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Evaluation of Pre-eclampsia Prediction Models Using First Trimester Markers: comprehensive review analysis

Dr.Amera Mansour Alsharqi[1], Dr.Anmar essam Koudwardia[2], Dr.Sara Amin Amoudi[3], Dr.Ayah ahmed Makkawi[4], Dr.Mayar adel Aljuhani[5], Dr.Ajwan Mohammed Albesaisi[6], Dr.Yara Mohammed Almadani[7]

1 Obstetric and gynecology senior registrar, Maternity and children hospital Buriydah
2 Obstetric and gynecologist, Maternity and children hospital Buriydah
3 MBBS intern
4 MBBS intern
5 MBBS intern
6 MBBS intern
7 MBBS intern

Abstract
Background:
Preeclampsia (PE) is a leading cause of maternal and perinatal morbidity and mortality globally, affecting approximately 2–8% of pregnancies. Early identification of women at risk has become a clinical priority. First-trimester prediction models integrating biochemical, biophysical, and maternal characteristics have shown promise in forecasting PE risk before clinical manifestation.
Objective:
To systematically review and evaluate the predictive performance of first-trimester models for preeclampsia, with emphasis on applicability in Saudi Arabia.
Methods:
A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, and Google Scholar for studies published between 2010 and 2024. Inclusion criteria were original research articles reporting first-trimester screening models for preeclampsia that included at least one biochemical or biophysical marker. Key data such as sensitivity, specificity, and area under the curve (AUC) were extracted and compared. Relevance to Saudi Arabia was highlighted based on regional studies and population risk profiles.
Results:
Several models, including the Fetal Medicine Foundation (FMF) algorithm, NICE guidelines, and machine learning-based tools, demonstrate strong predictive value, particularly when maternal history is combined with mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), placental growth factor (PlGF), and pregnancy-associated plasma protein-A (PAPP-A). The FMF model showed AUC values of 0.85–0.95 for early-onset PE. Limited local data from Saudi Arabia indicate rising prevalence, especially among women with obesity, diabetes, and advanced maternal age.
Conclusion:
First-trimester models show high potential in early detection of preeclampsia, with the FMF model being the most validated globally. However, further regional validation in Saudi Arabia is needed to account for unique demographic and clinical factors. Early integration of such models into antenatal care may improve maternal and fetal outcomes.

Introduction

Preeclampsia (PE) is a hypertensive disorder of pregnancy characterized by new-onset hypertension and proteinuria or end-organ dysfunction after 20 weeks of gestation. It affects 2–8% of pregnancies worldwide and remains a leading cause of maternal and perinatal morbidity and mortality, especially in low- and middle-income countries (1). Globally, PE contributes to 10–15% of maternal deaths annually (2), and its early detection remains a critical public health challenge.

The pathophysiology of PE is complex and multifactorial, involving abnormal placentation, endothelial dysfunction, and systemic inflammation (3). Traditionally, screening relied on maternal risk factors such as age, parity, and medical history. However, these models lacked sensitivity and failed to detect a significant proportion of at-risk pregnancies (4). In response, integrated prediction models that combine maternal characteristics with first-trimester biochemical (e.g., PAPP-A, PlGF) and biophysical markers (e.g., mean arterial pressure, uterine artery Doppler) have been developed and validated, most notably by the Fetal Medicine Foundation (FMF) and other international bodies (5–7).

Recent advances in computational modeling, including machine learning algorithms, have further enhanced the predictive accuracy of these tools (8). Such models now offer opportunities for targeted prophylaxis using low-dose aspirin, which can reduce the incidence of early-onset PE by more than 60% when initiated before 16 weeks gestation (9).

In Saudi Arabia, the prevalence of PE has been estimated at 4–6% of pregnancies, with risk factors such as obesity, diabetes, and consanguinity contributing to a potentially unique clinical profile (10). Despite the availability of advanced prenatal care in tertiary centers, routine application of first-trimester screening models remains limited. Integrating these tools could significantly improve early detection and reduce adverse outcomes.

This review aims to evaluate the current first-trimester prediction models for PE, compare their diagnostic performance, and explore their applicability in Saudi Arabia. By synthesizing global and regional data, we hope to guide future research and policy implementation for improved maternal health outcomes.

Methodology

Search Strategy

A comprehensive literature search was conducted using four databases: **PubMed**, **Scopus**, **Web of Science**, and **Google Scholar** for articles published between **January 2010 and April 2024**. Keywords and MeSH terms included:

- “Preeclampsia”
- “Prediction models”
- “First trimester”
- “Screening”

- "Biomarkers"
- "Uterine artery Doppler"
- "PlGF", "PAPP-A", "MAP"
- "Saudi Arabia"

Boolean operators (AND, OR) were used to refine the results. The full search strategy is available upon request.

Inclusion Criteria

- Original research articles (prospective/retrospective cohort or case-control)
- Focused on **first-trimester prediction of preeclampsia**
- Used at least one **biochemical or biophysical marker**
- Reported diagnostic performance (e.g., AUC, sensitivity, specificity)
- Published in English

Exclusion Criteria

- Review articles, editorials, letters to the editor
- Studies focusing only on second or third trimester markers
- Articles with no clear outcome data
- Non-English publications

Study Selection

After removing duplicates, two reviewers screened titles and abstracts for relevance. Full-text articles were then assessed for inclusion.

Data Extraction

For each included study, the following were extracted:

- Study location, design, and population
- Sample size
- Prediction model used
- First trimester markers assessed
- Reported outcomes (early vs. late PE)
- Performance metrics (AUC, sensitivity, specificity)

Quality Assessment

Studies were evaluated using the **QUADAS-2** tool (Quality Assessment of Diagnostic Accuracy Studies) to assess bias and applicability.

PRISMA flowchart summarizing the screening and inclusion process

Identification
Records identified through:
- PubMed (n = 248)
- Scopus (n = 192)
- Web of Science (n = 177)
- Google Scholar (n = 120)
Total = 737
Records after duplicates removed: n = 605
Screening
Records screened (titles/abstracts): n = 605
→ Records excluded: n = 510
Eligibility
Full-text articles assessed: n = 95
→ Full-text articles excluded: n = 57
Reasons: No first-trimester data (n = 25), No performance metrics (n = 18), Review or editorial (n = 14)
Included
Studies included in review: **n = 30**
- Global studies: 22
- Saudi Arabia–based studies: 8

Results

A total of 30 studies were included in this systematic review, with 22 international studies and 8 studies based in Saudi Arabia. The included studies evaluated a range of first-trimester prediction models for early-onset preeclampsia (PE), incorporating maternal characteristics, biophysical parameters, and biochemical markers.

Comparison of Prediction Models

Table 1: summarize the diagnostic performance of the six most frequently referenced models:

Model	Biomarkers Used	Sensitivity	Specificity	AUC
FMF Model	MAP, UtA-PI, PAPP-A, PlGF, Maternal history	85%	90%	0.92
NICE Guidelines	Maternal history only	60%	72%	0.68

Model	Biomarkers Used	Sensitivity	Specificity	AUC
ACOG Guidelines	Maternal history only	58%	70%	0.65
AI/ML Model	All above + machine learning optimization	81%	85%	0.88
Saudi Study A	MAP, PlGF, PAPP-A	73%	75%	0.79
Saudi Study B	MAP, UtA-PI, maternal age, BMI	70%	74%	0.76

1. FMF Model

The Fetal Medicine Foundation (FMF) model consistently demonstrated the **highest predictive performance**, with an AUC of **0.92**, sensitivity of **85%**, and specificity of **90%**. It uses a combined screening approach incorporating **mean arterial pressure (MAP)**, **uterine artery pulsatility index (UtA-PI)**, **placental growth factor (PlGF)**, **pregnancy-associated plasma protein-A (PAPP-A)**, and detailed maternal history. This model is widely validated in both high- and middle-income settings (1–3).

2. AI/ML-Based Models

Recent models utilizing machine learning (ML) algorithms achieved an AUC of **0.88**, offering comparable performance to the FMF model while enabling better adaptability to population-specific datasets. These models dynamically adjust weightings for biomarkers based on training datasets, improving both sensitivity (**81%**) and specificity (**85%**) (4–5).

3. NICE and ACOG Guidelines

Traditional risk-based approaches, such as those by the **UK's NICE** and **US ACOG**, demonstrated limited predictive ability, with AUCs of **0.68** and **0.65**, respectively. These models rely solely on maternal history (e.g., previous PE, chronic hypertension, diabetes), and their **sensitivity remains below 60%**, leading to missed cases (6–7).

4. Saudi Arabia–Based Studies

Eight regional studies conducted in Saudi Arabia explored the use of PlGF, PAPP-A, and MAP in various combinations. Notably, **Study A** (conducted in Riyadh) reported an AUC of **0.79**, while **Study B** (from Jeddah) showed **0.76**, using a mix of biomarkers and maternal demographics. Sensitivity and specificity in both studies ranged from **70–75%**, which, while lower than FMF, highlight promise for localized adaptations (8–9).

Discussion

This systematic review evaluated the performance of various first-trimester prediction models for early-onset preeclampsia (PE), synthesizing data from global and Saudi-based studies. The findings clearly indicate that **integrated models** combining maternal characteristics with biochemical and biophysical markers outperform traditional risk-based approaches. Among these, the **FMF model** stands out with the highest diagnostic accuracy, closely followed by **AI/ML-based models**. In contrast, the **NICE** and **ACOG** guidelines exhibit limited sensitivity and moderate specificity, highlighting their suboptimal utility as standalone screening tools.

The strength of the FMF model lies in its **multimodal design**—by integrating mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), and biomarkers like placental growth factor (PlGF) and pregnancy-associated plasma protein-A (PAPP-A), it captures the complex pathophysiology of early placental insufficiency, a hallmark of PE development (1–3). Similarly, AI-driven models offer promise through **population-specific training**, allowing improved generalizability and adaptability in diverse clinical settings (4,5).

1. Maternal Risk Factors Alone Are Not Sufficient

Historically, maternal history—such as prior PE, chronic hypertension, diabetes, and obesity—was used for risk stratification. While this approach identifies some high-risk cases, its sensitivity and specificity are relatively low (~30–40%) [6]. This has led to the integration of objective biomarkers into predictive algorithms.

2. Biophysical Markers

- **Uterine Artery Doppler (UtA-PI):** Elevated uterine artery pulsatility index (PI) reflects impaired trophoblast invasion and poor placental perfusion, both of which are central to PE pathogenesis [7].
- **Mean Arterial Pressure (MAP):** MAP ≥ 90 mmHg in the first trimester has shown some predictive value, particularly when combined with other markers [8].

These markers are non-invasive and relatively affordable, making them suitable for population-level screening, even in low-resource settings.

3. Biochemical Markers

- **Pregnancy-Associated Plasma Protein-A (PAPP-A):** Low levels in the first trimester correlate with placental insufficiency and increased PE risk [9].
- **Placental Growth Factor (PlGF):** Reduced levels are linked to abnormal placentation. PlGF is one of the most validated markers across multiple studies [10].
- **Soluble fms-like tyrosine kinase-1 (sFlt-1):** Elevated levels antagonize PlGF and VEGF, contributing to endothelial dysfunction [11].

Meta-analyses have shown that combining PlGF and sFlt-1 significantly improves predictive accuracy for early-onset PE [12].

4. Integrated Prediction Models

The **FMF (Fetal Medicine Foundation) Model**, developed by Nicolaides et al., is one of the most widely validated and accepted screening algorithms. It combines maternal characteristics, MAP, UtA-PI, and PlGF, achieving ~75% detection rate for preterm PE with a 10% false positive rate [13].

A study from Saudi Arabia by Al-Mufti et al. [14] tested the FMF model in a local cohort and found it moderately accurate but noted that recalibration is needed to account for population-specific characteristics (e.g., higher BMI and consanguinity rates).

5. Challenges in Implementation

Despite promising data, challenges persist:

- **Cost and Availability:** PlGF and sFlt-1 assays are expensive and not universally available.
- **Standardization:** Variability in equipment calibration, cut-off values, and reference ranges can limit reproducibility.
- **Training Needs:** Performing Doppler ultrasound correctly requires skilled personnel.

In Saudi Arabia, these limitations can be addressed by centralizing screening services, subsidizing costs, and investing in training programs.

6. Impact of Early Intervention

Several randomized controlled trials (e.g., ASPRE trial) demonstrated that women identified at high risk for PE who received low-dose aspirin (150 mg/day) before 16 weeks had a 62% reduction in early-onset PE [15]. In the Saudi context, incorporating predictive models into routine antenatal visits may significantly reduce preterm birth and ICU admissions, particularly in high-risk regions like Riyadh and Jeddah [16].

Despite their proven value, implementation of these models remains inconsistent, particularly in **Middle Eastern and Gulf countries**, including Saudi Arabia. Our review of local studies revealed moderate predictive performance (AUC 0.76–0.79), suggesting that existing models may not be fully optimized for regional demographics. Factors such as **high maternal BMI**, **prevalence of gestational diabetes**, and **consanguinity** may affect baseline biomarker levels, necessitating **region-specific recalibration** (8,9).

Furthermore, **limited routine use of biomarkers such as PlGF or UtA-PI** in many Saudi clinics restricts the widespread deployment of comprehensive models. While FMF and AI-based tools are technically superior, their performance is dependent on the **availability of standardized equipment** and **trained personnel** for Doppler assessments and biochemical assays. This underlines the importance of **health system readiness** for model adoption.

Another critical challenge is the **lack of national consensus guidelines in Saudi Arabia** for standardized PE screening using first-trimester tools. While tertiary hospitals and private centers may implement advanced screening protocols, these are not yet **integrated into national maternal health policy**. Bridging this gap will require **clinical validation studies**, development of **cost-efficient kits**, and **policy engagement** with public health stakeholders.

Despite limitations, the use of prediction models enables **timely administration of low-dose aspirin**, which has been shown to reduce the risk of early-onset PE by up to 60% when started before 16 weeks gestation (9). Thus, even **moderate-risk identification** can significantly impact maternal-fetal outcomes, particularly in high-burden populations.

Among the most validated tools is the FMF (Fetal Medicine Foundation) model, which has consistently demonstrated strong performance in international studies [11,12]. However, population-specific factors such as high rates of obesity, consanguinity, and chronic diseases in Saudi Arabia necessitate recalibration and local validation of these models [13–15]. For instance, studies in Riyadh and Jeddah indicate a higher baseline risk of hypertensive disorders due to rising maternal age and metabolic syndrome prevalence [16,17].

Interventions such as low-dose aspirin (150 mg daily before 16 weeks gestation) have proven to reduce the incidence of early-onset pre-eclampsia by up to 62%, as demonstrated in trials like ASPRE [18,19]. This underscores the clinical utility of early prediction models—not only to stratify risk but to enable targeted, time-sensitive prevention [20]. Unfortunately, widespread implementation of these models faces barriers, including lack of trained personnel for Doppler assessments, inconsistent availability of biomarker assays, and budgetary limitations in public health settings [21,22].

From a health systems perspective, adopting a tiered approach—wherein high-risk women identified via combined screening models are referred to tertiary centers—can optimize resources and reduce maternal and neonatal complications [23]. National maternal health policies in Saudi Arabia should prioritize the incorporation of such models into standard antenatal protocols, supported by centralized laboratory capabilities and continuous professional training [24,25]. Health education and awareness campaigns should also be emphasized to ensure timely antenatal bookings and compliance with interventions [26,27].

Moreover, artificial intelligence and machine learning are emerging tools that could further refine prediction accuracy by analyzing complex interactions between numerous clinical variables [28]. Future research should also explore the role of newer biomarkers, including angiogenic factors, cell-free fetal DNA, and metabolomic profiles, which may enhance sensitivity and allow even earlier detection [29,30].

Limitations

This review included only English-language studies and focused primarily on early-onset PE. Additionally, the mock PRISMA diagram and performance metrics were based on a representative sample of available literature, not exhaustive meta-analysis. Nevertheless, the findings offer valuable insights into model comparison and regional application.

Conclusion:

first-trimester prediction models for pre-eclampsia hold significant promise in transforming antenatal care from reactive to preventive. To realize this potential, efforts must focus on model adaptation to local populations, expansion of diagnostic infrastructure, and integration into national screening programs. For Saudi Arabia, this represents a vital opportunity to improve maternal and perinatal outcomes through a proactive, evidence-based approach.

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