Early preeclampsia screening and prevention: An update for general practice

Minh Hang Vu, Daniel L Rolnik, Timothy J Lee

Background
Preeclampsia is a disorder of pregnancy that causes significant adverse perinatal outcomes. Risk factor–based screening performs poorly when compared with algorithm-based approaches. The role of general practitioners in early screening for preeclampsia is crucial in predicting and preventing the condition.

Objective
This article discusses the different screening approaches and interventions available for prevention of preeclampsia, making the case for a screen-and-treat model based on individual risk calculation for all pregnant women.

Discussion
The Fetal Medicine Foundation (FMF) algorithm is the most effective validated tool for early preeclampsia screening. Where components of the full FMF algorithm are unavailable, a limited FMF model can be used as an alternative to risk factor–based screening alone. A screen-and-treat approach based on individual risk calculation should be provided to all pregnant women, and low-dose aspirin should be offered to women at high risk to reduce the risk of preterm preeclampsia by up to 62%.

PREECLAMPSIA IS A MULTISYSTEM DISORDER characterised by new-onset hypertension after 20 weeks of pregnancy. The condition is diagnosed by high blood pressure (systolic ≥140 mmHg or diastolic ≥90 mmHg on two or more measurements) accompanied by at least one other complication: new-onset proteinuria (>30 mg/mmol urinary protein–creatinine ratio), maternal organ dysfunction (renal function, liver function) or uteroplacental dysfunction (foetal growth restriction, angiogenic imbalance, placental abruption, abnormal Doppler studies).[1]

Recognised as one of the most severe complications of pregnancy, and a leading cause of maternal morbidity and mortality, preeclampsia affects approximately 1 in 33 women in Australia and 6 million women worldwide each year.[2,3] Preeclampsia increases the risk of maternal chronic disease (cardiovascular disease and diabetes) and infant morbidity and mortality (by increasing the risks of foetal growth restriction, preterm birth, perinatal death, neurodevelopmental delay and cardiovascular disease later in life).[1] Preeclampsia is classified as preterm or term if delivery occurred prior to or after 37 weeks gestation, respectively.[4]

Preterm preeclampsia is commonly thought to originate from impaired trophoblast invasion and incomplete remodelling of uterine spiral arteries during early pregnancy, causing uteroplacental malperfusion.[4] In response to placental hypoxia, placental epithelial cells release pro-inflammatory cytokines, exosomes and anti-angiogenic agents into the maternal circulation. This causes oxidative stress and disrupts maternal endothelial cell function, resulting in a systemic inflammatory response and formation of micro-emboli that impairs multiple organ systems.[4] Term preeclampsia is more often associated with poor maternal perfusion, failing to meet the metabolic demands of placenta and foetus, and maternal predisposition to inflammation.[5] It is likely that there is crossover of pathophysiology in many cases.

Screening for preeclampsia has for decades been performed by identifying maternal risk factors alone – but when evaluated as a screening test, this approach performs poorly.[6] In addition, aspirin for prevention of preeclampsia remains underprescribed.[6,7] Both these issues continue to limit the potential reduction in incidence of preeclampsia and its sequelae.

This article discusses the different screening approaches and interventions available for prevention of preeclampsia, making the case for a screen-and-treat model based on individual risk calculation for all pregnant women.

Risk factor–based screening

It is strongly recommended by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) that routine screening in early pregnancy for preeclampsia is offered to all women.[8]

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Table 1. Screening for preeclampsia based on risk factors alone[10,11]

High-risk factors	Moderate-risk factors
• History of preeclampsia	• Nulliparity
• Multifoetal gestation[A]	• Obesity
• Chronic hypertension	– BMI >30 kg/m^2 (ACOG)
• Type 1 or 2 diabetes	– BMI >35 kg/m^2 (NICE)
• Chronic kidney disease	• Family history of preeclampsia
• Autoimmune disease (systemic lupus erythematosus, antiphospholipid syndrome)	• Advanced maternal age
	– Age >35 years (ACOG)
	– Age >40 years (NICE)
	• Others[B]

[A] NICE categorises multifoetal gestation as a moderate-risk factor.

[B] ACOG also lists 'sociodemographic factors' and 'obstetric factors such as low birthweight or small for gestational age, previous adverse outcome, more than 10-year pregnancy interval' as moderate-risk factors.

ACOG, American College of Obstetricians and Gynecologists; BMI, body mass index; NICE, National Institute for Health and Care Excellence.

History taking to identify risk factors according to maternal characteristics and medical and obstetric history is the earliest and most convenient screening that can be performed by general practitioners (GPs) during early antenatal care. Guidelines have been published by the American College of Obstetricians and Gynecologists (ACOG) and the National Institute for Health and Care Excellence (NICE).[9,10] According to both guidelines, women with at least one high-risk factor or two or more moderate-risk factors (Table 1) should be started on aspirin.

Risk factor–based screening has the poorest performance when compared with other approaches, only identifying 30% of cases, with a screen-positive rate of 10%.[11,12] A screen-positive rate of 10% means 10 in 100 women tested will have an increased risk of preeclampsia. Although this screening method remains useful in resource-limited settings, there exist improved approaches to more accurately predict those who are truly at high risk of developing preeclampsia and rule out those who are not.

Algorithm-based screening

The Fetal Medicine Foundation (FMF) competing-risks model has been shown to be a superior screening tool than the risk factor–based screening guideline by NICE.[12] In predicting preterm preeclampsia, the FMF algorithm had a detection rate (or sensitivity) of 82.4%, whereas the NICE guidelines had a detection rate of 40% (at the same screen-positive rate of 10%).[12]

The FMF algorithm (freely available at https://fetalmedicine.org/research/assess/preeclampsia/first-trimester, and also embedded in commercial ultrasound reporting software packages) has been endorsed by several national and international organisations (including RANZCOG) as the most effective tool for detecting preterm disease.[6,8,13] The algorithm has been validated for use in large cohorts of women from different ethnicities and racial origins.[14] The algorithm incorporates maternal characteristics and medical and obstetric history in addition to mean arterial blood pressure (MAP), uterine artery pulsatility index (UtPI) on ultrasonography between 11 and 14 weeks gestation, and serum placental growth factor (PlGF) and/or pregnancy-associated plasma protein A (PAPP-A) levels measured between 11 and 14 weeks gestation (Table 2).[15]

Practicalities in general practice

Although women may not always attend appointments and review at these gestations, we present a suggested timeline to aid GPs in performing best practice, evidence-based early preeclampsia screening (Figure 1).

There are scenarios in which limited or no access to a combination of UtPI, PlGF or PAPP-A may occur because of service unavailability, inadequate accreditation/training or cost barriers. Additionally, PlGF is not covered by the Medicare Benefits Schedule and costs an out-of-pocket fee of $50–$100. Measuring MAP also requires dedicated time within a general practice consultation or availability of a practice nurse or other to assist in performing this task. For these reasons, it is important to note that partial combinations can be used to screen for preeclampsia using a limited FMF model at the expense of slightly lower detection rates (Table 3).

Prevention of preeclampsia

Low-dose aspirin

Women identified to be at high risk of preterm preeclampsia (greater than 1:100 assessed by the FMF algorithm) are recommended to commence low-dose aspirin (at least 100 mg, ideally 150 mg) at night from before 16 weeks of gestation until 36 weeks of gestation (or earlier in case of delivery) to effectively reduce the risk of preterm preeclampsia.[8,15] This recommendation is based on evidence from the Aspirin for Evidence-Based Preeclampsia (ASPRE) Prevention trial that showed a reduction in risk of preeclampsia causing birth at <34 weeks gestation of 90% and in risk of preterm preeclampsia of 62% (95% confidence interval [CI]: 20%–80%).[14]

Aspirin is available in Australia in the form of 300 mg tablets (which can be halved into the recommended 150 mg dose) or 100 mg tablets (which requires patients to take one and a half tablets). RANZCOG recommends a dose of at least 100 mg to be effective at preventing preeclampsia. Allergy to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin-sensitive asthma (Samter's triad), severe active bleeding, erosive gastritis, severe hepatic disease and renal impairment, and bleeding disorders are contraindications to aspirin use. Potential side effects of aspirin include gastrointestinal symptoms, worsening renal function, asymptomatic bleeding and nausea.[16] Low-dose aspirin does not increase the risk of placental abruption or postpartum haemorrhage, and it is safe for the foetus when used in early pregnancy, with evidence showing no increased risk of congenital anomalies, foetal ductal closure or neonatal intracranial haemorrhage.[17,18]

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Table 2. Components of the Fetal Medicine Foundation (FMF) algorithm for early preeclampsia screening[22]

FMF-specific maternal characteristics, medical, and obstetric history	• Age, height and weight, racial origin (White, Black, south Asian, east Asian, multiracial) • Smoking status • Parity • Interpregnancy interval • History of preeclampsia • Family history of preeclampsia in the patient's mother • Conception method (spontaneous, ovulation drugs, in-vitro fertilisation) • Chronic hypertension, diabetes types 1 and 2, systemic lupus erythematosus, antiphospholipid syndrome	
Mean arterial pressure (MAP)	**How to perform:** • Requires automated blood pressure measurement device(s) validated and calibrated for use in pregnancy • Ensure: – cuff is appropriate for the patient's arm circumference – at least 5 minutes of rest prior to recording – arms are supported at the level of the heart – blood pressured is measured in both arms simultaneously • Record two sets of readings at 1-minute intervals[13] • FMF website calculator automatically converts recordings to multiples of the median (MoM)	**Why:** • The MAP MoM value has been observed to be higher in women with preterm preeclampsia[13]
Uterine artery pulsatility index (UtPI)	**How to arrange:** • Add UtPI onto request form for routine first trimester 11–14-week ultrasound • Sonographer requires credentialing and/or specific training to perform	**Why:** • Higher UtPI indicates an increase in resistance and pulsatility of the uterine artery[23,24] • Higher UtPI MoM values imply increased risk of developing preeclampsia, foetal growth restriction, abruption and stillbirth[23]
Placental growth factor (PlGF) and/or pregnancy-associated plasma protein A (PAPP-A)	**How to arrange:** • Add PlGF and/or PAPP-A onto pathology request for combined first trimester screening (CFTS)[A] or non-invasive prenatal testing; or order separately if aneuploidy screening declined	**Why:** • Lower PlGF and PAPP-A MoM indicate higher risk of preeclampsia[25–27] • PlGF is a better biomarker of preeclampsia when compared with PAPP-A[26] • PAPP-A is a weak marker that only increases detection when PlGF is not available[12]

[A] PAPP-A is done as part of the CFTS.

Table 3. Performance of screening approaches for preterm preeclampsia[12,13,21]

Screening approach	Detection rate	Screen-positive rate
Full FMF algorithm	82.4%	10%
Limited FMF model (maternal characteristics + UtPI)	62%	10%
Limited FMF model (maternal characteristics + PlGF)	59.2%	10%
Limited FMF model (maternal characteristics + MAP)	49.3%	10%
Risk factor–based screening (NICE guideline)	40%	10%
Risk factor–based screening (ACOG guideline)	89%	66.1%[A]

[A] A high screen-positive can increase the false-positive rate in screening, causing unnecessary intervention and overtreatment with aspirin.

ACOG, American College of Obstetricians and Gynecologists; FMF, Fetal Medicine Foundation; MAP, mean arterial blood pressure; NICE, National Institute for Health and Care Excellence; PlGF, placental growth factor; UtPI, uterine artery pulsatility index.

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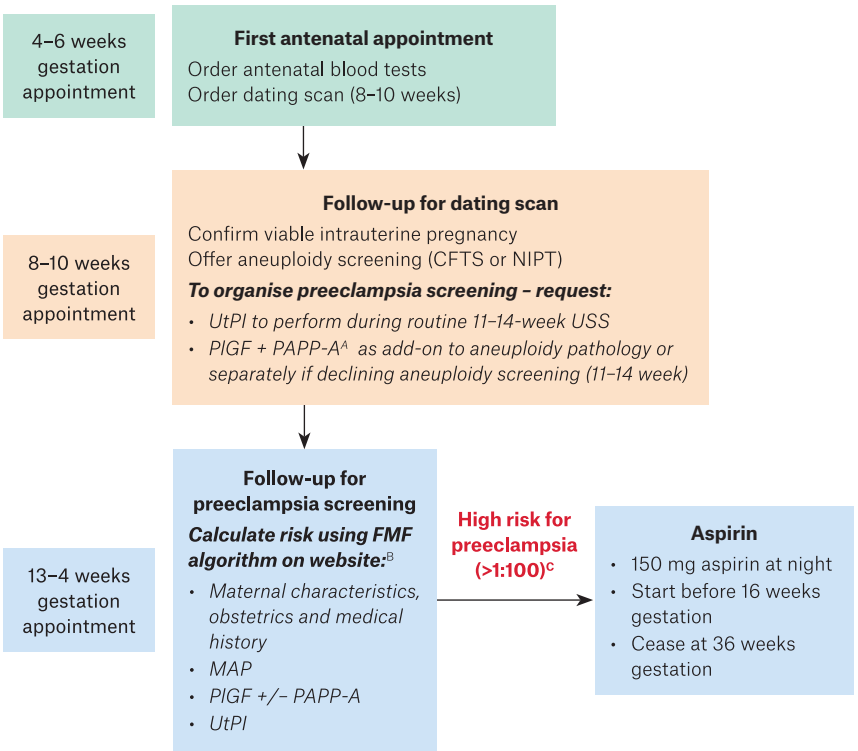

Figure 1. Flowchart for first-trimester preeclampsia screen-and-treat model using the FMF algorithm in a general practice setting.

[A] PAPP-A is performed routinely as part of CFTS.

[B] Preeclampsia risk can still be calculated using an incomplete FMF model. However, any additional components will improve the sensitivity and specificity of the algorithm.

[C] Risk cut off used by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists.[9]

CFTS, combined first trimester screening; FMF, Fetal Medicine Foundation; MAP, mean arterial pressure; NIPT, non-invasive prenatal testing; PAPP-A, pregnancy-associated plasma protein A; PlGF, placental growth factor; USS, ultrasound scan; UtPI, uterine artery pulsatility index.

Calcium supplementation and prenatal exercise

There exists inconsistent evidence to support the use of calcium and prenatal exercise in preventing preterm preeclampsia.[19] A recently published meta-analysis concluded that calcium supplementation, both high (>1 g/day) and low (<1 g/day) doses, prevented preeclampsia (relative risk 0.49, 95% CI: 0.36–0.66) in women with low dietary calcium intake, which may not be applicable to the general Australian population.[20]

Prenatal exercise has also been shown to reduce the odds of preeclampsia in a systematic review of 3322 women (odds ratio 0.59, 95% CI: 0.37–0.90), although data are limited.[21]

Conclusion

Early first trimester screening for preeclampsia allows identification of high-risk individuals who may benefit from timely intervention with aspirin to significantly reduce the risk of preterm preeclampsia. Where able to be performed, the full FMF algorithm is the most sensitive and specific screening tool. The limited FMF model or risk factor–based screening provide alternative screening options.

Key points

- General practice is a crucial point of care to provide routine early first trimester preeclampsia screening using risk factors or, more ideally, algorithm-based models
- Components of the FMF algorithm for preeclampsia risk assessment include: maternal characteristics, obstetric and medical history, MAP, UtPI, and PlGF and/or PAPP-A.
- Patients deemed to be at high risk of preeclampsia should be started on 150 mg of aspirin at night by 16 weeks of gestation until 36 weeks of gestation for prevention of preterm preeclampsia (unless they have allergies/contraindications).
- A screen-and-treat approach based on individual risk calculation should be provided to all pregnant women to reduce the risk of preterm preeclampsia by up to 62%.

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