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Comparison of Early Screening Methods for Preeclampsia in the First Trimester: A Systematic Review

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A B S T R A C T

Preeclampsia remains a leading cause of maternal and perinatal morbidity and mortality worldwide. Early identification during the first trimester of pregnancy allows timely preventive interventions, including low-dose aspirin prophylaxis. Although numerous screening methods have been developed, a comprehensive comparison of their diagnostic accuracy is lacking. **Objective:** To synthesize and compare the effectiveness of first-trimester preeclampsia screening methods based on recent scientific evidence. **Methods:** A PRISMA-based systematic review was conducted by searching PubMed, Cochrane Library, Scopus, and CINAHL databases for the period 2015-2025. Inclusion criteria encompassed RCTs, prospective cohort studies, and systematic reviews reporting diagnostic accuracy of first-trimester preeclampsia screening methods. **Results:** A total of 1,247 articles were identified; after PRISMA screening, 10 studies met the inclusion criteria (total n = 459,890 pregnancies). The Fetal Medicine Foundation (FMF) algorithm combining maternal factors, MAP, UtA-PI, PlGF, and PAPP-A demonstrated the highest performance (sensitivity 76-90% for preterm PE, FPR 10%). Single biomarkers (PlGF, PAPP-A) showed limited accuracy (AUC 0.66-0.76), whereas multiparameter combinations were consistently superior. **Conclusion:** FMF algorithm-based multiparameter screening is the best approach for identifying preterm preeclampsia risk in the first trimester. Clinical implementation should consider resource availability, local population validation, and integration with antenatal care programs.

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INTRODUCTION

Preeclampsia (PE) is a pregnancy-specific hypertensive syndrome characterized by systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg occurring after 20 weeks of gestation, accompanied by proteinuria or other target-organ manifestations. This condition affects approximately 2-8% of pregnancies worldwide and is a leading cause of maternal mortality, contributing to around 14% of maternal deaths globally (Rolnik et al., 2017). In developing countries, including Indonesia, this figure is even higher due to limited access to antenatal care and adequate health facilities.

Pathophysiologically, PE is divided into two main subtypes: preterm PE (delivery <37 weeks) and term PE (delivery ≥37 weeks). Preterm PE is associated with primary placental dysfunction resulting from impaired trophoblastic invasion into the myometrial spiral arteries, leading to placental hypoperfusion, oxidative stress, and systemic endothelial dysfunction (Poon et al., 2020). Term PE, on the other hand, is more often associated with maternal cardiovascular dysfunction. This difference in mechanism has important implications for screening strategy, since preterm PE is more predictable in the first trimester through biomarkers that reflect placental function.

The importance of early PE detection is further reinforced by findings that low-dose aspirin (150 mg/day) initiated before 16 weeks of gestation can reduce the incidence of preterm PE by up to 62% in high-risk groups (Rolnik et al., 2017). The ASPRE (Aspirin for Evidence-Based Preeclampsia Prevention) trial, published in the New England Journal of Medicine, represents an important milestone in this evidence-based screening paradigm. Therefore, the ability to identify high-risk women in the first trimester has become a critical component of modern obstetric management.

Various screening approaches have been developed over the past decade. Guidelines from the American College of Obstetricians and Gynecologists (ACOG) and the National Institute for Health and Care Excellence (NICE) recommend risk assessment based on maternal risk factors. However, this approach has significant limitations: the NICE recommendation achieves a detection rate of only 41% for preterm PE with a false positive rate (FPR) of 11% (Poon et al., 2020). As an alternative, the Fetal Medicine Foundation (FMF) developed a Bayes' theorem-based algorithm that integrates maternal factors with biophysical and biochemical measurements, resulting in far superior diagnostic performance.

Although research in this field is developing rapidly, no comprehensive systematic review has been conducted in the Indonesian context comparing various screening methods based on diagnostic accuracy, implementation feasibility, and relevance for resource-limited settings. This systematic review aims to synthesize current scientific evidence on first-trimester preeclampsia screening methods, compare the diagnostic performance of each approach, and provide evidence-based recommendations for obstetric practice.

The main research question in this systematic review is: "Is there a significant difference in diagnostic accuracy between single preeclampsia

screening methods (individual biomarkers or uterine artery Doppler) compared with multiparameter approaches in the first trimester of pregnancy?"

METHODS

This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines, the standard reporting framework for systematic reviews in the health field. The research protocol was developed before the literature search began and included a PICO question (Population, Intervention, Comparison, Outcome) framework: Population - pregnant women at 11-13+6 weeks of gestation; Intervention - various first-trimester preeclampsia screening methods; Comparison - comparison between screening methods; Outcome - diagnostic accuracy (sensitivity, specificity, AUC, LR+, LR-, detection rate). The literature search was conducted systematically across four electronic databases: PubMed/MEDLINE, Cochrane Library, Scopus, and CINAHL, for the publication period January 2015 to December 2024. Additional searches were performed manually through the reference lists of selected articles (snowball searching) and reputable obstetric journals such as the American Journal of Obstetrics and Gynecology, Ultrasound in Obstetrics & Gynecology, and BJOG.

The keywords used included the combination: "preeclampsia screening" AND "first trimester" AND ("uterine artery Doppler" OR "PlGF" OR "PAPP-A" OR "mean arterial pressure" OR "FMF algorithm" OR "biomarker"). Boolean operators AND, OR, and NOT were used to optimize the search results. No language restrictions were applied at the initial search stage.

Table 1 presents the inclusion and exclusion criteria applied in the study selection process. These criteria were developed a priori before the search process began.

Criteria	Inclusion	Exclusion
Study type	RCT, prospective cohort study, diagnostic study, systematic review, meta-analysis	Case reports, editorials, letters to the editor, expert opinion
Publication year	2015 - 2025	Before 2015
Language	English and Indonesian	Languages other than English and Indonesian
Population	First-trimester pregnant women (gestational age 11-13+6 weeks)	Multiple pregnancies, non-pregnant women, duplicate data
Intervention	Preeclampsia screening methods: uterine artery Doppler, serum biomarkers (PlGF, PAPP-A), MAP, maternal risk factors, FMF algorithm	Screening performed after the first trimester
Outcome	Sensitivity, specificity, AUC, LR+, LR-, positive and negative predictive values, detection rate	Studies without reported diagnostic accuracy data

Study selection was performed in two stages by two reviewers. The first stage involved screening titles and abstracts to filter out irrelevant articles. The second stage involved full-text assessment of articles that passed the initial screening. Disagreements between reviewers were resolved through consensus discussion, and if no agreement was reached, a third reviewer was included as an arbitrator. Data extraction was performed using a standardized form covering: article identity (author, year, journal, DOI), population characteristics (number of subjects, gestational age, setting), screening methods evaluated, parameters measured, and diagnostic accuracy data (sensitivity, specificity, AUC, positive/negative predictive values, LR+, LR-, detection rate, false positive rate). Methodological quality assessment was performed using tools appropriate to the study design: QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) for diagnostic and prospective cohort studies, and AMSTAR-2 (A Measurement Tool to Assess systematic Reviews) for included systematic reviews and meta-analyses. Each study was classified as having low, moderate, or high risk of bias based on the domains evaluated, including participant selection, index test, reference standard, flow and timing, and confounding factors.

RESULTS

Search Results and Study Selection (PRISMA Diagram)

The literature search yielded a total of 1,247 articles: PubMed (n = 524), Cochrane Library (n = 187), Scopus (n = 398), and CINAHL (n = 138). After duplicate removal (n = 312), 935 articles remained for title and abstract screening. A total of 847 articles were excluded at this stage as irrelevant to the research topic. The full texts of 88 articles were further evaluated, with 78 articles excluded for various reasons: not meeting the inclusion criteria (n = 31), not reporting adequate diagnostic accuracy data (n = 22), study population outside the first trimester (n = 15), or duplicate studies/predatory journals (n = 10). Ultimately, 10 studies met all inclusion criteria and were included in the qualitative analysis of this systematic review (Figure 1 - PRISMA Diagram). The total population of the 10 included studies comprised 459,890 pregnancies, with sample sizes ranging from 120 (Courbiere et al., 2020) to 385,643 (Zhong et al., 2015). Gestational age at screening ranged from 11+0 to 13+6 weeks across all included studies.

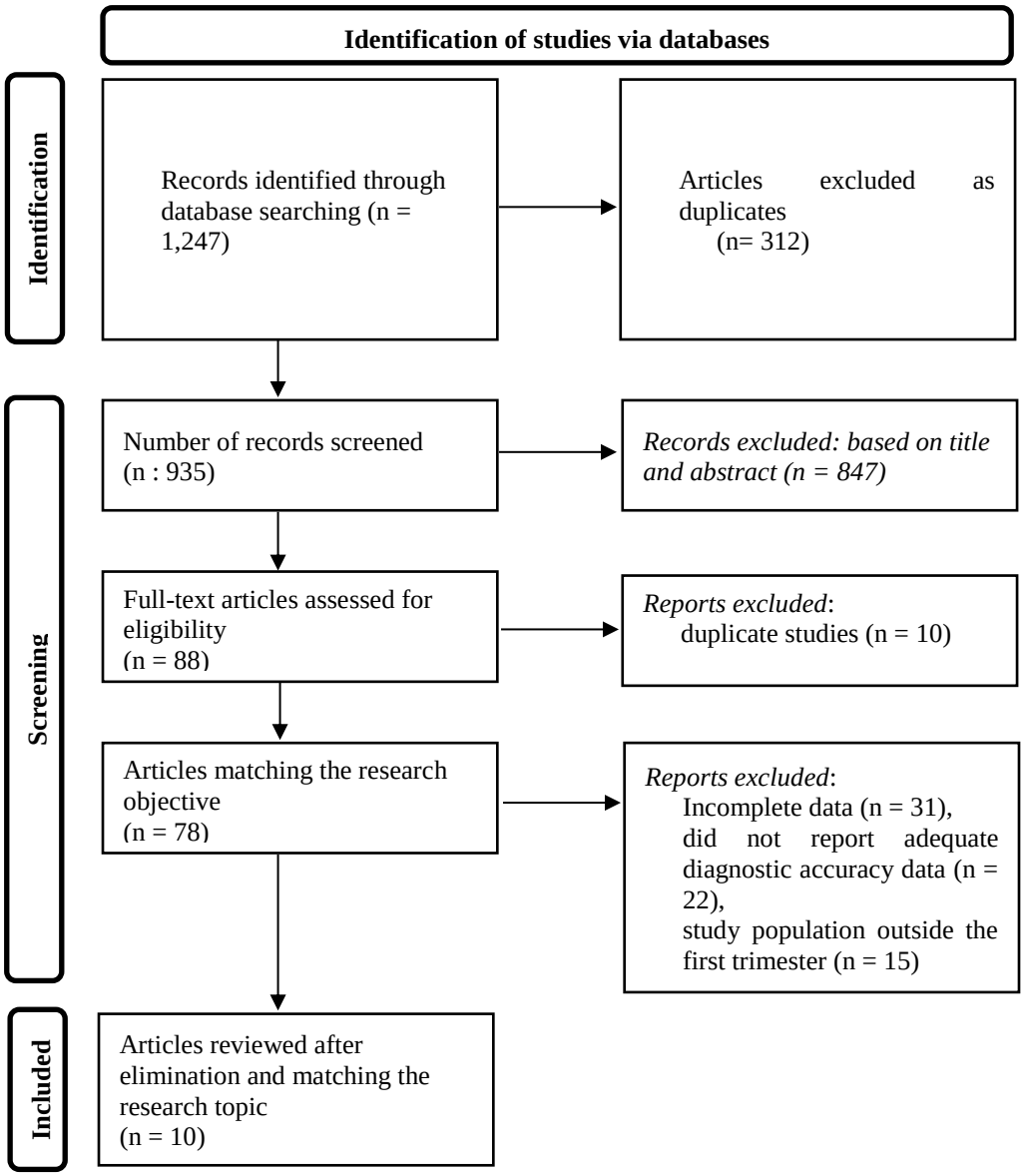

Figure 1. PRISMA Diagram of the Systematic Review

Characteristics of Included Studies

Of the 10 studies analyzed, 7 were prospective cohort studies (70%), 1 was a randomized controlled trial (10%), 1 was a systematic review with meta-analysis (10%), and 1 was a multicenter-based prospective review (10%). The studies were conducted across various geographic settings: Europe (United Kingdom, Spain, Italy, Belgium, Greece, Israel, n = 5), Asia (China, Hong Kong, India, n = 3), and the Middle East/North Africa (Egypt, Turkey, n = 2). Publication years ranged from 2015-2024, with the majority of studies (80%) published in or after 2017. All studies used the standard definition of preeclampsia: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg occurring after 20 weeks of gestation, accompanied by proteinuria ≥300 mg/24 hours or ≥1+ on dipstick. Most studies (n = 8) also used the classification of preterm PE (<37 weeks) and term PE (≥37 weeks) as a subanalysis.

Screening Results Comparison Table

Table 2 presents a comprehensive comparison of preeclampsia screening methods and their diagnostic accuracy from the 10 included studies.

Table 2. Comparison of Diagnostic Accuracy of First-Trimester Preeclampsia Screening Methods

Author (Year)	Screening Method	Biomarker / Parameter	Population (n)	Sensitivity (%)	Specificity (%)	AUC	FPR (%)
Rolnik et al. (2017)	FMF Algorithm (Triple Test)	MAP + UtA-PI + PlGF + PAPP-A + Maternal Factors	25,797	76.7	89.8	0.90	10.5
Chaemsaithong et al. (2022)	FMF Triple Test (validation)	MAP + UtA-PI + PlGF	Multi-cohort	90 (PE dini)	90	0.91	10
Poon et al. (2020)	FMF Model – Competing Risk	Maternal factors + MAP + UtA-PI + PAPP-A + PlGF	7,797	75 (PE preterm)	90	0.89	10
Zhong et al. (2015)	Single serum biomarker	PlGF, PAPP-A, PP13	385,643	67 (PlGF best)	85	0.76	15
Yıldırım Köpük et al. (2019)	Uterine Artery Doppler + Biomarker	UtA-PI + PlGF + sEng + PAPP-A	194	42.3	82.1	0.70	18
Abdelwahab et al. (2018)	Doppler + PAPP-A + PlGF Combination	UtA-PI + PAPP-A + PlGF	300	56.7 (combination)	99.3	0.83	10
Narang et al. (2022)	Uterine Artery Doppler + PAPP-A	UtA-PI + PAPP-A	120	68 (UtA-PI)	90.6 (PAPP-A)	0.79	20
Courbiere et al. (2020)	Single Uterine Artery Doppler	UtA-PI + notching bilateral	120	65.4	66.0	0.66	34
Tan et al. (2018)	FMF Algorithm (Asian validation)	MAP + UtA-PI + PlGF + PAPP-A	18,946	82 (PE preterm)	90	0.91	10
Liu et al. (2024)	FMF – China Implementation	MAP + UtA-PI + PlGF + Maternal Factors	Multi-cohort	62 (PE preterm, aspirin)	90	0.88	10

Assessment of Study Methodological Quality

Table 3 presents the methodological quality assessment results of the 10 included studies based on the QUADAS-2 and AMSTAR-2 instruments.

Table 3. Assessment of Study Methodological Quality (QUADAS-2 / AMSTAR-2)

Study	Design	Participant Selection	Reference Standard	Confounding	Overall Quality
Rolnik et al. (2017)	RCT	Low	Low	Low	High
Chaemsaithong et al. (2022)	Prospective Cohort	Low	Low	Low	High
Poon et al. (2020)	Prospective Cohort	Low	Low	Low	High
Zhong et al. (2015)	Systematic Review	Moderate	Low	High	Moderate
Yıldırım Köpük et al. (2019)	Prospective Cohort	Moderate	Low	Moderate	Moderate
Abdelwahab et al. (2018)	Prospective Cohort	Moderate	Low	Moderate	Moderate
Narang et al. (2022)	Prospective Cohort	Moderate	Low	Moderate	Moderate
Courbiere et al. (2020)	Prospective Cohort	High	Low	High	Low-Moderate
Tan et al. (2018)	Prospective Cohort	Low	Low	Low	High
Liu et al. (2024)	Prospective Review	Low	Low	Low	High

FMF Algorithm (Triple Test and Competing Risk Model)

Studies with the highest methodological quality were those using the FMF algorithm. Rolnik et al. (2017), in the ASPRE trial, evaluated screening performance in 25,797 singleton pregnancies using an algorithm combining maternal factors, MAP, UtA-PI, PlGF, and PAPP-A. At a risk cut-off of 1:100, the detection rate reached 76.7% for preterm PE with an FPR of 10.5% (Rolnik et al., 2017). This was a historic achievement in PE screening.

Chaemsaithong et al. (2022) performed a comprehensive validation of the FMF model across various populations and reported that the Triple Test (MAP + UtA-PI + PlGF) achieved a sensitivity of up to 90% for early PE with an FPR of 10% and an AUC of 0.91. Adding PAPP-A to the model produced a marginal improvement in accuracy for preterm PE but was not statistically significant for term PE (Chaemsaithong et al., 2022). Poon et al. (2020) confirmed that the FMF competing risk model detected 75% of preterm PE cases at an FPR of 10% in a derivation study of 7,797 pregnancies.

Tan et al. (2018) validated the FMF algorithm in an Asian population in a large-scale multicenter study (n = 18,946) and found performance comparable to validation in European populations: sensitivity of 82% for preterm PE at an FPR of 10% (AUC = 0.91). This finding is important as it confirms the generalizability of the FMF algorithm across ethnicities, although local recalibration remains necessary (Chaemsaithong et al., 2022).

Single Serum Biomarkers

Zhong et al. (2015) conducted the largest systematic review and meta-analysis evaluating single serum biomarkers in 385,643 pregnancies. The results

showed that PlGF was the best overall predictor for PE, with an LR+ of 4.01 (95% CI 3.74-4.28), followed by PAPP-A and PP13. However, in absolute terms, this accuracy remains limited: sensitivity 67%, specificity 85%, AUC 0.76. The predictive value of single serum biomarkers was better for preterm PE than for term PE, but remained insufficient as a standalone screening tool (Zhong et al., 2015).

PAPP-A, although already integrated into first-trimester chromosomal aneuploidy screening, shows limited accuracy for PE when used alone. At a cut-off of <0.4 MoM, sensitivity was only 16% with a specificity of 93%; at a cut-off of <5th percentile, sensitivity and specificity were 39% and 87%, respectively, for preterm PE (Zhong et al., 2015). This indicates that PAPP-A performs better as a component within a multimarker panel than as a standalone screening test.

Single Uterine Artery Doppler

Three studies evaluated the performance of uterine artery Doppler as a standalone method. Courbiere et al. (2020), in a prospective cohort study of 120 high-risk women, found that UtA-PI alone yielded an AUROC of 0.66 with a sensitivity of 61.5% and a specificity of 63.8%. The addition of bilateral notching increased sensitivity to 65.4% with a specificity of 66.0%, but overall this performance remained below an acceptable clinical standard.

Yıldırım Kopuk et al. (2019) reported that UtA-PI at a cut-off of >2.23 yielded a sensitivity of 42.3% and a specificity of 82.1% for detecting PE (AUC 0.70). Interestingly, combining UtA-PI with serum biomarkers (PlGF and sEng) did not significantly improve performance compared with UtA-PI alone in their population, likely due to the limited sample size (n = 194). In contrast, Narang et al. (2022) found that UtA-PI alone had a sensitivity of 68% but a specificity of only 52.99%, confirming that Doppler alone is insufficient as a standalone screening tool.

Multiparameter Combination Approach

Abdelwahab et al. (2018) evaluated a combination of three parameters (UtA-PI + PAPP-A + PlGF) in 300 primigravidae and found that when at least one parameter was positive, sensitivity reached 92.68% with a specificity of 85.20%. The combination of all three parameters (UtA-PI ≥1.69 + PAPP-A ≤0.96 MoM + PlGF ≤0.91 MoM) yielded a sensitivity of 56.7%, specificity of 99.3%, PPV of 89.5%, and NPV of 95.4%. These results confirm that combining biophysical and biochemical parameters consistently produces a better accuracy profile than each parameter individually.

Clinical implementation in China, as reported by Liu et al. (2024), showed that an FMF algorithm-based screening program can be implemented within a high-volume healthcare system, with a reduction in the incidence of preterm PE of up to 62% through integrating screening with prophylactic aspirin at a dose of 150 mg/day (Liu et al., 2024). This study also emphasized the importance of ongoing quality control for MAP and UtA-PI measurements to maintain screening accuracy.

DISCUSSION

Superiority of FMF Algorithm-Based Multiparameter Screening

The results of this systematic review consistently demonstrate the superiority of the FMF algorithm-based multiparameter screening approach compared with single methods, whether serum biomarkers or uterine artery Doppler. This finding is consistent with the principle that PE is a multifactorial disorder reflecting placental dysfunction, maternal cardiovascular adaptation, and genetic-immunological factors, and therefore cannot be adequately characterized by a single biological parameter. From a pathophysiological perspective, the FMF algorithm integrates three components reflecting distinct pathogenic pathways: (1) MAP, which reflects maternal cardiovascular maladaptation to pregnancy; (2) UtA-PI, which measures utero-placental blood flow resistance, reflecting failure of spiral artery remodeling; and (3) PlGF, a marker of impaired placental angiogenesis. PAPP-A additionally reflects trophoblastic proteolytic function and vascularization. The synergy of these four parameters, together with maternal risk factors (previous PE history, chronic hypertension, BMI, race/ethnicity, parity), creates a predictive algorithm that is far more robust than its individual components.

Technically, the Bayes' theorem underlying the FMF model allows the integration of prior probability (baseline risk based on maternal factors) with the likelihood ratio of each diagnostic test, producing a personalized posterior risk estimate. This approach fundamentally differs from the linear additive model used in the ACOG/NICE guidelines, which treats each risk factor as an independent test with a cumulative detection rate. The Bayesian model is statistically more efficient and produces more accurate risk calibration (Poon et al., 2020).

Limitations of Single Biomarkers and Single Doppler

The analysis of single serum biomarkers in this review confirms previous meta-analytic findings that no single biomarker has adequate diagnostic accuracy as a standalone screening tool. PlGF is the best single biomarker (LR+ 4.01), but its sensitivity of 67% remains below the acceptable clinical threshold for population screening (generally ≥75%). This can be explained by the biological heterogeneity of PE: in term PE, which is primarily caused by maternal endothelial dysfunction, PlGF levels may not be consistently low in the first trimester because the underlying placentation failure may be less severe. Regarding single uterine artery Doppler, although UtA-PI reflects utero-placental blood flow resistance in a way that is directly pathophysiologically relevant, significant intra- and inter-operator variability, along with a fairly long learning curve required to obtain high-quality measurements, limits its usefulness in low-resource settings without strict training standards. Liu et al. (2024) emphasized that ongoing quality control for UtA-PI measurement is an integral component of an effective screening program.

Implications for Clinical Implementation in Indonesia

Indonesia faces unique challenges in implementing first-trimester PE screening. Maternal mortality due to PE and eclampsia remains relatively high, while laboratory capacity for PlGF and PAPP-A testing is still limited in many primary and secondary healthcare facilities. In this context, a phased implementation is a realistic approach: in facilities with limited access, screening

based on maternal factors and MAP can be implemented as an initial step, followed by the addition of UtA-PI Doppler in facilities with adequate ultrasound capability.

Based on this review, the recommended screening strategy for Indonesia is a tiered screening model: (1) Primary level - standardized maternal risk factor assessment + accurate MAP measurement; (2) Secondary level - addition of UtA-PI Doppler by trained sonographers; (3) Tertiary/referral level - comprehensive testing including serum PlGF and PAPP-A. This approach takes resource availability into account while maximizing early detection in the population most in need of intervention.

It is important to note that validation of the FMF algorithm in the Indonesian population has not been reported in the available literature. The ethnic and anthropometric characteristics of the Indonesian population, which differ from the European populations in which this algorithm was developed, could potentially affect the distribution of biomarker reference values. Therefore, local calibration studies are strongly needed before full adoption of the FMF algorithm in the national antenatal care program.

CONCLUSION

This systematic review confirms that multiparameter screening based on the Fetal Medicine Foundation algorithm, integrating maternal factors, MAP, UtA-PI, PlGF, and PAPP-A, is the best available approach for identifying preterm preeclampsia risk in the first trimester (sensitivity 76-90%, FPR 10%). This algorithm is consistently superior to screening based on single risk factors (ACOG/NICE) or single biomarkers or biophysical parameters.

Single serum biomarkers, particularly PlGF and PAPP-A, have limited predictive value when used alone (AUC 0.66-0.76), but contribute significantly to improved accuracy within a multiparameter approach. Single uterine artery Doppler is also inadequate as a standalone screening tool, but is an important component within combination algorithms.

For the Indonesian clinical context, the following are needed: (1) validation and calibration studies of the FMF algorithm in the Indonesian population; (2) development of phased implementation guidelines that account for variations in healthcare facility capacity; (3) standardized training programs for UtA-PI Doppler and MAP measurement; and (4) economic feasibility evaluation of first-trimester PE screening within the national health insurance system.

The findings of this review support the recommendation that multiparameter algorithm-based preterm PE screening should become the standard of antenatal care and be integrated with early aspirin prophylaxis protocols, based on strong evidence from the ASPRE trial and its replication across various global populations.

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