International Journal of Women's Health

Dovepress

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REVIEW

Reviewing Accuracy of First Trimester Screening for Preeclampsia Using Maternal Factors and Biomarkers

Sarah L Malone[1], Rani Haj Yahya[1], Stefan C Kane[1,2]

[1]Department of Maternal Fetal Medicine, the Royal Women's Hospital, Parkville, Victoria, Australia; [2]The University of Melbourne, Department of Obstetrics and Gynaecology, Parkville, Victoria, Australia

Correspondence: Sarah L Malone, Department of Maternal Fetal Medicine, the Royal Women's Hospital, Parkville, Victoria, Australia, Tel +61 3 8345 2000, Email Sarah.Malone@thewomens.org.au

Abstract: Preeclampsia is a common and important complication of pregnancy, one with potentially significant morbidity and even mortality to both mother and baby. Identifying those at high risk of developing the condition is helpful as there is evidence that the incidence of preeclampsia can be reduced with low dose aspirin taken in pregnancy. Accurately predicting the risk of preeclampsia allows for more targeted aspirin prophylaxis and a greater opportunity for early detection of maternal and/or fetal complications associated with impaired placentation through a schedule of enhanced antenatal surveillance. Traditional preeclampsia prediction models use maternal characteristics and risk factors and have been shown to be of low predictive value. Multiparametric screening tests combine patient characteristics with serum biomarkers and ultrasound Doppler indices and have been shown to be more effective at detecting those at high risk of preeclampsia – more specifically, early-onset preeclampsia (onset of preeclampsia <34 weeks' gestation). Multiparametric screening has now been validated in different populations. The true cost effectiveness of a multiparametric screening model for preeclampsia screening is not yet fully known and will vary depending on the clinical setting. Despite the growing body of evidence for its improved detection rates, first trimester preeclampsia screening using multiparametric models is not widely implemented and is not part of the recommendations for antenatal screening from most international bodies. The International Federation of Gynecology and Obstetrics has advised universal preeclampsia screening using maternal risk factors and biomarkers and has strongly encouraged its promotion worldwide. Various barriers to implementation must be considered such as the immediate cost of equipment and training, the need for audit and quality control, and the expected benefit to the population. Low to middle income settings may require a pragmatic approach to the implementation of multiparametric screening given limited resources.

Keywords: preeclampsia, hypertensive disorders of pregnancy, screening, first trimester, serum biomarkers, ultrasound

Plain Language Summary

Preeclampsia is an illness which only develops in pregnancy and can seriously affect both mother and baby. In someone thought to be at high risk of preeclampsia, aspirin can reduce the risk of this condition developing. Identifying which pregnant women are at higher risk of preeclampsia has traditionally involved identifying the mother's age, race, certain medical problems or family history. If they score highly then they may be at higher risk. This has been shown to have limited accuracy. More recently, a different way of predicting risk of preeclampsia has been developed. This involves the mother's details and medical history but adds in results of blood tests (called Placental Growth Factor and Pregnancy Associated Plasma Protein A), blood pressure and the result of an ultrasound which can measure the flow of blood to the womb (Uterine artery pulsatility index). This has been shown in large studies, in many different areas of the world, to be more reliable at finding out who is more likely to get preeclampsia.

Although this new method of identifying those at risk of preeclampsia is more accurate, testing everyone this way would be expensive because of the equipment needed and the training to ensure it was being performed properly. Studies to check if it is financially worthwhile overall have not been done. In low-income settings, it may not be realistic to assess risk for preeclampsia with blood tests and scans as access to these are expensive and may not be a priority.

Received: 1 March 2022
Accepted: 25 August 2022
Published: 19 September 2022

Introduction

Preeclampsia has had varying degrees of incidence reported but is likely to affect between 2–8% of all pregnancies.[1] In the Australian population, the estimated incidence is 3–3.3% and early-onset disease as low as 0.4%.[2,3]

Hypertensive disorders encountered in pregnancy include preeclampsia, chronic hypertension that predates pregnancy, gestational hypertension (de novo hypertension identified in pregnancy without proteinuria or other features of preeclampsia), and superimposed preeclampsia: chronic hypertension with new onset proteinuria or other features after 20 weeks' gestation, or chronic proteinuria with new onset hypertension.[4]

Hypertension in pregnancy is defined as a systolic blood pressure (BP)≥ 140mmHg or diastolic ≥ 90mmHg.[5]

The definition of preeclampsia has evolved over time,[6] and conventionally was characterized by new onset hypertension and proteinuria. The International Society for the Study of Hypertension in Pregnancy (ISSHP) and the American College of Obstetricians and Gynaecologists[7] revised their guidelines to reflect the wide range of clinical manifestations of this condition. The definition was expanded to include cases with renal, hepatic, neurological and/or hematological dysfunction, with proteinuria no longer a requirement for the diagnosis. The Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) and ISSHP also consider fetal growth restriction as a marker of end organ involvement.[5,8,9]

There are two subtypes of preeclampsia, early and late, based on the gestational age at the time of diagnosis. Early preeclampsia is defined as a diagnosis before 34 weeks' gestation and late at ≥ 34 weeks' gestation.[10] Late-onset preeclampsia is more common than early-onset, and whilst it can have significant maternal health consequences, fetal growth is commonly unaffected.[11] Early-onset preeclampsia causes greater maternal morbidity, neonatal morbidity and perinatal death than late-onset, and is more likely to lead to a preterm birth.[12] Adverse short-term maternal outcomes from preeclampsia include acute kidney or hepatic failure, pulmonary edema, cerebral hemorrhage, disseminated intravascular coagulation and progression to eclampsia,[12] as well as an increased risk of a cesarean section.[13] Long-term maternal consequences of preeclampsia are now being increasingly recognized as increased risks of chronic hypertension, ischemic heart disease, cerebrovascular disease, renal disease, diabetes, thromboembolism, hypothyroidism and impaired memory.[14] It is yet to be determined whether preeclampsia is simply an early warning sign of these pathologies that would have developed in later life anyway, or whether its role is in some way causative. It has, however, been observed that preeclampsia is, in high risk women, the first "cardiovascular event" and requires appropriate secondary prevention and follow up.[15] There is a reported four-fold risk after preeclampsia of developing heart failure and a two-fold increase in stroke, cardiovascular disease and death after adjusting for other risk factors.[16] The fetus is at additional risk during pregnancy and in the neonatal period, with a seven-fold increase in stillbirth in pregnancies affected by early-onset preeclampsia compared to normotensive pregnancies, and surviving neonates have a 23% lower birth weight than expected for their gestational age.[12] The Barker hypothesis describes the fetal origins of adult disease: fetuses that are exposed to an adverse intrauterine environment respond by altering their gene expression which in turn leads to changes in metabolism and stress responses.[17] Ex-utero, these changes are maladaptive with the consequence of an increased risk of hypertension and cardiovascular disease in later life.[17,18]

There are estimated to be between 70–80,000 annual maternal deaths and 500,000 annual perinatal deaths secondary to preeclampsia, with 99% of these mortalities occurring in low to middle income countries (LMIC).[19] In high income countries, 90% of preeclampsia is late onset[20] which – although it carries maternal risk of eclampsia, HELLP and other hypertensive complications – has an improved neonatal prognosis. This is not the case in LMICs, where there is an increased incidence of early-onset disease of up to 30% of all preeclampsia.[20] This is a disproportionately high burden of both increased maternal, fetal and neonatal morbidity and mortality in LMICs where the effects are more likely to be "life-ending, life-threatening or life-altering".[19]

The Pathogenesis of Preeclampsia

The cause of preeclampsia is still debated and is likely to be a complex interplay of maternal, genetic and immune factors. There is evidence that, particularly in early-onset preeclampsia, pathological mechanisms originate at the fetal-maternal interface. In a pregnancy destined to develop preeclampsia, cytotrophoblast fails to develop into its endothelial subtype, leading to inadequate remodeling of the spiral arterioles.[4] A subsequent low-flow, high-resistance circulation is

created and this relative ischemia causes oxidative stress and damage to the placental villi.[6] The maternal response to the placental hypoperfusion is characterized by the release of inflammatory cytokines and antiangiogenic factors which cause widespread endothelial dysfunction and associated clinical manifestations thereof.[21,22] The pathophysiology of late-onset preeclampsia is less well understood, with minimal or no abnormal vascular remodeling of the spiral arteries.[12]

The definitive management of preeclampsia is delivery of the placenta and therefore the baby. The competing interests of the mother and the fetus and timing delivery accordingly is a challenge, particularly in early-onset preeclampsia.[12]

Can Preeclampsia Be Prevented?

Clearly, preeclampsia is an important global health concern which warrants attempts to reduce its incidence and associated morbidity. The Cochrane systematic review of the use of aspirin for prevention of preeclampsia and its complications included 40,249 pregnancies in both high and low risk populations, varying aspirin doses, and studies of both primary and secondary prevention.[23] It showed a reduction in the risk of proteinuric preeclampsia with the use of antiplatelet agents (RR 0.82, 95% CI 0.77–0.88) and a reduction in preterm birth <37 weeks gestation (RR 0.91, 95% 0.87–0.95).[23] One of the trials included in the Cochrane review was the ASPRE trial, which has provided evidence that low-dose aspirin is effective in high-risk populations as prophylaxis for preeclampsia.[24] This was a large multicenter prospective randomized controlled trial – with 1620 pregnant women included in the final analysis – which demonstrated that in singleton pregnancies at high risk for preeclampsia, aspirin (150 mg per day) vs placebo taken between 11 to 14 weeks' gestation until 36 weeks reduced the incidence of preterm preeclampsia by 62% (95% CI 0.26–0.8) but had no significant effect on the incidence of term preeclampsia.[24]

The results of ASPRE and 15 other trials were combined in another meta-analysis with a total of 18,907 participants.[25] This meta-analysis showed that aspirin reduces the rate of preterm preeclampsia <32 weeks' gestation (relative risk (RR) 0.62, 95% CI 0.45–0.87) but not that of term preeclampsia (RR 0.92, 95% CI 0.70–1.21). A subgroup analysis assessed the outcomes depending on the gestational age at which aspirin was commenced (≤ 16 weeks' gestation and > 16 weeks' gestation). The reduction in preterm preeclampsia was only observed when aspirin was initiated at ≤ 16 weeks' gestation and at a dose of ≥ 100 mg per day.

There are two hypotheses for this apparent benefit of the early commencement of aspirin:

1. The underlying pathophysiology of preterm preeclampsia differs to that of term preeclampsia, the latter of which has no pharmacological benefit from aspirin.
2. The potential that aspirin indeed does reduce the risk of both preterm and term preeclampsia. It may delay the onset of preeclampsia, meaning that the cases of preterm preeclampsia are prevented but then become term preeclampsia, and term preeclampsia does not eventuate as birth occurs prior.

Aspirin is considered safe and has been used extensively in obstetric practice, not only for the prevention of preeclampsia but also for other adverse pregnancy outcomes.[23] There has been no associated increase in congenital heart defects or other structural anomalies.[26] An early randomized trial on the use of aspirin (60mg per day) reported a significant increase in placental abruption.[27] A recent meta-analysis on the effect of aspirin used for preeclampsia prophylaxis on placental abruption and antepartum hemorrhage concluded that there was no increase in either event at any dose, initiated at any gestation.[28]

The risk of postpartum hemorrhage may be slightly increased with the use of aspirin (RR 1.06 95% CI 1.00–1.12) but the evidence included in this Cochrane review was of only moderate quality.[23] A recently published Swedish registry-based cohort study with 313,624 subjects investigated the association of aspirin with both maternal and neonatal bleeding complications.[29] This study also showed no increased rate of antepartum bleeding in those taking aspirin. However, there was an increased risk of intrapartum bleeding (2.9% in aspirin users vs 1.5% in non-users, adjusted OR 1.63, 95% CI 1.30–2.05), an increase in postpartum hemorrhage (10.2% aspirin users vs 7.8% non-users, aOR 2.21, 95% CI 1.08–1.39), and postpartum hematoma (0.4% aspirin users vs 0.1% non-users, adjusted OR 2.21, 95% CI 1.13–4.34).[29] There was also an increased rate of neonatal intracranial hemorrhage of 0.07% in the aspirin users vs 0.01% in the non-users (aOR 9.66 95% CI 1.88–49.48). Interestingly, when analyzed based on mode of birth, there was a higher incidence of bleeding in those who had a vaginal birth but not in the

cesarean group.[29] This study could not adjust for important confounders which may have made significant contributions to bleeding risk, but with such a large sample size, it does at a minimum challenge the perception that low-dose aspirin in pregnancy is a completely innocuous drug.

Other prophylactic measures for preeclampsia include calcium supplementation. A Cochrane review showed a reduction in preeclampsia (RR 0.45 95% 0.31–0.65) and in those with low calcium diets, the effect was more pronounced (RR 0.36 95% CI 0.2–0.65).[30]

Vitamin D deficiency has been associated with an increased risk of preeclampsia. A recent systematic review and meta-analysis of randomized controlled trials assessed the impact of Vitamin D supplementation on the incidence of preeclampsia. This showed that Vitamin D supplementation was associated with a reduced risk of preeclampsia (OR 0.37, 95% CI 0.24–0.50, p<0.001).[31] Varying preparations and dosages were used among the studies included. A previous meta-analysis of Vitamin D supplementation in pregnancy failed to see a reduction in the incidence of preeclampsia (RR 1.09 95% CI 0.43–2.76). The World Health Organization[32] advise against Vitamin D supplementation for the prevention of preeclampsia.[32] A large, prospective randomized controlled trial of a standardized dose and preparation would be helpful to clarify the efficacy of Vitamin D supplementation in the prevention of preeclampsia.

Several meta-analyses have been published regarding the effect of exercise in pregnancy. These have demonstrated reduced rates of gestational weight gain, gestational diabetes, gestational hypertensive disorders, preterm birth, cesarean delivery and lower birth weight with a higher incidence of vaginal birth.[33] A randomized controlled trial examined the impact of exercise in pregnancy on the incidence of pregnancy-induced hypertension. The participants were of all BMIs and were randomized to the control group or an intervention of an exercise group performing aerobic, strength and flexibility exercises for 3 days a week for 50 minutes. The women in the control group were excluded if they had high levels of baseline physical activity. The women who did not exercise were more likely to develop gestational hypertension (OR 2.96 95% CI 1.29–6.81, p=0.01), and were more likely to gain excessive weight in pregnancy (OR 1.47; 95% CI 1.06–2.03, p=0.02).[34] Although the primary outcome for the study was not preeclampsia, there was a statistically significant reduction in preeclampsia in the exercise group compared to the control group (0.5% vs 2.3%). This advice is part of the International Society for the Study of Hypertension in Pregnancy (ISSHP) recommendations for preeclampsia prevention.

The Role of Screening

Preeclampsia is a condition which lends itself to screening. It is justified for the following reasons:

- Opportunity for prevention through targeted prophylaxis.
- Allow early risk stratification and triage into high-risk care.
- Increased maternal and fetal surveillance. It is known that a delay in diagnosis of preeclampsia can contribute to maternal morbidity and mortality.[35]
- Identification of a population in which trials of novel prophylactic and/or treatment therapies can be performed.[11]

Although there would seem to be minimal confirmed major harm from a liberal use of aspirin, it has been observed that compliance rates are low in groups which are less stringently targeted. Those that are defined as high risk for preeclampsia by the NICE guidelines have a reported compliance rate of only 23%.[36] In the ASPRE trial, where risk was identified by the use of a multiparametric model, patients defined as high risk demonstrated a rate of good compliance – defined as consuming more than 85% of the prescribed tablets – of 79.9%.[24] Compliance in a trial setting is likely to be an inaccurate reflection of real-world use.

Predicting Preeclampsia

Screening by Risk Factors

Traditional assessment of preeclampsia risk has been by history taking, which is an essential part of any clinical encounter and is usually performed at the first antenatal visit. The NICE and ACOG guidelines recommend low-dose aspirin for preeclampsia prophylaxis if a woman has one high risk factor or more than 1 moderate risk factors[37] (Table 1).

Table 1 Current International Screening Guidelines for Identifying Those at High Risk of Developing Preeclampsia

	NICE Guidelines[37]	ACOG/ SMFM/ US Preventative Task Force (USPSTF) Guidelines[80]	ISSHP Guidelines[5]
Indications and prophylactic intervention	**Start 75–100 mg/day of aspirin from 12 weeks if**: **1 high risk factor**: • Hypertensive disease during a previous pregnancy • Chronic kidney disease • Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome • Type 1 or 2 diabetes • Chronic hypertension **Or >1 moderate risk factor**: • First pregnancy • Age 40 years or older • Pregnancy interval of >10 years • Body mass index (BMI) of 35 kg/m^2 or more at the first visit • Multifetal pregnancy.	**Start 81 mg/ day of aspirin between 12–28 weeks gestation (ideally <16 weeks) if**: **1 high risk factor**: • History of preeclampsia, especially when accompanied by an adverse outcome • Chronic hypertension • Pregestational type 1 or 2 diabetes • Autoimmune disease (ie Systemic lupus erythematosus or antiphospholipid syndrome) • Combinations of multiple moderate risk factors. **Or >1 moderate risk factor**: • Nulliparity • Obesity (BMI >30kg/m^2) • Family history of preeclampsia (mother or sister) • Black race (as a proxy for underlying racism) • Lower income • Age 35 or older • Personal history factors (eg low birth weight or small for gestational age, previous adverse pregnancy outcome, >10 year pregnancy interval) • In vitro fertilization.	**When it can be integrated into local health system, multiparametric screening is supported.** **Otherwise**: **Start low dose aspirin (150 mg/kg/day) <16 weeks gestation if high risk preeclampsia, particularly**: • Previous preeclampsia • Pre-existing medical conditions such as chronic hypertension, underlying renal disease or pregestational diabetes. • Multiple pregnancy • Maternal BMI >30 kg/m^2 • Assisted reproduction technology **All pregnant women**: Start calcium (1.2–2.5g/ day) in the face of low calcium intake (<600mg/day) Exercise at least 3 days per week for an average of 50 minutes using a combination of aerobic, strength and flexibility training.

Using this approach, each risk factor is taken as separate screening test with its own odds ratio and does not consider which factors may further increase or even decrease risk. The data informing the NICE guidelines were derived from a systematic review of controlled studies which assessed the individual risk factors for preeclampsia and their relative contribution to the risk of this condition.[38] This identified that the greatest risk factor for developing preeclampsia was the presence of antiphospholipid antibodies (RR 9.72 95% CI 4.34–21.75) and previous preeclampsia (RR 7.19 95% CI 5.85–8.83).[38] The review acknowledged the limitations of this model of prediction, as although the individual risk factors could be assessed, the interplay between them cannot be appreciated: for example, a patient with a high-risk factor who has already had pregnancies without complication may not be as likely to develop preeclampsia.[38] By using the NICE guidelines for preeclampsia screening, the detection rate is 41% for preterm preeclampsia and 34% for term preeclampsia with a false positive rate (FPR) of 10%.[39]

The maternal characteristics for developing preeclampsia are based on research performed in high income countries (HIC).[40] A secondary analysis of the WHO Global Survey on Maternal and Perinatal Health found the 3 most significant associations with the development of preeclampsia to be severe anemia F(AOR 2.98;95% CI 2.47–3.61), chronic hypertension (AOR 7.75; 95% CI 6.77–8.87) and raised BMI ≥ 35 kg/m2 (AOR 3.9; 95% CI 3.52–4.34).[40] Other factors more relevant to the developing-nation setting were also assessed including no maternal education (AOR 1.22 95% CI 1.07–1.39) and pyelonephritis or urinary tract infection (AOR 1.13 95% CI 1.03–1.24). This is important to highlight: since most data come from HIC, it is not known if LMICs – where there is a significant burden from preeclampsia – are being adequately served.

In a further attempt to improve risk estimation, maternal risk factors have been combined in a multivariate regression model to improve detection rates within a certain population. One prospective first trimester screening study identified

factors associated with the development of early-onset preeclampsia as being of Afro-Caribbean origin (OR 3.64 95% CI 1.84–7.21), chronic hypertension (OR 8.7 95% CI 2.77–27.33), history of preeclampsia (OR 4.02 95% CI 1.58–10.24) and conception by ovulation induction (OR 4.75 95% CI 1.55–14.53). The same study identified different associations for the development of late-onset preeclampsia, including maternal age (OR 1.01 95% CI 1.00–1.07), raised BMI (OR 1.10 95% 1.07–1.13), family history (OR 2.91 95% CI 1.63–5.21) or personal history of preeclampsia (OR 2.18 95% CI 1.24–3.83). Late-onset preeclampsia was also seen more frequently in those of Afro-Caribbean and South Asian descent (adjusted OR 2.66–3.31).[41] From this study, the detection rate using logistic regression of maternal demographics in isolation was 37% for early preeclampsia, 28.9% for late preeclampsia, and 20.87% for gestational hypertension at a 5% false positive rate (FPR).

Competing Risk Model Using Multiparametric Screening Tests

The competing risk model treats preeclampsia as an event in time.[42] It assumes that were a pregnancy to continue indefinitely, at some point, preeclampsia will develop. Whether this occurs prior to a specified gestational age is dependent on competition between delivery before or after the onset of preeclampsia.[43] Gestational age at delivery is plotted on a Gaussian curve based on maternal characteristics (including age, weight, height, race, personal and family history of preeclampsia, chronic hypertension, diabetes, systemic lupus erythematosus, antiphospholipid syndrome, method of conception and interpregnancy interval).[44] Those at low risk of preeclampsia would have the Gaussian distribution shifted to the right, and so in these pregnancies it is likely that delivery would occur prior to the development of preeclampsia. In those identified at high risk, the distribution and mean age of delivery is shifted to the left, meaning that delivery would likely occur at an earlier gestation. By combining these risks in a multiparametric model, including those factors that would reduce the risk, the detection rate for preeclampsia is improved. Using only maternal characteristics, the competing risks model could predict any preeclampsia, preeclampsia requiring delivery at <37 weeks and at <34 weeks' gestation at rates of 40%, 48% and 54% respectively, with a FPR of 11%. In comparison, the detection rates using the NICE guidelines are 35%, 40% and 44% respectively.[45] Maternal characteristics in isolation perform poorly as a screening test for hypertensive disorders of pregnancy. The addition of other biophysical or biochemical factors to the a priori risk further improves detection rates. This method is analogous to the model of first trimester combined screening for aneuploidy. This uses the principle of Bayes Theorem of multiplying an a priori risk with the additional likelihood ratio associated with each parameter.[46] Various combinations of biophysical and biochemical components provide different test performance in different populations.

In the following paragraphs we detail the commonly used additional biophysical parameters and biomarkers which have been commonly used in this multiparametric screening model.

Maternal Mean Arterial Pressure (MAP)

Measuring blood pressure (BP) is another routine component of an antenatal visit, and so minimal or no further resources should be required for its implementation in a preeclampsia screening program. Chronic hypertension is a known risk factor for the development of preeclampsia, and even "white coat" hypertension is not as benign as previously assumed.[47]

Blood pressure measured at 11–13+6 weeks' gestation is increased in pregnancies that subsequently develop preeclampsia and gestational hypertension, with a particularly marked increase in those that will develop early preeclampsia.[48] A systematic review and meta-analysis has identified that MAP is a better predictor for preeclampsia than either systolic or diastolic blood pressure taken in the first and second trimesters.[49]

To be a reliable tool, BP must be measured using a validated and reproducible method. The Fetal Medicine Foundation (FMF) protocol includes taking the measurement after five minutes of rest, with the arm at the level of the heart using a regularly calibrated and validated device with an appropriately sized cuff. BP is measured simultaneously in both arms, two measurements are obtained and the average of all four measurements is used.[50] MAP is calculated as 2/3 diastolic BP + 1/3 systolic BP.

Uterine Artery Doppler Analysis

The Doppler waveform of the uterine artery (Ut-A) is the most commonly studied vascular bed in relation to adverse pregnancy outcomes, including preeclampsia. It is possible to measure resistance through this vessel, usually by assessment of the pulsatility index (PI) which, when raised, can be associated with the development of preeclampsia and fetal growth restriction.[51] The convenience of the uterine artery is that it can be interrogated throughout pregnancy at the time of routine ultrasound examinations. Transabdominal or transvaginal approaches are possible, although transabdominal is preferred as transvaginal measurements produce higher PI values.[52]

The uterine artery Doppler parameter is the most at risk of error given that it is highly operator dependent.[53] Accurate acquisition can also be impacted by patient factors such as patient obesity. Again, a validated protocol for its measurement is necessary and should be subject to quality control and audit. Systematic error can potentially under- or overestimate the risk of preeclampsia and significantly change the screen positive rate.[53]

When used in isolation, the Ut-A PI in the first trimester has a sensitivity of 48% and specificity of 92% for the prediction of early-onset PE.[52]

Serum Biomarkers

Several candidate biomarkers have been investigated for preeclampsia prediction. These include serum biomarkers which would increase in preeclampsia, such as soluble endoglin (sEng), inhibin A, activin A, pentraxin-3 and p-selectin, and also those which would decrease such as pregnancy associated placental protein- A (PAPP-A), placental growth factor (PlGF) and placental protein-13 (PP13).[54]

For a given biomarker to be easily implemented in a screening test, it is desirable for it to be already used in other existing testing regimens. For this reason, PAPP-A and PlGF (already used in aneuploidy screening and prediction of preeclampsia in later stages of pregnancy) have been most extensively researched. PlGF is a vascular endothelial growth factor which is essential for angiogenesis of the uteroplacental circulation, low levels of which precede the clinical manifestations of disease.[52] PlGF measured at 11–13 weeks' gestation, as an isolated screening tool, has a detection rate for preeclampsia requiring delivery before and after 34 weeks' gestation of 51% and 32% respectively, at a 10% FPR.[55]

PAPP-A is a glycoprotein produced by the embryo and the trophoblast and has a role in the cleavage of insulin-like growth factor, which regulates placental and fetal development and growth.[52] It is reduced in pregnancies with preeclampsia and as an isolated screening tool has a detection rate of 21.9% at a FPR of 10%.[56]

The analysis of these biomarkers can be undertaken by automated machines, known to provide rapid and reproducible results.[54] Serum soluble fms-like tyrosine kinase-1 (sFLT-1) is also a clinically well-established biomarker for preeclampsia but it is only useful for screening in the third trimester and so has no role in first trimester screening.[42]

The fact that no single marker has been identified to be predictive of preeclampsia likely reflects the heterogenous nature of the disease. Using a competing risks model, various combinations of biophysical and/or biochemical markers can be appraised in addition to maternal characteristics to identify the most practical and accurate combination.

The False Positive Rate

The false positive rate can be set at any arbitrary figure according to the desired detection rate, as is done in first trimester combined screening for aneuploidy. The higher the false positive rate, the greater the detection rate. The consequence of a false positive result in preeclampsia screening is likely to be minimal (aspirin, closer surveillance) in comparison to aneuploidy screening (significant anxiety and invasive testing with risk of pregnancy loss, albeit small).[22]

The Screen Positive Rate (SPR)

A risk of 1:100 is usually deemed as a screen positive result for developing PE <37 weeks gestation.[46] The clinical value of using a risk cut-off that is similar to the background incidence of preeclampsia has been questioned, as have the inconsistent screen positive rates used in different studies.[57] The screen positive rate should be seen as something that could be modified to suit the needs of the population and be subject to regular review.

The Performance of Competing Risk Models

The first prospective study of the performance of the NICE guidelines was the SPREE trial, a prospective study of 17,051 patients comparing preeclampsia risk as defined by the NICE guidelines to risk as defined by a multiparametric competing risk model of screening including mean arterial pressure (MAP) uterine pulsatility index (UtA-PI), serum pregnancy associated plasma protein- A (PAPP-A) and serum placental growth factor (PlGF).[36] Using the NICE guidelines, the screen positive rate was 10.3% with a detection rate of all preeclampsia of 30.4% compared to a higher detection rate of 42.5% with the multiparametric model. The detection rate for preterm preeclampsia was 40.8% using NICE guidelines for screening and 82.4% using the same combination in a multiparametric screening test.

Although other groups have developed similar algorithms, that produced by the Fetal Medicine Foundation (FMF) in the UK is the most widely validated. The largest study of this algorithm combined data from three prospective studies[36,43,58] giving a total of 61,174 singleton pregnancies for analysis.[59] The study showed that the best individual biomarker for prediction of preeclampsia was PlGF, followed by Ut-A PI, MAP and then PAPP-A. The best screening performance was achieved with the combination of maternal factors, MAP, Ut-A PI and serum PlGF. This is now known as the FMF triple test. There was no additional benefit of PAPP-A. Figure 1 illustrates the varying detection rates at an FPR of 10% with a screen positive cut off of 1:100 using different combinations of parameters. For term PE, the FMF algorithm is less reliable. This is because the deviation of the biomarkers from normal is less pronounced in the prediction of term preeclampsia and this is particularly true of the UtA-PI, with which there is little discrimination between unaffected pregnancies and those destined to develop term preeclampsia.[59] This is in contrast to MAP, the performance of which in predicting preeclampsia at term is relatively good.[59]

The Performance of the FMF Algorithm for Demographic Subgroups

The performance of the FMF algorithm has been analyzed by demographic subgroup within the cohort studied. Caucasian parous patients with no history of preeclampsia were the lowest risk group: they accounted for a plurality of the population (34.7%) yet only 12.8% of preterm preeclampsia.[59] This equated to a detection rate for preterm preeclampsia of 54% and a screen positive rate of 3.7%. Likewise, the highest risk group was Afro-Caribbean patients with a history of preeclampsia, who accounted for 0.8% of the population but 7.3% of cases of preterm PE, and for whom the detection rate was 100% for preterm preeclampsia and the FPR 72.8%.[59] This translates to two extremes of screen performance, which is inevitable at a fixed cut off point. This does introduce the notion that an inherently high-risk population would derive negligible benefit from first trimester screening and favors a less judicious approach to empirical aspirin prophylaxis and close surveillance. This is also true of the data regarding performance of the FMF model in first trimester screening for twin pregnancies. These are pregnancies which have high rates of preeclampsia compared to singletons.[60] The FMF group applied combined screening for preeclampsia to 1100 twin pregnancies with the competing risks model using maternal characteristics, MAP, UtA PI and PlGF to predict preeclampsia at <32 weeks, <37 weeks and <42 weeks' gestation with detection rates of 100%, 99% and 97% with a SPR of 75%.[61] The screen-positive cut-off was 1:75.

Is the FMF Algorithm Externally Validated in Other Populations?

The FMF algorithm was derived from a European multi-ethnic population, and so its validity for other populations needs to be assessed. East Asian populations have a naturally lower incidence of preeclampsia, one study having an observed rate of 2.05% in their Chinese population of 10,935 participants. People of East Asian origin represented only 3.5% of the ASPRE cohort.[24] Several prospective studies have shown that the FMF model of screening has a lower detection rate for preterm preeclampsia in Asian populations (with Chinese/East Asian populations the most studied).[62–65] One prospective study identified the FMF algorithm (using maternal characteristics, MAP, Ut-A PI and PlGF) as achieving detection rates of 48.2%, 64%, 71.8% and 75.8% at 5%,10%, 15% and 20% fixed false positive rates, respectively.[64] Another prospective study in China showed similar detection rates of 65%, 72.6% and 76.1% in models using PAPP-A as the only biochemical biomarker and reduced performance using PlGF as the only biochemical biomarker with detection rates of 56.4%, 71.8% and 75.4% at 10%, 15% and 20% fixed positive rates, respectively.[65] This variable performance suggests that the distribution of individual parameters within normal and preeclamptic populations may need to be

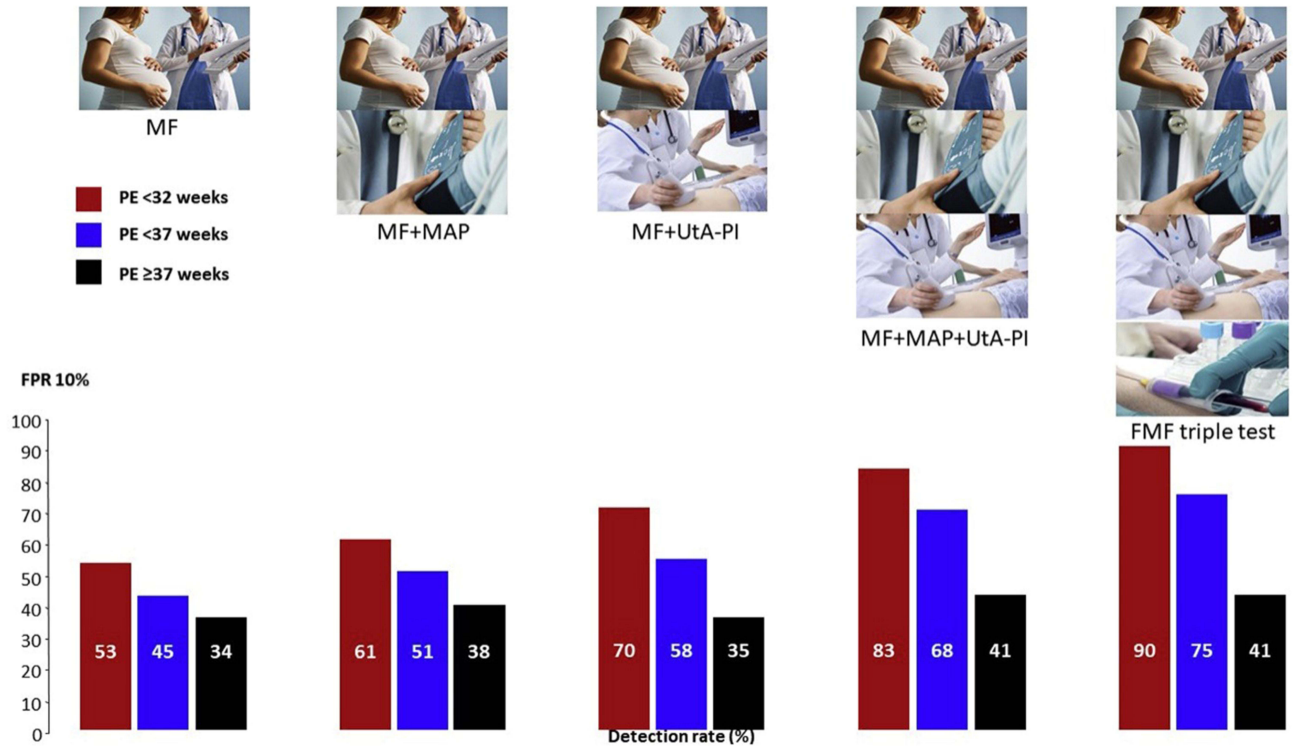

Figure 1 Screening performance of the first trimester FMF prediction model for preeclampsia according to the different combinations at FPR of 10%. Reproduced with permission from Chaemsaithong P, Sahota DS, Poon LC. First trimester preeclampsia screening and prediction. *American journal of obstetrics and gynecology.* Feb 2022;226(2S): S1071-S1097 e2, Copyright 2022, with permission from Elsevier.[22]

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

adjusted for the population in which the test is to be performed. Nevertheless, the FMF algorithm for preeclampsia screening in Asian populations resulted in improved detection rates as compared to either NICE or ACOG guidelines.[64] Other studies in European populations have also demonstrated the FMF algorithm to be effective.[66,67] A small study in Switzerland noted that Ut-A PI was lower in their population which may have been due to incorrect measurement technique[67] – this highlights the importance of correct protocol, training, and audit. A prospective study in Hungary found that, similar to the Asian populations, PAPP-A improved detection rates, whereas the addition of PlGF to the calculation did not.[66]

With this knowledge, introducing screening by the FMF algorithm would still be an improvement on current screening methods. With the acquisition of further population data, it will be possible to adjust the relative contribution of parameters specific to that population, as well as derive the combination with the highest detection rate and most acceptable false positive rate.

Barriers to Implementation

Is First Trimester Screening with Maternal Characteristics and Biomarkers Cost Effective?

Whilst first trimester screening for preeclampsia using the FMF algorithm would be more costly than current risk-based assessments, the cost of preeclampsia to the healthcare system and the community is significant. The average cost for a pregnancy affected by preeclampsia is higher than that of one without. Aside from the maternal cost, the neonatal care is the real short-term cost. Whilst the cost of maternal care rises 2.7 fold, for preterm birth <32 weeks' gestation, the cost of neonatal care increases 35 fold.[68] Although the ASPRE study did not identify a reduction in admissions to the neonatal unit between aspirin and placebo groups (6.8% vs 6.2%), the length of stay was significantly reduced (31.4 days vs 11.1 days respectively).[68] A study in Belgium assessed the cost utility of a first trimester screening strategy using the FMF combined risk algorithm versus screening by risk factors in a nulliparous

population. They factored in a prescription rate of only 50% in those identified as high risk and still found that the cost saving was €28.67 per patient by preventing 337 cases of preeclampsia per year.[69] This could be a conservative estimate given that one UK clinical effectiveness study saw a 99% prescription rate after implementing the FMF algorithm.[70] The study was conducted in a nulliparous population and so it may have proven more cost effective given that if participants were otherwise medically well and in the obvious absence of previous preeclampsia, they would have been deemed low risk.

Knowing that there are adverse health outcomes for people having suffered from preeclampsia and their offspring, one could postulate that preventing a case of preeclampsia may have further downstream long-term cost effectiveness which has the potential to impact generations to come. The true cost effectiveness of multiparametric screening for preeclampsia, both short and long term, is not yet fully known.

To reduce costs, a two-tier test has been proposed whereby patients undergo initial screening with varying combinations of a) maternal factors, b) maternal factors plus MAP and UtA-PI, or c) maternal factors, MAP and PlGF.[71] This is akin to the contingent screening approach for aneuploidy whereby those with intermediate risk for aneuploidy based on first trimester combined screening are offered screening with cell-free DNA (cfDNA), known to have a higher sensitivity and specificity.[72] This reserves the more costly screening test with superior performance (cfDNA) for those it is most likely to benefit, which in turn reduces costs of the screening program. By applying this similar 2 stage principle to first trimester preeclampsia screening, it was shown that in a Caucasian population, a similar screening performance can be achieved with a two-stage strategy using only maternal factors as an initial screen, reserving MAP, UtA-PI and PlGF for 70% of the remaining population.[71] Using maternal factors, MAP and UtA-Pi as a first-tier screen, only 30–40% need go onto PlGF testing.[71] If maternal factors, MAP and PlGF are used initially then only 20–30% go on to a UtA-PI measurement.[71] A two-tier strategy has been suggested by FIGO for low resource settings, with universal maternal factors and MAP, and UtA and PlGF reserved for a subgroup of those initially deemed high risk. Contingency screening has not been assessed in a population of mixed ethnicity: to set a screen positive rate to fit the White demographic would yield a high SPR in the Black and South Asian population.[71] It may be preferable for those high-risk populations to proceed directly to the full testing algorithm.

Multiparametric screening has been designed to be of practical convenience: for example, performance of the Ut-A PI at the time of the first trimester nuchal translucency scan, assessment of analytes as part of combined aneuploidy screening, and blood pressure measurements are already routine. Evidence supporting its improved performance in comparison to risk factor screening for the prediction of preeclampsia (and specifically early-onset preeclampsia) is convincing and consistent, and yet widespread implementation is yet to be seen. Most international bodies have not updated guidance regarding screening since the advent of multiparametric screening: ISSHP has acknowledged and supported the use of multiparametric screening when it can be integrated into the healthcare system and otherwise suggest risk factor screening.[5] FIGO, however, has embraced the concept of multiparametric screening for preeclampsia enthusiastically and has encouraged all countries to promote universal screening with a multiparametric test, ideally using maternal characteristics, MAP, Ut-PI and PlGF, but at a minimum, maternal characteristics and MAP with the option of contingent screening for those then identified as high risk.[68]

However, the infrastructure, provision of training, care pathways for those screened as high risk, rigorous audit and quality control are essential to the success of such a program and require initial and ongoing investment. The risk calculator is available free of charge on the Fetal Medicine website and so at a very minimum, it would seem easily achievable to assess risk using maternal characteristics and MAP with PAPP-A if it had been measured for Downs syndrome screening. Performing UtA-PI measurements is not particularly complex and has already been implemented in the second trimester in the UK as part of the RCOG's risk assessment of the small-for-gestational-age fetus in those who have multiple minor risk factors.[73] Based on the evidence which has been presented in this review, any combination of parameters would be an improvement on existing risk factor screening alone.

The Challenge in Low-Middle Income Countries

Such an undertaking is challenging enough in a high-income country, but the capacity for low-resource settings to support such a program is possibly unrealistic. Preeclampsia remains a critical health priority in LMICs, as hypertensive

disorders remain one of the major causes of maternal death.[22] Primary prevention of preeclampsia in these settings is therefore of great importance. This was addressed in the 2019 FIGO guidance on screening for preeclampsia, which acknowledged that in low resource settings, perfection is the enemy of the good and a pragmatic approach incorporating maternal characteristics and MAP should still be achievable.[68] This may not be the case across all settings as antenatal care can be non-existent in some circumstances.

In LMICs the focus has been more on raising awareness of the signs and symptoms of preeclampsia, providing general antenatal care, recognition and management of hypertensive disorders in pregnancy than perhaps primary prevention.[74,75]

Given aspirin's generally reassuring safety profile, there is an argument that a less judicious approach to its initiation would forego the need for an accurate screening test, particularly in LMICs where there may be minimal antenatal care. It is also a reasonable point given that aspirin can confer other benefits to pregnancy including reducing spontaneous preterm birth <37 weeks' gestation (RR 0.91 95% CI 0.87–0.95), reducing fetal deaths, neonatal deaths or death prior to discharge (RR 0.85 95% 0.76–0.95), small for gestational age babies (RR 0.84 95% CI 0.76–0.92) and pregnancies with serious adverse outcome (RR 0.90 95% CI 0.85–0.96) based on high-quality evidence.[23] The recent ASPIRIN trial was a multinational, randomized, double-masked placebo-controlled trial of low dose aspirin (81 mg per day) initiated in the first trimester to nulliparous women with a confirmed singleton pregnancy in low- to middle-income countries. The primary outcome was incidence of preterm birth < 37 weeks' gestation. Aspirin was shown to reduce perinatal mortality and fetal loss overall, and the preterm birth rate <37 weeks' gestation was reduced by 11% and for gestations <34 weeks' by 25%.[76] There was no difference in rates of hypertensive disorders in the aspirin and placebo groups: however, the study excluded participants who were hypertensive, had multiple pregnancies or medical problems such as diabetes (ie, those women who were more likely to develop preeclampsia). A secondary analysis of these data assessing any unexpected emergency medical visits and occurrence of side effects was performed. This showed no safety concerns, which is pleasing given the need for a low-cost, effective and safe intervention to reduce adverse pregnancy outcomes in low- to middle-income countries.[77]

The National Specialized Commission of Hypertension in Pregnancy of the Brazilian Association of Gynecology and Obstetrics Federation recently published their statement on preeclampsia screening, stating that given the cost and logistics required to implement universal multiparametric screening in a country with few resources, universal prophylaxis with low dose aspirin would be preferable, particularly in view of the other benefits such as reduced preterm birth and perinatal mortality as demonstrated in the ASPIRIN trial.[76,78] This is echoed even in a HIC, with the ACOG practice advisory recently stating that in some areas, there may be such a proportion of high risk groups that an institution may decide to adopt a policy of universal aspirin prophylaxis for their population.[79]

Conclusion

First trimester screening for preeclampsia has been shown to be an effective strategy for the detection of early-onset preeclampsia. A competing risks model incorporating maternal characteristics and biomarkers has an improved screening performance as compared to the traditional risk-based assessment. There is a strong argument that risk-based screening should be largely redundant in contemporary practice in high-income settings. In low to middle income countries, a competing risks model can still be used with the option of biophysical or biochemical biomarkers to improve detection rates dependent on resources. Implementing the FMF algorithm will require investment in local systems to support training, process, audit, and quality assurance. Accurately identifying those at high risk of preeclampsia will benefit them through targeted aspirin prophylaxis and increased pregnancy surveillance. The detection rates within different populations vary significantly, highlighting the importance of validating algorithms and modifying them for different patient groups. In LMICs, particularly where access to antenatal care is minimal, there is a valid argument for universal aspirin prophylaxis to reduce the incidence of preeclampsia as well as other placentally mediated complications of pregnancy.

Where possible, all settings should implement some form of first trimester screening for preeclampsia using a competing risks model with a combination of parameters that fits their population and resources.

Ethics

Institutional ethics review board approval was not required for this review article.

Funding

This work was not supported by grant funding of any sort.

Disclosure

The authors have no competing or conflicting interests to declare.

References

1. Ives CW, Sinkey R, Rajapreyar I, Tita ATN, Oparil S. Preeclampsia-Pathophysiology and Clinical Presentations: JACC State-of-The-Art Review. *J Am Coll Cardiol*. 2020;76(14):1690–1702. doi:10.1016/j.jacc.2020.08.014
2. Thornton C, Dahlen H, Korda A, Hennessy A. The incidence of preeclampsia and eclampsia and associated maternal mortality in Australia from population-linked datasets: 2000-2008. *Am J Obstet Gynecol*. 2013;208(6):476e1–5. doi:10.1016/j.ajog.2013.02.042
3. Thornton C, Tooher J, Ogle R, von Dadelszen P, Makris A, Hennessy A. Benchmarking the Hypertensive Disorders of Pregnancy. *Pregnancy Hypertens*. 2016;6(4):279–284. doi:10.1016/j.preghy.2016.04.009
4. Rana S, Granger J, Granger JP, Karumanchi SA. Preeclampsia: pathophysiology, challenges and perspecticves. *Circ Res*. 2019;124(7):1094–1112. doi:10.1161/CIRCRESAHA.118.313276
5. Brown MA, Kenny LC, Karumanchi SA, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens*. 2018;13:291–310. doi:10.1016/j.preghy.2018.05.004
6. Chappell LC, Cluver CA, Kingdom J, Tong S. Pre-eclampsia. *Lancet*. 2021;398(10297):341–354. doi:10.1016/S0140-6736(20
7. ACOG Committee on Obstetric Practice. ACOG Practice Bulletin No. 202: gestational Hypertension and Preeclampsia. *Obstet Gynecol*. 2019;133 (1):1. doi:10.1097/AOG.0000000000003018
8. Bouter AR, Duvekot JJ. Evaluation of the clinical impact of the revised ISSHP and ACOG definitions on preeclampsia. *Pregnancy Hypertens*. 2020;19:206–211. doi:10.1016/j.preghy.2019.11.011
9. Lowe SABL, Lust K, McMahon LP, et al. SOMANZ: guideline for the management of hypertensive disorders of pregnancy. *Australian N Zealand J*. 2014;55:e1.
10. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. *Lancet*. 2016;387(10022):999–1011. doi:10.1016/S0140-6736(15)00070-7
11. Kane SC. First trimester screening for pre-eclampsia. *Obstet Med*. 2016;9(3):106–112. doi:10.1177/1753495X16649074
12. Bokslag AVW, Mol B, de Groot C, de Groot CJM. Preeclampsia; short and long term consequences for the mother and the neonate. *Early Hum Dev*. 2016;102:47–50. doi:10.1016/j.earlhumdev.2016.09.007
13. Bhattacharya S, Campbell DM. The incidence of severe complications of preeclampsia. *Hypertension Pregnancy*. 2005;24(2):181–190. doi:10.1081/PRG-200059873
14. Williams D. Preeclampsia and long term mental health. *Obsetric Med*. 2012;5(3):98–104. doi:10.1258/om.2012.120013
15. Muijsers HR, van de Hejden N, Maas OWH, Consider JE. Preeclampsia as a first cardiovascular event. *Curr Cardiovasc Risk Rep*. 2019;13:21. doi:10.1007/s12170-019-0614-0
16. Elder PS, Gulati G, Michos M. Identification of female-specific risk enhances throughout the lifespan of women to improve cardiovascular disease prevention. *Am j Preventive Cardiol*. 2020;2:100028. doi:10.1016/j.ajpc.2020.100028
17. Turbeville HR, Sasser JM. Preeclampsia beyond pregnancy: long-term consequences for mother and child. *Am J Physiol Renal Physiol*. 2020;318 (6):F1315–F1326. doi:10.1152/ajprenal.00071.2020
18. Benagiano M, Mancuso S, Brosens JJ, Benagiano G. Long-term consequences of placental vascular pathology on the maternal and offspring cardiovascular systems. *Biomolecules*. 2021;11(11):1625. doi:10.3390/biom11111625
19. Von Dadelszen P, Sawchuck D, Justus Hofmeyr G. PRE-EMPT(PRE-eclampsia-Eclampsia Monitoring, Prevention and Treatment): a low and middle income country initiative to reduce the global burden of maternal, fetal and infant death and disease related to pre-eclampsia. *Pregnancy Hypertens*. 2013;3(4):199–202. doi:10.1016/j.preghy.2013.06.002
20. Pea R, Dekker G, Chaouat G, Elliot MG, Scioscia M. High Incidence of early onset preeclampsia is probably the rule and not the exception worldwide. 20th anniversary of the Reunion workshop. A summary. *J Reprod Immunol*. 2019;133:30–36. doi:10.1016/j.jri.2019.05.003
21. Rodriguez A, Tuuli MG, Odibo AO. First-, Second-, and Third-Trimester Screening for Preeclampsia and Intrauterine Growth Restriction. *Clin Lab Med*. 2016;36(2):331–351. doi:10.1016/j.cll.2016.01.007
22. Chaemsaithong P, Sahota DS, Poon LC. First trimester preeclampsia screening and prediction. *Am J Obstet Gynecol*. 2022;226(2S):S1071–S1097e2. doi:10.1016/j.ajog.2020.07.020
23. Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Sys Rev*. 2019;2019:10. doi:10.1002/14651858.CD004659.pub3
24. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. *N Engl J Med*. 2017;377 (7):613–622. doi:10.1056/NEJMoa1704559
25. Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and meta analysis. *Am J Obstet Gynecol*. 2018;218(3):287–293 e1. doi:10.1016/j.ajog.2017.11.561
26. Rolnik DL, Nicolaides KH, Poon LC. Prevention of preeclampsia with aspirin. *Am J Obstet Gynecol*. 2022;226(2S):S1108–S1119. doi:10.1016/j.ajog.2020.08.045

27. Sibai BM, Caritis SN, Thom E, et al. Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women. The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med*. 1993;329(17):1213–1218. doi:10.1056/NEJM199310213291701
28. Roberge SBE, Nicolaides K. Meta-analysis on the effect of aspirin use for prevention of preeclampsia on placental abruption and antepartum haemorrhage. *Am J Obstet Gynecol*. 2018;218(5):483–489. doi:10.1016/j.ajog.2017.12.238
29. Hastie CTS, Wikström A, Sandström A, Hesselman S, Bergman L. Aspirin use during pregnancy and the risk of bleeding complications: a Swedish population- based cohort study. *Am J Obstet Gynecol*. 2021;224(1):95.e1–95.e12. doi:10.1016/j.ajog.2020.07.023
30. Hofmeyr GJ, Lawrie TA, Atallah AN, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database Sys Rev*. 2018;10(10):CD001059. doi:10.1002/14651858.CD001059.pub5
31. Sea F, Fogacci F, Banach M. Vitamin D supplementation and inceident preeclampsia: a systematic review and meta-analysis of randomized clinial trials. *Clin Nutrition*. 2020;39:1742–1752. doi:10.1016/j.clnu.2019.08.015
32. WHO. *WHO Recommendations for Prevention and Treatment of Pre-Eclampsia and Eclampsia*. WHO; 2021.
33. Berghella V, Saccone G. Exercise in pregnancy! *Am J Obstet Gynecol*. 2017;216(4):335–337. doi:10.1016/j.ajog.2017.01.023
34. Rea B, Pelaez M, Cordero Y. Exercise during pregnancy protects against hypertension and macrosomia: randomized clinical trial. *Am j Obstetrics Gynecol Glob Rep*. 2016;214:649.e1–649.e8. doi:10.1016/j.ajog.2015.11.039
35. Sandstrom A, Snowden JM, Hoijer J, Bottai M, Wikstrom AK. Clinical risk assessment in early pregnancy for preeclampsia in nulliparous women: a population based cohort study. *PLoS One*. 2019;14(11):e0225716. doi:10.1371/journal.pone.0225716
36. Tan MY, Wright D, Syngelaki A, et al. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. *Ultrasound Obstetrics Gynecol*. 2018;51(6):743–750. doi:10.1002/uog.19039
37. NIfHaCE. *Hypertension in Pregnancy: Diagnosis and Management*. NICE; 2019.
38. Duckitt KH. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *Br Med J*. 2005;330(03):565–567. doi:10.1136/bmj.38380.674340.E0
39. O'Gorman N, Wright D, Poon LC, et al. Multicenter screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation: comparison with NICE guidelines and ACOG recommendations. *Ultrasound Obstetrics Gynecol*. 2017;49(6):756–760. doi:10.1002/uog.17455
40. Vea B. Risk factors of pre-eclampsia/ eclampsia and its adverse outcomes in low and middle income countries: a secondary WHO analysis. *PLoS One*. 2014;9(3):e91198. doi:10.1371/journal.pone.0091198
41. Poon LCK, Chelemen N. Maternal risk factorts for hypertensive disorders in pregnancy: a multivariate approach. *J Hum Hypertens*. 2010;24:104–110. doi:10.1038/jhh.2009.45
42. Wright D, Wright A, Nicolaides KH. The competing risk approach for prediction of preeclampsia. *Am J Obstet Gynecol*. 2020;223(1):12–23 e7. doi:10.1016/j.ajog.2019.11.1247
43. O'Gorman N, Wright D, Syngelaki A, et al. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks gestation. *Am J Obstet Gynecol*. 2016;214(1):103e1–103 e12. doi:10.1016/j.ajog.2015.08.034
44. Wright D, Tan MY, O'Gorman N, et al. Predictive performance of the competing risk model in screening for preeclampsia. *Am J Obstet Gynecol*. 2019;220(2):199e1–199 e13. doi:10.1016/j.ajog.2018.11.1087
45. Wright D, Syngelaki A, Akolekar R, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. *Am J Obstet Gynecol*. 2015;213(1):62e1–62 e10. doi:10.1016/j.ajog.2015.02.018
46. Vikraman SK, Elayedatt RA. Pre-eclampsia screening in the first trimester - preemptive action to prevent the peril. *j Maternal Fetal Neonatal Med*. 2020;1–9. doi:10.1080/14767058.2020.1767059
47. Johnson SLB, Kalafat E, Thilaganathan B, Khalil A. Maternal and Perinatal Outcomes of White Coat Hypertension During Pregnancy: a Systematic Review and Meta-Analysis. *Hypertension*. 2020;76(1):157–166. doi:10.1161/HYPERTENSIONAHA.119.14627
48. Poon LC, Kametas NA, Valencia C, Chelemen T, Nicolaides KH. Hypertensive disorders in pregnancy: screening by systolic diastolic and mean arterial pressure at 11-13 weeks. *Hypertension in Pregnancy*. 2011;30(1):93–107. doi:10.3109/10641955.2010.484086
49. Cnossen JS, Vollebregt KC, de Vrieze N, et al. Accuracy of mean arterial pressure and blood pressure measurements in predicting pre-eclampsia: systematic review and meta-analysis. *BMJ*. 2008;336(7653):1117–1120. doi:10.1136/bmj.39540.522049.BE
50. Poon LCZN, Zamprakou A, Syngelaki A, Nicolaides KH. Protocol for measurement of mean arterial pressure at 11-13 weeks' gestation. *Fetal Diagn Ther*. 2012;31(1):42–48. doi:10.1159/000335366
51. Park HJ, Shim SS, Cha DH. Combined Screening for Early Detection of Pre-Eclampsia. *Int J Mol Sci*. 2015;16(8):17952–17974. doi:10.3390/ijms160817952
52. Reddy M, Springhall EA, Rolnik DL, da Silva Costa F. How to perform first trimester combined screening for pre-eclampsia. *Australas J Ultrasound Med*. 2018;21(4):191–197. doi:10.1002/ajum.12111
53. Rolnik DL, da Silva Costa F, Sahota D, Hyett J, McLennan A. Quality assessment of uterine artery Doppler measurement in first-trimester combined screening for pre-eclampsia. *Ultrasound Obstetrics Gynecol*. 2019;53(2):245–250. doi:10.1002/uog.19116
54. Gallo DM, Poon LC, Akolekar R, Syngelaki A, Nicolaides KH. Prediction of preeclampsia by uterine artery Doppler at 20-24 weeks' gestation. *Fetal Diagn Ther*. 2013;34(4):241–247. doi:10.1159/000356171
55. Akolekar RZ, Poon E, Pepes LC, Nicolaides S. Maternal serum placental growth factor at 11+0 to 13+6 weeks gestation in the prediction of preeclampsia. *Ultrasound Obstetrics Gynecol*. 2008;32(6):732–739. doi:10.1002/uog.6244
56. Poon LCM, Valencia C, Plasencis W, Nicolaides W. First trimester maternal serrum pregnancy-associated plasma protein-A and pre-eclampsia. *Ultrasound Obstetrics Gynecol*. 2009;33:23–33. doi:10.1002/uog.6280
57. Prefumo F, Farina A. First-trimester screening for pre-eclampsia: time for reflection. *Ultrasound Obstetrics Gynecol*. 2017;50(5):662–663. doi:10.1002/uog.18893
58. O'Gorman N, Wright D, Poon LC, et al. Accuracy of competing-risks model in screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. *Ultrasound Obstetrics Gynecol*. 2017;49(6):751–755. doi:10.1002/uog.17399
59. Tan MY, Syngelaki A, Poon LC, et al. Screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. *Ultrasound Obstetrics Gynecol*. 2018;52(2):186–195. doi:10.1002/uog.19112
60. Khalil AL, State-of-The-Art Review B. Controversies in the management of twin pregnancy. *Ultrasound Obstetrics Gynecol*. 2021;57:888–902. doi:10.1002/uog.22181

61. Francisco C, Wright D, Benko Z, Syngelaki A, Nicolaides KH. Competing-risks model in screening for pre-eclampsia in twin pregnancy according to maternal factors and biomarkers at 11-13 weeks' gestation. *Ultrasound Obstetrics Gynecol*. 2017;50(5):589–595. doi:10.1002/uog.17531
62. Cheng Y, Leung TY, Law LW, Ting YH, Law KM, Sahota DS. First trimester screening for pre-eclampsia in Chinese pregnancies: case-control study. *BJOG*. 2018;125(4):442–449. doi:10.1111/1471-0528.14970
63. Zhang J, Han L, Li W, et al. Early prediction of preeclampsia and small-for-gestational-age via multi-marker model in Chinese pregnancies: a prospective screening study. *BMC Pregnancy Childbirth*. 2019;19(1):304. doi:10.1186/s12884-019-2455-8
64. Chaemsaithong P, Pooh RK, Zheng M, et al. Prospective evaluation of screening performance of first-trimester prediction models for preterm preeclampsia in an Asian population. *Am J Obstet Gynecol*. 2019;221(6):650e1–650 e16. doi:10.1016/j.ajog.2019.09.041
65. Hu J, Gao J, Liu J, et al. Prospective evaluation of first-trimester screening strategy for preterm pre-eclampsia and its clinical applicability in China. *Ultrasound Obstetrics Gynecol*. 2021;58(4):529–539. doi:10.1002/uog.23645
66. Orosz L, Orosz G, Veress L, et al. Screening for preeclampsia in the first trimester of pregnancy in routine clinical practice in Hungary. *J Biotechnol*. 2019;300:11–19. doi:10.1016/j.jbiotec.2019.04.017
67. Mosimann B, Pfiffner C, Amylidi-Mohr S, Risch L, Surbek D, Raio L. First trimester combined screening for preeclampsia and small for gestational age - a single centre experience and validation of the FMF screening algorithm. *Swiss Med Wkly*. 2017;147:w14498. doi:10.4414/smw.2017.14498
68. Poon LC, Shennan A, Hyett JA, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: a pragmatic guide for first-trimester screening and prevention. *Int J Gynaecol Obstet*. 2019;145(Suppl 1):1–33. doi:10.1002/ijgo.12802
69. Dubon Garcia A, Devlieger R, Redekop K, Vandeweyer K, Verlohren S, Poon LC. Cost-utility of a first-trimester screening strategy versus the standard of care for nulliparous women to prevent pre-term pre-eclampsia in Belgium. *Pregnancy Hypertens*. 2021;25:219–224. doi:10.1016/j.preghy.2021.06.012
70. Guy GP, Leslie K, Diaz Gomez D, et al. Implementation of routine first trimester combined screening for pre-eclampsia: a clinical effectiveness study. *BJOG*. 2021;128(2):149–156. doi:10.1111/1471-0528.16361
71. Wright A, Wright D, Syngelaki A, Georgantis A, Nicolaides KH. Two-stage screening for preterm preeclampsia at 11-13 weeks' gestation. *Am J Obstet Gynecol*. 2019;220(2):197e1–197 e11. doi:10.1016/j.ajog.2018.10.092
72. Chitty L, Cameron L, Daley R. RAPID Non-invasive prenatal testing (NIPT) evaluation study Executive summary. Executive summary. UK NSC; 2015.
73. Gynaecologists RCoOa. The Investigation and Management of the Small-for-Gestational-Age Fetus. *Green-Top Guideline No*. 2014;31:548.
74. Goldenberg RJ, Griffin B, Rouse J. Reducing maternal mortality from preeclampsia and eclampsia in low resource countries- what should work? *Acta Obstet Gynecol Scand*. 2014;94(2):148–155. doi:10.1111/aogs.12533
75. Warren CH, Ishaku SMI, Armbruster S. A primary health care model for manageing pre-eclampsia and eclampsia in low and middle income countries. *Reprod Health*. 2020;17(1):46. doi:10.1186/s12978-020-0897-0
76. Hoffman MK, Goudar SS, Kodkany BS, et al. Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2020;395(10220):285–293. doi:10.1016/S0140-6736(19)32973-3
77. Short VL, Metgud M. Safety of daily low-dose aspirin use during pregnancy in low-income and middle-income countries. *Am J Obstet Gynecol*. 2021;1:100003.
78. De Oliveira LD, Prado ALD, Cunha Fihlo CAC. Pre-eclampsia: universal Screening or Universal Prevention for Low and Middle-Income Settings? *Rev Bras Ginecol Obstet*. 2021;43(1):61–65. doi:10.1055/s-0040-1713803
79. Gynecologists ACoOa. Low Dose Aspirin Use for the Prevention of Preeclampsia and Related Morbidity and Mortality. *Practive Advisory*. 2021;1:548.
80. ACOG. Committee Opinion No.743: low dose Aspirin Use During Pregnancy. *Obstet Gynecol*. 2018;132:e44–e52. doi:10.1097/AOG.0000000000002708