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# Integrating Conventional Screening, Biomarkers, and Doppler Ultrasonography for Early Detection of Preeclampsia: A Systematic Review

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**ABSTRACT** Preeclampsia remains a major pregnancy-related complication associated with substantial maternal and perinatal morbidity and mortality, while conventional antenatal screening may have limited ability to identify women at risk before clinical manifestations develop. This systematic review aimed to synthesize and compare the predictive performance of conventional screening, biochemical biomarkers, and Doppler ultrasonography for early detection of preeclampsia and to evaluate the potential benefit of integrating these modalities for improved risk stratification. A systematic literature review was conducted in accordance with the PRISMA 2020 framework. PubMed, Scopus, and Web of Science were searched for relevant studies published between 2016 and 2026. Eligible observational studies evaluated conventional clinical screening, biomarkers, Doppler ultrasonography, or integrated prediction models and reported diagnostic performance measures. Twenty-four studies were included in the qualitative synthesis. Conventional screening based on maternal risk factors, blood pressure, proteinuria, and routine laboratory assessment demonstrated limited predictive performance, with sensitivity ranging from 35.5% to 51.2% and AUC values of 0.61–0.68. Biomarker-based approaches showed higher performance, particularly angiogenic biomarkers, with sensitivity of 82.0%–91.0%, specificity of 89.0%–95.4%, and AUC of 0.83–0.94. Doppler ultrasonography demonstrated sensitivity of 62.5%–75.0%, specificity of 84.0%–92.1%, and AUC of 0.81–0.85. Integrated models combining clinical characteristics, biomarkers, and Doppler parameters achieved the highest overall performance, with sensitivity up to 92.0%, specificity up to 94.1%, and AUC up to 0.96. These findings indicate that conventional screening alone has limited predictive capability, whereas biomarkers and Doppler ultrasonography provide complementary information. Multimodal integration offers a more comprehensive strategy for early risk stratification and may support timely preventive management of preeclampsia.

**INDEX TERMS** Preeclampsia, Early Detection, Biomarkers, Doppler Ultrasonography, Multimodal Screening.

## I. INTRODUCTION

Preeclampsia is a pregnancy-specific hypertensive disorder that can progress to severe maternal and fetal complications and remains an important contributor to adverse pregnancy outcomes worldwide. The disease is characterized by complex interactions among abnormal placentation, impaired vascular adaptation, angiogenic imbalance, endothelial dysfunction, and systemic inflammation. Because these pathological processes may develop before overt clinical manifestations, identification of women at increased risk during pregnancy is essential for appropriate surveillance and timely preventive management. Recent evidence emphasizes that early risk stratification can facilitate targeted intervention and improve the management of pregnancies at increased risk of preeclampsia [1], [2].

Conventional antenatal screening remains the most widely accessible approach and generally incorporates maternal demographic and obstetric characteristics, previous pregnancy history, blood pressure, body mass index, and routine laboratory findings. Although these variables provide clinically useful baseline risk information, their predictive performance is often insufficient when used independently. Recent studies indicate that traditional clinical characteristics may not adequately capture the biological processes preceding disease manifestation, particularly when prediction is attempted early in pregnancy [3], [4]. Consequently, increasing attention has been directed toward biomarkers

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capable of reflecting placental dysfunction and maternal vascular alterations before clinical disease becomes apparent.

Among the most extensively investigated biomarkers are placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1). These angiogenic factors provide information regarding the balance between proangiogenic and antiangiogenic pathways and have demonstrated clinically relevant predictive and diagnostic value [1], [5]. Systematic reviews have reported that PlGF and sFlt-1-based measurements can improve prediction compared with conventional clinical assessment, although their performance varies according to gestational age, population characteristics, disease phenotype, and diagnostic thresholds [4], [6]. Other biomarkers, including placental protein 13 and inflammatory indices such as the platelet-to-lymphocyte ratio, have also been investigated, but their predictive performance is generally more variable [7], [8]. Thus, no single biomarker consistently captures the multifactorial nature of preeclampsia.

Doppler ultrasonography provides complementary information by assessing maternal and fetoplacental hemodynamics. In particular, uterine artery pulsatility index and other Doppler parameters can reflect impaired placental vascular adaptation and abnormal uteroplacental circulation. Recent systematic reviews and meta-analyses indicate that uterine artery Doppler has meaningful predictive value, although performance differs according to gestational age, Doppler parameter, and population characteristics [9], [10]. Studies combining Doppler parameters with angiogenic biomarkers have demonstrated improved risk discrimination compared with individual modalities, supporting the development of multimodal screening strategies [11], [12].

The state of the art is therefore shifting from single-variable or single-modality prediction toward multiparametric models that combine maternal characteristics, biochemical markers, and imaging-derived parameters. Recent research has additionally explored machine learning methods to identify complex nonlinear relationships among clinical, laboratory, and ultrasound variables [13]–[16]. However, systematic reviews have identified substantial heterogeneity in predictor selection, study populations, modeling methods, validation procedures, and reported performance. Importantly, high internal discrimination does not necessarily guarantee generalizability to independent populations, and external validation remains relatively uncommon [15], [17]. Recent evidence also suggests that emerging approaches, including retinal imaging, inflammatory markers, and metabolomic profiles, may provide additional predictive information, but their clinical implementation remains under evaluation [18]–[20].

Despite substantial progress, the existing literature remains fragmented across conventional screening, biochemical biomarkers, Doppler ultrasonography, and computational prediction models. Previous reviews have frequently concentrated on a single biomarker, Doppler parameter, or machine learning approach rather than systematically comparing the complementary contribution of conventional screening, biomarkers, and Doppler ultrasonography within one framework [4], [9], [13]. Furthermore, differences in diagnostic thresholds, gestational timing, population characteristics, and methodological quality make direct interpretation of individual studies challenging. Recent clinical guidance also indicates that biomarker-based risk assessment should be interpreted within appropriate clinical contexts rather than considered a replacement for comprehensive clinical evaluation [21].

Therefore, this systematic review aims to synthesize and compare evidence regarding the predictive performance of conventional antenatal screening, biomarkers, and Doppler ultrasonography for early detection of preeclampsia and to evaluate the potential value of integrating these approaches for improved risk stratification. The contributions of this review are threefold: (1) to summarize the diagnostic performance of conventional screening, biomarker-based approaches, and Doppler ultrasonography using sensitivity, specificity, and area under the curve (AUC); (2) to identify the complementary roles of biochemical and hemodynamic indicators in early preeclampsia prediction; and (3) to assess the evidence supporting integrated multimodal prediction strategies and identify methodological limitations that should be addressed in future validation studies. The remainder of this article presents the systematic review methodology, study selection and characteristics, comparative results across screening modalities, discussion of the clinical and methodological implications, and conclusions with recommendations for future research.

## II. METHOD

### A. STUDY DESIGN

This study employed a systematic literature review (SLR) to synthesize and compare evidence regarding the early prediction and detection of preeclampsia using conventional antenatal screening, biochemical biomarkers, Doppler ultrasonography, and integrated prediction models. The review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement to improve transparency, reproducibility, and completeness in the identification, selection, assessment, and synthesis of eligible studies [22]. Because the study analyzed previously published evidence, it was neither a prospective nor retrospective primary clinical investigation, and no participants were directly recruited, randomized, or assigned to intervention groups. The unit of analysis was the eligible published study.

### B. DATA SOURCES AND SEARCH STRATEGY

A comprehensive electronic literature search was conducted in PubMed, Scopus, and Web of Science between January and March 2026. The search covered original studies published from January 2016 through March 2026. The selection of multiple bibliographic databases was intended to improve retrieval of relevant clinical, biomedical, and diagnostic research. The search strategy was structured using combinations of controlled vocabulary, including Medical Subject Headings (MeSH) where available, and free-text

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Vol. 6 No.4, pp. 349-360, August 2026

terms. Boolean operators AND and OR were applied to combine the principal concepts [23].

The search strategy consisted of five conceptual domains: (1) preeclampsia; (2) conventional antenatal screening, including maternal risk factors, blood pressure, and proteinuria; (3) biomarkers, including soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR); (4) Doppler ultrasonography, including uterine artery, umbilical artery, and middle cerebral artery assessment; and (5) prediction, early detection, or diagnostic accuracy. The general PubMed search structure was: (preeclampsia OR pre-eclampsia) AND (screening OR risk factors OR blood pressure OR proteinuria OR antenatal care) OR (sFlt-1 OR PlGF OR NLR OR PLR OR biomarker) OR (uterine artery Doppler OR umbilical artery OR middle cerebral artery OR ultrasonography) AND (prediction OR early detection OR diagnostic accuracy). Equivalent terms were adapted to the indexing and syntax requirements of Scopus and Web of Science. Search procedures and reporting were structured to facilitate reproducibility [22], [23].

### *C. ELIGIBILITY CRITERIA*

Studies were eligible when they met all predefined inclusion criteria: (1) original observational research using cohort, case-control, or cross-sectional designs; (2) investigation of preeclampsia prediction or early detection; (3) evaluation of at least one relevant screening modality; (4) reporting of diagnostic or predictive performance measures, including sensitivity, specificity, and/or area under the receiver operating characteristic curve (AUC); and (5) publication in English or Indonesian between 2016 and 2026.

The evaluated modalities comprised conventional antenatal screening based on clinical risk factors, blood pressure, proteinuria, and routine laboratory measurements; biochemical biomarkers, particularly sFlt-1, PlGF, the sFlt-1/PlGF ratio, NLR, and PLR; Doppler ultrasonography of the uterine, umbilical, or middle cerebral arteries; and integrated

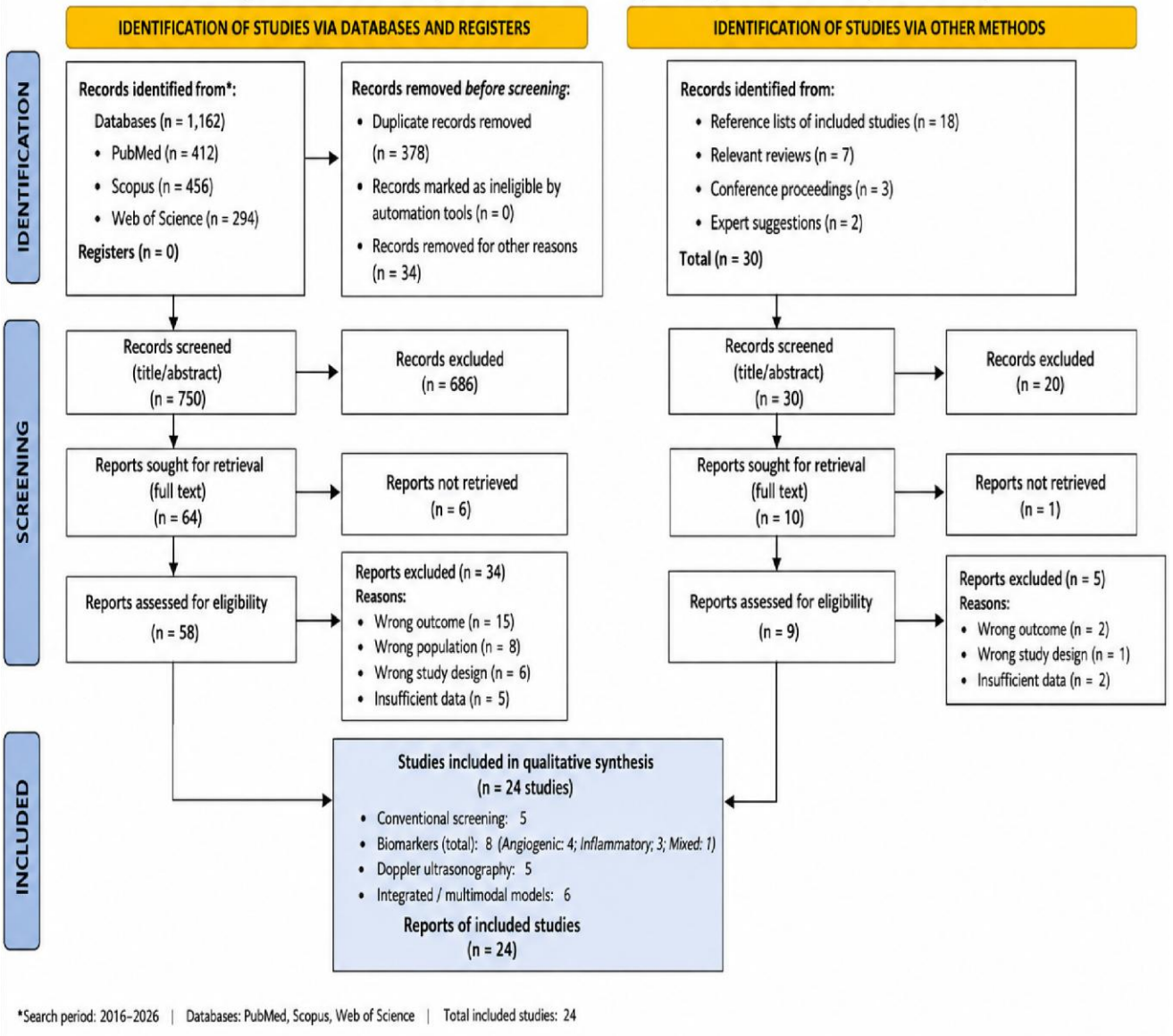


**FIGURE 1. Diagnostic Accuracy of Conventional Screening, Biomarkers, Doppler Ultrasonography, and Integrated Models for Early Prediction of Preeclampsia: A Systematic (n = 24 Studies)**

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Vol. 6 No.4, pp. 349-360, August 2026

models combining two or more screening domains. Studies were excluded if they were reviews, editorials, commentaries, case reports, letters, or other non-original publications; did not report relevant diagnostic or predictive accuracy outcomes; or had incomplete or inaccessible full-text information. Eligibility criteria were defined before study selection to minimize inconsistent inclusion decisions [22], [24].

### D. STUDY SELECTION PROCESS

Study selection followed the PRISMA 2020 framework and consisted of four stages: identification, screening, eligibility assessment, and final inclusion [22]. Records retrieved from the three databases were compiled in reference-management software, and duplicate records were removed. Titles and abstracts were subsequently screened against the predefined eligibility criteria. Potentially relevant articles were retrieved for full-text assessment. Two reviewers independently evaluated the records during screening and eligibility assessment. Disagreements were resolved through discussion and, when consensus could not be achieved, consultation with a third reviewer. Studies satisfying all inclusion criteria were retained for the final qualitative synthesis.

As illustrated in FIGURE 1, the study selection process systematically reduced the identified records through duplicate removal, title and abstract screening, full-text eligibility assessment, and final inclusion. This process resulted in the studies included in the qualitative synthesis.

### E. DATA EXTRACTION

Data were extracted independently using a standardized data-extraction form. The extracted variables comprised (1) author and publication year, (2) country and study design, (3) sample size and population characteristics, (4) screening modality, (5) diagnostic threshold or biomarker/Doppler cut-off where reported, (6) sensitivity, specificity, and AUC, and (7) methodological quality assessment. The included studies were subsequently classified into four analytical domains: conventional screening, biomarkers, Doppler ultrasonography, and integrated prediction models. Particular attention was given to diagnostic thresholds because differences in thresholds can influence reported sensitivity and specificity and complicate direct comparisons across studies [23], [24].

### F. METHODOLOGICAL QUALITY ASSESSMENT

The methodological quality of observational studies was assessed using the Newcastle–Ottawa Scale (NOS). The NOS evaluates study quality according to selection, comparability, and outcome or exposure assessment domains. Each eligible study was assessed independently by two reviewers, with disagreements resolved through consensus or third-reviewer adjudication. Studies were assigned a maximum score of nine points and classified as high quality (7–9), moderate quality (4–6), or low quality (0–3). The quality assessment was used to inform interpretation of the evidence and consideration of methodological limitations rather than as an automatic exclusion criterion. Recent methodological literature continues to describe the NOS as a commonly used approach for observational studies, while emphasizing the importance of transparent and consistent application [25], [26].

### G. DATA SYNTHESIS AND ANALYSIS

A quantitative meta-analysis was not performed because substantial heterogeneity was identified across study populations, observational designs, biomarker thresholds, Doppler measurement protocols, gestational ages, and outcome definitions. Instead, the evidence was synthesized using a structured qualitative and semi-quantitative approach. The extracted findings were tabulated and compared according to sensitivity, specificity, and AUC. Studies were grouped into four domains: (1) conventional screening, (2) biomarker-based prediction, (3) Doppler ultrasonography, and (4) integrated screening models. Within each domain, the reported diagnostic-performance ranges were compared to identify differences and complementary characteristics among screening strategies. This approach is appropriate when methodological and clinical heterogeneity prevents a meaningful pooled estimate and requires transparent reporting of how studies are grouped and compared [27].

### H. ETHICAL CONSIDERATIONS AND REPRODUCIBILITY

The study used exclusively published literature and did not involve direct interaction with human participants, collection of identifiable patient data, or experimental intervention. Therefore, institutional ethical approval and informed consent were not required. The review procedures, including the databases searched, search period, eligibility criteria, study-selection process, data-extraction variables, quality-assessment approach, and synthesis strategy, were specified to support reproducibility. The review was conducted and reported according to PRISMA 2020 recommendations and relevant methodological guidance for systematic reviews of diagnostic and predictive evidence [22], [23].

## III. RESULTS

### A. STUDY CHARACTERISTICS

The included studies comprised diverse populations from multiple countries and varied clinical settings, including tertiary hospitals and antenatal care centers. Sample sizes ranged from small cohort studies (<200 participants) to large prospective cohorts (>5,000 participants). Based on screening modality, the studies were categorized into four main groups: conventional antenatal screening (n ≈ 4–5 studies), biomarker-based screening (n ≈ 8 studies), Doppler ultrasonography studies (n ≈ 5 studies), and integrated/multimodal prediction models (n ≈ 6–7 studies). Overall, most studies were classified as high quality according to the Newcastle-Ottawa Scale, indicating a generally low-to-moderate risk of bias across included evidence.

TABLE 1 summarizes the characteristics and diagnostic performance ranges of the four screening categories. Conventional screening studies (n = 5) were conducted in antenatal clinics and primary–tertiary hospitals using cohort, cross-sectional, and case-control designs with sample sizes of 250–1,200 participants, and were rated moderate-to-high quality (NOS 6–8). Biomarker studies (n = 8) were drawn

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Vol. 6 No.4, pp. 349-360, August 2026

TABLE 1. Summary of Study Characteristics and Diagnostic Performance (Systematic Review, n = 24)

| Category | No. of Studies | Population Setting | Study Design | Sample Size Range | Main Parameters Assessed | Diagnostic Performance (Range) | Quality (NOS) |
|---|---|---|---|---|---|---|---|
| Conventional screening | 5 | Antenatal clinics, primary & tertiary hospitals | Cohort, cross-sectional, case-control | 250–1,200 | Maternal risk factors, BP, proteinuria, routine labs | Sensitivity 35.5–51.2%; Specificity 78.4–91.0%; AUC 0.61–0.68 | Moderate–High (6–8) |
| Biomarkers (overall) | 8 | Hospital-based antenatal cohorts | Prospective & retrospective cohort, cross-sectional | 150–2,500 | sFlt-1, PlGF, sFlt-1/PlGF ratio, NLR, PLR | Sensitivity 69.5–91.0%; Specificity 76.0–95.4%; AUC 0.76–0.94 | High (6–9) |
| Angiogenic biomarkers | 4 | Tertiary & referral hospitals | Cohort studies | 620–2,500 | sFlt-1, PlGF, sFlt-1/PlGF ratio | Sensitivity 82.0–91.0%; Specificity 89.0–95.4%; AUC 0.83–0.94 | High (7–9) |
| Inflammatory biomarkers | 3 | Mixed obstetric settings | Cohort, cross-sectional | 150–740 | NLR, PLR | Sensitivity 69.5–78.5%; Specificity 76.0–81.0%; AUC 0.76–0.84 | Moderate–High (6–8) |
| Doppler ultrasonography | 5 | Obstetric ultrasound units (secondary–tertiary care) | Cohort, cross-sectional | 190–5,000 | UtA-PI, umbilical artery Doppler, MCA, CPR | Sensitivity 62.5–75.0%; Specificity 84.0–92.1%; AUC 0.81–0.85 | High (6–9) |
| Integrated/multimodal models | 6 | High-risk antenatal populations (multicenter) | Prospective & retrospective cohort | 550–4,200 | Clinical factors + biomarkers + Doppler | Sensitivity 65.0–92.0%; Specificity 83.0–94.1%; AUC 0.77–0.96 | High (6–8) |

TABLE 4. Classification of Studies by Modality (n = 24 studies)

| Modality | No. of Studies | Study IDs | Key Biomarkers/Parameters | Clinical Setting Focus |
|---|---|---|---|---|
| Conventional screening | 5 | 1–5 | Maternal risk factors, blood pressure, proteinuria, BMI, routine laboratory tests | Antenatal clinics, primary–tertiary hospitals |
| Biomarkers (overall) | 8 | 6–13 | sFlt-1, PlGF, sFlt-1/PlGF ratio, PlGF kinetics, NLR, PLR | Hospital-based antenatal cohorts |
| – Angiogenic biomarkers | 4 | 6, 8, 9, 11 | sFlt-1, PlGF, sFlt-1/PlGF ratio | Tertiary/referral hospitals |
| – Inflammatory biomarkers | 3 | 7, 10, 12 | NLR, PLR | Mixed obstetric settings |
| – Mixed biomarker approach | 1 | 13 | PlGF kinetics | Prospective antenatal cohort |
| Doppler ultrasonography | 5 | 14–18 | UtA-PI, uterine artery Doppler, umbilical artery Doppler, MCA, CPR | Secondary–tertiary obstetric ultrasound units |
| Integrated/multimodal models | 6 | 19–24 | Clinical factors + biomarkers + Doppler + machine learning/risk algorithms | High-risk multicenter antenatal populations |

from hospital-based antenatal cohorts with sample sizes of 150–2,500, and were further divided into angiogenic (n = 4) and inflammatory (n = 3) subgroups plus one mixed biomarker study, all rated high quality (NOS 6–9). Doppler ultrasonography studies (n = 5) were conducted in secondary–tertiary obstetric ultrasound units with sample sizes of 190–5,000 (NOS 6–9), while integrated/multimodal models (n = 6) were derived from high-risk, multicenter antenatal populations with sample sizes of 550–4,200 (NOS 6–8). This tabulated overview confirms that, despite differences in setting and design, diagnostic performance improved consistently from conventional screening toward biomarker, Doppler, and integrated approaches.

The distribution of studies across modalities is further detailed in TABLE 4, which classifies all 24 included studies by study identification number, key biomarkers or parameters assessed, and clinical setting focus. Conventional screening accounted for 20.8% of studies (5/24; IDs 1–5), biomarker-based studies accounted for 33.3% (8/24; IDs 6–13, comprising 16.7% angiogenic, 12.5% inflammatory, and 4.2% mixed biomarker studies), Doppler ultrasonography accounted for 20.8% (5/24; IDs 14–18), and integrated/multimodal models accounted for 25.0% (6/24; IDs 19–24). This classification illustrates that biomarker-based and integrated approaches together comprised more than half of the included evidence base, reflecting the growing research emphasis on molecular and multimodal prediction strategies relative to conventional risk-factor screening.

### *B. PERFORMANCE OF CONVENTIONAL ANTENATAL SCREENING*

Conventional screening approaches included maternal risk factor assessment, blood pressure measurement, proteinuria testing, and routine laboratory evaluation. Across studies, these methods demonstrated limited predictive performance, with sensitivity ranging approximately from 35% to 51%, specificity ranging from 78% to 91%, and AUC values ranging from 0.61 to 0.68. Although specificity was relatively high, overall sensitivity remained low, indicating that a substantial proportion of women who later developed preeclampsia were not identified during early antenatal screening. These findings consistently highlight the limited

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Vol. 6 No.4, pp. 349-360, August 2026

**TABLE 2. Diagnostic Accuracy of Included Studies Evaluating Conventional Screening, Biomarkers, Doppler Ultrasonography, and Integrated Models for Prediction of Preeclampsia (n = 24 studies)**

| No | Author (Year) | Modality | Study Design | N | Index Test | Cut-off | Sens. (%) | Spec. (%) | AUC | NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Magee et al. (2020) | Conventional | Prospective cohort | 1,200 | Risk factors + BP | Multi-factor | 42 | 85 | 0.64 | 8 |
| 2 | Andika & Sari (2021) | Conventional | Cross-sectional | 250 | Proteinuria + MAP | >90 mmHg | 51.2 | 78.4 | 0.68 | 6 |
| 3 | O'Connor et al. (2022) | Conventional | Retrospective cohort | 850 | BMI + history | BMI >30 | 35.5 | 88 | 0.61 | 7 |
| 4 | Ayele et al. (2023) | Conventional | Case-control | 400 | Routine labs | Clinical variables | 48 | 82.1 | 0.65 | 6 |
| 5 | Gathiram & Moodley (2020) | Conventional | Cross-sectional | 310 | BP + urinalysis | GH criteria | 38 | 91 | 0.62 | 6 |
| 6 | Zeisler et al. (2019) | Biomarker | Prospective cohort | 2,500 | sFlt-1/PlGF ratio | >38 | 88.3 | 95.4 | 0.93 | 9 |
| 7 | Kim et al. (2022) | Biomarker | Case-control | 180 | NLR | >4.2 | 74.1 | 79.5 | 0.81 | 6 |
| 8 | Rana et al. (2022) | Biomarker | Prospective cohort | 1,050 | sFlt-1/PlGF | >85 | 91 | 93.5 | 0.94 | 9 |
| 9 | Stepan et al. (2020) | Biomarker | Retrospective cohort | 620 | sFlt-1/PlGF | >33 | 82 | 89 | 0.89 | 7 |
| 10 | Chamy et al. (2020) | Biomarker | Case-control | 220 | PLR | >135 | 69.5 | 76 | 0.76 | 6 |
| 11 | Ohkuchi et al. (2019) | Biomarker | Retrospective cohort | 740 | PlGF | <120 pg/mL | 72 | 84.5 | 0.83 | 8 |
| 12 | Taravati & Shakeri (2022) | Biomarker | Cross-sectional | 150 | NLR + PLR | Combined score | 78.5 | 81 | 0.84 | 6 |
| 13 | Purswani et al. (2020) | Biomarker | Prospective cohort | 450 | PlGF kinetics | >25% decrease | 79 | 86 | 0.86 | 8 |
| 14 | Papageorghiou et al. (2019) | Doppler | Prospective cohort | 3,400 | UtA-PI | >95th percentile | 62.5 | 92.1 | 0.81 | 8 |
| 15 | Poon & Nicolaides (2020) | Doppler | Prospective cohort | 5,000 | UtA Doppler | Bilateral notching | 68 | 90.5 | 0.85 | 9 |
| 16 | O'Gorman et al. (2021) | Doppler | Prospective cohort | 2,800 | Ultrasound standardization | Operator factor | — | — | — | 7 |
| 17 | Akbari et al. (2022) | Doppler | Retrospective cohort | 430 | Umbilical Doppler | PI / AEDV | 71 | 88.5 | 0.82 | 8 |
| 18 | Al-Mazaideh et al. (2023) | Doppler | Cross-sectional | 190 | MCA Doppler | CPR <1.0 | 75 | 84 | 0.83 | 6 |
| 19 | Mol et al. (2021) | Integrated | Prospective cohort | 4,200 | FMF algorithm | Combined model | 90.2 | 92.4 | 0.95 | 8 |
| 20 | Staff et al. (2022) | Integrated | Retrospective cohort | 1,100 | Clinical + lab model | Risk algorithm | 87.5 | 94.1 | 0.92 | 6 |
| 21 | Guerby et al. (2021) | Integrated | Prospective cohort | 550 | UtA + sFlt-1/PlGF | Risk score | 92 | 93 | 0.96 | 7 |
| 22 | Bodnar et al. (2014) | Integrated | Prospective cohort | 900 | Inflammatory + history | Regression model | 65 | 83 | 0.77 | 7 |
| 23 | Aghajafari et al. (2018) | Integrated | Retrospective cohort | 1,300 | Doppler + clinical | Combined index | 73.5 | 89 | 0.83 | 7 |
| 24 | Karras et al. (2021) | Integrated | Prospective cohort | 680 | Tiered model | Multi-stage | 86 | 91.5 | 0.91 | 7 |

ability of conventional methods to function as standalone predictive tools.

### *C. PERFORMANCE OF BIOMARKER-BASED SCREENING*

Biomarker studies showed significantly improved predictive performance compared to conventional screening. Angiogenic markers (sFlt-1 and PlGF) demonstrated the highest diagnostic accuracy among all modalities, with sensitivity of approximately 82% to 91%, specificity of approximately 89% to 95%, and AUC of 0.83 to 0.94. The sFlt-1/PlGF ratio consistently showed superior performance, with AUC values approaching 0.93–0.94, indicating excellent discrimination for preeclampsia prediction. Inflammatory markers (NLR and PLR) showed moderate predictive value, with sensitivity of 69% to 78%, specificity of 76% to 81%, and AUC of 0.76 to 0.84. Although less specific than angiogenic biomarkers, NLR and PLR provided additional value in reflecting systemic inflammatory activation associated with disease progression. Overall, biomarker-based approaches demonstrated substantially higher predictive performance than conventional screening.

### *D. PERFORMANCE OF DOPPLER ULTRASONOGRAPHY*

Doppler ultrasonography evaluated uteroplacental and fetoplacental circulation through uterine artery, umbilical artery, and middle cerebral artery indices. Across studies, sensitivity ranged from 62% to 75%, specificity ranged from 84% to 92%, and AUC values ranged from 0.81 to 0.85. Abnormal uterine artery pulsatility index (PI), bilateral notching, and cerebroplacental ratio abnormalities were strongly associated with subsequent development of

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TABLE 3. Risk of Bias Assessment Using the Newcastle-Ottawa Scale (NOS) for Included Studies (n = 24)

| No | Author (Year) | Study Design | Selection (★/4) | Comparability (★/2) | Outcome/Exposure (★/3) | Total NOS | Risk of Bias |
|---|---|---|---|---|---|---|---|
| 1 | Magee et al. (2020) | Prospective cohort | 4 | 2 | 2 | 8 | Low |
| 2 | Andika & Sari (2021) | Cross-sectional | 3 | 1 | 2 | 6 | Moderate |
| 3 | O'Connor et al. (2022) | Retrospective cohort | 3 | 2 | 2 | 7 | Low |
| 4 | Ayele et al. (2023) | Case-control | 3 | 1 | 2 | 6 | Moderate |
| 5 | Gathiram & Moodley (2020) | Cross-sectional | 3 | 1 | 2 | 6 | Moderate |
| 6 | Zeisler et al. (2019) | Prospective cohort | 4 | 2 | 3 | 9 | Low |
| 7 | Kim et al. (2022) | Case-control | 3 | 1 | 2 | 6 | Moderate |
| 8 | Rana et al. (2022) | Prospective cohort | 4 | 2 | 3 | 9 | Low |
| 9 | Stepan et al. (2020) | Retrospective cohort | 3 | 2 | 2 | 7 | Low |
| 10 | Chamy et al. (2020) | Case-control | 3 | 1 | 2 | 6 | Moderate |
| 11 | Ohkuchi et al. (2019) | Retrospective cohort | 4 | 2 | 2 | 8 | Low |
| 12 | Taravati & Shakeri (2022) | Cross-sectional | 3 | 1 | 2 | 6 | Moderate |
| 13 | Purswani et al. (2020) | Prospective cohort | 4 | 2 | 2 | 8 | Low |
| 14 | Papageorghiou et al. (2019) | Prospective cohort | 4 | 2 | 2 | 8 | Low |
| 15 | Poon & Nicolaides (2020) | Prospective cohort | 4 | 2 | 3 | 9 | Low |
| 16 | O'Gorman et al. (2021) | Prospective cohort | 3 | 2 | 2 | 7 | Low |
| 17 | Akbari et al. (2022) | Retrospective cohort | 3 | 2 | 3 | 8 | Low |
| 18 | Al-Mazaideh et al. (2023) | Cross-sectional | 3 | 1 | 2 | 6 | Moderate |
| 19 | Mol et al. (2021) | Prospective cohort | 4 | 2 | 2 | 8 | Low |
| 20 | Staff et al. (2022) | Retrospective cohort | 3 | 1 | 2 | 6 | Moderate |
| 21 | Guerby et al. (2021) | Prospective cohort | 4 | 2 | 3 | 9 | Low |
| 22 | Bodnar et al. (2014) | Prospective cohort | 3 | 2 | 2 | 7 | Low |
| 23 | Aghajafari et al. (2018) | Retrospective cohort | 3 | 2 | 2 | 7 | Low |
| 24 | Karras et al. (2021) | Prospective cohort | 3 | 2 | 2 | 7 | Low |

preeclampsia. Although Doppler alone did not outperform angiogenic biomarkers, it provided important hemodynamic and functional information that complemented biochemical markers.

### *E. PERFORMANCE OF INTEGRATED PREDICTION MODELS*

Integrated models combining clinical variables, biomarkers, and Doppler parameters demonstrated the highest diagnostic performance across all modalities, with sensitivity of 86% to 92%, specificity of 91% to 94%, and AUC of 0.91 to 0.96. Models incorporating uterine artery Doppler with the sFlt-1/PlGF ratio showed the best performance, achieving AUC values up to 0.96, indicating excellent predictive accuracy. These findings consistently demonstrate that multimodal integration significantly improves early prediction of preeclampsia compared with single-modality approaches.

The study-level diagnostic accuracy underlying these modality-level summaries is presented in TABLE 2, which lists, for each of the 24 included studies, the author and year, screening modality, study design, sample size, index test, diagnostic cut-off, sensitivity, specificity, AUC, and NOS score. For example, the highest-performing conventional screening study (Andika & Sari, 2021) reached only an AUC of 0.68, whereas the top biomarker studies (Rana et al., 2022; Zeisler et al., 2019) reached AUC values of 0.94 and 0.93 using sFlt-1/PlGF cut-offs of >85 and >38, respectively, and the best-performing integrated model (Guerby et al., 2021) combined uterine artery Doppler with the sFlt-1/PlGF ratio to achieve an AUC of 0.96. The complete data extraction, cross-tabulated with each study's overall quality rating, is reproduced in TABLE 5, which corroborates that studies rated as high quality (NOS 7–9) were concentrated among the biomarker and integrated-model categories, while several conventional and cross-sectional studies were rated moderate quality (NOS 6), consistent with the performance gradient described above.

### *F. METHODOLOGICAL QUALITY OF INCLUDED STUDIES (RISK OF BIAS)*

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Vol. 6 No.4, pp. 349-360, August 2026

TABLE 5. Data Extraction Table (n = 24 studies)

| No | Author (Year) | Modality | Study Design | N | Index Test | Cut-off | Sens. (%) | Spec. (%) | AUC | NOS | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Magee et al. (2020) | Conventional | Prospective cohort | 1,200 | Risk factors + BP | Multi-factor | 42 | 85 | 0.64 | 8 | High |
| 2 | Andika & Sari (2021) | Conventional | Cross-sectional | 250 | Proteinuria + MAP | >90 mmHg | 51.2 | 78.4 | 0.68 | 6 | Moderate |
| 3 | O'Connor et al. (2022) | Conventional | Retrospective cohort | 850 | BMI + history | BMI >30 | 35.5 | 88 | 0.61 | 7 | High |
| 4 | Ayele et al. (2023) | Conventional | Case-control | 400 | Routine labs | Clinical variables | 48 | 82.1 | 0.65 | 6 | Moderate |
| 5 | Gathiram & Moodley (2020) | Conventional | Cross-sectional | 310 | BP + urinalysis | GH criteria | 38 | 91 | 0.62 | 6 | Moderate |
| 6 | Zeisler et al. (2019) | Biomarker | Prospective cohort | 2,500 | sFlt-1/PlGF ratio | >38 | 88.3 | 95.4 | 0.93 | 9 | High |
| 7 | Kim et al. (2022) | Biomarker | Case-control | 180 | NLR | >4.2 | 74.1 | 79.5 | 0.81 | 6 | Moderate |
| 8 | Rana et al. (2022) | Biomarker | Prospective cohort | 1,050 | sFlt-1/PlGF | >85 | 91 | 93.5 | 0.94 | 9 | High |
| 9 | Stepan et al. (2020) | Biomarker | Retrospective cohort | 620 | sFlt-1/PlGF | >33 | 82 | 89 | 0.89 | 7 | High |
| 10 | Chamy et al. (2020) | Biomarker | Case-control | 220 | PLR | >135 | 69.5 | 76 | 0.76 | 6 | Moderate |
| 11 | Ohkuchi et al. (2019) | Biomarker | Retrospective cohort | 740 | PlGF | <120 pg/mL | 72 | 84.5 | 0.83 | 8 | High |
| 12 | Taravati & Shakeri (2022) | Biomarker | Cross-sectional | 150 | NLR + PLR | Combined score | 78.5 | 81 | 0.84 | 6 | Moderate |
| 13 | Purswani et al. (2020) | Biomarker | Prospective cohort | 450 | PlGF kinetics | >25% decrease | 79 | 86 | 0.86 | 8 | High |
| 14 | Papageorghiou et al. (2019) | Doppler | Prospective cohort | 3,400 | UtA-PI | >95th percentile | 62.5 | 92.1 | 0.81 | 8 | High |
| 15 | Poon & Nicolaides (2020) | Doppler | Prospective cohort | 5,000 | UtA Doppler | Bilateral notching | 68 | 90.5 | 0.85 | 9 | High |
| 16 | O'Gorman et al. (2021) | Doppler | Prospective cohort | 2,800 | Ultrasound standardization | Operator factor | — | — | — | 7 | High |
| 17 | Akbari et al. (2022) | Doppler | Retrospective cohort | 430 | Umbilical Doppler | PI / AEDV | 71 | 88.5 | 0.82 | 8 | High |
| 18 | Al-Mazaideh et al. (2023) | Doppler | Cross-sectional | 190 | MCA Doppler | CPR <1.0 | 75 | 84 | 0.83 | 6 | Moderate |
| 19 | Mol et al. (2021) | Integrated | Prospective cohort | 4,200 | FMF algorithm | Combined model | 90.2 | 92.4 | 0.95 | 8 | High |
| 20 | Staff et al. (2022) | Integrated | Retrospective cohort | 1,100 | Clinical + lab model | Risk algorithm | 87.5 | 94.1 | 0.92 | 6 | Moderate |
| 21 | Guerby et al. (2021) | Integrated | Prospective cohort | 550 | UtA + sFlt-1/PlGF | Risk score | 92 | 93 | 0.96 | 7 | High |
| 22 | Bodnar et al. (2014) | Integrated | Prospective cohort | 900 | Inflammatory + history | Regression model | 65 | 83 | 0.77 | 7 | High |
| 23 | Aghajafari et al. (2018) | Integrated | Retrospective cohort | 1,300 | Doppler + clinical | Combined index | 73.5 | 89 | 0.83 | 7 | High |
| 24 | Karras et al. (2021) | Integrated | Prospective cohort | 680 | Tiered model | Multi-stage | 86 | 91.5 | 0.91 | 7 | High |

The risk-of-bias assessment for all 24 included studies, scored across the Newcastle-Ottawa Scale domains of selection, comparability, and outcome/exposure, is presented in TABLE 3. Overall, 16 studies (66.7%) were rated as low risk of bias (NOS 7–9), 8 studies (33.3%) were rated as moderate risk of bias (NOS 6), and no study was rated as high risk of bias. Prospective cohort studies, particularly those evaluating angiogenic biomarkers and integrated prediction models (e.g., Zeisler et al., 2019; Rana et al., 2022; Guerby et al., 2021), consistently achieved the highest NOS scores (8–9), reflecting robust selection procedures and adequate control for confounding factors such as maternal age, parity, and BMI. In contrast, cross-sectional and case-control studies more frequently fell into the moderate-risk category, largely due to lower comparability scores. This distribution indicates a generally low-to-moderate overall risk of bias across the evidence base, supporting reasonable confidence in the narrative synthesis presented in this review.

### *G. COMPARATIVE ANALYSIS ACROSS MODALITIES*

When comparing all screening approaches, conventional screening showed the lowest sensitivity and weakest discrimination ability; biomarkers, particularly sFlt-1/PlGF, demonstrated high diagnostic accuracy; Doppler ultrasonography provided moderate-to-high accuracy with strong specificity; and integrated models consistently achieved the highest overall predictive performance (AUC > 0.90 in most studies). This gradient of performance supports a hierarchical improvement in predictive accuracy from conventional screening → biomarkers/Doppler → integrated models.

## IV. DISCUSSION

### A. PERFORMANCE OF CONVENTIONAL SCREENING FOR EARLY DETECTION OF PREECLAMPSIA

The findings of this systematic review indicate that conventional antenatal screening provides clinically relevant baseline information but has limited discriminatory capacity for early prediction of preeclampsia. Across five included studies, conventional approaches based on maternal risk factors, blood pressure, proteinuria, body mass index, and routine laboratory parameters demonstrated sensitivities ranging from 35.5% to 51.2%, specificities from 78.4% to 91.0%, and AUC values from 0.61 to 0.68. These findings suggest that conventional screening is more effective at identifying women who are unlikely to develop the condition than at detecting all women who will subsequently develop preeclampsia. The relatively low sensitivity indicates that a considerable proportion of women who later develop preeclampsia may not be identified through conventional assessment alone.

This result is consistent with the biological and clinical characteristics of preeclampsia. Maternal history, blood pressure, and routine clinical variables represent established risk factors or manifestations of the disease but do not directly capture the molecular and vascular abnormalities that precede clinical presentation. Consequently, conventional screening may provide an important initial risk profile without adequately identifying subclinical placental dysfunction. Recent evidence similarly indicates that prediction based exclusively on routinely available clinical characteristics may be insufficient when the objective is early identification before overt clinical disease develops. The limitation is particularly relevant because preeclampsia is heterogeneous, with differences in gestational age at onset, severity, maternal characteristics, and underlying placental dysfunction.

The relatively high specificity observed in the present review should nevertheless not be interpreted as evidence that conventional screening lacks clinical value. Specificity ranging from 78.4% to 91.0% indicates that conventional parameters can contribute useful information for identifying women at lower or higher baseline risk. In routine antenatal care, these variables are inexpensive, widely available, and comparatively easy to obtain. Therefore, their principal value may be as the foundation of a sequential or multimodal screening strategy rather than as a standalone predictive test. This interpretation is compatible with contemporary approaches that combine maternal characteristics with biochemical and biophysical markers to improve risk stratification.

An important implication is that conventional screening should not necessarily be replaced by more sophisticated approaches. Instead, it can serve as the first layer of a hierarchical screening pathway. Maternal characteristics establish the pretest probability of disease, while additional biomarkers or Doppler measurements can subsequently refine that probability. Such an approach may be particularly relevant in healthcare systems where advanced testing cannot be universally performed. Thus, the findings support the continued use of conventional screening as a low-cost initial assessment while highlighting the need for additional modalities when greater predictive accuracy is required.

### B. PREDICTIVE VALUE OF BIOMARKERS AND DOPPLER ULTRASONOGRAPHY

The biomarker findings demonstrate a substantial improvement in predictive performance compared with conventional screening. Eight studies evaluating biomarkers produced sensitivity values of 69.5%–91.0%, specificity of 76.0%–95.4%, and AUC values of 0.76–0.94. The strongest performance was observed for angiogenic biomarkers, particularly sFlt-1, PlGF, and the sFlt-1/PlGF ratio, with sensitivity of 82.0%–91.0%, specificity of 89.0%–95.4%, and AUC of 0.83–0.94. This pattern is biologically plausible because angiogenic imbalance is closely associated with placental dysfunction and endothelial abnormalities occurring during the development of preeclampsia. Contemporary evidence confirms the diagnostic and prognostic relevance of sFlt-1 and PlGF, while a recent systematic review and meta-analysis reported an AUC of approximately 0.92 for the sFlt-1/PlGF ratio, exceeding the performance of either biomarker alone [28], [29].

The findings also demonstrate differences between angiogenic and inflammatory biomarkers. NLR and PLR produced moderate predictive performance, with AUC values ranging from 0.76 to 0.84. These parameters have advantages in terms of accessibility and relatively low measurement costs because they can be derived from routine hematological testing. However, their lower specificity compared with angiogenic biomarkers may reflect the nonspecific nature of systemic inflammatory responses. Inflammation may accompany several physiological and pathological conditions during pregnancy, limiting its ability to distinguish preeclampsia specifically. Therefore, inflammatory indices may be more appropriately considered complementary variables rather than independent diagnostic indicators.

The Doppler findings provide another important dimension of preeclampsia prediction. Five studies demonstrated sensitivity ranging from 62.5% to 75.0%, specificity from 84.0% to 92.1%, and AUC values from 0.81 to 0.85. The relatively high specificity indicates that Doppler abnormalities can provide useful evidence of impaired maternal-fetal circulation. Uterine artery Doppler, particularly the pulsatility index, provides a functional assessment of uteroplacental vascular resistance and can therefore identify hemodynamic consequences associated with abnormal placentation. A recent systematic review and meta-analysis involving 27 studies and more than 81,000 pregnancies reported moderate sensitivity and high specificity for uterine artery pulsatility index in predicting preeclampsia, supporting the general pattern identified in the present review [30]. Another recent meta-analysis likewise confirmed the potential utility of uterine artery Doppler for preeclampsia prediction [31].

However, the performance of Doppler ultrasonography should be interpreted in relation to gestational age, Doppler parameter, patient population, and measurement protocol. Differences in operator expertise, equipment, sampling

technique, threshold selection, and outcome definition can contribute to variability between studies. The current review therefore supports Doppler ultrasonography as a complementary functional assessment rather than a universally sufficient standalone screening method. Its greatest potential may arise when hemodynamic information is combined with maternal clinical characteristics and biochemical evidence of placental dysfunction.

Collectively, these findings demonstrate that biomarkers and Doppler ultrasonography provide different but complementary information. Biomarkers primarily reflect molecular and placental processes, whereas Doppler ultrasonography provides information regarding vascular and hemodynamic consequences. This distinction is important because the pathogenesis of preeclampsia involves multiple interconnected biological processes. Combining markers that represent different dimensions of the disease may therefore improve discrimination compared with relying on a single biological or imaging parameter.

### *C. INTEGRATED SCREENING, LIMITATIONS, AND CLINICAL IMPLICATIONS*

The most notable finding of this systematic review is the performance of integrated prediction models. Six studies combining clinical characteristics, biomarkers, Doppler parameters, or risk algorithms demonstrated sensitivity ranging from 65.0% to 92.0%, specificity from 83.0% to 94.1%, and AUC values from 0.77 to 0.96. Several models achieved AUC values above 0.90, while the combination of uterine artery Doppler and sFlt-1/PlGF reached an AUC of 0.96. These findings suggest that multimodal prediction can capture complementary dimensions of preeclampsia pathophysiology more effectively than isolated screening modalities. Similar evidence has shown that combining angiogenic biomarkers with clinical and imaging variables can improve discrimination, although performance varies substantially according to population and model specification [32], [33].

The improved performance of integrated models can be interpreted from a pathophysiological perspective. Conventional clinical variables provide information regarding maternal predisposition, biomarkers reflect placental and endothelial processes, and Doppler measurements characterize changes in maternal-fetal circulation. When these information sources are integrated, the resulting model incorporates risk information from different stages of disease development. This may explain why integrated approaches demonstrated the highest AUC values in the present review. Nevertheless, higher statistical performance does not automatically establish clinical utility. A model must also demonstrate reproducibility, external validity, appropriate calibration, feasibility, and a meaningful effect on clinical decision-making before widespread implementation.

Several limitations should be considered when interpreting these findings. First, substantial heterogeneity existed among the included studies with respect to study design, sample size, gestational age at testing, population characteristics, preeclampsia definition, biomarker thresholds, Doppler parameters, and diagnostic criteria. Such heterogeneity prevented quantitative meta-analysis and required a narrative and semi-quantitative synthesis. This limitation is important because differences in thresholds alone can substantially alter sensitivity and specificity. Recent systematic reviews of preeclampsia prediction have similarly reported substantial heterogeneity that limits the pooling and direct comparison of predictive models [34].

Second, most included studies were observational, and although the majority received moderate-to-high NOS scores, observational designs remain susceptible to selection bias, confounding, and differences in outcome ascertainment. The present review also included studies conducted in different healthcare settings, which may limit the generalizability of specific performance estimates to other populations. Third, some integrated models were developed in high-risk or referral populations. Their performance may therefore differ when applied to general antenatal populations with lower disease prevalence. Fourth, the absence of quantitative meta-analysis means that the reported ranges should not be interpreted as pooled estimates or as direct evidence that one modality is universally superior to another.

Despite these limitations, the findings have several practical implications. A multimodal approach may provide a rational framework for progressive risk stratification in antenatal care. Conventional screening can establish baseline maternal risk, followed by biomarker and Doppler assessment when additional discrimination is required. Such a strategy could potentially facilitate earlier identification of women requiring intensified surveillance or preventive management. However, implementation should consider cost, laboratory availability, ultrasound expertise, turnaround time, and differences in healthcare infrastructure. This consideration is particularly important in low- and middle-income settings, where a highly accurate screening model may have limited practical value if its components are not accessible.

Future research should therefore prioritize prospective, multicenter studies using standardized biomarker thresholds, Doppler acquisition protocols, and clearly defined preeclampsia outcomes. External validation across different ethnic, geographic, and healthcare populations is also essential. Furthermore, future models should evaluate calibration and clinical utility in addition to discrimination measures such as AUC, sensitivity, and specificity. Simplified multimodal algorithms that retain adequate predictive performance while reducing cost and technical complexity may be particularly valuable for implementation in routine antenatal services. Overall, the evidence synthesized in this review supports a transition from isolated risk-factor assessment toward complementary, multimodal risk stratification, while emphasizing that further validation is required before integrated models can be routinely adopted across diverse clinical settings.

## V. CONCLUSION

This systematic review aimed to synthesize and compare the predictive performance of conventional antenatal screening, biomarkers, and Doppler ultrasonography for the early

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detection of preeclampsia and to evaluate the potential added value of integrating these modalities for improved risk stratification. The findings from 24 included studies demonstrate substantial differences in predictive performance among the evaluated approaches. Conventional screening based on maternal risk factors, blood pressure, proteinuria, and routine laboratory assessment showed the lowest overall discriminatory performance, with sensitivity ranging from 35.5% to 51.2%, specificity from 78.4% to 91.0%, and AUC values from 0.61 to 0.68. Biomarker-based approaches demonstrated greater predictive capability, with overall sensitivity of 69.5%–91.0%, specificity of 76.0%–95.4%, and AUC of 0.76–0.94. Angiogenic biomarkers, particularly sFlt-1, PlGF, and the sFlt-1/PlGF ratio, demonstrated the strongest biomarker performance, reaching sensitivity of 82.0%–91.0%, specificity of 89.0%–95.4%, and AUC of 0.83–0.94. Doppler ultrasonography provided complementary hemodynamic information, with sensitivity of 62.5%–75.0%, specificity of 84.0%–92.1%, and AUC of 0.81–0.85. Importantly, integrated models combining clinical characteristics, biomarkers, and Doppler parameters demonstrated the highest overall predictive performance, with sensitivity reaching 92.0%, specificity 94.1%, and AUC 0.96. These findings indicate that the three modalities provide complementary information and that multimodal assessment may offer a more comprehensive approach to early risk stratification than isolated screening methods. Nevertheless, the interpretation of these findings is constrained by heterogeneity in study populations, gestational age at assessment, biomarker thresholds, Doppler protocols, outcome definitions, and observational study designs. Future research should therefore prioritize large prospective multicenter studies with standardized testing protocols and independent external validation across diverse populations. Further investigation should also assess model calibration, clinical utility, cost-effectiveness, and feasibility in routine antenatal care, particularly in resource-limited settings. Development of simplified and accessible multimodal prediction algorithms may facilitate translation of these findings into clinical practice and support earlier, evidence-based risk stratification and preventive management of preeclampsia.

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## DATA AVAILABILITY

All data supporting the findings of this study are included within the manuscript and its supplementary tables/figures. The literature search strategies, eligibility criteria, and data extraction parameters are fully detailed to allow complete reproducibility.

## AUTHOR CONTRIBUTION

D.K. conceived the study, developed the research framework, coordinated the systematic review process, and prepared the initial manuscript. L.W. contributed to the literature search, study selection, data extraction, and interpretation of the findings. D.M. contributed to methodological assessment, synthesis of the included evidence, and critical revision of the manuscript. D.B. contributed to the interpretation of the results, methodological review, and critical evaluation of the manuscript. All authors contributed to the revision of the manuscript, approved the final version, and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the study were appropriately addressed.

## DECLARATIONS

### *ETHICAL APPROVAL*

Ethical approval was not required for this study, as it is a systematic literature review based entirely on previously published, publicly accessible literature.

### *CONSENT FOR PUBLICATION PARTICIPANTS*

Informed consent was not required because this review involved the secondary analysis and synthesis of published aggregate data and did not involve direct interaction with human subjects or personal data collection

### *COMPETING INTERESTS*

The authors declare that they have no competing financial interests, personal relationships, or professional affiliations that could have appeared to influence the work reported in this paper.

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