Hong Kong J Gynaecol Obstet Midwifery 2019;19(1):56-72 | https://doi.org/10.12809/hkjgom.19.1.07

Screening and prevention of pre-eclampsia: a review

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Pre-eclampsia (PE) is a major cause of maternal and perinatal morbidity and mortality. Early-onset PE requiring preterm delivery is associated with a higher risk of complications in both mothers and babies. It is important to identify pregnant women who are at high risk of developing PE in the first trimester, so that preventive measures can be initiated early to improve placentation and reduce the prevalence and severity of the disorder. This review illustrates that effective screening for early-onset PE can be performed in the first trimester of pregnancy by a combination of maternal risk factors, mean arterial pressure, uterine artery Doppler ultrasonography, and placental growth factor. This prediction algorithm has detection rates of 90%, 75%, and 41% for very-early (delivery <32 weeks), preterm (delivery <37 weeks), and term (delivery ≥37 weeks) PE at 10% false positive rate, respectively. This model has been validated in several populations. Recent evidence has demonstrated that administration of low-dose aspirin (150 mg/nightly) starting at 11-14 weeks of gestation to high-risk women is effective in reducing the risk of preterm PE and the length of stay in neonatal intensive care unit.

Introduction

Pre-eclampsia (PE) is a multisystem disorder of pregnancy characterised by new onset of hypertension and significant proteinuria after 20 weeks of gestation[1-7]. It affects 2% to 5% of pregnant women and is a leading cause of maternal and perinatal morbidity and mortality. Worldwide, 76 000 women and 500 000 babies die yearly from this disorder[8]. PE can be divided into early onset (with delivery at <34 weeks of gestation), late onset (with delivery at ≥34 weeks of gestation), preterm (with delivery at <37 weeks of gestation), and term (with delivery at ≥37 weeks of gestation). Early-onset or preterm PE is associated with a higher risk of adverse maternal and perinatal outcomes than late-onset or term PE[9,10].

PE is a two-stage process in which the first stage is caused by inadequate trophoblast invasion, resulting in failure of physiologic transformation of spiral arteries[1,11]. The second stage is characterised by placental dysfunction, followed by production of oxidative stress, inflammatory cytokines, angiotensin 1 autoantibodies, and imbalance in angiogenic/anti-angiogenic factors, causing widespread endothelial dysfunction and clinical features of this disorder[12].

It is important to identify pregnant women who are at high risk of developing PE in the first trimester, so that preventive measures can be initiated early to improve placentation and reduce the prevalence and severity of the disorder[13,14]. In addition, high-risk women can benefit from increased antenatal surveillance, thus allowing detection of PE at the earliest for appropriate management in order to minimise the risk of associated complications to both the women and babies[14]. Recent advances have made it possible to predict and prevent PE in the first trimester of pregnancy, but effective prediction and prevention of PE is limited to early-onset PE.

First trimester screening for pre-eclampsia

Maternal history

According to the National Institute for Health and Care Excellence (NICE)[15] in 2010, the presence of any one of the following high risk factors (hypertensive disease in previous pregnancy, chronic hypertension, chronic renal disease, diabetes mellitus or autoimmune disease) or any two or more moderate risk factors (nulliparity, age >40 years, body mass index [BMI] ≥35 kg/m^2, family history

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of PE, or inter-pregnancy interval >10 years) is considered high risk for PE (Table 1).

According to the American College of Obstetricians and Gynecologists (ACOG)[16-18] in 2013, women are classified as high risk if they have: (1) a history of early-onset PE and preterm delivery at <34 weeks of gestation, or (2) a history of recurrent PE (Table 1).

In 2014, the US Preventive Services Task Force expanded the indications for the use of low-dose aspirin for the prevention of PE[17]. Low-dose aspirin (81 mg/day, starting after 12 weeks) should be given to women with one or more high risk factor (history of PE, renal disease, autoimmune disease, type 1 or type 2 diabetes mellitus, or chronic hypertension) or two or more moderate risk factors (first pregnancy, age >35 years, BMI >30 kg/m^2, family history of PE, sociodemographic characteristics, and personal history factors)[17].

In 2018, ACOG endorsed these indications for the use of low-dose aspirin for the prevention of PE[18]. High risk women are recommended to commence daily low-dose aspirin (81 mg/day) starting between 12-28 weeks (optimally before 16 weeks) and continue until delivery (Table 1). The approach recommended by the NICE and ACOG essentially treats each risk factor as a separate screening test with additive detection rate (DR) and screen positive rate. Evidence supporting these recommendations is mainly based on retrospective epidemiological studies of associations between individual risk factor and the development of PE; and most studies have not differentiated between preterm and term PE.

A first trimester screening study of 9149 singleton pregnancies evaluated maternal risk factors profile according to the severity of PE using multivariable regression analysis[19]. An increased risk of early-onset PE was associated with women of Afro-Caribbean origin (adjusted odds ratio [OR]=3.64, 95% confidence interval [CI]=1.84-7.21, p<0.001), a history of PE (adjusted OR=4.02, 95% CI=1.58-10.24, p<0.001), chronic hypertension (adjusted OR=8.70, 95% CI=2.77-27.33, p<0.001), and those who conceived with ovulation induction (adjusted OR=4.75, 95% CI=1.55-14.53, p<0.001). For late-onset PE, the risk increased with maternal

Table 1. Women at risk for pre-eclampsia (PE) according to professional organisations

National Institute for Health and Care Excellence, 2010[15]	American College of Obstetrics and Gynecology, 2013[16]	American College of Obstetrics and Gynecology, 2018[17,18]
Any one of the high risk factors: • Hypertensive disease in a previous pregnancy • Chronic kidney disease • Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome • Type 1 or 2 diabetes mellitus • Chronic hypertension Or Any two of the moderate risk factors: • First pregnancy • Age >40 years • Pregnancy interval >10 years • Body mass index of ≥35 kg/m^2 at first prenatal visit • Family history of PE	Any one of the following: • Primiparity • Previous preeclamptic pregnancy • Chronic hypertension • Chronic renal disease • History of thrombophilia • In vitro fertilisation • Family history of PE • Type 1 or 2 diabetes mellitus • Body mass index of >30 kg/m^2 • Systemic lupus erythematosus • Age >40 years Aspirin (60-80 mg/day beginning in the late first trimester) is recommended if having: (1) history of early-onset PE and preterm delivery at <34 weeks of gestation, or (2) >1 previous history of PE	High risk factors: • History of PE, especially when accompanied by an adverse outcome • Chronic hypertension • Type 1 or 2 diabetes mellitus • Renal disease • Autoimmune disease (systemic lupus erythematosus, antiphospholipid syndrome) Moderate risk factors: • Nulliparity • Body mass index of >30 kg/m^2 • Family history of PE (mother or sister) • Sociodemographic characteristics (African American race, low socioeconomic status) • Age ≥35 years • Personal history factors (low birthweight or small for gestational age, previous pregnancy outcome, >10-year pregnancy interval) Aspirin (81 mg/day beginning between 12- 28 weeks) is recommended if the patient has ≥1 high risk factors or ≥2 moderate risk factors

age (adjusted OR=1.04, 95% CI=1.00-1.07, p<0.001), BMI (adjusted OR=1.10, 95% CI=1.07-1.13, p<0.001), family history (adjusted OR=2.91, 95% CI=1.63-5.21, p<0.001), and a history of PE (adjusted OR=2.18, 95% CI=1.24-3.83, p<0.001). Additionally, late-onset PE was more common in Afro-Caribbean and South Asian women (adjusted OR=2.66-3.31). Maternal risk factors alone yielded a detection rate of 37% for early-onset PE and 29% for late-onset PE at 5% false-positive rate (FPR)[19].

A large systematic review and meta-analysis of 92 studies, including 25 356 688 pregnancies, was conducted to determine the association between clinical risk factors identified before 16 weeks of gestations and the risk of PE[20]. The most significant risk factors for PE were women with a history of PE (relative risks [RR]=8.4, 95% CI=7.1-9.9) and chronic hypertension (RR=5.1, 95% CI=4.0-6.5). Other clinical risk factors for PE included nulliparity (RR=2.1, 95% CI=1.9-2.4), maternal age >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), pre-pregnancy 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)[20].

The performance of NICE and ACOG recommendations in screening was evaluated in about 9000 singleton pregnancies at 11-13 weeks of gestation. Screening by NICE recommendation detected 41% (95% CI=62-85) of preterm PE and 34% (95% CI=27-41) of term PE at 10% FPR[21]. Screening by 2013 ACOG recommendation detected 5% (95% CI=2-14) of preterm PE and 2% (95% CI=0.3-5) of term PE at 0.2% FPR[21]. Screening by 2018 ACOG recommendation detected 90% (95% CI=79-96) of preterm PE and 89% (95% CI=84-94) of term PE at a FPR of 64%[21]. Although recognition of maternal risk factors is useful in identifying at risk women in clinical practice, it is not sufficient for effective prediction of PE[22].

Biomarkers

Biomarkers can be used to predict PE in the first trimester of pregnancy. Combination of biomarkers has better predictive performance than single biomarker[13]. Thus, the combination of maternal risk factors, biophysical (mean arterial pressure [MAP] and uterine artery Doppler measurement) and biochemical (maternal serum placental growth factor [PLGF]) markers in a multivariable model is the best approach for PE screening in the first trimester of pregnancy.

Mean arterial pressure

Accurate measurement of maternal blood pressure (BP) antenatally is the mainstay for early detection and diagnosis of PE. Women who develop PE typically have an elevated BP in the first and second trimesters of pregnancy[23-26]. In a systematic review of 60 599 women including 3341 cases with PE, MAP predicted PE with a moderate area under the receiver-operating characteristic curve (AUC) of 0.76 (95% CI=0.70-0.82), whereas systolic and diastolic BP are less effective in predicting PE, with an AUC of <0.70[27]. The systematic review identified considerable heterogeneity between studies in terms of study design, study populations, sample size, and types of BP devices. Standardisation of BP measurement is essential for accurate prediction of PE, and thus it is important to use validated automated BP devices and apply a standard protocol for BP measurement.

The use of mercury sphygmomanometers for BP monitoring has been phased out owing to concerns about clinical performance and safety[28,29]. Methodological problems include inter-observer error, terminal digit preference, and inconsistent cuff deflation rates[30,31]. Automated BP monitors allow standardised measurements to be taken, but accurate measurements still require correct cuff size and patient positioning.

There is a need for specific guidelines for BP measurement in pregnancy. According to the National Heart Foundation of Australia (NHFA)[32], patients are asked to rest for 5 minutes in the sitting position with their backs leaning against the seat, their arms supported at the level of the heart, and legs uncrossed as well as the use of correct cuff size (Figure 1). BP is measured in both arms simultaneously and a minimum of two recordings are made at 1-minute intervals until variations between consecutive reading fall to within 10 mmHg in systolic BP and 6 mmHg in diastolic BP in both arms[32]. When this point of stability is achieved, the average of the last two stable measurements of the left and right arms is calculated and the highest of these two measurements from the two arms is used[33]. However, to achieve BP stability, it is necessary to perform two measurements in both arms in about 50% of cases, three measurements in 25% of cases, and four measurements in 25%[34]. In a prospective study of 5435 healthy women with singleton pregnancy, the prevalence of significant BP inter-arm difference (defined as >10 mmHg) of systolic BP and diastolic BP was 8.3% and 2.3%, respectively, supporting the need to measure BP in both arms[35].

A simplified protocol for BP measurement was

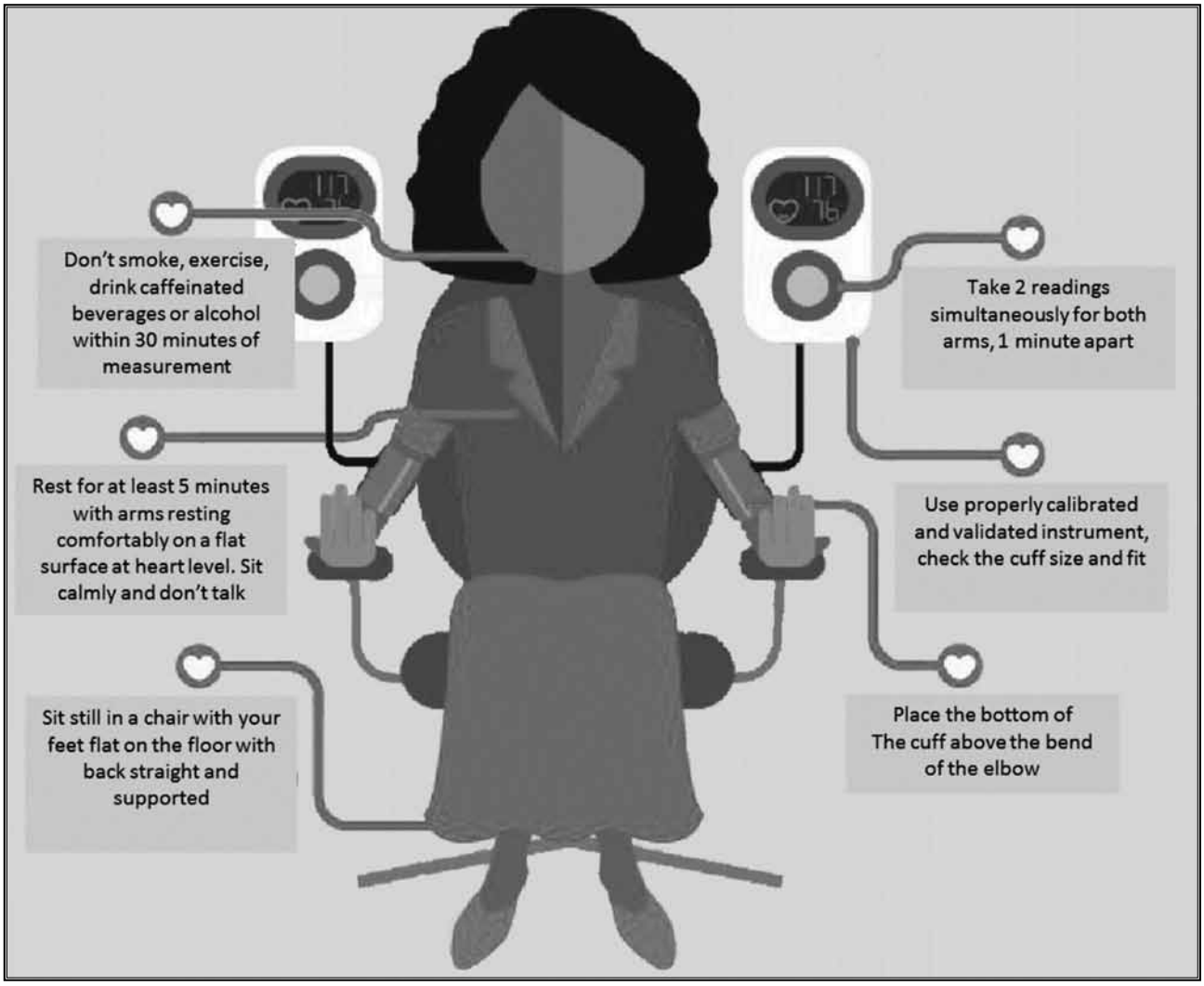

Figure 1. Correct position for blood pressure measurement.

developed in a study of 25505 women with singleton pregnancy where BP measurements were made at 11-13 weeks of gestation with the use of validated automatic devices[34]. The performance of screening for PE with the average of a minimum of two BP measurements from both arms was comparable to that of BP measurement according to the NHFA protocol. Thus, BP should be measured in both arms simultaneously with the correct positioning of patients and the final MAP is calculated from the average of the four measurements.

The measurement of MAP is affected by gestational age at screening, maternal age, racial origin, BMI, smoking, family history of PE, prior history of PE, and history of chronic hypertension and diabetes mellitus[36]. The MAP should be converted to multiple of median (MoM) adjusted for these variables in a multivariable prediction model. In a study of 5590 pregnant women with singleton pregnancy, detection rates for PE at 10% FPR were 43%, 38%, and 63% for maternal history alone, MAP alone, and combination of both, respectively[25]. In a study of >9000 singleton pregnancies screened at 11-13 weeks of gestation to compare the screening performance of systolic BP, diastolic BP, and MAP[26], the MAP performed best, with a detection rate of 76% for early-onset PE, which increased from 47% (based on maternal factors alone) at a FPR of 10%.

Uterine artery pulsatility index

Abnormal uteroplacental circulation can be observed as abnormal uterine arteries by Doppler velocimetry as early as the first trimester of pregnancy. To achieve reproducible, consistent, and accurate screening performance, standardisation for the measurement of uterine artery pulsatility index (PI) is required. According to the Fetal Medicine Foundation (FMF), transabdominal ultrasound is used to obtain a sagittal section of the uterus and to locate the internal cervical os. Then, ultrasound

transducer is kept in the midline and tilted to the lateral sides of the cervix. Colour 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 uterine artery PI and peak systolic velocity are measured by the ultrasound machine to obtain three similar consecutive waveforms. The peak systolic velocity must be >60 cm/s to ensure measurement of the uterine artery PI is performed at the level of the internal os (Figure 2)[37]. Evidence suggests that the uterine artery PI measurement taken at the level of internal os is more reproducible than that obtained at the level of external iliac vessels crossover[38]. The FMF provides a process of accreditation for sonographers to indicate uterine artery PI measurement competency. The measurement of uterine artery PI is associated with gestational age at screening, maternal age and weight, racial origin, history of PE, gestational age at birth of the last pregnancy, and birthweight Z-score[39]. The uterine artery PI needs to be adjusted for these variables by conversion to MoMs before comparing the values between affected and unaffected groups.

In a prospective PE-screening study evaluating the predictive value of the measurement of uterine artery Doppler at 11-13 weeks of gestation in 3107 singleton pregnancies that included 22 cases (0.7%) of early-onset PE and 71 cases (2.3%) of late-onset PE[40], the uterine artery PI MoM was significantly higher in women with PE than in unaffected women. The detection rates by uterine artery PI were 77% (95% CI=55-92) for early-onset PE and 27% (95% CI=17-39) for late-onset PE at a 10% FPR. These findings were confirmed in a follow-up study of 8366 women including 165 cases of PE[41].

In a meta-analysis of first trimester uterine artery Doppler measurement for the prediction of PE that included eight studies (n=41 692) for the prediction of early-onset PE and eleven studies (n=39 179) for prediction of PE of any gestations[42], the first trimester abnormal uterine artery Doppler was defined as the resistance index or PI ≥90th centile, with a pooled detection rate of 48% (95% CI=39-57) at 8% (95% CI=5-11) FPR for early-onset PE, and 22% (95% CI=18-25) at 10% (95% CI=9-10) FPR for late-onset PE. However, measurement of uterine artery PI is under scrutiny because of its methodological challenges and moderate reproducibility[43,44]. An alternative measurement approach through visualisation of the cervix in a transverse plane obtains the uterine artery PI comparable with that obtained through the conventional sagittal approach in terms of reliability, reproducibility, and time required, and is easier to perform[45].

Serum biochemical markers

Maternal serum PLGF has shown promising results in early prediction of PE. It can be measured by several commercially available automated analysers that provide reproducible results within 20-40 minutes of sampling. Similar to measurements of MAP and uterine artery PI, certain maternal and pregnancy characteristics affect the crude serum concentration of PLGF. It is therefore necessary to express the MoM values that adjust for confounders as well as analyser and reagents used[46].

PLGF is a glycosylated dimeric glycoprotein secreted by trophoblastic cells and is part of the angiogenic

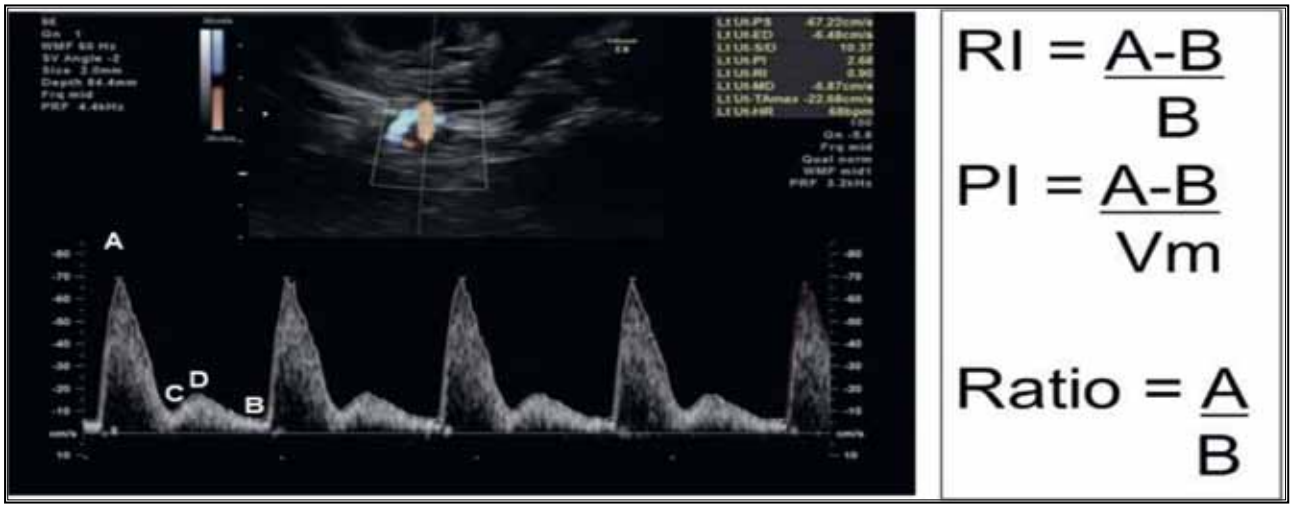

Figure 2: Measurement of uterine artery resistance indices in the first trimester: RI=resistance index, PI=pulsatility index, Vm=mean velocity, A=systolic peak; B=end-diastole, C=start of diastole, and D=maximum diastole

vascular endothelial growth factor family. It binds to vascular endothelial growth factor receptor-1, which increases in pregnancy. PLGF is synthesised in villous and extravillous cytotrophoblasts and has both vasculogenesis and angiogenetic functions. Its angiogenetic abilities may play a role in normal pregnancy, and changes in PLGF levels or its inhibitory receptors have been implicated in the development of PE[47-49].

PLGF can be detected in the maternal circulation from as early as 6 weeks of gestation[50]. Its concentrations increase with gestational age, peaking at 29-32 weeks of gestation and decrease thereafter[49]. Women who subsequently develop PE have significantly lower serum PLGF concentrations in the first trimester than those with unaffected pregnancy[50-53]. In a case-control study of 127 pregnant women with PE and 609 controls, PLGF has a detection rate of 55% (95% CI=33-71) for early-onset PE and 33% (95% CI=24-43) for late-onset PE at a 10% FPR[54]. Similar findings have been observed in larger studies[55,56]. In a systematic review and meta-analysis of performance of maternal serum pregnancy associated plasma protein-A (PAPP-A), human chorionic gonadotropin (hCG), PLGF, and placental protein-13 in the first trimester for the prediction of PE[57], PLGF is superior to the other biochemical markers for predicting PE. Specifically, serum PLGF concentrations alone achieve a detection rate of 40% at 10% FPR, with positive and negative likelihood ratios of 4.01 and 0.67, respectively[57]. The predictive performance is greater for early-onset PE, with a detection rate of 56% (95% CI=52-61), FPR of 9% (95% CI=8-41), positive likelihood ratio of 6.05 (95% CI=5.55-6.55), and negative likelihood ratio of 0.48 (95% CI=0.43-0.52)[57]. The addition of PLGF to maternal factors and uterine artery PI increases the detection rate for early-onset PE from 76% (95% CI=57-90) to 90% (95% CI=73-98) at 10% FPR[54]. Unlike PLGF, the significant increase in levels of soluble fms-like tyrosine kinase-1, an anti-angiogenic protein also binding vascular endothelial growth factor, is only apparent approximately 5 weeks prior to the onset of the condition[49]. Therefore, its contribution to the first trimester prediction algorithm is limited[55].

Pre-eclampsia prediction algorithms

In a systematic review comparing the performance between simple risk models (maternal characteristics only) and specialised models (measurements of MAP, uterine artery PI, and/or biochemical markers) for the prediction of PE[58], 70 models (from 29 studies) were identified: 17 to predict PE of any gestation, 31 to predict early-onset PE, and 22 to predict late-onset PE. Of the 70 models, 22 were simple risk models and 48 were specialised models. The latter performed better in predicting both early- and late-onset PE, with an additional detection rate of 18% (95% CI=0-56) for identification of PE at a FPR of 5% or 10%[58]. Therefore, a combination of various tests rather than a single test is recommended for the prediction of PE.

In a prospective PE-screening study by FMF of 7797 singleton pregnancies that included 157 (2%) cases of PE[59], a combination approach (of maternal factors, MAP, uterine artery PI, serum PAPP-A, and PLGF at 11-13 weeks of gestation) was superior to the traditional checklist-based approach that relies on maternal factors only in detecting PE. Using the first trimester combined test with four biomarkers, the detection rates of early- and late-onset PE at 5% FPR were 93% and 36%, respectively[59].

The first trimester combined test incorporates a novel analytical approach and evolves to the FMF 'competing risk model', which is based on a survival time model for the time of delivery for PE[60,61]. It hypothesised that all women would develop PE if pregnancy were to continue indefinitely. There is a competition between delivery before or after the development of PE. A model that represents the distribution of gestational age at delivery with PE is applied (Figure 3).

The largest study to date for the development of the first trimester PE prediction algorithm using the competing risk model included 61 174 mixed European pregnant women, with 1770 (2.9%) cases of PE[46]. A combination of maternal factors, MAP, uterine artery PI, and maternal serum PLGF yielded the best predictive performance, with detection rates of 90%, 75%, and 41% for very-early (delivery <32 weeks), preterm, and term PE, respectively, at 10% FPR. The incorporation of PAPP-A to the model did not improve the detection rate of PE of any gestational age at delivery[46]. These findings are in line with previous studies[21,55,56].

In a secondary analysis of data from the Aspirin for Evidence-Based Preeclampsia Prevention study that included 34 573 pregnant women, of which 239 (0.7%) cases developed preterm PE[62], at least one of the ACOG criteria was found in 22 287 (64.5%) pregnancies and the incidence of preterm PE was 0.97% (95% CI=0.9-1.1). The incidence of preterm PE increased substantially in those who were positive in the FMF test (4.8%, 95% CI=4.1%-5.6%). When screen negative by the FMF test, the incidence reduced to within or below background levels (0.3%, 95% CI=0.2%-0.3%). The relative incidence in FMF

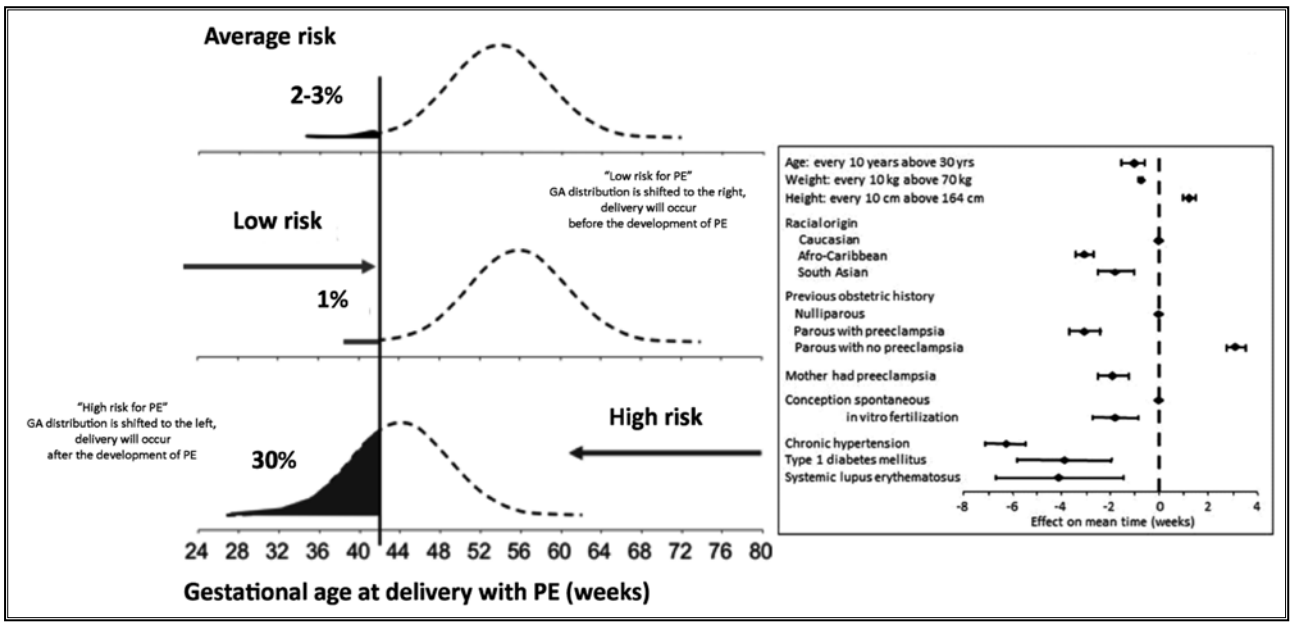

Figure 3: The competing risk model represents the distribution of gestational age at delivery with pre-eclampsia (PE). In women with a low risk for PE, the gestational age distribution is shifted to the right indicating that the gestational age for development of PE will be after delivery. In women with a high risk for PE, the gestational age distribution is shifted to the left indicating that the gestational age for development of PE will occur before delivery. The distribution of gestational age at delivery with PE is defined by two components: (1) the prior distribution based on maternal characteristics, and (2) the distribution of MoM biomarker values with gestational age in pregnancies affected by PE. (Modified from Wright D, Akolekar R, Syngelaki A, Poon LC, Nicolaides KH. A competing risks model in early screening for pre-eclampsia. Fetal Diagn Ther 2012;32:171-8.)

screen negative to FMF screen positive was 0.05% (95% CI=0.04%-0.07%). Similarly, in women fulfilling any of the NICE high risk criteria, the incidence of preterm PE in the subgroup of FMF negative pregnancies was 92% lower than in the positive group (8.7% [95% CI=6.9%-10.9%] vs 0.3% [95% CI=0.3%-1.7%]), and for those with any two or more moderate-risk factors the reduction was 91% (4.9% [95% CI=3.5%-6.8%] vs 0.4% [95% CI=0.2%-0.9%]). Hence, in pregnant women with ACOG/NICE-recognised risk factors who are negative by the FMF test, the risk of preterm PE is decreased to or below background levels[62].

Other first trimester combined prediction models have been developed in different populations (Table 2). Specifically, two Spanish cohort studies developed models that included maternal risk factors, uterine artery PI, MAP, and biochemical markers reported similar predictive performance with that derived from the FMF test[63,64]. In contrast, three combined PE prediction algorithms based on cohort studies in American populations demonstrated lower predictive performance than that from the FMF test[65-67].

Validation studies of existing pre-eclampsia prediction models

The prevalence of the disease, characteristics of the population (ie, low vs high risk, race, height, weight), and variations in biomarkers can influence the effectiveness of screening tests. Specifically, detection rate and FPR are characteristics of a screening test and are only influenced by the test characteristics and the criterion of screen positivity. In contrast, positive predictive value of a screening test is dependent on the prevalence of the disease in the population tested. It is necessary to validate prediction models that have been developed in specific study populations in different populations prospectively (Table 3). External validation 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[68] and it reflects generalisability of the prediction model[69].

In a systematic review[70] evaluating the benefits and harms of 16 PE-screening models that were validated in four studies (n=7123)[71-75], five models were considered good or better discrimination determined by C statistic score >0.8 (Table 4)[60,76-79]. Although all models had low positive predictive value, effective prediction of preterm PE, followed by prevention, was demonstrated in the Aspirin for Evidence-Based Preeclampsia Prevention trial[70].

Table 2. First trimester combined pre-eclampsia (PE) prediction models

Study	Populations	Pre-valence of PE	Model	Detection rate
Poon et al, 2009[59]	Total (n=7797), control (n=7504), PE (n=157), gestational hypertension (n=136)	2.0%	Maternal factors, uterine artery PI, MAP, serum PAPP-A and PLGF	At 5% FPR, 82.8% for early-onset PE, 35.7% for late-onset PE, 18.3% for gestational hypertension
Audibert et al, 2010[123]	Nulliparous women only, total (n=893), early-onset PE (n=9), late-onset PE (n=31), gestational hypertension (n=20)	4.5%	Maternal factors, PAPP-A, inhibin-A, PLGF	At 10% FPR, 31.8% for all PE, 75% for early-onset PE
Goetzinger et al, 2010[124]	Total (n=3716), control (n=3423), PE (n=293)	7.9%	Maternal factors, PAPP-A	At 10% FPR, 36.4% at 86.8% specificity for score of >2, positive likelihood ratio of 2.8, negative likelihood ratio of 0.73
Akolekar et al, 2011[125]	Total (n=33 602), control (n=32 850), PE (n=752)	2.2%	Maternal factors, uterine artery PI, MAP PAPP-A, PLGF, Inhibin-A, activin-A, soluble endoglin	At 10% FPR, 95.2% (95% CI=89.1%-98%) for early-onset PE, 88.3% (95% CI=80.5%-93.2%) for intermediate PE (delivery 34-37 weeks), and 71.1% (95% CI=61.6%-79.1%) for late-onset PE
Odibo et al, 2011[65]	Control (n=410), PE (n=42), early-onset PE (n=12)	9.3%	Placental protein-13, PAPP-A, mean uterine artery PI	At 10% FPR, 45%-50% for all PE by each individual biomarker; combinations of markers do not improve
Wright et al, 2012[60]	Control (n=57 458), PE (n=1426)	2.4%	Maternal factors, mean uterine artery PI, MAP	89.7% for early-onset PE, 71.5% for preterm PE, 56.6% for all PE
Akolekar et al, 2013[79]	Total (n=58 884), control (n=57 458), (n=1426)	2.4%	Maternal factors, uterine artery PI, MAP, PAPP-A and PLGF	At 10% FPR, 96.3% for early-onset PE, 76.6% for preterm PE, 53.6% for all PE
Scazzocchi et al, 2013[63]	Total (n=5170), PE (n=136), early-onset PE (n=26), late onset PE (n=110)	2.6%	Maternal factors, uterine artery PI, MAP, PAPP-A	At 10% FPR, 80.8% for early-onset PE, 39.6% for late-onset PE
Baschat et al, 2014[66]	Total (n=2441), PE (n=108), early- onset PE (n=18)	4.4%	Maternal factors, MAP, and PAPP-A	At 10% FPR, 55% for early-onset PE, 49% for all PE
Crovetto et al, 2015[64]	Total (n=9462), early-onset PE (n=57), late-onset PE (n=246) A subset of women had PLGF and soluble fms-like tyrosine kinase-1 (n=853)	3.2%	Maternal factors, MAP, uterine artery PI, PLGF, soluble fms-like tyrosine kinase-1	At 10% FPR, 91.2% for early-onset PE, 76.4% for late-onset PE
Gabbay-Benziv et al, 2016[126]	Total (n=2433), PE (n=108), early-onset PE (n=18)	4.4%	Maternal factor, diastolic blood pressure, PLGF	At 60% FPR, 90% for all PE
O'Gorman, et al, 2016[55]	Total (n=35 948), PE (n=1058), early-onset PE (n=18)	2.9%	Maternal factors, uterine artery PI, MAP, and PLGF	At 10% FPR, 75% (95% CI=70%-80%) for preterm PE, 47% (95% CI=44%-51%) for term PE
Yucel et al, 2016[127]	Total (n=490), PE (n=41)	8.37%	Uterine artery PI, placental volume, PAPP-A	92.68% at specificity of 85.2% for one abnormal parameter, 85.37% at specificity of 98.89% for 2 abnormal parameters
Sonek et al, 2018[67]	Total (n=1068), Total PE (n=46), early-onset PE (n=13), late-onset PE (n=33)	4.3%	Maternal characteristics, MAP, PLGF, PAPP-A, uterine artery PI and estimated placental volume	At 10% FPR, combination of maternal characteristics, PLGF, and PAPP-A had the best detection rate for PE: 85% for early-onset PE, 60% for preterm PE, 41% for all PE; addition of MAP, uterine artery PI, and estimated placental volume did not improve predictive performance.
Tan et al, 2018[46]	Total (n=61 174), Total PE (n=1770), early-onset PE (<32 weeks) (n=493), preterm PE (n=493), term PE (n=1277)	2.9%	Maternal factors, uterine artery PI, MAP and PLGF	At 10% FPR, 89.5% (95% CI=83%-94%) for early-onset PE, 74.8% (95% CI=71%-79%) for preterm PE, 41% (95% CI=38%-44%) for term PE

Abbreviations: CI=confidence interval, FPR=false-positive rate, MAP=mean arterial pressure, PAPP-A=pregnancy-associated plasma protein A, PI=pulsatility index, and PLGF=placental growth factor

Table 3. External validation studies of the first trimester pre-eclampsia (PE) prediction models

Study	Population	Sample size	Original models	Performance of validation studies (detection rate at 10% false-positive rate)	Performance of original studies (detection rate at 10% false-positive rate)
Farina et al, 2011[71]	Bologna, Italy	n=554, late-onset PE=7% (n=39)	Plasencia et al, 2008	41%	47%
			Plasencia et al, 2007	54%	52%
			Onwudiwe et al, 2008	74%	50%
			Poon et al, 2009	39%	45%
			Poon et al, 2009	41%	47%
			Poon et al, 2009	44%	46%
			Poon et al, 2009	36%	41%
			Poon et al, 2010	85%	57%
Park et al, 2013[72]	Sydney, Australia	n=3066, PE=2.8% (n=83), early-onset PE=0.4% (n=12)	Poon et al, 2010	92% for early-onset PE	95%
Oliveira et al, 2014[73]	Baltimore, Maryland	n=871-2962, early onset PE=1%-1.2%		Early-onset PE:	
			Parra-Cordero et al, 2013	29%	47%
			Scazzocchio et al, 2013	43%	81%
			Poon et al, 2009	53%	89%
			Poon et al, 2010	52%	95%
			Odibo et al, 2011	80%	68%
			Caradeux et al, 2013	30%	63%
				Late-onset PE:	
			Parra-Cordero et al, 2013	18%	29%
			Scazzocchio et al, 2013	31%	40%
Skrastad et al, 2015[75]	Throndheim, Norway	n=541, PE=3.9% (n=21), preterm PE=0.9% (n=5)	Akolekar et al, 2013	80% for preterm PE, 30% for late-onset PE	96% for early-onset PE, 54% for all PE
Allen et al, 2017[81]	Royal London Hospital, UK	n=2500, PE=2.4% (n=60		**Area under the curve**	**Area under the curve**
				Early-onset PE:	Early-onset PE:
			Akolekar et al, 2008	0.718	0.941
			DiLorenzo et al, 2012	0.504	0.893
			Plasencia et al, 2008	0.706	0.931
			Poon et al, 2009	0.765	0.905
			Poon et al, 2009	0.833	0.954
			Poon et al, 2009	0.824	Not reported
			Parra-Cordero et al, 2012	0.702	Not reported
			Scazzochio et al, 2013	0.831	0.960
			Baschat et al, 2014	0.624	0.830
				Late-onset PE:	Early-onset PE:
			Akolekar et al, 2008	0.737	0.941
			DiLorenzo et al, 2012	0.504	0.893
			Plasencia et al, 2008	0.659	0.779
			Poon et al, 2009	0.691	0.790
			Poon et al, 2009	0.828	0.863
			Poon et al, 2009	0.811	Not reported
			Parra-Cordero et al, 2012	0.644	Not reported
			Scazzochio et al, 2013	0.699	0.710
			Baschat et al, 2014	0.631	0.820
Guizani et al, 2017[82]	Brussels, Belgium	n=3239, PE=2.5%, preterm PE=1.1% (n=36), term PE=1.4% (n=44)	O'Gorman et al, 2016	83% for early-onset PE, 81% for preterm PE, 32% for term PE	89% for early-onset PE, 75% for preterm PE, 48% for term PE
Scazzocchio et al, 2017[128]	Barcelona, Spain	n=4203, PE=4% (n=169)	Scazzocchio et al, 2013	86% for early-onset PE, 43% for late-onset PE	75% for early-onset PE, 53% for late-onset PE
Lobo et al, 2017[80]	Sao Paulo, Brazil	n=617, PE=5.5% (n=34)	Akolekar et al, 2013	86% for early-onset PE, 67% for preterm PE, 53% for all PE	96% for early-onset PE, 77% for preterm PE, 53% for all PE
O'Gorman et al, 2017[21]	European populations	n=8775, PE=0.2% (n=17), preterm PE=0.7% (n=59), term PE=2.1% (n=180)	O'Gorman et al, 2016	100% for PE <32 weeks, 80% for preterm PE, 43% for term PE	82% for PE <32 weeks, 75% for preterm PE, 47% for term PE
Tan et al, 2018[85]	European populations	n=16 747, all PE=2.8% (n=473), preterm PE=0.8% (n=142)	O'Gorman et al, 2016	90% for early-onset PE, 82% for preterm PE, 43% for term PE	82% for early-onset PE, 75% for preterm PE, 47% for term PE

Table 4. Summary of five first trimester pre-eclampsia (PE) prediction models and their external validation (Modified from Henderson JT, Thompson JH, Burda BU, Cantor A. Preeclampsia screening: evidence report and systematic review for the US Preventive Services Task Force. JAMA 2017;317:1668-83.)

	PE <34weeks			PE <37weeks	PE ≥34weeks	
Model	Poon et al, 2010	Poon et al, 2010	Odibo et al, 2011	Akolekar et al, 2013	Onwudiwe et al, 2008	Poon et al, 2010
Model variables	Maternal factors, MAP, PAPP-A, uterine artery PI	Maternal factors, MAP, PAPP-A, uterine artery PI	Chronic hypertension, PAPP-A, placental protein-13, uterine artery PI	Maternal factors, MAP, PAPP-A, PLGF, uterine artery PI	Maternal factors, MAP, uterine artery PI	Maternal factors, MAP, uterine artery PI
External validation study	Oliveira et al, 2014	Park et al, 2013	Oliveira et al, 2014	Skrastad et al, 2014	Farina et al, 2011	Farina et al, 2011
Population tested	United States of America	Australia	United States of America	Norway	Italy	Italy
No. (%)	2833 (1.0)	3014 (0.4)	871 (1.1)	541 (0.9)	554 (7.0)	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)	0.85 (0.78-0.93)	0.93 (0.88-0.98)
Detection rate, % (95% CI)	52	91.7 (61.5-98.6)	80	80 (28.4-99.5)	74.4 (60.7-88.1)	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)	36.3	39.3
Negative predictive value	99.6 (99-100)	99.9 (99.7-99.9)	99.8 (99-100)	99.8 (98.8-100)	97.9	98.7

Abbreviations: MAP=mean arterial pressure, PAPP-A=Pregnancy associated plasma protein-A, PI=pulsatility index, PLGF=placental growth factor

Several FMF prediction models have been evaluated in different populations, including Italian[71], Australian[72], American[73], Brazilian[80], mixed European[21,56,75,81-83], and South Chinese[84]. Some validation studies have reported comparable predictive performance corresponding to the original studies[55,56,72,75,82], but some have not[71,73,84]. In a European-wide multicentre, prospective non-intervention study to validate the FMF prediction model that included 8775 pregnant women with 239 (2.7%) having PE[56], the screening performance was comparable to that obtained from the original study and reported detection rates of 100%, 75%, and 43% at 10% FPR for very-early, preterm, and term PE, respectively. In a validation study of the FMF test conducted in a multicentre UK population that included 16747 singleton pregnancies with 473 (2.9%) of cases developing PE[85], predictive performance was similar to the original study in which detection rates were 90% (95% CI=80-96) for early-onset PE, 82% (95% CI=59-75) for preterm PE, and 43% (95% CI=37-48) for term PE at a FPR of 10%.

On contrary, a validation study performed in the American population demonstrated discrepancies of prediction algorithms between validated and original studies[73]. Predictive performance of six first trimester algorithms in 2969 women was evaluated, with rates of early-onset PE being 1.0% to 1.2% and late-onset PE being 4.1% to 5.0%. Maternal characteristics, MAP, and uterine artery PI were recorded in all patients, whereas maternal blood samples for PAPP-A (n=2833), free β-hCG (n=2833), PLGF (n=1565), and placental protein-13 (n=957) were available in subsets of patients. For the prediction of early-onset PE, detection rates (range, 29%-80%) of all models except one[65] at a fixed 10% FPR were lower than those derived from the original studies. Similar observations were reported for the prediction of late-onset PE, with a detection rate of 18% to 31%[73].

First trimester pre-eclampsia prediction in Chinese populations

Biomarker values differ between Chinese and non-Chinese populations[84,86-88]. Specifically, Chinese women have higher median serum PAPP-A, PLGF, β-hCG concentrations in the first trimester of pregnancy than Caucasian women, after adjusting for weight and gestational age[84,89-91]. These variations can affect the screening performance.

In a case-control study of 3330 South Chinese women (3000 in control group, 30 in PE group) evaluated

in the first trimester PE prediction test[84], MAP was measured once from each woman's left arm using a non-pregnancy specific automated BP monitor, uterine artery PI was measured according to the FMF protocol[37,92], and maternal serum PLGF concentrations were measured using the AutoDELFIA platform. Biomarker values were transformed to MoMs and adjusted for maternal and pregnancy characteristics with the use of published expected values from the FMF[79]. The MoM values of MAP and uterine artery PI in the control group based on the FMF model were significantly lower than the original values (mean log10 MAP=0.04, mean log10 uterine artery PI= -0.03, p<0.0001 for both)[84]. Using published models from the FMF and from Spain, predictive performance derived from the South Chinese population was lower than those obtained from the original studies. The poor performance of screening may be due to the lower rate of PE in Chinese population and under measurement of the MAP and uterine artery PI[84]. An Asia-wide prospective validation study of the FMF test is underway and results are expected in early 2019 (ClinicalTrials.gov Identifier: NCT03554681).

Quality assessment

Tools to access quality control include the sequential probability ratio test, cumulative sum[93,94], and target plot. Cumulative sum assesses changes in means or slopes of trend of sequential data (Figure 4)[95]. Target plot evaluates central tendency (deviation from expected median MoM) and dispersion (deviation from expected median standard deviation) [Figure 5]. Cumulative sum is sensitive to detect small shifts over time and the point of shift can be easily visualised[96]. However, its design is more complicated than target plot, which is easy to construct and visualised but requires large datasets and is insensitive.

Quality assessment is relevant in the context of screening for PE, as each biomarker is susceptible to inaccurate measurements, thus affecting performance of screening[97]. The biophysical markers MAP and uterine artery PI are susceptible to significant variability in measurements, mainly as a result from poor adherence to well-defined protocols. Quality control of the uterine artery PI Doppler by using cumulative sum and target

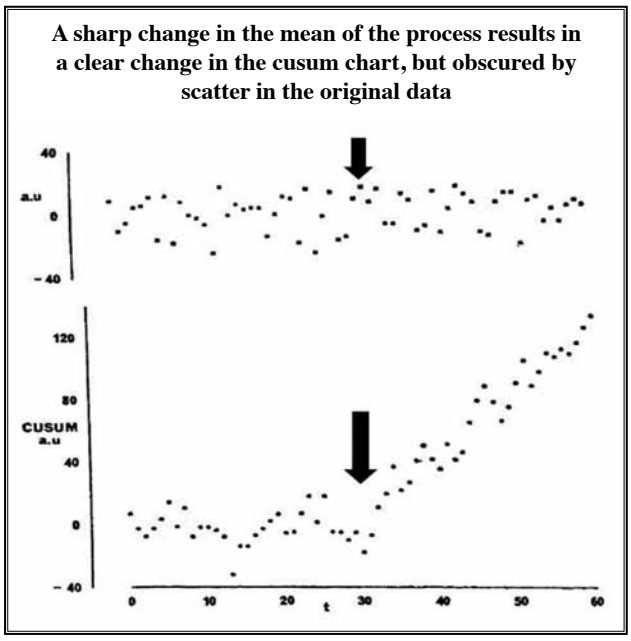

Figure 4: Cumulative sum: the reference value (mean or common reference point) is selected and this value is subtracted from each data point in succession. The successive deviations of the data from the reference value are then added to the previous sum. Changes in the cumulative sum indicate changes 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 (Modified from Chaput de Saintonge DM, Vere DW. Why don't doctors use cusums? Lancet 1974;1:120-1.)

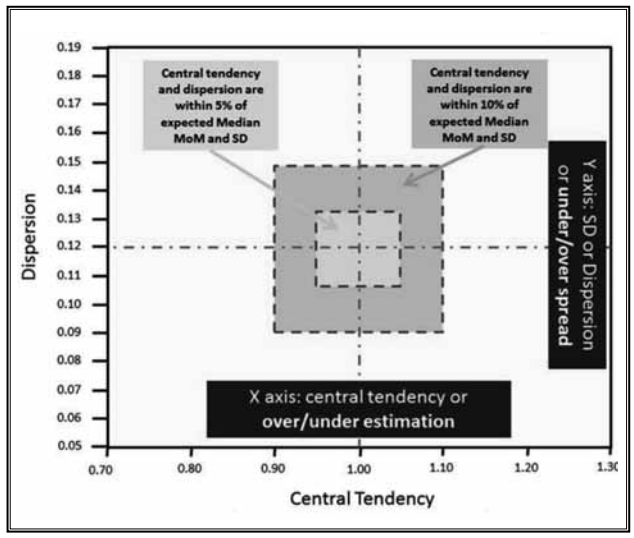

Figure 5: Target plot is a common tool to evaluate central tendency (deviation from expected median multiple of median [MoM]) and dispersion (deviation from expected median standard deviation [SD]). Central tendency is plotted against the X-axis and dispersion is plotted against the Y-axis. Acceptable performance is considered if the central tendency and dispersion are within 10% of the expected median MoM and SD (represented as outer square box, light grey). The inner square box (dark grey) represents that central tendency and dispersion that are within 5% of the expected median MoM and SD. (Modified from Ridding G, Hyett JA, Sahota D, McLennan AC. Assessing quality standards in measurement of uterine artery pulsatility index at 11 to 13 + 6 weeks of gestation. Ultrasound Obstet Gynecol 2015;46:299-305.)

plot demonstrated that detection rates of early-onset PE improved in ultrasonographers who received feedback on their performance than those without any feedback (screen positive rate for early-onset PE, 10% vs 2.7%)[43]. Furthermore, a retrospective cohort study of 21010 first trimester pregnant women showed that overall uterine artery PI MoM was 1.042 (interquartile range=0.85-1.26). Of 46 operators, 42 (91.3%) had more than 50 examinations; 24 (57.1%) of 42 had mean values in the ideal range of 0.95 to 1.05 MoM and 41 (97.6%) of 42 had mean values within the acceptable limits of 0.90 and 1.10 MoM. Ultrasonographers measuring PI <0.95 MoM and >1.05 MoM had, respectively, lower and higher screen positive rates when compared to those with measurements within the 0.95-1.05 MoM range (7.2% vs 13.2% vs 11.2%, p<0.001)[97]. Similarly, inaccurate biochemical marker results may occur because of changes in batch of reagent used, changes in temperature[98], and deviation from the manufacturer's protocol, and failure to implement a continuous quality control process. Therefore, a process for quality control must be performed regularly to ensure data standardisation, reliability, and accuracy. Any deviations of screening values should be promptly investigated for the causes and retraining of the measurement may be required.

Prevention of pre-eclampsia

Effective screening to identify women at risk of developing preterm PE allows early prophylactic treatment and therapeutic intervention. Approaches to prevent PE include administration of low-dose aspirin, heparin, anti-oxidants, calcium supplementation, proton pump inhibitor or metformin. The only proven effective preventive strategy is administration of low-dose aspirin to high-risk women for preterm PE at <16 weeks of gestation[99,100].

Prostacyclin-thromboxane imbalance contributes to vasospasm and coagulation abnormalities and is an underlying mechanism for development of PE. Aspirin is a potential prophylactic agent because it targets prostaglandin pathways and modifies the imbalance between thromboxane A2 and prostacyclin. In 1978, a patient with recurrent PE and thrombocytopenia was reported to benefit from aspirin prophylaxis[101]. Nulliparous women who took aspirin or aspirin-containing compounds for more than once a fortnight throughout pregnancy had a lower risk of PE than those with no aspirin consumption[102]. A randomised, open-labelled trial showed that women at risk of PE or fetal growth restriction, based on obstetric history, who received 300 mg of dipyridamole and 150 mg of aspirin since 12 weeks of gestation until delivery was not complicated by PE, fetal loss, or severe fetal growth restriction, compared to those in the non-intervention group[103].

In an individual patient data meta-analysis of 32217 women including 31 randomised trials of PE prevention, patients who received anti-platelet agents especially aspirin for prevention of PE had a 10% reduction in the rates of PE (RR=0.90, 95% CI=0.84-0.97), preterm birth at <34 weeks of gestation, and serious adverse pregnancy outcomes (a composite of PE, delivery at <34 weeks of gestation, small for gestational age neonates, fetal or maternal death), irrespective of aspirin dosage, starting time and indications[104]. Low-dose aspirin started at 16 weeks or earlier in patients at risk of PE substantially reduced the rate of PE (RR=0.47, 95% CI=0.34-0.65); however, aspirin started after 16 weeks of gestation did not decrease the rate of PE (RR=0.81, 95% CI=0.87-1.10)[105]. Subsequent meta-analyses consistently demonstrated that the administration of low-dose aspirin (50-150 mg/day) to women at risk of PE prior to 16 weeks of gestation significantly reduced the risk of PE[106,107], especially for severe PE with a 78% risk reduction (RR=0.22, 95% CI=0.080-0.567)[106]. Early aspirin was associated with a 50% reduction in the rate of fetal growth restriction and 60% reduction in the rate of perinatal death[100,105].

In a retrospective study comparing a non-intervention cohort with an intervention cohort of women at high risk for PE in the first trimester, the rates of early-onset PE (p<0.01) and preterm PE (p=0.03) significantly reduced in the intervention cohort who were prescribed 150 mg of aspirin[74]. The effect of aspirin is most pronounced in those who are at high risk of early-onset or preterm PE, as a consequence of improved placentation. However, a triple blinded randomised controlled trial of 150 mg of aspirin or placebo to women with abnormal uterine artery Doppler in the first trimester of pregnancy reported no improvement in placentation as represented by the mean value of uterine artery PI at 28 weeks of gestation[108]. Nonetheless, this study excluded women with high risk factors for PE.

In the Aspirin for Evidence-Based Preeclampsia Prevention trial that compared placebo with low-dose (150 mg per night) aspirin started at 11-14 until 36 weeks of gestation, the rate of preterm PE can be reduced by >60% by low-dose aspirin started in high-risk women identified by the FMF prediction model[99]. In this multicentre, double-blind, placebo-controlled trial, 1776 women with singleton pregnancies at high risk of preterm PE were randomly assigned to receive aspirin at a dose of 150 mg per night or placebo from 11 to 14 weeks of gestation until 36 weeks. According to the intention-to-treat principle, logistic

regression analysis was used to determine differences in the incidence of preterm PE between the aspirin and placebo groups, adjusting for the effect of the estimated risk for PE at the screening and participating centres. Excluding those withdrawn and lost to follow-up, 798 participants in the aspirin group and 822 participants in the placebo group were included for analysis. Preterm PE occurred in 13 (1.6%) and 35 (4.3%) participants in the respective groups (OR=0.38, 95% CI=0.20-0.74, p=0.004). Adherence was good with a reported intake of ≥85% of the required number of tablets in 80% of the participants. Low-dose aspirin was safe, with no significant between-group differences in adverse events and serious adverse events. In a secondary analysis of data of 1620 participants with 1571 liveborn neonates, the total (1696 vs 531 days) and mean (31.4 vs 11.1 days) length of stay in neonatal intensive care unit was significantly longer in the placebo than aspirin group[109]. Overall, including those not admitted to the neonatal intensive care unit, the mean length of stay was longer in the placebo than aspirin group (2.06 vs 0.66 days), corresponding a reduction of 68%[109].

In the latest meta-analysis of 16 randomised controlled trials with 18 907 participants[100], administration of aspirin was associated with a reduction in the preterm PE rate (RR=0.62, 95% CI=0.45-0.87) but not with term PE (RR=0.92, 95% CI=0.70-1.21). Only when aspirin was started at ≤16 weeks of gestation at a dose of ≥100 mg/day was associated with a reduction in the frequency of preterm PE (RR=0.33, 95% CI=0.19-0.57, p=0.0001); initiation of aspirin at >16 weeks or the daily dose of <100 mg was not associated with a reduction in preterm or term PE[100].

Evidence is not well established in other potential prophylaxes such as exercise[110,111], heparin[112,113], vitamin C and E[114-117], magnesium[118], folate[119], metformin[120], statin[121], and proton pump inhibitor[122].

Conclusion

Traditional PE screening based on maternal risk factors as proposed by the NICE or ACOG has limited predictive performance. The most promising PE prediction model is the first trimester combined test developed by the FMF that comprises maternal risk factors, MAP, uterine artery PI, and maternal serum PLGF concentration. Measurement of biomarkers can be performed in the same setting for routine screening of common trisomies. The first trimester combined test can identify a high proportion of women that will develop preterm PE, but the performance of screening for term PE is suboptimal[21,46,55,59,60,63-67,71-73,75,80-82,85,123-128]. The first trimester combined test is clinically useful because prophylactic low-dose aspirin (150 mg starting at <16 weeks, nightly) is effective in preventing preterm PE rather than term PE. Low-dose aspirin is safe for both the mother and fetus. Appropriate pre- and post-test counselling and surveillance throughout pregnancy should be provided to high risk women. Further studies are needed to evaluate whether the same PE screening and prevention program is effective in both developing and developed regions of Asia.

Declaration

All authors have no conflicts of interest to disclose.

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