

Study Characteristics and Risk of Bias

Table S1 summarizes the overall features of all qualified studies. The potential for bias in this study was due to the use of two types of assessments, depending on the type of study. Twelve studies (1,2,5-7,13,15-17,19,22,23) were included in the NOS risk of bias assessment for non-diagnostic test accuracy studies (Table S2), and the other five studies (8,14,18,20,21) were included in the QUADAS-2 for diagnostic test studies (Figure S1). All studies demonstrated low concern regarding applicability across all domains. However, some domains had an unclear risk of bias, particularly in patient selection, index test interpretation, and flow and timing. These issues were identified in two studies: Olatunji et al (18) and Oliveira et al (8)

Both studies showed an ambiguous risk of bias under several QUADAS-2 domains, which may affect the reliability of their findings. In the patient selection domain, neither study reported whether patients were enrolled consecutively or randomly, which is crucial for most studies. As per QUADAS-2 guidelines, not

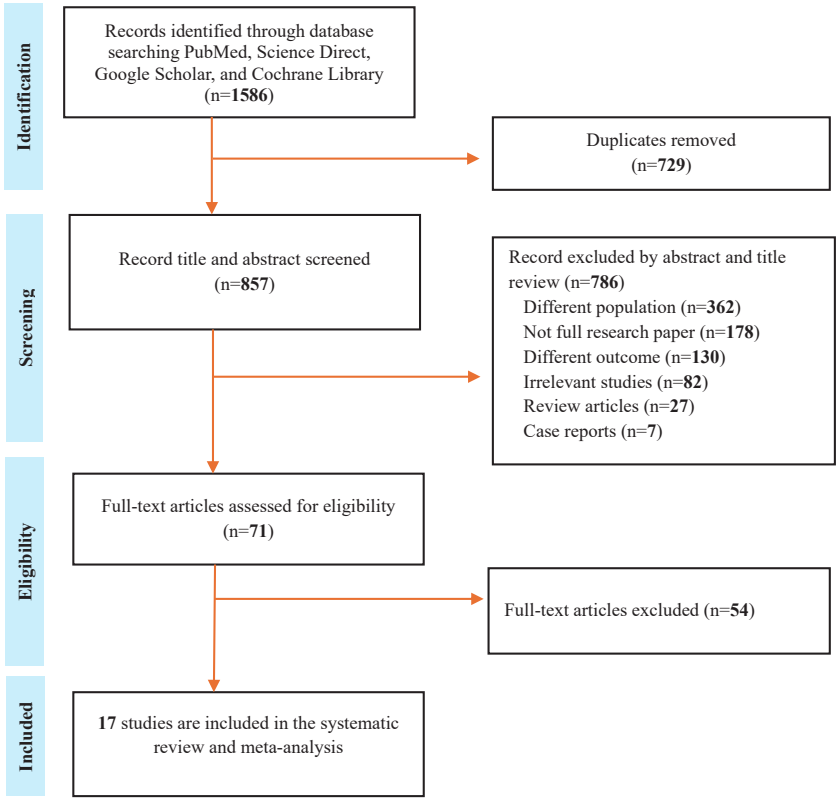

Figure 1. PRISMA Flowchart of the Study.

specifying either random or successive sampling raises significant concerns because purposive sampling can produce selection bias, which harms the representability of the population, which could affect the diagnostic accuracy. Although appropriate exclusion criteria were applied, the lack of clarity on enrollment methods leads to an unclear risk of bias. In the index test domain, both studies were unclear on whether the index test results were interpreted independently of the reference standard. QUADAS-2 emphasizes that if index test interpretation is not blinded to the reference standard, observer bias may occur, potentially overestimating test accuracy. This lack of blinding thus introduces an unclear risk of bias. Regarding flow and timing, Olatunji et al did not include all recruited patients in the final analysis and failed to meet the predetermined minimum sample size. QUADAS-2 specifies that exclusion of patients after enrollment and insufficient sample size can lead to attrition bias and reduce statistical power, which can affect the accuracy of the result.

Quantitative Analysis

When comparing overall PE with normotensive pregnancies (Table 1), PE patients exhibit significantly lower PI mean difference (MD) of -0.36 (95% CI: -0.56; -0.15; $P < 0.001$; $I^2 = 92\%$) and RI MD of -0.06 (95% CI: -0.08; -0.03; $P < 0.001$; $I^2 = 89\%$). In contrast, the PR showed a higher value in PE patients, with an MD of 0.14 (95% CI: 0.02; 0.25; $P = 0.02$; $I^2 = 98\%$). The second systolic velocity (P2) was significantly higher in PE patients, with an MD of 8.67 cm/s (95% CI: 1.02; 16.32; $P = 0.003$; $I^2 = 95\%$), and the end diastolic velocity also showed an MD of 2.13 cm/s (95% CI: 0.08; 4.17; $P = 0.04$; $I^2 = 94\%$). Conversely, the PSV did not differ significantly, with an MD of 0.47 (95% CI: -5.50; 6.44; $P = 0.88$; $I^2 = 95\%$). These findings underscore consistent Doppler alterations in PE, particularly in vascular resistance and flow augmentation parameters.

In comparisons between mild PE and normotensive pregnancies (Table 2), the PI was significantly lower in PE patients, with an MD of -0.54 (95% CI: -0.77; -0.31; $P < 0.001$; $I^2 = 95\%$), and the RI showed an MD of -0.07 (95% CI: -0.12; -0.02; $P < 0.001$; $I^2 = 84\%$). This was alongside an increase in PR, with an MD of 0.14 (95% CI: 0.04; 0.24; $P = 0.004$; $I^2 = 95\%$). The second systolic velocity peak also showed significantly higher values in mild PE patients, with an MD of 3.87 cm/s (95% CI: 1.15; 6.59; $P = 0.005$; $I^2 = 0\%$). However, no significant differences were found for PSV or end diastolic velocity, with MDs of -1.28 (95% CI: -5.30; 2.74; $P = 0.53$; $I^2 = 86\%$) and 0.68 (95% CI: -1.43; 2.79; $P = 0.53$; $I^2 = 90\%$), respectively. These findings suggest that mild PE is associated with altered Doppler flow parameters, particularly impedance-related parameters.

A pooled study of severe PE and normotensive pregnancies (Table 3) revealed that OAD values differed substantially between the groups. Severe PE patients had significantly lower PI with an MD of -0.60 (95% CI: -0.77,

Table 1. Summary of the Pooled Mean Difference of Ophthalmic Artery Doppler Parameters for Overall Preeclampsia and Normotensive Pregnant Women

Parameter	No. of Studies	Total Population	Mean Difference OR (95% CI)	*P* Value	Heterogeneity
PI	7	1712	-0.36 (-0.56;-0.15)	<0.001	92%
RI	10	1600	-0.06 (-0.08;-0.03)	<0.001	89%
PR	6	1544	0.14 (0.02;0.25)	0.02	98%
Second systolic velocity peak	3	451	8.67 (1.02-16.32)	0.003	95%
PSV	6	1363	0.47 (-5.50;6.44)	0.88	95%
EDV	5	923	2.13 (0.08;4.17)	0.04	94%

Abbreviations: PI, pulsatility index; RI, resistance index; PR, peak ratio; PSV, peak systolic velocity;EDV, end-diastolic velocity; OR, odds ratio.

Table 2. Summary of the Pooled Mean Difference of Ophthalmic Artery Doppler Parameters for Mild Preeclampsia and Normotensive Pregnant Women

Parameter	No. of Studies	Total Population	Mean Difference OR (95% CI)	*P* Value	Heterogeneity
PI	10	1535	-0.54 (-0.77;-0.31)	<0.001	95%
RI	7	1092	-0.07 (-0.12;-0.02)	<0.001	84%
PR	6	1266	0.14 (0.04;0.24)	0.004	95%
Second systolic velocity peak	2	109	3.87 (1.15;6.59)	0.005	0%
PSV	7	1093	-1.28 (-5.30;2.74)	0.53	86%
EDV	5	343	0.68 (-1.43;2.79)	0.53	90%

Abbreviations: PI, pulsatility index; RI, resistance index; PR, peak ratio; PSV, peak systolic velocity;EDV, end-diastolic velocity; OR, odds ratio.

Table 3. Summary of the Pooled Mean Difference of Ophthalmic Artery Doppler Parameters for Severe Preeclampsia and Normotensive Pregnant Women

Parameter	No. of Studies	Total Population	Mean Difference OR (95% CI)	*P* Value	Heterogeneity
PI	9	1,419	-0.60 (-0.77;-0.43)	<0.001	93%
RI	7	1,071	-0.13 (-0.15;-0.11)	<0.001	0%
PR	6	1,216	0.26 (0.18;0.35)	<0.001	96%
Second systolic velocity peak	2	96	4.48 (0.51;8.46)	0.03	0%
PSV	7	1,072	-0.19 (-5.79;5.41)	0.95	89%
EDV	5	334	3.17 (0.37;5.97)	0.03	92%

Abbreviations: PI, pulsatility index; RI, resistance index; PR, peak ratio; PSV, peak systolic velocity;EDV, end-diastolic velocity; OR, odds ratio.

-0.43) and RI with an MD of -0.13 (95% CI: -0.15, -0.11; $P < 0.001$), with considerable heterogeneity for the former ($I^2 = 93\%$) and none for the latter ($I^2 = 0\%$). The PR was significantly elevated, with an MD of 0.26 (95% CI: 0.18; 0.35; $P < 0.001$; $I^2 = 96\%$), as was the second systolic velocity peak, with an MD of 4.48 (95% CI: 0.51; 8.46; $P = 0.03$; $I^2 = 0\%$), and the EDV with an MD of 3.17 (95% CI: 0.37; 5.97; $P = 0.03$; $I^2 = 92\%$). In contrast, the PSV showed no significant difference, with an MD of -0.19 (95% CI: -5.79; 5.41; $P = 0.95$; $I^2 = 89\%$). These findings indicate significant alterations in several Doppler parameters in severe PE, although high heterogeneity was observed in most.

In a subgroup analysis of OAD parameters between mild and severe PE (Table 4), only the RI showed a statistically significant difference, with a reduction in the mild group, MD of -0.10 (95% CI: -0.13; -0.06; $P = 0.04$), despite significant heterogeneity ($I^2 = 76\%$). In the mild group, the PI decreased with an MD of -0.60 (95% CI: -0.77; -0.43), with no heterogeneity ($I^2 = 0\%$), although the difference was not significant ($P = 0.45$). The PR indicated a non-significant tendency toward an increase in mild instances (MD 0.20, 95% CI: 0.12; 0.28; $P = 0.07$), with moderate-to-high heterogeneity ($I^2 = 69.8\%$). There were no significant changes in the second systolic velocity peak, PSV, or end diastolic velocity. However, the latter exhibited a possible rising tendency (MD 1.86, 95% CI: 0.23; 3.50; $P = 0.16$; $I^2 = 48.3\%$). These findings suggest that only the RI may distinguish between mild and severe PE among the evaluated parameters, though variability among studies should be considered. The forest plot analysis of the mean difference between the groups for PI, RI, PR, second systolic velocity peak, PSV, and end diastolic velocity can be found in Figures S2-S7.

The high heterogeneity observed in this meta-analysis, particularly for parameters such as PR and PI, likely

Table 4. Summary for Subgroup Difference of Ophthalmic Artery Doppler Parameters: Mean Difference Between Mild Preeclampsia and Control Group and Severe Preeclampsia and Control Group

Parameter	No. of Studies	Total Population	Mean Difference OR (95% CI)	*P* Value	Heterogeneity
PI	10	2954	-0.60 (-0.77;-0.43)	0.45	0%
RI	7	2163	-0.10 (-0.13;-0.06)	0.04	76%
PR	6	2482	0.20 (0.12;0.28)	0.07	69.8%
Second systolic velocity peak	2	205	4.07 (1.82;6.31)	0.8	0%
PSV	7	2165	-0.76 (-3.95;2.42)	0.76	0%
EDV	5	677	1.86 (0.23;3.50)	0.16	48.3%

Abbreviations: PI, pulsatility index; RI, resistance index; PR, peak ratio; PSV, peak systolic velocity;EDV, end-diastolic velocity; OR, odds ratio.

stems from multiple differences across included studies. One major source of heterogeneity is the variation in how PE was defined and classified. Some studies applied different diagnostic thresholds or timing of diagnosis, and the gestational age at Doppler measurement. The proportion of severe PE cases also varied, and this may have influenced the Doppler indices due to changes in vascular resistance and cerebral autoregulation associated with disease progression. In addition to clinical differences, methodological variations were significant. The studies used different ultrasound machines and Doppler protocols. Some measured the ophthalmic artery in one eye, while others measured both, and some averaged multiple waveforms, while others used a single reading. These variations affect parameters such as PR and PI, which are sensitive to technical and operator-related factors. The administration of anti-hypertensive treatment before Doppler assessment, reported in some studies and excluded in others, may have also altered vascular indices and introduced further variability. Population characteristics contributed additional complexity. Maternal age, body mass index, parity, and other demographic factors differed across studies and were not always controlled for or reported consistently. These differences in study design, measurement technique, treatment status, and population demographics likely account for the high heterogeneity in pooled results.

In addition to the high heterogeneity, specific outcomes warrant closer consideration due to limited study representation. For instance, the second systolic velocity peak consistently demonstrated significant differences between preeclamptic and normotensive groups across Tables 1, 2, and 3, indicating lower vascular resistance and potential diagnostic utility. However, despite its statistical significance, the number of studies contributing data for this parameter remains limited. This small sample size reduces the confidence in the subgroup findings and limits the generalizability of the results.

Diagnostic Meta-Analysis

Pulsatility Index

A total of two studies, involving 399 patients, were included in the analysis of PI. The pooled sensitivity for PI was 0.69 (95% CI: 0.58-0.78), with low heterogeneity (I^2 = 0%), indicating consistency across the studies. Given the low heterogeneity, a fixed-effects model was applied. This sensitivity value suggests that PI can detect PE moderately (Figure 2a). The pooled specificity for PI was 0.86 (95% CI: 0.64-0.96), with high heterogeneity (I^2 = 91%), prompting using a random-effects model in the analysis. Despite considerable variability across the studies, this high specificity indicates that PI effectively identifies pregnant women without PE (Figure 2b). The pooled diagnostic odds ratio (DOR) for PI was 12.89 (95% CI: 5.40-30.78), with significant heterogeneity (I^2 = 50.5%, P = 0.155), leading to a random-effects model. This value suggests that PI has good diagnostic accuracy as an indicator, although variability between the studies was observed (Figure 2c). The SROC analysis demonstrated that PI performs well in terms of sensitivity and an acceptable false positive rate (Figure 3)

Complementary analyses combining data from two studies provided further insight into the diagnostic performance of OAD parameters for identifying PE. The pooled PPV was 0.5861 (95% CI: 0.2481–0.8587), while the NPV was 0.8991 (95% CI: 0.4649–0.9892), both calculated using random-effects models due to substantial heterogeneity between studies (I^2 = 91.0% for PPV and 96.6% for NPV). These findings suggest that while the test may have a moderate ability to confirm disease presence (PPV), it performs better in ruling out PE (NPV). Furthermore, the pooled PLR was 4.9337 (95% confidence interval: 1.9124-12.7284), indicating a significant increase in the probability of illness following a positive test. In contrast, the NLR was 0.3837 (95% CI: 0.2311-0.6371), computed using a fixed-effects model due to no observed heterogeneity (I^2 = 0%), suggesting consistent disease elimination.

The diagnostic values observed in the analysis underscore the clinical utility of PI as a tool for detecting PE. A PPV of 0.8444 indicates that approximately 84% of individuals with a positive PI test have PE, reflecting a strong ability to confirm the condition. Conversely, the NPV of 0.8976 suggests that nearly 90% of individuals with

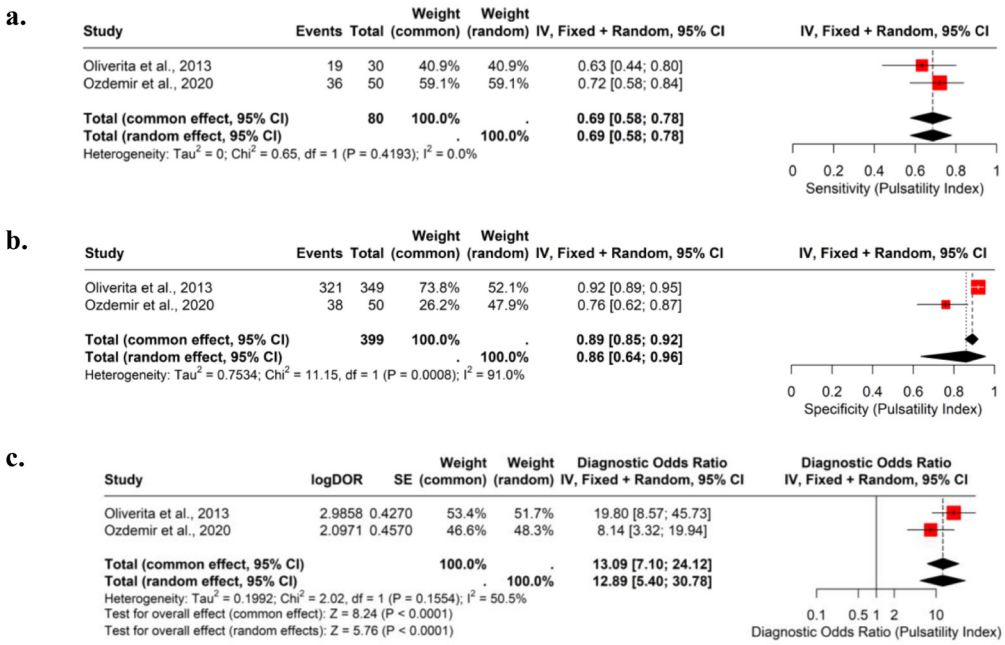

Figure 2. Forest Plot Analysis for (a) Sensitivity, (b) Specificity, and (c) Diagnostic Odds Ratio for Pulsatility Index of Ophthalmic Artery Doppler in Preeclampsia Patients.

a negative result are accurately identified as not having the disease, which is crucial for ruling out PE in clinical practice. A PLR of 10.2084 signifies that a positive test result increases the likelihood of having PE by more than tenfold, representing strong diagnostic utility. Meanwhile, an NLR of 0.2214 indicates a substantial reduction in disease probability following a negative result. The AUC was 0.768, denoting PI's acceptable overall discriminative capacity for identifying PE.

Resistance Index

A total of four studies, involving 499 patients, were included in the analysis of RI. The pooled sensitivity for RI was 0.76 (95% CI: 0.68-0.82), with very low heterogeneity (I^2 = 0%), indicating consistent results across the studies included in the analysis. Given the low heterogeneity, a fixed-effects model was applied. This sensitivity value suggests that RI has a relatively good ability to detect PE, with a low likelihood of false negatives (Figure 4a). The pooled specificity for RI was 0.76 (95% CI: 0.57-0.88), with very high heterogeneity (I^2 = 93.2%), prompting the use of a random-effects model in the analysis. Despite the considerable variability across studies, the high specificity indicates that RI effectively identifies pregnant women without PE (Figure 4b). The pooled DOR for RI was 11.14 (95% CI: 6.01-20.64), with low heterogeneity (I^2 = 35.6%, P = 0.195). Given the low heterogeneity, a fixed-effects model was applied. This high DOR value indicates that RI has good diagnostic capability as an indicator, with stable accuracy across the studies analyzed (Figure 4c). The SROC analysis demonstrated that RI performs well in terms of sensitivity and an acceptable false positive rate (Figure 5).

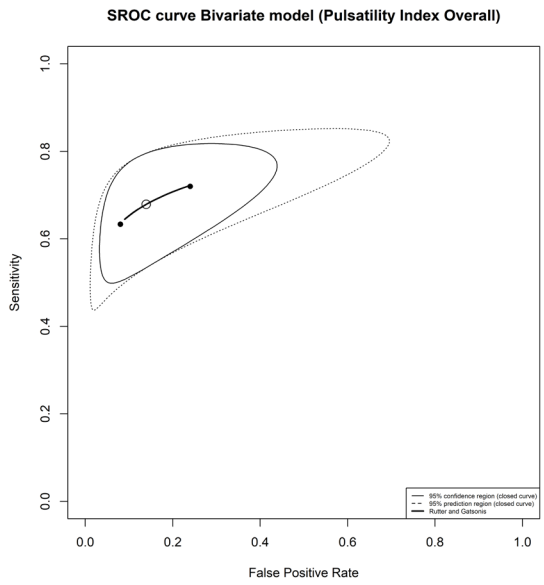

Figure 3. Summary Receiver Operating Characteristics Analysis for Pulsatility Index of Ophthalmic Artery Doppler in Preeclamptic Patients

Complementary analyses from four studies further evaluated the diagnostic performance of the RI in detecting PE. The pooled PPV was 0.5506 (95% CI: 0.2858–0.7895), indicating that approximately 55% of patients with a positive RI test result truly had PE. Meanwhile, the NPV was 0.8867 (95% CI: 0.7012–0.9631), suggesting that nearly 89% of those with a negative result were correctly identified as not having the disease. Both values were derived using random-effects models due to high heterogeneity (I^2 > 91%). The pooled PLR was 3.4533 (95% CI: 1.9414-6.1425), demonstrating a significant increase in the probability of PE following a positive test.

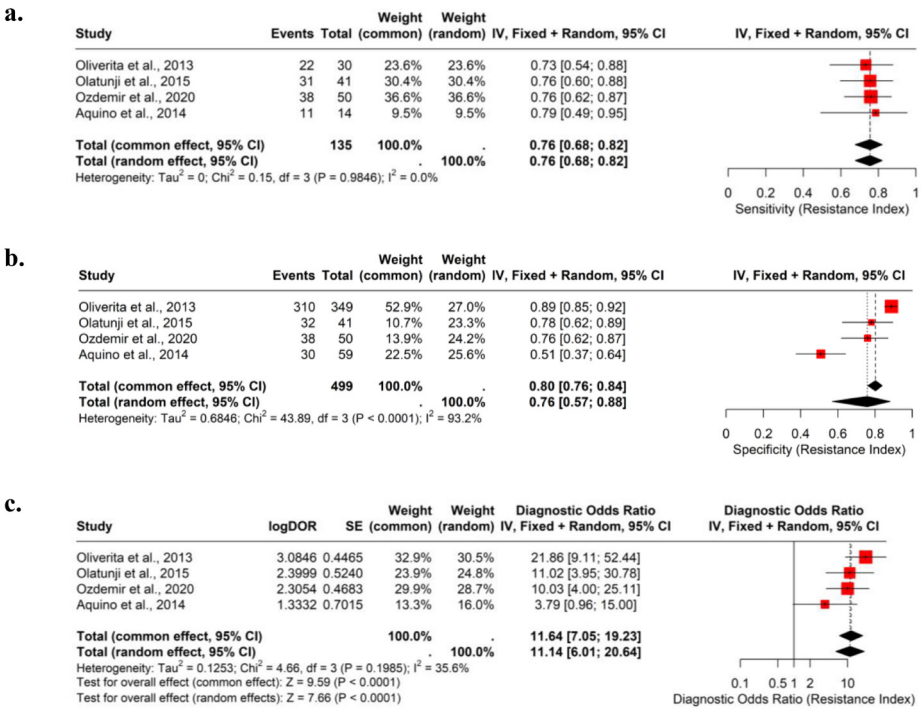

Figure 4. Forest Plot Analysis for (a) Sensitivity, (b) Specificity, and (c) Diagnostic Odds Ratio for Resistance Index of Ophthalmic Artery Doppler in Preeclamptic Patients.

The fixed-effects model with no heterogeneity (I^2 = 0%) resulted in an NLR of 0.3199 (95% CI: 0.2076-0.4932), showing that a negative RI test significantly decreases the risk of PE.

The RI demonstrated solid diagnostic potential in detecting PE. A PPV of 0.5506 suggests that around 55% of individuals with a positive RI test have PE, reflecting moderate accuracy in confirming the disease. In contrast, the NPV of 0.8867 indicates that nearly 89% of individuals with a negative test result are correctly identified as not having PE, highlighting RI's strength in ruling out the condition. A PLR of 3.4533 indicates that a positive test result raises the probability of PE by more than three times. In contrast, an NLR of 0.3199 suggests a significant reduction in the likelihood of illness following a negative test. These probability ratios emphasize RI's diagnostic value. Furthermore, an AUC of 0.774 indicates that RI has adequate overall discriminative accuracy for discriminating between normotensive and preeclamptic pregnancies.

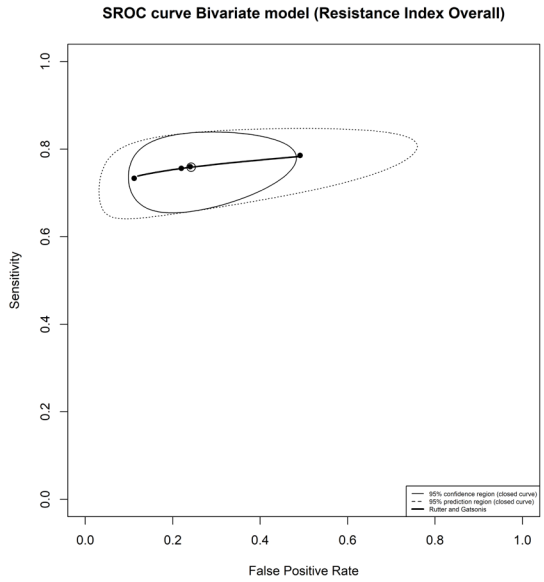

Figure 5. Summary Receiver Operating Characteristics Analysis for Resistance Index of Ophthalmic Artery Doppler in Preeclamptic Patients.

Peak Ratio

A total of four studies, involving 575 patients, were included in the analysis of PR. The pooled sensitivity for PR was 0.80 (95% CI: 0.66-0.89), with moderate heterogeneity (I^2 = 75.2%), prompting the use of a random-effects model in the analysis. This sensitivity value indicates that PR can detect PE, with a relatively low possibility of false negatives (Figure 6a). The pooled specificity for PR was 0.92 (95% CI: 0.80-0.97), with high heterogeneity (I^2 = 88.2%), indicating substantial variability between the studies. Given the high heterogeneity, a random-effects model was applied. Despite the variability across studies, the high specificity suggests that PR is excellent at identifying pregnant women without PE (Figure 6b). The pooled DOR for PR was 48.85 (95% CI: 12.79-186.53), with significantly high heterogeneity (I^2 = 86.5%, P < 0.0001). Due to the high heterogeneity, a random-effects model was applied. This very high DOR indicates that PR has exceptional diagnostic accuracy as an indicator for

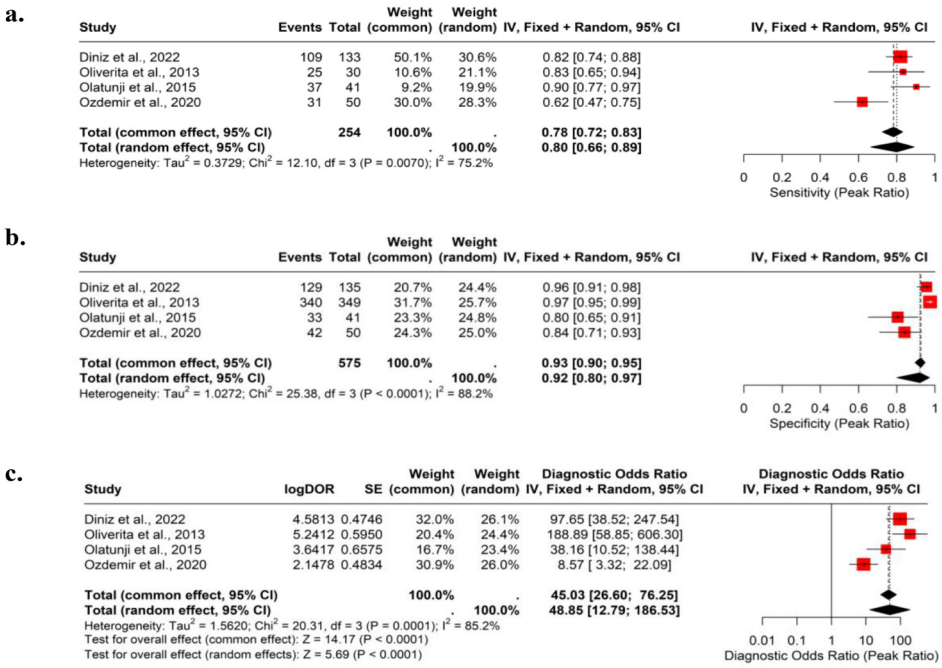

Figure 6. Forest Plot Analysis for (a) Sensitivity, (b) Specificity, and (c) Diagnostic Odds Ratio for Peak Ratio of Ophthalmic Artery Doppler in Preeclamptic Patients

detecting PE, although substantial variation exists among the studies analyzed (Figure 6c). The SROC analysis demonstrated that PR performs well in terms of sensitivity and an acceptable false positive rate (Figure 7).

Complementary analyses from four studies examined the diagnostic accuracy of OAD parameters in detecting PE. The PPV was 0.8444 (95% CI: 0.7097–0.9234), indicating that approximately 84% of patients with a positive test result had PE, reflecting a strong ability to confirm the disease. The NPV was 0.8976 (95% CI: 0.6795–0.9731), showing that nearly 90% of those with a negative result were correctly identified as not having PE, which is crucial for ruling out the condition. Additionally, a PLR of 10.2084 (95% CI: 3.6823–28.3007) demonstrates that a positive test increases the likelihood of PE by over tenfold. The NLR was 0.2214 (95% CI: 0.1278–0.3837), indicating a substantial decrease in the probability of PE following a negative result. These findings, derived from random-effects models due to significant heterogeneity (I^2 ranging from 51.1% to 93.0%), underscore the diagnostic value of OAD parameters for PE detection.

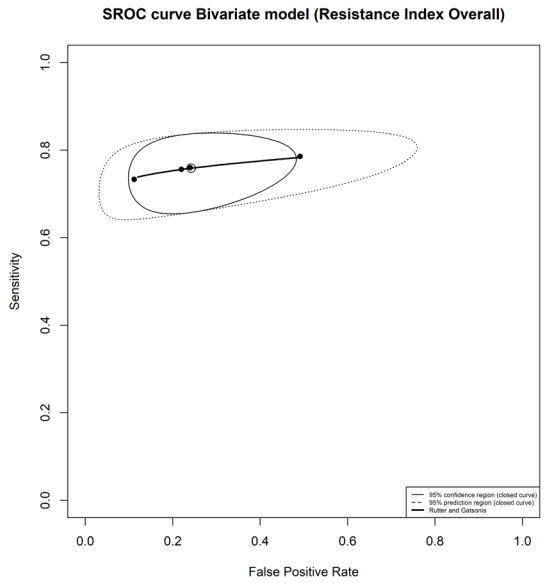

Figure 7. Summary Receiver Operating Characteristics Analysis for Peak Ratio of Ophthalmic Artery Doppler in Preeclamptic Patients

A PPV of 0.5861 indicates that approximately 59% of patients with a positive PR test truly have PE, while an NPV of 0.8991 means that about 90% of patients with a negative result are correctly identified as not having PE; furthermore, a PLR of 4.9337 suggests that a positive result increases the likelihood of PE nearly fivefold, whereas an NLR of 0.3837 demonstrates that a negative test substantially lowers the probability of PE. Finally, the AUC was 0.911, demonstrating high discriminative performance of PR in diagnosing PE.

Publication Bias

Based on funnel plot analysis, the symmetric dispersion of study estimates around the pooled OR 0.3–0.4, which is tightly clustered at high precision and appropriately fanned out at low precision within the 95 % pseudo-confidence funnel. However, mild asymmetry and the presence of some outliers suggest potential publication bias. Egger's test was not performed due to the limited number of included studies (Figure 8).

Quality of Evidence

The GRADE technique was used in this study to assess

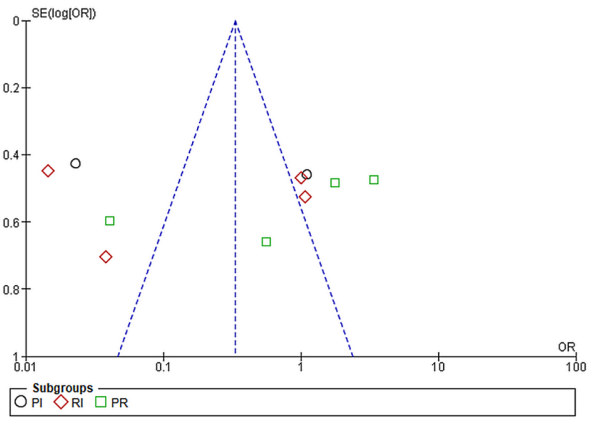

Figure 8. Funnel Plot of Ophthalmic Artery Doppler Parameters in Preeclamptic Patients.

the confidence level in the diagnostic meta-analysis data. Tables S3-S5 provide comprehensive GRADE evidence profiles for sensitivity and specificity for the PI, RI, and PR. Only two studies were identified as having an unknown risk of bias, meaning that overall, the research was found to have a low risk. For the index of pulsatility (Table S3), the sensitivity of 0.69 (95% CI: 0.58 to 0.78) was classified as a high class of evidence (CoE), indicating high confidence that this effect estimate is accurate and that further research is very unlikely to alter this estimate. In contrast, the specificity of 0.86 (95% CI: 0.64 to 0.96) was given moderate CoE, suggesting that additional research might impact our confidence and potentially modify the effect estimate. The RI, which has a sensitivity of 0.76 (95% CI: 0.68 to 0.82), was classified as high CoE and moderate CoE, with a specificity of 0.76 (95% CI: 0.57 to 0.88), even though the included studies have some inconsistencies, which may be seen in the wide confidence interval. Interestingly, the PR had high CoE on sensitivity of 0.80 (95% CI: 0.66 to 0.89) and specificity. Still, both had high inconsistencies in the included studies, which may be due to the large population and heterogeneity.

Overall, the PR parameter exhibited high sensitivity and high specificity with high certainty, suggesting that this metric reliably identifies PE and that additional research is unlikely to alter these estimates substantially. These findings underscore the potential of the PR as a robust diagnostic marker for PE. In contrast, despite their promising performance, the pulsatility and ratio indices may benefit from further confirmatory research to solidify their diagnostic precision.

Discussion

Doppler sonography is widely recognized as the primary non-invasive imaging modality for evaluating blood flow and tissue perfusion in various human organs. Among its many clinical applications, Doppler velocimetry, particularly when applied to the orbital vessels such as the ophthalmic artery, has emerged as a promising tool in assessing pregnant women with hypertensive disorders. This technique enables clinicians to measure blood flow velocity and vascular resistance, which can reflect systemic hemodynamic changes associated with conditions such as PE and chronic arterial hypertension. In the context of obstetric care, differentiating between PE and chronic hypertension is crucial, as their management and associated risks differ significantly. Doppler assessment of orbital blood flow offers a unique advantage by providing indirect yet reliable information on cerebral perfusion, which is often compromised in severe cases of PE. Studies have shown that abnormal flow patterns in the ophthalmic artery, such as increased PR, PI, and RI, may serve as indicators of elevated intracranial pressure or systemic vascular dysfunction. These changes are more pronounced in severe PE, thereby aiding in risk stratification and potentially guiding clinical decision-making regarding monitoring intensity, timing of delivery, and maternal-fetal intervention strategies. Furthermore, the utility of this technique lies in its non-invasiveness, ease of performance, and relatively low cost, making it accessible and practical for routine use, even in resource-limited settings. Its integration into standard prenatal care protocols for high-risk pregnancies could enhance early detection and outcomes for mothers and their infants (8).

This study was primarily designed to assess the diagnostic utility of various OAD parameters in identifying and differentiating PE. Out of the five OAD parameters initially considered, PR, PI, and RI met the criteria for inclusion in the final analysis based on data completeness and measurement reliability. All three parameters demonstrated a clinically acceptable level of diagnostic accuracy in detecting PE, reinforcing the potential role of OAD in the evaluation of hypertensive disorders during pregnancy. Notably, the PR parameter stood out by achieving the highest diagnostic performance, with a sensitivity of 0.80 and specificity of 0.92. These values indicate a strong ability of PR to correctly identify both true positive and true negative cases of PE, suggesting a high level of reliability in distinguishing affected individuals from normotensive pregnant women. While PI and RI also showed favourable diagnostic capabilities, their performance metrics were somewhat lower. PI exhibited a sensitivity of 0.69 and specificity of 0.86, whereas RI yielded sensitivity and specificity values of 0.76 for both. Although these parameters still offer diagnostic value, their relatively lower accuracy metrics underscore the superior predictive strength of PR. These findings highlight PR as the most promising and reliable OAD parameter among those evaluated, supporting its potential use as a supplementary, non-invasive diagnostic tool for PE. Incorporating PR into routine screening protocols could enhance early detection efforts and facilitate timely clinical interventions, ultimately improving maternal and fetal outcomes.

OAD generally shows good but variable accuracy. A recent meta-analysis study indicated that ophthalmic

PR yields the highest AUC (~0.88–0.90) among OAD measures, which is similar to our result (24). Olatunji et al found that the PR AUC = 0.900 (95% CI 0.84–0.96) distinguishes PE from normotensive pregnancies, but the RI and PI are consistently lower (18). When a PR cutoff is used, reported sensitivities range from ~80% up to 100% (especially for preterm/severe PE) with specificities ~88–92% (24,25). By contrast, RI/PI cutoffs tend to have lower sensitivity or specificity. In diagnostic-model terms, adding PR to traditional screens raises detection of preterm-PE by ~10–20 percentage points at a fixed false positivity rate (FPR) (26,27).

Several recent studies have assessed OAD in early pregnancy. Gana et al prospectively measured the ophthalmic PSV ratio (second/first peak, PR) at 11–13 weeks in 4066 women. They found PR was significantly elevated in those who later developed PE (especially preterm PE) and that adding PR to standard first-trimester markers such as maternal factors, uterine artery pulsatility index (UtA-PI), mean arterial pressure (MAP), serum PlGF, and serum pregnancy-associated plasma protein-A (PAPP-A) modestly improved detection of preterm PE. For example, at a 10% FPR, detection of preterm PE rose from 46.3% (maternal history alone) to 58.4% when PR was added; similarly, models already including UtA-PI+PlGF saw a rise from 74.6% to 76.7% detection (27). Kusuma et al used a Bayesian model combining first-trimester PR with MAP, UtA-PI, and PlGF in 946 women. They achieved very high accuracy: their composite model had an AUC of 0.981 (95% CI 0.965–0.998) for early-onset PE, with 100% detection at 10% FPR. These results suggest that, alone or in combination, OAD PR in the first trimester is a promising predictor. However, on its own, it adds only modest incremental value beyond established markers (28).

By contrast, the other OAD indices, RI and PI, have been less informative in early pregnancy. In the 19–23 weeks, the Sapantzoglou et al study reported that only PR discriminated PE, while RI and the first peak did not change significantly. No first-trimester study has reported standalone RI/PI performance in isolation comparable to PR. In general, first-trimester uterine artery Doppler (UtA-PI) combined with maternal factors and PlGF remains the most validated screen with roughly 75%–80% detection of preterm PE at 10% FPR in large cohorts, compared to RI and PI (26). One recent prospective observational study from India notes that ophthalmic Doppler is "simple, accurate, and objective" with predictive value similar to or even better than UtA Doppler and OAD PR in early pregnancy. It shows statistically significant differences in eventual PE (especially early-onset) and can improve model AUC when added to standard screening. However, its standalone sensitivity/specificity in the first trimester is generally lower than combined UtA/PlGF approaches (29).

A meta-analysis by Velauthar et al evaluated the effectiveness of first-trimester uterine artery Doppler screening for PE and found a sensitivity of 47.8% (95% CI 39.0–56.8%) and a specificity of 92.1% (95% CI 88.6–94.6%). In comparison, OAD assessed using the first diastolic peak velocity demonstrated a sensitivity of 61.0% (95% CI 44.2–76.1%) and a specificity of 73.2% (95% CI 66.9–78.7%). Although this study did not evaluate the same parameters as Velauthar et al's analysis, the findings suggest that OAD may be just as effective as uterine artery Doppler for screening PE. The higher sensitivity of OAD in this context could indicate that it may be more capable of detecting PE in its early stages. In contrast, with its higher specificity, uterine artery Doppler may be more useful for confirming the diagnosis in later stages. These results highlight the potential of OAD as an alternative or complementary screening tool for PE, particularly in settings where uterine artery Doppler might be less accessible or feasible (30).

A recent meta-analysis found that certain OAD parameters, assessed during the second trimester or above, significantly correlated with the later development of early-onset PE. The observed effect sizes were consistent across included studies, and the diagnostic accuracy of these OAD parameters was comparable to that of uterine artery Doppler in detecting early-onset PE. Specifically, the PR demonstrated moderate predictive ability for early-onset PE, with a sensitivity of 51.3% (95% CI, 31.4–70.9%), specificity of 82.3% (95% CI, 71.3–89.7%), and AUC of 0.67 (95% CI, 0.58–0.77). For late-onset PE, the same parameter showed a lower sensitivity of 19.4% (95% CI, 11.9–30.1%) but maintained the same specificity, with an AUC of 0.57 (95% CI, 0.51–0.63). In contrast, the PI did not achieve clinically relevant diagnostic performance for any threshold. For instance, a PI cut-off below 2.4 yielded a sensitivity of 24.8% (95% CI, 12.0–44.2%) and specificity of 71.6% (95% CI, 61.5–79.9%) in predicting early-onset PE, with an AUC of 0.54 (95% CI, 0.45–0.64). Despite limitations such as the small number of included studies, all of which were conducted in South America and displayed methodological variability, the analysis highlights a potentially important insight: the predictive value of uterine and OAD assessments for PE may be more closely linked to maternal cardiovascular adaptations during pregnancy than to placental invasion or spiral artery remodeling. This observation warrants further investigation into how Doppler indices of two distinct maternal vascular territories can reflect the risk of a condition predominantly considered a placental disorder (31).

Studies in late pregnancy (late 2nd or 3rd trimester) have found stronger OAD signals. In the extensive prospective study at 35–37 weeks with a population of 2300 women, Sarno et al reported that the ophthalmic PR was higher in women who soon developed PE. Using a competing-risks model, adding PR to maternal factors roughly doubled the detection rate of PE at 10% FPR: it rose from 25.0% to

50.0% for any-time PE onset, and from 31.6% to 57.9% for PE delivering within 3 weeks (32) Similarly, Saleh et al measured OAD at 28–32 weeks in 795 women and found all OAD indices differed between eventual PE and controls. Although confidence intervals were wide, the average PR had 100% sensitivity (95% CI 81–100%) and 90% specificity for later PE (25). A multivariable model combining PR with PI (averaged between eyes), PAPP-A, and UtA-PI yielded 94% sensitivity and 93% specificity for predicting third-trimester PE onset. These data suggest that in late pregnancy, OAD can be very sensitive for identifying at-risk women, and this study indicates that combining OAD parameters may also aid in its predictive value. A recent systematic review/meta-analysis of OAD (all pooled gestations) reported that PR outperforms RI and PI. Across eight studies (n=1425), PR had a pooled AUC of 0.885 with a sensitivity of 84% and a specificity of 92%. In comparison, RI showed sensitivity was 0.765 (95% CI 0.692-0.826), the pooled specificity was 0.793 (95% CI 0.724 - 0.848), and the AUC was 0,833. PI showed sensitivity was 0.768 (95% CI 0.658-0.851), specificity was 0.813 (95% CI 0.692-0.894), and AUC was 0.794. For severe or overall PE, PR remained the best OAD index (24). Thus, PR is consistently the most accurate OAD parameter by the third trimester, with sensitivity often in the 80–100% range and specificity ~90% (24,25).

The overall comparison between OAD parameters and other biomarkers such as sFlt-1, PlGF, or uterine artery doppler between multiple recent meta-analyses is summarized in Table 5. The table shows that OAD, especially the PR parameter, demonstrated the highest diagnostic performance, with a pooled sensitivity of 0.80 (95% CI: 0.66–0.89), a specificity of 0.92 (0.80–0.97), a DOR of 48.85 (12.79–186.53), and an AUC of 0.911. The PI marker yielded a sensitivity of 0.69 (0.58–0.78) and specificity of 0.86 (0.64–0.96), with a DOR of 12.89 and AUC of 0.768. Meanwhile, the RI marker showed slightly lower discriminative power, with sensitivity and specificity of 0.76 (0.68–0.82) and 0.76 (0.57–0.88), respectively, a DOR of 11.4, and an AUC of 0.774. When compared to established biomarkers, sFlt-1 alone demonstrated moderate diagnostic capacity (sensitivity 0.76–0.79, specificity 0.71–0.86, DOR up to 22.68, AUC up to 0.89), whereas the sFlt-1/PlGF ratio exhibited superior performance (e.g., Zhang: sensitivity 0.83, specificity 0.88, DOR 36.21, AUC 0.92). In contrast, UtA-PI, as reported by Liu et al, revealed lower sensitivity (0.59) despite comparable specificity (0.88), with no DOR or AUC reported.

Among the evaluated OAD parameters, the PR marker demonstrated the most favorable diagnostic profile for PE, outperforming both PI and RI indices in sensitivity, specificity, and overall diagnostic efficiency. These findings underscore the potential of PR as a reliable OAD-based single biomarker for PE screening. Although PI and RI markers also exhibited moderate predictive value, their relatively lower DORs and AUCs suggest limited standalone utility. When juxtaposed with conventional angiogenic biomarkers, such as sFlt-1 and the sFlt-1/PlGF ratio, PR remains competitive, particularly in contexts prioritizing cost-efficiency and accessibility. Notably, uterine artery Doppler—despite high specificity—continues to demonstrate suboptimal sensitivity, reinforcing limitations in its screening application.

Another important finding in this study is that overall, PE patients have a significantly lower PI (MD -0.36; 95% CI: -0.56 to -0.15) and a lower RI (MD -0.06; 95% CI: -0.08 to -0.03), but the PR was found to be higher in PE patients (MD 0.14; 95% CI: 0.02 to 0.25). These findings align with the previous meta-analysis conducted by Xinxin Dai et al.

Table 5. Summary of Recent Meta-Analysis for Each Diagnostic Accuracy Results from Parameters Used in Predicting Preeclampsia (33–37)

Study	Sensitivity	Specificity	DOR	AUC
OAD parameter				
PR				
This meta-analysis	0.80 (0.66–0.89)	0.92 (0.80–0.97)	48.85 (12.79–186.53)	0.911
PI				
This meta-analysis	0.69 (0.58–0.78)	0.86 (0.64–0.96)	12.89 (5.40–30.78)	0.768
RI				
This meta-analysis	0.76 (0.68–0.82)	0.76 (0.57-0.88)	11.4 (6.01–20.64)	0.774
sFlt-1 Biomarker				
Zhang 2025	0.79 (0.68–0.87)	0.86 (0.77–0.92)	22.68	0.89 (0.86–0.92)
Lim 2020	0.76 (0.54–0.89)	0.71 (0.55–0.83)	7.43	0.79 (0.75–0.82)
sFlt-1/PlGF biomarker				
Zhang 2025	0.83 (0.77–0.88)	0.88 (0.82–0.92)	36.21	0.92 (0.89–0.94)
Gómez 2022	0.78 (0.65-0.87)	0.75 (0.67-0.82)	Not mentioned	Not mentioned
Lim 2020	0.67 (0.46–0.82)	0.77 (0.66–0.86)	4.65	0.79 (0.76–0.83)
Agrawal 2017	0.80 (0.68-0.88)	0.92 (0.87-0.96)	47.7	Not mentioned
Uterine arteries PI				
Liu et al 2024	0.59 (0.49-0.68)	0.88 (0.83-0.92)	Not mentioned	Not mentioned

Abbreviations: PI, pulsatility index; RI, resistance index; PR, peak ratio; PSV, peak systolic velocity;EDV, end-diastolic velocity; sFlt-1, soluble fms-like tyrosine kinase-1; PlGF, placental growth factor; DOR, diagnostic odds ratio; OAD, ophthalmic artery Doppler; AUC, area under the curve.

(2022), which found that PE patients had lower RI and PI with standardized mean differences (SMDs) of −0.18 (95% CI: −1.90 to 1.53) and −2.05 (95% CI: −3.12 to −0.98), respectively. The study also found higher PR in PE patients, with an SMD of 1.46 (95% CI: −1.30 to 4.22). However, the study did not differentiate between early and late PE; it only found a significant difference in the PI parameter. The main reason for this likely stems from variability among the included studies. Additionally, the study did not conduct meta-regression or subgroup analyses due to the limited number of extractable covariates and the small sample size within each subgroup (38).

This meta-analysis study population predominantly comprised pregnant women in the late second and early third trimesters of gestation, reflecting a period during which hypertensive disorders such as PE commonly become clinically evident. Although including participants across a range of gestational ages could be perceived as a potential source of variability, this was not considered a methodological limitation. This is because previous literature has consistently demonstrated that key OAD parameters remain relatively stable throughout normal pregnancy. A notable prospective cross-sectional study conducted in 2008 provided empirical support for this assumption. The results revealed no statistically significant correlation between gestational age and any measured Doppler parameters, suggesting a gestational age-independent behavior of OAD indices. This stability across gestational ages strengthens the reliability and generalizability of the current study's findings, as it supports the interpretation of OAD measurements without the need for gestational age-specific adjustments. Consequently, using these Doppler parameters, particularly in assessing hypertensive disorders like PE, is validated across the studied gestational window and enhances the practical utility of OAD as a diagnostic adjunct in obstetric care (39).

Diniz et al's study assessed how gestational age affected OAD parameters in pregnant women with normotension and offered crucial information about how stable these indices were throughout the pregnancy. A total of 51 healthy pregnant women with singleton pregnancies, ranging in gestational age from 20 to 38.5 weeks, including both the second and third trimesters, were included in the research. The researchers conducted in-depth Doppler ultrasonography of the ophthalmic artery to evaluate important hemodynamic parameters, such as the RI, PI, PR, and PSV. Their analysis revealed no statistically significant variations in these Doppler measurements throughout the gestational period under investigation. This suggests that OAD parameters remain relatively stable as pregnancy progresses, at least in normotensive individuals. These findings are particularly relevant in the context of research and clinical practice involving hypertensive disorders of pregnancy, such as PE, as they support the validity of comparing Doppler values without needing gestational age-specific adjustments. The gestational age independence of OAD indices enhances their reliability and usability as diagnostic tools, particularly in studies evaluating their performance in detecting PE or other hypertensive complications during pregnancy (19).

Nonetheless, the investigators observed a non-significant trend suggesting that the RI of the ophthalmic artery may slightly decline as gestational age advances. Although this trend did not reach statistical significance, it points to a potential physiological adaptation in vascular resistance during the later stages of pregnancy. This observation aligns with findings from other reference-value studies, which have also reported subtle inverse correlations between gestational age and the ophthalmic artery's PI and RI. These indices reflect downstream vascular resistance and pulsatile blood flow, and their gradual reduction may correspond with the regular hemodynamic changes that occur as pregnancy progresses, including increased blood volume, reduced systemic vascular resistance, and enhanced placental circulation. However, despite these minor trends, the overall consensus remains that the variations in OAD parameters across gestation are minimal and not of clinical significance, especially in normotensive pregnancies. The relatively stable nature of PI and RI throughout the second and third trimesters supports the robustness of OAD as a diagnostic modality that can be applied consistently across a wide gestational age range. This reinforces the value of these parameters, particularly when used to evaluate pathologic states such as PE, without the need for gestational age-adjusted reference values (40,41).

In another noteworthy investigation examining the relationship between gestational age and OAD parameters, researchers identified statistically significant inverse correlations between RI and PI and advancing gestation, specifically across the 20 to 40-week range. These findings indicate that RI and PI values tended to decline as pregnancy progressed. This trend reflects the physiological reduction in systemic vascular resistance and cerebral perfusion changes naturally occurring with increasing gestational age. However, despite the statistical significance of these correlations, the associated R^2 values were notably low. This suggests that while gestational age may contribute to the decline in RI and PI, it is not the sole influencing factor; other physiological or pathological variables likely play a role in modulating these Doppler indices. Interestingly, the PR remained stable throughout gestation among the measured parameters and did not show any significant association with gestational age. This lack of variability with advancing gestation underscores PR's potential clinical advantage. Its stability enhances its reliability and diagnostic consistency, making it particularly valuable for evaluating hypertensive disorders in pregnancy, such as PE, where minimizing the influence of gestational age is crucial for accurate and timely

interpretation of Doppler findings (42).

OAD ultrasound has demonstrated strong diagnostic consistency, making it a reliable tool for assessing conditions such as PE. Previous studies have evaluated the reproducibility of Doppler ultrasound measurements by assessing both intra-observer consistency and inter-observer agreement. Intra-observer consistency refers to the ability of a single examiner to obtain the exact measurements during repeated assessments. At the same time, inter-observer agreement evaluates the consistency between different examiners performing the same procedure. Research has shown that OAD ultrasound exhibits excellent intra-observer consistency, with minimal variation between repeated measurements by the same clinician. This suggests that a single examiner can reliably perform the technique, ensuring consistent results over time. Furthermore, high inter-observer agreement has been reported, indicating that different clinicians can achieve similar results when performing the Doppler ultrasound (24,41,42). In a prospective cohort of women at 35–37 weeks' gestation, repeat measurements of the second-to-first PSV ratio (PR) demonstrated strong within-eye agreement (right eye r = 0.823; left eye r = 0.840) but more modest between-eye reproducibility (first ratio r = 0.690; second ratio r = 0.682), underscoring the benefit of averaging bilateral readings to minimize variability (43). This reinforces the technique's reliability across multiple practitioners, which is crucial for clinical settings where various healthcare providers may be involved in patient care. Data specific to the PI and RI in PE are sparse. However, earlier work in healthy pregnancies indicates that these angle-independent metrics exhibit high intra- and inter-observer concordance when measured by experienced sonographers (39).

Overall intra- and inter-observer reproducibility of OAD indices in preeclamptic patients has generally been acceptable but remains understudied. Common limitations across these studies include small sample sizes, single-center designs, and reliance on highly trained operators; technical factors such as Doppler beam insonation angle, sample-volume placement, probe pressure, and inconsistent patient positioning may further contribute to measurement error. Future research should therefore prioritize standardized measurement protocols, multi-center operator-comparison studies in preeclamptic populations, and assessment of test–retest reliability over time to better define the true operator-dependent variability in clinical practice.

One primary study cohort was carefully selected to minimize potential biases, enhancing the reliability and generalizability of the findings. Women without PE risk factors, those free from prior endothelial injury, and individuals not receiving first-trimester prophylaxis were included in the study. This selection strategy ensured a homogeneous group, reducing confounding variables that could affect the outcomes and allowing for more accurate assessments of the diagnostic capabilities of OAD ultrasound. By excluding individuals with a higher risk for PE or pre-existing endothelial damage, the study focused on a population that was less likely to exhibit abnormalities unrelated to the condition being studied. The OAD procedure was typically performed with the patient in the supine position, with the head elevated at about a 30-degree angle. This positioning helped provide optimal access to the ocular area for accurate imaging. The examination usually lasted between 30 and 40 minutes, ensuring sufficient time for a thorough assessment. The ultrasound transducer was placed gently on the closed eyelid, applying minimal pressure to avoid distorting the flow measurements. This careful technique helped maintain the accuracy of Doppler readings, ensuring that the results reflected the true flow characteristics of the ophthalmic artery without external interference (44).

Abnormal trophoblast development and failure in the conversion of maternal spiral arteries are considered pivotal factors in the onset of PE. During normal pregnancy, trophoblast cells invade the uterine wall and remodel the spiral arteries to ensure adequate blood flow to the placenta. In PE, this process is impaired, leading to poor placental perfusion and ischemia. The lack of proper arterial remodelling results in increased vascular resistance and endothelial dysfunction, contributing to the hypertension and organ damage characteristic of PE. These disturbances are central to the pathophysiology of PE, affecting maternal and fetal health (45-47).

Most PE prediction models depend on biomarkers that provide information on placentation and placental function and serve as stand-ins for placental health. Essential indicators that indicate the placenta's health and development include PlGF, which is secreted by the organ. One of the hallmarks of PE is poor placentation, which is frequently linked to low levels of PlGF. Furthermore, uterine blood flow and vascular resistance are frequently evaluated using uterine artery Doppler measures, such as the PI and RI. Abnormalities in these Doppler measurements, such as increased resistance, suggest poor placental perfusion and are predictive of PE. These biomarkers and Doppler parameters provide valuable information for early detection, helping to identify women at risk for PE, even before clinical symptoms appear (48-52).

Compared to uterine artery Doppler, ophthalmic PR often performs at least as well. In many studies, PR either matched or exceeded UtA-PI's predictive power. For instance, Sapantzoglou et al found that adding PR to an UtA-PI+MAP model raised preterm-PE detection from 80.7% to 87.9% (10% FPR) (26). In Saleh et al, adding PR and PI to UtA-PI/PAPP-A raised sensitivity to 94% (25). Conversely, standalone UtA-PI in late pregnancy is not usually used, and in early pregnancy, UtA-PI alone may detect around 75–90% early-PE (10% FPR) by FMF criteria. By comparison, Kusuma et al's model (UtA+PlGF+PR)

reached AUC 0.98, indicating PR can boost an already high-performing test (28). When compared to angiogenic biomarkers, OAD is sometimes surprisingly strong. The AJOG review notes that the ophthalmic PR outperformed PlGF and sFlt-1 individually in predicting both term and preterm PE. However, in practice, PlGF/sFlt-1 ratios (e.g., sFlt-1/PlGF) have become highly accurate for ruling out imminent PE in late gestation, whereas OAD has been tested mainly for screening earlier. In low- to middle-resource settings where biomarkers are unavailable, OAD offers an ultrasound-based analogue to gauge cerebral perfusion (53).

Because ocular measures are suggestive of maternal hemodynamic adaptations during pregnancy rather than the particularity of trophoblast development, the result that OAD may equal the uterine artery Doppler in predicting PE contradicts the accepted long-held belief that PE is a placental disorder based on the fundamental associations between PE and placental histological abnormalities. It is also crucial to remember that PE is linked to cardiovascular abnormalities that appear months before the clinical development of hypertension, such as decreased cardiac index, elevated vascular resistance, and impaired myocardial relaxation. Additionally, cardiovascular dysfunction is more prominent in early-onset PE, which probably explains the ocular artery Doppler changes seen in this investigation (54).

One of the studies included in the research by Hata et al examined OAD assessments and revealed a reduction in the PI among women with PE. This reduction was interpreted as indicative of maternal central nervous system (CNS) hyperperfusion, suggesting that there may be an adaptive mechanism similar to the fetal circulatory response to hypoxia in PE. In the fetus, hypoxia triggers a compensatory mechanism to prioritize blood flow to vital organs, including the brain. Similarly, in preeclamptic women, a decrease in PI could indicate that the maternal CNS is receiving a disproportionate amount of blood flow in an attempt to preserve brain function despite impaired placental perfusion. This compensatory hyperperfusion may be part of the pathophysiological response to the compromised uteroplacental circulation seen in PE, and it provides a potential explanation for the observed changes in ocular Doppler parameters, reflecting broader vascular alterations in the maternal body (7).

Another study by Diniz et al further underscores the utility of ocular arterial Doppler, particularly highlighting the strong association between PR values and the severity of PE. The study demonstrated that PR values could be a reliable marker for the condition's progression. The mean PR value in healthy pregnancies was 0.499 (0.092), reflecting normal placental and circulatory function. In contrast, women with mild PE exhibited a significantly higher mean PR of 0.81 (0.09), and those with severe PE had an even higher mean PR of 0.84 (0.08). These findings suggest that elevated PR values are closely linked to worsening disease severity in PE, potentially offering a non-invasive and reliable diagnostic tool to monitor and assess the severity of the condition. As the PR increases, it may indicate worsening placental dysfunction and impaired blood flow, which are central to the pathophysiology of PE. This study reinforces the importance of Doppler ultrasound in assessing maternal vascular health and aiding in the early detection and management of PE (19).

More recently, Chaves et al expanded on previous research by demonstrating that women with significant CNS hyperperfusion, as indicated by highly abnormal PR values (PR ≥ 0.99), are at a heightened risk of adverse maternal outcomes. This study reinforces the emerging hypothesis that systemic vasoconstriction and hypertensive crises—common features of PE—trigger vasodilation in the CNS. This compensatory response to impaired placental perfusion and systemic hypertension could potentially lead to barotrauma-induced brain lesions, a serious complication of PE. The high PR values reflect a marked alteration in vascular dynamics, suggesting that CNS hyperperfusion could be an early indicator of vascular maladaptation in PE. As the brain attempts to protect itself by increasing blood flow, it may inadvertently expose itself to damage from excessive pressure, contributing to the neurological complications associated with the condition. These findings highlight the potential for PR measurements, particularly those ≥0.99, to serve as an essential biomarker for predicting severe maternal complications, underscoring the critical need for timely diagnosis and intervention to prevent adverse outcomes in women with PE (55).

Additional contemporary research has further emphasized that the robust performance of OAD measurements may parallel that of uterine artery doppler and offer unique insights into cerebral circulation changes in preeclamptic women. One key advantage of OAD is its ability to circumvent some limitations associated with uterine artery Doppler, such as interference from a gravid uterus or maternal obesity, which can complicate accurate assessments of uterine artery flow. This is particularly significant because changes in cerebral circulation often occur before the onset of clinical hypertension in preeclamptic pregnancies, providing an early warning system for clinicians. By detecting these circulatory alterations earlier, OAD can serve as a predictive and supplementary diagnostic marker, potentially identifying women at risk for severe PE before other clinical signs emerge. In high-risk pregnancies, this early detection can lead to more proactive monitoring and management, which may help improve maternal and fetal outcomes. Thus, OAD offers an additional layer of diagnostic capability, enhancing the overall precision and effectiveness of PE screening, particularly in women who may be difficult to assess with uterine artery Doppler alone (31,42).

Maternal hemodynamic state may be easily, reliably,

and objectively assessed using OAD, which makes it very useful in resource-constrained environments. The meta-analysis's conclusions show that this method can predict PE independently, particularly the severe or early-onset types of PE. Instead of changes associated with trophoblast invasion or the conversion of maternal spiral arteries, the screening value of OAD may come from its capacity to detect maternal hemodynamic modifications throughout pregnancy (31). Importantly, OAD indices provide information different from that of placental biomarkers. The ophthalmic artery reflects maternal/cerebral hemodynamic (orbital hyperperfusion in PE), whereas PlGF/sFlt-1 reflect placental angiogenesis. Nicolaides et al report that at mid-trimester (19–23 weeks), the ophthalmic PR was superior to each of UtA-PI, MAP, PlGF, and sFlt-1 when considered alone. Additionally, adding PR to a model that includes all other markers further improved both preterm and term PE prediction. Likewise, at 35–37 weeks, adding PR to maternal+UtA+PlGF models increased detection markedly. This suggests that OAD can complement biomarkers, even in high-resource screening programs, PR may add modest gain in AUC or sensitivity above state-of-the-art algorithms (53).

One of the other essential advantages of OAD is its feasibility. It is cost-effective, non-invasive, repeatable, and radiation-free (56). Compared to specialized tests (PlGF/sFlt-1 assays or MRI perfusion), OAD requires only conventional ultrasound machine equipment, widespread in many low-resource obstetric clinics (24) Even in these machines, rural Indonesia's primary health care center has already been reached. As Kumari et al note, "ocular sonography is technically feasible as eyeballs lack bone, fat, or gas." In other words, virtually any Doppler-capable scanner and trained sonographer can perform OAD without added consumableS (56).

This is a key benefit in low-resource settings. Biomarker kits for PlGF or sFlt-1 are expensive and require laboratory infrastructure, limiting their availability in many developing countries. By contrast, ultrasound is usually consolidated in clinical obstetric practice and widely available even in low-income areas. Therefore, incorporating OAD into routine antenatal visits could improve early identification of high-risk women without significant extra cost or logistics. In a context of high PE burden and low resources, an objective ultrasound marker like OAD is attractive. In high-resource settings, OAD might serve as an adjunct to existing screening. Current first-trimester screening (maternal factors + UtA-PI + PlGF) is already very sensitive for preterm PE, and the National Institute for Health and Care Excellence (NICE) guidelines often use PlGF/sFlt-1 in symptomatic late pregnancy (24,28).

To date, major obstetric guidelines do not yet include OAD. The International Federation of Gynecology and Obstetrics (FIGO) 2019 statement urges universal first-trimester screening using maternal history, blood pressure, and optionally biomarkers (MAP, UtA-PI, PlGF) (57). International Society for the Study of Hypertension (ISSHP) 2021 recommendations focus on classification and management of hypertensive disorders but similarly emphasize early risk assessment and prophylaxis, but do not specify new ultrasound tests and currently suggest that available biomarkers are not recommended for general screening without symptoms (58). The World Health Organization (WHO) antenatal care guidelines prioritize identification of high-risk women by history, clinical exam, and preventive measures (low-dose aspirin, calcium) (59). In summary, FIGO/ISSHP/WHO all endorse early PE risk assessment by prioritizing maternal risk factors and blood pressure, but do not yet address OAD in their algorithms. Although OAD is not yet standard, pilot data suggest it could provide incremental accuracy. For example, adding OAD PR to multivariable models modestly improved AUC even when PlGF was included. OAD could also be helpful in the surveillance of severe PE to assess cerebral flow or in cases where PlGF is equivocal.

We suggest that OAD could be integrated with existing ultrasound programs in low-resource settings lacking biochemical assays. For instance, during the routine mid-trimester anomaly scan around 20 weeks or the third-trimester growth scan, sonographers could add a quick OAD assessment. OAD could also be used in high-risk clinics to triage women for intensified surveillance. Training materials and standard operating procedures would be needed; studies indicate OAD protocols (probe placement, angle, waveform analysis) can be standardized and taught globally. Given the evidence that combining multiple screening tools yields the best sensitivity, programs might use OAD in addition to risk-factor screening. For example, pregnant women with borderline MAP or a previous history could receive an OAD scan to refine risk stratification. Pilot implementation could focus on referral centers first, assessing feasibility and outcomes before scale-up. Importantly, such strategies align with the WHO's call to strengthen health systems and train providers for early PE detection.

Limitations of the Study

The criteria used by the authors to define PE varied across the included studies, likely contributing to the heterogeneity of the results and complicating comparisons of parameter means. Most of the manuscripts in this meta-analysis employed the traditional PE definition: a blood pressure reading of 140/90 mm Hg and, after the 20th week of pregnancy, proteinuria of more than 300 mg in a 24-hour urine collection (or a dipstick test result of 1+ or a protein-to-creatinine ratio of 0.30 mg/mg). However, various changes have been made to the criteria that define PE.

OAD screening is operator-dependent and may be influenced by technical factors (e.g., poor insonation angle, patient movement). It also requires the patient to be

still and cooperative (eyes closed, lying supine), which is generally feasible in antenatal clinics. In very low-resource settings, the availability of any ultrasound can be a barrier; however, mobile and pocket ultrasounds are increasingly deployed even in rural primary care settings. We suggest that, to assess better the role of OAD in predicting and diagnosing PE, particularly in low-resource settings where its simplicity could be advantageous as a point-of-care test, training programs could integrate OAD into the existing antenatal ultrasound curriculum, with a standardized examination procedure of OAD that needs to be implemented.

Future research should use uniform disease definitions, adopt longitudinal study designs, and incorporate Doppler assessments of both eyes. More diagnostic studies are needed to investigate the accuracy with prospective cohort design is the preferred standard, to assess the sensitivity, and specificity of these Doppler parameters, furthermore, the inclusion of different percentages of early or late onset of PE, as well as variations in statistical power and confidence intervals between the studies, are probably the reasons for the substantial heterogeneity shown across all OAD characteristics in the general PE group.

Conclusions

OAD is an effective complementary non-invasive diagnostic method for overall and early or severe PE. The PSV ratio (PR) consistently and accurately predicts PE among ophthalmic Doppler indices. In the first trimester, OAD PR differs significantly in those who will develop PE and can modestly improve early-PE detection when added to uterine Doppler/biomarker screening. In late pregnancy, OAD can be highly sensitive for identifying women close to manifesting PE. Crucially, OAD is an ultrasound-based marker that is easy to perform and low-cost, making it particularly appealing for low-resource implementation. In high-resource settings, OAD could complement and improve existing protocol screening. In contrast, it may improve early risk stratification in low-resource settings and allow timely preventive interventions to reduce PE morbidity.

Authors' Contribution

Conceptualization: I Wayan Agus Surya Pradnyana, Endang Sri Widiyanti.
Data curation: I Wayan Agus Surya Pradnyana, Ni Nengah Devianti Wulan Pradnyani.
Formal analysis: I Gde Arie Kusuma Wijaya, Made Favian Budi Gunawan, I Gusti Ayu Cintya Paramyta.
Funding acquisition: I Wayan Agus Surya Pradnyana.
Investigation: I Wayan Agus Surya Pradnyana, Ni Nengah Devianti Wulan Pradnyani.
Methodology: I Wayan Agus Surya Pradnyana, Endang Sri Widiyanti.
Project administration: I Wayan Agus Surya Pradnyana, Endang Sri Widiyanti.
Resources: I Wayan Agus Surya Pradnyana, Endang Sri Widiyanti.
Software: I Gde Arie Kusuma Wijaya, Made Favian Budi Gunawan.
Supervision: Endang Sri Widiyanti.
Validation: Endang Sri Widiyanti.
Visualization: I Gusti Ayu Cintya Paramyta.
Writing–original draft: I Wayan Agus Surya Pradnyana, I Gde Arie Kusuma Wijaya, Made Favian Budi Gunawan.
Writing–review & editing: I Wayan Agus Surya Pradnyana, I Gde Arie Kusuma Wijaya, Endang Sri Widiyanti.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

Not applicable.

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Supplementary files

Supplementary file 1 contain supplementary data for this study, including additional tables (S1-S5), figures (S1-S7), and GRADE assessment.

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