Review

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First Trimester Preeclampsia Screening and Prevention: Perspective in Chinese Mainland

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Abstract

Preeclampsia (PE), a multisystem disorder in pregnancy, is one of the leading causes of perinatal morbidity and mortality that poses financial and physical burdens worldwide. Preterm PE with delivery at <37 weeks of gestation is associated with a higher risk of adverse maternal and perinatal outcomes than term PE with delivery at ≥37 weeks of gestation. A myriad of first trimester screening models have been developed to identifying women at risk of preterm PE. In fact, the Fetal Medicine Foundation (FMF) first trimester prediction model has undergone successful internal and external validation. The FMF triple test enables the estimation of patient-specific risks, using Bayes theorem to combine maternal characteristics and medical history together with measurements of mean arterial pressure, uterine artery pulsatility index, and serum placental growth factor. Establishing a quality control process for regular monitoring and to ensure data standardization, reliability, and accuracy is key to maintaining optimal screening performance. The rate of preterm PE can be reduced by 62% by using the FMF prediction model, followed by the administration of low-dose aspirin. Recent evidence has also demonstrated that metformin has the potential for preventing PE in patients at high-risk of the disorder. In this article, we will summarize the existing literature on the different screening methods, different components of risk assessment, therapeutic interventions, and clinical implementation of the first trimester screening and prevention program for PE with specific considerations for Chinese mainland.

Keywords: Preeclampsia; Chinese population; First trimester; Screening; Prevention

Introduction

Preeclampsia (PE) is a multisystem, progressive, and pregnancy-associated disorder that typically manifests with new onset of hypertension and significant proteinuria after 20 weeks of gestation. It affects approximately 2%–5% of Chinese pregnant women and remains one of the main causes of maternal and perinatal morbidity and mortality.[1–4] PE is associated with maternal complications, including cerebral hemorrhage, impaired renal, hepatic, hematological, and placental functions.[5] The offspring of patients with preeclamptic pregnancies are predisposed to the risk of hypertension, diabetes mellitus, insulin resistance, stroke, and mental disorders in the future.[6]

By characterizing the subtypes of PE, our understanding of PE can be enhanced. The International Federation of Gynecology and Obstetrics (FIGO) has proposed to subclassify PE according to gestational age at delivery as follows: early-onset PE (with delivery at $<34^{+0}$ weeks' gestation), preterm PE (with delivery at $<37^{+0}$ weeks' gestation), late-onset PE (with delivery at $\geq 34^{+0}$ weeks' gestation), and term PE (with delivery at $\geq 37^{+0}$ weeks' gestation).[7] These subtypes of PE are nonmutually exclusive. Early-onset PE is associated with increased risks of fetal growth restriction (FGR) and maternal and perinatal morbidity and mortality.[8]

To date, despite the heterogeneity of clinical presentation, disease severity, and outcomes, recent advances in medicine have made early prediction and prevention of early-onset PE possible.

The current guidelines in Chinese mainland recommend that women should be risk stratified for developing PE using a checklist of maternal factors, and the proposed strategy in preventing PE is to treat with aspirin prophylaxis at 50–150 mg daily from 12–16 weeks' gestation until 26–28 weeks' gestation.[2] Therefore, this review primarily aims to critically appraise the contemporary risk prediction models for PE and the evidence on the prevention action of aspirin and metformin; this review also discusses the specific considerations for implementing the first trimester screening and prevention program for PE in Chinese mainland.

First trimester screening for Preeclampsia

Clinical risk factors of Preeclampsia

A systematic review and meta-analysis of 92 studies involving 25,356,688 pregnancies demonstrated that the most remarkable risk factors for PE are a history of PE (relative risk (*RR*): 8.4; 95% confidence interval (*CI*): 7.1–9.9), followed by chronic hypertension (*RR*: 5.1; 95% *CI*: 4.0–6.5), pregestational diabetes mellitus (*RR*: 3.7; 95% *CI*: 3.1–4.3), pregestational body mass index of >30 kg/m^2 (*RR*: 2.8; 95% *CI*: 2.6–3.1), nulliparity (*RR*: 2.1; 95% *CI*: 1.9–2.4), 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), and maternal age of >35 years (*RR*: 1.2; 95% *CI*: 1.1–1.3).[9]

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Conventionally, the risk of PE in pregnant women has been assessed according to risk factors, maternal characteristics, and medical history, as recommended by several professional organizations, such as the American College of Obstetricians and Gynecologists (ACOG)[10] and the United Kingdom National Institute for Health and Care Excellence (NICE).[11] These approaches are simple to implement. However, these methods result in a binary classification of risk, with consequent suboptimal screening performance, and do not quantify individual patient-specific risks, as they treat each of the risk factors, such as age of 40 years or older, nulliparity, and family history or history of PE, as separate screening tests with additive detection and false-positive rates (FPRs). Screening based on the NICE recommendation in mixed-European populations achieved detection rates of 41% (95% *CI*: 62–85%) and 34% (95% *CI*: 27–41%), at a 10% FPR for preterm and term PE, respectively. The ACOG guidelines achieve detection rates of 90% (95% *CI*: 79–96%) and 89% (95% *CI*: 84–94%), respectively, for preterm and term PE, at an FPR of 64%.[10]

The use of the NICE and ACOG screening recommendations in Asian pregnant women, with the majority of cases Southern Chinese, reportedly achieved detection rates of 26.3% (95% *CI*: 16.3–36.3%) at 5.5% FPR and 54.6% (95% *CI*: 43.5–65.9%) at 20.4% FPR for preterm PE, respectively.[12] The current guidelines in Chinese mainland recommend risk stratification for PE based on a checklist of maternal demographic characteristics and medical and obstetric history, similar to the aforementioned ACOG and NICE guidelines.

Prediction by probability models

Given that the screening performance of the traditional checklist-based approach is limited; alternative screening methods are needed to enhance the prediction of PE. A different approach to screening involves the application of probability models that treat PE as a binary outcome. The approach is based on maternal factors alone or a combination of biophysical and biochemical markers to quantify the individual patient-specific risks for PE.[13–17] In addition, biophysical and biochemical marker values are converted to multiples of the expected normal median (MoM) corrected for the effects of gestational age determined by the fetal crown rump length and maternal characteristics. However, these probability models lack the flexibility of selecting different gestational age cut-offs for categorizing the severity of PE, and these models cannot be easily expanded to include new biomarkers; therefore, separate models are needed for each subtype of PE.

Prediction by Gaussian algorithm

The multivariate Gaussian distribution model is an alternative screening method for early-onset PE. This model has been adopted widely in the routine care settings in Spain.[18] The algorithm combines the a priori risk (based on maternal factor) with the results of placental growth factor (PlGF) and biophysical markers, including mean arterial pressure (MAP) and uterine artery pulsatility index (UtA-PI), to estimate the individual posteriori risk for PE, which is used to classify a pregnant individual as high or low risk for PE. This approach was developed using the data of a small number of patients with early-onset PE, and the detection rates for early-onset PE were 59% and 94%, at 5% and 10% FPR, respectively.[18]

The specification of the Gaussian algorithm is that the likelihood ratio (LR) for the a priori risk estimation was based on information from a meta-analysis and large-scale prospective study that included >25 million pregnancies, instead of that from the study population in which the efficacy of the algorithm was investigated.[18] These factors make the Gaussian algorithm less overfitted than probability models and therefore, more adaptable for patients with different characteristics. However, the Gaussian algorithm has been explored only in a single cohort of subjects, and its predictive performance has not been evaluated in other populations.

Prediction by Bayes' theorem-based method

Another approach for PE screening has been developed by the Fetal Medicine Foundation (FMF), which has been endorsed by the FIGO.[7] This screening approach applies Bayes theorem to combine the a priori risk from maternal characteristics and medical and obstetrical history with MoM values of MAP, UtA-PI, and PlGF (known as the first trimester triple test).[19] Based on this approach, a competing risk model treats the gestational age at delivery with PE as an event in time by a survival-time model. It is assumed that all women would develop PE if the pregnancy were to continue indefinitely and whether they do so or not before a specified gestational age depends on a competition between delivery before or after the development of PE.[20]

This approach showed superior screening performance to others in a study in England as it achieved detection rates of 90%, 75%, and 47% for early-onset, preterm, and term PE, respectively, at an FPR of 10%.[19] The FMF first trimester prediction algorithm was successfully validated for 10,935 singleton pregnancies in Asia, with the majority of patients being of Southern Chinese origin, achieving detection rates of 48.2%, 64.0%, 71.8%, and 75.8% at 5%, 10%, 15%, and 20% FPRs, respectively, for the prediction of preterm PE by the triple test.[12]

In addition, the FMF first trimester prediction algorithm has also been prospectively validated in Australian,[21] American,[22] Brazilian,[23] British,[24] and mixed-European populations.[25–28] Almost all validation studies have reported comparable predictive performance corresponding to the original studies.[21–28]

The algorithm has some advantageous features that confer advantages. It allows the estimation of individual patient-specific risks of PE requiring delivery before the specified gestation and the addition of new biomarkers.[20]

Biomarkers for early prediction of preeclampsia

Numerous studies have investigated the value of potential biophysical and biochemical markers in the prediction of PE in the first trimester. They have demonstrated that a combination of biomarkers is better at predicting PE than single biomarkers.[29,30] The most frequently used biophysical and biochemical markers in PE prediction models are MAP, UtA-PI, and PlGF. These biomarkers have been shown to be affected by gestational age at screening, maternal characteristics, and medical history. For their use in PE screening, conversion of the biomarker values into MoMs after adjustment for confounding variables is essential.[31–33]

Mean arterial pressure

A systematic review involving 60,599 women has demonstrated that MAP serves as a better predictor of PE than systolic and diastolic blood pressure (BP): area under the receiver operating characteristic curve (AUC): 0.76 (95% *CI*: 0.70–0.82) *vs*. 0.68 (95% *CI*: 0.64–0.72) *vs*. 0.66 (95% *CI*: 0.59–0.72).[34] Specifically, in a prospective screening study for PE involving 5,590 singleton pregnancies, the measurement of MAP using validated automated BP devices has been reported to achieved a detection rate of 37.5% at a 10% FPR. A combination of MAP with maternal factors has been found to improve the detection rate to 62.5%.[35]

In a study of a mixed-European cohort comprising 75,841 women with singleton pregnancy, MAP was found to be affected by maternal height, weight, Afro-Caribbean racial origin, cigarette smoking, prior history of PE, family history of PE, interpregnancy interval, chronic hypertension, and diabetes mellitus.[33] After the application of the MoMing formula, the MAP MoM levels of the among Asian pregnant women were found to be 4% lower than that those of the mixed-European women.[36] It is important to account for this regional difference in the MoMing of MAP.

A standardized protocol for MAP measurement has been developed. Pregnant 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. The BP should be measured twice from both arms simultaneously, and the final MAP is calculated from the average of the 4 measurements.

Uterine artery Doppler

In a prospective PE screening study, UtA Doppler was conducted in 3,107 women singleton pregnancies at 11–13 weeks of gestation. The combination of maternal factors and UtA-PI achieved detection rates of 77.3% (95% *CI*: 54.6–92.1%) and 42.3% (95% *CI*: 30.6–54.6%) for early-onset and late-onset PE, respectively, at a 10% FPR.[37] A meta-analysis has investigated the accuracy of 15 UtA Doppler indices in predicting PE in 74 studies and suggested that UtA-PI alone or in combination with notching was the best predictive Doppler parameter. However, the details on the method of determining UtA Doppler indices and reference standards were not uniform in the included studies.[38]

Based on the data of 90,484 women with singleton pregnancy in the first trimester in a mixed-European cohort, UtA-PI was found to be affected by maternal age, weight, racial origin, and prior history of PE.[31] The UtA-PI MoM levels in the Asian population were found to be similar to that expected in the mixed-European population in a nonintervention, multicenter study of 4,023 singleton pregnancies in Asia that applied the MoMing formula.[36]

A standardized protocol for the measurement of UtA-PI has been developed, and the FMF has established an accreditation process (www.fetalmedicine.org). Transabdominal ultrasonography is used to obtain the sagittal section of the uterus and locate the internal cervical os. 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 three similar consecutive waveforms are obtained. The PSV must be at >60 cm/s to ensure that PI measurement is of the uterine artery.

Serum placental growth factor

An imbalance between angiogenic and antiangiogenic factors has been demonstrated to play a fundamental role in the pathogenesis of PE.[39] Serum levels of PlGF, a factor promoting angiogenesis, are significantly lower in patients with PE than in those without PE.[40]

PlGF concentrations in women with normotensive pregnancy increase during the first two trimesters, peaking at 29 to 32 weeks, and decreasing thereafter.[41] Women with low concentrations of PlGF during early gestation have an increased risk of early-onset PE.[42] Specifically, women with a low PlGF level (≤100 pg/mL) have a hazard ratio of 7.17 (95% *CI*: 5.08–10.13) in Cox regression for time to delivery, indicating that a low PlGF correlates with preterm delivery, independent of a diagnosis of PE or gestational age at presentation.[43]

In a meta-analysis of 16 studies including 84,424 subjects to investigate the accuracy of a number of biochemical markers (PlGF, pregnancy-associated plasma protein-A, human chorionic gonadotropin, and placental protein 13) for the prediction of PE, PlGF has been reported as the best predictor for PE (LR+ = 4.01 (95% *CI*: 3.74–4.28), LR– = 0.67 (95% *CI*: 0.64–0.69)).[44] First trimester PlGF has been shown to be predictive of PE, with detection rates of 51.7% (95% *CI*: 32.5%–70.5%) and 32.7% (95% *CI*: 23.5%–42.9%) provided by PlGF alone for early-onset and late-onset PE, respectively, at 10% FPR.[45] Effective PE screening can be conducted with a combination of maternal factors, UtA-PI and PlGF at 11–13 weeks' gestation.[45]

In a study of 38,002 women with singleton pregnancy in a mixed-European cohort, PlGF has been shown to be affected by maternal age, weight, and racial origin.[32] After the application of the MoMing formula, the PlGF MoM levels among Asian pregnant women were found to be 11% lower than that among European pregnant women. Variations in the MoM values according to different PlGF analyzers have also been observed. Therefore, further need for regional adjustment or specific MoMing formulas and corrections for specific PlGF analyzers are needed.

Quality assessment of biomarkers

The importance of accurate measurements of these biomarkers cannot be underestimated, as they impact the risk ascribed to the patients and the screening performance. Establishing standardized methods for biomarker measurements and regular biomarker quality assessment (QA) is relevant in the context of PE prediction.

Two tools are used frequently in medicine to assess quality control including cumulative sum (CUSUM) and target plot. CUSUM is a rapid approach for assessing changes in means or slopes of the trend of sequential data.[46] A change in the CUSUM represents a change in the mean or the trend of the data from the baseline (mean or reference point), allowing the detection of small but persistent changes that are obscured by conventional methods or original data.[47] Therefore, a prospective data monitoring process in combination with feedback provision is feasible with the CUSUM. The target plot is a tool to evaluate the central tendency

(deviation from expected median MoM) and dispersion (deviation from expected median standard deviation (*SD*)). Central tendency and dispersion within 10% of the expected median MoM and *SD* indicate acceptable performance. CUSUM is a sensitive method for detecting small shifts over time and the time point of the shift, and the target plot is easy to interpret and visualize.

In a study of first trimester PE screening, assessing quality assurance of the measurement of UtA-PI using CUSUM and the target plot resulted in improved performance of the measurements in detecting early-onset PE in a group of sonographers who received regular feedback on their performance compared with those who did not receive any feedback (screen-positive rate for early-onset PE: 10% *vs*. 2.7%).[48]

Prevention of preeclampsia

To date, aspirin is the only drug with high-quality evidence demonstrating its benefit in the prevention of PE, and it is recommended for women at high-risk of PE by professional associations.[10] In addition, use of low dose of aspirin is only effective for the prevention of PE when started before 16 weeks' gestation.[49,50] Recently, the use of metformin for the prevention of PE has also gained attention. Increasing evidence from experimental studies and randomized clinical trials (RCTs) indicates that metformin may play a role in preventing PE.[51–53]

Prevention of preeclampsia with aspirin

Various studies have demonstrated that early low-dose aspirin can reduce the risk of preterm PE in pregnant women.[49,50,54,55] In 1979, Crandon and Isherwood[56] proposed that nulliparous women who had taken aspirin during pregnancy (at least once every 2 weeks) were less likely to develop PE than women who did not in a retrospective study. In 2007, a meta-analysis of 31 RCTs including 32,217 women reported that low-dose aspirin reduced the incidence of PE by approximately 10% in pregnant women at risk of PE.[57]

In 2017, the largest multicenter, double-blind, RCT (ASPRE trial) in Europe randomly assigned 1776 singleton pregnant women at high risk for preterm PE, determined by the FMF combined algorithm, to receive aspirin, at a dosage of 150 mg every night or placebo from 11 to 14 weeks of gestation until 36 weeks of gestation.[58] Treatment with low-dose aspirin in women at high-risk for preterm PE resulted in a lower incidence of preterm PE than placebo (odds ratio (*OR*): 0.38; 95% *CI*: 0.20–0.74).[50] In addition, several studies have suggested that starting low-dose aspirin before 16 weeks of gestation can effectively reduce the incidence of preterm PE, FGR, preterm birth, and placental abruption, without increasing maternal and fetal bleeding risk,[49,54,59] while low-dose aspirin initiated at >16 weeks of gestation had a modest or no impact on the risk of PE, severe PE, and FGR.[54] Key international professional bodies such as the International Society for the Study of Hypertension in Pregnancy, FIGO, the International Society of Ultrasound in Obstetrics and Gynecology, etc recommend that women at increased risk of PE receive low-dose aspirin (100–150 mg/d) before 16 weeks of gestation.[7,60,61]

Despite the results of the ASPRE trial demonstrating that aspirin prophylaxis is routinely recommended for women at high risk of PE, there is still some degree of controversy in relation to the optimal dose of aspirin in the context of PE prevention. Studies have demonstrated that a daily dosage ≥100 mg is more effective in the prevention of PE.[49] A meta-analysis including 16 studies with 18,907 participants showed that aspirin reduced the risk of preterm PE only at a daily dosage ≥100 mg (*RR*: 0.33; 95% *CI*: 0.19–0.57).[49] Although 2 other meta-analyses have reported a dose-response effect of aspirin in the prevention of PE up to 150 mg/d,[55,62] the limitation of these meta-analyses is the lack of large RCTs and inclusion of patients in early pregnancy, specifically at ≤16 weeks of gestation. A prospective RCT comparing the efficacy of different dosages of aspirin for the prevention of PE in women who are identified as high risk is needed.

In the last 15 years, an increasing proportion of aspirin-treated patients failed to exhibit optimal platelet response after receiving aspirin treatment, as determined by biochemical and clinical tests. This phenomenon is referred to as "aspirin non-responsiveness."[63,64] Approximately 30% of pregnant women showed a lack of change in platelet function with dosage of 81 mg, as assessed by the closure time obtained with epinephrine cartridges in the PFA-100 Platelet Function Analyzer.[65] Another retrospective cohort study that assessed platelet function using the PFA-100 reported that women determined resistant to 81 mg of aspirin had a lower risk of severe PE when the dose of aspirin was increased from 81 to 162 mg than those who continued with 81 mg.[66] Therefore, trials on the effectiveness of low-dose aspirin in the prevention of preterm PE should use a dose closer to 160 mg rather than 80 mg.

According to the current guidelines in Chinese mainland, the recommended strategy for preventing PE is to initiate aspirin prophylaxis at 50–150 mg daily from 12 to 16 weeks' gestation until 26 to 28 weeks' gestation.[2] Meanwhile, the ACOG recommends aspirin prophylaxis at 81 mg, commencing at 12–28 weeks of gestation (optimally before 16 weeks) until delivery for women at high risk of PE.[10] It is noted that 28 weeks of gestation is the latest recommended time to start aspirin instead of the end time of aspirin prophylaxis. In relation to the dosage of aspirin for the prevention of PE, it is common that different regions adopt different dosages. Overall, aspirin dosage below 100 mg/d is currently used in the mainstream practice. Considering the ASPRE trial included in a mixed-European population with a small number of East Asian women, future prospective multicenter RCTs with larger samples are required to determine the optimal dosage of aspirin for preventing preterm PE in East Asian populations. A recent multicenter RCT including a total of 1000 eligible women demonstrated that aspirin at 100 mg daily did not reduce the incidence of preterm PE, compared with no treatment in pregnant women with conventionally reported high-risk factors in Chinese mainland.[67] However, in another RCT in Chinese mainland, including 1,105 high-risk patients randomized into placebo (n = 284) or aspirin groups (including 3 subgroups: 272 patients in aspirin 25 mg group, 278 patients in aspirin 50 mg group and 271 patients in aspirin 75 mg group), the results showed that low-dose aspirin significantly reduced the incidence of PE and that such prevention was associated with a dose-response effect.[68]

The mechanism by which aspirin can prevent PE has not been fully elucidated. There are many relevant theories on the role of aspirin. There is some evidence showing that aspirin prevents PE by way of improving the function of

trophoblast cells and increasing cell invasiveness.[69,70] Some studies have reported that aspirin may also prevent PE through anti-inflammatory effect by inhibiting the release of inflammatory factors in the placenta.[71,72] Recently, Li *et al.*[73] investigated the impact of aspirin on gestational age advancement by metabolomics analysis and found that aspirin significantly slowed down metabolic gestational age by 1.27 weeks (95% *CI*: 0.66–1.88 weeks) in aspirin-treated high-risk women, compared to in those on placebo, and partially reversed various metabolic changes with the gestational age advancement.

The relative safety of low-dose aspirin in the first trimester has been investigated in large cohort studies, supporting that aspirin is not teratogenic and not associated with increased risk of structural anomalies.[74,75] Furthermore, the use of low-dose aspirin (60–150 mg) in the third trimester has not been associated with premature closure of ductus arteriosus.[76] Lastly, no increased risk of maternal-neonatal bleeding complications and no adverse effects related to epidural anesthesia for women treated with aspirin have been reported.[77–79]

Prevention of preeclampsia with metformin

The incidence of gestational diabetes mellitus (GDM) is increasing annually in Chinese mainland. A meta-analysis of 25 studies involving 79,064 Chinese pregnant women demonstrates that the total incidence of GDM in Chinese mainland was 14.8% (95% *CI*: 12.8–16.7%).[80] Other studies have demonstrated that the incidence of GDM in Chinese mainland varies between 5.1% and 33.3%.[81,82] Advanced maternal age, overweight status, and family history of diabetes mellitus could significantly increase the prevalence of GDM with incidence of 26.7% (95% *CI*: 23.2–30.3%), 30.3% (95% *CI*: 25.9–34.7%), and 32.9% (95% *CI*: 27.5–38.4%), respectively.[80] Despite the most recent survey in Chinese mainland demonstrating an increasing trend of obesity, the prevalence of obesity is still significantly lower than that in Western populations, largely attributed to differences in dietary and lifestyle factors.[83]

Women with GDM have an increased risk of developing PE. Although the pathogenesis of PE remains unclear, it has been accepted that abnormal lipid metabolism caused by GDM leads to dysfunction of vascular endothelial cells and atherosclerosis, resulting in the onset of PE.[84] Population-based retrospective cohort studies in several countries have shown that GDM is independently associated with the occurrence of PE.[85,86] PE also affects the occurrence of GDM. A retrospective cohort study in Korea has demonstrated that women with PE alone during the first pregnancy had an increased risk of GDM during the second pregnancy when compared with women who did not have PE during their first pregnancy (*OR*: 1.2; 95% *CI*: 1.1–1.3), indicating that PE in the first pregnancy serves as an additional risk factor for GDM in subsequent pregnancies.[87] These mentioned studies provide evidence for a positive association between GDM and PE.

In the latest Chinese guidelines on diagnosis and management of GDM, metformin is recommended to control the blood glucose level when patients opt not to use insulin, cannot inject insulin safely, or cannot afford the cost of insulin.[88] In relation to the systematic review and meta-analysis of Chinese RCT with 4663 patients, metformin is a safe and effective alternative to insulin for the management of GDM if patients opt not to receive insulin for any reasons in China.[89] A number of studies have demonstrated that the use of metformin for the treatment of GDM and polycystic ovarian syndrome in pregnancy is not associated with adverse fetal effects.[51] In addition, metformin is associated with a lower risk of pregnancy-induced hypertension and PE. Metformin can reduce the risk of PE by reducing sFlt-1 and soluble endoglin secretion from endothelial cells and primary trophoblasts.[51] These 2 anti-angiogenic molecules derived from the placenta are responsible for endothelial dysfunction and impaired vascular relaxation that have been observed frequently in PE pathogenesis.[51]

A recent RCT reported by Cluver *et al.*,[52] that evaluated metformin versus placebo given to women with preterm PE indicated that women in the metformin group delivered their newborns at a median of 17.5 days after randomization, 9.6 days longer than the 7.9 days in the placebo group. This trial provided proof of concept that metformin treatment for preterm PE is feasible. Furthermore, a meta-analysis of 15 studies including 3,124 pregnant women demonstrated posterior probabilities of metformin, at a median dosage of 1.5 g, having a beneficial effect on the prevention of PE, pregnancy-induced hypertension, and hypertensive disorders of pregnancy (HDP) of 92.7%, 92.8%, and 99.2%, respectively, compared with any other treatment or placebo. These results suggest that metformin treatment is associated with a lower incidence of HDP than other treatments.[53]

Implementation

The FMF competing risk model was developed for providing personalized risk assessment (RA) for PE risk stratification. High-risk women identified through first trimester screening for PE would benefit from timely preventative therapeutic interventions.[20]

Screening for PE using maternal factors and biomarkers in low- and middle-income countries (LMICs) is considered challenging, as nearly all RA tools have been explored exclusively in high-income countries. It is important to identify risk factors for high-risk women in LMICs. Therefore, the existing RA models need to be further validated in LMICs.[90]

The current guidelines on the prediction and prevention of PE in Chinese mainland have acknowledged that the FMF triple test provides accurate results in the first trimester based on the results of the ASPRE trial.[2,50] However, the expert panel has not explicitly suggested this test as a routine first trimester screening tool for PE in Chinese mainland, and recommends that prospective, large-scale studies should take into account the unique characteristics of the Chinese population.[2] An Asia-wide cohort study including pregnant women from Chinese mainland has demonstrated that the FMF first trimester triple test was effective in predicting preterm PE in Asian populations.[12] Regarding clinical implementation of first trimester screening for PE in Chinese mainland, there are various levels of implications and complexity in terms of clinical application and costs of various components of the FMF screening test. The recording of maternal characteristics, medical history, and BP measurements are recorded in antenatal clinics of obstetrics and gynecology departments, while ultrasonography at 11–13 weeks of gestation is performed at ultrasonography departments and/or prenatal diagnostic departments in the

majority of the hospitals in Chinese mainland. Therefore, ultrasonography providers need specific training and accreditation for UtA-PI measurement and a process of QA must be put in place.

In addition, the measurement of serum PlGF has not been widely implemented in daily clinical practice for the early prediction of PE in the Chinese mainland. Especially in settings with limited resources in non–first-tier cities of Chinese mainland, healthcare institutions may face challenges in implementing routine screening for PE with PlGF because of the additional costs associated with the necessary equipment, reagents, and technical support. It is important to be pragmatic about clinical implementation. In settings where the measurements of UtA-PI and PlGF are more readily available and training can be provided, the triple test could be implemented for the early prediction of PE, whereas in settings where it is not possible to measure the UtA-PI and PlGF, the baseline screening should be a combination of maternal factors with MAP, and not maternal factors alone.[7] The proposed PE management for Chinese mainland is presented in Supplementary Figure 1 (http://links.lww.com/MFM/A49).

Currently, a double-blind RCT titled "Aspirin versus Metformin in Pregnancies at High Risk of Preterm PE: a 3-arm Randomized Controlled Trial" is being conducted in Chinese mainland, which is funded by the National Key Research and Development Program of China (no. 2021YFC2701600 and 2021YFC2701604). This study aims to evaluate the optimal dosage of aspirin (75 *vs.* 150 mg) for the prevention of PE and the role of metformin in reducing the incidence of PE. Bayes theorem–based method that combines maternal factors together with MAP and PlGF has been used for risk stratification of PE at 11–13 weeks of gestation to facilitate the implementation within the current infrastructure of antenatal care in Chinese mainland while still achieving an acceptable screening performance for PE.[19] Women who are regarded as high-risk patients for PE following first trimester combined test will be invited to participate in the 3-arm RCT to explore the optimal dosage of aspirin and the role of metformin for the prevention of PE (trial identifier: NCT05580523). The AVERT trial is another important step in clinical research, widespread clinical implementation, and guideline improvement in Chinese mainland with regard to PE prevention strategies.

Conclusion

PE remains one of the leading causes of morbidity and mortality for both mothers and newborns worldwide. Efforts have been made to find strategies for prediction and prevention of PE. Incorporation of screening for preterm PE using the Bayes' theorem-based method that combines maternal factors and biomarkers and offers prophylactic low-dose aspirin before 16 weeks' gestation to high-risk women would be effective approaches for reducing the incidence and severity of preterm PE. In Chinese mainland, awareness of the first trimester screening and prevention of PE has increased. However, prospective research is needed to evaluate the applicability and clinical utility of this "screen and prevent" program in Chinese mainland. There is also a need to compare different dosages of aspirin in preventing PE in women at high-risk and explore other therapeutic interventions for the effective prevention of PE.

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Conflicts of Interest

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