First trimester preeclampsia screening and prediction

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Preeclampsia is a major cause of maternal and perinatal morbidity and mortality. Early-onset disease requiring preterm delivery is associated with a higher risk of complications in both mothers and babies. Evidence suggests that the administration of low-dose aspirin initiated before 16 weeks' gestation significantly reduces the rate of preterm preeclampsia. Therefore, it is important to identify pregnant women at risk of developing preeclampsia during the first trimester of pregnancy, thus allowing timely therapeutic intervention. Several professional organizations such as the American College of Obstetricians and Gynecologists (ACOG) and National Institute for Health and Care Excellence (NICE) have proposed screening for preeclampsia based on maternal risk factors. The approach recommended by ACOG and NICE essentially treats each risk factor as a separate screening test with additive detection rate and screen-positive rate. Evidence has shown that preeclampsia screening based on the NICE and ACOG approach has suboptimal performance, as the NICE recommendation only achieves detection rates of 41% and 34%, with a 10% false-positive rate, for preterm and term preeclampsia, respectively. Screening based on the 2013 ACOG recommendation can only achieve detection rates of 5% and 2% for preterm and term preeclampsia, respectively, with a 0.2% false-positive rate. Various first trimester prediction models have been developed. Most of them have not undergone or failed external validation. However, it is worthy of note that the Fetal Medicine Foundation (FMF) first trimester prediction model (namely the triple test), which consists of a combination of maternal factors and measurements of mean arterial pressure, uterine artery pulsatility index, and serum placental growth factor, has undergone successful internal and external validation. The FMF triple test has detection rates of 90% and 75% for the prediction of early and preterm preeclampsia, respectively, with a 10% false-positive rate. Such performance of screening is superior to that of the traditional method by maternal risk factors alone. The use of the FMF prediction model, followed by the administration of low-dose aspirin, has been shown to reduce the rate of preterm preeclampsia by 62%. The number needed to screen to prevent 1 case of preterm preeclampsia by the FMF triple test is 250. The key to maintaining optimal screening performance is to establish standardized protocols for biomarker measurements and regular biomarker quality assessment, as inaccurate measurement can affect screening performance. Tools frequently used to assess quality control include the cumulative sum and target plot. Cumulative sum is a sensitive method to detect small shifts over time, and point of shift can be easily identified. Target plot is a tool to evaluate deviation from the expected multiple of median and the expected median of standard deviation. Target plot is easy to interpret and visualize. However, it is insensitive to detecting small deviations. Adherence to well-defined protocols for the measurements of mean arterial pressure, uterine artery pulsatility index, and placental growth factor is required. This article summarizes the existing literature on the different methods, recommendations by professional organizations, quality assessment of different components of risk assessment, and clinical implementation of the first trimester screening for preeclampsia.

Key words: abruption, algorithm, ASPRE, adverse pregnancy outcome, aspirin, blood pressure, competing risk, CUSUM, fetal growth restriction, first trimester, FMF, Fetal Medicine Foundation, FGR, hypertension, IUGR, mean arterial pressure, morbidity, mortality, NNS, NNT, number needed to screen, number needed to treat, perinatal, placental insufficiency, PLGF, placental growth factor, prediction, preeclampsia, pregnancy, pregnancy complications, prematurity, preterm, prevention, prophylaxis, pulsatility index, quality assessment, quality assurance, resistant index, risk factor, safety, stillbirth, UtA-PI, target plot, uterine artery, validation

Preeclampsia is a multisystem disorder of pregnancy characterized by new onset of hypertension with significant proteinuria after 20 weeks' gestation.[1–7] This disorder affects 2% to 8% of pregnant women and is one of the leading causes of maternal and perinatal morbidity and mortality. Worldwide, 76,000 women and 500,000 babies die yearly from this disorder.[4,8,9] Preeclampsia causes immediate maternal adverse effects, including impairment of hepatorenal and coagulation systems.[10] If left untreated or in severe form, maternal pulmonary edema, eclampsia, brain injury, and death can occur.[11–13] Inadequate uteroplacental perfusion leads to fetal growth restriction and/or placental abruption, resulting in indicated preterm birth or stillbirth. Moreover, preeclampsia is associated with an increased risk of long-term cardiovascular and chronic diseases in both the mothers and their children from the affected pregnancy.[14] Specifically, women with preeclampsia are at elevated risk for chronic hypertension, future cardiovascular disease, stroke, metabolic syndromes, cognitive impairment, and chronic end-stage renal disease later in life.[15–22] Infants born to mothers affected by preeclampsia are also at risk of having medium- and long-term

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complications, such as neurodevelopmental impairment, insulin resistance, diabetes mellitus, coronary heart disease, and hypertension.[23–26]

The International Society for the Study of Hypertension in Pregnancy (ISSHP) has proposed to subclassify preeclampsia according to gestational age at delivery because evidence suggests that early- and late-onset disease have different pathophysiologic and etiologic pathways.[27] Early-onset preeclampsia (with delivery at <34 weeks' gestation) and preterm preeclampsia (with delivery at <37 weeks' gestation) are associated with a higher risk of adverse maternal and perinatal outcomes than late-onset (delivery at ≥34 weeks' gestation) and term preeclampsia (delivery ≥37 weeks' gestation).[28,29]

A long-held belief of the underlying pathophysiology of preeclampsia is that it is a 2-stage process in which genetic factors (fms-related receptor tyrosine kinase 1 single-nucleotide polymorphism and trisomy 13), maternal factors (chronic hypertension, diabetes, and antiphospholipid antibodies), and immunologic factors (decidual natural killer cells and regulatory T-cell imbalance) may cause inadequate trophoblast invasion that leads to shallow placentation (also known as stage I).[1,30–35] Reduced placental perfusion leads to the second stage (also known as stage II), which is characterized by oxidative stress that stimulates the release of inflammatory cytokines, angiotensin 1 autoantibodies, antiangiogenic factors, and microparticles, causing widespread endothelial dysfunction resulting in the clinical manifestations of preeclampsia.[36,37]

Stage I usually occurs in the first trimester of pregnancy and is considered the subclinical phase. This stage creates a window of opportunity for the prediction and prevention of preeclampsia. Low-dose aspirin at 150 mg daily administered to high-risk women from <16 weeks until 36 weeks' gestation has been shown to reduce the rate of preterm preeclampsia.[38–46] A key question that has arisen from recent research relates to what should be the appropriate screening approach to identifying women at risk of preeclampsia. Thus far, there are a myriad of prediction models for preeclampsia. In this article, we will summarize and critically appraise some of the models that are worthy of consideration.

Maternal History

A large systematic review and meta-analysis of 92 studies, including 25,356,688 pregnancies, have been conducted to evaluate the association among clinical risk factors identified before 16 weeks' gestation and the risk of preeclampsia.[47] The most remarkable risk factors for preeclampsia are history of preeclampsia (relative risk [RR], 8.4; 95% confidence interval [CI], 7.1–9.9) and chronic hypertension (RR, 5.1; 95% CI, 4.0–6.5). Other clinical risk factors for preeclampsia include nulliparity (RR, 2.1; 95% CI, 1.9–2.4), maternal age of >35 years (RR, 1.2; 95% CI, 1.1–1.3), chronic kidney disease (RR, 1.8; 95% CI, 1.5–2.1), conception by assisted reproductive technology (RR, 1.8; 95% CI: 1.6–2.1), prepregnancy body mass index (BMI) of >30 kg/m^2 (RR, 2.8; 95% CI 2.6–3.1), and pregestational diabetes mellitus (RR, 3.7; 95% CI, 3.1–4.3).[47]

Several professional organizations, such as the National Institute for Health and Care Excellence (NICE) and the American College of Obstetricians and Gynecologists (ACOG), have proposed screening for preeclampsia based on maternal risk factors (Table 1). According to the NICE recommendation, the presence of any 1 of the following high-risk factors (hypertensive disease in previous pregnancy, chronic hypertension, chronic renal disease, diabetes mellitus, or autoimmune disease) or more than 1 moderate risk factor (nulliparity, aged ≥40 years, BMI of ≥35 kg/m^2, family history of preeclampsia, or interpregnancy interval of >10 years) is considered high risk for preeclampsia. Women at high risk are advised to take 75 to 150 mg of aspirin daily from 12 weeks' gestation until the birth of the baby.[49,54]

The ACOG issued the Hypertension in Pregnancy Task Force Report (2013) recommending daily low-dose aspirin from the late first trimester for women with a history of early-onset preeclampsia and preterm delivery at <34 weeks' gestation or for women with more than 1 previous pregnancy complicated by preeclampsia.[55] The United States Preventive Services Task Force (USPSTF) published a similar guideline, although the list of indications for low-dose aspirin use was more expansive.[56] An updated version of the USPSTF guideline has now been endorsed by the ACOG,[48] the Society for Maternal-Fetal Medicine,[52] and the American Diabetes Association.[57] Low-dose aspirin prophylaxis at 81 mg/d from 12 and 28 weeks' gestation (optimally at <16 weeks' gestation), continued daily until delivery, should be considered for women with 1 or more high-risk factors (history of preeclampsia, renal disease, autoimmune disease, type 1 or type 2 diabetes, and chronic hypertension) or more than 1 of several moderate risk factors (first pregnancy, age of ≥35 years, BMI >30 kg/m^2, family history of preeclampsia, sociodemographic characteristics, and personal history factors). The approach recommended by NICE and ACOG essentially treats each risk factor as a separate screening test, with additive detection rate and screen-positive rate. Evidence supporting these recommendations is mainly based on retrospective epidemiologic studies of associations between individual risk factors and the development of preeclampsia. In addition, most studies have not differentiated the risk factors according to the severity of preeclampsia.

Recent evidence has shown that preeclampsia screening based on the NICE and ACOG approach has suboptimal performance, as the NICE recommendation only achieves detection rates of 41% (95% CI, 62–85) and 34% (95% CI, 27–41), with a 10% false-positive rate (FPR) for preterm and term preeclampsia, respectively.[58] Screening based on the 2013 ACOG recommendation[59] can only achieve detection rates of 5% (95% CI, 2–14) and 2% (95% CI, 0.3–5) for preterm and term preeclampsia, respectively, with a 0.2% FPR.[58] The expanded list of clinical risk factors included in the USPSTF

TABLE 1
Maternal risk factors for preeclampsia according to professional organizations

ACOG 2018[48] (United States of America)	NICE 2019[49] (United Kingdom)	SOGC 2014[50] (Canada)	SOMANZ 2014[51] (Australia)	ISSHP 2018[52]	WHO 2011[53]
High-risk factors	High-risk factors	High-risk factors	Risk factors	High-risk factors	Risk factors
☐ Previous pregnancy with PE ☐ Chronic hypertension ☐ Systemic lupus erythematosus ☐ Type 1 or type 2 diabetes mellitus ☐ Renal disease ☐ Multifetal gestation ☐ Antiphospholipid syndrome	• Previous pregnancy with PE • Chronic hypertension • Autoimmune disease • Type 1 or type 2 diabetes mellitus • Chronic kidney disease • Antiphospholipid syndrome	• Previous pregnancy with PE • Antiphospholipid syndrome • Preexisting diabetes mellitus • Renal disease or proteinuria • Chronic hypertension or booking diastolic BP, ≥90 mm Hg	• Nulliparity • Multiple pregnancy • Previous history of PE • Family history of PE • Overweight • Obesity (BMI, ≥30 kg/m^2) • Age, ≥40 y • Systolic BP, >130 mm Hg or diastolic BP, >80 mm Hg before 20 wk • Antiphospholipid syndrome • Preexisting diabetes mellitus • Underlying renal disease • Chronic autoimmune disease • Interpregnancy interval, >10 y	• Prior PE • Chronic hypertension • Pregestational diabetes mellitus • BMI, >30 kg/m^2 • Chronic kidney disease • Antiphospholipid syndrome	• Previous PE • Diabetes • Chronic hypertension • Renal disease • Autoimmune disease • Multifetal pregnancy
Moderate risk factors	Moderate risk factors	Moderate risk factors (first trimester)		Moderate risk factors	
☐ Nulliparity ☐ Age, ≥35 y ☐ Interpregnancy interval, >10 y ☐ BMI, >30 kg/m^2 • Family history of PE (mother or sister) • History of SGA or adverse outcome • Sociodemographic characteristics (African American race or low socioeconomic status)	• Nulliparity • Age, ≥40 y • Interpregnancy interval, >10 y • BMI at first visit, ≥35 kg/m^2 • Family history of PE • Multifetal pregnancy	☐ Age, 40 y ☐ Family history of PE (mother or sister) ☐ Family history of early-onset cardiovascular disease ☐ Lower maternal birthweight or preterm delivery ☐ Heritable thrombophilia ☐ Nonsmoking ☐ Increased prepregnancy triglycerides ☐ Previous miscarriage of <10 wk with same partner ☐ Cocaine and methamphetamine use ☐ Booking systolic of BP ≥130 mm Hg or diastolic BP of ≥90 mm Hg ☐ Vaginal bleeding in early pregnancy ☐ Gestational trophoblastic disease ☐ Abnormal PAPP-A or free beta-hCG		☐ Advanced maternal age, >35 y ☐ Family history of preeclampsia ☐ Short duration of sexual relationship (<6 mo) before the pregnancy ☐ Primiparity ☐ Primipaternity (both changed paternity and an interpregnancy interval of >5 y have been associated with an increased risk for preeclampsia) ☐ Connective tissue disorder	

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(continued)

TABLE 1
Maternal risk factors for preeclampsia according to professional organizations *(continued)*

ACOG 2018[48] (United States of America)	NICE 2019[49] (United Kingdom)	SOGC 2014[50] (Canada)	SOMANZ 2014[51] (Australia)	ISSHP 2018[52]	WHO 2011[53]
Indications for aspirin	Indications for aspirin	Indications for aspirin	Indication for aspirin	Indications for aspirin	Indications for aspirin
• 1 or more high-risk factors • Consider if 2 or more moderate risk factors • Dose: 81 mg/d initiated between 12 and 28 wk, optimally before 16 wk • Continue daily until delivery	• 1 or more high-risk factors • 2 or more moderate risk factors • Dose: 75 to 150 mg/d from 12 wk • Continue daily until delivery	• 1 or more high-risk factors • 2 or more moderate risk factors • Dose: 81 to 162 mg/d from before 16 wk • Continue daily until delivery	• Women with at least moderate- to high-risk of PE • Dose: unclear • Continue until 37 wk or delivery	• 1 or more high-risk factors • 2 or more moderate risk factors • Dose: 100 to 150 mg/d before 16 wk • Continue daily until 37 wk	• 1 or more risk factors • Dose: 75 mg before 20 wk, and, if possible, as early as 12 wk of gestation

ACOG, American College of Obstetricians and Gynecologists; *BMI*, body mass index; *BP*, blood pressure; *hCG*, human chorionic gonadotrophin; *ISSHP*, International Society for the Study of Hypertension in Pregnancy; *NICE*, National Institute for Health and Care Excellence; *PAPP-A*, pregnancy-associated plasma protein A; *PE*, preeclampsia; *SGA*, small-for-gestational-age; *SOGC*, Society of Obstetricians and Gynaecologists of Canada; *SOMANZ*, Society of Obstetric Medicine of Australia and New Zealand; *WHO*, World Health Organization.

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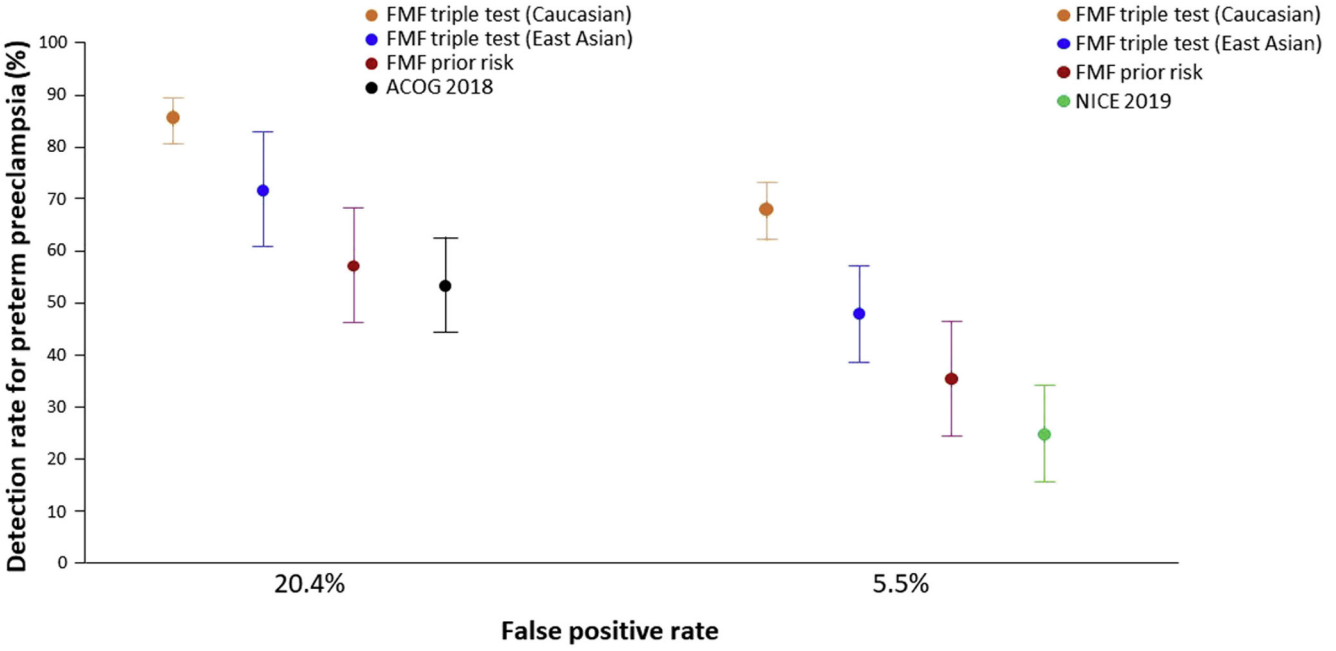
recommendation has led to a considerable improvement in the detection rates to 90% (95% CI, 79–96) and 89% (95% CI, 84–94) for preterm and term preeclampsia, respectively; however, the FPR has also increased to as high as 64% (Figure 1).[60]

A different approach for the development of a preeclampsia prediction algorithm is to use logistic regression analysis. A first trimester screening study of preeclampsia based on maternal history developed from logistic regression analysis has demonstrated that women of Afro-Caribbean racial origin (odds ratio [OR], 3.64; 95% CI, 1.84–7.21), with history of preeclampsia (OR, 4.02; 95% CI, 1.58–10.24) and chronic hypertension (OR, 8.70; 95% CI, 2.77–27.33), and those who conceive with ovulation induction (OR, 4.75; 95% CI, 1.55–14.53) are associated with an increased risk of early-onset preeclampsia. For late-onset preeclampsia, the risk increases with maternal age (OR, 1.04; 95% CI, 1.00–1.07), BMI (OR, 1.10; 95% CI, 1.07–1.13), family history (OR, 2.91; 95% CI, 1.63–5.21), or history of preeclampsia (OR, 2.18; 95% CI, 1.24–3.83).[62] In addition, late-onset preeclampsia is more common in Afro-Caribbean and South Asian women (adjusted OR, 2.66–3.31). However, maternal risk factors alone yield detection rates of 37% and 29% for early- and late- onset preeclampsia, respectively, at 5% FPR.[62] The advantage of the logistic regression approach is that it can be used to combine maternal factors with various biophysical and biochemical markers. Biomarker values are transformed into multiples of the median (MoM) to account for the effects of gestational age and maternal characteristics, such as weight and racial origin, associated with individual biomarkers. The MoM value is calculated by dividing the observed value by the expected value of the biomarker. The expected value is estimated by a formula that incorporates all factors that are identified to be independent predictors of the biomarker, based on a multivariate regression analysis. However, the drawbacks of this approach are that it assumes a binary or dichotomous outcome and that separate

FIGURE 1
Screening performance for preterm preeclampsia according to the FMF triple test, FMF prior risk, NICE 2019, and ACOG 2018 guidelines



Screening performance is derived from Tan et al[62] and Chaemsaithong et al.[60]

ACOG, American College of Obstetricians and Gynecologists; *FMF*, Fetal Medicine Foundation; *NICE*, National Institute for Health and Care Excellence.

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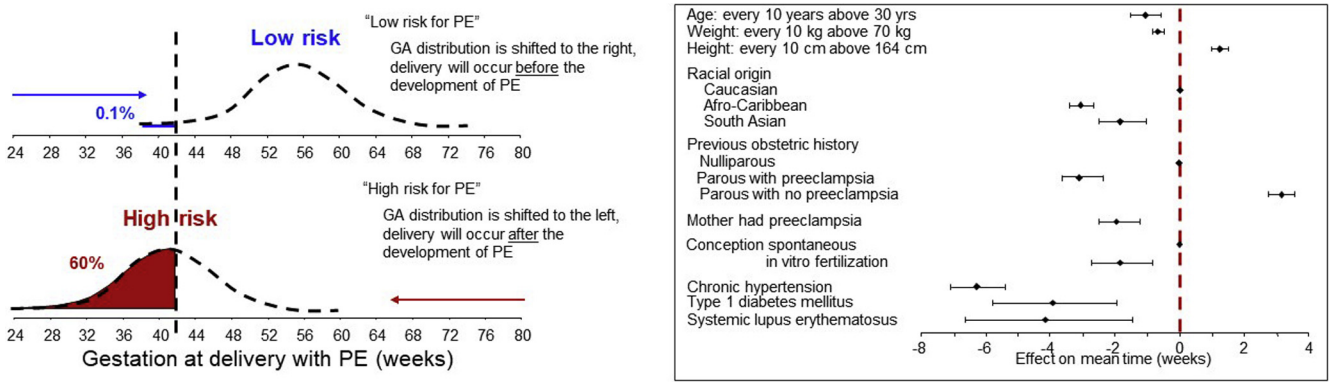
models are needed for each subtype of preeclampsia.[62–67]

An alternative approach to screening for preeclampsia is to use Bayes theorem to combine the a priori risk from maternal characteristics and medical and obstetrical history with the results of various biomarkers.[62,65] The advantage of this approach is that it allows the assessment of individual patient-specific risks of preeclampsia that require delivery before a specified gestation.[62,65] In addition, Bayes theorem provides a natural framework for dynamic prediction, in which risk assessment is updated as new information becomes available during pregnancy. Incorporation of biomarker information using likelihoods means that new markers can be added by extending an existing model rather than developing a completely new model. On the basis of Bayes theorem, a competing risk model, which is based on a survival-time model for the gestational age at delivery with preeclampsia, has been developed.[68–70] This approach assumes that if the pregnancy were to continue indefinitely, all women would experience preeclampsia, and whether they do so or not before a specified gestational age depends on competition between delivery before or after the development of preeclampsia (Figure 2). The effect of variables from maternal characteristics and history is to modify the mean of the distribution of gestational age at delivery with preeclampsia so that in pregnancies at low risk of preeclampsia, the gestational age distribution is shifted to the right with the implication that in most pregnancies, delivery occurs before the development of preeclampsia. In high-risk pregnancies, the distribution is shifted to the left, and the smaller the mean gestational age at delivery, the higher the risk of preeclampsia.

In a study of 120,492 singleton pregnancies, including 2704 pregnancies with preeclampsia (2.2%), using the competing risk model, the risk factors of advancing maternal age, increasing weight, Afro-Caribbean and South Asian racial origin, medical history of chronic hypertension, diabetes mellitus and systemic lupus erythematosus or antiphospholipid syndrome, family and history of preeclampsia, and conception by in vitro fertilization have been shown to increase the risk for preeclampsia by shifting the Gaussian distribution of the gestational age at delivery with preeclampsia to the left.[70] In contrast, the risk for preeclampsia decreases with increasing maternal height and in parous women with no history of preeclampsia. For example, in women with chronic hypertension without diabetes mellitus and no family history of preeclampsia, the mean gestational age for delivery with preeclampsia is reduced by 7.3 weeks. Of note, the effects of chronic hypertension are complicated because of interactions with other factors.[70] The survival-time model based on maternal factors achieves detection rates of 40%, 48%, and 54%, at 10% FPR, for all, preterm, and early-onset preeclampsia,

FIGURE 2
The competing risk model



A model that represents the distribution of gestational age at delivery with PE is applied. In women with a low risk for PE, the gestational age distribution is shifted to the right, meaning that gestational age for development of PE will be after delivery. Thus, in most pregnancies, delivery will occur before the development of PE. In pregnancies at high risk for PE, the gestational age distribution is shifted to the left, indicating that gestational age for development of PE will occur before delivery. Therefore, delivery will occur after the development of PE. The distribution of gestational age at delivery with PE is defined by the following 2 components: the prior distribution based on maternal characteristics and obstetrical and medical history, and the distribution of MoM biomarker values with gestational age in pregnancies affected by PE. Adapted from Wright et al.[68]

GA, Gaussian; *MoM*, multiples of the median; *PE*, preeclampsia.

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respectively.[70] These figures are considerably greater than those derived from the NICE approach.[70] Although recognition of maternal risk factors might be useful in identifying at-risk women in clinical practice, it is not a sufficient tool for the effective prediction of preeclampsia.[71]

Most recently, a multivariate Gaussian distribution approach has been used to develop models for the prediction of early-onset preeclampsia.[72] Such models are constructed using different sources such as previous knowledge, specific population marker medians, risk factor metaanalysis, and published literature. Hence, this approach might reduce the overfitting problem, which is particularly related to models derived from logistic regression analysis.

In summary, the checklist-based approach recommended by NICE and ACOG only allows an increase in a woman's risk of preeclampsia with additional risk factors that come with an accompanying increase in both the detection rate and the FPR. The logistic regression approach allows the incorporation of biomarkers. However, it does not provide patient-specific risk of preeclampsia and requires a specific model for each subtype of the disorder. Finally, the Bayes theorem method with the use of the competing risk approach allows for personalization of risk assessment, incorporating both the risk factors and the protective factors, such as no history of preeclampsia.

First Trimester Combined Preeclampsia Risk Assessment

Considerable efforts have been made to identify biomarkers that can predict preeclampsia in the first trimester of pregnancy. Evidence suggests that combinations of biomarkers have better predictive performance than single biomarkers.[73,74]

A systematic review evaluating the benefits and harms of preeclampsia screening models has indicated that among 16 models that have been validated in 4 studies (n=7123), only 5 models (4 first trimester models and 1 second trimester model) are considered good or with better discrimination, with c statistics ≥0.80 (Table 2).[75] Of these, the model developed by Poon et al[65] was the only model with successful external validation in more than 1 population, including the United States (n=2833),[76] Australia (n=3014),[77] and Italy (n=554).[78] The model developed by Odibo et al[79] has undergone external validation in a similar population (United States). This logistic regression model was developed by the Fetal Medicine Foundation (FMF) with a combination of maternal factors, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), and serum pregnancy-associated plasma protein A (PAPP-A).[80]

A recent systematic review including 68 preeclampsia prediction models from 70 studies with 425,125 participants has demonstrated that the most frequently used predictors are medical history, blood pressure, and UtA-PI.[81] Most models are neither internally nor externally validated.[81] Only 1 study of a combined first trimester prediction model divided data into training and validation datasets for internal validation, in which there was high concordance of areas under the curves (AUCs) between the 2 datasets (training, 0.76; validation, 0.78).[82] For external validation, 1 combined first trimester prediction model has been successfully

TABLE 2
Summary of 4 good first trimester preeclampsia prediction models and their external validation

	Preeclampsia, <34 wk		Preeclampsia, <37wk	Preeclampsia, ≥34 wk
Model	Poon et al[80] 2010	Poon et al[80] 2010	Odibo et al[79] 2011	Akolekar et al[69] 2013	Poon et al[80] 2010
Model variables	Maternal factors, MAP, PAPP-A, UtA-PI	Maternal factors, MAP, PAPP-A, UtA-PI	Chronic hypertension, PAPP-A, PP-13, UtA-PI	Maternal factors, MAP, PAPP-A, PLGF, UtA-PI	Maternal factors, MAP, UtA-PI
External validation study	Oliveira et al[76] 2014 (United States)	Park et al[77] 2013 (Australia)	Oliveira et al[76] 2014 (United States)	Skråstad et al[85] 2014 (Norway)	Farina et al[78] 2011 (Italy)
n (%)	2833 (1.0)	3014 (0.4)	871 (1.1)	541 (0.9)	554 (7.0)
C statistic (95% CI)	0.8 (0.7–0.9)	0.93 (0.92–0.94)	0.86 (0.73–0.99)	0.94 (0.86–1.00)	0.93 (0.88–0.98)
Detection rate (95% CI)	52	91.7 (61.5–98.6)	80	80 (28.4–99.5)	84.6 (73.3–95.9)
Positive predictive value	4.2 (2.6–6.5)	3.6 (2–7)	11.3 (5.3–21.5)	6.8 (1.9–16.5)	39.3
Negative predictive value	99.6 (99–100)	99.9 (99.7–99.9)	99.8 (99–100)	99.8 (98.8–100)	98.7

Modified from Henderson et al.[76]

CI, confidence interval; *MAP*, mean arterial pressure; *PAPP-A*, pregnancy-associated plasma protein A; *PLGF*, placental growth factor; *PP-13*, placental protein-13; *UtA-PI*, uterine artery pulsatility index.

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validated in an independent population with similar demographics and geographic settings to those of the original model.[83] There are only 2 combined first trimester prediction models[69,84] that have undergone external validation in an independent population with different demographics and geographic settings than those of the original models.[58,85–87] Table 3 showed external validation studies of the first trimester preeclampsia prediction model.

In summary, a major limitation of the existing prediction models is that only a few of them have undergone external validation.[75,81,88,89] The models that have been developed by the logistic regression approach are prone to overfitting, which can overestimate screening performance; however, the models are likely to perform poorly on data that have not been used to fit the model.[90]

It is well recognized that the prevalence of the disease, characteristics of the population (ie, low vs high risk, race, and height), and variations in the biomarkers can influence the effectiveness of screening tests. Therefore, it is necessary to validate prediction models that have been developed in specific study populations in different populations prospectively. This process is considered the optimal approach for evaluating a prediction model, which should be tested in independent validation samples with patients from a different but plausibly related population, and it reflects the generalizability of the prediction model.[91,92]

Thus far, there are a series of first trimester combined prediction models developed from cohort studies (Supplemental Table 1). In the following section, we will summarize some of the key first trimester combined prediction models developed from prospective cohort studies that have undergone external validation.

Summary of Combined First Trimester Preeclampsia Prediction Models

The Fetal Medicine Foundation prediction models

Model development. Originally, the FMF prediction models were derived from

FIGURE 3
Countries and regions with successful external validation of the first trimester FMF preeclampsia prediction models

Modified from google.com.hk

FMF, Fetal Medicine Foundation.

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data of pregnant women of various racial groups collected from hospitals in and around London, United Kingdom. The first version of the prediction models was described in a prospective screening study including 7797 singleton pregnancies with 157 cases (2%) of preeclampsia.[64] Using multivariate logistic regression analysis, a combination of maternal factors, MAP, UtA-PI, serum PAPP-A, and placental growth factor (PLGF) at 11 to 13 weeks' gestation, namely the first trimester combined test, was developed, which yielded detection rates of 93% and 36% for the prediction of early- and late-onset preeclampsia, respectively, at 5% FPR, which were superior to the detection rates of the traditional checklist-based approach, which relies on maternal factors only.[64] The FMF first trimester combined test has since evolved with the incorporation of the aforementioned competing risk model.[68,70]

The competing risk algorithm was first developed from a study of 58,884 singleton pregnancies at 11 to 13 weeks' gestation, including 1426 (2.4%) that subsequently developed preeclampsia; the estimated detection rates of preterm preeclampsia and all cases of preeclampsia, at a fixed FPR of 10%, were 77% and 54%, respectively.[69] Subsequently, data from prospective screening in 35,948 singleton pregnancies, including 1058 pregnancies (2.9%) that experienced preeclampsia, were used to update the original algorithm; the detection rates of preterm and term preeclampsia were 75% and 47%, respectively, at an FPR of 10%.[84]

In the screened population in the ASPRE (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention) trial involving 26,941 singleton pregnancies from 13 maternity hospitals in 6 countries (the United Kingdom, Spain, Italy, Belgium, Greece, and Israel), the detection rates of preterm and term preeclampsia, after adjustment for the effect of aspirin, were 77% and 43%, respectively, at an FPR of 9.2%.[101]

The largest study to date for the development of the FMF first trimester combined test using the competing risk model was reported by Tan et al.[61] The study included data from 3 reported prospective nonintervention screening studies at 11 to 13 weeks' gestation in a combined total of 61,174 mixed-European pregnant women, including 1770 cases of preeclampsia (2.9%). The best predictive performance was achieved by a combination of maternal factors with MAP, UtA-PI, and serum PLGF (also known as the FMF triple test), with detection rates of 90%, 75%, and 41% for very early (with delivery at <32 weeks), preterm, and term preeclampsia, respectively, at 10% FPR.[61] Using a risk cutoff of 1 in 100 for preterm preeclampsia in white women, the screen-positive rate was 10%, and detection rates for early, preterm, and term preeclampsia were 88%, 69%, and 40%, respectively.[61] With the same method of screening and risk cutoff, in women of Afro-Caribbean racial origin, the screen-positive rate was 34%, and detection rates for early, preterm, and term preeclampsia were 100%, 92%, and 75%, respectively. These findings are in line with previous studies.[58,84,102] The latest FMF triple test has undergone successful internal validation and calibration.[103]

Validation of the models. The FMF prediction models have been prospectively evaluated in Italian,[78] Australian,[77] American,[76] Brazilian,[86,104,105] mixed-European,[58,66,85,87,102,106–108] Dutch,[109,110] and Asian populations (Figure 3).[60] Almost all validation studies have reported comparable predictive performance corresponding to the original studies.[60,77,78,83,85–87,102,106–110] Below, we summarize 3 major validation studies that have been performed in large populations[58,60,108]:

1. O'Gorman et al[58] conducted a European-wide multicenter, prospective, nonintervention study to validate the FMF first trimester combined test in 8775 pregnant women, including 239 (2.7%) with preeclampsia. The screening performance was similar to that obtained from the original study[84] and reported detection rates of 100%, 75%, and 43%, at 10% FPR, for very early, preterm, and term preeclampsia, respectively.
2. In a National Institute for Health Research (United Kingdom)–commissioned prospective validation study of the algorithm in 16,747 pregnancies, including 473 (2.8%)

women who developed preeclampsia, the screen-positive rate by the NICE method was 10.3% and the detection rate for all preeclampsia was 30%; for preterm preeclampsia, it was 41%. The detection rate of the mini−combined test (maternal factors, MAP, and PAPP-A) for all preeclampsia was 43%, which was superior to that of the NICE method by 12.1% (95% CI, 7.9−16.2).[108] In screening for preterm preeclampsia by a combination of maternal factors, MAP, UtA-PI, and serum PLGF (FMF triple test), the detection rate was 82%, which was higher than that of the NICE method by 41.6% (95% CI, 33.2−49.9).[108]

3. Recently, the FMF triple test has been successfully validated in a multicenter study in Asia, including 10,935 women with 73 cases (0.67%) of preterm preeclampsia.[60] The FMF triple test achieved detection rates of 48.2%, 64.0%, 71.8%, and 75.8% at 5%, 10%, 15%, and 20% fixed FPRs, respectively, for the prediction of preterm preeclampsia. The screening performance was comparable with that of East Asian women in previously published data from the FMF study[61] and was superior to the approach recommended by ACOG and NICE.[60] This study is considered a landmark study for the external validation of preeclampsia prediction models because the study population is totally different from the original population utilized for model development.

Further evidence to support the use of the FMF risk-based screening using biomarkers derives from a secondary analysis of the ASPRE data of a total of 34,573 women that underwent prospective screening for preterm preeclampsia, including 239 (0.7%) cases of preterm preeclampsia.[111] In women who were screened positive by the ACOG or NICE method but screened negative by the Bayes theorem−based method, the risk of preterm preeclampsia was reduced to within or below background levels. The study demonstrated that at least 1 of the ACOG criteria was fulfilled in 22,287 (64.5%) pregnancies and the incidence of preterm preeclampsia was 0.97% (95% CI, 0.85−1.11). In the subgroup that was Bayes method screen−positive, the incidence was 4.80% (95% CI, 4.14−5.55); in those that were screen-negative, it was 0.25% (95% CI, 0.18−0.33); and the relative incidence in Bayes method−negative to Bayes method−positive was 0.051 (95% CI, 0.037−0.071). In 1392 (4.0%) pregnancies, at least 1 of the NICE high-risk criteria was fulfilled, and in this group, the incidence of preterm preeclampsia was 5.17% (95% CI, 4.13−6.46); in the subgroups of screen-positive and screen-negative by the Bayes method, the incidence of preterm preeclampsia was 8.71% (95% CI, 6.93−10.89) and 0.65% (95% CI, 0.25−1.67), respectively, and the relative incidence was 0.075 (95% CI, 0.028−0.205). In 2360 (6.8%) pregnancies with at least 2 of the NICE moderate risk criteria, the incidence of preterm preeclampsia was 1.74% (95% CI, 1.28−2.35); in the subgroups of screen-positive and screen-negative by the Bayes method, the incidence was 4.91% (95% CI, 3.54−6.79) and 0.42% (95% CI, 0.20−0.86), respectively, and the relative incidence was 0.085 (95% CI, 0.038−0.192).[111]

Table 4 and Figure 4 illustrate the predictive performance of the latest FMF first trimester prediction models according to the different combinations of biomarkers.[61]

Models developed from North American populations

To date, there are several models that have been developed from prospective cohort studies in the United States and Canada.[67,82,93−99] The first model was reported in 2010 and was developed from 893 nulliparous women including 40 (4.5%) cases of preeclampsia.[93] The combination of maternal characteristics, PAPP-A, inhibin-A, and PLGF yielded a detection rate of 75% for early-onset preeclampsia, at 10% FPR. However, this model has not gained attention because the model is limited to nulliparous women, and the measurement of PLGF was only done in half of the study population (n=531). This model has failed external validation in a Dutch population.[110] The second model was reported in 2011 and originated from 452 women including 42 (9.3%) affected by preeclampsia.[79] The components of this model included placental protein 13, PAPP-A, or mean UtA-PI. A combination of maternal factors and biomarkers achieved detection rates of 60% and 79% for all and early-onset preeclampsia, respectively, at 20% FPR. This model has undergone successful external validation within the United States[76] but failed external validation in a Dutch population.[110] The third model was reported by Baschat et al[67] in 2014 involving 2441 singleton pregnancies with rates of all and early-onset preeclampsia of 4.4% and 0.7%, respectively. Prediction components for all preeclampsia consisted of maternal factors, MAP, and PAPP-A. For early-onset preeclampsia, the model consisted of maternal factors and MAP. The prediction algorithms for all and early-onset preeclampsia achieved AUCs of 0.82 and 0.83, respectively, and the respective detection rates were 49% and 55%, at 10% FPR. These models have been externally evaluated in the United Kingdom; however, the predictive performance is lower than that of the original study (all preeclampsia: AUC, 0.63; 95% CI, 0.55−0.71; early-onset preeclampsia: AUC, 0.62; 95% CI, 0.55−0.70).[106] A recently developed combined model with maternal factors, UtA-PI, PAPP-A, and alpha-feto protein was evaluated in 1068 pregnant women with the rate of all preeclampsia of 4.3%.[99] The model achieved detection rates of 85%, 60%, and 24% for the prediction of early-onset, preterm, and term preeclampsia, respectively, at 10% FPR. This model has not undergone internal or external validation.

Altogether, the models developed in the United States and Canada were derived from the logistic regression approach in small populations and are therefore predisposed to overfitting. In addition, none of the models have undergone successful external validation.

Models developed from Spanish populations

To date, there are 3 major cohort studies that have reported on the first trimester

TABLE 3
External validation studies of the first trimester preeclampsia prediction models

First author, year	Population tested	Sample size	Original models (First author, year)	Performance of validation studies	Performance of original studies
Farina et al,[78] 2011	Bologna, Italy	n=554; late-onset PE, 7% (n=39)		DRs at 10% FPR	DRs at 10% FPR
			Plasencia et al,[112] 2008	41%	47%
			Plasencia et al,[63] 2007	54%	52%
			Onwudiwe et al,[113] 2008	74%	50%
			Poon et al,[64] 2009	39%	45%
			Poon et al,[64] 2009	41%	47%
			Poon et al,[64] 2009	44%	46%
			Poon et al,[114] 2009	36%	41%
			Poon et al,[80] 2010	85%	57%
Park et al,[77] 2013	Sydney, Australia	n=3066; PE, 2.8% (n=83); early-onset PE, 0.4% (n=12)	Poon et al,[80] 2010	DRs at 10% FPR	DRs at 10% FPR
			Early-onset PE	92%	95%
Oliveira et al,[76] 2014	Baltimore, Maryland	n=871−2962; early-onset PE, 1% −1.2%	Early-onset PE	Dtpgoto "Rs at 10% FPR	DRs at 10% FPR
			Parra-Cordero et al,[115] 2013	29%	47%
			Scazzocchio et al,[66] 2013	43%	81%
			Poon et al,[116] 2009	53%	89%
			Poon et al,[80] 2010	52%	95%
			Odibo et al,[79] 2011	80%	68%
			Caradeux et al,[117] 2013	30%	63%
			Late-onset PE		
			Parra-Cordero et al,[115] 2013	18%	29%
			Scazzocchio et al,[66] 2013	31%	40%
Skråstad et al,[85] 2015	Throndheim,	n=541; PE, 3.9% (n=21); preterm PE, 0.9% (n=5)	Akolekar et al,[69] 2013	DRs at 10% FPR	DRs at 10% FPR
	Norway			Preterm PE 80%	Early-onset PE 96%
				Late-onset PE 30%	All PE 54%

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(continued)

TABLE 3
External validation studies of the first trimester preeclampsia prediction models *(continued)*

First author, year	Population tested	Sample size	Original models (First author, year)	Performance of validation studies	Performance of original studies
Allen et al,[105] 2017	Royal London Hospital, United Kingdom	n=2500; PE, 2.4% (n=60)	Early-onset PE	AUC	AUC
			Akolekar et al,[118] 2008	0.718	0.941
			DiLorenzo et al,[172] 2012	0.504	0.893
			Plasencia et al,[112] 2008	0.706	0.931
			Poon et al,[114] 2009	0.765	0.905
			Poon et al,[120] 2009	0.833	0.954
			Poon et al,[64] 2009	0.824	NR
			Parra-Cordero et al,[115] 2012	0.702	NR
			Scazzocchio et al,[66] 2013	0.831	0.960
			Baschat et al,[67] 2014	0.624	0.830
			Late-onset PE		
			Akolekar et al,[118] 2008	0.737	0.941
			DiLorenzo et al,[119] 2012	0.504	0.893
			Plasencia et al,[112] 2008	0.659	0.779
			Poon et al,[114] 2009	0.691	0.790
			Poon et al,[120] 2009	0.828	0.863
			Poon et al,[64] 2009	0.811	NR
			Parra-Cordero et al,[115] 2012	0.644	NR
			Scazzocchio et al,[66] 2013	0.699	0.710
			Baschat et al,[67] 2014	0.631	0.820
Guizani et al,[107] 2017	Brussels, Belgium	n=3239; PE, 2.5%; preterm PE, 1.1% (n=36); term PE, 1.4% (n=44)	O'Gorman et al,[83] 2016	DRs at 10% FPR	DRs at 10% FPR
			Early-onset PE	83%	89%
			Preterm PE	81%	75%
			Term PE	32%	48%

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TABLE 3
External validation studies of the first trimester preeclampsia prediction models *(continued)*

First author, year	Population tested	Sample size	Original models (First author, year)	Performance of validation studies	Performance of original studies
Scazzocchio et al,[83] 2017	Barcelona, Spain	n=4203; PE, 4% (n=169)	Scazzocchio et al,[66] 2013	DRs at 10% FPR	DRs at 10% FPR
			Early-onset PE	86%	75%
			Late-onset PE	43%	53%
Lobo et al,[86] 2017	Sao Paulo, Brazil	n= 617; PE, 5.5% (n=34)	Akolekar et al,[69] 2013	DRs at 10% FPR	DRs at 10% FPR
			Early-onset PE	86%	96%
			Preterm PE	67%	77%
			All PE	53%	53%
O'Gorman et al,[58] 2017	Multicenter studies, European populations	n=8775; PE, <32 wk, 0.2% (n=17); preterm PE, 0.7% (n=59); term PE 2.1% (n=180)	O'Gorman et al,[84] 2016	DRs at 10% FPR	DRs at 10% FPR
			PE <32 weeks	100%	82%
			Preterm PE	80%	75%
			Term PE	43%	47%
Mosimann et al,[87] 2017	Swiss	n=1129; all PE, 1.68% (n=19); preterm PE, 0.44% (n=5); early-onset PE, 0.18% (n=2); term PE, 1.24% (n=14)	O'Gorman et al,[84] 2016	DR 81% at 10% FPR (preterm PE)	DR 80%, FPR 8.3%
Tan et al,[108] 2018	European population	n=16,747; all PE 2.8% (n=473); preterm PE, 0.8% (n=142)	Tan et al,[61] 2018	DRs at 10% FPR	DRs at 10% FPR
			Early-onset PE	90%	90%
			Preterm PE	82%	75%
			Term PE	43%	41%

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(continued)

TABLE 3
External validation studies of the first trimester preeclampsia prediction models *(continued)*

First author, year	Population tested	Sample size	Original models (First author, year)	Performance of validation studies	Performance of original studies
Lamain-de Ruiter et al,[110] 2019	Dutch population	n=3736; all PE, 2.3% (n=87); late-onset PE, 0.4% (n=71); early-onset PE 0.9% (n=14)	All PE	AUC	AUC
			Baschat et al,[67] 2014	0.82	0.76
			Giguère et al,[121] 2015	0.75	0.64
			Goetzinger et al,[94] 2010	0.70	0.55
			Goetzinger et al,[82] 2013	0.76	0.56
			Myatt et al,[122] 2012	0.65	0.64
			Odibo et al,[79] 2011	0.77	0.57
			Plasencia et al,[63] 2007	0.81	0.73
			Poon et al,[123] 2008	0.85	0.76
			Syngelaki et al,[124] 2011	NR	0.75
			Late-onset PE		
			Akolekar et al,[95] 2011	NR	0.72
			Crovetto et al,[96] 2014	0.72	0.73
			Crovetto et al,[125] 2014	0.75	0.58
			Kuc et al,[126] 2013	NR	0.68
			Kuc et al,[127] 2014	0.79	0.68
			Plasencia et al,[63] 2007	0.80	0.60
			Poon et al,[114] 2009	0.79	0.73
			Poon et al,[62] 2010	0.80	0.73
			Scazzocchio et al,[66] 2013	0.81	0.69
Rezende et al,[105] 2019	Brazilian population	n=1531; PE, 7.8% (n=120); preterm PE, 1.7% (n=26); early-onset PE 0.65% (n=11)	Wright et al,[68] 2012	DRs at 10% FPR	DRs at 10% FPR
			Early-onset PE	54.0%	89.7%
			Preterm PE	38.0%	71.5%
			Total PE	26.7%	56.6%

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(continued)

TABLE 3
External validation studies of the first trimester preeclampsia prediction models *(continued)*

First author, year	Population tested	Sample size	Original models (First author, year)	Performance of validation studies	Performance of original studies
Meertens et al,[109] 2019	Dutch population	n=2,614; all PE, 2.9% (n=76)		AUC	AUC
			Macdonald-Wallis et al,[128] 2015	0.77	0.73
			Kenny et al,[129] 2014	0.73	0.60
			Direkvand-Monghadam et al,[130] 2013	0.67	0.56
			Syngelaki et al,[124] 2011	NR	0.52
			North et al,[131] 2011	0.76	0.58
			Seed et al,[132] 2011	0.70	0.52
			Audibert et al,[93] 2010	0.75	0.56
			Poon et al,[133] 2008	0.85	0.74
			Poon et al,[123] 2008	0.85	0.63
			Plasencia et al,[63] 2007	0.81	0.74
Chaemsaithong P et al,[60] 2019	Asian population	n=10,935; all PE, 2.05% (n=224); early-onset PE, 0.23% (n=25); preterm PE, 0.67% (n=73); term PE, 1.38% (n=151)		DRs at 10% FPR	DRs at 10% FPR
			Tan et al,[61] 2018	64.03%	50.0% (East Asian population)

AUC, area under the curve; *DR*, detection rate; *FPR*, false-positive rate; *PE*, preeclampsia; *NR*, not reported.

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TABLE 4
Predictive performance of the first trimester Fetal Medicine Foundation preeclampsia prediction algorithm at screen-positive rate of 10%

	Preterm PE			Term PE	
Method of screening	Risk cutoff for preterm PE	AUC	DR% (95% CI)	AUC	DR% (95% CI)
Maternal risk factors	1 in 62	0.788	44.8 (40.5–49.2)	0.735	33.5 (31.0–36.2)
Maternal risk factors plus					
MAP	1 in 61	0.841	50.5 (46.1–54.9)	0.776	38.2 (35.6–40.9)
UtA-PI	1 in 60	0.853	58.4 (54.0–62.7)	0.733	35.2 (32.6–37.8)
PAPP-A	1 in 61	0.810	48.5 (44.1–52.9)	0.734	35.2 (32.7–37.9)
PLGF	1 in 62	0.868	60.6 (56.3–64.9)	0.745	34.5 (32.0–37.2)
MAP, UtA-PI	1 in 61	0.891	68.4 (64.1–72.3)	0.772	41.4 (38.8–44.2)
MAP, PAPP-A	1 in 60	0.855	55.8 (51.4–60.1)	0.774	39.1 (36.4–41.8)
MAP, PLGF	1 in 65	0.895	66.1 (61.8–70.2)	0.777	39.3 (36.7–42.0)
UtA-PI, PAPP-A	1 in 60	0.861	59.2 (54.8–63.5)	0.735	36.3 (33.7–39.0)
UtA-PI, PLGF	1 in 62	0.892	66.9 (62.7–70.9)	0.744	36.9 (34.3–39.6)
PLGF, PAPP-A	1 in 62	0.869	63.5 (59.2–67.6)	0.745	35.7 (33.1–38.4)
MAP, UtA-PI, PAPP-A	1 in 61	0.896	68.2 (63.9–72.1)	0.773	40.6 (37.9–43.3)
MAP, PAPP-A, PLGF	1 in 65	0.896	67.3 (63.1–71.3)	0.777	39.3 (36.7–42.0)
MAP, UtA-PI, PLGF	1 in 66	0.915	74.8 (70.8–78.5)	0.776	41.0 (38.3–43.7)
UtA-PI, PAPP-A, PLGF	1 in 63	0.892	68.2 (63.9–72.1)	0.745	36.9 (34.3–39.6)
MAP, UtA-PI, PAPP-A, PLGF	1 in 66	0.916	74.8 (70.8–-78.5)	0.777	41.3 (38.7–-44.1)

Adapted from Tan et al.[87]

AUC, area under the curve; *CI*, confidence interval; *DR*, detection rate; *MAP*, mean arterial pressure; *PAPP-A*, pregnancy-associated plasma protein A; *PE*, preeclampsia; *PLGF*, placental growth factor; *UtA-PI*, uterine artery pulsatility index.

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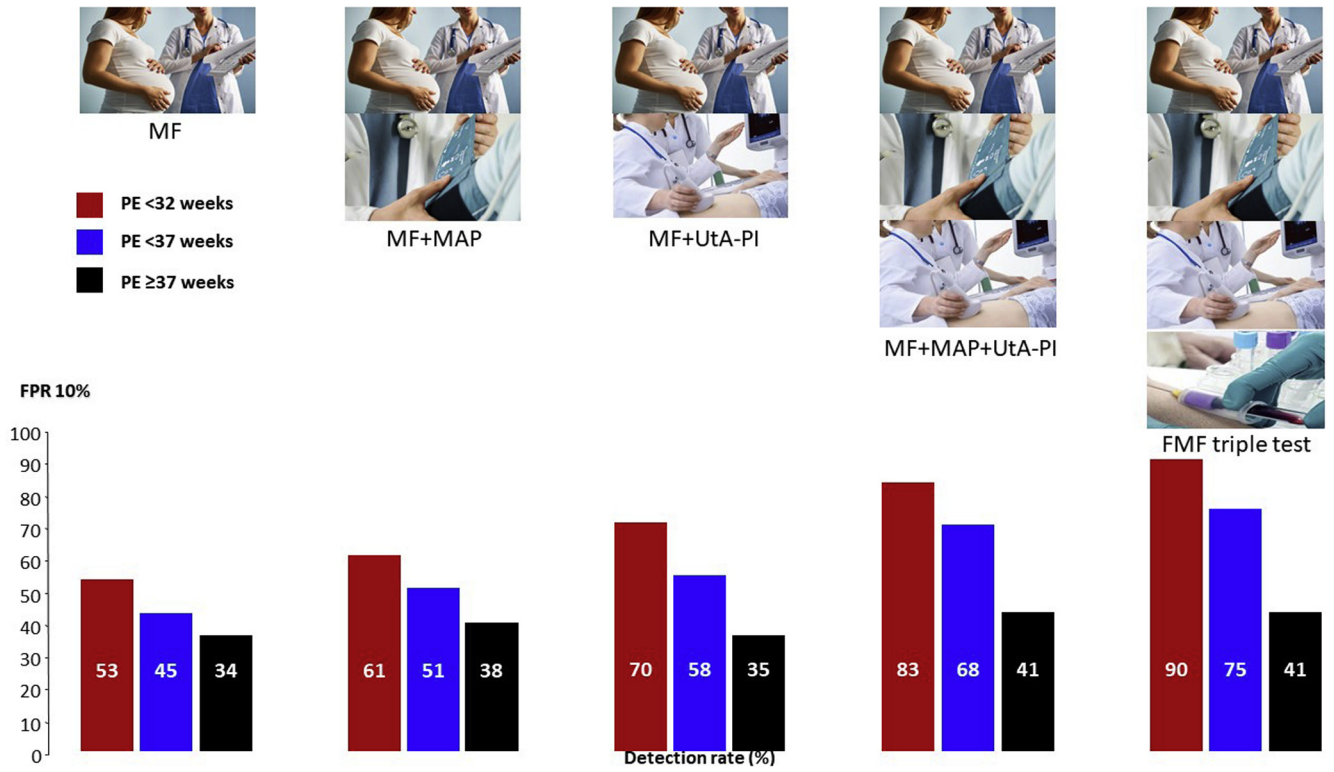
combined prediction models developed from the Spanish population.[66,72,96] Scazzocchio et al[66] developed combined prediction models for early- and late-onset preeclampsia from 5759 singleton pregnancies in 2013, with rates of all, early-, and late-onset preeclampsia of 2.6%, 0.5%, and 2.1%, respectively. The prediction algorithm for early-onset preeclampsia was based on maternal factors, mean UtA-PI, and MAP, whereas the prediction algorithm for late-onset preeclampsia was based on maternal factors and PAPP-A. The combination of maternal factors and biomarkers achieved an AUC of 0.960 (95% CI, 0.940–0.980) with a detection rate of 80.2%, at 10% FPR, for early-onset preeclampsia. For late-onset preeclampsia, the AUC was 0.710 (95% CI, 0.658–0.763) and the detection rate was 39.6% at 10% FPR.

In 2017, the same group of researchers internally validated the performance of their prediction algorithms in 4203 singleton pregnancies with rates of all, early-, and late-onset preeclampsia of 4.0%, 0.7%, and 3.4%, respectively. In this internal validation study, the predictive performance of preeclampsia was similar to that derived from the original cohort.[83]

For external validation, there are 4 studies that have prospectively evaluated Scazzocchio et al's prediction algorithms.[76,83,106,110] Notably, 3 studies, 1 each in United States, United Kingdom, and Dutch populations, have reported underperformance,[76,106,110] contrary to the internal validation study performed by the original investigators.

The same group of researchers later developed another prediction algorithm for preeclampsia using maternal factors, MAP, UtA-PI, plasma PLGF, and soluble fms-like tyrosine kinase-1 (sFlt-1) based on a study population of 9462 singleton pregnancies with 57 (0.6%) and 246 (2.6%) cases with early- and late-onset preeclampsia, respectively.[96] Maternal PLGF and sFlt-1 concentrations were available in a subset of patients (303 preeclampsia cases and 853 controls). The best algorithms for early- and late-onset preeclampsia consisted of a combination of maternal factors, MAP, UtA-PI, PLGF, and sFlt-1. The models achieved detection rates of 91.2% and 76.4%, at 10% FPR, for early- and late-onset preeclampsia, respectively. These models have undergone external validation in a Dutch study including 3736 women with 87 (2.3%) affected by preeclampsia;

FIGURE 4
Screening performance of the first trimester FMF prediction model for preeclampsia according to the different combinations at FPR of 10%



Screening performance derived from Tan et al.[61]

FMF, Fetal Medicine Foundation; *FPR*, false-positive rate; *MAP*, mean arterial pressure; *MF*, maternal factors; *PE*, preeclampsia; *UtA-PI*, uterine artery pulsatility index.

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however, the calibration was reported to be suboptimal.[110]

Most recently, a new model for screening for early-onset preeclampsia was developed by another group of Spanish investigators in a cohort study of 7908 pregnancies with 17 cases (0.2%) of early-onset preeclampsia.[72] A multivariate Gaussian distribution model including maternal factors, MAP, and UtA-PI at 11 to 13^{+6} (13 gestational weeks and 6 days) weeks' gestation, and PLGF at 8 to 13^{+6} weeks' gestation had been shown to achieve a detection rate of 94.1% at 10% FPR for the identification of early-onset preeclampsia.[72] This model used a new approach called multivariate Gaussian distribution models, which might potentially allow adaptation to a variety of populations. In addition, multiple approaches for UtA-PI determination (transabdominal or transvaginal) and PLGF measurement from as early as 8 weeks' gestation would allow flexibility for routine clinical practice in a setting in which Down syndrome screening is performed using a 2-step procedure.[72] However, the major limitations of these models were related to the fact that they were developed on the basis of a small number of early-onset preeclampsia cases and the lack of internal and external validation.

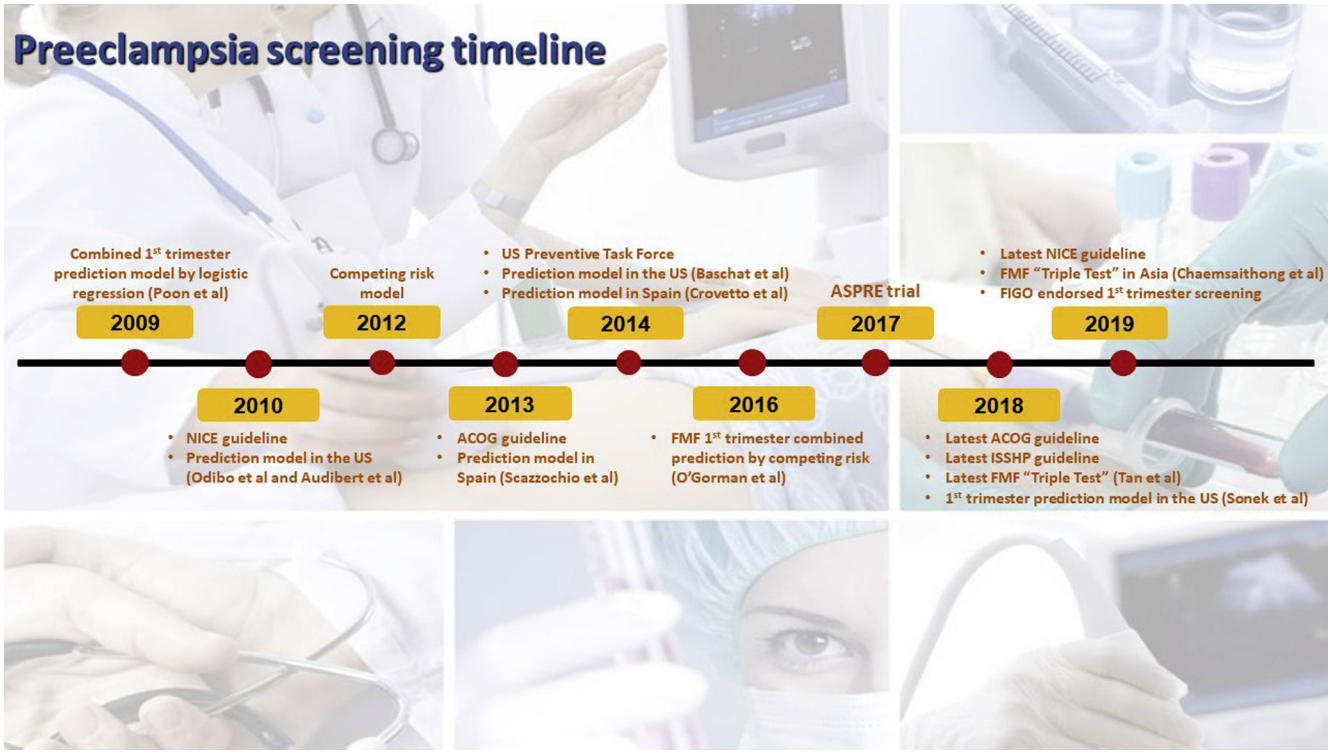
In conclusion, thus far, the FMF first trimester combined models are the only models that have undergone extensive internal and external validations.[58,60,108] The FMF triple test has been endorsed by the International Federation of Gynecology and Obstetrics (FIGO).[42] The models developed by the United States and the Spanish researchers have failed or not undergone external validation, a process that is considered essential before clinical implementation. The timeline of the development of preeclampsia prediction models is illustrated in Figure 5.

The key to maintaining optimal screening performance is to establish standardized methods for biomarker measurements and regular biomarker quality assessment. The latter has an important role in the context of preeclampsia screening, as each biomarker is susceptible to inaccurate measurement, thus affecting performance of screening.[134]

Quality Assessment

In medicine, the development of quality assurance and quality control systems has arisen after the report of the Bristol Royal Infirmary Inquiry[135] and the Harold Shipman case.[136] These are historical examples of unnoticed poor healthcare

FIGURE 5
Timeline of important developments in preeclampsia screening



ACOG, American College of Obstetricians and Gynecologists; *ASPRE*, Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention; *FMF*, Fetal Medicine Foundation; *FIGO*, International Federation of Gynecology and Obstetrics; *ISSHP*, International Society for the Study of Hypertension in Pregnancy; *NICE*, National Institute for Health and Care Excellence; *PE*, preeclampsia.

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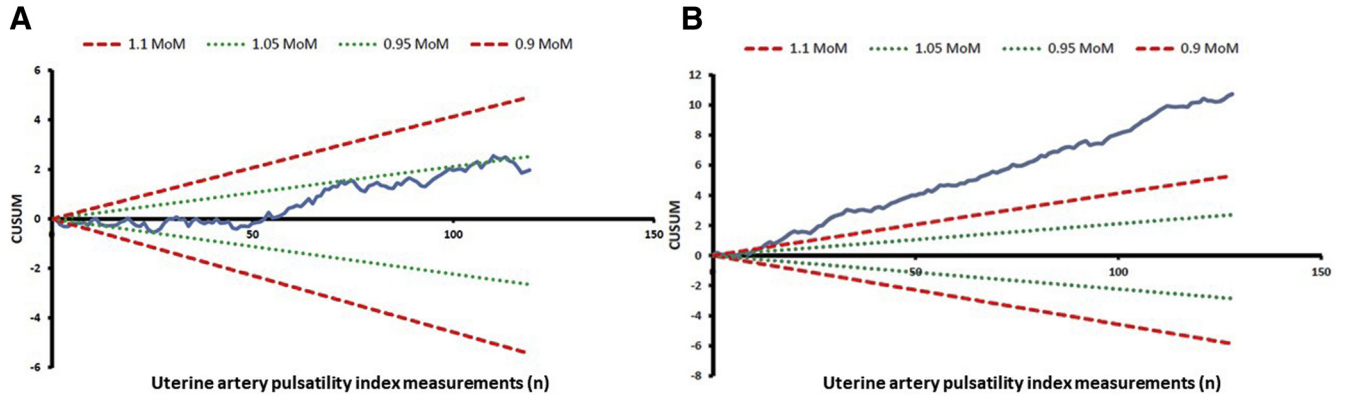
leading to widespread criticisms of how the medical profession regulates itself and recommendations of how matters should be dealt with in the future.

Tools that are used frequently to assess quality control include the sequential probability ratio test, cumulative sum (CUSUM), and target plot.[137,138] CUSUM is a rapid and powerful approach to assess changes in means or slopes of trend of sequential data (Figure 6).[139] Briefly, the reference value (mean or common reference point) is selected, and this value is subtracted from each data point in succession. The successive deviations of the data from the reference value are then added to the previous sum.[139,140] Changes in the CUSUM indicate changes in the mean or trend of data from the baseline (mean or reference point), which allow the detection of small but sustained changes that are obscured by conventional methods or original data.[141] The target plot is a tool to evaluate central tendency (deviation from expected MoM) and dispersion (deviation from expected median standard deviation [SD]) (Figure 7). Central tendency is plotted against the X-axis and dispersion is plotted against the Y-axis. Acceptable performance is considered if the central tendency and dispersion are within 10% of the expected median MoM and SD (represented as outer square box, blue color). The inner square box (yellow color) corresponds to central tendency and dispersion that are within 5% of the expected median MoM and SD. Disadvantages of the target plot include the requirement of large datasets and its insensitivity to detect small deviation. In contrast, CUSUM is a sensitive method to detect small shifts over time and the point of shift can be easily visualized.[141] However, its design is more complicated than the target plot.

The need for quality assessment is relevant in the context of screening for preeclampsia, as each biomarker is susceptible to inaccurate measurements, thus impacting on the risk given to patients and the performance of screening.[134,142,143] As mentioned previously, the most frequently used biomarkers in the preeclampsia prediction models are MAP and UtA-PI. These biophysical markers are susceptible to considerable variability in their measurements, mainly as a result of poor adherence to well-defined protocols.[142,143]

Based on the protocol for MAP measurement,[42,144–146] women are placed in a standardized sitting posture with their back resting against the seat, their arms supported at the level of the heart, and legs uncrossed (Figure 8). Blood pressure should be measured from both arms simultaneously with validated automated blood pressure devices and correct size cuffs. A total of 2 readings should be

FIGURE 6
Cumulative sum



The reference value (mean or common reference point) is selected, and this value is subtracted from each data point in succession. The successive deviations of the data from the reference value are then added to the previous sum. Changes in the CUSUM indicate changes in the mean or trend of data from the baseline (mean or reference point), which allow the detection of small but sustained changes that are obscured by conventional. **A,** The measurements are within 0.95 to 1.05 MoM. **B,** The overmeasurement requires biomarker acquisition reassessment or biomarker adjustment factor.

CUSUM, cumulative sum; *MoM*, multiples of the median.

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recorded from each arm, and each reading is 1 minute apart. The final MAP is calculated from the average of the 4 measurements.

For UtA-PI measurement, according to FMF, transabdominal ultrasound is used to obtain a sagittal section of the uterus and to locate the internal cervical os (www.fetalmedicine.org). Then, the ultrasound transducer is kept in the midline and tilted to the lateral sides of the cervix. Color Doppler flow mapping is used to identify the uterine arteries at the level of the internal cervical os. Pulsed wave Doppler is then performed with the sampling gate set at 2 mm to cover the vessel. The UtA-PI and peak systolic velocity (PSV) are measured automatically when 3 similar consecutive waveforms are obtained. The PSV must be at >60 cm/s to ensure that measurement of the UtA-PI is performed at the level of the internal os (Figure 9).[147] An alternative measurement approach has recently emerged, and the measurement of UtA-PI is performed through the visualization of the cervix in a transverse plane. The UtA-PI values acquired through this new approach seem to be comparable with those obtained through the conventional sagittal approach, in terms of reliability, reproducibility, and time required, and may it be easier to perform.[147-149] The transverse approach is not the approved technique according to FMF; however, it can be used in challenging cases.

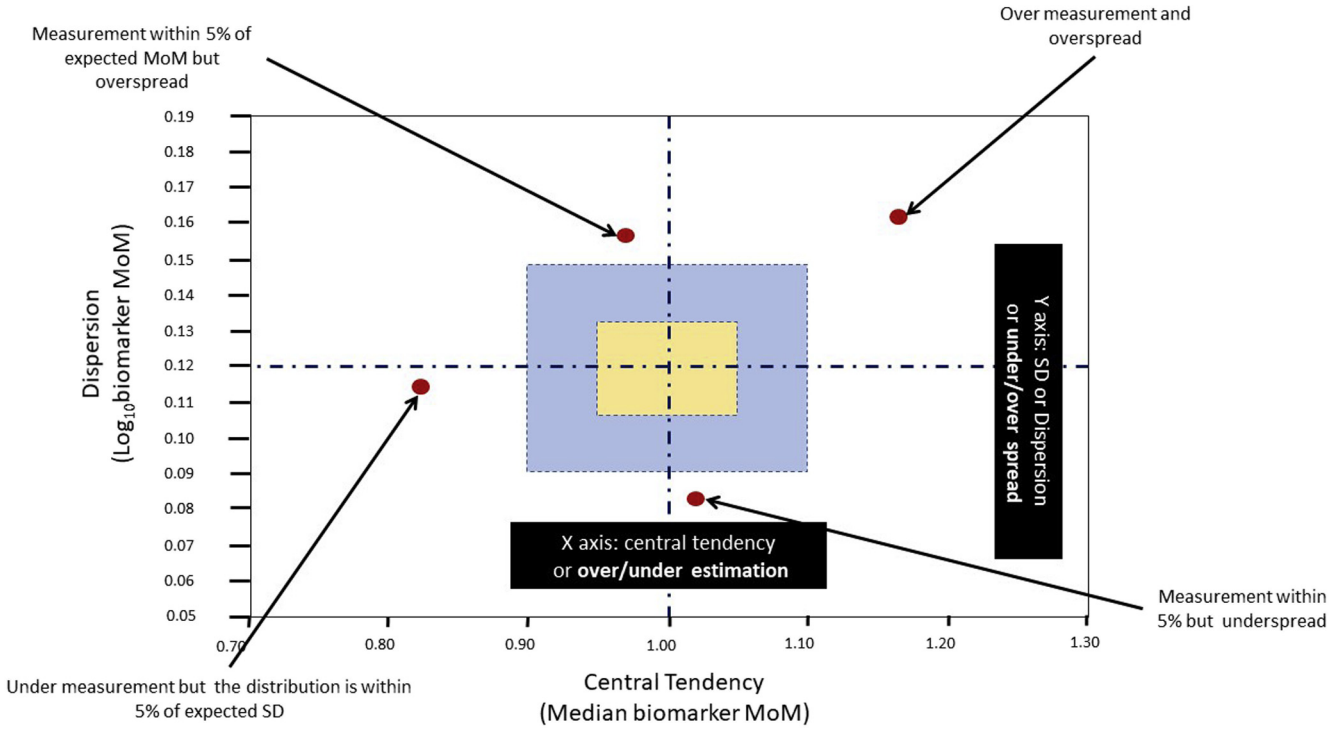
In the context of preeclampsia screening, using CUSUM and target plot for quality control of UtA-PI has improved the performance for the detection of early-onset preeclampsia in the group of sonographers who received regular feedback on their performance compared with those without any feedback (screen-positive rate for early-onset preeclampsia, 10% vs 2.7%).[142] Furthermore, a retrospective cohort study involving 21,010 first trimester pregnant women demonstrated that 24 of 42 ultrasound operators (57.1%) had mean UtA-PI values in the ideal range (0.95−1.05 MoM) and 41 of 42 (97.6%) had mean values within the acceptable limits of 0.90 and 1.10 MoM. Ultrasound operators measuring UtA-PI below 0.95 MoM and above 1.05 MoM had, respectively, lower and higher screen-positive rates than those with measurements within the 0.95 to 1.05 MoM range (7.2% and 13.2% vs 11.2%, respectively, $P<.001$).[134] Other than for quality assessment, our group has also utilized these tools to determine differences in biomarker profiles in Asian women compared with the European population.[143] Any biomarker deviation would indicate a potentially substantial underlying difference in population characteristics. We have reported that, in the Asian population, the MoM values of MAP and PLGF are overall 4% and 11% lower, respectively, than those obtained from the European population.[143] These findings highlight the need for adjustment or regional-specific formulas for the normalization of the biomarkers before their incorporation for the calculation of patient-specific risks of preeclampsia.

Similarly, inaccurate biochemical marker results may occur because of changes in the batch of reagent used, changes in temperature,[150] deviation from the manufacturer's protocol, and failure to implement a continuous quality control process. Therefore, a process for quality control must be established and performed regularly to ensure data standardization, reliability, and accuracy. Any deviations of screening values should be promptly investigated for the causes, and retraining of the biomarker measurement may be required.

Clinical Implementation of the First Trimester Preeclampsia Prediction Model

Clinical implementation is defined as the ability to accomplish any type of strategy

FIGURE 7
Target plot



Target plot is a common tool to evaluate central tendency (deviation from expected median MoM) and dispersion (deviation from expected median SD). Central tendency is plotted against the X-axis and dispersion is plotted against the Y-axis. Acceptable performance is considered if the central tendency and dispersion are within 10% of the expected median MoM and SD (represented as outer square box, blue). The inner square box (yellow) corresponds to central tendency and dispersion that are within 5% of the expected median MoM and SD.

MoM, multiples of the median; *SD*, standard deviation.

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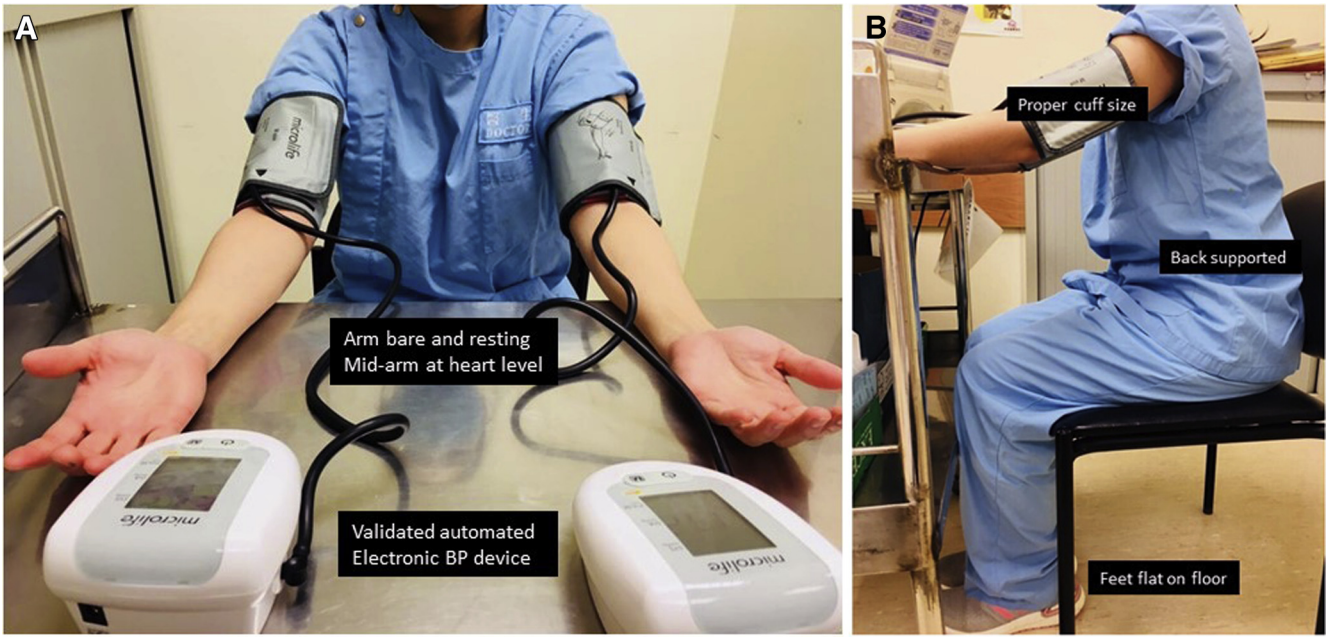
to provide practical effects or to be officially used.[151] Regarding the implementation of a new screening strategy, this process requires external validation of the prediction algorithm for the local population and continuous quality control, in addition to ongoing research in evaluating cost effectiveness and impact on maternal and perinatal morbidity and mortality.

The principle of first trimester preeclampsia screening has been established. Regarding clinical implementation, there are various levels of complexity and implications in terms of general applicability and costs for the various components of the FMF triple test. First, the collection of maternal demographic data, medical and obstetrical history, and the measurement of weight and height need to be done by trained staff with the use of a standardized data collection form. Transcribing data into the risk calculator, followed by regular review of the collected data with the use of quality assessment tools, are essential to ensure data accuracy.

Second, measurement of MAP is considered as a part of routine prenatal care and can be undertaken by healthcare assistants after minimal training with the use of inexpensive equipment and takes a few minutes to perform. Third, measurement of UtA-PI can be undertaken within a few minutes by the same ultrasound operators and machines as part of the current routine first trimester scan. However, the ultrasound operators will require specific training and accreditation for this measurement and quality assessment of their results. It is recognized that the measurement of UtA-PI is sampling site—dependent, and the measurement acquired distal from the internal os leads to a reduction in the UtA-PI values and, thus, a reduction in the detection rate for preeclampsia.[152,153] Finally, measurement of serum PLGF can be undertaken on the same blood sample and by the same automated analyzers as for PAPP-A (at an additional cost) for the routine Down syndrome screening. Frequent calibrations of the analyzers and appropriate adjustment for confounding factors are essential. Such considerations are also applicable to other prediction models for other pregnancy complications that include a series of biophysical and biochemical markers.

The optimal cutoff value of the FMF triple test for preterm preeclampsia is 1:100, which is applicable in the Asian population.[38] This risk cutoff is

FIGURE 8
Correct position for BP measurement in pregnant women



A, face front; **B**, side view.

BP, blood pressure.

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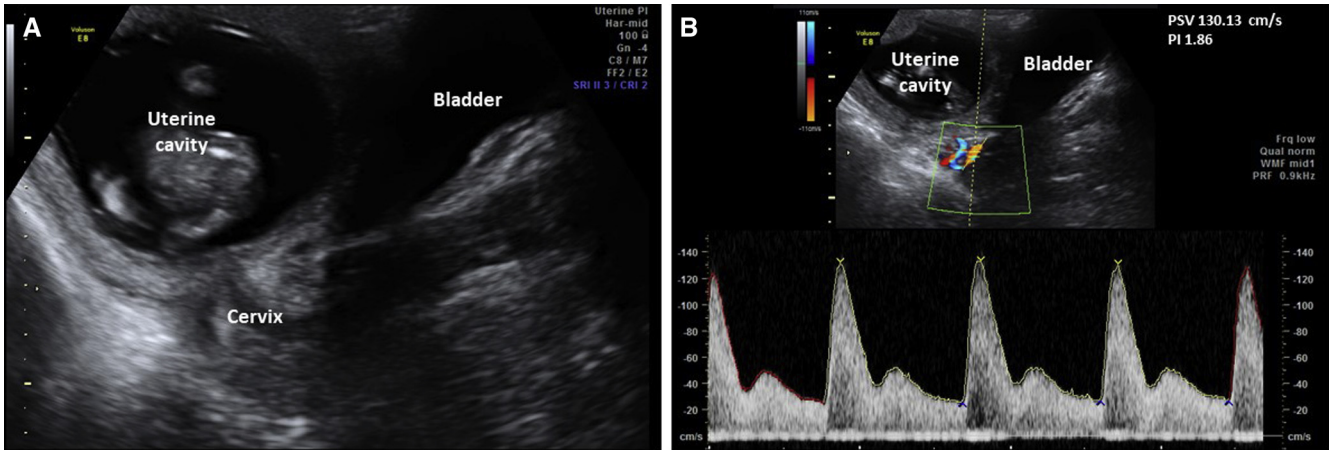
determined according to the desired FPR and/or detection rate. For example, in Down syndrome screening, the cutoff is selected for a lower FPR to avoid unnecessary invasive prenatal testing. In contrast, a higher FPR for preeclampsia screening is acceptable because low-dose aspirin has limited serious adverse effects compared with failure of identification of women who subsequently develop preeclampsia. The optimal cutoff might vary according to characteristics of the women and the different combinations of biomarkers.

FIGURE 9
Measurement of uterine artery resistance indices in the first trimester



A, Sagittal section of cervix is identified. Then ultrasound probe is tilted to see uterine artery. **B**, Uterine artery is identified at the level of cervical os.

PSV, peak systolic velocity; *PI*, pulsatility index.

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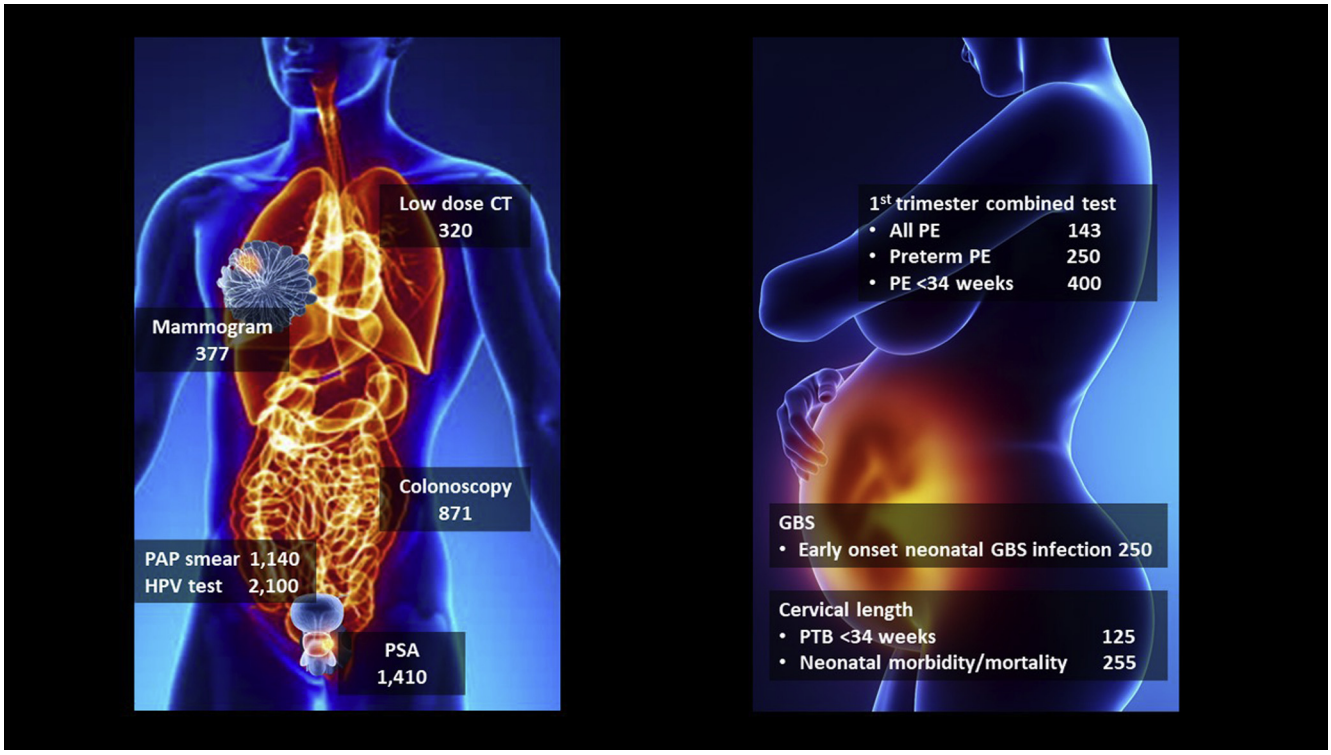
FIGURE 10
NNS in clinical oncology (left) and obstetrics (right)



The number represent NNS for each condition. Numbers derived from the following publications: lung cancer, National Lung Screening in Trial Research Team et al[164]; breast cancer, Nelson et al[165]; colorectal cancer, Schoen et al[166]; cervical cancer, Benedet et al[167] and Ronco et al[168]; prostate cancer, Hugosson et al[169]; PE, ASPRE trial, Rolnik et al[38] and Rolnik et al[101]; preterm birth, Conde-Agudelo and Romero[170]; GBS, Ohlsson and Shah.[171]

CT, computerized tomography; *GBS*, Group B Streptococcus; *HPV*, human papilloma virus; *NNS*, number needed to screen; *PAP*, Papanicolaou; *PE*, preeclampsia; *PSA*, prostate-specific antigen; *PTB*, preterm birth.

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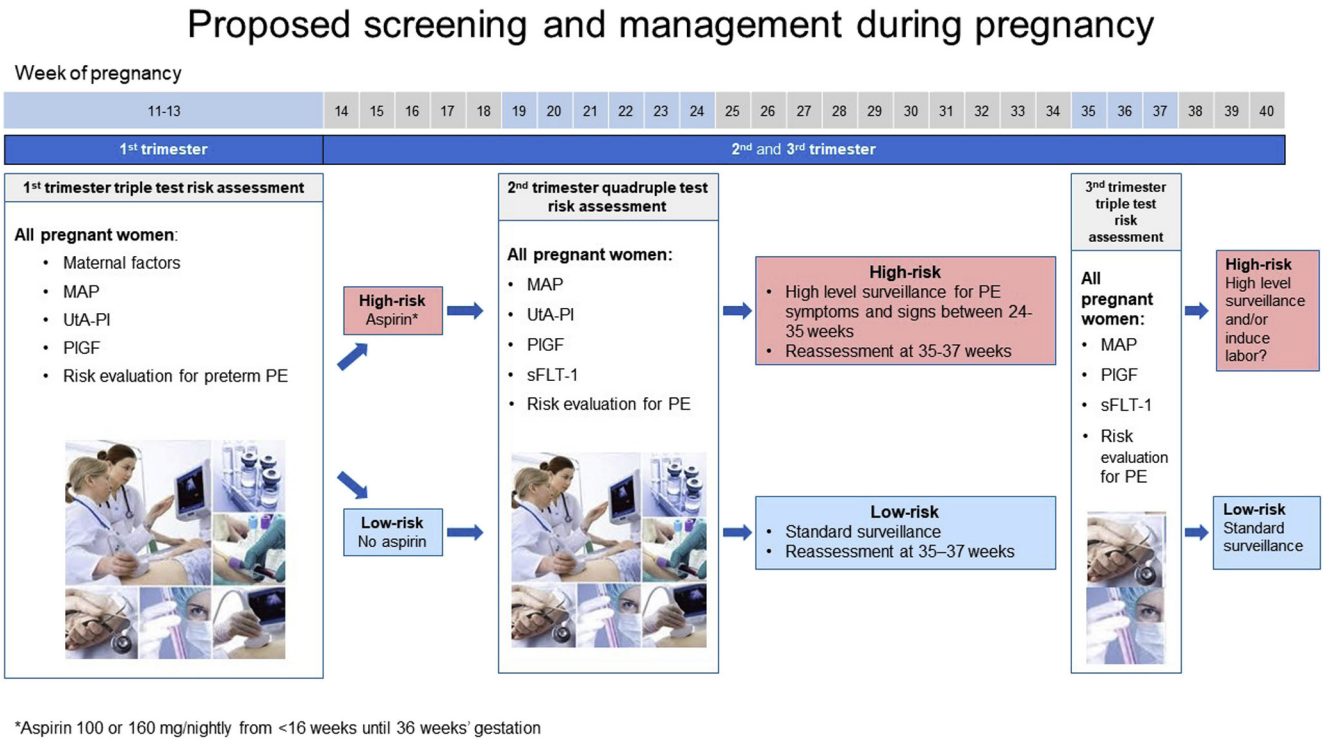
Preeclampsia Prediction In a Low-Resource Setting

In low- and middle-income countries (LMICs), preeclampsia is prevalent, and it is one of the major causes of maternal deaths. In Latin America, including Brazil, hypertensive disorders, mainly preeclampsia, account for 26% of all causes of maternal deaths.[4] Screening of preeclampsia using maternal factors and biomarkers in LMICs is considered challenging as nearly all risk assessment tools have been developed exclusively in high-income countries. It is important to determine whether high-risk women in LMICs have the same risk factors as those in high-income countries and to determine that they have unique risk factors, such as malaria[154] and human immunodeficiency virus.[155] Some factors (eg, diet, smoking status, and coital and partner history) may alter the risk, severity, and pertinent pathophysiology of preeclampsia compared with that observed in high-income countries.[156] Therefore, the prior risk models developed in high-income populations require evaluation in LMICs. Furthermore, tests such as UtA-PI and PLGF are not readily available in primary healthcare settings in LMICs. In contrast, it is anticipated that a combined test with maternal history and MAP can be relatively easier to implement but requires prospective validation. Maternal factors alone or together with MAP can achieve detection rates of 44.8% and 50.5%, respectively, for preterm preeclampsia, at 10% FPR.[61] In view of the lack of resources in these countries, a simplified approach for the measurement of MAP by a validated semiautomated blood pressure device should be considered.[157,158] FIGO recommends that in LMICs, where resources are limited, variations of the first trimester combined test can be considered but the baseline test is one that combines maternal factors with MAP.[43] FIGO encourages all countries and its member associations to ensure that risk assessment and resource-appropriate testing for preterm preeclampsia become an integral part of routine first trimester evaluation protocol offered at all maternal health services.[43]

Most importantly, the biggest challenge for first trimester preeclampsia prediction is that most women in LMICs do not receive prenatal care until late pregnancy. Therefore, an enormous effort must be made to provide education and early access to prenatal care. In addition, there is a need to explore and

FIGURE 11
Proposed model for screening, prediction, and management of preeclampsia starting from the first trimester throughout pregnancy



*Aspirin 100 or 160 mg/nightly from <16 weeks until 36 weeks' gestation

Preeclampsia risk assessment is based on the FMF algorithms.

FMF, Fetal Medicine Foundation; *MAP*, mean arterial pressure; *PE*, preeclampsia; *PLGF*, placental growth factor; *sFLT-1*, soluble fms-like tyrosine kinase-1; *UtA-PI*, uterine artery pulsatility index.

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investigate point-of-care biomarker test(s), which can be easily added to the Bayes theorem–based combined test to improve the predictive performance for preeclampsia.

Number Needed to Screen

Benefits from screening include early awareness by both the physicians and the patients that the pregnancy is at an increased risk of developing preterm preeclampsia and prompt clinical interventions to reduce the severity of or prevent the condition, thus reducing neonatal intensive care unit admission duration, and ultimately, with potential in reducing future risks of adverse outcomes in both the mothers and their children from the affected pregnancy.[159–161] Potential harms from screening include unnecessary anxiety and side effects or complications associated with therapeutic prophylaxis.[162]

In clinical medicine, number needed to screen (NNS) is a tool for measuring screening benefit. This number is defined as the number of people that need to be screened for a given duration to prevent 1 adverse event or outcome of interest. It can be directly calculated from clinical trials of disease screening and can also be estimated from clinical trials of treatment and the prevalence of so far unrecognized or untreated disease.[163]

According to the data from the ASPRE trial, the NNSs based on the use of the first trimester combined test to prevent 1 case of all and preterm preeclampsia are 143 and 250, respectively (Figure 10).[38,101] The NNS for preterm preeclampsia is equivalent to the NNS for the prevention of 1 case of early infection by Group B Streptococcus (GBS) through universal screening for GBS colonization in women at 35 to 37 weeks' gestation (NNS=250).[170,171] Compared with screening tools in clinical oncology, this number is lower than the NNS for the prevention of 1 case of the following: (1) breast cancer through screening with mammography (NNS=377),[165] (2) lung cancer by the use of low-dose computerized tomography (NNS=320),[164] (3) colon cancer by the use of colonoscopy (NNS=871),[166] (4) prostate cancer by the use of prostate-specific antigen (NNS=1410),[169] and (5) cervical cancer through screening with Papanicolaou smear (NNS=1140) and human papilloma virus test (NNS=2100).[167,168]

Future Studies

The FMF first trimester prediction algorithm for preterm preeclampsia performs well and can successfully identify a high proportion of women who will develop the disorder. However, owing to

the complex nature of preeclampsia, no single predictive marker exists. Identifying potential predictive markers, including cardiovascular, immunologic, or inflammatory-related biomarkers and the use of system biology approach to improve overall screening performance for preterm preeclampsia is the focus of ongoing research.[172–189] In addition, the first trimester prediction algorithm is ineffective for the screening of term preeclampsia, raising the hypothesis that the underlying pathophysiology of term preeclampsia is different to that of preterm preeclampsia.[190] Although term preeclampsia is considered to be the milder form of the disorder, it constitutes most preeclampsia cases and, therefore, has a substantial impact on the healthcare system. Furthermore, low-dose aspirin is not effective in preventing term preeclampsia, and this may be because of, first, the suboptimal screening performance of the first trimester prediction algorithm, such that only a small number of high-risk women are given prophylaxis and, therefore, a reduction in the rate of the disorder is not observed, and second, the hypothesis that term preeclampsia is not a placenta-mediated complication and is, therefore, not amenable to aspirin prophylaxis.[190,191] There is a need for better methods of prediction and prevention of term preeclampsia. Another direction for future research is to evaluate a comprehensive approach for preeclampsia management from first trimester screening to risk stratification of evolving preeclampsia in the second and third trimester of pregnancy (Figure 11).

Conclusion

Major advances in preeclampsia screening have been made over the last decade. The traditional approach to screening, as proposed by the NICE or ACOG guidelines, which are based on a checklist of maternal risk factors, has limited predictive performance, and can no longer be considered sufficient for predicting preeclampsia effectively. Such guidelines should be updated to reflect recent scientific evidence that the target of screening should be preterm preeclampsia, the best way to identify the high-risk group is the Bayes theorem–based method that combines maternal factors and biomarkers, aspirin should be started before 16 weeks' gestation, and screening should be done during the first trimester of pregnancy. ■

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SUPPLEMENTAL TABLE 1

Combined first trimester preeclampsia prediction model developed from cohort studies

First author, year	Populations	Prevalence of PE (%)	Model	Detection rates
Poon et al,[64] 2009	Total (n=7797), control (n=7504), PE (n=157), GH (n=136)	2.0	Maternal factors, UtA-PI, MAP, serum PAPP-A, and PLGF	At 5% FPR • Early-onset PE, 82.8% • Late-onset PE, 35.7% • GH 18.3%
Audibert et al,[93] 2010	Nulliparous women only, total (n=893), early-onset PE (n=9), late-onset PE (n=31), GH (n=20)	4.5	Maternal factors, PAPP-A, inhibin-A, PLGF	At 10% FPR • All PE, 31.8% • Early-onset PE, 75%
Goetzinger et al,[94] 2010	Total (n=3716), control (n=3423), PE (n=293)	7.9	Maternal factors, PAPP-A	At 10% FPR • Model based on score; score of $\geq$2 had DR of 36.4% at 86.8% specificity, LR+2.8, LR−0.73
Akolekar et al,[95] 2011	Total (n=33,602), control (n=32,850), PE (n=752)	2.2	Maternal factors, UtA-PI, MAP PAPP-A, PLGF, inhibin-A, activin-A, sEng	At 10% FPR • Early-onset PE, 95.2% (95% CI, 89.1−98) • Intermediate PE (delivery 34−37 wk) 88.3% (80.5−93.2) • Late-onset PE, 71.1% (95% CI, 61.6−79.1)
Odibo et al,[79] 2011	Control (n=410), PE (n=42), early-onset PE (n=12)	9.3	PP-13, PAPP-A, mean UtA-PI	At 10% FPR • All PE: each individual biomarker had DR of 45%−50% • Combinations of markers do not improve
Wright et al,[68] 2012	Control (n=57,458), PE (n=1426)	2.4	Maternal factors, mean UtA-PI, MAP	• Early-onset PE, 89.7% • Preterm PE, 71.5% • All PE, 56.6%
Akolekar et al,[69] 2013	Total (n=58,884), control (n=57,458), PE (n=1426)	2.4	Maternal factors, UtA-PI, MAP, PAPP-A and PLGF	At 10% FPR • Early-onset PE, 96.3% • Preterm PE, 76.6% • All PE, 53.6%
Scazzocchio et al,[66] 2013	Total (n=5170), PE (n=136), early-onset PE (n=26), late-onset PE (n=110)	2.6	Maternal factors, UtA-PI, MAP, PAPP-A	At 10% FPR • Early-onset PE, 80.8% • Late-onset PE, 39.6%
Baschat et al,[67] 2014	Total (n=2441), PE (n=108), early-onset PE (n=18)	4.4	Maternal factors, MAP, and PAPP-A	At 10% FPR • Early-onset PE, 55% • All PE, 49%

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(continued)

SUPPLEMENTAL TABLE 1

Combined first trimester preeclampsia prediction model developed from cohort studies *(continued)*

First author, year	Populations	Prevalence of PE (%)	Model	Detection rates
Crovetto et al,[96] 2015	Total (n=9462), early-onset PE (n=57), late-onset PE (n=246) A subset of women had PLGF and sFlt-1 (n=853)	3.2	Maternal factors, MAP, UtA-PI, PLGF, sFlt-1	At 10% FPR • Early-onset PE, 91.2% • Late-onset PE, 76.4%
Gabbay-Benziv et al,[97] 2016	Total (n=2433), PE (n=108), early-onset PE (n=18)	4.4	Maternal factor, diastolic BP, PLGF	At 60% FPR • All PE, 90%
O'Gorman N et al,[84] 2016	Total (n=35,948), PE (n=1058), early-onset PE (n=18)	2.9	Maternal factors, UtA-PI, MAP and PLGF	At 10% FPR • Preterm PE, 75% (95% CI, 70–80) • Term PE, 47% (95% CI, 44–51)
Yücel et al,[98] 2016	Total (n=490), PE (n=41)	8.37	UtA-PI, placental volume, PAPP-A	• One parameter abnormal: DR, 92.68%; specificity, 85.2% • 2 parameters abnormal: DR, 85.37%; specificity, 98.89%
Tan et al,[61] 2018	Total (n=61,174), total PE (n=1770), early-onset PE <32 wk (n=493), preterm PE (n=493), term PE (n=1277)	2.9	Maternal factors, UtA-PI, MAP, and PLGF	At 10% FPR • Early-onset PE, 89.5% (95% CI, 83–94) • Preterm PE, 74.8% (95% CI, 71–79) • Term PE, 41% (95% CI, 38–44)
Sonek et al,[99] 2018	Total (n=1068), total PE (n=46), early-onset PE (<34 wk) (n=13), late-onset PE (n=33)	4.3	Maternal factors, UtA-PI, PAPP-A, and AFP	At 10% FPR • Early-onset PE, 85% • Late-onset PE, 27% • Preterm PE, 60% • Term PE, 24% • All PE, 43%
Leite et al,[100] 2019	Total (n=605), total PE (n=34), early-onset PE (<34 wk) (n=18), preterm PE (n=18)	5.6	Maternal factors, MAP and, mean UtA-PI	At 10% FPR • Early-onset PE, 71.4% • Preterm PE, 50% • All PE, 41.2%
Serra et al,[72] 2020	Total (n=7908), total PE (n=161), early-onset PE (n=17)	2.3	Maternal factors, MAP, mean UtA-PI, and PLGF	At 10% FPR • Early-onset PE, 94.1%

AFP, alpha-fetoprotein; *BP*, blood pressure; *CI*, confidence interval; *DR*, detection rate; *FPR*, false-positive rate; *GH*, gestational hypertension; *LR*, likelihood ratio; *MAP*, mean arterial pressure; *PAPP-A*, pregnancy-associated plasma protein A; *PE*, preeclampsia, *PI*, pulsatility index; *PLGF*, placental growth factor; *PP-13*, placental protein 13; *sFlt-1*, soluble fms-like tyrosine kinase; *sEng*, soluble endoglin; *UtA-PI*, uterine artery pulsatility index.

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