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Narrative review

EARLY PREDICTION OF PREECLAMPSIA RISK: THE EVOLUTION OF SCREENING STRATEGIES AND THE ROLE OF PROPHYLACTIC INTERVENTION

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ABSTRACT

Preeclampsia (PE) is a complex multisystem disorder in pregnancy and a leading cause of maternal and perinatal morbidity and mortality worldwide. Early prediction and timely prophylactic intervention can significantly improve pregnancy outcomes. Over the past decades, the strategy for PE screening has undergone a revolution, shifting from a low-efficiency model based on single clinical risk factors to a combined multifactorial screening model in the first trimester. This model, which integrates maternal risk factors, physiological measurements (mean arterial pressure), biochemical markers (PAPP-A, PlGF), and uterine artery Doppler ultrasound, has demonstrated superior efficacy in identifying the high-risk group of pregnant women. This review will examine the evolution of screening methods, analyze the effectiveness of the modern combined model, the role of novel biomarkers, and the importance of applying screening results to clinical practice for prophylaxis with low-dose Aspirin, based on the most up-to-date scientific evidence.

Key words: Preeclampsia, first-trimester screening, combined model, PlGF, PAPP-A, Uterine artery Doppler, Aspirin

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INTRODUCTION

Preeclampsia is a pregnancy syndrome characterized by the onset of hypertension and proteinuria after 20 weeks of gestation, or hypertension accompanied by signs of end-organ damage [1] . The prevalence of PE ranges from 2-8% of all pregnancies and is responsible for more than 70,000 maternal deaths and 500,000 fetal deaths worldwide each year [2,3] . The pathophysiology of PE is complex but is primarily believed to stem from abnormal placentation and development, leading to placental ischemia and the release of anti-angiogenic factors into the maternal circulation, causing systemic endothelial dysfunction [4] . Notably, early-onset PE (before 34 weeks) and PE requiring delivery before 37 weeks are associated with the most severe adverse outcomes for both mother and child. Therefore, the early identification of pregnant women at high risk of developing PE, particularly the severe form, is a primary objective of modern obstetrics. This allows for the implementation of effective prophylactic interventions, most notably the use of low-dose Aspirin.

Methodologically, this manuscript is structured as a narrative review. To identify relevant literature, we conducted a search of major databases including PubMed and Scopus. The search strategy focused on literature published primarily within the last 15 years, using key search terms such as Preeclampsia, First-trimester screening, Aspirin prophylaxis. We prioritized the inclusion of randomized controlled trials (RCTs), meta-analyses, and updated guidelines from major international organizations, while excluding case reports and non-peer-reviewed data.

THE EVOLUTION OF SCREENING STRATEGIES

Traditional Risk Factor-Based Screening Model

For many years, the primary method for PE screening relied on identifying risk factors from the pregnant woman's medical and personal history, guided by major organizations such as the American College of Obstetricians and Gynecologists (ACOG) or the National Institute for Health and Care Excellence (NICE) in the UK [1,5] . "High-risk" factors included a history of PE, multiple pregnancies, chronic kidney disease, diabetes mellitus, chronic hypertension, and autoimmune diseases. "Moderate-risk" factors included nulliparity, obesity, maternal age >35 or 40, a family history of PE, etc. However, this method has a very low sensitivity. Studies have shown that applying these criteria can only detect about 34-41% of cases that will develop PE, with a false-positive rate of

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10%[6]. The main limitation of this model is its inability to quantify individualized risk, thus missing a large proportion of PE cases that occur in women with no apparent risk factors.

The First-Trimester Combined Screening Model

A revolution in PE screening occurred with the introduction of the combined screening model in the first trimester (11 weeks to 13 weeks 6 days), pioneered and developed by the Fetal Medicine Foundation (FMF). This model is based on Bayes' theorem, combining the mother's a priori risk with physiological, biochemical, and ultrasound markers to calculate an individualized risk[7]. This model includes four main components:

- **Maternal factors:** Detailed recording of obstetric history, medical conditions, and demographic characteristics (age, race, weight, height).
- **Mean Arterial Pressure (MAP):** Blood pressure is measured in both arms following a standardized protocol, and the average value is calculated. MAP is a powerful and independent predictor of PE risk[8].
- **Uterine Artery Pulsatility Index (UtA-PI) Doppler Ultrasound:** This measures the resistance to blood flow in the uterine arteries. A high UtA-PI reflects the failure of spiral artery remodeling, a key feature in the pathophysiology of PE[9].
- **Maternal Serum Biochemical Markers:**
- **Pregnancy-associated plasma protein-A (PAPP-A):** A protein produced by the placenta. Low levels of PAPP-A in the first trimester are associated with poor placental function and an increased risk of PE[10].
- **Placental Growth Factor (PlGF):** An angiogenic factor secreted by the placenta, playing a crucial role in the development of the placental vasculature. Low PlGF concentration is one of the earliest and most sensitive markers of abnormal placentation and impending PE risk[11].

The combination of these factors through an FMF algorithm achieves superior screening performance. Large-scale studies have demonstrated that, at a 10% false-positive rate, this model can detect approximately 90% of early-onset PE cases (<34 weeks), 75% of preterm PE cases (<37 weeks), and 45% of term PE cases (≥37 weeks)[7,12].

However, critical appraisal of the evidence suggests that the performance of these models requires rigorous validation across different settings. A systematic evidence review by Henderson et al. for the USPSTF evaluated various prediction models, highlighting studies with good discrimination such as those by Poon et al. and Odibo et al.[13–15]. Nevertheless, external validation studies, including those by Farina et al., Park et al., Skråstad et al., and Oliveira et al., indicate that the performance of first-trimester prediction models can vary significantly. These variations are often attributed to differences in ethnicity and healthcare settings, suggesting that models developed primarily in European populations may require recalibration to ensure accuracy and generalizability in non-European or mixed populations.

THE ROLE OF PROPHYLACTIC INTERVENTION AFTER SCREENING

Several previous meta-analyses suggested that low-dose Aspirin had a modest effect in reducing the risk of PE. However, these studies often did not effectively screen patients and used varying dosages and timings for the initiation of treatment.

The landmark ASPRE trial addressed these shortcomings. It was a double-blind, placebo-controlled, multicenter randomized controlled trial (RCT).

- **Design:** Nearly 27,000 pregnant women were screened using the FMF combined model. 1,776 women at high risk for preterm PE (>1 in 100) were randomly assigned to receive either Aspirin 150 mg/day or a placebo from 11-14 weeks until 36 weeks of gestation.
- **Primary Outcome:** Compared to the placebo group, the Aspirin group had a significantly lower rate of preterm PE: 1.6% vs. 4.3% (Hazard Ratio 0.38; 95% CI, 0.20 to 0.74; p=0.004). This equates to a 62% reduction in risk. The impact was even greater for early-onset PE (<34 weeks), with an 82% reduction[20].

Despite these promising results, it is important to acknowledge the limitations of the ASPRE trial. The strict inclusion criteria and the controlled environment of an RCT may limit the generalizability of the findings to real-world settings, particularly where screening coverage is lower or where compliance with daily aspirin intake may be suboptimal.

The ASPRE study including 47 RCTs (n > 36,000) also confirmed that low-dose Aspirin reduces the risk of PE (RR 0.83, 95% CI 0.77-0.89), with greater efficacy when started before 16 weeks and at a dose of ≥100 mg/day[21]. In this study, results showed that the Aspirin group had a 62% reduction in the rate of preterm PE compared to the placebo group. The effect was even more pronounced for early-onset PE (<34 weeks), with a reduction of up to 82%[22].

The findings from ASPRE have strongly reinforced the recommendations of major health organizations like International Federation of Gynecology and Obstetrics (FIGO) to implement universal first-trimester

Table 1: Prospective cohort studies for external validation of preeclampsia risk prediction models

Author, Year	Location & Period	Study Population	Sample Size (N)	Outcome Prevalence % (No. of cases)	Funding
Farina et al (2011) [16]	Bologna, Italy (Dec 2007–Apr 2010)	Women with singleton pregnancies enrolled at screening visit; delivery in tertiary care center.	554	Late PE: 7.0% (39)	Ricerca Fondamentale Orientata
Park et al (2013) [17]	Sydney, Australia (Apr 2010–Mar 2012)	Women with singleton pregnancies presenting for aneuploidy screening.	3,066	Early PE: 0.4% (12)	NR (Not Reported)
Oliveira et al (2014) [18]	Baltimore, Maryland, USA (2007–2010)	Women with singleton pregnancies.	871–2,962	Early PE: 1.0–1.2% (10–30) Late PE: 4.1–5.0% (78–116)	Diagnostic Technologies Limited
Skråstad et al (2014) [19]	Trondheim, Norway (Sep 2010–Mar 2012)	Nulliparous women.	541	Any PE: 3.9% (21) Preterm PE (<37 wk): 0.9% (5)	Norwegian University of Science and Technology; National Center for Fetal Medicine

screening for all pregnant women using the combined model and to prescribe low-dose Aspirin (150 mg/day) for those at high risk [23] .

CHALLENGES AND FUTURE DIRECTIONS

Although the combined screening model has proven effective, its widespread implementation still faces several challenges:

• **Cost and Availability:** PlGF testing and Doppler ultrasound performed by well-trained operators are not available in all healthcare facilities, especially in resource-limited areas. However, evidence regarding cost-effectiveness supports this approach. For instance, Mallampati et al. demonstrated that first-trimester screening for preeclampsia followed by aspirin prophylaxis is a cost-effective strategy compared to no screening or screening based solely on maternal history, as it significantly reduces the financial burden associated with preterm birth and neonatal intensive care [24] .

• **Standardization of Procedures:** The measurement of MAP and UtA-PI requires strict adherence to standardized protocols to ensure accuracy and consistency.

• **Acceptance and Compliance:** Implementing universal screening and ensuring that high-risk pregnant women adhere to daily Aspirin therapy remains a practical challenge.

In the future, research will focus on optimizing predictive algorithms by integrating more data, applying artificial intelligence (AI), and developing population-specific screening models.

CONCLUSION

The strategy for screening and early prediction of preeclampsia risk has undergone a fundamental paradigm shift, moving from reliance on low-performance clinical risk factors to a multifactorial combined screening model in the first trimester. The FMF model, with its integration of maternal history, MAP, UtA-PI, and PlGF, has become the gold standard in research, allowing for the accurate identification of the majority of severe and early-onset PE cases. This effective screening creates an opportunity for prophylactic intervention with low-dose Aspirin, a measure proven by the ASPRE trial to significantly reduce the incidence of preterm PE.

However, in the conclusion, we must explicitly address that although combined first-trimester models demonstrate good discrimination (high detection rates), they often suffer from poor calibration when applied to external populations without local adjustment. The ”one-size-fits-all” application of the FMF algorithm can lead to variable false-positive rates and

potential mismanagement if not validated for the specific demographic characteristics of the local population.

The widespread adoption of the universal screening - risk-based intervention strategy holds immense potential for improving maternal and child health. However, success depends not merely on adopting the algorithm, but on rigorous local validation, quality control of biophysical and biochemical markers, and a healthcare infrastructure capable of ensuring adherence to prophylactic aspirin. Future research must focus on closing the validation gap and developing cost-effective, simplified models for low-resource settings to ensure that the benefits of early prediction reach all women at risk.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest in conducting this research.

AUTHOR CONTRIBUTIONS

Ho Minh Tuan: Conceptualization, Methodology, Formal analysis, Writing - Original Draft

Nguyen Thi Yen: Software, Validation, Formal analysis, Writing - Review & Editing.

ABBREVIATIONS

ACOG: American College of Obstetricians and Gynecologists

AI: Artificial intelligence

FIGO: International Federation of Gynecology and Obstetrics

FMF: Fetal Medicine Foundation

MAP: Mean Arterial Pressure

NICE: National Institute for Health and Care Excellence

PAPP-A: Pregnancy-associated plasma protein-A

PE: Preeclampsia

PlGF: Placental Growth Factor

RCT: Randomized controlled trial

UtA-PI: Uterine Artery Pulsatility Index

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Bài tổng quan

DỰ ĐOÁN SỚM NGUY CƠ TIỀN SẢN GIẬT: SỰ TIẾN HÓA CỦA CHIẾN LƯỢC SÀNG LỌC VÀ VAI TRÒ CỦA CAN THIỆP DỰ PHÒNG

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TÓM TẮT

Tiền sản giật (TSG) là một rối loạn đa hệ thống phức tạp trong thai kỳ, là một trong những nguyên nhân hàng đầu gây ra bệnh suất và tử suất cho cả mẹ và thai nhi trên toàn cầu. Việc dự đoán sớm và can thiệp dự phòng kịp thời có khả năng cải thiện đáng kể kết cục thai kỳ. Trong những thập kỷ qua, chiến lược sàng lọc TSG đã có một cuộc cách mạng, chuyển đổi từ mô hình dựa trên các yếu tố nguy cơ lâm sàng đơn lẻ với hiệu quả thấp sang mô hình sàng lọc kết hợp đa yếu tố ở tam cá nguyệt thứ nhất. Mô hình này, tích hợp các yếu tố nguy cơ từ tiền sử mẹ, các chỉ số sinh lý (huyết áp động mạch trung bình), các dấu ấn sinh hóa (PAPP-A, PlGF) và siêu âm Doppler động mạch tử cung, đã chứng tỏ hiệu quả vượt trội trong việc xác định nhóm thai phụ nguy cơ cao. Bài tổng quan này sẽ nhìn lại sự phát triển của các phương pháp sàng lọc, phân tích hiệu quả của mô hình kết hợp hiện đại, vai trò của các dấu ấn sinh học mới, và tầm quan trọng của việc áp dụng kết quả sàng lọc vào thực hành lâm sàng để dự phòng bằng Aspirin liều thấp, dựa trên các bằng chứng khoa học cập nhật nhất.

Từ khoá: Tiền sản giật, sàng lọc tam cá nguyệt thứ nhất, mô hình kết hợp, PlGF, PAPP-A, Doppler động mạch tử cung, Aspirin

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