Prediction and Prophylaxis of Preeclampsia: An Expert Review

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ABSTRACT

Preeclampsia remains one of the leading causes of global maternal and perinatal morbidity and mortality. This review aims to provide a comprehensive, up-to-date synthesis of the current evidence on prediction and prophylaxis strategies for preeclampsia. It particularly emphasizes the role of mean arterial pressure and combined screening models. A comprehensive literature review was conducted using PubMed and other relevant databases, focusing on studies published over the last two decades. Predictive approaches were evaluated, including maternal risk factors, biochemical markers, uterine artery Doppler scan, and mean arterial pressure. The review also discusses prophylactic interventions such as low-dose aspirin and calcium supplementation. Results from recent multicenter trials highlight the value of integrating maternal history with mean arterial pressure and biochemical markers. This approach improves screening performance in early pregnancy. This review underscores the importance of early risk stratification and timely initiation of preventive strategies to reduce the burden of preeclampsia. Its original value lies in presenting a concise, evidence-based update for clinical practice by integrating current guidelines with recent trial outcomes.

Keywords: Mean arterial pressure; Preeclampsia; Pregnancy complications; Prophylaxis

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Introduction

Preeclampsia is classically defined as the onset of hypertension and proteinuria in the second half of pregnancy (1). However, the current understanding has evolved beyond this definition. Preeclampsia is now recognized as a systemic and complex syndrome involving multiple organ systems (2). It remains one of the leading causes of maternal and perinatal morbidity and mortality worldwide (1). In developed countries, preeclampsia accounts for approximately 10-15% of maternal deaths and 10-25% of perinatal deaths. In developing countries, it is responsible for 20-25% of maternal deaths (1,3). Globally, an estimated 40,000-70,000 women and 500,000-700,000 fetuses and neonates lose their lives each year due to preeclampsia (4). For every maternal death, 50 to 100 women experience severe maternal morbidity and near-miss mortality (4). Women who develop preeclampsia during pregnancy also have an increased risk of developing long-term cardiometabolic diseases and death (5).

This expert review was prepared through a comprehensive search of the medical literature to provide an updated synthesis on the prediction and prophylaxis of preeclampsia. The databases PubMed, Scopus, and Web of Science were searched for studies published between January 2000 and June 2024. Keyword combinations included: “preeclampsia”, “prediction”, “screening”, “prevention”, “prophylaxis”, “mean arterial pressure”, and “aspirin”. Only English-language human studies were included. Priority was given to original research articles, meta-analyses, systematic reviews, and major international guidelines. Exclusions were made for case reports, non-English publications, conference abstracts, and experimental animal studies. The reference lists of relevant articles were also manually reviewed to identify additional sources.

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From an etiological and epidemiological perspective, the preeclampsia syndrome can be categorized into two distinct phenotypes: early-onset (before 34 weeks of gestation) and late-onset (after 34 weeks of gestation) preeclampsia (Table I) (6). From a maternal cardiovascular perspective, early-onset preeclampsia is characterized by low cardiac output and high peripheral vascular resistance. In contrast, late-onset preeclampsia is associated with high cardiac output and low peripheral vascular resistance (7). Early-onset preeclampsia is typically associated with inadequate trophoblastic invasion, abnormal placentation, and fetal growth restriction (FGR) (6). Placental development and fetal growth are generally normal in cases of late-onset preeclampsia (6).

According to the proposed two-stage mechanism of preeclampsia pathogenesis (8), the initial stage involves impaired placentation. This may result from genetic predisposition, immunologic maladaptation, or a primary trophoblastic defect. Abnormal placentation sets the stage for the second phase. In this phase, abnormal cytokines and antiangiogenic factors are released from the placenta. There is oxidative stress, increased generation of reactive oxygen species, apoptosis, activation of leukocytes and macrophages, stimulation of the complement system, and release of microparticles into the maternal circulation. These processes together lead to widespread maternal endothelial dysfunction. Such dysfunction underlies the clinical manifestations of preeclampsia (Figure 1). This pathophysiological cascade is especially central to the development of early-onset preeclampsia.

The second theory is the maternal cardiac maladaptation hypothesis. Pregnancy leads to a significant increase in both intravascular and extravascular fluid volume (6). This expanded fluid volume imposes a substantial hemodynamic load on the maternal cardiovascular system. The load may result in endothelial dysfunction (9). Pregnancy itself is also a state of physiological inflammatory stress. Under normal circumstances, women adapt to the cardiovascular and inflammatory stress of pregnancy through protective compensatory mechanisms (9,10). When protective mechanisms are inadequate and the necessary adaptation does not occur, preeclampsia can develop (9,10). This form can be referred to as "maternal preeclampsia". Both placental and maternal theories may also contribute to the development of preeclampsia.

Prediction of Preeclampsia: The pathology (disease process) associated with preeclampsia is present from the onset of pregnancy, whereas the clinical picture (observable symptoms and signs) emerges in the later weeks of pregnancy. Therefore, many tests have been proposed to identify the underlying pathology before clinical findings appear; these are referred to as preeclampsia prediction tests.

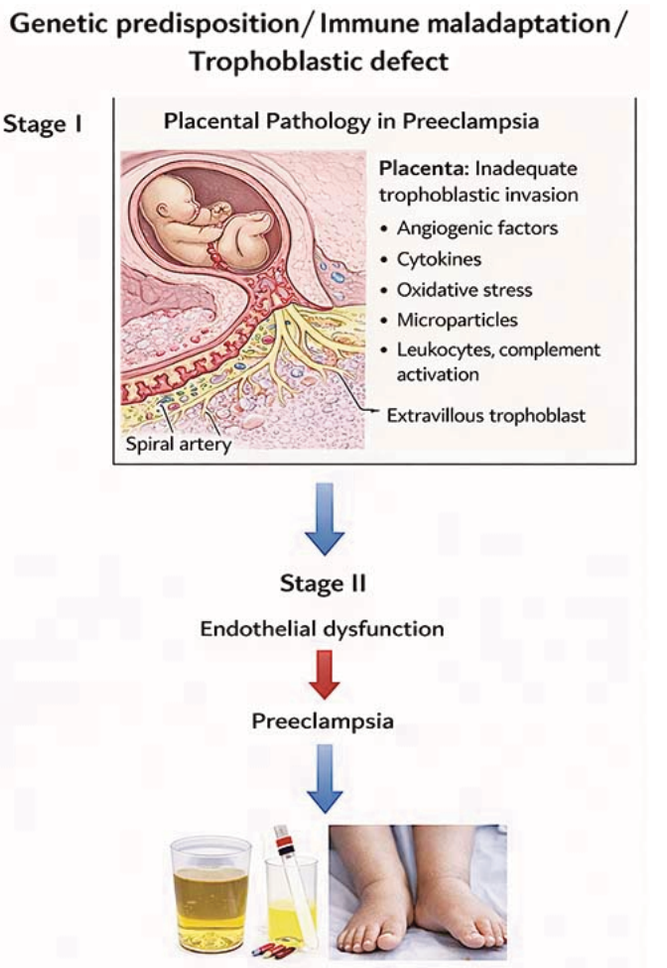

Figure 1: *Two-stage placental theory in the pathogenesis of preeclampsia*

Maternal Factors: The underlying pathology of preeclampsia is present from the onset of pregnancy and increases the risk of developing the disease. Certain maternal characteristics and obstetric history factors also contribute to increased risk. Some guidelines recommend identifying high-risk groups for preeclampsia using maternal factors and history, which can be determined at the first antenatal visit. Based on this, they rec-

Table I: *Characteristics of early- and late-onset preeclampsia*

Early-onset preeclampsia (<34 weeks of gestation)	Late-onset preeclampsia (≥34 weeks of gestation)
Placental preeclampsia	Maternal preeclampsia
Impaired placentation	Exaggerated maternal inflammatory response
Abnormal uterine artery Doppler	Normal uterine artery Doppler
Low maternal cardiac output	High maternal cardiac output
High maternal systemic vascular resistance	Low maternal systemic vascular resistance
High rate of fetal growth restriction	Low rate of fetal growth restriction
High perinatal and maternal mortality and morbidity	Low perinatal and maternal mortality and morbidity

ommend initiating prophylactic low-dose aspirin (LDA) therapy (11-13). Advanced maternal age, nulliparity, multiple pregnancy, ethnicity, maternal weight, history of preeclampsia, family history of preeclampsia, chronic hypertension, diabetes, systemic lupus erythematosus, and antiphospholipid syndrome all increase the risk of preeclampsia (Table II) (14-16). However, the predictive value of maternal risk factors alone is quite limited. According to the National Institute for Health and Care Excellence (NICE), the sensitivity of these risk factors for predicting preterm (<37 weeks of gestation) and term preeclampsia at a 10% false-positive rate is 41% and 34%, respectively (17). Similarly, data from the Fetal Medicine Foundation (FMF) indicate that maternal risk factors alone predict early-onset (<32 weeks of gestation), preterm (<37 weeks of gestation), and term preeclampsia with sensitivities of 53%, 45%, and 34%, respectively, at a 10% false-positive rate (18). These findings confirm that maternal history and risk factors alone are insufficient for accurate prediction of preeclampsia. For effective risk stratification, they should be used with other predictive biomarkers and biophysical parameters (19).

Mean Arterial Pressure: Mean arterial pressure (MAP) is calculated by dividing the sum of systolic (SBP) and two diastolic blood pressures (DBP) by three (MAP=SBP + 2DBP/3). In a meta-analysis by Cnossen et al., it was found that MAP in the first and second trimesters was more effective than diastolic and systolic blood pressure measurements for predicting preeclampsia in low-risk pregnant populations (20). Therefore, MAP is a weak to moderate predictor of preeclampsia (20). The MAP value depends on factors such as the pregnant woman's weight, parity, race, and the presence of diabetes and chronic hypertension. In predicting preeclampsia, it is recommended to use multiples of median (MoM) values, calculated by accounting for these parameters (21). Tayyar et al. showed that MAP and maternal risk factors at 12 weeks of gestation together predicted 66% of preeclampsia cases born before 32 weeks and 45% of cases born after 37 weeks, with a false-positive rate of 10%. MAP and maternal risk factors at 22 weeks of gestation accounted for 72% of preeclampsia cases born before 32 weeks and 43% of cases born after 37 weeks, with a false-positive rate of 10% (22). According to FMF data, the effectiveness of maternal factors + MAP in determining early (<32 weeks of gestation), preterm (<37 weeks of gestation), and term preeclampsia in the first trimester is reported as 71, 47, and 37%, respectively, with a false-positive rate of 10% (18). MAP alone has very low efficacy in predicting preeclampsia. It is often used as a supplementary factor in combined tests to predict (or risk-assess) first-trimester preeclampsia.

Artery Doppler: Doppler ultrasonography is a non-invasive technique used to assess blood flow velocity in vessels. The uterine artery (UtA) demonstrates a characteristic waveform pattern. In non-pregnant women, the waveform typically reflects high vascular resistance, characterized by a rapid systolic upstroke, an early diastolic notch, and low diastolic flow. Physiological changes in the spiral arteries during pregnancy decrease vascular resistance, increase diastolic flow, and eliminate the notch. (Figure 2) Consequently, the UtA Doppler waveform shows high diastolic flow throughout diastole, indicating low vascular resistance. Diastolic flow increases with advancing gestational age. There is a close relationship between UtA Doppler findings and histological changes in the

Table II: *Risk factors increasing the risk of developing preeclampsia*

Risk factor	RR (95% CI)
High risk	
History of preeclampsia	7.19 (5.85-8.83)
Antiphospholipid syndrome	9.72 (4.34-21.75)
Systemic lupus erythematosus	7.8 (4.8-12.9)
Chronic hypertension	5.1 (4.0-6.5)
Chronic kidney disease	10.36 (6.28-17.09)
Pregestational diabetes	3.7 (3.1-4.3)
BMI >35	4.29 (3.52-5.49)
Moderate risk	
Family history of preeclampsia	2.90 (1.70-4.93)
Nulliparity	2.91 (1.28-6.61)
Multiple pregnancy	2.93 (2.04-4.21)
Maternal age <17	2.98 (0.39-22.76)
Maternal age >40	1.68 (1.23-2.29)
History of stillbirth	2.4 (1.7-3.4)
History of placental abruption	2.0 (1.4-2.7)
Short sperm exposure	3.1 (1.59-6.73)
Oocyte donation	3.31 (1.61-6.80)
Assisted reproductive technologies	1.8 (1.6-2.1)
Abnormal maternal serum markers (AFP, hCG, inhibin A >2 MoM)	2.39 (1.75-3.26)
Two abnormal markers	3.65 (2.79-4.78)

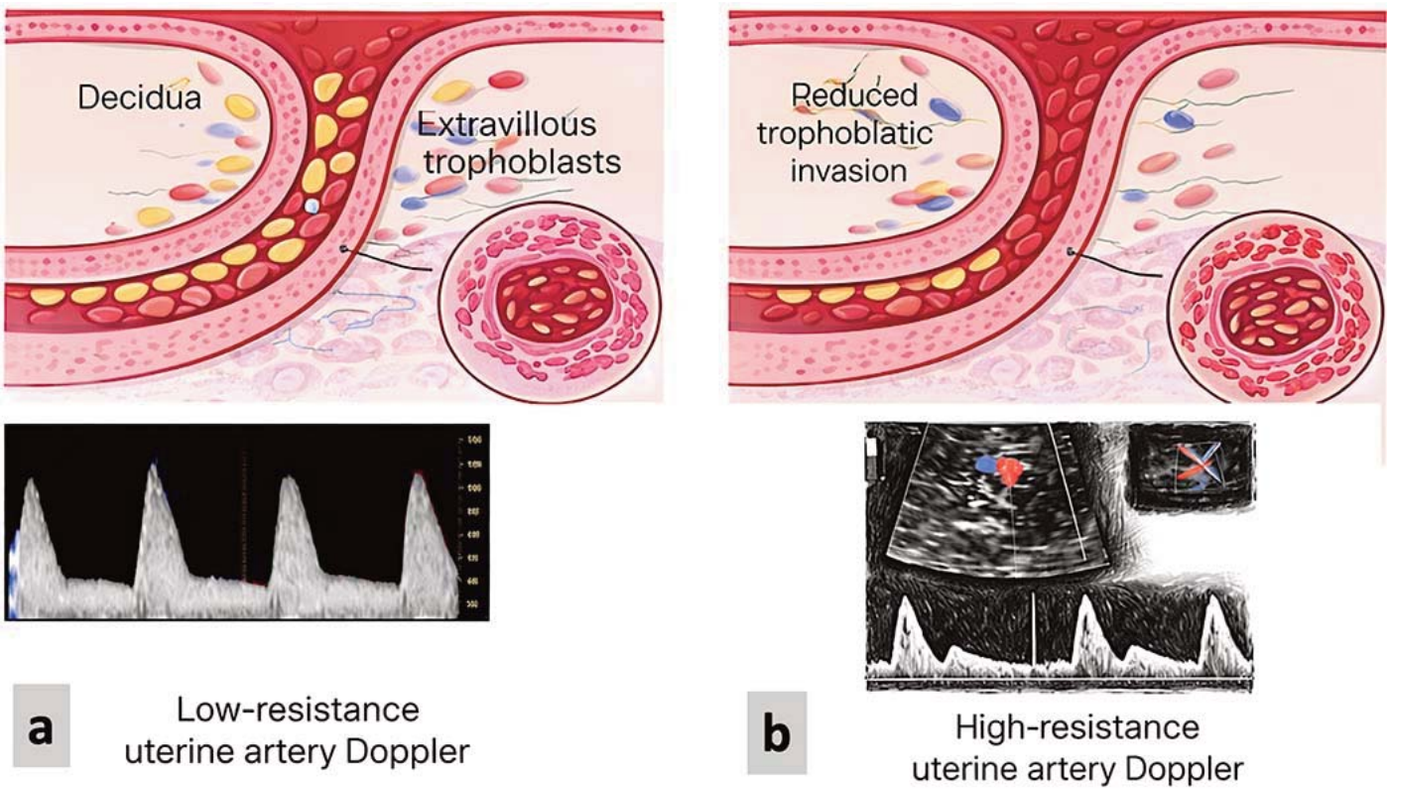

Figure 2: a. *In normotensive pregnancies, adequate trophoblastic invasion in the spiral arteries, decidual biopsy, vascular imaging, and Doppler findings.* ***b.*** *In preeclampsia, inadequate trophoblastic invasion in the spiral arteries, decidual biopsy, vascular imaging, and Doppler findings.*

spiral arteries. A Doppler examination can assess the uteroplacental circulation and pregnancy-specific changes in the spiral arteries (23). In cases of inadequate trophoblastic invasion, particularly in placentation problems, increased resistance is observed on UtA Doppler examination (24). The assessment is performed by identifying the uterine arteries bilaterally on color flow, either transabdominally or transvaginally (in the first trimester). The right and left uterine arteries are identified using color Doppler flow mapping on either side of the uterus. The sampling chamber should be at least 2 mm wide, encompass the entire vessel, and have an angle of <30º. The vessel's peak systolic velocity (PSV) should be >50-60 cm/s (indicating the absence of an arcuate artery) (25). Because uterine arterial resistance is typically lower on the placental side, pulsatility index (PI) values may differ between the right and left uterine arteries (24). Therefore, in UtA Doppler prediction, the average of the right and left UtA PI values (UtAright PI+UtAleft PI/2) or the lower PI value is used (24). Gómez et al. found bilateral notching rates in UtA to be 46.3% between 11 and 14 weeks, 16.5% between 15 and 24 weeks, and 5% between 25 and 41 weeks of gestation (26). The 95th percentile of the mean uterine artery pulsatility index (PI) is roughly 2.5 and 1.5 at 12 and 22 weeks of gestation (24). FMF determined that the UtA PI value was associated with ethnicity, parity, BMI, smoking status, and history of preeclampsia (27). FMF therefore recommends using UtA PI MoM values specific to gestational weeks, taking into account the parameters mentioned above.

In their meta-analysis of 18 studies (15 of which were low-risk pregnant women) published up to 2013, Velauthar et al. reported that the sensitivity, specificity and positive (+LR) and negative likelihood ratio (–LR) of the first-trimester UtA Doppler analysis in detecting early-onset preeclampsia were 47.8%, 92.1%, 6.1%, and 0.57%, respectively, and the sensitivity, specificity, +LR, and –LR in detecting late-onset preeclampsia were 21.5%, 90.3%, 2.2%, and 0.87%, respectively (28). According to FMF data, the sensitivities of maternal factors + average UtA Doppler in the first-trimester for detecting early (<32 weeks of gestation), preterm (<37 weeks of gestation), and term preeclampsia are 82%, 61%, and 39%, respectively, with a false-positive rate of 10% (18).

Detecting increased resistance in the second-trimester Doppler examination (abnormal Doppler findings) increases the risk of developing preeclampsia approximately 6-7 times, while normal Doppler results reduce it by half (24).

An important finding from the studies is that uterine artery Doppler is much more effective at predicting early-onset preeclampsia, the main clinical problem that occurs in early pregnancy (24). Analysis of 90.000 pregnancies, Conde-Agudelo et al. found that the sensitivity and specificity of sec-

ond-trimester uterine artery Doppler for preeclampsia ranged from 34-76% and 83-93%, respectively (29). Among UtA Doppler findings, the presence of bilateral notching and aPI > 95. The percentile was found to be the most predictive parameter (+LR = 5.1) (29).

A Doppler screening test is considered a moderate-to-good predictor of early-onset preeclampsia and can be easily integrated into routine ultrasonography at 11-14 and 22-24 weeks of gestation without additional cost. Second-trimester Doppler appears to be more effective than first-trimester screening; however, since prophylactic interventions (e.g., aspirin therapy)must begin before 16 weeks, early Doppler screening gains additional importance in clinical practice.

Angiogenic Biomarkers: Preeclampsia is characterized by a shift in the balance between angiogenic and anti-angiogenic factors toward an anti-angiogenic state (30). In women who develop preeclampsia, there is a decrease in angiogenic proteins, such as placental growth factor (PlGF) and vascular endothelial growth factor (VEGF), along with elevated levels of anti-angiogenic markers, such as soluble FLT-1 (sFLT-1) and soluble endoglin (sEng) (30). Before the clinical signs of preeclampsia appear, maternal PIGF and VEGF levels decrease, whereas maternal sFLT-1 and sEng levels increase (31).In their meta-analysis, Kleinrouweler et al. found that maternal serum PIGF levels were reduced in 27 studies and VEGF levels were reduced in 3 studies in pregnant women who developed preeclampsia compared to those who did not, while sFLT-1 and sEng levels were increased in 10 studies. They also found that, at a 5% false-positive rate, the sensitivities of PlGF, sFLT-1, and sEng in predicting preeclampsia were 32%, 26%, and 18%, respectively (32). Akolekar et al. determined that the sensitivity of PIGF measured between 11 and 14 weeks of gestation for predicting early-onset and late-onset preeclampsia was 55% and 33%, respectively, with a false-positive rate of 10% (33).et al. reported that the combined assessment of PIGF and maternal factors at 12 weeks of gestation had a false-positive rate of 10%, with sensitivities of 79% and 40%, respectively, in predicting early- and late-onset preeclampsia (34). Although angiogenic markers alone are insufficient, they are valuable components of multiparametric screening models (31).

Placenta-Derived Proteins: Early-onset preeclampsia results from a placental defect. Placentation defects cause changes in the release and levels of placenta-derived proteins in maternal blood. Human chorionic gonadotropin (β-hCG), pregnancy-associated plasma protein-A (PAPP-A), alpha-fetoprotein (AFP), and inhibin-A are placental-derived proteins used in first- and second-trimester aneuploidy screening. Conde-Agudelo et al., in a meta-analysis of 18 studies involving 105.639 pregnant women, determined the sensitivity, specificity, positive, and negative likelihood ratios for hCG levels above 2.0-2.5 MoM in predicting preeclampsia to be 21%, 91%, 2.4, and 0.9, respectively (29). For AFP, in a meta-analysis of 11 studies including 115.419 pregnant women, the sensitivity, specificity, and positive and negative likelihood ratios for predicting preeclampsia at values above 2.0 MoM were reported as 13%, 96%, 3.3, and 0.9, respectively (35). In another study on PAPP-A, a meta-analysis of 7 studies including 99.449 pregnant women showed that the sensitivity, specificity, and positive and negative likelihood ratios for predicting preeclampsia with a value below 0.4 MoM were 10%, 95%, 2.0, and 0.9, respectively (35). Wright et Wright et al. demonstrated that the combination of maternal factors and PAPP-A in 94,989 pregnant women at 11-13 weeks of gestation predicted early-onset preeclampsia with 51% sensitivity and a 10% false-positive rate (36).alysis of 7 studies including 45.274 pregnant women on inhibin-A found that sensitivity, specificity, and positive and negative likelihood ratios for predicting preeclampsia at values above 2.0 MoM were 21%, 95%, 4.2, and 0.8, respectively (35).

In conclusion, placental proteins alone are not sufficiently effective in predicting preeclampsia. They are used in multiparametric combined tests. However, low PAPP-A, high hCG, AFP, and inhibin levels during biochemical aneuploidy screening should also be evaluated for placental problems.

Other Tests: The amount of cell-free fetal DNA (cffDNA), derived from apoptotic trophoblasts, in maternal blood has been shown to be significantly increased in preeclamptic pregnant women (37). Based on these observations, studies on the effectiveness of cffDNA in predicting preeclampsia have begun to be reported. In their systematic review of 13 studies, Martin et al. showed that, in 11 of the 13 studies, cffDNA levels were significantly higher in patients who developed preeclampsia during follow-up than in those who did not, and this increase was particularly pronounced in patients with early-onset preeclampsia (37). Therefore, cffDNA in maternal blood is considered a potential marker for predicting preeclampsia. In recent years, a group of proteins, metabolites, and mRNAs has been used to uncover the pathophysiological mechanisms of certain diseases. The effectiveness of these metabolites in predicting preeclampsia in the first trimester is also being evaluated. Although an effective screening profile has not yet been established, studies are ongoing (24).

Multiparametric Combined Tests: None of the tests predicting preeclampsia is sufficiently effective on its own. Therefore, the aim was to increase the effectiveness of preeclampsia prediction by combining multiple tests. The general approach is to combine biophysical tests, such as UtA Doppler, with biochemical parameters such as placental proteins and angiogenic factors. Overall, the predictive effectiveness of combined tests is low to moderate for all cases of preeclampsia, but moderate to high for early-onset preeclampsia (35).

The modeling recommended by FMF in the first trimester between 11 and 14 weeks of gestation includes maternal char-

acteristics, MBP, UtA Doppler, and PIGF, and is referred to as the "triple test" (38). The predictive effectiveness of the markers used in the FMF model for preeclampsia is presented in Table III (38). The sensitivities of the triple test in predicting early- and late-onset preeclampsia were reported as 91.2% and 76.4%, with a false-positive rate of 10% (38). Based on FMF data, the International Federation of Gynecology and Obstetrics (FIGO) recommends routine first-trimester screening for preeclampsia using this model (39).

Prediction and prevention of preeclampsia remain some of the most intensively studied subjects in obstetrics. Given the significant maternal and perinatal morbidity and mortality associated with preeclampsia, its prevention offers a critical opportunity to reduce maternal and neonatal deaths.

Lifestyle and Diet: Before pregnancy, appropriate treatment and management of chronic conditions, such as chronic hypertension, diabetes, and obesity, which increase the likelihood of developing preeclampsia, are essential (40). The risk of preeclampsia increases with increasing BMI (41). Reducing weight to appropriate levels before pregnancy is important for reducing the risk of preeclampsia (40). A healthy lifestyle, good nutrition, and appropriate physical activity are important factors for positive pregnancy outcomes (40). No data demonstrates that salt restriction and bed rest during pregnancy reduce the risk of preeclampsia (40). A meta-analysis found that aerobic exercise performed 2-7 times a week for 30-60 minutes reduced the risk of hypertension in pregnancy overall (5.9% vs. 8.5%; RR 0.70, 95% CI 0.53-0.83; 7 studies in 2517 pregnant women), but this reduction was not significant for gestational hypertension. It was reported that there was no significant difference in terms of preeclampsia (42). A Cochrane review found that 1.5-2 grams of calcium supplementation per day reduced the risk of preeclampsia in pregnant women with low calcium intake (43). The International Society for the Study of Hypertension in Pregnancy (ISSHP) (44), ACOG (11), and FIGO (45) recommend 1.5-2 grams of calcium supplementation per day in high-risk pregnant women, if their calcium intake is inadequate (<600 mg/day).

Low-Dose Aspirin: Aspirin (acetylsalicylic acid) is a member of the nonsteroidal anti-inflammatory drug family and has analgesic, antipyretic, and anti-inflammatory effects (46). Low-dose aspirin (LDA) includes aspirin doses below 300 mg. At doses below 300 mg, aspirin selectively and irreversibly inactivates the cyclooxygenase (COX)-1 enzyme, inhibiting the production of prostaglandins and thromboxanes and preventing platelet aggregation (47). LDA is effective in preeclampsia prophylaxis by positively influencing placentation, preventing platelet aggregation, and exerting anti-inflammatory and endothelial-stabilizing effects (46). LDA is considered to play a positive role in placental formation by increasing the release of PIGF and other cytokines from cytotrophoblasts and decreasing apoptosis and early trophoblast differentiation (46,48).

The use of 75-150 mg/day LDA for preeclampsia prophylaxis has been studied for many years. The Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) study is the largest randomized controlled trial conducted at 13 centers in 6 countries (49). In the study, 1.776 of 26.941 pregnant women identified as high risk (risk >1/100) by the FMF preeclampsia screening test at 11-14 weeks of gestation were given 150 mg of aspirin daily at bedtime, and the other half received a placebo. This continued until 36 weeks of gestation. The rate of preterm preeclampsia (<37 weeks' gestation) was reduced by 62% (1.6% vs. 4.3%; OR 0.38, 95% CI 0.20–0.74) with aspirin prophylaxis (49). Aspirin prophylaxis did not cause a significant change in the rate of term preeclampsia (49). Park et al. reported that 80 mg/day LDA prophylaxis reduced the risk of developing early-onset preeclampsia by 90% in the high-risk group identified by maternal characteristics, MAP, UtA Doppler, and PAPP-A at 11-13 weeks' gestation (50). Roberge et al. in their meta-analysis on low-dose aspirin prophylaxis in pregnancies at high risk for developing preeclampsia, demonstrated that when prophylaxis was initiated before 16 weeks of gestation, the risk of preeclampsia was reduced by 50% (RR 0.47, 95% CI 0.36–0.62), whereas initiation after 16 weeks of gestation reduced the risk by 20% (RR 0.78, 95% CI 0.61–0.99) (51). Furthermore, initiation of LDA prophylaxis before 16 weeks of gestation was found to reduce the risk of preterm preeclampsia more significantly than term preeclampsia (RR 0.11, 95% CI 0.04–0.33 vs RR 0.98, 95% CI 0.42–2.33), and severe preeclampsia more significantly than mild preeclampsia (RR 0.22, 95% CI 0.08–0.57 vs RR 0.81, 95% CI 0.33–1.96) (52,53). her meta-analysis by Roberge et al., it was determined that LDA prophylaxis started before 16 weeks of gestation in a dose-dependent manner, significantly reduced the risks of preeclampsia (RR 0.57, 95% CI 0.43–0.75), severe preeclampsia (RR 0.47, 95% CI 0.26–0.83) and fetal growth restriction, while LDA prophy-

Table III: *Sensitivities of markers used in the FMF model for preeclampsia prediction (at 10% false positive rate)*

Markers	<32 weeks (%)	<37 weeks (%)	≥37 weeks (%)
Maternal characteristics (MC)	53	45	34
MC + MAP	61	51	38
MC + UtAPI	70	58	35
MC + MAP + UtAPI	83	68	41
MC + MAP + UtAPI + PlGF (Triple test)	90	75	41

MC: maternal characteristics; MAP: mean arterial pressure; UtAPI: uterine artery pulsatility index; PlGF: placental growth factor

laxis started after 16 weeks of gestation slightly reduced the risk of preeclampsia (RR 0.81, 95% CI 0.66–0.99) and did not cause a significant change in the risks of severe preeclampsia and fetal growth restriction (54).

In conclusion, in pregnant women at high risk for preeclampsia, LDA prophylaxis at 100-150 mg/day, initiated before 16 weeks of gestation, significantly reduces the risk of early-onset preeclampsia. The effectiveness of LDA prophylaxis in preventing preeclampsia is presented in Table IV.

In pregnancies at high risk of developing preeclampsia, ACOG (55) recommends 81 mg/day starting between 12 and 28 weeks of gestation (preferably <16 weeks), NICE (12) recommends 75-150 mg/day starting at 12 weeks of gestation, and FIGO (39) recommends 100-150 mg/day starting between 11 and 13 weeks of gestation. Many guidelines recommend 75-162 mg/day of LDA prophylaxis starting before 16 weeks of gestation and continuing until 36 weeks of gestation in high-risk pregnancies (56).

Aspirin use in pregnant women causes a slightly increased risk of postpartum hemorrhage (57). Empirical aspirin prophylaxis is not recommended for low-risk pregnant women (46). Guideline recommendations for the use of LDA for preeclampsia prophylaxis, taking into account maternal risk factors, are presented in Table V.

Conclusion and Recommendations

• Since early-onset and late-onset preeclampsia arise through different mechanisms, the effectiveness of predictive tests also varies between them.

• Preeclampsia prediction tests are more effective in detecting early-onset (placental-origin) preeclampsia, whereas their effectiveness is lower for late-onset or term preeclampsia.

• No single test is sufficiently accurate for predicting preeclampsia. A multiparametric approach provides better predictive value. The method is the triple test, which combines maternal characteristics, mean arterial pressure, uterine artery Doppler, and PlGF.

• The triple test is highly effective in detecting preeclampsia, particularly before 32 weeks of gestation, with an accuracy of 90%, but its positive predictive value is very low, ranging from 3% to 10%. In other words, among cases where tests indicate preeclampsia may develop, only a small proportion actually develop preeclampsia. Arterial Doppler is a valuable method for assessing placental insufficiency and is especially effective in detecting placenta-mediated pathologies.

• The effectiveness of uterine artery Doppler in the first trimester at 12 weeks of gestation is lower than that in the second trimester at 22-24 weeks of gestation. Notching should not be considered in the first-trimester uterine artery Doppler assessment; the average uterine artery Doppler PI value should be considered. In second-trimester Doppler assessment, bilateral notches and elevated mean PI are the most effective parameters. In the second trimester, unilateral elevation of uterine artery Doppler resistance on the non-placental side is a normal finding. mended prophylactic treatment for preeclampsia is slow-dose aspirin (LDA) at 75–150 mg/day.0 mg/day.

• Especially when initiated before 16 weeks at a dose of ≥100 mg (e.g., 100 or 150 mg/day), LDA can reduce the risk of early-onset preeclampsia by up to 70%. We recommend initiating LDA prophylaxis in women with high-risk features(e.g., previous preeclampsia, chronic kidney disease) based on maternal history.

• To enable early initiation of aspirin (by 12 weeks),early preeclampsia screening is recommended at the same time.

• The triple test in the first trimester (12 weeks)is the most effective screening approach. However, in settings with lim-

Table IV: *The effectiveness of low-dose aspirin prophylaxis in preventing preeclampsia*

• **Preterm PE (<37 GW)** **RR 0.62, 95% CI, 0.45-0.87**	• **Term PE** **RR 0.92, 95% CI, 0.70-1.21**
• **≤16 GW and ≥ 100 mg** **RR 0.33, 95% CI 0.19-0.57**	• >16 GW and ≥ 100 mg RR 0.88, 95% CI 0.54-1.43
• ≤16 GW and < 100 mg RR 0.59, 95% CI 0.29-1.19	• >16 GW and < 100 mg RR 1.00, 95% CI 0.80-1.25

Table V: *Guideline recommendations for low-dose aspirin prophylaxis*

Criteria	WHO, 2011	ACOG, 2018	NICE, 2019
Risk Criteria	≥1 risk factor	≥1 high risk factor or ≥2 moderate risk factors	≥1 high risk factor or ≥2 moderate risk factors
Recommended dose	75 mg/day	81 mg/day	75–150 mg/day
Duration	<20 weeks gestational age (preferably by 12 weeks) until delivery	12-28 weeks gestational age (preferably by 12 weeks) until delivery	From 12 weeks gestational age until delivery

ited resources, screening can be conducted using only maternal characteristics + MAP.

• First-trimFirst-trimester UtA Doppler screenings should be widely implemented. If bilateral UTAs are identified,LDA prophylaxis may be started, though its positive predictive value is low. A follow-up Doppler at the second trimester can be used to re-evaluate and discontinue aspirin in those with normal findings.ntIf placental protein abnormalities such as low PAPP-A, high hCG, and high AFP are present, an UtA Doppler scan should be performed; if abnormal results are obtained, LDA prophylaxis may be initiated.d be noted that initiating LDA prophylaxis in cases where UtA Doppler pathology is detected during the second trimester (18-22 weeks of gestation) is likely to be ineffective. In such cases, the decision to initiate prophylaxis is left to clinical judgment as a matter of personal preference.

Declarations

Ethical Considerations: This article is an expert opinion based on a review of previously published literature and does not include any individual patient data. Therefore, ethics committee approval and informed consent were not required. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Competing interests: The authors declare that they have no competing interests.

Authors' contributions: RM, OO, and IM raised the presented idea. RM, AE, OO, and IM designed the study. RM conducted the analyses. RM and OO developed the first draft of the manuscript. All authors contributed to the writing of the paper, and have read and approved the final manuscript.

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