UK National Screening Committee

Screening for the Prevention and Prediction of Pre-Eclampsia

External review against programme appraisal criteria for the UK National Screening Committee

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Author: Costello Medical

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UK National Screening Committee, Southside, 39 Victoria Street, London, SW1H 0EU

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Plain English summary

UK National Screening Committee currently does not recommend screening for pre-eclampsia.

Pre-eclampsia is a condition that can develop during pregnancy. It is currently unclear what causes pre-eclampsia. Women usually experience it in the second half of pregnancy (from 20 weeks). The most common symptoms are increased blood pressure (called hypertension) and an unusually high level of protein in the urine (called proteinuria). But other, less common symptoms can also occur and be diagnosed as pre-eclampsia.

Pre-eclampsia can lead to serious consequences like stroke, seizures or even death of the mother. Because of it babies can suffer from restricted growth, which means that they are at risk of being born early (prematurely) and of being small for the stage of pregnancy at which they are born (gestational age). If pre-eclampsia requires birth after a pregnancy has reached 37 weeks, it is called term pre-eclampsia, when the best treatment is an early birth of the baby. When pre-eclampsia requires birth before a pregnancy reaches 37 weeks it is called preterm pre-eclampsia. This is commonly considered a more severe and complicated form of pre-eclampsia, but the decision to induce birth to prevent possible harm to both the mother and the baby must to be balanced against the dangers to the baby of being born prematurely.

To prevent pre-eclampsia, it is important to know which pregnancies are at risk of it. We know that older mothers, women who are overweight or obese (with higher body-mass index), and women who had pre-eclampsia before are more likely to develop pre-eclampsia than mothers without those risk factors. Yet many mothers with these risk factors will go on to have uneventful pregnancies, and some mothers with no risk factors will develop pre-eclampsia. To put in place a screening programme for all pregnant women, it is important to have a test that is good at predicting who will develop pre-eclampsia and who will not. It is also necessary to have a preventive treatment that mothers who are at risk can receive. This review looked at evidence to see if there is a good test to find the women at risk, and a treatment that can prevent pre-eclampsia developing in women identified by a screening programme.

Because the consequences of pre-eclampsia are different depending on when it happens during pregnancy, the review divided the evidence in two separate groups: preterm pre-eclampsia, and term pre-eclampsia.

The review concluded that there may be sufficient evidence to support screening for pre-term pre-eclampsia but not term pre-eclampsia. This is because:

- there is no test that is reliable at predicting mothers that will develop pre-eclampsia in general or term pre-eclampsia

- there is a test that can reliably predict which mothers are at high risk of developing preterm pre-eclampsia. This test uses maternal risk factors together with results from prenatal ultrasound and blood tests
- there is evidence from one good quality trial that a low dose (150 mg) of aspirin given from 11 to 14 weeks of pregnancy until 36 weeks is safe, and can reduce the risk of developing preterm pre-eclampsia in mothers shown to be at risk. Because this was only found in one clinical trial, it is recommended that other studies should confirm this finding
- there is not enough evidence for a treatment to prevent term pre-eclampsia in mothers at risk.

Executive summary

Purpose of the review

This review was conducted to check whether a programme of routine screening for risk of pre-eclampsia (PE) should be recommended.

Background

PE is a multi-system disorder of unknown aetiology and is part of a spectrum of conditions referred to as hypertensive disorders of pregnancy (HDPs). It is defined by the National Institute for Health and Care and Excellence (NICE) in their 2019 guideline update (NG133) as new onset hypertension (≥140 mmHg systolic or ≥90 mmHg diastolic) presenting after 20 weeks of pregnancy with one or more new-onset conditions, including significant proteinuria or maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological complications or haematological complications.[1-3] NICE also defines severe PE as having a blood pressure of >160 mmHg systolic or >110 mmHg diastolic, with worsening maternal organ dysfunction (such as haemolysis, elevated liver function tests and low platelets, also known as HELLP syndrome) or worsening fetal growth restriction.[1] Incidence of PE varies between 1.4% and 4% in unselected populations, and in the UK, PE is responsible for 8% of maternal deaths.[4, 5] PE also increases the risk of perinatal mortality and morbidity, with approximately 20% of antenatal admissions and two-thirds of referrals to day care assessment units in the UK having been attributed to PE.[6]

Currently, management of PE is focused on general monitoring, controlling maternal hypertension, and ultimately, birth of the baby. Early identification of women at high risk of PE would facilitate monitoring and administration of secondary preventive measures, to mitigate adverse maternal and fetal outcomes. However, most of the major PE guidelines do not currently recommend routine screening for the whole population, due to insufficient evidence of clinical and/or cost-benefit. In the UK, high-risk women are identified based on the presence of risk factors and are advised to take low-dose aspirin until birth of the baby. This approach has been shown to be of limited value, especially in the low-risk population (where no risk factors are present).

PE remains a significant burden with adverse maternal and fetal/neonatal outcomes, and it is unclear whether currently available evidence could support the recommendation of a screening programme. As such, the UK NSC commissioned a rapid review to ascertain if there is sufficient evidence to consider introducing a population screening programme for PE.

Recommendation under review

Based on the 2011 UK NSC review of the evidence, a population screening for PE is not currently recommended in the UK. However, NICE antenatal care guidance (NG201), last updated in 2021, recommends that at the first antenatal (booking) appointment, women should be assessed for PE risk factors, and those with at least 2 moderate risk factors (first pregnancy, age 40 years or older, pregnancy interval of more than 10 years, body mass index (BMI) of 35 kg/m2 or more at first visit, family history of pre-eclampsia and multi-fetal pregnancy) or at least 1 major risk factor (hypertensive disease during a previous pregnancy. chronic kidney disease, autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome, type 1 or type 2 diabetes and chronic hypertension) for PE should be advised to take aspirin.7 The 2011 review found that there were no appropriate, validated predictive test(s) or preventive treatments with suitable efficacy and safety profile that could be given to women that were identified by a universal screening programme. Additionally, the review also emphasised the need for more studies evaluating biochemical and ultrasound tests, as well as the evidence behind treatment with antiplatelet agents. Finally, the review suggested there was not enough information on the natural history of PE that would allow understanding of the causes of the condition.

Focus of the review

The evidence summary aimed to identify evidence published since the previous UK NSC review in order to provide an overview of the current landscape of screening and interventions for PE. Specifically, new evidence was collected to answer the following 2 questions:

- What is the most effective screening test to predict PE? (criterion 4)
- Is there an effective intervention for preventing PE in screen-detected women? (criterion 9)

Findings and gaps in the evidence of this review

The searches for the UK NSC evidence summary update were conducted in December 2018. Due to a high number of relevant studies identified, retrospective and case-control studies were not selected for extraction, as these study designs are generally of lower methodological quality and at a higher risk of bias and confounding. The search was updated in October 2021, and an additional 22 studies were included. Ultimately, 97 publications representing 52 unique studies were extracted and synthesised. A summary of question level results is presented below.

Criterion 4: 'There should be a simple, safe, precise and validated screening test.'

A total of 75 publications reporting on 37 primary studies were included and extracted, evaluating the use of screening tests for the prediction of PE.

The evidence was split into test predicting preterm PE (defined as either <34 or <37 weeks of gestation), term PE (defined as >37 or >34 weeks gestation) and All PE (studies lacking specification or including pregnancies across term and pre-term). Amongst preterm PE studies, for tests using only single factors, the sensitivity ranged between 10% and 70.6%, and for tests utilising combinations of factors, between 35% and 100%. Specificity range was mostly set at 10% false positive rate (FPR). Where the specificity was measured alongside sensitivity, it ranged from 32.2% to 99.8% for single factors and 80.9% to 95% for combinations of factors tests. For term PE, the ranges of sensitivity were 21% to 34% for single factors, 15% to 60.5% for detecting PE >34 weeks of gestational age and 6% to 60% for detecting PE at >37 weeks of gestation by combinations of factors. Specificity was mostly set at 90% for reporting sensitivity; where it wasn't the range was 80.9% to 90.8%. The one approach that outperformed all others at 89.4% sensitivity was following the recommendation of the American College of Obstetricians and Gynecologists (ACOG), however, the specificity of this approach was 32.2%. For all PE, sensitivity for single factor tests range between 7.4% and 83.3%, and specificity was between 61.2% and 98.2%. For combinations of factors, sensitivity was between 17% and 93% and specificity between 36.5% and 95%.

The results were considered in light of some limitations. Full and transparent reporting of test accuracy for each screening test was often lacking; often only sensitivity was reported. Whilst the ability of a test to correctly identify women at risk of PE is paramount, others measures such as PPV, NPV and LRs facilitate evaluation of effectiveness of screening. Furthermore, for some results, the confidence intervals were large, thereby diminishing the confidence in the point estimates. Similarly, it is important to consider the high risk of intervention bias in some of the included screening studies where pregnant women and health providers were not blinded to test results. Knowledge of the pregnancy being at high risk of an adverse outcome would have likely prompted an intervention or enhanced pregnancy monitoring, therefore an effective screening test could paradoxically lead to underestimation of its predictive accuracy.

Based on the evidence assessed by this evidence summary, the performance of a competing risks approach using a combination of maternal factors, uterine artery pulsatility index (UtA-PI), mean arterial pressure (MAP), pregnancy-associated plasma protein A (PAPP-A) and placental growth factor (PlGF) could be considered sufficiently reliable for use in a screening programme aimed at predicting pregnancies at risk of preterm PE. This is because the approach was consistently shown to achieve over 80% sensitivity at ~10% false-positive rate for predicting which women are likely to develop preterm PE. For the identification of women at risk of term PE no test can be recommended for use in a screening programme in clinical practice. Based on these findings, criterion 4 is met for preterm but not met for term PE or for PE in general.

Criterion 9: There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered'

A total of 25 articles on 17 unique cohorts were selected for extraction, reporting on possible interventions for pregnancies at risk of PE. Randomised controlled trials (RCTs) accounted for the majority of studies (n=12); 3 were prospective cohorts, 1 was a pilot observational study and 1 was a systematic literature review (SLR)/meta-analysis. Four studies reported outcomes for preterm PE, 3 reported outcomes for term PE and 12 reportedoutcomes for 'all PE', without stratificiation by gestational age. The preventive interventions investigated were aspirin (11 studies; 1 also looking at low molecular weight heparin [LMWH]), enoxaparin (1 study), metformin (2 studies), pravastatin (2 studies), LMWH (1 SLR). Four studies looked at prevention of preterm PE (all using aspirin, at 60 mg – 150 mg doses); 1 trial found a significant effect for PE prevention by 62% with 150 mg aspirin (13/798 in the aspirin group and 35/822 in the placebo group, OR [odds ratio]: 0.38; 95% CI [confidence interval]: 0.20 to 0.74, p=0.004), whereas the other studies showed no significant difference in PE reduction for 100 mg aspirin vs placebo, 81 mg vs placebo, or between 60 mg and 80 mg aspirin. Three studies specifically looked at term PE prevention, evaluating aspirin (150 mg vs placebo or 160 mg vs 80 mg) and pravastatin (20 mg), and all found no effect of their intervention. Most (12) studies reported on all PE prevention, with mixed results. Two studies found no effect of aspirin (100 mg and 150 mg), whereas 1 study of found a weak effect with 100 mg aspirin (p=0.041). Comparison between 160 mg and 80 mg aspirin yielded no significant results in all PE prevention. Similarly, for LMWH, 1 study found no preventive effect, whereas the SLR and meta-analysis (MA) showed a protective effect of the intervention (OR: 0.62; 95% CI: 0.43 to 0.90 p=0.010). Metformin was also found to be protective in 1 study (OR 0.24, 95% CI 0.10 to 0.61, p=0.001) but not in another (OR 2.39, 95% CI 0.62 to 9.36; p=0.21). Pravastatin showed no effect on PE prevention.

Based on this review and previous work, there is a low volume of high-quality evidence that aspirin may prevent preterm PE in screen-detected women and decrease the length of NICU stay (1.4 days, 68% reduction; 95% CI 20 to 86%). Additionally, interventions were well tolerated with no safety concerns, and have shown some benefit in other maternal and neonatal outcomes, such as admission to the NICU and birth weight, although further study is required to support these findings. Conversely, no clearly effective intervention to prevent term PE has been identified. Based on these findings, criterion 9 is met for preterm PE but not met for term PE, or for PE in general.

Recommendations on screening

Based on the overall synthesis of evidence against the UK NSC criteria, screening of pregnant women to prevent preterm PE could be pursued as a candidate for a screening programme pending further work, whilst screening of pregnant women to prevent term PE is still not recommended.

The evidence was considered separately for preterm, term and all PE although separate conclusions were made for preterm and term PE only, as question-level conclusions differed considerably between the preterm and term PE settings.

For preterm PE, there is a large volume of high-quality evidence indicating that a screening test based on a combination of maternal factors, MAP, UtA-PI and PlGF/PAPP-A for this population could be adequate. Furthermore, there is a low volume of high-quality evidence that daily 150 mg aspirin up to 36 weeks of gestation decreases the incidence of preterm PE in screen-detected at-risk women. This dose is somewhat in line with NICE recommendation of 75 mg or 150 mg aspirin for at-risk women, and aligned to the recommendations made in the Saving Babies' Lives Care Bundle v2.[1, 8] Further work investigating the safety of the intervention and the impact of introducing a screening programme for preterm PE is recommended.

For term PE, there is a moderate volume of high-quality evidence which does not support any test as adequate for screening in this setting. In addition, no intervention was demonstrated to be effective at preventing term PE, based on a low volume of high-quality evidence. Although not investigated in this review, it is noted that induction of labour at term has been shown to be safe and effective at reducing HDP in low-risk primiparous women.[9] It is also noted that it may not be possible for any test to accurately predict term PE and instead, screening to detect placenta-related disease at term (such labour can be induced when diagnosed) may need to be considered. Further work to identify relevant studies reporting on test accuracies and effectiveness of labour induction for women at risk of placental disorders at term may thus be indicated.

For all PE, screening tests appear to be appropriate to predict PE but with lower accuracy than if applied to detect preterm PE only, and studies of interventions show mixed results in terms of preventive power. There is a large volume of mostly high-quality evidence that generally supports the conclusions separately reached for preterm and term PE. Given the difference between preterm and term PE findings, there is a risk that lack of predictive power or effect in term PE pregnancies may be diluting the effect of the test or intervention amongst preterm pregnancies in the 'all PE' cohorts.

Limitations

A main limitation of this review was that studies of a retrospective and case-control design were not extracted in the evidence synthesis. This decision was taken *a posteriori* because of the high number of relevant studies identified in the review initially. Prospective and cohort studies have fewer potential sources of bias and confounding than retrospective and case-control studies, hence the reason for exclusion, however, it is noted that this may potentially increase the overall risk of bias.
Methodological limitations included limiting the searches to only including peer-reviewed, English-language journal articles. The titles, abstracts and full texts were screened by one reviewer, with a second reviewer verifying all included, 10% of excluded decisions and any articles where there was uncertainty about their inclusion. Systematic reviews were identified through a separate search and were pre-screened based on title by a single, senior reviewer.

Expert advice

This review was conducted with expert advice from:

Professor Jenny Myers — Professor Obstetrics & Maternal Medicine; Maternal & Fetal Health Research Centre; School of Medicial Sciences, Faculty Biology, Medicine & Health; University of Manchester.

Introduction and approach

Background

Pre-eclampsia (PE) is a multi-system disorder of unknown aetiology and is part of a spectrum of conditions referred to as hypertensive disorders of pregnancy (HDPs). Forming a continuum with normal pregnancy, these disorders include chronic hypertension, gestational hypertension and PE.[10-13]

In the past, a variety of definitions of PE have been used in studies and guidelines, however, recently, efforts have been made towards standardisation.[12, 14] In 2010, NICE guidelines defined PE as new hypertension (persistent systolic blood pressure [SBP] ≥140 mmHg or diastolic blood pressure [DBP] ≥90 mmHg) presenting after 20 weeks with significant proteinuria, defined as >300 mg protein in a 24-hour urine collection or >30 mg/mmol urinary protein/creatinine ratio in a sample.[7] Despite the requirement for significant proteinuria in this definition, it is widely recognised that both clinical symptoms and haematological or biochemical abnormalities can occur in the absence of proteinuria.[7, 13, 15] As a result and to reflect the heterogeneity of the condition, the ACOG 2013 guidelines broadened the diagnostic criteria for PE.[15, 16] In the absence of proteinuria, ACOG 2013 define PE as hypertension in association with thrombocytopenia (platelet count <100,000/µL), impaired liver function (double the normal concentration of elevated liver transaminase levels), new development of renal insufficiency (elevated serum creatinine >1.1 mg/dL or a doubling of serum creatinine in the absence of other renal disease), pulmonary oedema, or new-onset cerebral or visual disturbances.[15] In 2019, NICE updated their definition to define PE as new onset hypertension (≥140 mmHg systolic or ≥90 mmHg diastolic) presenting after 20 weeks of pregnancy with one or more new-onset conditions, including significant proteinuria or maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological complications or haematological complications.[1]

Severe PE, as defined by NICE, is a blood pressure of >160 mmHg systolic or >110 mmHg diastolic, with worsening maternal organ dysfunction (such as haemolysis, elevated liver function tests and low platelets, also known as HELLP syndrome) or worsening fetal growth restriction. “Early-onset” PE is a term sometimes used to refer to PE cases manifesting before 34 weeks gestation.[10, 17] Early-onset PE is usually associated with more severe adverse maternal and neonatal outcomes than “late onset” PE, which refers to cases developing at or after 34 weeks gestation.[10, 17, 18] PE can be further subclassified based on the gestational age at birth, with preterm PE referring to PE requiring birth before 37 weeks gestation and term PE referring to PE with birth at or after 37 weeks gestation. Currently the general consensus is that preterm and term PE may have distinct aetiologies and thus suspected to be different forms of the condition.[19, 20]

Condition progression

PE can lead to stroke, a syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP syndrome), disseminated intravascular coagulation and eclampsia, which is the development of seizures in a woman with severe PE.[12] PE has a 1.8% mortality rate and a further 35% of women experience a serious complication due to PE.[21] Women with PE are also at an increased risk of developing gestational hypertension and PE in a future pregnancy.[7] Furthermore, PE has been linked to a number of long-term effects on maternal health, including increased risk for subsequent cardiovascular complications, chronic inflammation indicative of immunological memory and autoimmune diseases.[22] It is estimated that over the 5 to 15 years after birth women with PE have twice the risk of cardiovascular complications such as heart disease, stroke, and venous thromboembolism.[22]

In addition to impacting the mother, PE can also affect the baby. Consequences include problems with growth due to impaired placentation, such as FGR, or prematurity, due to the need for an earlier birth;[12] an estimated 20–25% of preterm babies will be born small for gestational age (SGA).[7] PE can also have more long-term effects on the child, with an increased risk of hospitalisation for many diseases, including endocrine, nutritional, and metabolic diseases in children born at term who were exposed to PE.[23]

Pathogenesis, aetiology and risk factors associated with pre-eclampsia

The pathogenesis of PE is still not well understood, though there is increasing evidence that it is not a single condition, but a collection of syndromes varying in origin and outcome.[24] Based on the findings that PE resolves after the placenta has been expelled and can still occur in the absence of a viable fetus, the placenta is implicated in the causal pathway for PE.[12, 25] Villous and vascular placental lesions have also been implicated in PE pregnancies, however, their role in aetiology is unclear as they are not specific to only PE.[26] It has also been suggested that PE is a two-stage condition with an imbalance between angiogenic and anti-antigenic factors at the heart of the pathogenic mechanism.[13, 20, 27]

Interestingly, placental pathology may have less of an important role in later-onset PE, an observation based on the seemingly fewer histological pathologies observed.[28] Additionally, PE with earlier and later onsets have been shown to be most strongly associated with different risk factors and different outcomes.[29] If the aetiology of PE with an earlier or later onset differs, the consequence could be that different screening tests may be more suited to predict early onset than late onset PE. For example, placental growth factor (PlGF) could be a useful test for early onset, but less accurate for predicting late onset PE.[30] Other factors that appear to have a role in causing PE include the maternal immune response, genetic predisposition, maternal vascular disease, and

diet; whether a woman will develop PE is likely to depend on the presence and interaction of these.[14]

The incidence of PE is increased in women with risk factors such as nulliparity, advanced maternal age, multiple births, diabetes, obesity, family history of PE, a new partner and/or more than 10 years since last pregnancy, renal disease, and the presence of antiphospholipid antibodies, as well as prior PE and chronic hypertension.[18, 31-37] Thrombophilia and autoimmune disease also have a strong association with severe early-onset PE.[14] Current national and international guidelines provide a list of risk factors, the presence of which indicates further assessment based on clinical characteristics of the woman.[7, 10, 15] However, there is little evidence on the risk of PE associated with each factor individually and how these may interact.[14]

Burden of pre-eclampsia

An overall prevalence of gestational hypertension has been reported to range from 3.6 to 9.1%.[4] In unselected populations, the incidence of PE varies between 1.4% and 4%,[4, 12] with a lower prevalence of PE with onset before 34 weeks gestation (0.38%) compared with PE with onset at or after 34 weeks (2.7%).[29] Globally, it has been estimated that 14% of maternal deaths are due to hypertensive disorders, and 10% are associated with eclampsia.[38, 39] In the UK, while PE is less prevalent than in other countries, it is still responsible for 8% of maternal deaths.[5] In addition, PE also increases the risk of perinatal mortality and morbidity; 1 in 20 (5%) stillbirths in infants without congenital abnormality occurred in women with PE,[7] and approximately 20% of antenatal admissions and two-thirds of referrals to day care assessment units in the UK have been attributed to PE.[12] As mentioned previously, PE also substantially contributes to the number of preterm births; it is estimated that about 13% of PE cases will develop before 34 weeks and 32% between 34 and 37 weeks, with as many as 1 in 250 (0.4%) nulliparous women giving birth before 34 weeks as a result of PE.[7, 40]

The increased likelihood of complications in pregnancy, labour or perinatal death in women with PE often leads to increased psychological morbidity, hence developing PE can also be a significant psychological burden and a challenging experience for many women.[12] Women who have suffered from PE have been shown to experience more cognitive problems and have a significantly reduced quality of life and social functioning compared with women with normotensive pregnancies.[41]

Current clinical practice

It is widely recognised that evidence is lacking for the prediction, prevention and treatment of PE. In the absence of such evidence, the focus of management is on general monitoring, controlling maternal hypertension, and ultimately, birth of the baby and the placenta.[42] Where possible

(specifically, in cases occurring with mild to moderate hypertension), planned birth at 37 weeks gestation is standard care in the UK,[7] and reduces PE morbidity compared with expectant monitoring.[43] By contrast, birth before 37 weeks is associated with a significantly higher risk of adverse neonatal outcomes,[44] and thus in women developing preterm PE any management strategies should aim to balance minimising maternal risks due to worsening PE with fetal risks of prematurity.[11]

Pharmacological interventions

There exists a variety of pharmacological interventions whose efficacy in the prevention of PE in women at high risk has been tested in clinical trials. Potentially promising interventions include anti-coagulants such as aspirin, anti-oxidants such as vitamin C and E (with nitric oxide donors) and calcium supplementation.[6, 12, 42, 45] More recently, metformin and statins have been proposed as candidate interventions for reducing the risk of PE.[46] [47] Many interventions, such as fish oil, evening primrose oil, salt restriction, diuretics,[42, 48] bed rest or progesterone,[6] among others, have been investigated but there is insufficient data to draw reliable conclusions for those.

Low-dose aspirin, started before 16 weeks of gestation and taken until the birth of the baby is the only treatment consistently indicated to be effective for the prevention of PE in high-risk groups.[48] Available evidence suggests that aspirin has a good safety profile, and it would be reasonable to continue with low-dose aspirin well into the third trimester of pregnancy.[18] However, aspirin is not entirely effective for secondary prevention in all cases of PE, as a recent meta-analysis (MA) including 16 trials and 18,907 participants found that despite reducing the risk of preterm PE, a daily dose of ≥100 mg aspirin initiated at or before 16 weeks of gestation does not reduce the risk of term PE.[49]

Current guidance on assessing risk

Most of the major PE guidelines do not currently recommend routine screening (such as biomarker measurements) for the whole population, due to insufficient evidence of clinical and/or cost-benefit. Instead, the recommended approach is to identify those at “high risk” and administer prophylactic treatment, such as low-dose aspirin.[7, 15, 50] In the UK, NICE recommends that a woman’s risk of PE should be evaluated at her first visit by collecting information on maternal characteristics, such as age, body mass index (BMI) and previous and family history of PE.[1, 51] For women with one major or two or more moderate risk factors, those who present with mild hypertension before 32 weeks gestation, or experience symptoms of PE, measurements of blood pressure and urine are also recommended at every routine face-to-face antenatal appointment.[7, 15, 52] Major risk factors are hypertensive disease during a previous pregnancy, chronic kidney disease, autoimmune disease, type 1 or type 2 diabetes or chronic hypertension. Moderate risk factors are first pregnancy, age 40

years or older, pregnancy interval >10 years, BMI of 35 kg/m^2 or more at first visit, family history of PE and multi-fetal pregnancy.

Current guidance for secondary prevention

The 2019 NICE guideline (NG133) recommends that pregnant women with one major or more than one moderate risk factor for pre-eclampsia take 75 to 150 mg of aspirin daily from 12 weeks until birth.[1] Similarly, the ACOG guideline recommends that women at high risk of PE take 60 to 80 mg aspirin daily, beginning late in the first trimester,[15] and the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) guidelines advise low-dose aspirin for the secondary prevention of PE in women with moderate to high risk.[50] NICE and ACOG guidelines also consider interventions such as antioxidants (vitamin C and E), salt restriction and nutritional supplements but conclude that there is insufficient evidence to recommend them.[7, 15] The WHO recommends low-dose aspirin (75 mg), antihypertensive drugs and calcium supplementation.[53] ACOG acknowledges that whilst calcium supplementation may be of benefit to populations who are deficient, it is unlikely to be of relevance to developed countries. Interventions not recommended include bed rest, restriction in dietary salt intake, vitamin C, D and E supplementation or diuretics.[53] No differentiation is made between early onset and late onset PE in any of the treatment guidelines.

Screening for pre-eclampsia

Early identification of women at high risk of PE would facilitate monitoring and administration of secondary preventive measures, to mitigate adverse maternal and fetal outcomes. Screening measures that have been explored in the experimental setting include imaging techniques and the measurement of biomarkers. One well studied imaging technique is the uteroplacental Doppler ultrasound, widely used for predicting PE by identifying impaired placental perfusion and defective placentation.[10, 25] It reportedly predicts 48% of early onset PE cases and 26% of any PE when conducted in the first trimester.[10] Biomarkers suggested as possible predictors of PE include angiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1), vascular endothelial growth factor (VEGF), PlGF and soluble endoglin,[15, 25] markers of fetoplacental endocrinological dysfunction such as pregnancy-associated plasma protein A (PAPP-A) and inhibin A,[25] or more novel markers such as cell-free fetal DNA (cffDNA),[24] fibronectin,[54] or placental protein-13 (PP13).[15]

Numerous large reviews have evaluated a broad range of possible screening tests for PE, all reaching the conclusion that available tests are not sufficiently accurate or validated to be used in routine clinical practice.[12, 55] Overall, there is consensus that a single marker is unlikely to provide an accurate prediction, given that it is unclear how individual factors interact and contribute to the risk of PE. However, sensitivity increases with the monitoring of multiple markers in parallel.[14]

Recent developments have seen an emergence of a risk prediction tool based on an algorithmic approach with the use of Bayes' theorem, combining risk from different factors, including maternal characteristics, uterine artery pulsatility index (UtA-PI) and biomarkers.[18, 56, 57] The model assumes that all pregnancies would ultimately result in PE, if they continued for long enough.[57] The performance of models in predicting PE has been promising, with sensitivity for predicting preterm PE up to 75% at 11 to 13 weeks,[58, 59] and 85% at 19 to 24 weeks, at 10% false-positive rate.[34, 59 60] On the other hand, a recent Health Technology Assessment (HTA) conducted by the National Institute for Health Research (NIHR) externally validated 24 of the 131 published prediction models in 11 UK cohorts and found that predictive performance was poor to average across data sets, with large heterogeneity.[61] However, a large number of published models were not able to be validated because the models' predictors were unavailable in the individual participant data.[61] When 12 new models were developed and validated using 78 data sets, with adjustment for overfitting, these showed good predictive performance on average across data sets, demonstrating a potential benefit to the singleton, nulliparous UK pregnant population.[61] However, in clinical practice, the models would need to be recalibrated to particular settings and populations, which would require local data.[61] Future research is still needed to validate the large number of models which have not yet been validated.[61]

Risk prediction models out-perform the current risk approach recommended by NICE, which identifies only 30% to 40% of pregnancies that develop PE.[56] Along with a low sensitivity, identifying women at high risk based on risk factors (as recommended by NICE) has a number of other limitations. These include a limited ability to detect PE in the low-risk population (i.e. those for whom risk factors are not evident), and the fact that many women who do have risk factors (such as increased maternal age, a pre-existing condition, family history of PE) do not suffer PE. ACOG guidance recommends considering all risk factors, which results in an extremely high screen-positive rate, with almost two-thirds of the screened population identified as high risk.[15]

In contrast to most recommendations, the US Preventive Services Task Force (USPSTF) does recommend PE screening for the whole population in the form of blood pressure measurements at each prenatal visit,[62] which is already a routine part of antenatal care for every pregnant woman in the UK.[52] Further evaluation is then indicated for those with repeatedly elevated blood pressure. However, more detailed recommendations on, for example, specific biomarker measurements are not given.[62]

In 2021, the USPSTF updated its recommendations for the prevention of PE, based on results from a systematic review, and now advises the use of daily low-dose aspirin as a preventivie medication for PE after 12 weeks gestation in women deemed high risk.[63] It has been suggested that treatment of all pregnant women with aspirin may be more cost-effective than screening for PE, however, there are ethical implications to consider as even with a relatively safe drug like aspirin this would involve administering unnecessary treatment to a high number of women.

Nevertheless, screening for PE may be cost-effective compared with not carrying out screening or administering treatment at all.[64] The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guideline also recommends Doppler US screening of the uterine artery in the first and second trimester.[10] Regardless of its potential for cost-effectiveness, current evidence surrounding test accuracy is not strong enough to support this.[65]

Current policy context and previous reviews

All population screening for PE is not currently recommended in the UK. This is based on the 2011 UK NSC review of the evidence, which found that there were no appropriate, validated predictive test(s) or preventive treatments with suitable efficacy and safety profile that could be given to high-risk (screen-positive) women. Additionally, the review suggested there was not enough information on the natural history of PE that would allow understanding of the causes of the condition. The review further emphasised the need for more studies evaluating biochemical and ultrasound tests as well as the evidence behind treatment with antiplatelet agents. Finally, the review acknowledged that diagnosis and management of PE are currently covered by the NICE CG62 (in terms of identifying women with risk factors) and NICE CG107 (in terms of further management) guidelines.

PE remains a significant burden with adverse maternal and fetal/neonatal outcomes, and it is unclear whether there is new evidence that could support recommendation of a screening programme. This rapid review aims to identify and synthesise evidence published since the most recent UK NSC review (2011) to provide an overview of the current landscape of screening and interventions for PE. Specifically, new evidence was collected to answer the following 2 questions:
1) What is the most accurate screening test to predict PE?
2) Is there an effective intervention for preventing PE in screen-detected women?

A key focus was put on distinguishing between preterm and term PE as these may be considered separate in terms of aetiology, and thus, differ in the appropriate tests and interventions.

Objectives

This review aims to assess whether there is sufficient evidence to consider introducing a screening programme for PE. The review will appraise evidence on the questions in

Table 1, which each relate to the criteria set out by the UK NSC for assessing the suitability of a screening programme.

Table 1. Key questions for the evidence summary, and relationship to UK NSC screening criteria

	Criterion	Key questions	Studies Included
	THE TEST		
4	There should be a simple, safe, precise and validated screening test.	What is the most effective screening test to predict preterm and term pre-eclampsia?	75 publications on 37 unique cohorts
	THE INTERVENTION		
9	There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.	Is there an effective intervention for preventing preterm or term pre-eclampsia in screen-detected women?	25 publications on 17 unique cohorts

Methods

The current review was conducted by Costello Medical, in keeping with the UK National Screening Committee evidence review process.

Database searches were conducted on **5 December 2018** to identify studies relevant to the questions detailed in

Table 1.

The review was subsequently **updated on 11 October 2021**.

Eligibility for inclusion in the review

The following review process was followed:

- Two separate searches were run – one aimed at identifying primary studies and one aimed at identifying systematic reviews (though it is noted that systematic reviews were not specifically excluded from the search or primary studies). The search for systematic reviews was to ensure no relevant evidence syntheses would be missed.
- Records identified though the systematic reviews search were pre-screened based on title by a single, senior reviewer. In cases of uncertainty, reviews were included. All included reviews were then added to the pool of the main database search and duplicates were removed prior to the abstract review stage.
- Each abstract was reviewed against the inclusion/exclusion criteria by one reviewer. Where the applicability of the inclusion criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies are captured. A second independent reviewer provided input in cases of uncertainty, and validated all included and 10% of excluded articles. Any disagreements were resolved by discussion until a consensus was met.
- Full-text articles required for the full-text review stage were acquired if freely available at the Cambridge University Library. For any paywalled articles unavailable at the Cambridge University Library, the authors were contacted to provide the full texts and any articles that were not available were purchased.
- Due to the high volume of evidence identified, retrospective or nested case-control studies were not analysed. Any such studies that were unavailable were not purchased but tagged separately should they need to be reviewed in the future.
- Each full-text article was then reviewed against the inclusion/exclusion criteria by one reviewer, who determined whether the article was relevant to one or more of the review questions. A second independent reviewer provided input in cases of uncertainty and validated all included and 10% of excluded articles. Any disagreements were resolved by discussion until a consensus was met.

Eligibility criteria for each question are presented in Table 2 and Table 3. For all questions, systematic literature reviews (SLRs) and MAs were considered for inclusion. If the scope of an SLR or MA was very closely aligned to one of the topics of this review, it was included in its own right. However, where the scope was not closely aligned to one of the topics of this review but some of the included articles may have been of interest, the reference list of the SLR or MA was hand-searched. Any relevant primary research articles identified were included, but the SLR itself was excluded.

Table 2. Inclusion and exclusion criteria for question 1 — screening for pre-eclampsia

Domain	Target condition	Population	Intervention	Outcome	Study type	Setting	Other considerations
Inclusion criteria	Pre-eclampsia	All pregnant women (unselected or low-risk)	Index test (before 20 weeks of gestation): Risk of pre-eclampsia determined by individual or combined assessment of maternal characteristics, medical history or ultrasound or biochemical markers, including, but not limited to: • Mean arterial pressure (MAP); • Uterine artery pulsatility index (UtA-PI); • Serum placental growth factor (PlGF); and • serum pregnancy-associated plasma protein-A (PAPP-A) Maternal characteristics, medical history and measurements of: • MAP and PAPP-A; • MAP and PlGF; • MAP, UtA-PI and PlGF • MAP, UtA-PI and PAPP-A Reference standard (applied at or after 20 weeks of gestation): New onset hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) and the coexistence of 1 or more of the following new-onset conditions • (1) Proteinuria (urine protein:creatinine ratio of ≥0.30 mg/mmol or ≥1+ dipstick testing • (2) Other maternal organ dysfunction including: acute kidney injury (creatinine ≥90 µmol/L, ≥1 mg/dL), liver	Measures of screening accuracy: • Competing risk • Sensitivity • Specificity • Positive predictive value • Negative predictive value • Accuracy • Likelihood ratio	RCTs and interventional studies, cross-sectional studies, cohort studies, case-control studies, systematic reviews	Studies conducted in the UK Studies conducted in high-income countries where the screening methods and technology are expected to be similar to that of the UK (OECD and EEA countries excluding South Korea and Mexico)	Peer-reviewed studies in the English language Studies published in 2011 or later

		involvement (elevated transaminases, for example ALT or AST >40 IU/L) with or without right upper quadrant or epigastric abdominal pain, neurological complications (eclampsia, altered mental status, blindness, stroke, clonus, severe headaches or visual scotomata) or haematological complications (thrombocytopenia–platelet count <150,000/μL, disseminated intravascular coagulation, haemolysis) • (3) Uteroplacental dysfunction (such as fetal growth restriction, abdnormal umbilical artery doppler waveform analysis or stillbirth). OR Definition of pre-eclampsia as defined by the study authors OR Gestational hypertension OR Hypertensive disorders of pregnancy				
Exclusion criteria	Women who are not pregnant Pregnant women known to have specific conditions (for example, polycystic ovary syndrome) or risk factors (for example, twin pregnancies)	Index tests performed after 20 weeks of gestation Index test aiming to predict gestational hypertension or hypertensive disorders of pregnancy	Any other outcomes (including area under the receiver-operator curve or measures of association between risk factors/test values and risk of pre-eclampsia)	Case reports, case series, narrative reviews, editorials, commentaries, letters, conference abstracts or other publication types that have not been peer-reviewed	Studies in ineligible countries, or international studies that consider eligible and ineligible countries, but outcomes for eligible countries are not presented separately to outcomes from ineligible countries	Studies with full text not in the English language Studies published pre-2011

Table 3. Inclusion and exclusion criteria for question 2 — interventions to prevent pre-eclampsia

Domain	Target condition	Population	Intervention	Comparator	Outcome	Study type	Setting	Other considerations
Inclusion criteria	Pre-eclampsia	All pregnant women	Pharmacological intervention of the type: • Anti-coagulant • Anti-thrombotic • Anti-oxidants	• Normal care (defined as 75 to 150 mg aspirin) • No treatment • Placebo	• Maternal outcomes • Death and short and long-term morbidity including: eclampsia, stroke, a syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP syndrome) and disseminated intravascular coagulation • Newborn outcomes: small for gestational age (SGA), perinatal mortality, neonatal intensive care unit (NICU) admission • Pre-eclampsia • Harms of treatment	RCTs and interventional studies, cohort studies, case-control studies, systematic reviews	Studies conducted in the UK Studies conducted in high-income countries where the screening methods and technology are expected to be similar to that of the UK (OECD and EEA countries excluding South Korea and Mexico)	Peer-reviewed studies in the English language Studies published in 2011 or later
Exclusion criteria		Women who are not pregnant	Any other intervention	Any other comparator	Any other outcomes, for example quality of life or costs	Cross-sectional studies, case reports, case series, narrative reviews, editorials, commentaries, letters, conference abstracts or other publication types that have not been peer-reviewed	Studies in ineligible countries, or international studies that consider eligible and ineligible countries, but outcomes for eligible countries are not presented separately to outcomes from ineligible countries	Studies with full text not in the English language Studies published pre-2011

Appraisal for quality/risk of bias tool

The following tools were used to assess the quality and risk of bias of each study included in the review

- Diagnostic accuracy studies: adapted Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool[66]
- Observational and interventional studies: adapted Downs and Black Checklist[67]
- Systematic reviews: AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews) instrument

The full guidance used for the quality assessments is available in Appendix 3

Databases/sources searched

The following databases were searched:

- MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print
- Embase
- The Cochrane Library, including the following:
    - Cochrane Database of Systematic Reviews (CDSR)
    - Cochrane Central Register of Controlled Trials (CENTRAL)
- Database of Abstracts of Reviews of Effects (DARE)

MEDLINE databases and Embase were searched simultaneously via the Ovid SP platform. The Cochrane Library databases were searched via the Wiley Online platform. While the Database of Reviews of Effects of Interventions (DARE) was searched in the original review, this database was not searched during the review update as the records were last updated in 2015.

Searches were initially conducted in December 2018, followed by an an update in October 2021. Full details of the searches, including the search strategy for each database, are presented in Appendix 1 — Search strategy.

Overall results

In the original search (2018), database searches yielded 4223 results for primary studies and 748 results for SLRs, of which 117 articles were judged to be relevant to one or more questions. An additional 14 references were identified through hand-searching reference lists, so 131 articles were considered. Ultimately, 75 articles from this original review were included.

In the update searches (2021), database searches yielded 4534 results, (3929 primary studies and 605 SLRs). A total of 22 of these articles were judged to be relevant to one or more questions. No additional relevant references were identified through hand-searching reference lists. Therefore, this update adds 22 new publications to the 75 publications identified in the original review. In total, 97 publications reporting on 52 unique studies were included.

Appendix 2 — Included and excluded studies contains a full PRISMA flow diagram (Figure 1), along with a table of the included publications and details of which questions these publications were identified as being relevant for (Table 23).

Question level synthesis

Criterion 4 — Screening tests for pre-eclampsia

4: 'There should be a simple, safe, precise and validated screening test.'

In 2011, the UK NSC summarised the findings of the 2008 health technology assessment (HTA) report 'Methods of prediction and prevention of PE: systematic reviews of accuracy and effectiveness literature with economic Modelling' that included a review of predictive tests. The report found that although tests were relatively safe, their sensitivities and specificities were not sufficient to be useful for general screening of the UK population in the first or second trimester.[6, 12]

In current practice, as recommended by the NICE NG133 guideline for hypertension in pregnancy, the risk of PE in pregnant women in the UK is evaluated by collecting information on maternal characteristics and obstetric history.[1] Those identified as "high-risk" are then administered prophylactic treatment, such as low-dose aspirin.[1] Women without risk factors identified are not currently offered additional screening or prevention and the current approach identifies only 30% to 40% of pregnancies that develop PE.[56]

The aim of this question was to identify and synthesise evidence published since 2011 on accuracy parameters of tests that predict PE, with results classified into preterm (before 37 weeks), term (from 37 weeks) and all PE (results not stratified by gestational age) in low-risk or unselected UK women, or women similar to a low-risk or unselected UK population. Studies which defined outcomes using the terminology 'early-onset' and 'late-onset' were classified into preterm or term based on how the study authors defined these outcomes. The decision to categorise results in this way is further elaborated on below.

Question 1 — Is there an effective test to predict the risk of preterm or term PE?

Eligibility for inclusion in the review

This review searched for cohort, cross-sectional and case-control studies, randomised controlled trials (RCTs) and interventional studies with an appropriate screening component, along with SLRs or MAs. Studies were eligible if they assessed the performance of an index test that aimed to predict the risk of PE administered before 20 weeks of gestation. The reference standard was PE, GH or HDP. Eligible studies were required to use a definition for PE consistent with the UK: GH (persistent SBP ≥140 mmHg and/or DBP ≥90 mmHg) accompanied by ≥1 of the following new onset conditions at or after 20 weeks of gestation: proteinuria, acute kidney injury, liver involvement with or without right upper quadrant or epigastric pain, neurological complications,

haematological complications, and/or uteroplacental dysfunction.[68] Studies were only included if they directly reported test accuracy parameters; no calculations were performed in this review to obtain such measures.

The eligible population was unselected or low-risk pregnant women, as specified by the NICE NG201 guideline for antenatal care.[52] Studies that only included women with high-risk pregnancies, such as those who had previous complications or maternal comorbidities, were excluded. These women would already be identified as being at risk through, and receive care under, existing antenatal care pathways, and would therefore fall outside of the expected screening population.

Full details of the eligibility criteria are presented in Table 2.

Description of the evidence

From the 2018 search, 107 publications were initially included for Criterion 4. Due to a high number of studies identified, retrospective and case-control studies were deprioritised and not extracted, as these study designs are generally of lower methodological quality and at a higher risk of bias and confounding. The same approach was taken for when the search was updated. A list of all included but not extracted studies is available in Table 24.

In total, 75 primary publications reporting on 37 unique cohorts of women were extracted for this criterion. In a number of cases, cohorts overlapped between different studies, for example reports spanned different time frames but had substantial cross-over of women. The most prominent example of this are 22 publications reporting on a large prospective screening programme conducted in the UK, based at the King's College Hospital and Medway Maritime Hospital, with some records also recruiting at University College London Hospital, University Hospital Lewisham, Homerton University Hospital, North Middlesex University Hospital, Southend University Hospital and Royal London Hospital, henceforth referred to as 'London Cohorts'.[69] For these and similar studies, baseline characteristics were extracted for the most representative cohort whilst results for different specific tests were still extracted separately.

No systematic reviews which closely aligned with the scope of this review question were identified; the main reason for this was that the majority of studies included in each systematic review were conducted prior to 2011. As case-controls and retrospective study designs were ultimately not included in data synthesis, all extracted studies were of a prospective cohort design. The majority of studies (N=28, 8 unique cohorts)[69-78] were conducted in the UK, with the remaining studies conducted in Australia (N=4, 3 unique cohorts),[79-82] Austria (N=1),[83] Canada (N=7, 3 unique cohorts),[84-90] Chile (N=1),[91] Israel (N=2),[92, 93] Italy (N=3),[94-96] Japan (N=2),[97, 98] The Netherlands (N=1)[99] Norway (N=1),[100] Spain (N=5, 3 unique cohorts),[101-105] Sweden (N=1),[106] Turkey (N=2)[107,

[108] and United States (N=9, 7 unique cohorts).[109-116] All studies used confirmed PE as the reference standard.

All screening tests were performed before 20 weeks gestation, and included single or combination tests of maternal characteristics and history, 21 distinct biomarkers and 9 distinct ultrasound-based markers:

- Biomarkers
    - A-disintegrin and metalloprotease 12 (ADAM-12)
    - Albumin: creatinine ratio (ACR)
    - Fructose-biphosphate aldolase A (ALDOA)
    - Alpha-fetoprotein (AFP)
    - Augmentation index (AIx-75)
    - Central aortic systolic blood pressure (SBPAo)
    - Extracellular matrix protein 1 (ECM1)
    - Free beta-human chorionic gonadotropin (fβ-hCG)
    - Inhibin-A
    - Insulin-like growth factor acid labile subunit (IGFALS)
    - Microtubule-associated protein RP/EB family member 1 or 3 (MAPRE1/3)
    - Mean arterial pressure (MAP)
    - Mean platelet volume (MPV)
    - Melanoma cell adhesion molecule (MCAM)
    - Multimerin-2 (MMRN2)
    - Neutrophil gelatinase-associated lipochalin (NGAL)
    - Pregnancy associated plasma protein (PAPP-A)
    - Placental growth factor (PlGF)
    - Placental protein 13 (PP13)
    - Placental quotient (PQ)
    - Placental volume (PV)
    - P-selectin
    - Pulse wave velocity (PWV)
    - Selenoprotein (SEPP1)
    - Serine peptidase inhibitor Kunitz type 1 (SPINT1)
    - Soluble endoglin (sEng)
    - Soluble fms-like tyrosine kinase (sFlt-1)
    - Total human chorionic gonadotropin (hCG)
    - Unconjugated estriol (uE3)
- Ultrasound-based markers
    - Notch/bilateral notch
    - Highest uterine artery pulsatility index (hUtA-PI)
    - Mean notch depth index (mNDI)

- Power Doppler vascularization index of the placental bed (PBVI)
- Uterine artery pulsatility index (UtA-PI)
- Uterine artery resistance index (UtA-RI)
- Vascularisation flow index (VFI)
- Vascularisation index (VI)

Thirty-one studies developed and evaluated predictive models using a combination of maternal factors and biomarkers,[72-74, 78, 80-82, 84, 86-88, 90-93, 96, 97, 99, 101, 106-109, 111, 112, 114-119] and 8 studies evaluated existing algorithms or clinical guidelines.[69-71, 76, 79, 95, 100, 111] Twenty-six studies in 6 unique, non-overlapping cohorts (including the majority of those in the 'London Cohorts') used a "competing risks" model approach (currently part of the Fetal Medicine Foundation [FMF] risk assessment algorithm): a combination of risk factors (including maternal history), and biomarkers (such as MAP, UtA-PI, serum PlGF, PAPP-A), [34, 79, 120] and the application of Bayes' theorem to estimate individual patient-specific risk of PE requiring birth before any specified gestation (i.e. as a continuous variable).[32-34, 56, 58, 59, 69, 71, 75, 77, 79, 89, 98, 100, 103-105, 111, 121-128] The Preeclampsia Predictor TM version 1 revision 2 by Perkin Elmer (PREDICTOR) algorithm was also evaluated by one study; this calculates a 'prior risk' of PE based on the same factors used in the FMF algorithm.[100] The accuracy of predicting PE using risk-factor based clinical guidelines, such as NICE guidelines or ACOG recommendations, was evaluated in 2 cohorts.[69, 79]

Summary of findings

A study-level summary of data extracted from each included publication is presented in the summary and appraisal of individual studies in Appendix 3.

Quality Assessment

The quality of the included studies was appraised using an adapted QUADAS-2 checklist (Table 29; Appendix 3). A summary of the risk of bias and applicability to the UK setting is presented in Table 4, Table 5 and Table 6, and the full appraisal is presented in Appendix 3(Table 30, Table 31, and Table 32).

Table 4. Summary of QUADAS-2 assessments for pre-eclampsia screening studies (part 1)

Question	Al-Amin 2018[79]	Allen 2018[73]	ASPRE[74]	Baweja 2011[81]	Boucoiran 20123a[86]	Boucoiran 2013b[87]	Caradeux 2013[91]	Carter 2015[110]	Di Lorenzo 2012[94]	Di Martino 2019[95]	Erkamp 2020[99]	Gabbay-Benziv 2016[118]	Goetzinger 2013[109, 112]
PARTICIPANT SELECTION													
Risk of bias	Unclear	Low	Low	High	Low	Low	Unclear	Low	Low	Low	High	High	Low

Question	Al-Amin 2018[79]	Allen 2018[73]	ASPRE[74]	Baweja 2011[81]	Boucoiran 2012a[86]	Boucoiran 2013b[87]	Caradeux 2013[91]	Carter 2015[110]	Di Lorenzo 2012[94]	Di Martino 2019[95]	Erkamp 2020[99]	Gabbay-Benziv 2016[118]	Goetzinger 2013[109, 112]
Concern about applicability	High	Low	Low	Low	Low	High	High	High	Low	Low	Low	Low	Low
INDEX TESTS													
Risk of bias	Low	High	Low	Unclear	Low	Unclear	High	High	Low	Unclear	Low	High	Low
Concern about applicability	High	Low	Low	Low	Low	Low	High	Low	High	Low	Low	Low	High
REFERENCE STANDARD													
Risk of bias	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Concern about applicability	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
PARTICIPANT FLOW													
Risk of bias	High	High	High	High	High	Low	High	High	High	High	High	High	Low

Table 5. Summary of QUADAS-2 assessments for pre-eclampsia screening studies (part 2)

Question	GOS study [84, 88, 89]	Goto 2021[98]	Hafner 2013[83]	Honigberg 2016[117]	Kanat-Pektas 2014[108]	Khalil 2012[74]	Maymon 2017[93]	Meiri 2014[92]	Metcalfe 2014[90]	Myatt 2012[114]	Odibo 2011a[115]	Odibo 2011b[116]
PARTICIPANT SELECTION												
Risk of bias	Low	Low	Low	Low	High	Low	Low	Low	Low	High	Low	Low
Concern about applicability	Low	Low	Low	High	Low	Low	Unclear	Low	Low	Low	Low	Low
INDEX TESTS												
Risk of bias	Unclear	Low	Unclear	High	Low	Unclear	Unclear	Low	High	Low	Low	Low
Concern about applicability	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
REFERENCE STANDARD												
Risk of bias	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Concern about applicability	Low	Low	Low	Low	Low	Low	Low	Low	Unclear	Low	Low	Unclear
PARTICIPANT FLOW												
Risk of bias	Low	High	High	High	High	High	Low	Low	High	Low	High	High

Table 6. Summary of QUADAS-2 assessments for pre-eclampsia screening studies (part 3)

Question	POP study[76]	Sandström 2019[106]	Scazzocchio 2013[101]	SCOPE [72, 119]	Schneuer 2012[80, 82]	Serra 2020[103]	Skrastad 2015[100]	Sonek 2018[111]	Takahashi 2012[97]	Tan 2018a[69]	Tsiakkas 2016b[127]	Youssef 2011[96]	Yucel 2016[107]
PARTICIPANT SELECTION													
Risk of bias	Low	Low	Low	Low	Unclear	Low	Low	Low	Low	Low	Low	High	Low
Concern about applicability	Low	Low	High	Low	Low	Low	High	High	High	Low	High	High	Low
INDEX TESTS													
Risk of bias	Unclear	Unclear	High	Low	Low	Unclear	Low	Low	High	Low	High	Low	Low
Concern about applicability	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
REFERENCE STANDARD													
Risk of bias	Low	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear
Concern about applicability	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
PARTICIPANT FLOW													
Risk of bias	High	High	High	Low	Low	High	Low	High	Low	High	High	High	High

Participant selection

Studies were considered to be at a high risk of bias with regard to participant selection if they made inappropriate exclusions. Overall, the risk of bias was judged low in 28 out of 37 cohorts of pregnant women, as they recruited pregnant women consecutively from unselected or low-risk populations and did not inappropriately exclude any women.[69, 70, 72-74, 76, 83, 84, 86, 87, 90, 92-95, 97, 98, 100, 101, 103, 106, 107, 109-111, 115-117, 127] Six studies were judged to be high risk due to recruiting women non-consecutively or inappropriately excluding certain women.[81, 96, 99, 108, 114, 118] Three studies did not report eligibility criteria and therefore the risk of selection bias was unclear.[79, 80, 91]

The concern about applicability was high in 10 studies.[79, 87, 91, 96, 97, 100, 110, 111, 117, 127] These studies either recruited pregnant women from a specialised maternity hospital (and therefore this study population may have been at a higher risk of PE than the general population of pregnant women), and/or a proportion of enrolled women had pre-existing health conditions including chronic hypertension, diabetes mellitus and systemic lupus erythematosus (SLE). These cohorts may therefore not be entirely representative of a low-risk or unselected population of pregnant women in the UK.

Index tests

Studies were at high risk of bias if the index test results were interpreted with knowledge of who developed PE, and if the threshold for which an index test result was considered positive or negative was not pre-specified. If the cut-off values were not pre-specified, the results of the index test may have influenced the chosen thresholds, allowing for the potential overestimation of test accuracy.

Overall, there was a low risk of bias in the conduct of the index tests. In 18 out of 37 studies it was specifically reported that the index test was performed/interpreted while blind to study outcomes.[69, 72, 79, 80, 86, 92, 94, 96, 98-100, 108, 111, 114-116] In 10 other studies, it was not reported whether screening test results were interpreted without knowledge of PE outcomes, and therefore these studies were at an unclear risk of bias.[74, 76, 81, 83, 84, 87, 93, 95, 103, 106] Ten studies were at high risk of bias for this domain; interpretation of the index test results were not blinded to PE diagnosis and/or thresholds for the index test were not pre-specified.[71, 73, 90, 91, 97, 101, 110, 117, 118]

There was little concern that the index test may have differed from the review question in the majority of included studies (N=33); 4 studies assessed screening algorithms that classify women at risk of PE according to pre-existing health conditions such as thrombophilia and diabetes mellitus,[79, 91, 94, 109] and while these women with these conditions are already covered by the NICE guideline CG107, it was not considered that this would have affected the applicability of the index test used.[7]

Reference standard

The lack of information provided regarding the conduct of the reference standard made it difficult to ascertain whether PE was diagnosed with knowledge of the index test results; the risk of bias for this domain was therefore unclear in 29 studies.[69, 70, 72-74, 79-81, 83, 87, 90-96, 98, 99, 103, 107-110, 115-117, 127] If the results of the index test were known at diagnosis or confirmation of diagnosis, this could have led to bias in the recording of HDP outcomes including gestational hypertension and PE. Risk of bias was low for 7 studies in which it was directly stated that diagnoses of PE were confirmed by blinded clinical staff.[76, 84, 86, 101, 106, 114, 118] No included studies explicitly stated if labour was induced in any women to prevent PE; this may have led to an underestimation of test accuracy if cases of PE were prevented through induced labour. Conversely, studies using a competing risks model are at risk of underperformance, especially at term, For example, pregnancies considered to be at "high-risk" could end up in giving birth (spotanueus or induced) before the pre-specified cut-off date for reasons other than PE. These would be considered as false positives (because they were predicted to develop PE but had not actually developed it). For example, a competing risks model could predict PE developing at 39 weeks. A pregnancy may be induced at 38 weeks for another

reason, but will have to be classed as 'wrongly' predicted (false positive), by the model, because it had not developed PE at 39 weeks. There was no concern about applicability of the reference standard in the majority of studies; PE was diagnosed using the definition used in the UK in 35 studies, and only in 2 studies was the applicability of the reference standard unclear, as PE was not adequately defined.[90, 116]

Participant flow

While PE was generally consistently defined by the included studies, the methods for confirming the diagnosis of PE were poorly described in the majority of studies, for example, it was unclear if the PE diagnosis was confirmed by hospital staff or the researchers. This raises the possibility of bias, as there may have been differences in the methods of diagnosis between staff of different hospitals or with different training backgrounds.

In 27 studies, a considerable number of women were not included in the analyses due to missing index test or outcome data.[69-71, 73, 74, 76, 79, 81, 83, 86, 90, 91, 94-96, 98, 99, 103, 106-108, 110, 111, 115-118] This could have introduced selection bias, potentially leading to under- or overestimation of test accuracy.

Results

A ‘perfect’ diagnostic test is one that is able to discriminate between test subjects who truly have and truly do not have the test condition (that is, 100% sensitivity and 100% specificity/false-positive rate [FPR] of 0%); however, this is rarely achievable clinically. The general consensus is that tests with a positive likelihood ratio (LR) greater than 10 and a negative LR of less than 0.1 are considered to have an acceptable accuracy, and could be considered for use in screening for a condition in clinical practice.[129, 130] Nevertheless, LRs were not widely-reported amongst the eligible studies. Instead, sensitivity, specificity, positive predictive values (PPVs) and negative predictive values (NPVs) were synthesised to discuss the accuracy of diagnostic tests. However, this is under the caveat that such values are variable depending on the study population and prevalence of disease, making it difficult to draw comparisons across different studies.
The results for a test’s accuracy at predicting preterm, term and all PE are presented in Table 7,

Table 8 and Table 9. Ideally, studies would have been grouped by gestational age at PE onset, however, the precise time of PE onset is difficult to ascertain. For example, a woman may have PE onset at 32 weeks of gestation, but this may not be detected until her next routine antenatal visit. Therefore, while some studies report results by week of PE onset, unless the woman was having weekly antental visits (which is not standard practice in the UK) the majority of these studies are more likely to actually be reporting on time of PE detection. In addition, the majority of studies report results by gestational age at birth with PE, rather than onset of PE, with onset not being uniformly comparable across all studies. Therefore, results were categorised by gestational age at

birth, defining preterm PE as birth <37 weeks, term PE as birth ≥37 weeks, and all PE when results were not stratified by gestational age. Studies which report results exclusively by gestational age at PE onset and/or detection are categorised into either preterm or term PE as most appropriate, and this differing definition is highlighted in the reporting of results. Furthermore, where studies reported results for multiple test combinations, the best-performing combination is presented, and where studies reported results for multiple FPRs, results for 10% FPR are presented. The sensitivities from studies that evaluated a test at different gestational ages at birth are presented in Table 10. Full study results and details are provided in the extraction tables in Appendix 3.

Preterm pre-eclampsia

Thirty-six studies on 23 unique, non-overlapping cohorts reported measures of screening test accuracy for preterm PE, which includes any studies specifically reporting on PE before 37 weeks or studies where PE was only defined as "preterm". All studies reported on PE with birth before 32, 34 or 37 weeks of gestation except for 5 studies which reported only gestational age of PE onset (<32 or <34 weeks) rather than gestational age at birth.[84, 91, 94, 97, 111] The results are presented in Table 7. Eight cohorts reported on predicting preterm PE with single factors,[72, 80, 83, 84, 97, 109, 110, 117] and 18 cohorts reported on predicting preterm PE using at least one combination of factors;[69-72, 74, 76, 79, 84, 85, 94, 99-101, 103, 106, 109, 111, 128, 131-133] a competing risks model was used in 4 of these cohorts.[69, 79, 100, 111] Five of the studies also included comparisons to guidelines.[56, 76, 79, 95, 106]

The best-performing single factors were MAP in the Great Obstetrical Syndromes (GOS) study (Canada), yielding a 60% detection rate(DR) at a 10% FPR,[84] and PlGF (cut off 25th percentile), yielding a 70.6% sensitivity at 75.4% specificity.[117] However, no measures of variance were provided in either study, so these results are highly uncertain. The worst-performing single factor for predicting PE with birth <34 weeks was abnormal uterine artery (UtA) Doppler measurement in an American cohort, with a sensitivity of 10% at 10% FPR,[109] while the worst-performing single factor predicting PE with birth <37 weeks was PAPP-A in the GOS study with a sensitivity of 17.2% at a 7.5% FPR.[84]
Overall, combinations of factors demonstrated a better performance than individual ones. Sensitivities ranged from 35% for predicting PE with birth <34 weeks in a United States cohort (using ADAM-12 + PAPP-A + UtA Doppler)[109] to 100% for predicting PE with birth both <34 and <37 weeks (95% confidence interval [CI] 29.2 to 100.0 and 63.0 to 100.0, respectively) for the FMF algorithm (based on a competing risks model) in an Australian cohort at both 1:100 and 1:60 risk cut-offs (FPRs of 19.1% and 12.7%).[79] It is worthwhile noting that the 95% CI's were considerably wide, particularly for birth <34 weeks, and so the robustness of these results is low.[79] Interestingly, a study conducted in Norway with the same sample size as the Australian cohort, found the FMF algorithm (with measures of UtA-PI + MAP + PAPP-A + PlGF) to have 80% sensitivity at 10% FPR, but again, the uncertainty around the result was high, with 95% CI's 28.4 to 99.5%.[100] A

Spanish cohort demonstrated similar predictive accuracies, combining risk factors with MAP, mean UtA-PI and PlGF to produce a 94.1% sensitivity for predicting PE with birth <34 weeks (at 10% FPR).[103] However, no measures of variance were provided and so the result is highly uncertain. Secondary analyses of this cohort compared the predictive accuracy of the model depending on whether predictors were measured between 8^{+0} and 10^{+6} weeks or between 11^{+0} and 13^{+6} weeks.[104] The sensitivities demonstrated no difference, with wide, overlapping confidence intervals; for predicting PE with birth <34 weeks, the sensitivity was 80% (95% CI 20 to 100) with measurement between 8^{+0} and 10^{+6} weeks, and 83.3% (95% CI 50 to 100) between 11^{+0} and 13^{+6} weeks (10% FPR). For predicting PE with birth <37 weeks, the sensitivity was 50.0 (95% CI 25 to 75) with measurement between 8^{+0} and 10^{+6} weeks and 64.3% (95% CI 35.7 to 85.7) between 11^{+0} and 13^{+6} weeks (10% FPRs).[104]

Four studies looked at the test accuracy of NICE guidelines in predicting preterm PE.[56, 76, 79, 106] The best sensitivity identified was 75% (FPR 22.4%),[79] followed by 53.6% (FPR 10.6%),[76] and 40.8% (FPR not reported).[56] The lowest sensitivity for NICE guidelines for predicting preterm PE was found to be 19.5 (FPR 5.5%).[106] There is greater uncertainty around the results from the 2 studies demonstrating the best predictive performance for NICE guidelines, both of which had smaller cohorts and wider confidence intervals (95% CI 34.9 to 96.8[79] and 34.3 to 71.8[76]), compared with the 2 larger studies that achieved lower sensitivities (95% CI 32.8% to 48.8%[56] and 16.1% to 23.3%). This could possibly explain the variation in the studies' findings. Alternatively, these differences could also arise because of variability in the study setting or populations (i.e. different eligibility criteria leading to the exclusion of different subgroups), emphasising the importance of considering whether a study population is reflective of the whole UK population.

The most promising screening test results were reported by the studies extracted as part of the 'London Cohorts', where the competing risks approach was used on data from over 61,000 pregnancies and the models consisting of maternal factors and combinations of MAP, UtA-PI, PlGF and serum PAPP-A.[32-34, 56, 58, 59, 69, 71, 75, 77, 78, 121-128, 134-136] Of these, the best-performing combination for predicting PE with birth <32 weeks was: maternal factors, MAP, UtA-PI and PlGF at a 1:100 risk cut-off, which had 94.0% (95% CI 88.1 to 97.1) sensitivity; inclusion of PAPP-A provided no additional sensitivity.[69] Similarly, at a 1:66 risk cut-off, this combination of the same factors achieved 89.7% (95% CI 82.8 to 94.0) sensitivity with an increase in sensitivity to 91.4% with the addition of PAPP-A.[69] At birth <37 weeks, the best performing test for the prediction of PE was a combination of MF + MAP + UtA-PI + PAPP-A + PlGF, which achieved a sensitivity of 76.1% at a 1:70 risk cut-off and 80.7% at a 1:100 risk cut-off.[69] One study that was part of the 'London Cohorts' took a population of 16,747 pregnancies and explored the incremental benefit of adding single biomarkers to a specific combination of one or more biomarkers.[56] The greatest beneficial effect was seen when the measurement of UtA-PI was added to maternal factors + MAP, which increased sensitivity from 49.3% to 73.9% (a difference of 24.7%) at a screen-positive rate of 10%. These results constitute high-quality evidence for the effectiveness of screening for

preterm PE, with birth <32 or <37 weeks gestation, using this combination of maternal factors and biomarkers. The FMF screening algorithm based on the competing risks model was subsequently validated in a study which used data from 3 prior prospective screening studies of singleton pregnancies between 11^{+0} and 13^{+6} weeks of gestation, further supporting the predictive value of this screening test.[128]

Table 7. Measures of test accuracy for screening tests for preterm pre-eclampsia

Study	Test	Gestational age at birth [onset]*	Pregnancies included in analysis	Sens (%)**	Spec (%)	PPV	NPV
†**Al-Amin 2018**[79] *Australia*	NICE guidelines	<34 weeks	543	33.3[a] (0.8–90.5)	22.4% FPR	NR	NR
	ACOG recommendations			66.6[a] (9.4–99.1)	67.8% FPR	NR	NR
	FMF: MF+ MAP + UtA-PI (cut-off 1:100)			100.0[a] (29.2–100.0)	19.1% FPR	NR	NR
	FMF: MF+ MAP + UtA-PI (cut-off 1:60)			100.0[a] (29.2–100.0)	12.7% FPR	NR	NR
	NICE guidelines	<37 weeks		75.0[a] (34.9–96.8)	22.4% FPR	NR	NR
	ACOG recommendations			87.5[a] (47.3–99.6)	67.8% FPR	NR	NR
	FMF: MF+ MAP + UtA-PI (cut-off 1:100)			100.0[a] (63.0–100.0)	19.1% FPR	NR	NR
	FMF: MF+ MAP + UtA-PI (cut-off 1:60)			100.0[a] (63.0–100.0)	12.7% FPR	NR	NR
ASPRE[70] *United Kingdom*	Predictive model: maternal factors, MAP, UtA-PI, maternal serum PAPP-A, PlGF	<37 weeks	25,797	76.7[a]	9.2% FPR	NR	NR
Caradeux 2013[91] *Chile*	Predictive model: age, weight, SBP, DBP, MAP, parity, history of PE, hypertension, diabetes mellitus, log UtA-PI, history of preterm labour	[<34 weeks]	NR[b]	62.5[a]	95.5	NR	NR
Carter 2015[110] *United States*	Mean UtA PI >75th percentile	<34 weeks	1,192	16.7	75.3	0.5	99.2
Di Lorenzo 2012[94] *Italy*	Predictive model: maternal factors (BMI, black vs other, parity, chronic hypertension), biomarkers (log fβ-hCG, log PAPP-A, log PlGF), UtA-PI	[<34 weeks]	2,118	75	10% FPR	NR	NR
Di Martino 2019[95] *Italy*	FMF algorithm	<34 weeks	11,632	58.2[a] (45.5–70.2)	10% FPR	NR	NR
	BCNatal algorithm			41.8[a] (29.6–54.5)	10% FPR	NR	NR
Erkamp 2020[99] *The Netherlands*	Maternal characteristics + MAP	<34 weeks	7,124	57	90	NR	NR
Goetzinger 2013[109] *United States*	Maternal characteristics	<34 weeks	578	55	10% FPR	NR	NR
	ADAM-12			22	10% FPR	NR	NR
	PAPP-A			16	10% FPR	NR	NR
	UtA Doppler			10	10% FPR	NR	NR
	ADAM-12 + PAPP-A + UtA Doppler			35	10% FPR	NR	NR

Study	Test	Gestational age at birth [onset]*	Pregnancies included in analysis	Sens (%)**	Spec (%)	PPV	NPV
	Maternal characteristics + ADAM-12/UtA Doppler[c]			54	10% FPR	NR	NR
GOS[84] *Canada*	MAP	[<34 weeks]	4,700	60[a]	10% FPR	NR	NR
GOS[89] *Canada*	Maternal characteristics + MAP + serum biomarkers + UtA-PI FMF risk cutoff of 1 in 70	<34 weeks	4,575	70.0[a]	10.7% FPR	1.4	99.9
	Maternal characteristics + MAP + serum biomarkers + UtA-PI FMF risk cutoff of 1 in 100			70.0[a]	15.8% FPR	1.0	99.9
	Maternal characteristics + MAP + serum biomarkers + UtA-PI FMF risk cutoff of 1 in 70	<37 weeks		55.2[a]	10.5% FPR	3.2	99.7
	Maternal characteristics + MAP + serum biomarkers + UtA-PI FMF risk cutoff of 1 in 100			69.0[a]	15.6% FPR	2.7	99.8
GOS[88] *Canada*	MAP MoM, log_{10}PlGF MoM, log_{10}AFP MoM, log_{10}UtA-PI MoM	<37 weeks	4,531	55.2[a] (37.1–73.3)	10% FPR	NR	NR
GOS[84, 85, 131, 132] *Canada*	MAP	<37 weeks	4,700	48[a]	10% FPR	NR	NR
	PAPP-A <0.4 MoM			17.2[a]	7.5% FPR	1.4	99.4
	Log_{10}PlGF <0.8537 MoM			40[a]	10% FPR	NR	NR
	Log_{10}PlGF <0.8537 MoM + maternal characteristics			55[a]	10% FPR	NR	NR
	PlGF <10th percentile (0.59 MoM)			NR	10% FPR	7.2	NR
	UtA-PI			40[a]	10% FPR	NR	NR
	UtA-PI + maternal characteristics			45[a]	10% FPR	NR	NR
Goto 2021[98] *Japan*	Maternal characteristics + MAP + UtA-PI + PlGF	<37 weeks	913	91[a]	10% FPR	NR	NR
Hafner 2013[83] *Austria*	PBVI (≤18.05)	≤34 weeks	4,325	51.6	90.6	NR	NR
	PQ (≤0.63)			12.9	90.9	NR	NR
	Uterina12[d] (≥5.18)			22.6	90.1	NR	NR

Study	Test	Gestational age at birth [onset]*	Pregnancies included in analysis	Sens (%)**	Spec (%)	PPV	NPV
	Uterina22[e] (≥3.11)			43.5	90.5	NR	NR
	PAPP-A (≤0.51)			19.4	90.4	NR	NR
Honigberg 2016[117] *United States*	PlGF (cut-off empirical)	<34 weeks	2,355	70.6	70.6	2.0	99.6
	PlGF (cut-off 25th percentile)			70.6	75.4	2.4	99.7
	sFlt-1 (cut-off empirical)			64.7	64.8	1.6	99.5
	sFlt-1 (cut-off 75th percentile)			29.4	75.0	1.0	99.2
Khalil 2012[74] *United Kingdom*	History + vascular-derived risk (AIx-75, PWV, SBPAO) + UtA-PI + PAPP-A	<34 weeks	7,084	71.4[a]	10% FPR	NR	NR
†London Cohorts[69] *United Kingdom*	MF (cut-off 1:62)	<32 weeks	61,174	52.6 (43.6–61.4)	NR	NR	NR
	MF + MAP + UtA-PI + PlGF (cut-off 1:66)			89.7 (82.8–94.0)	NR	NR	NR
	MF (cut-off 1:70)			53.4 (44.4–62.3)	11.7% FPR	NR	NR
	MF + MAP + UtA-PI + PAPP-A + PlGF (cut-off 1:70)			91.4 (84.9–95.3)	10.4% FPR	NR	NR
	MF (cut-off 1:100)			62.9 (53.9–71.2)	19.1% FPR	NR	NR
	MF + MAP + UtA-PI + PlGF (cut-off 1:100)			94.0 (88.1–97.1)	14.5% FPR	NR	NR
	MF (cut-off 1:62)	<37 weeks	61,174	44.8 (40.5–49.2)	NR	NR	NR
	MF + MAP + UtA-PI + PlGF (cut-off 1:66)			74.8 (70.8–78.5)	NR	NR	NR
	MF (cut-off 1:70)			48.3 (43.9–52.7)	11.5% FPR	NR	NR
	MF + MAP + UtA-PI + PAPP-A + PlGF (cut-off 1:70)			76.1 (72.1–79.6)	10.0% FPR	NR	NR
	MF (cut-off 1:100)			59.4 (55.0–63.7)	18.8% FPR	NR	NR
	MF + MAP + UtA-PI + PAPP-A + PlGF (cut-off 1:100)			80.7 (77.0–84.0)	14.1% FPR	NR	NR
†London Cohorts[77] *United Kingdom*	MF + MAP + UtA-PI + PlGF	<32 weeks	16,747	100[a] (69–100)	10% FPR	NR	NR
	MF + MAP + UtA-PI + PlGF	<37 weeks		80[a] (65–90)	10% FPR	NR	NR
POP study[76] *United Kingdom*	NICE guidelines	<37 weeks	4,184	53.6 (34.3–71.8)	10.6% FPR	3.3 (2.0–5.4)	99.7 (99.4–99.8)

Study	Test	Gestational age at birth [onset]*	Pregnancies included in analysis	Sens (%)**	Spec (%)	PPV	NPV
	Risk score derieved from the ASPRE trial's prior history model [PGAPE algorithm]			57.1 (37.5–74.8)	8.8% FPR	4.2 (2.6–6.7)	99.7 (99.4–99.8)
	Maternal history (PGAPE) algorithm			60.7 (40.8–77.6)	9.6% FPR	4.1 (2.6–6.5)	99.7 (99.5–99.8)
Sandström 2019[106] *Sweden*	Pre-specified variables model[f]	<34 weeks	62,562[i]	30.6 (24.5–37.2)	10% FPR	NR	NR
	Backwards selection model[g]			26.9 (21.1–33.3)	10% FPR	NR	NR
	Random forest model[h]			18.5 (13.6–24.4)	10% FPR	NR	NR
	Risk classification based on NICE guidelines binary clinical decision rule			22.2 (16.8–28.4)	5.5% FPR	NR	NR
	Pre-specified variables model[f]	<37 weeks	62,562[i]	29.2 (25.2–33.4)	10% FPR	NR	NR
	Backwards selection model[g]			25.8 (22.0–29.8)	10% FPR	NR	NR
	Random forest model[h]			24.3 (20.6–28.4)	10% FPR	NR	NR
	Risk classification based on NICE guidelines binary clinical decision rule			19.5 (16.1–23.3)	5.5% FPR	NR	NR
Scazzocchio 2013[101] *Spain*	Maternal characteristics, PAPP-A, fβ-hCG, MAP, UtA-PI	<34 weeks	5,170	80.0[a]	10% FPR	NR	NR
Scazzocchio 2017[102j] *Spain*	Maternal characteristics, MAP, UtA Doppler, PAPP-A Construction cohort	<34 weeks	4,621	75.0[a] (59.8–85.3)	10% FPR	3.0 (2.4–3.4)	99.9 (99.8–99.9)
	Maternal characteristics, MAP, UtA Doppler, PAPP-A Validation cohort			85.7[a] (71.3–96.4)	10% FPR	5.6 (4.7–6.3)	99.9 (99.8–100)
Schneuer 2012[80] *Australia*	PP13 (univariate model)	≤34 weeks	NR[k]	40.0 (5.3–85.3)	5% FPR	1.5 (0.2–5.3)	99.9 (99.6–100)
	PP13 (adjusted model)			20.0 (0.5–71.6)	5% FPR	0.7 (0–3.6)	99.8 (99.6–100)
SCOPE[72] *United Kingdom*	MAP, mUtA-RI, cystatitin C/PlGF Training set	<34 weeks	5,623	67 (41–85)	95	5 (3–10)	100 (100–100)
	MAP, mUtA-RI, cystatitin C/PlGF Validation set			44 (19–74)	95	4 (2–11)	100 (99–100)
SCOPE[72, 133] *United Kingdom*	MAP, mUtA-RI, interleukin receptor antagonist/PlGF Training set	<37 weeks	5,623	41 (28–57)	95	9 (6–14)	99 (99–100)

Study	Test	Gestational age at birth [onset]*	Pregnancies included in analysis	Sens (%)**	Spec (%)	PPV	NPV
	MAP, mUtA-RI, interleukin receptor antagonist/PlGF Validation set			42 (24–61)	95	10 (5–17)	99 (99–99)
	PlGF at 15 weeks			22 (12–35)	95	NR	NR
	sEng at 20 weeks			28 (17–43)	95	NR	NR
	Clinical risk			34 (22–48)	95	NR	NR
	Clinical risk + PlGF + UtA Doppler + sEng			52 (38–66)	95	NR	NR
Serra 2020[103] *Spain*	Risk factors + MAP + mean UtA-PI + PlGF	<34 weeks	6,893	94.1[a]	10% FPR	2.27	99.98
Mendoza 2021a[104l] *Spain*	Risk factors + MAP + UtA-PI + PlGF Measured between 8^{+0} and 10^{+6} weeks	<34 weeks	2,641	80.0[a] (20.0–100)	10% FPR	NR	NR
	Risk factors + MAP + UtA-PI + PlGF Measured between 11^{+0} and 13^{+6} weeks			83.3[a] (50.0–100)	10% FPR	NR	NR
	Risk factors + MAP + UtA-PI + PlGF + PAPP-A Measured between 8^{+0} and 10^{+6} weeks	<37 weeks		50.0[a] (25.0–75.0)	10% FPR	NR	NR
	Risk factors + MAP + UtA-PI + PlGF + PAPP-A Measured between 11^{+0} and 13^{+6} weeks			64.3[a] (35.7–85.7)	10% FPR	NR	NR
Mendoza 2021b[105l] *Spain*	Risk factors + MAP + UtA-PI + PlGF Cut-off 1/115	<34 weeks	2,641	81.8[a] (54.6–100)	10% FPR	NR	NR
†Skrastad 2015[100] *Norway*	FMF: MF + MAP + UtA-PI + PAPP-A + PlGF	<37 weeks	541	80.0 (28.4–99.5)	10% FPR	6.8 (1.9–16.5)	99.8 (98.8–100)
†Sonek 2018[111] *United States*	Maternal characteristics	[<34 weeks]	1,068	62	10% FPR	NR	NR
	PlGF + PAPP-A + AFP			85	10% FPR	NR	NR
	Maternal characteristics	<37 weeks	1,068	60	10% FPR	NR	NR
	PlGF + PAPP-A + AFP + MAP + UtA-PI + EPV			68	10% FPR	NR	NR
Takahashi 2012[97m] *Japan*	mNDI (cut-off 90th percentile)	[<32 weeks]	1,266	5.9	99.6	68.8	88.6
	mPI-SDS (cut-off SDS = 1.38)			6.7	99.7	75.0	88.9
	mRI-SDS (cut-off SDS = 0.98)			4.3	99.8	81.3	80.9

Study	Test	Gestational age at birth [onset]*	Pregnancies included in analysis	Sens (%)**	Spec (%)	PPV	NPV
	BN (positive)			4.9	99.7	75.0	94.5
†Tan 2018a[56n] *United Kingdom*	NICE guidelines	<37 weeks	16,747	40.8 (32.8–48.9)	NR	NR	NR
	MF + MAP + PAPP-A			53.5 (45.3–61.7)	NR	NR	NR
	MF + MAP + PlGF			69.0 (61.4–76.6)	NR	NR	NR
	MF + MAP + PlGF + UtA-PI			82.4 (76.1–88.7)	NR	NR	NR
†Tsiakkas 2016b[71n] *United Kingdom*	MF Empirical	<32 weeks	7,066	60 (26–88)	10% FPR	NR	NR
	MF Model-based			52	10% FPR	NR	NR
	MF + serum sFlt-1 Empirical			60 (26–88)	10% FPR	NR	NR
	MF + serum sFlt-1 Model-based			52	10% FPR	NR	NR
	MF Empirical	<37 weeks	7,066	54 (39–68)	10% FPR	NR	NR
	MF Model-based			47	10% FPR	NR	NR
	MF + serum sFlt-1 Empirical			54 (39–68)	10% FPR	NR	NR
	MF + serum sFlt-1 Model-based			46	10% FPR	NR	NR
†Wright 2019[128n] *United Kingdom*	MF + MAP + UtA-PI + PlGF Training set[o]	<34 weeks	35,948	87[a] (80–92)	10% SPR	NR	NR
	MF + MAP + UtA-PI + PlGF Validation set 1: SQS[p]		8,775	93[a] (76–99)	10% SPR	NR	NR
	MF + MAP + UtA-PI + PlGF Validation set 2: SPREE[q]		16,451	90[a] (78–96)	10% SPR	NR	NR
	MF + MAP + UtA-PI + PlGF Training set[o]	<37 weeks	35,948	75[a] (70–80)	10% SPR	NR	NR
	MF + MAP + UtA-PI + PlGF Validation set 1: SQS[p]		8,775	75[a] (62–85)	10% SPR	NR	NR
	MF + MAP + UtA-PI + PlGF Validation set 2: SPREE[q]		16,451	83[a] (76–89)	10% SPR	NR	NR

In cases where results were presented for multiple combinations of factors within the same study, the test which gave the 'best' result (in terms of sensitivity/specificity) is reported. If different combinations gave the same 'best' result, the test containing the lowest number of factors is reported. Where results were reported for different FPRs, the results for 10% FPR are reported in the specificity column.

* Where a study only reported gestational age at PE onset rather than at birth , this is reported in brackets

** Where available, results are reported as % (95% CI)

† Study/cohort used a competing risks model

[a] Sensitivity reported as detection rate

[b] 627 women enrolled in the study but it is not clear if data from all women informed the predictive model

[c] Maternal characteristics + ADAM-12 and maternal characteristics + UtA Doppler had equal best sensitivity

[d] Uterina12 is the addition of mean uterine PI and mean notch measured at 12 weeks

[e] Uterina22 is the addition of mean uterine PI and mean notch measured at 22 weeks

[f] Family history of PE + country of birth + method of conception + gestational length at registration + maternal age + height + weight + smoking habits in early pregnancy + pre-existing type I and type II diabetes + chronic hypertension + SLE + MAP

[g] Maternal age, BMI, MAP, protein in urine, infertility treatment, diabetes, blood group, alcohol consumption at registration, gestational length at registration, capillary glucose, haemoglobin, infertility duration, family history of PE, family history of hypertension, alcohol consumptions 3 months before registration, chronic kidney disease, family situation, smoking 3 months before pregnancy, snuff 3 months before pregnancy, snuff at registration, region of birth, hepatitis, morbus chron/ulcerous colitis, and psychiatric disease

[h] 36 candidate predictors, using a machine learning, ensemble method making use of multiple decision tree; for each tree, a bootstrap sample was drawn, from which the tree was built

[i] Total study population, which included pregnancies with major malformations or treatment with aspirin

[j] Cohort overlaps with Scazzocchio 2013

[k] 2,784 women were eligible for the study, but it is not clear if data from all women was used in the analysis

[l] Cohort overlaps with Serra 2020

[m] Authors of this review believe that the values reported in the publication for sensitivity and PPV were switched; the authors believe that the way the values are presented here is correct

[n] Cohort overlaps with the London Cohorts

[o] Pregnancy data for analysis derived from O'Gorman 2016; the data set used to develop the competing risks model[58]

[p] Pregnancy data for analysis derived from O'Gorman 2017, which used the developed competing risk model[124]

[q] Pregnancy data for analysis derived from Tan 2018a; a study specifically designed to compare the performance of screening by the competing risks algorithm to the method advocated by NICE[56]

Abbreviations: ACOG: American College of Obstetricians and Gynecologists; ADAM-12: A-disintegrin and metalloprotease 12; AFP: alpha-fetoprotein; ASPRE: Combined Multimarker Screening and Randomised Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention trial; BMI: body mass index; BN: bilateral notching; DBP: diastolic blood pressure; EPV: estimated placental volume; fβ-hCG: free β-human chorionic gonadotropin; FMF: Fetal Medicine Foundation; FPR: false positive rate; GOS: Great Obstetrical Syndromes study; MAP: mean arterial pressure; MF: maternal factors; mNDI: mean notch depth index; MoM: multiple of the median; mPI-SDS: mean pulsatility index standard deviation score; mRI-SDS: mean resistance index standard deviation score; mUtA-RI: mean uterine artery resistance index; NICE: National Institute for Health and Care Excellence; NPV: negative predictive value; NR: not reported; PAPP-A: pregnancy associated plasma protein A; PBVI: placental bed vascularisation index; PE: pre-eclampsia; PI: pulsatility index; PlGF; placental growth factor; PP13: placental protein 13; PPV: positive predictive value; PQ: placental quotient; SBP: systolic blood pressure; SCOPE: Screening for Pregnancy Endpoints study; SDS: standard deviation score; sEng: soluble endoglin; sFlt-1: soluble fms-like tyrosine kinase 1; SPR: screen positive rate; SPREE: Superior Province Rifting EarthScope Experiment; SQS: screening quality study; UtA-PI: uterine artery pulsatility index

Term pre-eclampsia (≥37 weeks) and pre-eclampsia ≥34 weeks

Eighteen studies of 14 unique non-overlapping cohorts reported measures of screening test accuracy for detecting PE at or after 34 or 37 weeks of gestation (often referred to as 'late onset PE' and 'term PE' respectively). The results are presented in

Table 8. While studies reporting on PE ≥34 weeks have been included here, it is important to note that it is possible that these studies included preterm PE (<37 weeks) as well as term PE (≥37 weeks). Therefore, it is difficult to directly compare the results of studies that reported results in this way to those of studies which reported results for term PE specifically.

Only the studies for the GOS cohort reported accuracy values for prediction from individual factors;[84, 85, 132] of these, MAP performed the best with 34% sensitivity, and the logarithm of PlGF at a multiple of median (MoM) <0.85 had the worst sensitivity of 21%.[84] All other studies reported on at least one combination of factors,[69-72, 74, 79, 84, 85, 91, 94, 95, 98, 100-102, 106, 111, 132], including 5 studies on applying the competing risks approach to predict PE.[69, 71, 79, 100, 111] Two studies reported on the performance of NICE and ACOG guidelines[69, 71, 79, 100, 111] and one compared the predictive performance of the FMF and BCNatal algorithms.[79, 95, 106]

Eight studies reported measures of screening test accuracy specifically for detecting PE at or after 34 weeks.[74, 91, 94, 95, 100-102, 111] The performance of the models evaluated in these studies ranged from a low 15% sensitivity (10% FPR) for the 'PREDICTOR prior' algorithm,[100] which calculated prior risk based on BMI, ethnicity, parity, family history of PE, chronic hypertension and MAP, in 541 pregnancies in Norway, to a 60.5% detection rate (DR [10% FPR]) for a model which combined maternal history with vascular derived risk factors, including Aix-75, PWV and SBP_{AO}, in 7,084 pregnancies in the UK.[74] However, certainty in these findings is low, as the Norwegian study reports a wide confidence interval (95% CI 3.2 to 37.9) and a confidence interval is not reported for the result of the UK-based study.

The remaining studies reported on measures of screening test accuracy for predicting PE at or after 37 weeks. In the 'London Cohorts', accuracy of combination tests, as evaluated by the competing risks model, ranged from 46.5 to 55.1% sensitivity at a risk cut-off of 1:100;[69] the best-performing combination test was maternal factors + MAP (sensitivity 55.1 [95% CI 52.3 to 57.8] at a FPR of 17.5%).[56] A model that applied the FMF Bayes theorem, combining maternal factors and MAP in a Japanese cohort, demonstrated an even greater accuracy of a 60% DR (FPR 10%).[98] The worst performance was reported in the validation cohort of the UK-based SCOPE study, for a combination of high fruit intake + MAP + BMI + tissue inhibitor of metalloproteinase 1, which yielded a sensitivity of just 6% and an LR+ of 1.1.[72] NICE and ACOG guidelines were found to have sensitivities of 47.3% (at a FPR of 22.4%) and 89.4% (at a FPR of 67.8%).[79]

Table 8. Measures of test accuracy for screening tests for term pre-eclampsia (≥37 weeks) and pre-eclampsia ≥34 weeks

Gestational age at birth	Study	Test	Pregnancies included in analysis	Sens (%)*	Spec (%)	PPV	NPV
≥34 weeks	**Caradeux 2013**[91] *Chile*	Predictive model: age, weight, SBP, DBP, MAP, parity, history of PE, hypertension, diabetes mellitus, log UtA-PI, history of preterm labour	NR[b]	31.6[a]	5% FPR	NR	NR
	Di Lorenzo[94] *Italy*	Predictive model: maternal factors (BMI, black vs other, parity, chronic hypertension), biomarkers (log fβ-hCG, log PAPP-A, log PlGF), UtA-PI	2,118	31	10% FPR	NR	NR
	Di Martino 2019[95] *Italy*	FMF algorithm	11,632	44.1[a] (37.3–51.1)	10% FPR	NR	NR
		BCNatal Algorithm		38.0[a] (31.3–44.8)	10% FPR	NR	NR
	Khalil 2012[74] *United Kingdom*	History + vascular-derived risk (AIx-75, PWV, SBPAO)	7,084	60.5[a]	10% FPR	NR	NR
	Scazzocchio 2013[101] *Spain*	Maternal characteristics, PAPP-A, fβ-hCG, MAP, UtA-PI	5,170	39.6[a]	10% FPR	NR	NR
	Scazzocchio 2017[102c] *Spain*	Maternal characteristics, MAP, UtA Doppler, PAPP-A Construction cohort	4,621	52.6[a] (42.3–62.9)	10% FPR	7.8 (6.4–9.2)	99.2 (99.0–99.3)
		Maternal characteristics, MAP, UtA Doppler, PAPP-A Validation cohort		43.4[a] (37.6–51.1)	10% FPR	13.1 (11.6–15.2)	97.8 (97.6–98.1)
	†**Skrastad 2015**[100] *Norway*	FMF: MF + MAP + UtA-PI + PAPP-A + PlGF	541	30.0 (11.9–54.3)	10% FPR	10.3 (3.9–21.2)	97.1 (95.2–98.4)
		PREDICTOR prior		15.0 (3.2–37.9)	10% FPR	5.6 (1.2–15.4)	96.5 (94.5–98)
		PREDICTOR posterior		30.0 (11.9–54.3)	10% FPR	10.3 (3.9–21.2)	97.1 (95.2–98.4)
	†**Sonek 2018**[111] *United States*	Maternal characteristics	1,068	48	10% FPR	NR	NR
		PlGF + PAPP-A + AFP + MAP + UtA-PI + EPV		36	10% FPR	NR	NR
≥37 weeks	†**Al-Amin 2018**[79] *Australia*	NICE guidelines	543	47.3[a] (24.4–71.1)	22.4% FPR	NR	NR
		ACOG recommendations		89.4[a] (66.8–98.7)	67.8% FPR	NR	NR
		FMF: MF + MAP + UtA-PI (cut-off 1:100)		42.1[a] (20.2–66.5)	19.1% FPR	NR	NR

Gestational age at birth	Study	Test	Pregnancies included in analysis	Sens (%)*	Spec (%)	PPV	NPV
		FMF: MF + MAP + UtA-PI (cut-off 1:60)		26.3[a] (9.1–51.2)	12.7% FPR	NR	NR
	ASPRE[70] *United Kingdom*	Predictive model: maternal factors, MAP, UtA-PI, maternal serum PAPP-A, PlGF	25,797	43.1[a]	9.2% FPR	NR	NR
	GOS[84, 85, 132] *Canada*	MAP	4,700	34[a]	10% FPR	NR	NR
		Log_{10}PlGF <0.8537 MoM		21[a]	10% FPR	NR	NR
		Log_{10}PlGF <0.8537 MoM + maternal characteristics		26[a]	10% FPR	NR	NR
		PlGF <10th percentile (0.59 MoM)		NR	10% FPR	2.5	NR
		UtA-PI		16	10% FPR	NR	NR
		UtA-PI + maternal characteristics		25	10% FPR	NR	NR
	Goto 2021[98] *Japan*	Maternal characteristics + MAP	913	60[a]	10% FPR	NR	NR
	†**London Cohorts**[69] *United Kingdom*	MF (cut-off 1:62)	61,174	33.5 (31.0–36.2)	NR	NR	NR
		MF + MAP + UtA-PI + PAPP-A + PlGF (cut-off 1:66)		41.3 (38.7–44.1)	NR	NR	NR
		MF (cut-off 1:70)		41.3 (38.7–44.1)	11.2% FPR	NR	NR
		MF + MAP + UtA-PI (cut-off 1:70)		44.6 (41.9–47.4)	11.0% FPR	NR	NR
		MF (cut-off 1:100)		48.5 (45.7–51.2)	18.5% FPR	NR	NR
		MF + MAP (cut-off 1:100)		55.1 (52.3–57.8)	17.5% FPR	NR	NR
	Sandström 2019[106] *Sweden*	Pre-specified variables model[d]	62,562[g]	28.1 (26.3–30.0)	10% FPR	NR	NR
		Backwards selection model[e]		28.2 (26.4–30.1)	10% FPR	NR	NR
		Random forest model[f]		22.4 (20.7–24.2)	10% FPR	NR	NR
		Risk classification based on NICE guidelines binary clinical decision rule		12.2 (10.9–13.7)	5.5%	NR	NR
	SCOPE[72] *United Kingdom*	High fruit intake, MAP, BMI, tissue inhibitor of metalloproteinase 1 Training set	5,623	19 (13–26)	95	14 (10–20)	96 (96–97)

Gestational age at birth	Study	Test	Pregnancies included in analysis	Sens (%)*	Spec (%)	PPV	NPV
		High fruit intake, MAP, BMI, tissue inhibitor of metalloproteinase 1 Validation set		6 (2–16)	95	3 (1–9)	97 (96–98)
	†**Sonek 2018**[111] *United States*	Maternal characteristics	1,068	43	10% FPR	NR	NR
		PlGF + PAPP-A + AFP + MAP + UtA-PI + EPV		29	10% FPR	NR	NR
	†**Tsiakkas 2016b**[71h] *United Kingdom*	MF Empirical	7,066	35 (26–44)	10% FPR	NR	NR
		MF Model-based		37	10% FPR	NR	NR
		MF + serum sFlt-1 Empirical		35 (26–44)	10% FPR	NR	NR
		MF + serum sFlt-1 Model-based		37	10% FPR	NR	NR

In cases where results were presented for multiple combinations of factors within the same study, the test which gave the 'best' result (in terms of sensitivity/specificity) is reported. If different combinations gave the same 'best' result, the test containing the lowest number of factors is reported. Where results were reported for different FPRs, the results for 10% FPR are reported in the specificity column.
* Where available, results are reported as % (95% CI)
† Study/cohort used a competing risks model
[a] Sensitivity reported as detection rate
[b] 627 women enrolled in the study but it is not clear if data from all women informed the predictive model
[c] Cohort overlaps with Scazzocchio 2013
[d] Family history of PE + country of birth + method of conception + gestational length at registration + maternal age + height + weight + smoking habits in early pregnancy + pre-existing type I and type II diabetes + chronic hypertension + SLE + MAP
[e] Maternal age, BMI, MAP, protein in urine, infertility treatment, diabetes, blood group, alcohol consumption at registration, gestational length at registration, capillary glucose, haemoglobin, infertility duration, family history of PE, family history of hypertension, alcohol consumptions 3 months before registration, chronic kidney disease, family situation, smoking 3 months before pregnancy, snuff 3 months before pregnancy, snuff at registration, region of birth, hepatitis, morbus chron/ulcerous colitis, and psychiatric disease
[f] 36 candidate predictors, using a machine learning, ensemble method making use of multiple decision tree; for each tree, a bootstrap sample was drawn, from which the tree was built
[g] Total study population, which included pregnancies with major malformations or treatment with aspirin
[h] Cohort overlaps with the London Cohorts
Abbreviations: ACOG: American College of Obstetricians and Gynecologists; AFP: alpha-fetoprotein; ASPRE: Combined Multimarker Screening and Randomised Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention trial; BMI: body mass index; DBP: diastolic blood pressure; EPV: estimated placental volume; fβ-hCG: free β-human chorionic gonadotropin; FMF: Fetal Medicine Foundation; FPR: false positive rate; GOS: Great Obstetrical Syndromes study; MAP: mean arterial pressure; MF: maternal factors; MoM: multiple of median; mUtA-RI: mean uterine artery resistance index; NICE: National Institute for Health and Care Excellence; NPV: negative predictive value; PAPP-A: pregnancy associated plasma protein A; PE: pre-eclampsia; PI: pulsatility index; PlGF; placental growth factor; PPV: positive predictive value; SBP: systolic blood pressure; SCOPE: Screening for Pregnancy Endpoints study; sEng: soluble endoglin; sFlt-1: soluble fms-like tyrosine kinase 1; SLE: systemic lupus erythematosus; UtA-PI: uterine artery pulsatility index

All pre-eclampsia

Thirty-three studies on 25 unique, non-overlapping cohorts, reported measures of screening test accuracy for PE without stratification by gestational age. The results are presented in Table 9.

The highest performing single factor was median spot urinary ACR, which yielded an 83.3% sensitivity at 63% specificity.[81] Mean UtA-PI[116] and SBP_{AO}[73] yielded sensitivities of 51% and 50%, respectively (both 10% FPR). One study reported on the predictive accuracy of maternal and clinical information alone, and this yielded a sensitivity of 25% at a 5% FPR;[82] performance did not improve when the biomarkers PlGF, sFlt-1 and PAPP-A were added. Another study that evaluated maternal characteristics alone yielded a predictive accuracy of sensitivity of 52% at a 10% FPR.[111]

The worst-performing single factors were PAPP-A in the GOS study, with a sensitivity of 9.8% at a 7.4% FPR,[84] PP13 in a univariate model, with a sensitivity of 5.6% at a 5% FPR[80] and the standard deviation score of mean resistance index (mRI-SDS) in a Japanese cohort, with a sensitivity of 7.6% at a 98.1% specifity.[97]

The best predictive performances were identified in a study in which the screening test was considered positive if at least one or two of the following parameters were abnormal: UtA-PI (>90th centile), placental volume (PV [<10th centile]), and/or PAPP-A (<10th centile).[107] Both models had high predictive capabilities, with the model for one abnormal parameter yielding a sensitivity of 92.68% (95% CI 80.08 to 98.46%) at a specificity of 85.20% (95% CI: 81.56 to 88.37%) and the model for two abnormal parameters yielding a sensitivity of 85.37% (95% CI 70.83 to 94.43%) at a specificity of 98.89% (95% CI 97.42 to 99.64%).[107] This study had a low risk of bias for most domains and there were no concerns regarding the applicability of the study to the general UK pregnant population. Additionally, the cut-off values used for considering indices 'abnormal' were justified based on the same methodology having been used in 3 prior studies.[137-139] However, a lack of information regarding whether PE was diagnosed without knowledge of the index test results, and the exclusion of some pregnancies from the analysis due to loss to follow up, are important considerations when interpreting these findings. Furthermore, these screening tests were evaluated using a small sample of 490 pregnancies from a single centre; evaluation of these tests in a larger cohort would improve confidence in the the findings.

Another high performing model, evaluated in an Israeli cohort of 820 pregnant women, included a combination of risk factors, PP13 and MAP, and yielded a 93% sensitivity (95% CI 87 to 100) for predicting PE at a 10% FPR.[92] However, while the study that evaluated this model was judged to be at low risk of bias for all domains, increasing confidence in the result, the study population included a disproportionate number of pregnancies with prior risk factors compared with the country's general population.[92] This brings into question the applicability of the screening test to the low-risk pregnant population of interest. Other high performing models included a combination of PlGF, sFlt-1 and NGAL (77% DR at a 10% FPR),[96] a combination of risk factors, MAP, UtA-PI, PlGF, PAPP-A and PP13 (79% DR at a 10% FPR)[93] and a combination of history, vascular-derived risk (AIx-75, PWV and SBP_{AO}), UtA-PI and PAPP-A (61.9% DR [95% CI 54.1 to 69.3%] at a 10% FPR).[74] Worse performing models included a model assessing the predictive capabilities of Slft1:PlGF ratio (25% DR at a 10% FPR),[87] a model combining maternal characteristics and MAP (33% sensitivity at a 90% specificity),[99] and a model combining maternal characteristics and PlGF (35.3% DR at a 10% FPR).[86]

Two studies used a combination of maternal characteristics, serum biomarkers and ultrasound parameters, however, neither demonstrated strong predictive accuracies. One study of 1200 patients, which used maternal characteristics, serum biomarkers and ultrasound parameters to develop individual weighted risk scores, demonstrated a 36.7% sensitivity (95% CI 23.4 to 51.7%)

at a 93.2% specificity (95% CI 90.7 to 95.2%) in the 'study cohort', consisting of the first 578 consecutive patients in the study. A 25.6% sensitivity (95% CI 13.0 to 42.1%]) at a 94.9% specificity (95% CI 92.3 to 96.8%) was further demonstrated in the 'validation cohort', the second half of the original study cohort.[112] A study from the GOS cohort used the FMF algorithm to calculate risk using a combination of maternal characteristics, MAP, serum biomarkers and UtA-PI. At risk cutoff of 1:70, the DR for PE in this study was 27.4% (9.9% FPR).[89]

Table 9. Measures of test accuracy for screening tests for all pre-eclampsia

Study	Test	Pregnancies included in analysis	Sens (%)*	Spec (%)	PPV	NPV
Allen 2018[73] *United Kingdom*	SBP_{AO}	1,045[a]	50	10% FPR	NR	NR
Baweja 2011[81] *Australia*	Median spot urinary ACR (35.5 mg/mmol)	265	83.3	61.2	63	78.6
Boucoiran 2013a[86] *Canada*	Maternal characteristics + PlGF	NR[b]	35.3[c]	10% FPR	13.5	96.9
Boucoiran 2013b[87] *Canada*	PlGF	772	21.4[c]	10% FPR	NR	NR
	Slft1:PlGF ratio		25.0[c]	10% FPR	NR	NR
	Inhibin A		21.4[c]	10% FPR	NR	NR
Di Lorenzo 2012[94] ***Italy***	Predictive model: maternal factors (BMI, black vs other, parity, chronic hypertension), biomarkers (log fβ-hCG, log PAPP-A, log PlGF), UtA-PI	2,118	40	10% FPR	NR	NR
Erkamp 2020[99] *The Netherlands*	Maternal characteristics + MAP	7,124	33	90	NR	NR
Gabbay-Benziv 2016[118] *United States*	Cardiovascular risk factors + metabolic risk factors + personal risk factors	2,433	90 (79.5–96.2)	40.2 (37.4–43.0)	7 (5.3–9)	98.8 (97.3–99.5)
Goetzinger 2014[112d] *United States*	Risk-based scoring system[e] Study cohort	578	36.7 (23.4–51.7)	93.2 (90.7–95.2)	34.0 (21.5–48.3)	93.9 (91.5–95.8)
	Risk-based scoring system[e] Validation cohort	622	25.6 (13.0–42.1)	94.9 (92.3–96.8)	32.3 (16.7–51.4)	93.1 (90.3–95.3)
GOS[89] *Canada*	FMF: maternal characteristics + MAP + serum biomarkers + UtA-PI Risk cutoff of 1 in 70	4,575	27.4[c]	9.9% FPR	12.3	96.0
	FMF: maternal characteristics + MAP + serum biomarkers + UtA-PI Risk cutoff of 1 in 100		35.4[c]	14.9% FPR	10.9	96.3
GOS[84] *Canada*	MAP	4,700	36	10% FPR	NR	NR
	PAPP-A <0.4 MoM		9.8[c]	7.4% FPR	6.3	95.2

Study	Test	Pregnancies included in analysis	Sens (%)*	Spec (%)	PPV	NPV
	Maternal characteristics		23	10% FPR	NR	NR
	PlGF <10th percentile (0.59 MoM)		NR	NR	9.7	NR
Hafner 2013[83] *Austria*	PBVI (≤18.05)	4,325	51.6	90.6	NR	NR
	PQ (≤0.63)		12.9	90.9	NR	NR
	Uterina12[f] (≥5.18)		22.6	90.1	NR	NR
	Uterina22[g] (≥3.11)		43.5	90.5	NR	NR
	PAPP-A (≤0.51)		19.4	90.4	NR	NR
Kanat-Pektas 2014[108] *Turkey*	MPV + PAPP-A MoM	196	75	70	NR	NR
Khalil 2012[74] *United Kingdom*	History + vascular-derived risk (AIx-75, PWV, SBPAO) + UtA-PI + PAPP-A	7,084	61.9[c] (54.1–69.3)	10% FPR	NR	NR
London Cohorts[78] *United Kingdom*	Average of left and right arm; MAP 1 + 2 + 3 + 4[h]	24,142	44.3[c] (40.2–48.4)	10% FPR	NR	NR
†London Cohorts[56] *United Kingdom*	NICE guidelines	16,747	30.4 (26.3–34.6)	NR	NR	NR
	Maternal factors + MAP + PAPP-A		42.5 (38.0–46.9)	NR	NR	NR
Maymon 2017[93] *Israel*	Maternal prior risk factors + MAP + UtA-PI, + PlGF + PAPP-A + PP13	467	79[c]	10% FPR	NR	NR
Meiri 2014[92] *Israel*	Risk factors + PP13 + MAP	820	93 (87–100)	10% FPR	NR	NR
Metcalfe 2014[90] *Canada*	Risk factors + AFP + hCG + Inhibin A + uE_3 + PAPP-A Predicted probability ≥0.5	45,287	81	41.4% FPR	NR	NR
Myatt 2012[114] *United States*	Presence of uterine artery notch or RI or PI MoM ≥75th percentile	2,188	43 (35–51)	67 (65–69)	10 (8–12)	93 (92–95)
Odibo 2011a[115] *United States*	VI	388	22[c]	10% FPR	NR	NR
	VFI		22[c]	10% FPR	NR	NR
Odibo 2011b[116] *United States*	Mean UtA-PI	452	51	10% FPR	NR	NR
Schneuer 2012[80] *Australia*	PP13 (univariate model)	NR[i]	5.6 (1.6–13.8)	5% FPR	3.0 (0.8–7.4)	97.4 (96.7–98.0)

Study	Test	Pregnancies included in analysis	Sens (%)*	Spec (%)	PPV	NPV
	PP13 (adjusted model)		15.5 (8–26)	5% FPR	7.7 (3.9–13.4)	97.6 (97.0–98.2)
Schneuer 2013[82j] *Australia*	Maternal characteristics	2,681	25.0 (15.3–37.0)	5% FPR	12.0 (7.1–18.5)	97.9 (97.3–98.4)
SCOPE[72] *United Kingdom*	High fruit intake + BMI + MAP + mean UT-RI + PlGF Training model	5,623	22 (17–29)	95	20 (15–26)	95 (95–96)
	High fruit intake + BMI + MAP + mean UT-RI + PlGF Validation model		17 (10–27)	95	13 (8–21)	96 (95–97)
SCOPE[119] *United Kingdom*	MAP, sEng, SPINT1, IGFALS, MCAM, PlGF Training model	100	67 (54–80)	80	NR	NR
	MAP, sEng, SPINT1, IGFALS, MCAM, PlGF Validation model	50	59 (45–73)	80	NR	NR
†**Sonek 2018**[111] *United States*	Maternal characteristics	1,068	52	10% FPR	NR	NR
	PlGF + PAPP-A + AFP		41	10% FPR	NR	NR
	PlGF + PAPP-A + AFP + UtA-PI		43	10% FPR	NR	NR
	PlGF + PAPP-A + AFP + MAP		39	10% FPR	NR	NR
	PlGF + PAPP-A + AFP + MAP + UtA-PI		41	10% FPR	NR	NR
	PlGF + PAPP-A + AFP + MAP + UtA-PI + EPV		50	10% FPR	NR	NR
Takahahi 2012[97k] *Japan*	mNDI (cut-off 90th percentile)	1,266	12.4	98.2	48.9	89.1
	mPI-SDS (cut-off SDS = 1.38)		12.2	98.2	46.8	89.4
	mRI-SDS (cut-off SDS = 0.98)		7.6	98.1	48.9	81.2
	BN (positive)		9.3	98.1	49.8	85.0
†**Wright 2019**[128l] *United Kindom*	MF + MAP + UtA-PI + PlGF Training set[m]	35,948	52[c] (49–55)	10% SPR	NR	NR
	MF + MAP + UtA-PI + PlGF Validation set 1: SQS[n]	8,775	49[c] (43–56)	10% SPR	NR	NR
	MF + MAP + UtA-PI + PlGF Validation set 2: SPREE[o]	16,451	53[c] (49–58)	10% SPR	NR	NR
Youssef 2011[96] *Italy*	PlGF+sFlt-1+NGAL	528	77[c]	10% FPR	NR	NR
Yucel 2016[107] *Turkey*	At least one abnormal parameter: UtA-PI >90th	490	92.68 (80.08–98.46)	85.20 (81.56–88.37)	36.54 (27.31–46.55)	99.22 (97.73–99.84)

Study	Test	Pregnancies included in analysis	Sens (%)*	Spec (%)	PPV	NPV
	centile, PV <10th centile, PAPP-A <10th centile					
	At least two abnormal parameters: UtA-PI >90th centile, PV <10th centile, PAPP-A <10th centile		85.37 (70.83–94.43)	98.89 (97.42–99.64)	87.50 (73.20–95.81)	98.67 (97.12–99.51)

In cases where results were presented for multiple combinations of factors within the same study, the test which gave the 'best' result (in terms of sensitivity/specificity) is reported. If different combinations gave the same 'best' result, the test containing the lowest number of factors is reported. Where results were reported for different FPRs, the results for 10% FPR are reported in the specificity column.
* Where available, results are reported as % (95% CI)
† Study/cohort used a competing risks model
[a] When an analysis was conducted with an additional cohort of 1141 women, who were recruited prospectively for research in the first trimester of pregnancy (2010 to 2012) for the prediction of PE, and their PlGF and AFP data were added, creating a larger sample size of 2,186 participants, the results remained unchanged
[b] 893 women enrolled in the study but it is not clear if data from all women informed the predictive model
[c] Sensitivity reported as detection rate
[d] Cohort overlaps with Goetzinger 2013
[e] Maternal characteristics, serum markers, and ultrasound parameters were used to develop individual risk scores; a weighted score was assigned by rounding the raw unadjusted odds ratio to the nearest whole number, and a total score for an individual patient was calculated by adding together the individual component scores; weighted scores were as follows: chronic hypertension, 4; past history of PE, 3, pre-gestational diabetes, 2; BMI ≥30 kg/m^2, 2; PAPP-A MoM <10th percentile, 1; bilateral uterine artery notching, 1
[f] Uterina12 is the addition of mean uterine PI and mean notch measured at 12 weeks
[g] Uterina22 is the addition of mean uterine PI and mean notch measured at 22 weeks
[h] The MAP of each arm was calculated as the average of the last 2 stable measurements and the arm with the highest final MAP was taken for subsequent analysis of results. Based on the first 4 recordings from both arms, 50 possible combinations of MAP were generated
[i] 2,784 women were eligible for the study, but it is not clear if data from all women was used in the analysis
[j] Cohort overlaps with Schneuer 2012
[k] Authors of this review believe that the values reported in the publication for sensitivity and PPV were switched; the authors believe that the way the values are presented here is correct
[l] Cohort overlaps with the London Cohorts
[m] Pregnancy data for analysis derived from O'Gorman 2016; the data set used to develop the competing risks model[58]
[n] Pregnancy data for analysis derived from O'Gorman 2017, which used the developed competing risk model[124]
[o] Pregnancy data for analysis derived from Tan 2018a; a study specifically designed to compare the performance of screening by the competing risks algorithm to the method advocated by NICE[56]
Abbreviations: ACR: albumin: creatinine ratio; AFP: alpha fetoprotein; AIx: augmentation index; BMI: body mass index; hCG: human chorionic gonadotropin; IGFALS: insulin-like growth factor acid labile subunit; MAP: mean arterial pressure; MCAM: melanoma cell adhesion molecule; MoM; multiples of the median; MPV: mean platelet volume; NGAL: neutrophil gelatinase-associated lipochalin; PAPP-A: pregnancy associated plasma protein-A; PE: pre-eclampsia; PI: pulsatility index; PlGF; placental growth factor; PP13: placental protein 13; PPV: positive predictive value; PV, placental volume; PWV, pulse wave velocity; NPV, negative predictive value; RI: resistance index; SBP_{AO}: systolic blood pressure in the aorta; SPR: screen positive rate; sens: sensitivity; sEng: soluble endoglin; sFlt-1: soluble fms-like tyrosine kinase 1; spec: specificity; SPINT1: serine peptidase inhibitor Kunitz type 1; uE_3: unconjugated estriol; UtA-PI: uterine artery pulsatility index; VFI: vascularisation flow index; VI: vascularisation index.

Comparison of screening tests for different gestational ages at birth

Seventeen studies representing 13 unique, non-overlapping 'cohorts' reported the accuracy of a screening test or algorithm for predicting PE at different gestational ages at birth, allowing for comparison of screening accuracy for preterm (<37 weeks) and term (≥37 weeks) PE.[69, 70, 74, 79, 84, 91, 94, 95, 98, 100, 101, 106, 111] Competing risks were used in 4 of these cohorts.[69, 71, 79, 100, 111, 128] Results of these studies are presented in Table 10.

Sonek 2018 reported on the accuracy of screening tests using maternal characteristics alone or 2 tests combining biochemical and ultrasound markers for the prediction of preterm and term PE. It appears that for all 3 tests, the DR decreased the later in pregnancy the PE prediction was being made, although this was less pronounced for maternal characteristics alone.[111] This trend in test accuracy was also observed in 2 other unique cohorts.[69, 84] For example, results of the competing risks model evaluated in the 'London Cohorts' indicated that the best performing screening test was a combination of maternal factors + MAP + UtA-PI + PAPP-A + PlGF at a 1:100 risk cut-off, achieving a high 80.7% sensitivity (95% CI 77 to 84%) for detecting preterm PE; but sensitivity for term PE for the same factor combination was markedly lower at 51.0%.[127] Predictive accuracy for this screening test was even higher (94% sensitivity) for detecting PE with birth <32 weeks.

Interestingly, the competing risks model reported in Tan 2018c also found that the combinations of factors producing the best performance in PE prediction was dependent on gestational age. For example, at a 1:66 risk cut-off, maternal factors + MAP + UtA-PI + PlGF had the highest sensitivity for preterm PE (74.8% sensitivity), whereas the best-performing combination for term PE included the addition of PAPP-A (41.3% sensitivity). Conversely, at 1:70 risk cut-off, the best combination for preterm PE was maternal factors + MAP + UtA-PI + PAPP-A + PlGF, whereas term PE required fewer factors achieved similar test performance with maternal + MAP + UtA-PI as with same test with the addition of PAPP-A and PlGF.[69]

The FMF algorithm as evaluated by Al-Amin 2018 reportedly identified all women who developed preterm PE (100% sensitivity, 95% CI 63.0 to 100.0), but only 26.3% of those who developed term PE, demonstrating a substantial drop in test accuracy.[79] It should, however, be noted that this study was judged to be at an uncertain and high risk of bias with concerns about applicability and the uncertainty around the results was high. Nevertheless, other studies demonstrated similar findings. One study evaluating a model combining maternal characteristics and MAP identified a 91% detection rate for preterm PE and a substantially lower 60% detection rate for term PE.[98] Three further studies evaluated screening for PE <34 and ≥34 weeks, and all reported substantially higher DRs (at least 2-fold) for <34 weeks compared with ≥34 weeks .[91, 94, 101]

Overall, the evidence suggests that the predictive accuracy of screening tests may be highest for preterm PE, particularly before 34 weeks gestation, relative to PE at term. This finding is supported

by multiple studies, most notably the high-quality studies in the ‘London Cohorts’, though it is acknowledged that the competing risks approach is likely to underperform for term PE detection. This is due to the model being influenced by the number of births. As the majority of births naturally occur after 37 weeks gestation, rather than due to PE, the risk of PE appears lower. However, this conclusion cannot be made for risk-based screening approaches. Use of ACOG recommendations yielded higher sensitivity for term PE than for PE <34 weeks (89.4% vs 66.6%) and preterm PE (89.4% vs 87.5%), although it should be noted that FPR was high at 67.8%.[79] Demonstrating further inconsistency, application of NICE guidelines predicted 47.3% of term PE pregnancies, 75% of preterm pregnancies with birth <37 weeks, but only 33.3% of preterm pregnancies with birth <34 weeks (suggesting that the majority of preterm PE diagnoses were at a later gestational age).[79]

Table 10. Comparison of sensitivity of screening tests for pre-eclampsia at different gestational ages at birth

Study	Test	Women included in analysis	Sensitivity*	
			Preterm birth [a]	Term birth [b]
†**Al-Amin 2018**[79] *Australia*	NICE guidelines	543	75.0[c] (34.9–96.8)	47.3[c] (24.4–71.1)
	ACOG recommendations		87.5[c] (47.3–99.6)	89.4[c] (66.8–98.7)
	FMF: MF+ MAP + UtA-PI (cut-off 1:100)		100.0[c] (63.0–100.0)	42.1[c] (20.2–66.5)
	FMF: MF+ MAP + UtA-PI (cut-off 1:60)		100.0[c] (63.0–100.0)	26.3[c] (9.1–51.2)
ASPRE[70] *United Kingdom*	Predictive model: maternal factors, MAP, UtA-PI, maternal serum PAPP-A, PlGF	25,797	76.7[c]	43.1[c]
Caradeux 2013[91] *Chile*	Predictive model: age, weight, SBP, DBP, MAP, parity, history of PE, hypertension, diabetes mellitus, log UtA-PI, history of preterm labour	NR[d]	62.5[ce]	31.6[cf]
Di Lorenzo[94] *Italy*	Predictive model: maternal factors (BMI, black vs other, parity, chronic hypertension), biomarkers (log fβ-hCG, log PAPP-A, log PlGF), UtA-PI	2,118	75[e]	31[f]
Di Martino 2019[95] *Italy*	FMF algorithm	11,632	58.2[ce] (45.5–70.2)	44.1[cf] (37.3–51.1)
	BCNatal Algorithm		41.8[ce] (29.6–54.5)	38.0[cf] (31.3–44.8)
GOS[84, 132] *Canada*	MAP	4,700	48[c]	34[c]
	Log_{10}PlGF <0.8537 MoM		40[c]	21
	Log_{10}PlGF <0.8537 MoM + maternal characteristics		55[c]	26
Goto 2021[98] *Japan*	Maternal characteristics + MAP	913	91[c]	60[c]
Khalil 2012[74] *United Kingdom*	History + vascular-derived risk (AIx-75, PWV, SBPAO)	7,084	71.4[ce]	60.5[cf]
†**London Cohorts**[69] *United Kingdom*	MF (cut-off 1:62)	61,174	44.8 (40.5–49.2)	33.5 (31.0–36.2)
	MF + MAP + UtA-PI + PlGF (cut-off 1:66)		***74.8 (70.8–78.5)***	41.0 (38.3–43.7)
	MF + MAP + UtA-PI + PAPP-A + PlGF (cut-off 1:66)		74.8 (70.8–78.5)	***41.3 (38.7–44.1)***
	MF (cut-off 1:70)		48.3 (43.9–52.7)	41.3 (38.7–44.1)
	MF + MAP + UtA-PI + PAPP-A + PlGF (cut-off 1:70)		***76.1 (72.1–79.6)***	42.4 (39.7–45.1)
	MF + MAP + UtA-PI (cut-off 1:70)		70.6 (66.4–74.4)	***44.6 (41.9–47.4)***
	MF (cut-off 1:100)		59.4 (55.0–63.7)	48.5 (45.7–51.2)

Study	Test	Women included in analysis	Sensitivity*	
			Preterm birth [a]	Term birth [b]
	MF + MAP + UtA-PI + PlGF (cut-off 1:100)		79.9 (76.2–83.2)	51.3 (48.6–54.0)
	MF + MAP + UtA-PI + PAPP-A + PlGF (cut-off 1:100)		***80.7 (77.0–84.0)***	51.0 (48.2–53.7)
	MF + MAP (cut-off 1:100)		66.7 (62.5–70.8)	***55.1 (52.3–57.8)***
Sandström 2019[106] *Sweden*	Pre-specified variables model[g]	62,562[j]	29.2 (25.2–33.4)	28.1(26.3–30.0)
	Backwards selection model[h]		25.8 (22.0–29.8)	28.2(26.4–30.1)
	Random forest model[i]		24.3 (20.6–28.4)	22.4(20.7–24.2)
	Risk classification based on NICE guidelines binary clinical decision rule		19.5 (16.1–23.3)	12.2(10.9–13.7) [5.5% FPR]
Scazzocchio 2013[101] *Spain*	Maternal characteristics, PAPP-A, fβ-hCG, MAP, UtA-PI	5,170	80.0[ce]	39.6[cf]
Scazzocchio 2017[102k] *Spain*	Maternal characteristics, MAP, UtA Doppler, PAPP-A Construction cohort	4,621	75.0[ce] (59.8–85.3)	52.6[cf] (42.3–62.9)
	Maternal characteristics, MAP, UtA Doppler, PAPP-A Validation cohort		85.7[ce] (71.3–96.4)	43.4[cf] (37.6–51.1)
†Skrastad 2015[100] *Norway*	FMF: MF + MAP + UtA-PI + PAPP-A + PlGF	541	80.0 (28.4–99.5)	30.0[f] (11.9–54.3)
†Sonek 2018[111] *United States*	Maternal characteristics	1,068	60	43
	PlGF + PAPP-A + AFP		60	19
	PlGF + PAPP-A + AFP + MAP + UtA-PI + EPV		***68***	***29***
†Tsiakkas 2016b[71l] *United Kingdom*	MF Empirical	7,066	54 (39–68)	35 (26–44)
	MF Model-based		47	37
	MF + serum sFlt-1 Empirical		54 (39–68)	35 (26–44)
	MF + serum sFlt-1 Model-based		46	37

In cases where results were presented for multiple combinations of factors within the same study, the test which gave the 'best' result (in terms of sensitivity/specificity) is highlighted in ***bold italic***.

* Where available, results are reported as % (95% CI)

† Study/cohort used a competing risks model

[a] Gestational age at birth <37 weeks

[b] Gestational age at birth ≥37 weeks

[c] Sensitivity reported as detection rate

[d] 627 women enrolled in the study but it is not clear if data from all women informed the predictive model

[e] <34 weeks

[f] ≥34 weeks

[g] Family history of PE + country of birth + method of conception + gestational length at registration + maternal age + height + weight + smoking habits in early pregnancy + pre-existing type I and type II diabetes + chronic hypertension + SLE + MAP

[h] Maternal age, BMI, MAP, protein in urine, infertility treatment, diabetes, blood group, alcohol consumption at registration, gestational length at registration, capillary glucose, haemoglobin, infertility duration, family history of PE, family history of hypertension, alcohol consumptions 3 months before registration, chronic kidney disease, family situation, smoking 3 months before pregnancy, snuff 3 months before pregnancy, snuff at registration, region of birth, hepatitis, morbus chron/ulcerous colitis, and psychiatric disease

[i] 36 candidate predictors, using a machine learning, ensemble method making use of multiple decision tree; for each tree, a bootstrap sample was drawn, from which the tree was built

[j] Total study population, which included pregnancies with major malformations or treatment with aspirin

[k] Cohort overlaps with Scazzocchio 2013

[l] Cohort overlaps with the London Cohorts

Abbreviations: ACOG: American College of Obstetricians and Gynecologists; AFP: alpha-fetoprotein; ASPRE: Combined Multimarker Screening and Randomised Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention trial; BMI: body mass index; DBP: diastolic blood pressure; EPV: estimated placental volume; fβ-hCG: free β-human chorionic gonadotropin; FMF: Fetal Medicine Foundation; GOS: Great Obstetrical Syndromes study; MAP: mean arterial pressure; MF: maternal factors; MoM: multiple of median; NICE: National Institute for Health and Care Excellence; PAPP-A: pregnancy associated plasma protein A; PE: pre-eclampsia; PlGF; placental growth factor; SBP: systolic blood pressure; sFlt-1: soluble fms-like tyrosine kinase 1; SPREE: Superior Province Rifting EarthScope Experiment; SQS: screening quality study; UtA-PI: uterine artery pulsatility index

Conclusion

This evidence summary included 72 publications reporting on 35 unique prospective cohorts that evaluated the use of screening tests for the prediction of PE. Three studies were conducted in large cohorts of 25,797, 61,174 and 62,562 pregnant women,[69, 70, 106] with remaining sample sizes ranging from 543 to 11,632. Data reported by these studies suggests that the accuracy of screening tests may be higher for preterm PE than for term PE, though this finding was not consistent for risk-factor based approaches such as those described by the NICE guidelines.

The evidence suggests that risk assessment strategies currently used in clinical practice (for example, guideline-based), perform worse than combination tests of maternal factors and biomarkers for all pre-eclampsia, as directly demonstrated in 2 studies.[69, 79] In particular, the FMF and similar screening algorithms were capable of achieving high sensitivity (≥80%) for preterm PE thereby representing a highly promising screening approach identified by this review. Of these, the results of the competing risks models represent a source of high-quality evidence for the effectiveness of screening for preterm PE. Furthermore, their performance was externally validated using two external validation data sets (Wright 2019),[128] thus providing an effective and reproducible method for first-trimester prediction of preterm PE as long as the various components of screening are carried out by appropriately trained and audited practitioners.[128]

Summary of Findings Relevant to Criterion 4

Preterm pre-eclampsia: criterion met

Quantity: A large volume of evidence was identified by this evidence review, and ultimately 36 publications reporting on 23 unique prospective observational studies with results for preterm PE were included for extraction. Three large cohorts of 25,797, 61,174 and 62,562 pregnant women were included in the review;[69, 70, 106] the remaining cohorts included between approximately 500 to 12,000 women.
Quality: All examined studies were of a prospective cohort design, and therefore were at a reduced risk of selection bias and confounding compared with case-controls and retrospective studies, which were not selected for extraction. The studies were generally of moderate quality, with 5 studies judged to be at high risk of bias or with concerns about applicability for at least 3 domains; this included 2 studies that used a competing risks approach. This was mostly due to inclusion of high-risk pregnant women within unselected populations, unblinded interpretation of index test results and omission of screened women from analyses, which could have led to under- or overestimation of test accuracy. The reference standard was generally well described.
Applicability: All of the studies included in this review were conducted in high-income countries that are considered to be reflective of the UK setting. The majority of the biomarkers investigated

by the included studies are already used in guideline-directed monitoring of high-risk pregnancies in the UK, and all studies used the same definition of PE as used in the UK.
Consistency: Comparisons in sensitivity/specificity and PPV/NPV are difficult due to the distribution of risk factors across different populations. A wide range of tests was investigated, with only a small number of individual tests investigated by multiple studies. The FMF algorithm and similar combination screening tests were found to be capable of achieving high sensitivity (≥80%) for preterm PE, particularly <34 weeks, in 8 unique, non-overlapping cohorts (7 studies, 2 validation cohorts).[69, 79, 100, 101, 111, 56, 77, 98, 102-105, 128] Two of these evaluated a combination of maternal factors, UtA-PI, MAP, PAPP-A and PlGF as part of the FMF algorithm for prediction of preterm PE, with consistent sensitivities of 80% (10% FPR) and 80.7% (14.1% FPR);[69, 100] with the validation study of the same factors minus PAPP-A yielding similar results in 2 validation sets of 75% (10% FPR) and 83% (10% SPR).[128] Another study (ASPRE) also developed a prediction model based on this specific combination, achieving 76.1% sensitivity at 10% FPR,[70] increasing confidence in the results.
Conclusions: Based on the evidence assessed by this review, a competing risks approach based on a combination of maternal factors, UtA-PI, MAP, PAPP-A and PlGF could be considered in a screening programme aimed at predicting pregnancies at risk of preterm PE in clinical practice.

Term pre-eclampsia: criterion not met

Quantity: A large volume of evidence was identified by this evidence review, and ultimately 22 publications reporting on 10 unique prospective observational studies with results for term PE were included for extraction. This included three large cohorts of 25,797, 61,174 and 62,562 pregnant women;[69, 70, 106] the 7 remaining cohorts ranged from approximately 500 to 11,600 women.[72, 79, 111, 140]
Quality: All examined studies were of a prospective cohort design, and therefore were at a reduced risk of selection bias and confounding than case-controls and retrospective studies, which were not selected for extraction. The studies were generally of moderate quality, with 2 studies judged to be at high risk of bias or with concerns about applicability for at least 3 domains. This was mostly due to inclusion of high-risk pregnant women, unblinded interpretation of index test results and omission of screened women from analyses, which could have led to under- or over-estimation of test accuracy. The reference standard was generally well described, but it was unclear if any deliveries were induced, and therefore it is possible that PE may have been prevented in some pregnancies.
Applicability: All of the studies included in this review were conducted in high-income countries that are considered to be reflective of the UK setting. The majority of the biomarkers investigated by the included studies are already used in guideline-directed monitoring of high-risk pregnancies in the UK, and all studies used the same definition of PE as used in the UK.

Consistency: Comparisons in sensitivity/specificity and PPV/NPV are difficult due to the distribution of risk factors across different populations. The range of tests investigated for the prediction of term PE was smaller than for preterm PE. There were fewer instances of the same individual test investigated in multiple studies for term PE compared with preterm PE. The FMF algorithm and similar combination screening tests were assessed in 4 studies, with no validation cohorts.[69, 70, 79, 95] Despite this, the performance of the tests was fairly consistent. The 2 studies using a competing risks model had similar sensitivities for a combination of maternal characteristics + MAP + UtA-PI (an iteration of the FMF algorithm)[69, 79] and the ASPRE study reported a similar sensitivity with the additional markers PAPP-A and PlGF.[70]
Conclusions: Based on the evidence assessed by this review, no test can be recommended for use in a screening programme aimed at predicting pregnancies at risk of term PE in clinical practice. There is evidence that combination tests have only a moderate sensitivity for detecting term PE, and differences in risk thresholds and study quality along with a wide range of different tests limit comparability between studies. Furthermore, these results have not been validated in separate cohorts, or been shown to demonstrate superiority against the risk-based approaches used in current clinical practice. Finally, due to many term pregnancies being delivered naturally after 37 weeks' gestation, rather than due to PE, it may not be feasible to achieve high levels of sensitivity and specificity in any predictive test for this gestational period. As such, approaches other than screening may need to be considered to prevent term PE.

Pre-eclampsia (all): criterion not met

Quantity: A large volume of evidence was identified by this evidence review, and ultimately 33 publications reporting on 25 unique prospective observational studies with results for PE without stratification by gestational age were included for extraction. Cohorts ranged widely in size, from 50 to 45,287 pregnancies.
Quality: All examined studies were of a prospective cohort design, and therefore were at a reduced risk of selection bias and confounding compared with case-controls and retrospective studies, which were not selected for extraction.The studies were generally of moderate quality, with 3 studies judged to be at high risk of bias or with concerns about applicability for at least 3 domains. This was mostly due to inclusion of high-risk pregnant women, unblinded interpretation of index test results and omission of screened women from analyses, which could have led to under- or overestimation of test accuracy. The reference standard was generally well described.
Applicability: All of the studies included in this review were conducted in high-income countries that are considered to be reflective of the UK setting. The majority of the biomarkers investigated by the included studies are already used in guideline-directed monitoring of high-risk pregnancies in the UK, and all studies used the same definition of PE as used in the UK.
Consistency: Comparisons in sensitivity/specificity and PPV/NPV are difficult due to the distribution of risk factors across different populations. A wide range of tests was investigated. Fewer than half of the studies that reported on prevalence of all PE (that is, without stratification

by gestational age) also reported results for preterm PE and/or term PE. Predictive accuracies for single factors ranged from 9.8% DR (7.4% FPR) to 83.3% sensitivity (63% specificity). For models that included multiple factors, sensitivities >75% at 10% FPRs were identified in 4 separate studies. Two studies that evaluated individual risk-based scoring systems did not demonstrate strong performance for predicting PE.

Conclusions: Over half of studies that reported on the accuracies of screening tests for predicting all PE cases failed to provide results for these tests stratified by gestational age. However, based on the overall body of evidence, there are multiple high-quality studies that provide results supporting screening tests for predicting PE; these tests would be effective for predicting preterm PE cases, and less effective for predicting term PE cases indicating that alternative strategies should be considered for term PE cases (see above for term PE). For example, as PE resolves with birth, and induction of labour has been shown to be relatively safe after 37 weeks, a possible strategy may be to shift efforts to focus on effectively diagnosing, rather than predicting, term PE cases. This would prompt identification and birth for such pregnancies, which may improve maternal and neonatal outcomes.

Criterion 9 — Intervention for preventing pre-eclampsia in screen-detected women

9: 'There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme should not be further considered'

In 2011, the UK NSC summarised the findings of the 2008 HTA report 'Methods of prediction and prevention of PE: systematic reviews of accuracy and effectiveness literature with economic Modelling'. Four interventions were found to reduce the risk of PE with statistically significant results; antioxidants, antiplatelets, calcium supplementation and rest in women with normal blood pressure. In addition, the evidence suggests that there were no suitable primary prevention interventions available that could be used in a UK population.

Currently, low-dose aspirin is the only intervention used in clinical practice to prevent PE. Antioxidants (vitamin C and E), and nutritional supplements were considered in NICE and ACOG guidelines, but were not recommended due to insufficient evidence.[7, 15] This review searched for relevant data published since 2011 relating to the effectiveness of interventions for preventing PE in screen-detected or otherwise high-risk women.

Question 2 — Is there an effective intervention for preventing pre-eclampsia in screen-detected women?

Eligibility for inclusion in the review

This review searched for RCTs, interventional studies, cohort and case-control studies, as well as SLRs and MAs of the above. Studies were included if the population comprised pregnant women at high risk of PE due to having a combination of maternal risk factors, or as determined through screening or testing. Once identified, women could receive interventions directed at preventing PE; aspirin, anticoagulants, antiplatelets, anti-thrombotics, metformin, statins, calcium supplementation or anti-oxidants. Publications were only included if they reported risk of PE or other relevant maternal or neonatal outcomes. Studies had to be conducted in the UK or other high-income countries.

Full details of the eligibility criteria are presented in Table 3.

Description of the evidence

Due to the high number of studies initially included in the review, and to remain consistent between data included for criterion 4, retrospective and case-control studies were not selected for extraction in the review. Therefore, in total, 25 articles reporting on 17 unique cohorts were selected for extraction for question 2.[70, 92, 102, 141-153] RCTs accounted for the majority of studies (n=13),[70, 102, 136, 141-144, 146, 147, 149, 151-153] with 2 prospective cohort studies,[92, 150] 1 SLR and MA[145] and 1 pilot observational study[148] comprising the remaining 4. Of the RCTs, 7 explored the use of aspirin in pregnancy, comparing it with placebo (6 studies);[70, 102, 141, 149, 151, 152] or comparing different doses of aspirin (1 study).[146] One study investigated enoxaparin and high-risk care compared with high-risk care alone; standard high-risk care involved no intervention.[142] Further studies explored metformin compared with placebo (2 studies)[143, 153] and pravastatin compared with placebo (2 studies).[144, 147] The 2 prospective cohort studies compared aspirin to no aspirin,[92, 150] and the pilot observational study addressed the impact of LMWH and aspirin compared with aspirin alone.[148] Lastly, the SLR and MA included studies exploring LMWH or unfractionated heparin (with or without low dose aspirin) compared were against a variety of measures including folic acid, standard high-risk care and some versus no intervention.[145] Studies of 4 unique cohorts were conducted in the UK or England.[70, 143, 147, 153]

Four identified studies provided data on the incidence of preterm PE[70, 146, 149, 151] and 3 studies reported incidence of term PE.[70, 146, 147] Most studies (n=12) recorded incidence of ‘all PE’, without stratification by gestational age.[92, 102, 141-148, 151, 153] Amongst notable maternal and fetal outcomes reported by included studies were admission to the NICU and maternal haemorrhage, and many studies also reported safety outcomes.

Summary of findings

Quality assessment

The quality of all included primary studies was appraised using an adapted Downs and Black checklist (Appendix 3, Table 33); a summary of the risk of bias and applicability to the UK setting (external validity) is presented in Table 11 and Table 12, and the full appraisal is presented in Appendix 3(Table 34 and Table 35). The quality of the included SLR and MA was appraised using an adapted AMSTAR-2 checklist. A summary of the assessment is presented in Table 13, with the full appraisal presented in Appendix 3(Table 36).

Primary studies

Table 11. Summary of Downs and Black assessments for studies of interventions to prevent PE

Question	ASPRE Rolnik 2017[70]	Ayala 2013[141]	Bella 2020[142]	Chiswick 2015[143]	Costantine 2016 Costantine 2016[144]	Dobert 2021[147]	McLaughlin 2021[148]	Meiri 2014[92]
Reporting	Low	Low	Low	Low	Low	Low	Low	Low
External validity	Low	High	Probably high	High	High	Low	Low	High
Internal validity – bias	Low	Low	High	High	Low	Low	High	High
Internal validity – confounding	Low	Low	High	Low	Low	Low	High	High
Power	Low	Low	Probably high	Low	High	Low	Unclear	Unclear

Table 12. Summary of Downs and Black assessments for interventions to prevent PE studies (continued)

Question	Odibo 2015[149]	Park 2021 Park 2021[150]	PREDO Villa 2013[151]	Scazzocchio 2017[102]	Stanescu 2018[152]	Syngelaki 2016[153]	Tapp 2020[146]
Reporting	Low	Low	Low	Low	Probably low	Low	Low
External validity	High	Low	High	Low	Low	High	High
Internal validity – bias	Probably low	High	Probably low	Low	High	Probably low	Low
Internal validity – confounding	Probably high	High	Low	Probably high	Unclear	Probably high	Probably low
Power	High	Unclear	Probably high	High	Unclear	High	High

Reporting

The risk of bias arising from reporting was judged to be probably low or low across all trials, as the distributions of principal confounders in each group of women to be compared were clearly described in all studies. Additionally, statistical significance was typically either reported exactly or indicated through confidence intervals. Stanescu 2018 was the only study for which risk of bias in this area was not judged as low; however, as a p value was reported for birth weight, the risk of bias was instead considered to be probably low.[152]

External validity

Six studies included a population directly applicable to the review question,[70, 102, 147, 148, 150, 152] that is, screen-detected women from a prospective, low-risk population. In all other studies except one where it was unclear,[92] women were at risk of PE due to the presence of risk factors, rather than

selected through screening (or testing).[141, 143, 144, 146, 149, 151, 153] Risk factors included medical history, such as previous history of PE, and anthropometry, such as BMI[146, 153]. As the presence of risk factors can only approximately indicate that a pregnancy is also at an increased risk for PE (in contrast to a more accurate detection of PE risk established via screening or testing), the results from these studies may not be fully applicable to the review question. Bella 2020 was an exception, as the study recruited some participants on the basis of risk factors and others based on screening.[142]

Internal validity — bias

In most of the studies , neither the participants nor the individuals carrying out the study knew the individuals' treatment assignments.[70, 102, 141, 143, 144, 146, 147, 149, 151, 153] Furthermore, 3 studies were open-label[92, 142, 150] and 2 studies incorporated elements of blinding, where participants were not blinded to the treatment they received but certain indivividuals, such as adjudicators, were unaware of treatment allocations.[148, 152] Most studies showed no evidence of data dredging, such as 'cherry-picking' the most promising findings and presenting the results of unplanned statistical tests as statistically significant,[70, 102, 142, 144, 146-148, 150, 151, 153] though in 2 studies dredging was unclear.[141, 152] In Odibo 2015 and Chiswick 2015, there was evidence of dredging, with the latter reporting post-hoc analyses.[143, 149] In all studies, statistical tests were appropriate, except for one study where these were not specified and therefore suitability was unclear.[152] One concern that may increase the uncertainty around the results is that compliance with the intervention was not clearly described in many studies.[142, 148-153] Compliance with the intervention was reliably reported in only 6 studies, where adherence was reported to be high[70, 102, 141, 144, 146, 147] and was unreliable in one study;[143] for 7 studies compliance and adherence to the intervention was unclear, as this was largely unreported .[142, 148-153] Eight studies were aligned with the UK definition of PE, namely GH (SBP ≥140 mmHg or DBP ≥90 mmHg) with or without proteinuria (≥0.3 g of protein in a 24-hour urine specimen or ≥1+ score on a dipstick test).[70, 102, 142, 144, 147-149, 151] One study did not use the UK definition of PE[141] and in 5 studies it was unclear whether the definition of PE used aligned with that of the UK,[143, 146, 150, 152, 153] primarily due to these studies not specifying the definition they used.

Internal validity — confounding (selection bias)

The majority of studies reported adjustment for confounding, with only 3 studies not making any adjustments to address their statistically significant difference in baseline characteristics between intervention groups.[142, 149, 153] Additionally, whilst McLaughlin 2021 failed to report any measures of statistical significance for baseline characteristics between groups or whether adjustment was necessary or performed, they did state that participants in one of the groups were initially assessed and identified at a later gestational age than those of the 2 other groups (12 and 16 weeks gestation in groups 1 and 2, respectively, compared with 22 weeks in group 3), which could be a potential source of bias.[148] In all but 2 studies in which participants were randomised to their respective treatment groups, the allocation sequence was concealed until recruitment was

complete and irrevocable. These studies all had appropriate randomisation and allocation sequence concealment that was unlikely to result in bias. The one exception was Bella 2020, where details of concealment were not reported.[142] Three studies (the pilot observational study and 2 prospective cohort studies) did not randomise participants to their treatment groups.[92, 148, 150] One of the studies for which the intervention groups were not recruited over a continuous period of time was the ASPRE group; the ASPRE trial recruitment stopped and started due to administrative reasons, resulting in 2 separated cohorts over different periods.[70] However, it appears that the distribution of women between arms was not affected, though there could still be differences in the population the authors did not test for. Park 2021 was the only other study in which participants in were sourced from two different cohorts which were recruited over different periods of time.[150] Although in the Ayala 2013 the study dates are not explicitly recorded, patients were recruited from a single centre and it could be reasonably assumed that individuals in different intervention groups were recruited consecutively over the same time period.. By contrast, Stanescu 2018 did not explicitly report the period of time, setting orpopulation the trial participants were recruited from, meaning the risk of bias in this area was unclear.

Participant losses either did not occur or were appropriately considered, for example using intention-to-treat analyses, in nine studies,[70, 141-144, 146-149, 151] Four studies did not consider participant losses[92, 102, 149, 150] and in a further 2 studies it was unclear if loss was accounted for.[152, 153] However, in one of these, the data presented implied there were no dropouts, in which case adjustment would not be necessary.[152]

Power

Four identified studies were adequately powered for incidence of PE.[70, 141, 143, 147] Tapp 2020 and Syngelaki 2016 were partially powered;[146, 153] these studies were underpowered for secondary outcomes, which included PE, and therefore these were judged at a high risk of bias in this domain.[146, 153] The PREDO trial failed to include sufficient numbers of participants for a power of 0.80 and instead had a 0.62 power to detect a 10% change in the incidence of PE and GH at 0.05 significance level and therefore was judged to have a probably high risk of bias in this domain.[151] Therefore, in total, studies had insufficient power and were considered to have a high or probably high risk of bias in this domain;[102, 142, 144, 146, 149, 151, 153] this was reported to be for a variety of reasons, for example under-recruitment[102] and lack of intention for the study to achieve power.[144] For 4 studies power was not reported and the risk of bias was therefore judged as unclear.[92, 148, 150, 152]

SLRs and MAs

The quality of the included SLR and MA was appraised using the AMSTAR-2 checklist. The full appraisal is available in Table 36 (Appendix 3).

Table 13. Summary of AMSTAR-2 assessments for interventions to prevent PE studies

Question	Cruz-Lemini 2021[145]
Was an 'a priori' design provided?	Yes
Was there duplicate study selection and data extraction?	Yes
Was a comprehensive literature search performed?	Yes
Was the status of the publication (e.g. grey literature) used as an inclusion criterion?	No
Was a list of studies (included and excluded) provided?	No
Were the characteristics of the included studies provided?	Yes
Was the scientific quality of the included studies assessed and documented?	Yes
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes
Were the methods used to combine the findings of studies appropriate?	Yes
Was the likelihood of publication bias assessed?	Yes
Was the conflict of interest included?	Yes

Study design

Overall, the study design of the SLR/MA was robust; the study protocol was registered with PROSPERO and abstract screening, full-text review and data extraction were performed independently by at least 2 individuals. The literature search was detailed in the supplementary materials and was deemed comprehensive and the methods used to combine the findings of studies was appropriate.

Quality of included studies

Whilst a list of included studies and their characteristics was provided, neither a list of excluded studies, nor reasons for their exclusion, were given. Furthermore, the status of publications (e.g. grey literature) was not used as an inclusion criterion. However, risk of bias was assessed and documented for all included studies and this was used appropriately in formulating conclusions.

Bias and disclosures

The likelihood of publication bias was assessed via a funnel plot, which suggested no bias, and there were no conflicts of interest in included studies.

Results

Identified studies were split into those reporting on preterm PE, term PE and PE (overall) to understand how effective interventions were at preventing PE. Studies could be included in more than one group. Other than PE incidence, maternal and fetal outcomes also considered relevant were: admission to the NICU, Apgar score and maternal haemorrhage. The risk of preterm PE in the included studies is detailed in Table 14, with term PE detailed in Table 15 and PE (overall) in Table 16. Additional maternal and fetal outcomes are detailed in Table 17. Full study results and details are provided in the extraction tables in Appendix 3.

Preterm PE

The only intervention assessed by identified studies for reducing the risk of preterm PE was aspirin, with varying results. The ASPRE study found that daily 150 mg aspirin until 36 weeks of gestation reduced incidence of preterm PE by 62% compared with placebo (OR 0.38 [95% CI 0.20 to 0.74]; p=0.004).[70] It appears that this effect is strongly associated with regular aspirin intake, as results of a secondary analysis suggest that the reduction in the incidence of preterm PE may be about 75% in women with ≥90% medication compliance and only 40% in those with compliance of <90%.[154] By contrast, PREDO found no statistically significant benefit for the effect of low-dose aspirin in preventing preterm PE.[151] ASPRE used a higher dose of aspirin (150 mg) compared with PREDO (100 mg),[70] which could explain the difference in results. Tapp 2020 also found no significant difference between the effect of 2 different doses of aspirin (80 mg and 160 mg) on the incidence of preterm PE (RR 0.5, 95% CI 0.04 to 5.25, p=0.556), however, the sample sizes in both arms were small and, without an untreated arm within the study, it is not possible to ascertain whether both doses had an effect or neither dose had an effect. Furthermore, all 16 women who had a history of preterm PE (8 in each arm), did not experience preterm PE during the study, and the occurrence of fetal growth restrictions was low despite this being a high-risk population, highlighting the efficacy of aspirin overall. It is worthwhile noting that the incidence of PE in this study was in line with UK estimates of preterm PE (2.4%)[155].[146] Overall, the evidence base had mixed results, and while data suggests that aspirin in general potentially is beneficial in preventing preterm PE, it is overall unclear whether a higher dose of aspirin (>100 mg) is more beneficial than a lower dose..

Table 14. Summary of the effectiveness of interventions to prevent preterm PE

Study	Intervention	Comparator	Risk of PE
ASPRE[70] Rolnik 2017	Aspirin 150 mg (N=798)	Placebo (N=822)	*PE <34 weeks*: Aspirin: 3/798 (0.4%) Placebo: 15/822 (1.8%) OR NS *PE <37 weeks):* Aspirin: 13/798 (1.6%) Placebo: 35/822 (4.3%) **p=0.004**
PREDO[151] Villa 2013	Aspirin 100 mg per day (N=61)	Placebo (N=60)	*PE <34^{+0} weeks:* Aspirin: 1/61 (1.6%) Placebo: 4/60 (6.7%) *PE with birth <37^{+0} weeks:* Aspirin:3/61 (4.2%) Placebo: 5/60 (8.3%)
Odibo 2015[149]	Aspirin 81 mg	Placebo	*PE* Aspirin: 3/14 Placebo: 3/16 RR: 0.88; 95% CI: 0.21 to 3.66

Study	Intervention	Comparator	Risk of PE
Tapp 2020[146]	160 mg aspirin daily (n=54)	80 mg aspirin daily (n=53)	*PE <34 weeks* 80 mg aspirin: 0/51 (0%) 160 mg aspirin: 1/53 (2%) RR: 2.8 (0.12 to 68.08); p=0.520 *PE <37 weeks* 80 mg aspirin: 2/51 (4%) 160 mg aspirin: 1/53 (2%) RR: 0.5 (0.04 to 5.25); p=0.556

Abbreviations: CI: confidence interval; IU: international unit; NS: not significant; OR: odds ratio; PE: pre-eclampsia; RR: risk ratio.

Term PE

Both aspirin and pravastatin were evaluated by identified studies for their ability to prevent term PE. However, no studies reporting on term PE found either intervention to have a significant impact on this outcome.[70] Despite aspirin having had a significant beneficial effect on reducing preterm PE incidence, it had no effect on the incidence of term PE in the ASPRE trial.[70] Aspirin dose appeared not to have a significant impact on the results, as Tapp 2020 found no statistically significant difference in PE risk in women with previous history of PE when 160 mg of aspirin was administered, compared with 80 mg. However, there was a low incidence of fetal growth restriction and preterm pre-eclampsia reoccurrence in this high-risk population, suggesting that aspirin overall is effective at reducing adverse clinical outcomes.[146] Pravastatin was similarly found by Dobert 2021 to have no significant impact on term PE (95% CI 0.76 to 1.33; p=0.96).[151] Therefore, no intervention was identified that showed potential benefit in reducing risk of term PE.

Table 15. Summary of the effectiveness of interventions to prevent term PE

Study	Intervention	Comparator	Risk of PE
ASPRE[70] Rolnik 2017	Aspirin 150 mg (N=798)	Placebo (N=822)	*PE ≥37 weeks*: Aspirin: 53/798 (6.6%) Placebo: 59/822 (7.2%) OR NS
Dobert 2021[147]	Pravastatin 20 mg (n=548)	Placebo (n=543)	*PE ≥37 weeks* Pravastatin: 79/548 (14.7) Placebo: 74/543 (14.0%) RR: 1.01 (0.76 to 1.33); p=0.96
Tapp 2020[146]	160 mg aspirin daily (n=54)	80 mg aspirin daily (n=53)	*PE >37 weeks* 80 mg aspirin: 4/51 (8%) 160 mg aspirin: 7/53 (13%) RR: 1.8 (0.54 to 5.53); p=0.546

* Event size too small for analysis
Abbreviations: N/A: not applicable; NS: not significant; OR: odds ratio; PE: pre-eclampsia; RR: risk ratio.

All PE

A variety of interventions were explored in terms of their ability to prevent PE overall. Whilst results were mixed, most studies did not find a significant positive impact of interventions on PE incidence.

The effect of aspirin on rates of all PE was explored in 3 identified RCTs. Both PREDO (100 mg per day) and Scazzocchio 2017 (150 mg per day) found it had no significant benefit over placebo in reducing the incidence of PE (95% CI 0.3 to 1.7; p value NR and 95% CI NR; p=0.76 respectively).[102, 151] However, the latter was not powered to assess the effect of aspirin on placenta-related diseases. By contrast, Ayala 2013 reported a significant reduction in the incidence of PE among women receiving aspirin (100 mg per day) versus placebo (p=0.041, CI not reported).[141] This study noted that the benefits were dependent on the time of day aspirin was administered, describing the impact as negligible when aspirin was taken first-thing in the morning, but significantly beneficial when taken at bedtime. Nevertheless, participants were advised to take their tablet in the evening in the Scazzocchio 2017 trial, and since no benefit was observed there (albeit in an underpowered study), it is unclear what the true effect of aspirin is for overall PE prevention.[102] No details were reported on what time of day aspirin was administered in the PREDO trial.

A similar trend was seen for heparin. McLaughlin 2021 commented their findings did not provide evidence for the preventative use of LMWH for placenta-mediated complications (which include PE).[148] However, the MA performed by Cruz-Lemini 2021, incorporating data from 15 trials, showed incidence of PE to be significantly lower among women treated with LMWH (95% CI 0.36 to 1.16; p=0.010).[145] The results of this MA potentially suggest that timing of LMWH administration can have an effect on PE prevention; the preventive effect was stronger upon exclusion of studies where LMWH administration commenced after 16 weeks (OR 0.62, 95%CI 0.41 to 0.95, p=0.030).[145] Given that McLaughlin 2021 was a single underpowered study, whereas Cruz-Lemini 2021 was a good quality SLR that incorporated data from 15 studies, it is likely that the direction of evidence towards a positive effect of LMWH on preventing PE.

Mixed results were encountered when assessing the impact of metformin on PE incidence; whilst Chiswick 2015 observed no significant benefit over placebo (95% CI 0.61 to 9.36, p=0.21),[143] Syngelaki 2016 found incidence to be significantly lower in the metformin arm (95% CI 0.10 to 0.61; p=0.001).[153] One potential explanation is a much higher dose was used by Syngelaki 2016, where participants started on a dose of 1 g metformin and could increase to a maximum of 3 g,[153] compared with 500 mg used by Chiswick 2015.[143] While these results are promising, the discrepancy between the studies suggests that metformin should be evalutated in further trials before the direction of effect can be ascertained.

Pravastatin was the only intervention for which results from both identified studies concurred; Costantine 2016 and Dobert 2021 found the intervention to have no significant impact on PE prevention.[144, 147] Notably, Costantine 2016 was intended to detect any safety risks of pravastatin, not evaluate its effectiveness in preventing PE, thus the authors concluded their results justify a larger trial with PE prevention as the primary aim.[144]

Table 16. Summary of the effectiveness of interventions to prevent all PE

Study	Intervention	Comparator	Risk of PE
PREDO[151] Villa 2013	Aspirin 100 mg per day (N=61)	Placebo (N=60)	Aspirin: 8/61 (13.1%) Placebo: 11/60 (18.3%) RR 0.7; OR: 0.3–1.7
Ayala 2013[141]	Aspirin 100 mg per day (n=76)	Placebo (n=174)	Aspirin: 6.3 (95% CI 2.7 to 9.8)[a] Placebo: 12.6[a] (95% CI 7.7 to 17.6)[a] **p=0.041**
Bella 2020[142]	Standard high-risk care + enoxaparin 40 mg SC (dose adjusted to 60 mg if maternal weight was above 90 kg) (n=144)	Standard high-risk care	Standard high-risk care + enoxaparin: 13 (9.7%) Standard high-risk care: 11 (7.6%) OR: 0.77 (0.33 to 1.78) *In women included due to previous obstetric complications* Standard high-risk care + enoxaparin (n=39): 6 (17.1%) Standard high-risk care only (n=35): 4 (10.2%) OR: 0.55 (0.14 to 2.15)
Chiswick 2015[143]	Metformin 500 mg (started at 1 500 mg tablet escalated by 1 tablet a day each week over 5 weeks, to reach either the maximum tolerable dose or the maximum permitted dose of 2500 mg, whichever was lower) (214 in ITT)	Placebo (220 in ITT)	Metformin: 7/221 (3%) Placebo: 3/222 (1%) OR: 2.39 (0.62 to 9.36); p=0.21
Costantine 2016[144]	Pravastatin 10 mg (n=10)**	Placebo (n=10)**	*Costantine 2016:* Pravastatin: 0/10 (0%) Placebo: 4/10 (40%) NS *Costantine 2021:* Pravastatin: 2/10 (20%) Placebo: 5/10 (50%) NS
Cruz-Lemini 2021[145]	LMWH or unfractionated heparin (with or without LDA)	No treatment or LDA alone	Data from 15 trials included (2795 women) showed participants treated with LMWH vs those not treated with LMWH OR: 0.62; 95% CI: 0.43 to 0.90 **p=0.010**

Study	Intervention	Comparator	Risk of PE
			Analysis by type of LMWH showed both enoxaparin and dalteparin each associated with significant reduction in PE with no statistical differences between them Enoxaparin: OR: 0.58; 95% CI: 0.39 to 0.87; p=0.008 Dalteparin: OR: 0.50; 95% CI: 0.25 to 0.97; **p=0.040**
Dobert 2021[147]	Pravastatin 20 mg (n=548)	Placebo (n=543)	Pravastatin: 80/548 (14.6%) Placebo: 74/543 (13.6%) RR: 1.08 (0.78 to 1.49); p=0.65
McLaughlin 2021[148]	LMWH (40 mg per day enoxaparin) + aspirin (women at risk of severe placental dysfunction received 162 mg LDA nightly) (n=7)	Aspirin alone (n=5)	LMWH: 4/7 (57%) No LMWH: 0/5 (0%)
Meiri 2014[92]	Aspirin – physicians decided whether to prescribe 75 mg per day aspirin or not based on major RFs alone, based on PP13 test results alone or based on both	No aspirin	*Treatment effectiveness by risk group:* Only low PP13: RR 8.43 Only RF: RR 0.21 Low PP13 and RFs: 1.73
Scazzocchio 2017[102]	150 mg extended-release aspirin (n=80)	Placebo (n=75)	Aspirin: 4/80 (5%) Placebo: 3/75 (4%) p=0.76
Syngelaki 2016[153]	1 g metformin per day increasing to a maximum dose of 5.0 g per day (n=225)	Placebo (n=225)	Metformin: 6/202 (3.0%) Placebo: 22/195 (11.3%) OR: 0.24 (0.10 to 0.61) **p=0.001**
Tapp 2020	160 mg aspirin daily (n=54)	80 mg aspirin daily (n=53)	80 mg group: 6/51 (12%) 160 mg group: 8/53 (15%) RR: 1.3 (0.49 to 3.58); p=0.775

* Event size too small for analysis
**Women's pregnancy management including use of low-dose aspirin was left to the discretion of the treating physician and performed as recommended by standard prenatal care as defined by the respective participating institution
[a]Event rates (95% CIs) are expressed as the percent ratio of observed number of events to total number of women per group
[b]This study only reported risk of severe PE
Abbreviations: CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; IU: international unit; LDA: low-dose aspirin; LMWH: low molecular weight heparin; N/A: not applicable; NS: not significant; OR: odds ratio; PE: pre-eclampsia; PP13: placental protein 13; RR: risk ratio; SC: subcutaneous; UFH: unfractionated heparin.

Other maternal and neonatal outcomes

While conclusions regarding the impact of interventions on preventing PE varied, several treatments were found to significantly improve other pregnancy outcomes. In some cases, this may have been as a result of reducing incidence of PE; for example, the ASPRE sub-analysis found that in pregnancies at high risk of PE, administration of aspirin reduced the length of stay in

the NICU by approximately 70% compared with placebo (2.06 vs 0.66 days [95% CI 0.45 to 2.81]; p=0.014).[156] This significant reduction in NICU stay may have been as a result of a reduction in birth rate at <32 weeks gestation, mainly due to the prevention of preterm PE. Interventions were also found to have a positive impact on neonatal outcomes; for example, Chiswick 2015 observed infants of women treated with metformin were significantly less likely to require admission to the neonatal unit (95% CI 0.236 to 0.899; p=0.02),[143] although this was not corroborated by Syngelaki 2016 who found no significant difference with metformin.[153] Apgar scores were another neonatal outcome of interest but neither study providing data on this outcome observed a benefit on infants' Apgar scores.[151, 153]

A maternal outcome of interest was haemorrhage, particularly considering that several interventions, such as aspirin and heparin, can cause bleeding in the mother.[157] Incidence of both antepartum and postpartum haemorrhage did not differ among studies' treatment arms, suggesting interventions may not pose a bleeding risk for pregnant women, though incidence of antepartum haemorrhage in Bella 2020 was close to being singifincantly higher in the enoxaparin-containing arm compared with standard care (which did not include any anticoagulants) (OR 2.43, 95% CI 0.97 to 6.06).[102, 141, 142, 153]

Table 17. Summary of the effectiveness of interventions to prevent maternal and neonatal outcomes other than PE incidence

Study	Intervention	Comparator	Other maternal outcomes	Neonatal outcomes
ASPRE[70] Rolnik 2017	Aspirin 150 mg (N=789)	Placebo (N=822)	*Death or complications:* Aspirin: 32/798 (4.0%) Placebo:48/822 (5.8%) OR NS *Stillbirth or death – with placental abruption or bleeding:* Aspirin: 0/798 (0%) Placebo: 2/822 (2.02%) OR (95% or 99% CI): 0.00 (0.00 to ∞)	*Stillbirth or death with PE or status of being SGA:* Aspirin: 3/798 (0.4%) Placebo: 6/822 (0.7%) OR NS *SGA <3rd centile:* Aspirin: 57/785 (7.3%) Placebo: 63/807 (7.8%) OR NS *Mean length of stay in NICU (SD):* Aspirin: 0.66 (6.3) days Placebo: 2.06 (15.5) days 95% CI 0.45 to 2.81; **p=0.014**
Ayala 2013[141]	Aspirin 100 mg per day (n=176)	Placebo (n=174)	*Antepartum haemorrhage:* Aspirin: 3.4[a] (95% CI 0.7 to 6.1) Placebo: 5.2[a] (95% CI 1.9 to 5.4) p=0.415	No outcomes of interest reported

Study	Intervention	Comparator	Other maternal outcomes	Neonatal outcomes
			Postpartum haemorrhage: Aspirin: 1.7[a] (–0.2 to 3.6) Placebo: 3.5[a] (0.7 to 6.2) p=0.303	
Bella 2020[142]	Standard high-risk care + enoxaparin 40 mg SC (dose adjusted to 60 mg if maternal weight was above 90 kg) (n=144)	Standard high-risk care	*Antepartum haemorrhage/abruption:* Standard high-risk care and enoxaparin: 17/144 (11.8%) Standard high-risk care only: 7/134 (5.2%) OR (95% CI): 2.43 (0.97–6.06)	NICU admission: Standard high-risk care and enoxaparin: 8/144 (5.5%) Standard high-risk care only: 8/134 (5.9%) p=0.88
Chiswick 2015[143]	Metformin 500 mg (started at 1 500 mg tablet escalated by 1 tablet a day each week over 5 weeks, to reach either the maximum tolerable dose or the maximum permitted dose of 2500 mg, whichever was lower) (214 in ITT)	Placebo (220 in ITT)	No outcomes of interest reported	*Admission to neonatal unit:* Metformin: 14/213 (7%) Placebo: 29/219 (13%) OR (95% CI): 0.461 (0.236–0.899)*; **p=0.02**
Costantine 2016 Costantine 2016[144]	Pravastatin 10 mg (n=10)**	Placebo (n=10)**	No outcomes of interest reported	*Highest level of care – intermediate (level 2) or NICU:* Pravastatin: 4/10 (40%) Placebo: 6/10 (60%)
Dobert 2021[147]	Pravastatin 20 mg (n=548)	Placebo (n=543)	No outcomes of interest reported	*NICU admission:* Pravastatin: 10/548 (1.8%) Placebo: 16/543 (2.9%)
PREDO[151] Villa 2013	Aspirin 100 mg per day (N=61)	Placebo (N=60)	NR	*SGA:* Aspirin: 2/61 (3.3%) Placebo: 6/60 (10.0%) RR NS
Park 2021[150]	Interventional cohort, women identified as high-risk prescribed 150 mg aspirin per day	Observational cohort, no treatment	No outcomes of interest reported	*SGA* No effect from aspirin therapy on preterm or term infants classified as SGA. For infants classified as birthweight <3rd centile, the OR was 0.37 (0.11–1.26, p=0.112), <5th centile the OR was 0.55 (0.25–1.22, p=0.14) and for the <10th centile, the OR was 0.75 (0.45–1.24, p =0.26).

Study	Intervention	Comparator	Other maternal outcomes	Neonatal outcomes
				PPROM There was no statistically significant difference in the prevalence of PPROM between the 2 cohorts or between the high-risk subgroups that were observed and treated with low dose aspirin (p=0.31).
Scazzocchio 2017[102]	150 mg extended-release aspirin (n=80)	Placebo (n=75)	*Postpartum haemorrhage:* Aspirin: 2/80 (2.5%) Placebo: 5/75 (6.7%) p=0.21 *Uterine bleeding during follow-up:* Aspirin: 9/80 (11.3%) Placebo: 11/75 (14.7%) p=0.53	No outcomes of interest reported
Stanescu 2018[152]	Group B: 150 mg aspirin until 32 weeks gestation Group C: 150 mg aspirin until 36 weeks gestation	Group A: Placebo	No outcomes of interest reported	*FGR:* In group C, there were fewer cases of FGR compared with other groups: 6% vs. 10% in group B vs. 24% in controls. *Birth weight:* There was a significant birth weight improvement in this group with a median of 3180 grams compared with 2950 grams in group B and 2760 g in group A (**p=0.01**).
Syngelaki 2016[153]	1 g metformin per day increasing to a maximum dose of 5.0 g per day (n=225)	Placebo (n=225)	*Postpartum haemorrhage:* Metformin: 19/202 (9.4%) Placebo: 16/295 (8.2%) OR (95% CI): 1.16 (0.58 to 2.33); p=0.67	*Apgar score at 5 min <7:* Metformin: 1/202 (0.5%) Placebo: 3/195 (1.5%) OR (95% CI): 0.32 (0.03 to 3.09) p=0.36 *Admission to NICU:* Metformin: 11/202 (5.4%) 14/195 (7.2%)

Study	Intervention	Comparator	Other maternal outcomes	Neonatal outcomes
				OR (95% CI): 0.74 (0.33 to 1.68) p=0.47

[a]Percent ratio of observed number of events to total number of women per group
[b]Non-adjusted analysis
[c]Denominator for standard care is 15 because 1 infant was stillborn
* post-hoc analysis
** Women's pregnancy managhement including use of low-dose aspirin was left to the discretion of the treating physician and performed as recommended by standard prenatal care as defined by the respective participating institution
*** Event size too small for analysis
Abbreviations: aOR, adjusted odds ratio; CI: confidence interval; FGR: fetal growth rate; HELLP: haemolysis, elevated liver enzymes and low platelet count; HR: hazard ratio; ITT: intention-to-treat; IU: international unit; LDA: low-dose aspirin; LMWH: low molecular weight heparin; NICU: neonatal intensive care unit; NR: not reported; NS: not significant; OR: odds ratio; PE: pre-eclampsia; PPROM: preterm premature rupture of membranes; RR: risk ratio; SC: subcutaneous; SD: standard deviation; SGA: small for gestational age; UFH: unfractionated heparin.

Harms of treatments

Many studies provided insight into the safety of various interventions used to prevent PE. A range of trials reporting on several interventions found no significant difference in adverse events between treatment and placebo arms (Table 18).

Table 18. Harms of treatmens in the identified studies

Study	Intervention	Comparator	Adverse event	Risk or occurrence (intervention/comparator, if reported separately)
ASPRE[70] Rolnik 2017	Aspirin 150 mg (N=789)	Placebo (N=822)	≥1 serious adverse event ≥1 adverse event	13 (1.6%)/26 (3.2%) 207 (25.9%) 210 (25.5%)
Ayala 2013[141]	Aspirin 100 mg per day (n=176)	Placebo (n=174)	Heamorrhage:	HR: 0.62, 95% CI:.25 to 1.59; p = 0.321
Bella 2020[142]	Standard high-risk care + enoxaparin 40 mg SC (dose adjusted to 60 mg if maternal weight was above 90 kg) (n=144)	Standard high-risk care	Epistaxis Irritation Bruising Thrombocytopenia	8 (1.98%) 2 (0.49%) 2 (0.49%) 2 (0.49%)
Chiswick 2015[143]	Metformin 500 mg (started at 1 500 mg tablet escalated by 1 tablet a day each week over 5 weeks, to reach either the maximum tolerable dose or the maximum permitted dose of 2500 mg, whichever was lower) (214 in ITT)	Placebo (220 in ITT)	No adverse events of metforming recorded in post-hoc safety analyses	
Costantine 2016 Costantine 2016[144]	Pravastatin 10 mg (n=10)*	Placebo (n=10)*	Headache Heartburn Muscoskeletal pain	3 (30%)/5 (50%) 1 (10%)/4 (40%) 4 (40%)/4(40%)

Study	Intervention	Comparator	Adverse event	Risk or occurrence (intervention/comparator, if reported separately)
			Muscle weakness	0 (0)/2 (20%)
			Dizziness**	1 (10%)/2 (20%)
Dobert 2021[147]	Pravastatin 20 mg (n=548)	Placebo (n=543)	Headache and/or dizziness	52 (9.5%)/ 45 (8.3%)
			Nausea and/or vomiting	34 (6.2%)/ 26 (4.8)
			Abdominal and/or pelvic pain	9 (1.6%)/6 (1.1%)
			Dyspepsia and/or heartburn	6 (1.1%)/6 (1.1%)
			Nasal bleeding	2 (0.4%)/1 (0.2%)
Scazzocchio 2017[102]	150 mg extended-release aspirin (n=80)	Placebo (n=75)	Postpartum heamorrhage	5 (6.7%)/2 (2/5%)
			Uterine bleeding during follow-up	11 (14.7%)/9 (11.3%)
Syngelaki 2016[153]	1 g metformin per day increasing to a maximum dose of 5.0 g per day (n=225)	Placebo (n=225)	Incidence of side effects significantly higher in the metforming group	

* Women's pregnancy managhement including use of low-dose aspirin was left to the discretion of the treating physician and performed as recommended by standard prenatal care as defined by the respective participating institution

** Only the 5 most common adverse events presented here. For more, please refer to the Table 28e.

The ASPRE trial, exploring the effect of aspirin, and Syngelaki 2016, exploring the effect of metformin, both compared with placebo, found no significant difference between treatment arms in the incidence of adverse events (AEs) and serious AEs (SAEs), respectively (p-values >0.05 for all AEs in the ASPRE trial; p-values not explicitly reported for SAEs in the Syngelaki 2016 study).[70, 153] Chiswick 2015 also used post-hoc analyses to compare women in the metformin and placebo groups with a recordable SAE and found no adverse effects of the intervention.[143] Similarly, in both the Costantine 2016 cohort and Dobert 2021 study the occurrence of SAEs was not significantly different between pravastatin and placebo treatment arms.[144, 147]

Several additional studies reported specific AEs to be no more frequent amongst women receiving the intervention versus placebo; for example, neither Ayala 2013 nor Scazzocchio 2017 found the risk of postpartum haemorrhage to be increased by the use of aspirin during pregnancy (p>0.05).[102, 141] Although interventions appeared to be typically well-tolerated, Cruz-Lemini 2021 noted a significantly greater incidence of allergies and skin reactions in women treated with LMWH compared with non-treated women (95% CI 2.04 to 11.62; p=0.0004) when analysing data across 6 RCTs in 'all PE'.[145] However, the certainty of these results is impeded by the small number of events and wide CIs. Additionally, despite post-hoc safety analyses finding no adverse effects of metformin, Chiswick 2015 also noted both diarrhoea and vomiting to be more common amongst women who received the intervention, compared with placebo in 'all PE'.[143]

Overall, the data obtained from studies identified in this review indicate few safety concerns associated with the use of interventions to prevent PE. These findings are positive with regards to the use of such interventions, suggesting they do not generally lead to detrimental impacts on the pregnant woman or the fetus.

Conclusions

Evidence for a beneficial effect of an intervention was mixed across both specific intervention and identified studies; however, more often than not interventions were not successful in reducing incidence of PE in high-risk pregnant women.

The ASPRE trial found that a daily dose of 150 mg aspirin significantly lowered the incidence of preterm PE by 62% compared with placebo.[70] As this was a study conducted in screen-detected women, this result is highly applicable to the review question and provides evidence of the benefit of aspirin for preventing preterm PE in women at risk. Additionally, it is important to note for this study that the aspirin intervention was assessed compared to placebo, rather than the current 'usual care' of 75 mg aspirin. Therefore, this study cannot indicate whether this intervention is superior to usual care in reducing PE incidence. However, the evidence supports 150 mg aspirin as an effective intervention to prevent PE and therefore does provide an intervention that is effective in preventing PE. Similarly, Tapp 2020 found that amongst women with a previous history of preterm PE, none of them had a reoccurrence of preterm PE when receiving 80 mg or 160 mg aspirin, with no significant difference between the two dosages.[155] While the lower dose of 80 mg in Tapp 2020 was more closely aligned with 'usual care', the study was not powered to assess whether there was a difference between 80 mg or 160 mg aspirin in terms of clinical outcomes. The study did however demonstrate the beneficial effect of aspirin overall. By contrast, the PREDO trial found no statistically significant benefit for the effect of 100 mg aspirin in preventing preterm PE.[151] Many factors can be speculated to determine whether interventions are successful in reducing the incidence of PE, including compliance, intervention dose and the specific intervention used. For example, the beneficial effect of aspirin in the prevention of preterm PE appears to depend on compliance, which is an important consideration for the practicality of introducing aspirin as an intervention.[154] The positive findings of the ASPRE and Tapp 2020 trials are further confirmed by the Roberge 2017 SLR (excluded from this evidence summary as the majority of trials within it predated 2011, the pre-set date limit for the evidence).[49] The Roberge 2017 SLR found that women taking at least 100 mg daily aspirin from before 16 weeks of gestation were protected from preterm PE, but no such effects were seen for term PE. It may be that the 100 mg dose (as used in the PREDO study) is on the lowest end of effectiveness and so some studies using this dose will not show a protective effect, and a higher dose, such as 150 mg is required. Based on the evidence and given that there is clinical consensus that aspirin is safe and beneficial, daily aspirin at a dose of at least 100 mg should be considered as an intervention to prevent preterm PE.

No studies identified in this review found a significantly beneficial effect of interventions for preventing term PE and the evidence based for all PE was mixed. One study found a significant reduction in the incidence of all PE among women receiving 100 mg aspirin when compared to placebo, and noted that benefits were dependent on the time of day aspirin was administered.[141]

This was in contrast to the findings in the PREDO trial and Scazzocchio 2017, which both found that aspirin had no significant benefit over placebo in reducing the incidence of PE.[102, 151] Interventions may therefore have a role in reducing the incidence of PE earlier in pregnancy, but not in PE that occurs ≥37 weeks of gestation. This suggests that the benefit found by some studies of interventions on PE overall may be driven by reductions in preterm PE.

Evidence was found by several other studies for improved neonatal and maternal outcomes for all gestational ages (aside from PE) when various interventions were used, which may have implications for both short-term and long-term health care costs, as well as for infant survival and handicap.

Furthermore, the data obtained from studies identified in this review indicate few safety concerns associated with the use of interventions to prevent PE. These findings are positive with regards to the use of such interventions, suggesting they do not generally lead to detrimental impacts on the pregnant woman or the fetus.

Summary of Findings Relevant to Criterion 9

Preterm pre-eclampsia: criterion met

Quantity: Four studies reported in 12 articles were selected for data extraction and synthesis. The cohorts investigated ranged from 30 to 1,620 women.
Quality: All studies were RCTs in which reporting and interval validity were generally good but external validity and power were a potential sources of bias.
Applicability: There was some concern about applicability to the review question. Only one of the 4 studies recruited screen-detected women from a prospective, low-risk population. In the remaining 3 studies, women were at risk of PE due to the presence of risk factors, rather than detected through screening or testing.
Consistency: Similar interventions were used across the included studies, with 3 trials comparing aspirin with placebo and the remaining study comparing 2 different doses of aspirin. However, the dose of aspirin used was not consistent between the studies. Only one study detected a significant decrease in preterm PE risk; however, maternal and neonatal outcomes were rare events in all of the studies, limiting the reliability of a comparison for these outcomes. The studies where aspirin did not significantly protect women from preterm PE used at most 100 mg aspirin, which may be too low a dose.
Conclusions: The ASPRE trial, a high-quality RCT, provided strong evidence to support daily aspirin 150 mg as an effective intervention for preventing preterm PE in screen-detected women. In addition, a sub-analysis of ASPRE found that the administration of aspirin in high-risk pregnancies significantly reduced the length of NICU stay, which may have implications for both short-term and long-term health care costs, as well as infant survival and handicap. Based on

this review, previous work and clinical consensus, 150 mg aspirin daily could be an intervention considered for preventing PE in screen-detected women.

Term pre-eclampsia: criterion not met

Quantity: There were 3 studies on interventions for the risk of term PE. These studies had cohort sizes ranging from 107 to 1,620 women.
Quality: All 3 studies were RCTs. Two were at a low risk of bias overall, though it is noted these studies were underpowered to assess the effect of the intervention on the risk of term PE, which was a secondary outcome. The remaining trial was not powered for secondary outcomes, which included PE, and this study had a higher risk of bias overall.
Applicability: There was no concern about applicability to the review question for 2 trials reporting the effect of intervention on the risk of term PE. These 2 studies recruited screen-detected women from a prospective, low-risk population. By contrast, women participating in the remaining study were identified as high risk of PE due to having a history of PE in a previous pregnancy.
Consistency: All 3 included RCTs explored the effect of different combinations of interventions and comparators, thus scope for comparison between the studies was limited. One studied the effect of aspirin compared with placebo whilst another compared pravastatin with placebo. The third study compared 2 doses of aspirin (80 mg and 160 mg). None of the studies found a significant difference of term PE incidence between the study arms.
Conclusions: Neither aspirin nor pravastatin was shown to be effective at reducing the risk of term PE, both compared with placebo and, in the case of aspirin, compared to a different dose. While this review was unable to demonstrate evidence of an effective pharmacological intervention for prevention of term PE, it is important to consider that induction of labour from 39 weeks of gestation, which by definition will prevent some of term PE, was shown to be safe and effective at reducing hypertensive disorders of pregnancy in low-risk nulliparous women.[9] As such, studies investigating the effectiveness and safety of labour induction in screen-detected high-risk women at ≥37 weeks of gestation may provide more relevant insight into term PE prevention.

Pre-eclampsia (all): criterion not met

Quantity: There were 12 studies on interventions for the risk of term PE. These studies had cohort sizes ranging from 12 to 1,101 women.
Quality: One study was an SLR of 15 trials, 9 studies were RCTs and 2 were prospective observational studies. Most studies were at a low risk of bias in reporting and internal validity; where risk of bias was higher this was due to lack of blinding, insufficient descriptions of interventions or compliance with interventions. Three trials were adequately powered and 2 trials partially powered for measuring the incidence of PE.

Applicability: There was no concern about applicability to the review question for 3 trials reporting the effect of intervention on the risk of all PE. These 2 studies recruited screen-detected women from a prospective, low-risk population. By contrast, women participating in the remaining 8 studies were identified as high risk of PE due to having various risk factors for PE.
Consistency: Where RCTs explored the effect of similar interventions and comparators, the results were mostly mixed (aspirin – 2 studies with no difference and 1 with a benefit; heparin 1 study no difference, and benefit in the SLR/MA; metformin – 1 study no difference and 1 study benefit). Only pravastatin studies were consistent in showing no benefit of this intervention in reducing the incidence of all PE.
Conclusions: Aspirin, heparin, metformin and pravastatin were investigated for reducing the incidence of PE in women at risk, but none have shown to be decisively effective for the all PE population. Given the disparity in results seen between pre-term and term PE prevention, it is unsurprising that the results for the broader category of all PE are inconsistent.

Review summary

Conclusions and implications for policy

Based on the overall synthesis of evidence against the UK NSC criteria, screening of pregnant women could be pursued as a candidate screening programme to prevent preterm PE, pending further work.

Two questions were considered in this rapid review: (1) whether an appropriate screening test exists for identification of women at risk of preterm or term PE and (2) whether there is evidence for an effective pharmacological intervention to prevent preterm or term PE in high-risk women. The evidence was considered separately for preterm and term PE, as well as for PE overall.

Preterm PE

This report found a large volume of high-quality and highly applicable evidence indicating that there exists an adequate screening test for predicting preterm PE. Specifically, algorithms based on a competing risks approach using combinations of maternal factors, MAP, UtA-PI and PlGF/PAPP-A can provide patient-specific risks that identify women at risk of preterm PE with high sensitivity and specificity (e.g. 94% sensitivity at 14.1% FPR with PlGF and 91.4% sensitivity at 10.4% FPR with PAPP-A instead of PlGF). The strong predictive performance of screening tests based on the competing risks approach has been corroborated through 2 validation studies comprised of 8,775 and 16,451 women.[128] A recent health technology assessment (HTA) externally validated existing PE prediction models and identified suboptimal predictive performances across data sets, suggesting limited application to the clinical setting.[61] However,

only around one-third of the existing models were validated in the MA, and approximately one-third of the data sets included only women with high-risk pregnancies.[61] By contrast, the present review focusses on screening of the low-risk or unselected pregnant population. Given the different populations and additional models it is not surprising that the conclusion of the current review is different that of the HTA assessment. The findings of this review are more applicable to the screening setting than the HTA results.

This review also found high-quality evidence from one RCT that daily 150 mg aspirin up to 36 weeks of gestation decreases the incidence of preterm PE in screen-detected at-risk women (OR 0.38 [95% CI 0.20 to 0.74]; p=0.004). A recent overview of MAs (not included in this rapid review do to study design) exploring aspirin's preventive qualities against PE showed mixed results.[158] Furthermore, a more recent SLR and MA (not included in this review due to the date range of the included evidence mostly being before 2018), included women with moderate or high risk factors. This finding is also corroborated by a 2021 evidence report, which concluded that daily low-dose aspirin (81 mg) should be prescribed to women at high risk of PE and systematic review finding aspirin reduced risk of PE for women at increased PE risk.[63] This review found that doses of less than 150 mg were ineffective in reducing the incidence of PE.[159] Selection of the daily dose and the start of aspirin may well be the reason behind some of the inconsistencies seen in the review; Roberge 2017 (also not included here due to the age of its evidence) confirmed that aspirin is effective in preventing specifically preterm PE, if at a dose ot at least 100 mg and initiated before or at 16 weeks of gestation.[49] This may explain why other reviews and some studies included in this review were unable to demonstrate a beneficial effect.[159] All interventions, including aspirin, were found to be safe and generally well tolerated. Nevertheless, further analysis of potential harms associated with daily 150 mg aspirin intake would be particularly relevant given that strongest effects of aspirin in PE prevention were observed in women with high (≥90%) compliance.

The present review demonstrates there exists a promising screening approach and a potentially effective preventive intervention for preterm PE, for which further work should be considered. Whilst the ASPRE study did not find aspirin to lead to increased incidence of AEs or SAEs, studies specifically investigating the intervention's safety would be integral in building an evidence base to further support aspirin's tolerability.

Term PE

For term PE, there is a moderate volume of high-quality evidence which does not support any test as adequate for screening in this setting. Similar tests were investigated for term PE as for preterm PE, but the sensitivity and specificity were low and insufficient for any of the tests to be considered a possible candidate for use in a screening programme. In addition, in the only RCT comparing aspirin to placebo where results were specifically reported for term PE, aspirin was not shown to

be effective in preventing PE. Pravastatin was also investigated for benefit in preventing term PE, but was not found to reduce its incidence.

The conclusion of this evidence synthesis is that a screening programme aimed at this subgroup should not be recommended. However, it is important to consider that a likely safe intervention in the form of labour induction for women who present present with PE at term may be available without the requirement for screening. In a subgroup abalysis of low-risk primiparous women in the ARRIVE study, labour induction significantly decreased incidence of hypertensive disorders of pregnancy.[9] Evidence of safety and effectiveness of labour induction from 37 weeks of gestation in screen-detected women at risk of PE is necessary to support this conclusion. Concomitantly, given that PE is a placenta-related disorder, a test to diagnose women with a placental dysfunction at term may have more use than tests aiming to identify women at risk of term PE. Importantly, at term, induction of labour could also be safe and effective for all placenta-related disorders. Further work to identify relevant studies reporting on diagnostic test accuracies and effectiveness of labour induction for women with placental disorders at term may thus be indicated.

A significant limitation of the evidence base was that full and transparent reporting of test accuracy for each screening test was often lacking; often only sensitivity and specificity were reported. Whilst the ability of a test to correctly identify women at risk of PE is paramount, other measures such as PPV, NPV and LRs greatly facilitate evaluation of effectiveness of screening. Furthermore, for some promising results, the confidence intervals were large, thereby diminishing the confidence in these. Similarly, it is important to consider the high risk of intervention bias in some of the included screening studies where pregnant women and health providers were not blinded to test results. Knowledge of the pregnancy being at high risk of an adverse outcome would have likely prompted an intervention or enhanced pregnancy monitoring, therefore an effective screening test could paradoxically lead to underestimation of its predictive accuracy.

Overall conclusions and further work

The review addressed criteria 4 and 9, which are relevant to the test and the intervention domains of assessing new screening programmes. The UK NSC considers 20 criteria across 5 domains, when introducing new screening programmes.[160] In this case, it may be particularly beneficial for further work to address relevant criteria under the Screening Programme domain (criteria 11 to 14), and, should this lead to a positive decision on programme recommendation, further work on the Implementation domain (criteria 15 to 20). Decision-analytical modelling could be of value to understand the cost-effectiveness and health sytem resource consequences of introducing a potential screening programme in the UK (addressing criterium 14). A model could also address the question of the benefit gained by individuals versus potential overdiagnosis and overtreatment; while aspirin is generally safe, its use may elicit allergic reactions, including worsening of respiratory conditions like asthma, in some individuals (addressing criteria 12 and 13).[161]

Limitations

This section considers limitations of the review methodology. Limitations of the evidence and evidence gaps are discussed in the section above.

The main limitation of this review was that studies of a retrospective and case-control design were included but not extracted or considered in the evidence synthesis. This decision was taken *a posteriori* because of the high number of relevant studies identified in the review initially. Prospective and cohort studies have fewer potential sources of bias and confounding than retrospective and case-control studies, hence the reason for exclusion, however, it is noted that this may potentially increase the overall risk of bias. The depriositised studies would have provided an increased evidence base. This could have been beneficial for the somewhat limited size of the evidence base for the intervention studies. Thus, inclusion of retrospective/case-control studies could be considered specifically for question 2, where less evidence was included.

This rapid review was conducted in line with the UK NSC requirements for evidence summaries, as described at https://www.gov.uk/government/publications/uk-nsc-evidence-review-process/appendix-f-requirements-for-uk-nsc-evidence-summaries. All items on the UK NSC Reporting Checklist for Evidence Summaries have been addressed in this report. A summary of the checklist, along with the page or pages where each item can be found in this report, is presented in Table 37 in Appendix 4.

Searches of multiple databases were conducted (see Appendix 1 — Search strategy). Database search terms were restricted by study design and interventions and limited to studies published since 2011. Published and well validated filters were used to limit by study design,[162-164] searches were supplemented with SLR reference list searches, and expert clinical opinion was sought on the completeness of the list of relevant records identified, which decreases the likelihood that major important studies were missed.

Included publication types

This review only included peer-reviewed journal publications and excluded publications that were not peer-reviewed and grey literature. This may have led to the exclusion of relevant evidence. However, this is an accepted methodological adjustment for a rapid review and is unlikely to miss any pivotal studies.

For question 1, publications were excluded if they only presented data allowing the calculation of test accuracy parameters. This was taken as a pragmatic approach and was unlikely to result in key screening studies being missed.

Language

Only studies published in English were included. Given that this review was focusing on evidence relevant to the UK setting, this limitation should not have led to the exclusion of any pivotal studies.

Review methodology

Articles were reviewed by a single reviewer in the first instance. A second reviewer examined all included articles, 10% of excluded articles, and any articles where there was uncertainty about inclusion. Systematic reviews were identified through a separate search and were pre-screened based on title by a single, senior reviewer. This pragmatic strategy should have minimised the risk of errors.

Articles not freely available

Searches for full-text articles were carried out at Cambridge University Library. For any paywalled articles unavailable at the Cambridge University Library, the authors were contacted to provide the full texts. Any unavailable articles were purchased (unless they were not selected for extraction based on study design, see the Methods section and below).

Risk management

Due to the high number of studies initially included in the review, retrospective and case-control studies were ultimately selected for extraction, as these study designs are generally of lower methodological quality and at a higher risk of bias and confounding.

Appendix 1 — Search strategy

Electronic databases

The search strategy included searches of the databases shown in Table 19. MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print and Embase.

Table 19. Summary of electronic database searches and dates

Database	Platform	Searched on date	Date range of search
MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print	Ovid SP	11 October 2021	1946 to 8 October 2021
Embase	Ovid SP	11 October 2021	1974 to 8 October 2021
The Cochrane Library, including: - Cochrane Database of Systematic Reviews (CDSR) - Cochrane Central Register of Controlled Trials (CENTRAL) -	Wiley Online	11 October 2021	CDSR: Issue 10 of 12, October 2021 CENTRAL: Issue 10 of 12, October 2021
Database of Abstracts of Reviews of Effects (DARE)	Centre for Reviews and Dissemination, University of York	5 December 2019	DARE: Issue 2 of 4, April 2015

Search Terms

Search terms included combinations of free text and subject headings (Medical Subject Headings [MeSH] for MEDLINE, and Emtree terms for Embase), grouped into the following categories:

- disease area: pre-eclampsia, pregnancy and hypertension
- study design: interventional and observational studies, systematic reviews and MAs
- other term group: interventions
    - screening terms (generic and specific for question 1)
    - intervention terms (for question 2)

Search terms for MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print and Embase are shown in Table 20, and search terms for the Cochrane Library databases are shown in Table 21. and search terms for DARE are shown in Table 22.

Table 20. Search strategy for MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print and Embase

Term Group	#	Search terms	Results (original)	Results (update)
Pre-eclampsia terms	1	exp pregnancy/ or pregnancy trimester, first/ or pregnancy trimester, second/ or pregnancy trimester, third/	1464975	1638243
	2	hypertension/	746203	876122

	3	1 and 2	25808	29240
	4	pre-eclampsia/ or hypertension, pregnancy-induced/ or gestosis, EPH/ or "eclampsia and preeclampsia"/	55502	75523
	5	(preeclamp$ or pre-eclamp$ or gestosis or ((gestational or pregnan$) and (tox?emi$ or hyperten$ or blood pressure or HDP))).ti,ab.	124170	151723
	6	or/3-5	143103	174833
	7	mass screening/ or prenatal diagnosis/ or maternal serum screening tests/ or Biological Markers/ or screen$.ti,ab. or (detect$ or predict$ or identif$ or diagnos$ or test$).ti. or "sensitivity and specificity"/ or (sensitiv$ or specific$ or accura$ or precis$ or predictive value$ or likelihood ratio$).ti,ab.	13707160	16555025
	8	Uterine Artery/us	0	0
	9	Pregnancy Proteins/	7856	8348
	10	Creatinine/ur	13465	14205
	11	Proteinuria/	89107	104945
	12	Uric acid/	59093	71868
	13	Urinalysis/	94771	110311
	14	((biological or serum) adj3 (marker$ or biomarker$)).ti,ab.	77295	96724
	15	(proteinuria or albuminuria or urine albumin).ti,ab.	109288	132202
	16	(urine adj (measur$ or analy$ or test$ or collect$)).ti,ab.	29342	34145
	17	urinalys$.ti,ab.	19776	24029
	18	exp creatinine urine level/	9978	12563
	19	albuminuria/	27973	33698
	20	calcium excretion/	2692	3037
Screening terms	21	(PIGF or placenta$ growth factor or tyrosine kinase or PAPP A or pregnancy-associated plasma protein A or fibronectin or (f?etal adj (cfDNA or cf DNA or cell-free DNA)) or cell-free f?etal DNA or fDNA or PP13 or placental protein 13 or PP 13 or "disintegrin and metalloproteinase 12" or ADAM12 or cystatin C or pentraxin 3 or PTX3 or P selectin or (maternal serum adj (AfP or alpha f?etoprotein or A-FP or HCG)) or free hCG or unconjugated estriol or inhibin A or activin A or estradiol or oestradiol or oestriol or estriol or human placental lactogen or hPL or f?etal h?emoglobin or extracellular HbF or sFlt-1 or soluble FMT-1 or vascular endothelial growth factor or VEGF or endoglin or seng or serum uric acid or sUA or kallikrein or albumin creatinine or SDS-PAGE or "sodium dodecyl sulfate polyacrylamide gel electrophoresis").ti,ab.	814375	933926
	22	exp estradiol/ or exp placental lactogen/ or exp Pregnancy-Specific beta 1-Glycoproteins/ or exp Pregnancy-Associated Plasma Protein-A/ or exp endoglin/ or exp vegf/ or ADAM12/ or cystatin C/ or pentraxin/ or PADGEM protein/ or hemoglobin F/	397951	449114
	23	(((f?etal or f?etus or maternal) adj blood flow) or ultraso$ or TAU or TVS or sonogra$ or pulsatility or resistance or (uterine artery adj2 (notching or ratio$)) or mean arterial pressure or peripheral waveform or (Doppler adj2 (velocimetry or uterine artery or flow velocity))).ti,ab.	2435669	2971499

	24	exp "Ultrasonography, Doppler, Pulsed"/ or exp Ultrasonography, Doppler/ or exp Doppler ultrasound/	148415	174071
	25	(maternal history or maternal risk factors or maternal age).ti,ab. or maternal age/ or Risk assessment/ or risk factors/ or medical history/	2014567	2591563
	26	or/8-25	5614187	6879365
Combined	27	7 and 26	1856711	2325668
	28	(Antiplatelet$ or aspirin or acetylsalicylic acid or dipyridamole or heparin$ or ozagrel).ti,ab. or acetylsalicylic acid/ or antithrombocytic agent/ or dipyridamole/ or Aspirin, Dipyridamole Drug Combination/ or heparin/ or Heparin, low-molecular-weight/ or ozagrel/	584875	661063
	29	(Anti-oxidant$ or antioxidant$ or vitamin$ C or ascorbic acid or vitamin$ E or alpha tocopherol or vitamin$ A or retino$ or all-trans-retino$ or palm oil$ or selenium or lycopene$ or beta carotene$ or lutein$ or xanthophyll$).ti,ab. or antioxidant/ or antioxidants/ or ascorbic acid/ or alpha tocopherol/ or selenium/ or lycopene/ or palm oil/ or red palm oil/ or beta carotene/ or retinol/ or vitamin A/ or xantophyll/ or lutein/	1058415	1273096
Intervention terms	30	((Calcium adj1 supplement$) or (calcium adj1 intake) or (calcium adj1 imbalance)).ti,ab. or Micronutrients/ or calcium balance/ or mineral balance/ or Nutritional advice.ti,ab. or nutrition/ or diet/ or dietary intake/ or food intake/ or maternal nutrition/	678885	792256
	31	(metformin or Glucophage).ti,ab. or exp metformin/ or exp hydroxymethylglutaryl coenzyme A reductase inhibitor/ or (statin$ or atorvastatin$ or pravastatin$ or bervastatin$ or cerivastatin$ or compactin$ or crilvastatin$ or dalvastatin$ or simvastatin$ or rosuvastatin$ or fluindostatin$ or glenvastatin$ or lovastatin$ or mevinolin$ or monacolin$ or pitavastatin$ or tenivastatin$ or "hydroxymethylglutaryl coenzyme A reductase" or HMGCoA).ti,ab.	272532	341072
	32	or/28-31	2457095	2902277
Interventional and observational study terms	33	exp Randomized Controlled Trials as Topic/	276001	365004
	34	exp Randomized Controlled Trial/	999342	1227163
	35	exp Random Allocation/	177167	198185
	36	exp Randomization/	177167	198185
	37	exp Double Blind Method/	304410	355978
	38	exp Single Blind Method/	59231	74937
	39	exp Single Blind Procedure/	33280	43953
	40	exp Double Blind Procedure/	156011	188444
	41	exp Crossover Procedure/	57554	68330
	42	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	378739	439145
	43	exp Clinical Trial/	2162905	2548150
	44	Clinical trial, phase i.pt.	18474	22431
	45	Clinical trial, phase ii.pt.	29822	35959
	46	Clinical trial, phase iii.pt.	14376	19192
	47	Clinical trial, phase iv.pt.	1613	2195
	48	exp Phase 1 Clinical Trial/ or exp Clinical trial, phase I/	67957	88929
	49	exp Phase 2 Clinical Trial/ or exp Clinical trial, phase II/	99162	127864

	50	exp Phase 3 Clinical Trial/ or exp Clinical trial, phase III/	51225	75806
	51	exp Phase 4 Clinical Trial/ or exp Clinical trial, phase IV/	4784	6681
	52	Controlled clinical trial.pt.	92771	94451
	53	Randomized controlled trial.pt.	472059	545909
	54	Multicenter study.pt.	242022	305118
	55	Clinical trial.pt.	513459	531367
	56	exp Clinical Trials as Topic/	602375	734676
	57	trial$.ti.	598810	779039
	58	(clinical adj trial$).tw.	772931	1005513
	59	exp Placebos/	361659	410655
	60	exp Placebo/	327507	372009
	61	placebo$.tw.	481925	561738
	62	randomly allocated.tw.	56639	71528
	63	(allocated adj2 random$).tw.	63396	79180
	64	random allocation.tw.	3372	4051
	65	random assignment.tw.	4819	5628
	66	randomized.ti,ab.	1118480	1418192
	67	randomised.ti,ab.	226940	284046
	68	randomisation.tw.	18853	25139
	69	randomization.tw.	62993	84314
	70	randomly.ti,ab.	697587	856363
	71	RCT.tw.	47700	69154
	72	Open-label trial$.tw.	8372	10538
	73	Open-label stud$.tw.	19434	23970
	74	Non-blinded stud$.tw.	283	331
	75	exp Cohort Studies/	2224847	2981084
	76	exp Cohort Analysis/	2224847	2981084
	77	cohort analy$.tw.	16945	24783
	78	(cohort adj (study or studies)).tw.	405557	610076
	79	exp Cross-sectional studies/	558169	829116
	80	(cross-sectional adj (study or studies)).tw.	308574	466615
	81	exp Longitudinal Studies/ or exp Longitudinal study/	238654	312654
	82	Longitudinal.tw.	495129	648024
	83	exp Follow-Up Studies/	1942472	2418546
	84	exp Follow-Up/	1339586	1746136
	85	(follow up adj (study or studies)).tw.	104350	119325
	86	exp Prospective Studies/ or exp Prospective study/	976370	1314291
	87	(Prospective adj (study or studies)).tw.	389528	470345
	88	(evaluation adj (study or studies)).tw.	11293	14198
	89	exp Retrospective Studies/ or exp Retrospective study/	1435027	2091651
	90	retrospective$.ti,ab.	1660459	2279307
	91	(chart adj3 review).tw.	102382	138071
	92	exp Observational studies/ or exp Observational study/	213889	358989
	93	(observational adj (study or studies)).tw.	222522	329260
	94	((single arm or single-arm) adj3 (study or studies or trial$)).tw.	12444	21251
	95	or/33-94	9276568	11756179

	96	("Conference Abstract" or "Conference Review" or comment or letter or editorial or note or case reports).pt.	8992372	10987979
	97	(case stud$ or case report$).ti.	586924	731890
Exclusion terms	98	Letter/ or historical article/ or case study/	4113297	4710098
	99	exp Animals/ not exp Humans/	8868082	9742378
	100	or/96-99	18106021	20962170
	101	95 not 100	7184751	8997992
	102	limit 101 to yr=2011-current	3300365	2289227
	103	6 and 27 and 102	3332	3042
Combined	104	6 and 32 and 102	1996	1645
	105	103 or 104	5011	4341
Total (interventional and observational)	106	remove duplicates from 105	3480	3092
	107	Meta-Analysis as Topic/	42835	55006
	108	meta analy$.tw.	315383	485188
	109	metaanaly$.tw.	10609	13187
	110	exp Meta-Analysis/	248808	370964
	111	(systematic adj (review$1 or overview$1)).tw.	294581	487741
	112	exp Review Literature as Topic/	223154	254838
	113	cancerlit.ab.	1346	1375
	114	cochrane.ab.	151122	237241
	115	embase.ab.	159654	263030
	116	(psychlit or psyclit).ab.	1903	1921
	117	(psychinfo or psycinfo).ab.	49480	88411
	118	(cinahl or cinhal).ab.	48413	76522
	119	science citation index.ab.	6146	7264
	120	bids.ab.	1075	1310
Systematic reviews and MAs	121	cancerlit.ab.	1346	1375
	122	reference list$.ab.	34553	43197
	123	bibliograph$.ab.	36804	45397
	124	hand-search$.ab.	13475	16978
	125	relevant journals.ab.	2374	2752
	126	manual search$.ab.	8536	11175
	127	or/107-126	873104	1211076
	128	selection criteria.ab.	61559	73075
	129	data extraction.ab.	38346	56919
	130	128 or 129	95693	125102
	131	Review/ or review.pt.	4928554	5766622
	132	130 and 131	54937	63285
	133	Comment/	742589	932400
	134	Letter/ or letter.pt.	2060606	2355095
	135	Editorial/ or editorial.pt.	1106525	1330440
	136	animal/	7692754	8468902
	137	human/	36383931	42424981

	138	136 not (136 and 137)	5503193	5985677
	139	or/133-135,138	8775808	9836525
	140	127 or 132	881468	1220955
	141	140 not 139	777023	1097744
	142	limit 141 to yr=2011-current	497958	403545
Total (SLRs	143	6 and (27 or 32) and 142	935	771
and MAs)	144	Remove duplicates from 143	653	557

Table 21. Search strategy for the Cochrane Library Databases (Searched via the Wiley Online platform)

Term Group	#	Search terms	Results (original)	Results (update)
Pre-eclampsia terms	1	[mh pregnancy] or [mh ^"pregnancy trimester, first"] or [mh ^"pregnancy trimester, second"] or [mh ^"pregnancy trimester, third"]	8029	23282
	2	[mh ^hypertension]	16137	18127
	3	#1 and #2	138	361
	4	[mh ^"pre-eclampsia"] or [mh ^"hypertension, pregnancy-induced"] or [mh ^"gestosis, EPH"] or [mh ^"eclampsia and preeclampsia"]	862	1143
	5	(preeclamp* or "pre-eclamp*" or gestosis or ((gestational or pregnan*) and (toxemi* or hyperten* or blood pressure or HDP))):ti,ab	3980	8793
	6	{or #3-#5}	4056	8915
	7	[mh ^"mass screening"] or [mh ^"prenatal diagnosis"] or [mh ^"maternal serum screening tests"] or [mh ^"Biological Markers"] or [mh ^"sensitivity and specificity"] or (detect* or predict* or identif* or diagnos* or test*):ti or (screen* or sensitive* or specific* or accura* or precis* or "predictive value*" or "likelihood ratio*"):ti,ab	218094	308545
Screening terms	8	[mh ^"Pregnancy Proteins"]	65	63
	9	[mh ^Creatinine/ur]	983	1035
	10	[mh ^Proteinuria]	980	1053
	11	[mh ^"Uric acid"]	1045	1179
	12	[mh ^Urinalysis]	223	244
	13	((biological or serum) near3 marker* or (biological or serum) near3 biomarker*):ti,ab	117902	175405
	14	(proteinuria or albuminuria or "urine albumin"):ti,ab	4084	6447
	15	(urine next (measure* or analy* or test* or collect*)):ti,ab	2394	4088
	16	urinalys*:ti,ab	1189	2795
	17	[mh ^albuminuria]	1208	1331
	18	(PIGF or "placenta* growth factor" or "tyrosine kinase" or "PAPP A" or "pregnancy-associated plasma protein A" or fibronectin or (fetal next (cfDNA or cf DNA or cell-free DNA)) or fDNA or PP13 or "placental protein 13" or "PP 13" or "disintegrin and metalloproteinase 12" or ADAM12 or "cystatin C" or "pentraxin 3" or PTX3 or "P selectin" or ("maternal serum" next (AfP or "alpha fetoprotein" or A-FP or HCG)) or "free hCG" or "unconjugated estriol" or "inhibin A" or "activin A" or	16759	

		estradiol or oestradiol or oestriol or estriol or "human placental lactogen" or hPL or "fetal hemoglobin" or "extracellular HbF" or sFlt-1 or "soluble FMT-1" or "vascular endothelial growth factor" or VEGF or endoglin or seng or "serum uric acid" or sUA or kallikrein or "albumin creatinine" or SDS-PAGE or "sodium dodecyl sulfate polyacrylamide gel electrophoresis"):ti,ab		
	19	[mh estradiol] or [mh "placental lactogen"] or [mh "Pregnancy-Specific beta 1-Glycoproteins"] or [mh "Pregnancy-Associated Plasma Protein-A"] or [mh endoglin] or [mh vegf] or [mh ^ADAM12] or [mh ^"cystatin C"] or [mh ^pentraxin] or [mh ^"PADGEM protein"] or [mh ^"hemoglobin F"]	5428	6105
	20	(((fetal or fetus or maternal) next "blood flow") or ultraso* or TAU or TVS or sonogram* or pulsatility or resistance or ("uterine artery" near2 notching) or ("uterine artery" near2 ratio*) or "mean arterial pressure" or "peripheral waveform analysis" (Doppler near2 velocimetry or Doppler near 2 "uterine artery" or Doppler near2 "flow velocity")):ti,ab	165670	243940
	21	[mh "Ultrasonography, Doppler, Pulsed"] or [mh "Ultrasonography, Doppler"] or [mh "Doppler ultrasound"]	2819	2923
	22	(maternal history or maternal risk factors or maternal age):ti,ab or [mh ^"maternal age"] or [mh ^"Risk assessment"] or [mh ^"risk factors"] or [mh ^"medical history"]	33538	39371
	23	{or #8-#22}	294194	425379
	24	#7 and #23	76992	106963
Intervention terms	25	(Antiplatelet* or aspirin or "acetylsalicylic acid" or dipyridamole or heparin* or ozagrel):ti,ab or [mh "^acetylsalicylic acid"] or [mh ^"antithrombocytic agent"] or [mh ^dipyridamole] or [mh ^"Aspirin, Dipyridamole Drug Combination"] or [mh ^heparin] or [mh ^"Heparin, low-molecular-weight"] or [mh ^ozagrel]	22643	30038
	26	(Anti-oxidant* or antioxidant* or "vitamin* C" or "ascorbic acid" or "vitamin* E" or "alpha tocopherol" or "vitamin* A" or retino* or all-trans-retino* or "palm oil*" or selenium or lycopene* or "beta carotene*" or lutein* or xanthophyll*):ti,ab or [mh ^antioxidants] or [mh ^"ascorbic acid"] or [mh ^"alpha tocopherol"] or [mh ^selenium] or [mh ^"palm oil"] or [mh ^"beta carotene"] or [mh ^retinol] or [mh ^"vitamin A"] or [mh lutein]	24236	34354
	27	((Calcium near11 supplement*) or (calcium near1 intake) or (calcium near1 imbalance)):ti,ab or [mh ^Micronutrients] or [mh ^"calcium balance"] or [mh ^"mineral balance"] or "Nutritional advice":ti,ab or [mh ^nutrition] or [mh ^diet] or [mh ^"dietary intake"] or [mh ^"food intake"] or [mh ^"maternal nutrition"]	93865	137897
	28	(metformin or Glucophage):ti,ab or [mh metformin] or [mh "hydroxymethylglutaryl coenzyme A reductase inhibitor"] or (statin* or atorvastatin* or pravastatin* or bervastatin* or cerivastatin* or compactin* or crilvastatin* or dalvastatin* or simvastatin* or rosuvastatin* or fluindostatin* or glenvastatin* or lovastatin* or mevinolin* or monacolin* or pitavastatin* or tenivastatin* or "hydroxymethylglutaryl coenzyme A reductase" or HMGCoA):ti,ab	18930	28041

	29	{or #25-#28}	147028	211760
Exclusions	30	("Conference review" or "conference abstract"):pt	124087	182954
Combined	31	(#6 and (#24 or #29)) not #30	1433	3258
	32	#31 with Cochrane Library publication date from Jan 2011 to Dec 2018, in Cochrane Reviews	95	837
	33	#31 with Publication Year from 2011 to 2018, in Trials	616	48

Table 22. Search strategy for DARE (Searched via the CRD website)

Term Group	#	Search terms	Results (original)
Pre-eclampsia terms	1	MeSH DESCRIPTOR pregnancy	798
	2	MeSH DESCRIPTOR pregnancy trimester, first	20
	3	MeSH DESCRIPTOR pregnancy trimester, second	14
	4	MeSH DESCRIPTOR pregnancy trimester, third	3
	5	MeSH DESCRIPTOR hypertension	256
	6	1 or 2 or 3 or 4	798
	7	5 and 6	2
	8	MeSH DESCRIPTOR Pre-eclampsia	51
	9	MeSH DESCRIPTOR hypertension, pregnancy-induced	12
	10	MeSH DESCRIPTOR gestosis, EPH	0
	11	MeSH DESCRIPTOR "eclampsia and preeclampsia"	0
	12	preeclamp* or pre-eclamp* or gestosis in Any field	87
	13	gestational or pregnan* in Any field	1,475
	14	toxemi* or toxaemi* or hyperten* or blood pressure in Any field	883
	15	13 and 14	68
	16	7 or 8 or 9 or 10 or 11 or 12 or 15 in DARE in 2011 to 2018	127

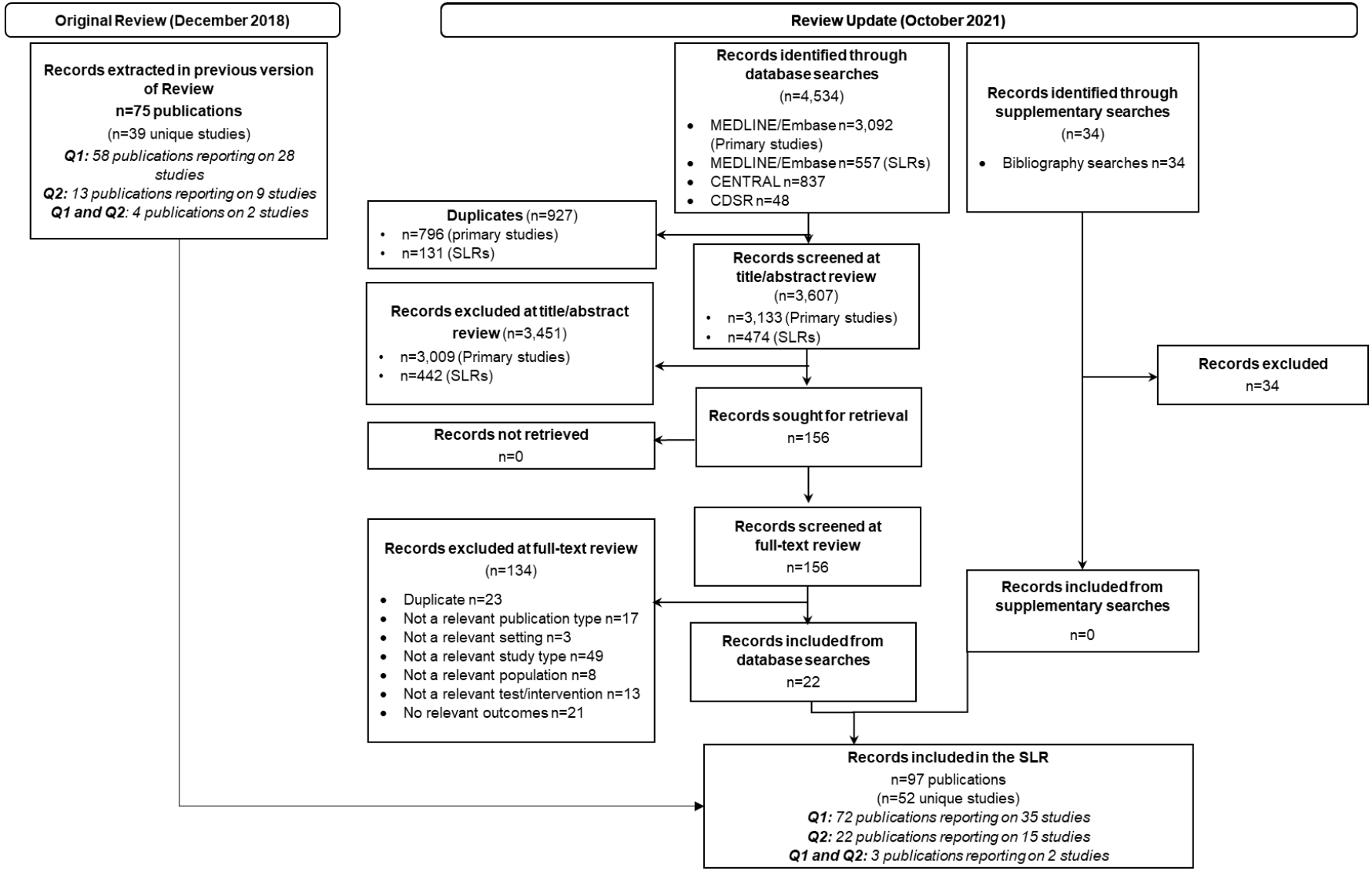
Results for interventional and observational studies (line 105 in Table 20, line 33 in Table 21 and line 16 in Table 22) and results for SLRs/MAs (line 144 in Table 20 and line 32 in Table 21) were imported into EndNote separately and de-duplicated.

Appendix 2 — Included and excluded studies

PRISMA flowchart

Figure 1 summarises the volume of publications included and excluded at each stage of the review. A total of 97 publications representing 52 unique studies were judged to be relevant to one or more review questions and were extracted and synthesised. Publications that were included or excluded after the review of full-text articles are detailed below.

Figure 1. Summary of publications included and excluded at each stage of the review



Publications included after review of full-text articles

The publications included after review of full-texts are summarised in Table 23 below.
Some studies were prioritised for extraction and data synthesis: after assessing the overall volume of evidence identified in the review, studies of prospective design (excluding nested case-control studies within prospective cohort studies) and SLRs were prioritised.

Publications not selected for extraction and data synthesis are detailed in Table 24 below.

Table 23. Summary of publications included after review of full-text articles, and the question(s) each publication was identified as being relevant to

Study	Question	The test (Q1)/intervention (Q2)	Comments
Studies selected for extraction			
Allen 2018[73]	Q1	SBP_{AO}	
Akolekar 2011[165]	Q1	Maternal factors, UtA PI, MAP, PAPP-A, PlGF, PPA-13, inhibin-A, activin-A, sEng, pentraxin-3, p-selectin	London Cohorts
Akolekar 2013[121]	Q1	MAP, UtA PI, PlGF, PAPP-A	London Cohorts
Al-Amin 2018[79]	Q1	NICE guidelines, ACOG guidelines, FMF algorithm (maternal factors, MAP, UtA-PI)	
Ayala 2013[141]	Q2	Aspirin (100mg/day)	
Baweja 2011[81]	Q1	Median spot urinary ACR	
Bella 2020[142]	Q2	Standard high-risk care + enoxaparin 40 mg SC (dose adjusted to 60 mg if maternal weight was above 90 kg)	
Boucoiran 2013a[86]	Q1	Maternal characteristics, PlGF	
Boucoiran 2013b[87]	Q1	PlGf, Slft1:PlGF ratio, Inhibin A	
Boutin 2018a[166]	Q1	PAPP-A	GOS Study
Boutin 2018b[131]	Q1	Maternal factors	GOS Study
Boutin 2018c[132]	Q1	PlGF	GOS Study
Boutin 2021a[88]	Q1	MAP, PlGF, AFP, Uta-PI	GOS study
Boutin 2021b[89]	Q1	FMF algorithm	GOS study
Caradeux 2013[91]	Q1	Maternal factors (age, weight, SBP, DBP, MAP), maternal medical history/characteristics (parity, history of PE, hypertension, diabetes mellitus, log UtA-PI, history of preterm labour)	
Carter 2015[110]	Q1	UtA-PI, UtA-RI, BN	
Chiswick 2015[143]	Q2	Metformin 500 mg (started at 1 500 mg tablet escalated by 1 tablet a day each week over 5 weeks, to reach either the maximum tolerable dose or the maximum permitted dose of 2500 mg, whichever was lower)	
Costantine 2016[144]	Q2	Pravastatin 10mg	
Costantine 2021[167]	Q2	Pravastatin 10 mg	
Cruz-Lemini 2021[145]	Q2	LMWH or unfractionated heparin (with or without LDA)	
Demers 2018[85]	Q1	UtA-PI	GOS Study

Study	Question	The test (Q1)/intervention (Q2)	Comments
Di Lorenzo 2012[94]	Q1	Maternal factors (age, BMI, ethnicity, parity, conception, smoking during pregnancy, diabetes mellitus, sex of child, chronic hypertension), biomarkers (log free β-hCG, log PAPP-A, log PlGF, log PP-13), UtA variables (BN, UtA-PI)	
Di Martino 2019[95]	Q1	FMF algorithm; BCNatal algorithm	
Dobert 2021[147]	Q2	Pravastatin 20 mg	
El-Achi 2021[168]	Q2	Aspirin (150mg/day)	Cohort overlaps with Park 2021
Erkamp 2020[99]	Q1	Maternal characteristic, MAP	
Francisco 2017[122]	Q1	MAP, UtA PI, PlGF, PAPP-A	London Cohorts
Gabbay-Benziv 2016[118]	Q1	Cardiovascular risk factors, metabolic risk factors, personal risk factors	
Gallo 2016[34]	Q1	MAP, UtA PI, PlGF, sFlt-1	London Cohorts
Gallo 2014[123]	Q1	MAP	London Cohorts
Gasse 2018[84]	Q1	MAP	GOS Study
Goetzinger 2013[109]	Q1	Maternal factors, ADAM12, PAPP-A, UtA Doppler	
Goetzinger 2014[112]	Q1	Risk-based scoring system	Cohort overlaps with Goetzinger 2013
Goto 2021[98]	Q1	Maternal characteristics, MAP, UtA-PI, PlGF	
Hafner 2013[83]	Q1	PBVI, PQ, UtA-PI, BN, PAPP-A	
Honigberg 2016[117]	Q1	PlGF, sFlt-1	
Kanat-Pektas 2014[108]	Q1	MPV, PAPP-A	
Kenny 2014[72]	Q1	High fruit intake, BMI, MAP, Ut-RI, PlGF, BMI, tissue inhibitor of metalloproteinase 1, interleukin receptor antagonist/PlGF, cystatin C/PlGF	SCOPE
Maymon 2017[93]	Q1	Maternal prior risk factors, MAP, UtA-PI, PlGF, PAPP-A, PP13	
Mazer Zumaeta 2020[75]	Q1	Maternal factors, MAP, Uta-PI, PlGF, PAPP-A	London Cohorts
McElrath 2012[169]	Q1	PlGF, sFlt-1	
McLaughlin 2021[148]	Q2	LMWH (40 mg per day enoxaparin) + aspirin (women at risk of severe placental dysfunction received 162 mg LDA nightly)	
Meiri 2014[92]	Q1 and Q2	Risk factors, PP13, MAP; Aspirin (75mg/day)	
Mendoza 2021a[104]	Q1	Risk factors, MAP, UtA-PI, PlGF, PAPP-A (measured between 8^{+0} and 10^{+6} weeks and 11^{+0} and 13^{+6} weeks)	Cohort overlaps with Serra 2020
Mendoza 2021b[105]	Q1	Risk factors, MAP, UtA-PI, PlGF	Cohort overlaps with Serra 2020
Metcalfe 2014[90]	Q1	Risk factors, AFP, hCG, Inhibin A, uE_3, PAPP-A	
Murtoniemi 2018[170]	Q2	Aspirin (100 mg/day)	PREDO
Myatt 2012a[113]	Q1	Uterine artery notch, RI, PI	
Myatt 2012b[114]	Q1	Uterine artery notch, RI, PI	Cohort overlaps with Myatt 2012a
Myatt 2013[171]	Q1	Uterine artery notch, RI, PI	Cohort overlaps with Myatt 2012a
Myers 2013a[133]	Q1	PlGF, sEng, clinical risk, UtA Doppler	SCOPE
Myers 2013b[119]	Q1	PlGF, sEng, clinical risk, UtA Doppler	**SCOPE**
North 2011[172]	Q1	Maternal factors, UtA RI	SCOPE
Odibo 2011a[115]	Q1	VI, VFI	

Study	Question	The test (Q1)/intervention (Q2)	Comments
Odibo 2011b[116]	Q1	UtA-PI	
O'Gorman 2017a[125]	Q1	FMF (MAP, UtA PI, PlGF), NICE risk factors, ACOG risk factors	London Cohorts
O'Gorman 2017b[124]	Q1	MAP, UtA PI, PlGF, PAPP-A	London Cohorts
O'Gorman 2016a[126]	Q1	UtA PI	London Cohorts
O'Gorman 2016b[18]	Q2	Aspirin (150 mg/day)	ASPRE
O'Gorman 2016c[58]	Q1	MAP, UtA PI, PlGF, PAPP-A	London Cohorts
Park 2021[150]	Q2	Aspirin (150mg/day)	
Poon 2012[78]	Q1	MAP	London Cohorts
Poon 2017[173]	Q2	Aspirin (150 mg/day)	ASPRE
Poon 2018[174]	Q2	Aspirin (150 mg/day)	ASPRE (erratum)
Poon 2020[77]	Q1	MF, MAP, UtA-PI, PlGF, inhibin-A	London Cohorts
Rolnik 2017a[70]	Q1 and Q2	Maternal factors, MAP, UtA-PI, PAPP-A, PlGF (Q1) Aspirin (150 mg/day) (Q2)	ASPRE
Rolnik 2017b[175]	Q2	Aspirin (150 mg/day)	ASPRE
Sandström 2019[106]	Q1	Pre-specified variables model, backwards selection model, random forest model, risk classification based on NICE guidelines binary decision rule	
Scazzocchio 2013[101]	Q1	Maternal characteristics, PAPP-A, fβ-hCG, MAP, UtA-PI	
Scazzocchio 2017a[102]	Q1	Maternal characteristics, MAP, UtA Doppler, PAPP-A	Cohort overlaps with Scazzocchio 2013
Schneuer 2012a[80]	Q1	PP-13	
Schneuer 2012b[176]	Q1	PP-13	Erratum to Schneuer 2012a
Schneuer 2013[82]	Q1	Maternal characteristics	Cohort overlaps with Schneuer 2012a
Serra 2020[103]	Q1	Risk factors, MAP, UtA-P, PlGF	
Skrastad 2015[100]	Q1	FMF algorithm (maternal factors, UtA-PI, MAP, PAPP-A, PlGF), PREDICTOR prior algorithm (BMI, ethnicity, parity, family history of PE, chronic hypertension, MAP), PREDICTOR posterior algorithm (prior risk, MAP, UtA-PI, PlGF, PAPP-A)	
Sonek 2018[111]	Q1	PAPP-A, PlGF, AFP, UtA-PI, MAP, EPV	
Sovio 2019a[76]	Q1	NICE guidelines, Risk score derived from the ASPRE trial's prior history model (PGAPE algorithm), maternal history (PGAPE) algorithm	POP study
Stanescu 2018[152]	Q2	Asprin (150mg until 32 or 36 weeks)	
Syngelaki 2016[153]	Q2	Metformin (1g/day) increasing to a maximum dose of 5g/day	
Takahashi 2012[97]	Q1	mNDI, mPI-SDS, mRI-SDS, BN	
Tan 2018a[56]	Q1	Maternal factors, MAP, UtA-PI, PAPP-A, PlGF, NICE guidelines	London Cohorts
Tan 2018b[136]	Q1 and Q2	Maternal factors, MAP, UtA-PI, PlGF (Q1) Aspirin (150 mg/day) (Q2)	London Cohorts and ASPRE
Tan 2018c[69]	Q1	Maternal factors, MAP, UtA-PI, PAPP-A, PlGF	London Cohorts
Tan 2017[135]	Q1	Maternal factors, MAP, UtA PI, PAPP-A, PlGF	London Cohorts
Tapp 2020[146]	Q2	160 mg aspirin daily	

Study	Question	The test (Q1)/intervention (Q2)	Comments
Tsiakkas 2016a[127]	Q1	Maternal factors, sFlt-1	London Cohorts
Tsiakkas 2016b[71]	Q1	maternal factors, sFlt-1	Cohort overlaps with London Cohorts
Villa 2013[151]	Q2	Aspirin (100 mg/day)	PREDO
Wright 2019[128]	Q1	Maternal factors, MAP, UtA PI, PlGF	London Cohorts
Wright 2019[177]	Q2	Aspirin (150 mg/day)	ASPRE
Wright 2018[156]	Q2	Aspirin (150 mg/day)	ASPRE
Wright 2017[154]	Q2	Aspirin (150 mg/day)	ASPRE
Wright 2016[59]	Q1	Maternal factors, MAP, UtA PI, PlGF	London Cohorts
Wright 2015[32]	Q1	Maternal factors, serum-free β-hCG	London Cohorts
Wright 2012[33]	Q1	Maternal factors, MAP, UtA PI	London Cohorts
Youssef 2011[96]	Q1	PlGF, sFlt-1, NGAL	
Yucel 2016[107]	Q1	At least one or two abnormal parameter: UtA-PI >90th centile, PV <10th centile, PAPP-A <10th centile	

Table 24. Studies de-prioritised and not extracted (due to study design)

Studies not selected for extraction		
Study	**Question**	**Reason for de-prioritisation**
Al-Rubaie 2020[178]	Q1	Restrospective
Anand 2016[179]	Q1	Retrospective
Anand 2015[180]	Q1	Retrospective
Bahado-Singh 2015[181]	Q1	Retrospective; case-control
Bahado-Singh 2013[182]	Q1	Retrospective; case-control
Bahado-Singh 2012[183]	Q1	Retrospective; case-control
Benovska 2018[184]	Q1	Retrospective; case-control
Bolin 2012[185]	Q1	Retrospective; case-control
Brunelli 2020[186]	Q1	Retrospective
Caliskan 2021[187]	Q1	Retrospective
Ceylan 2014[188]	Q1	Case-control
Cohen 2014[189]	Q1	Retrospective
Cordisco 2021[190]	Q1	Retrospective
Crovetto 2015a[191]	Q1	Case-control
Crovetto 2015b[192]	Q1	Case-control
Crovetto 2014[193]	Q1	Case-control
D'Antonio 2013a[194]	Q1	Retrospective
D'Antonio 2013b[195]	Q1	Retrospective
de la Serna Gamboa 2019[196]	Q1 and Q2	Retrospective
Erez 2017[197]	Q1	Retrospective; case-control
Giguere 2015[198]	Q1	Case-control
Gris 2011[199]	Q2	Included in Cruz-Lemini 2021 SLR
Groom 2017[200]	Q2	Included in Cruz-Lemini 2021 SLR
Groom 2016[201]	Q2	Included in Cruz-Lemini 2021 SLR
Guy 2021[202]	Q1 and Q2	Retrospective
Haddad 2016[203]	Q2	Included in Cruz-Lemini 2021 SLR

Hannaford 2015[204]	Q1	Retrospective
Hromadnikova 2017[205]	Q1	Retrospective
Karampas 2016[206]	Q1	Case-control
Keikkala 2013[207]	Q1	Case-control
Khalil 2012[74]	Q1	Case-control
Khan 2020[208]	Q1	Retrospective
Kingdom 2011[209]	Q2	Included in Cruz-Lemini 2021 SLR
Kirbas 2015[210]	Q1	Retrospective; case-control
Koninger 2018[211]	Q1	Retrospective; case-control
Kose 2020[212]	Q1	Restrospective
Kuc 2013[213]	Q1	Retrospective; case-control
Kuessel 2016[214]	Q1	Retrospective; case-control
Mannaerts 2017[215]	Q1	Retrospective
Mansilla 2018[216]	Q1	Retrospective
Maric 2020[217]	Q1	Retrospective
Martinelli 2012[218]	Q2	Included in Cruz-Lemini 2021 SLR
Mayer-Pickel 2021[219]	Q1	Case-control
McElrath 2012[169]	Q1	Case-control
Monckeberg 2020[220]	Q1 and Q2	Retrospective
Mone 2019[221]	Q2	Retrospective
Moore 2015[222]	Q2	Retrospective
Nanda 2011[223]	Q1	Retrospective; case-control
Nevalainen 2017[224]	Q1	Retrospective
Noel 2021[225]	Q1	Retrospective
Odibo 2015[149]	Q2	Case-control
Odibo 2013[226]	Q1	Case-control
Olsen 2012[227]	Q1	Retrospective
Orosz 2019[228]	Q1	Case-control
Ozdamar 2014[229]	Q1	Retrospective; case-control
Papantoniou 2013[230]	Q1	Retrospective; case-control
Papastefanou 2018[231]	Q1	Case-control
Park 2015[232]	Q1	Retrospective
Park 2014[233]	Q2	Retrospective
Park 2013[234]	Q2	Retrospective
Parra-Cordero 2013[235]	Q1	Retrospective; case-control
Pihl 2020[236]	Q1	Restrospective, case-control
Sammar 2017[237]	Q1	Retrospective
Schaller 2020[238]	Q1	Retrospective
Sepulveda-Martinez 2017[239]	Q1	Retrospective; case-control
Siljee 2013[240]	Q1	Retrospective; case-control
Sovio 2019b[241]	Q1	Case-control
Tarca 2019[242]	Q1	Case-control
Tarca 2021a[243]	Q1	Case-control
Tarca 2021b[244]	Q1	Retrospective; case-control
Teixeira 2014[245]	Q1	Retrospective
Teoh 2019[246]	Q1	Case-control
Tramontana 2018[247]	Q1	Retrospective; case-control

Verghese 2012[248]	Q1	Retrospective; case-control
Villa 2013[249]	Q1	Retrospective; case-control
Winger 2018[250]	Q1	Retrospective
Yliniemi 2015[251]	Q1	Retrospective

Table 25. Unavailable publications not reviewed for eligibility at full text stage

Reference
Alahakoon TI, Zhang W, Trudinger BJ, et al. Discordant clinical presentations of preeclampsia and intrauterine fetal growth restriction with similar pro-and anti-angiogenic profiles. Journal of Maternal-Fetal and Neonatal Medicine 2014;27:1854-1859.
Andersen LB, Frederiksen-Moller B, Work Havelund K, et al. Diagnosis of preeclampsia with soluble Fms-like tyrosine kinase 1/placental growth factor ratio: An inter-assay comparison. Journal of the American Society of Hypertension 2015;9:86-96.
Anderson UD, Olsson MG, Rutardottir S. Fetal haemoglobin and alpha1-microglobulin as first- and early second-trimester predictive biomarkers for preeclampsia. American Journal of Obstetrics and Gynaecology 2011;204:520.e1
Arcangeli T, Giorgetta F, Farina A, et al. Significance of uteroplacental Doppler at midtrimester in patients with favourable obstetric history. Journal of Maternal-Fetal and Neonatal Medicine 2013;26:299-302.
Birdir C, Janssen K, Stanescu A. Maternal serum copeptin, MR-proANP and procalcitonin levels at 11-13 weeks gestation inthe prediction of preeclampsia. Archives of Gynecology and Obstetrics 2015;292:1033-1042
Cantu JA, Jauk VR, Owen J, et al. Is low-dose aspirin therapy to prevent preeclampsia more efficacious in non-obese women or when initiated early in pregnancy? Journal of Maternal-Fetal and Neonatal Medicine 2015;28:1128-1132.
Deurloo KL, Linskens IH, Heymans MW, et al. ADAM12s and PP13 as first trimester screening markers for adverse pregnancy outcome. Clinical Chemistry and Laboratory Medicine 2013;51:1279-1284.
Engels T, Pape J, Schoofs K, et al. Automated measurement of sFlt1, PlGF and sFlt1/PlGF ratio in differential diagnosis of hypertensive pregnancy disorders. Hypertension in Pregnancy 2013;32:459-473.
Inan C, Varol FG, Erzincan SG, et al. Use of prokineticin-1 (PROK1), pregnancy-associated plasma protein A (PAPP-A) and PROK1/PAPP-A ratio to predict adverse pregnancy outcomes in the first trimester: a prospective study. Journal of Maternal-Fetal and Neonatal Medicine 2018;31:2685-2692.
Karahasanovic A, Sorensen S, Nilas L. First trimester pregnancy associated plasma protein A and human chorionic gonadotropin beta in early and late pre-eclampsia. Clinical Chemistry and Laboratory Medicine 2014;52:521-525.
Lakovschek IC, Csapo B, Kolovetsiou-Kreiner V, et al. Comparison of two-risk assessment algorithms for preeclampsia in first trimester with consecutive intake of low-dose aspirin in the high-risk group-an observational study. Journal of Maternal-Fetal and Neonatal Medicine 2018;31:549-552.
Lan PG, Gillin AG, Pelosi M, et al. Effect of early use of low-dose aspirin therapy on late-onset preeclampsia. Journal of Maternal-Fetal and Neonatal Medicine 2018:1-6.
Moon M, Odibo A. First-trimester screening for preeclampsia: Impact of maternal parity on modeling and screening effectiveness. Journal of Maternal-Fetal and Neonatal Medicine 2015;28:2028-2033.
Mula R, Meler E, Albaiges G, et al. Strategies for the prediction of late preeclampsia. Journal of Maternal-Fetal and Neonatal Medicine 2018:1-5.
Quattrocchi T, Baviera G, Pochiero T, et al. Maternal serum PAPP-A as an early marker of obstetric complications? Fetal Diagnosis and Therapy 2015;37:33-36.
Risch M, Purde MT, Baumann M, et al. High first-trimester maternal blood cystatin C levels despite normal serum creatinine predict pre-eclampsia in singleton pregnancies. Scandinavian Journal of Clinical and Laboratory Investigation 2017;77:634-643.
Wolak T, Sergienko R, Wiznitzer A, et al. High uric acid level during the first 20 weeks of pregnancy is associated with higher risk for gestational diabetes mellitus and mild preeclampsia. Hypertension in Pregnancy 2012;31:307-15.
Yefet E, Kuzmin O, Schwartz N, et al. Predictive Value of Second-Trimester Biomarkers and Maternal Features for Adverse Pregnancy Outcomes. Fetal Diagnosis and Therapy 2017;42:285-293.

Publications excluded after review of full-text articles

Of the 437 publications included after the review of titles and abstracts, 313 were ultimately judged not to be relevant to this review. These publications, along with reasons for exclusion, are listed in Table 26.

Table 26. Publications excluded after review of full-text articles

Reference	Reason for exclusion
Abd El-Latif M, Azzam H, Othman M, et al. Assessment of annexin A5 and annexin A2 levels as biomarkers for pre-eclampsia: A pilot study. Pregnancy Hypertension 2017;8:65-69.	Not a relevant setting
Abdi F, Aghaie Z, Rahnemaie S, et al. A systematic review of first trimester biochemical and molecular predictive tests for preeclampsia. Current Hypertension Reviews 2018;14:21-28	Not a relevant study or publication type
Abramovici A, Jauk V, Wetta L, et al. Low-dose aspirin, smoking status, and the risk of spontaneous pre-term birth. American Journal of Perinatology 2015;32:445-450.	Not in a relevant population
Adali E, Kurdoglu M, Adali F, et al. The relationship between brachial artery flow-mediated dilatation, high sensitivity C-reactive protein, and uterine artery doppler velocimetry in women with pre-eclampsia. Journal of clinical ultrasound : JCU 2011;39:191-197.	No relevant results
Adekola H, Romero R, Chaemsaithong P, et al. Endocan, a putative endothelial cell marker, is elevated in preeclampsia, decreased in acute pyelonephritis, and unchanged in other obstetrical syndromes. Journal of Maternal-Fetal and Neonatal Medicine 2015;28:1621-1632.	Not a relevant intervention
Adkins K, Allshouse AA, Metz TD, et al. Impact of aspirin on fetal growth in diabetic pregnancies according to White classification. American Journal of Obstetrics and Gynecology 2017;217:465.e1-465.e5.	Not in a relevant population
Afshani N, Moustaqim-Barrette A, Biccard M, et al. Utility of B-type natriuretic peptides in preeclampsia: a systematic review. International Journal of Obstetric Anesthesia 2013;22:96-103	Not a relevant study or publication type
Aggarwal S, Sunderland N, Thornton C, et al. A longitudinal analysis of angiotensin II type 1 receptor antibody and angiogenic markers in pregnancy. American Journal of Obstetrics and Gynecology 2017;216:170.e1-170.e8.	No relevant results
Agrawal S, Cerdeira AS, Redman C, et al. Meta-analysis and systematic review to assess the role of soluble FMS-like tyrosine kinase-1 and placenta growth factor ratio in prediction of preeclampsia: The SaPPPhirE study. Hypertension 2018;71:306-316.	Not a relevant intervention
Akolekar R, Cruz JDJ, Penco JMP, et al. Maternal plasma plasminogen activator inhibitor-2 at 11 to 13 weeks of gestation in hypertensive disorders of pregnancy. Hypertension in Pregnancy 2011;30:194-202.	No relevant results
Alemu T, and Taddese H. Micronutrients and pregnancy; effect of supplementation on pregnancy and pregnancy outcomes: A systematic review. Annals of Nutrition and Metabolism 2013:1449	Not a relevant study or publication type
Alici Davutoglu E, Akkaya Firat A, Ozel A, et al. Evaluation of maternal serum hypoxia inducible factor-1alpha, progranulin and syndecan-1 levels in pregnancies with early- and late-onset preeclampsia. Journal of Maternal-Fetal & Neonatal Medicine 2018;31:1976-1982.	No relevant results
Allen E, Rogozinska E, Cleverly K, et al. Abnormal blood biomarkers in early pregnancy are associated with preeclampsia: a meta-analysis. European Journal of Obstetrics, Gynecology, & Reproductive Biology 2014;182:194-201	Not a relevant study or publication type
Allen E, Sivarajasingam S, Rogozinska E, et al. Effects of diet and lipid lowering interventions in the prevention of pre-eclampsia: A meta-analysis. Archives of Disease in Childhood: Fetal and Neonatal Edition 2012:A34	Not a relevant study or publication type
Allen E, Zamora J, Arroyo-Manzano J, et al. External validation of pre-existing first trimester preeclampsia prediction models. European Journal of Obstetrics Gynecology and Reproductive Biology 2017;217:119-125	Not a relevant study or publication type

Reference	Reason for exclusion
Allen KM, Green A, Wallace SVF. Use of low-dose aspirin in pregnancy - How will the nice 'Hypertension in Pregnancy' guideline alter current practice? Archives of Disease in Childhood: Fetal and Neonatal Edition 2011;1):Fa112-Fa113.	Published pre-2011
Allen R, Aquilina J. Prospective observational study to determine the accuracy of first-trimester serum biomarkers and uterine artery Dopplers in combination with maternal characteristics and arteriography for the prediction of women at risk of preeclampsia and other adverse pregnancy outcomes. Journal of Maternal-Fetal and Neonatal Medicine 2018;31:2789-2806.	Not a relevant intervention
Allen R, Rogozinska E, Sivarajasingam P, et al. Effect of diet- And lifestyle-based metabolic risk-modifying interventions on preeclampsia: A meta-analysis. Acta Obstetricia et Gynecologica Scandinavica 2014;93:973-985	Not a relevant study or publication type
Allshouse AA, Jessel RH, Heyborne KD. The impact of low-dose aspirin on pre-term birth: Secondary analysis of a randomized controlled trial. Journal of Perinatology 2016;36:427-431.	No relevant results
Alqudah A, McKinley MC, McNally R, et al. Risk of pre-eclampsia in women taking metformin: a systematic review and meta-analysis. Diabetic Medicine 2018;35:160-172.	Not in a relevant population
Al-Rubaie ZTA, Askie LM, Hudson HM, et al. Assessment of NICE and USPSTF guidelines for identifying women at high risk of pre-eclampsia for tailoring aspirin prophylaxis in pregnancy: An individual participant data meta-analysis. European Journal of Obstetrics Gynecology and Reproductive Biology 2018;229:159-166.	Not in a relevant population
Al-Rubaie ZTA, Askie LM, Ray JG, et al. The performance of risk prediction models for pre-eclampsia using routinely collected maternal characteristics and comparison with models that include specialised tests and with clinical guideline decision rules: a systematic review. BJOG: An International Journal of Obstetrics and Gynaecology 2016;123:1441-1452.	No relevant results
Altorjay AT, Suranyi A, Nyari T, et al. Use of placental vascularization indices and uterine artery peak systolic velocity in early detection of pregnancies complicated by gestational diabetes, chronic or gestational hypertension, and preeclampsia at risk. Croatian Medical Journal 2017;58:161-169.	Not a relevant intervention
Alves JAG, Miyague AH, De Sousa PCP, et al. Brachial artery flow mediated dilation in the first trimester to predict the occurrence of hypertensive disorders during pregnancy. Fetal Diagnosis and Therapy 2015;37:316-320.	Not a relevant setting
Ammon FJ, Kohlhaas A, Elshaarawy O, et al. Liver stiffness reversibly increases during pregnancy and independently predicts preeclampsia. World Journal of Gastroenterology 2018;24:4393-4402.	No relevant results
An L, Li W, Xie S, et al. Calcium supplementation reducing risk of hypertensive disorders complicating pregnancy: A meta analysis of multi-center RCTs. Circulation 2012;125 (19):e714	Not a relevant study or publication type
An L, Li W, Xie T, et al. Calcium supplementation reducing the risk of hypertensive disorders of pregnancy and related problems: A meta-analysis of multicentre randomized controlled trials. International journal of nursing practice 2015;21:19-31	Not a relevant study or publication type
Andersen LB, Dechend R, Jorgensen JS, et al. Prediction of preeclampsia with angiogenic biomarkers. Results from the prospective Odense Child Cohort. Hypertension in Pregnancy 2016;35:405-419.	No relevant results
Andersen LB, Jorgensen JS, Herse F, et al. The association between angiogenic markers and fetal sex: Implications for preeclampsia research. Journal of Reproductive Immunology 2016;117:24-29.	Not a relevant intervention
Anderson NH, Sadler LC, Stewart AW, et al. Ethnicity, body mass index and risk of pre-eclampsia in a multiethnic New Zealand population. Australian and New Zealand Journal of Obstetrics and Gynaecology 2012;52:552-558.	Not a relevant intervention
Andraweera PH, Dekker GA, Thompson SD, et al. A functional variant in ANGPT1 and the risk of pregnancies with hypertensive disorders and small-for-gestational-age infants. Molecular Human Reproduction 2012;18:325-32.	Not a relevant intervention
Andrietti S, Carlucci S, Wright A, et al. Repeat measurements of uterine artery pulsatility index, mean arterial pressure and serum placental growth factor at 12, 22 and 32 weeks in prediction of pre-eclampsia. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2017;50:221-227.	Not a relevant intervention
Angeli E, Verdecchia P, Narducci P, et al. Additive value of standard ECG for the risk prediction of hypertensive disorders during pregnancy. Hypertension Research 2011;34:707-713.	Not a relevant intervention
*Anness, A. R., et al. Effect of metformin on biomarkers of placental- mediated disease: A systematic review and meta-analysis. Placenta 2021;107: 51-58	Not a relevant study or publication type

Reference	Reason for exclusion
Anonymous. Corrigendum to: The performance of risk prediction models for pre-eclampsia using routinely collected maternal characteristics and comparison with models that include specialised tests and with clinical guideline decision rules: a systematic review (BJOG: An International Journal of Obstetrics & Gynaecology, (2016), 123, 9, (1441-1452), 10.1111/1471-0528.14029). BJOG: An International Journal of Obstetrics and Gynaecology 2018;125:635.	Not a relevant study or publication type
Antartani R, Ashok K. Effect of lycopene in prevention of preeclampsia in high risk pregnant women. Journal of the turkish german gynecology association artemis 2011;12:35-38.	Not a relevant setting
Anton L, Olarerin-George AO, Schwartz N, et al. MiR-210 inhibits trophoblast invasion and is a serum biomarker for preeclampsia. American Journal of Pathology 2013;183:1437-1445.	Not a relevant intervention
Antonios TFT, Nama V, Wang D, et al. Microvascular remodelling in preeclampsia: Quantifying capillary rarefaction accurately and independently predicts preeclampsia. American Journal of Hypertension 2013;26:1162-1169.	No relevant results
Artunc-Ulkumen B, Guvenc Y, Goker A, et al. Maternal Serum S100-B, PAPP-A and IL-6 levels in severe preeclampsia. Archives of Gynecology & Obstetrics 2015;292:97-102.	Not a relevant intervention
Baba Y, Ohkuchi A, Usui R, et al. Urinary protein-to-creatinine ratio indicative of significant proteinuria in normotensive pregnant women. Journal of Obstetrics and Gynaecology Research 2016;42:784-788.	Not a relevant intervention
Baba Y, Yamada T, Obata-Yasuoka M, et al. Urinary protein-to-creatinine ratio in pregnant women after dipstick testing: Prospective observational study. BMC Pregnancy and Childbirth 2015;15 (1) (no pagination).	Not a relevant intervention
Babic I, Ferraro ZM, Garbedian K, et al. Intraplacental villous artery resistance indices and identification of placenta-mediated diseases. Journal of Perinatology 2015;35:793-798.	Not in a relevant population
Bahser N, Godehardt E, Hess AP, et al. Examination of intrarenal resistance indices indicate the involvement of renal pathology as a significant diagnostic classifier of preeclampsia. American Journal of Hypertension 2014;27:742-749.	Not a relevant intervention
Baschat AA, Dewberry D, Seravalli V, et al. Maternal blood-pressure trends throughout pregnancy and development of pre-eclampsia in women receiving first-trimester aspirin prophylaxis. Ultrasound in Obstetrics & Gynecology 2017;20:20.	No relevant results
Becker R, Keller T, Kiesewetter H, et al. Individual risk assessment of adverse pregnancy outcome by multivariate regression analysis may serve as basis for drug intervention studies: Retrospective analysis of 426 high-risk patients including ethical aspects. Archives of Gynecology and Obstetrics 2013;288:41-48.	Not in a relevant population
*Bellos, I., et al. Serum cystatin-c as predictive factor of preeclampsia: A meta-analysis of 27 observational studies. Pregnancy Hypertension 2019;16: 97-104.	Not a relevant study or publication type
Benton SJ, Hu Y, Xie F, et al. Angiogenic factors as diagnostic tests for preeclampsia: a performance comparison between two commercial immunoassays. American Journal of Obstetrics & Gynecology 2011;205:469.e1-8.	Not a relevant intervention
Bergeron TS, Roberge S, Carpentier C, et al. Prevention of Preeclampsia with Aspirin in Multiple Gestations: A Systematic Review and Meta-analysis. American Journal of Perinatology 2016;33:605-610.	Not a relevant study or publication type
Bergman L, Zetterberg H, Kaihola H, et al. Blood-based cerebral biomarkers in preeclampsia: Plasma concentrations of NfL, tau, S100B and NSE during pregnancy in women who later develop preeclampsia - A nested case control study. PLoS ONE 2018;13 (5) (no pagination).	No relevant results
Bezerra Maia EHMS, Praciano PC, Gurgel Alves JA, et al. Renal Interlobar Vein Impedance Index as a First-Trimester Marker Does Not Predict Hypertensive Disorders of Pregnancy. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine 2016;35:2641-2648.	Not a relevant setting
Bigelow CA, Pereira GA, Warmsley A, et al. Risk factors for new-onset late postpartum preeclampsia in women without a history of preeclampsia. American Journal of Obstetrics & Gynecology 2014;210:338.e1-338.e8.	Not a relevant intervention
Biyik I. Maternal serum soluble HLA-G in complicated pregnancies. Journal of Maternal-Fetal & Neonatal Medicine 2014;27:381-4.	No relevant results

Reference	Reason for exclusion
Block-Abraham DM, Turan OM, Doyle LE, et al. First-trimester risk factors for preeclampsia development in women initiating aspirin by 16 weeks of gestation. Obstetrics and Gynecology 2014;123:611-617.	Not a relevant intervention
Bouvier S, Cochery-Nouvellon E, Lavigne-Lissalde G, et al. Comparative incidence of pregnancy outcomes in treated obstetric antiphospholipid syndrome: the NOH-APS observational study. Blood 2014;123:404-413.	Not a relevant intervention
Bramham K, Seed PT, Lightstone L, et al. Diagnostic and predictive biomarkers for pre-eclampsia in patients with established hypertension and chronic kidney disease. Kidney International 2016;89:874-885.	Not a relevant intervention
Bredaki FE, Sciorio C, Wright A, et al. Serum alpha-fetoprotein in the three trimesters of pregnancy: effects of maternal characteristics and medical history. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2015;46:34-41.	Not a relevant intervention
Brennan MC, Wolfe MD, Murray-Krezan CM, et al. First-trimester hyperglycosylated human chorionic gonadotropin and development of hypertension. Prenatal Diagnosis 2013;33:1075-1079.	No relevant results
Brunelli B, and Prefumo F. Quality of first trimester risk prediction models for pre-eclampsia: A systematic review. BJOG: An International Journal of Obstetrics and Gynaecology 2015;122:904-914	Not a relevant study or publication type
Bujold E, Roberge S, Nicolaides KH. Low-dose aspirin for prevention of adverse outcomes related to abnormal placentation. Prenatal Diagnosis 2014;34:642-648.	Not a relevant study or publication type
Burke O, Benton S, Szafranski P, et al. Extending the scope of pooled analyses of individual patient biomarker data from heterogeneous laboratory platforms and cohorts using merging algorithms. Pregnancy Hypertension 2016;6:53-59.	Not a relevant study or publication type
Cade TJ, Gilbert SA, Polyakov A, et al. The accuracy of spot urinary protein-to-creatinine ratio in confirming proteinuria in pre-eclampsia. Australian & New Zealand Journal of Obstetrics & Gynaecology 2012;52:179-82.	Not in a relevant population
Carbone IF, Cruz JJ, Sarquis R, et al. Assisted conception and placental perfusion assessed by uterine artery Doppler at 11-13 weeks' gestation. Human Reproduction 2011;26:1659-64.	No relevant results
Cetin O, Kurdoglu Z, Kurdoglu M, et al. Chemerin level in pregnancies complicated by preeclampsia and its relation with disease severity and neonatal outcomes. Journal of Obstetrics and Gynaecology 2017;37:195-199.	Not a relevant intervention
*Chaemsaithong, P., et al. Does low-dose aspirin initiated before 11 weeks' gestation reduce the rate of preeclampsia? American Journal of Obstetrics and Gynecology 2020;222(5): 437-450	Not a relevant study or publication type
Cheng D, Hao Y, Zhou W, et al. Vascular endothelial growth factor +936C/T, -634G/C, -2578C/A, and -1154G/A polymorphisms with risk of preeclampsia: a meta-analysis. Plos One 2013;8:e78173.	Not a relevant study or publication type
*Choi, Y. J. and S. Shin Aspirin Prophylaxis During Pregnancy: A Systematic Review and Meta-Analysis. American Journal of Preventive Medicine 2021;61(1): e31-e45	Not a relevant study or publication type
Conde-Agudelo A, Romero R, Kusanovic JP, et al. Supplementation with vitamins C and e during pregnancy for the prevention of preeclampsia and other adverse maternal and perinatal outcomes: A systematic review and metaanalysis. American Journal of Obstetrics and Gynecology 2011;204:503.e1-503.e12.	Published pre-2011
Conserva V, Muggiasca M, Arrigoni L, et al. Recurrence and severity of abnormal pregnancy outcome in patients treated by low-molecular-weight heparin: A prospective pilot study. Journal of Maternal-Fetal and Neonatal Medicine 2012;25:1467-1473.	Not in a relevant population
Contro E, Bernabini D, and Farina A. Cell-Free Fetal DNA for the Prediction of Pre-Eclampsia at the First and Second Trimesters: A Systematic Review and Meta-Analysis. Molecular Diagnosis and Therapy 2017;21:125-135	Not a relevant study or publication type
Cui Y, Zhu B, Zheng F. Low-dose aspirin at <=16 weeks of gestation for preventing preeclampsia and its maternal and neonatal adverse outcomes: A systematic review and meta-analysis. Experimental and Therapeutic Medicine 2018;15:4361-4369.	Not a relevant study or publication type
Da Silva Calestini L, Patrici B, Reis N, et al. The role of placenta growth factor as predictor of Preeclampsia. Pregnancy Hypertension 2015;5 (1):88-89	Not a relevant study or publication type
D'Angelo A, Valsecchi L. High dose antithrombin supplementation in early preeclampsia: a randomized, double blind, placebo-controlled study. Thrombosis research 2016;140:7-13.	Not a relevant intervention

Reference	Reason for exclusion
De Jonge LL, Steegers EAP, Ernst GDS, et al. C-reactive protein levels, blood pressure and the risks of gestational hypertensive complications: The Generation R Study. Journal of Hypertension 2011;29:2413-2421.	No relevant results
De Leo V, Musacchio MC, Piomboni P, et al. The administration of metformin during pregnancy reduces polycystic ovary syndrome related gestational complications. European Journal of Obstetrics Gynecology and Reproductive Biology 2011;157:63-66.	Not in a relevant population
De Ruiter M, Kwee A, Naaktgeboren CA, et al. A systematic review and external validation of prediction models for pregnancy complications: The RESPECT study. American Journal of Obstetrics and Gynecology 2016;1):S243.	Not a relevant study or publication type
De Vries JIP, van Pampus MG, Hague WM, et al. Low-molecular-weight heparin added to aspirin in the prevention of recurrent early-onset pre-eclampsia in women with inheritable thrombophilia: The FRUIT-RCT. Journal of Thrombosis and Haemostasis 2012;10:64-72.	Not in a relevant population
Delic R, Stefanovic M, Krivec S, et al. Statistical regression model of standard and new laboratory markers and its usefulness in prediction of preeclampsia. Journal of Maternal-Fetal and Neonatal Medicine 2014;27:388-392.	No relevant results
Demirci O, Kumru P, Arinkan A, et al. Spot protein/creatinine ratio in preeclampsia as an alternative for 24-hour urine protein. Balkan Medical Journal 2015;32:51-55.	Not a relevant intervention
Di Martino DD, Stampalija T, Rosti E, et al. Bedside cardiovascular maternal interrogation in the first trimester to predict different phenotypes of hypertensive disorders in pregnancy. Pregnancy Hypertension 2016;6:300-305.	No relevant results
Diaz Cobos D, Laparte C, Ruiz-Zambrana A, et al. [First trimester screening of late-onset preeclampsia in a low risk and low volume obstetrical setting: external validation of a predictive model]. Anales del Sistema Sanitario de Navarra 2015;38:387-96.	Not in a relevant population
Dixon CL, Marrs C, Costantine MM, et al. Effect of Low-Dose Aspirin on the Time of Onset of Preeclampsia and Time of Delivery. American Journal of Perinatology 2017;34:1219-1226.	No relevant results
Dodd M, McLeod A, Windrim C, et al. Antithrombotic therapy for improving maternal or infant health outcomes in women considered at risk of placental dysfunction. The Cochrane database of systematic reviews 2013;7:CD006780	Not a relevant study or publication type
Dotan K, Guraslan H, Cankaya A, et al. Ischemia-modified albumin (IMA): A novel marker for preeclampsia independent of uterine artery notching identified by doppler ultrasound. Hypertension in Pregnancy 2015;34:516-524.	No relevant results
Dover N, Gulerman HC, Celen S, et al. Placental growth factor: As an early second trimester predictive marker for preeclampsia in normal and high-risk pregnancies in a turkish population. Journal of Obstetrics and Gynecology of India 2013;63:158-163.	Not a relevant intervention
Droge L, Herraiz I, Zeisler H, et al. Maternal serum sFlt-1/PlGF ratio in twin pregnancies with and without pre-eclampsia in comparison with singleton pregnancies. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2015;45:286-293.	Not a relevant intervention
Dror K, and Allen H. Interventions with Vitamins B6, B12 and C in pregnancy. Paediatric and Perinatal Epidemiology 2012;26:55-74	Not a relevant study or publication type
Duley L, Meher S, and Jones L. Drugs for treatment of very high blood pressure during pregnancy. Cochrane Database of Systematic Reviews 2013	Not a relevant study or publication type
*Duley L, Meher S, Hunter KE,Seidler AL and Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database of Systematic Reviews 2019 (10) (no pagination).	Not a relevant study or publication type
Duley L. Pre-eclampsia, eclampsia, and hypertension. BMJ clinical evidence 2011	Not a relevant study or publication type
Eastwood KA, Patterson C, Hunter AJ, et al. Evaluation of the predictive value of placental vascularisation indices derived from 3-Dimensional power Doppler whole placental volume scanning for prediction of pre-eclampsia: A systematic review and meta-analysis. Placenta 2017;51:89-97.	Not a relevant intervention
Ebina Y, Ieko M, Naito S, et al. Low levels of plasma protein S, protein C and coagulation factor XII during early pregnancy and adverse pregnancy outcome. Thrombosis & Haemostasis 2015;114:65-9.	No relevant results

Reference	Reason for exclusion
Elmas O, Aliciguzel Y, Simsek T. The relationship between hypertension and plasma allantoin, uric acid, xanthine oxidase activity and nitrite, and their predictive capacity in severe preeclampsia. Journal of Obstetrics and Gynaecology 2016;36:34-38.	Not a relevant intervention
Emet T, Ustuner I, Guven SG, et al. Plasma lipids and lipoproteins during pregnancy and related pregnancy outcomes. Archives of Gynecology and Obstetrics 2013;288:49-55.	Not a relevant intervention
Enrique Valdes R, Karina Lattes A, Hernan Munoz S, et al. Sex-hormone binding globulin (SHBG) levels during pregnancy as predictors for pre-eclampsia and fetal growth restriction. Revista Medica de Chile 2012;140:589-594.	No relevant results
Esteve-Valverde E, Ferrer-Oliveras R, Gil-Aliberas N, et al. Pravastatin for Preventing and Treating Preeclampsia: A Systematic Review. Obstetrical and Gynecological Survey 2018;73:40-55	Not a relevant study or publication type
Etwel F, and Koren G. When positive studies of novel therapies are subsequently nullified: cumulative meta-analyses in preeclampsia. Clinical and investigative medicine 2015;Medecine clinique et experimentale. 38:E274-E283	Not a relevant study or publication type
Euser AG, Metz TD, Allshouse AA, et al. Low-dose aspirin for pre-eclampsia prevention in twins with elevated human chorionic gonadotropin. Journal of Perinatology 2016;36:601-605.	Not a relevant intervention
Farina A, Rapacchia G, Freni Sterrantino A, et al. Prospective evaluation of ultrasound and biochemical-based multivariable models for the prediction of late pre-eclampsia. Prenatal Diagnosis 2011;31:1147-1152.	Not a relevant intervention
Farina A. Evaluation of different model for the prediction of late preeclampsia at the 1st trimester of pregnancy. Pregnancy Hypertension 2011;1 (3-4):242	Not a relevant study or publication type
Feig DS, Murphy K, Asztalos E, et al. Metformin in women with type 2 diabetes in pregnancy (MiTy): a multi-center randomized controlled trial. BMC pregnancy and childbirth 2016;16:173.	Not in a relevant population
Ferguson KK, Meeker JD, McElrath TF, et al. Repeated measures of inflammation and oxidative stress biomarkers in preeclamptic and normotensive pregnancies. American Journal of Obstetrics and Gynecology 2017;216:527.e1-527.e9.	No relevant results
Ferreira AF, Rezende JC, de Cassia COR, et al. Maternal serum visfatin at 11-13 weeks' gestation in preeclampsia. Journal of Human Hypertension 2013;27:261-4.	No relevant results
*Fogacci, S., et al. Nutraceuticals and hypertensive disorders in pregnancy: The available clinical evidence. Nutrients 2020;12(2) (no pagination).	Not a relevant study or publication type
Forest JC, Theriault S, Masse J, et al. Soluble Fms-like tyrosine kinase-1 to placental growth factor ratio in mid-pregnancy as a predictor of pre-term preeclampsia in asymptomatic pregnant women. Clinical Chemistry and Laboratory Medicine 2014;52:1169-1178.	Not a relevant intervention
Fruscalzo A, Londero AP, Biasizzo J, et al. Second trimester amniotic fluid retinol in patients developing preeclampsia. Archives of Gynecology and Obstetrics 2015;291:831-836.	No relevant results
Fu M, Ma Z, Liu G, et al. Vitamins supplementation affects the onset of preeclampsia. Journal of the Formosan Medical Association 2018;117:41426	Not a relevant study or publication type
Gabbay A, Tzur T, Weintraub AY, et al. Calcium level during the first trimester of pregnancy as a predictor of preeclampsia. Hypertension in Pregnancy 2014;33:311-321.	No relevant results
Gallo DM, Poon LC, Akolekar R, et al. Prediction of preeclampsia by uterine artery doppler at 20-24 weeks' gestation. Fetal Diagnosis and Therapy 2013;34:241-247.	Not a relevant intervention
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Gibbins KJ, Mumford SL, Sjaarda LA, et al. Preconception antiphospholipid antibodies and risk of subsequent early pregnancy loss. Lupus 2018;27:1437-1445.	Not a relevant intervention
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*Hamadeh, R., et al. C-Reactive Protein for Prediction or Early Detection of Pre-Eclampsia: A Systematic Review. Gynecologic and Obstetric Investigation 2021;86(1-2): 13-26	Not a relevant study or publication type
Hauspurg A, Sutton EF, Catov JM, et al. Aspirin effect on adverse pregnancy outcomes associated with stage 1 hypertension in a high-risk cohort. Hypertension 2018;72:202-207.	No relevant results
Heazell E, Whitworth M, Duley L, et al. Use of biochemical tests of placental function for improving pregnancy outcome. The Cochrane database of systematic reviews 2015;11:CD011202	Not a relevant study or publication type
Henderson JT, Thompson JH, Burda BU, et al. Agency for Healthcare Research and Quality 2017:04.	Not a relevant intervention
Henderson JT, Whitlock EP, O'Conner E, et al. Agency for Healthcare Research and Quality 2014:04.	Not a relevant study or publication type
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Henderson T, Thompson H, Burda U, et al. Preeclampsia screening evidence report and systematic review for the US preventive services task force. JAMA - Journal of the American Medical Association 2017;317:1668-1683	Not a relevant study or publication type
Henderson T, Whitlock P, Conner, E, et al. Low-dose aspirin for the prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the US Preventive Services Task Force. 2014:1-123	Not a relevant study or publication type
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Hirashima C, Ohkuchi A, Takahashi K, et al. A novel three-step approach for predicting the imminent onset of preeclampsia within 4 weeks after blood sampling at 19-31 weeks of gestation. Hypertension Research - Clinical & Experimental 2014;37:519-25.	Not a relevant intervention
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Hofmeyr J, and Manyame S. Calcium supplementation commencing before or early in pregnancy, or food fortification with calcium, for preventing hypertensive disorders of pregnancy. Cochrane Database of Systematic Reviews 2017;2017 (9)	Not a relevant study or publication type
Hofmeyr J, Belizan M, Von Dadelszen P, et al. Low-dose calcium supplementation for preventing pre-eclampsia: A systematic review and commentary. BJOG: An International Journal of Obstetrics and Gynaecology 2014;121:951-957	Not a relevant study or publication type
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Huhtala MS, Tertti K, Pellonpera O, et al. Amino acid profile in women with gestational diabetes mellitus treated with metformin or insulin. Diabetes Research and Clinical Practice 2018;146:8-17.	Not in a relevant population
Hui D, Okun N, Murphy K, et al. Combinations of Maternal Serum Markers to Predict Preeclampsia, Small for Gestational Age, and Stillbirth: A Systematic Review. Journal of Obstetrics and Gynaecology Canada 2012;34:142-153	Not a relevant study or publication type
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Jacobs M, Nassar N, Roberts L, et al. Levels of soluble fms-like tyrosine kinase one in first trimester and outcomes of pregnancy: A systematic review. Reproductive Biology and Endocrinology 2011;9	Not a relevant study or publication type
Jim B, Mehta S, Qipo A, et al. A comparison of podocyturia, albuminuria and nephrinuria in predicting the development of preeclampsia: A prospective study. PLoS ONE 2014;9 (7) (no pagination).	Not a relevant intervention
Johnston PC, McCance DR, Holmes VA, et al. Placental antioxidant enzyme status and lipid peroxidation in pregnant women with type 1 diabetes: The effect of Vitamin C and e supplementation. Journal of Diabetes and its Complications 2016;30:109-114.	No relevant results
Jwa SC, Arata N, Sakamoto N, et al. Prediction of pregnancy-induced hypertension by a shift of blood pressure class according to the JSH 2009 guidelines. Hypertension Research - Clinical & Experimental 2011;34:1203-8.	Not a relevant intervention
Kagan O, Sonek J, Wagner P, et al. Principles of first trimester screening in the age of non-invasive prenatal diagnosis: screening for other major defects and pregnancy complications. Archives of Gynecology and Obstetrics 2017;296:635-643	Not a relevant study or publication type
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Khaing W, Vallibhakara O, Tantrakul V, et al. Calcium and vitamin D supplementation for prevention of preeclampsia: A systematic review and network meta-analysis. Nutrients 2017;9	Not a relevant study or publication type
Khalil AA, Tsikas D, Akolekar R, et al. Asymmetric dimethylarginine, arginine and homoarginine at 11-13 weeks gestation and preeclampsia: A case-control study. Journal of Human Hypertension 2013;27:38-43.	No relevant results
Kleinrouweler CE, Bossuyt PM, Thilaganathan B, et al. Value of adding second-trimester uterine artery Doppler to patient characteristics in identification of nulliparous women at increased risk for pre-eclampsia: an individual patient data meta-analysis. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2013;42:257-267.	Not a relevant study or publication type
Kleinrouweler E, Wiegerinck J, Ris-Stalpers C, et al. Accuracy of circulating placental growth factor, vascular endothelial growth factor, soluble fms-like tyrosine kinase 1 and soluble endoglin in the prediction of pre-eclampsia: A systematic review and meta-analysis. BJOG: An International Journal of Obstetrics and Gynaecology 2012;119:778-787	Not a relevant study or publication type
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Lai J, Pinas A, Syngelaki A, et al. Maternal serum activin-A at 30-33 weeks in the prediction of preeclampsia. Journal of Maternal-Fetal and Neonatal Medicine 2013;26:733-737.	Not a relevant intervention
Lakovschek IC, Ulrich D, Jauk S, et al. Risk assessment for pre-term preeclampsia in first trimester: Comparison of three calculation algorithms. European Journal of Obstetrics Gynecology and Reproductive Biology 2018;231:241-247.	No relevant results
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Lee WY, Yang LY, Lim SLQ, et al. The role of calcium supplements in reducing risk of gestational hypertension or preeclampsia: A meta-analysis. Proceedings of Singapore Healthcare 2012;1):S55.	Not in a relevant population
LeFevre L. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement. Annals of Internal Medicine 2014;161:819-826	Not a relevant study or publication type
Lehnen H, Mosblech N, Reineke T, et al. Prenatal clinical assessment of sFlt-1 (Soluble fms-like tyrosine kinase-1)/PlGF (placental growth factor) ratio as a diagnostic tool for preeclampsia, pregnancy-induced hypertension, and proteinuria. Geburtshilfe und Frauenheilkunde 2013;73:440-445.	Not a relevant intervention
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Litwinska M, Syngelaki A, Wright A, et al. Management of pregnancies after combined screening for pre-eclampsia at 19-24 weeks' gestation. Ultrasound in Obstetrics & Gynecology 2018;52:365-372.	Not a relevant intervention
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Lowe A, Bowyer L, Lust K, et al. SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014. Australian and New Zealand Journal of Obstetrics and Gynaecology 2015;55:e1-e29	Not a relevant study or publication type
Lu P, Hasan A, Zeng S, et al. Plasma ET-1 Concentrations Are Elevated in Pregnant Women with Hypertension-Meta-Analysis of Clinical Studies. Kidney and Blood Pressure Research 2017;42:654-663	Not a relevant study or publication type
Macdonald-Wallis C, Silverwood RJ, De Stavola BL, et al. Antenatal blood pressure for prediction of pre-eclampsia, pre-term birth, and small for gestational age babies: Development and validation in two general population cohorts. BMJ (Online) 2015;351 (no pagination).	No relevant results
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Madazli R, Bulut B, Tuten A, et al. First-trimester maternal serum metastin, placental growth factor and chitotriosidase levels in pre-eclampsia. European Journal of Obstetrics, Gynecology, & Reproductive Biology 2012;164:146-9.	No relevant results

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*Man, R., et al. Aspirin for preventing adverse outcomes in low risk nulliparous women with singleton pregnancies: A systematic review and meta-analysis. European Journal of Obstetrics and Gynecology and Reproductive Biology 2021;262: 105-112	Not a relevant study or publication type
Martell-Claros N, Blanco-Kelly F, Abad-Cardiel M, et al. Early predictors of gestational hypertension in a low-risk cohort. Results of a pilot study. Journal of Hypertension 2013;31:2380-2385.	Not a relevant intervention
Martin A, Krishna I, Martina B, et al. Can the quantity of cell-free fetal DNA predict preeclampsia: A systematic review. Prenatal Diagnosis 2014;34:685-691	Not a relevant study or publication type
Mastrolia A, Novack L, Thachil J, et al. in the prevention of preeclampsia and fetal growth restriction in women without thrombophilia: A systematic review and meta-analysis. Thrombosis and Haemostasis 2016;116:868-878	Not a relevant study or publication type
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McGrogan A, Snowball J, Charlton RA. Statins during pregnancy: a cohort study using the General Practice Research Database to investigate pregnancy loss. Pharmacoepidemiology and Drug Safety 2017;26:843-852.	Not a relevant study or publication type
McLaughlin K, Baczyk D, Potts A, et al. Low Molecular Weight Heparin Improves Endothelial Function in Pregnant Women at High Risk of Preeclampsia. Hypertension 2017;69:180-188.	No relevant results
Meertens LJE, Scheepers HCJ, van Kuijk SMJ, et al. External Validation and Clinical Usefulness of First Trimester Prediction Models for the Risk of Preeclampsia: A Prospective Cohort Study. Fetal Diagnosis and Therapy 2018:1-13.	No relevant results
Meher S, Duley L, Hunter K, et al. Antiplatelet therapy before or after 16 weeks' gestation for preventing preeclampsia: an individual participant data meta-analysis. American Journal of Obstetrics and Gynecology 2017;216:121-128.e2.	Not a relevant study or publication type
Mekinian A, Loire-Berson P, Nicaise-Roland P, et al. Outcomes and treatment of obstetrical antiphospholipid syndrome in women with low antiphospholipid antibody levels. Journal of Reproductive Immunology 2012;94:222-226.	Not in a relevant population
Meler E, Scazzocchio E, Peguero A, et al. Role of maternal plasma levels of placental growth factor for the prediction of maternal complications in preeclampsia according to the gestational age at onset. Prenatal Diagnosis 2014;34:706-710.	Not a relevant intervention
Mihalceanu E, Nemescu D, Gavrilut M, et al. The Correlation between Markers of Systemic Inflammation and Angiogenic Markers in Pre-Eclampsia. Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi 2015;119:473-483.	No relevant results
Moe K, Heidecke H, Dechend R, et al. Dysregulation of circulating autoantibodies against VEGF-A, VEGFR-1 and PlGF in preeclampsia - A role in placental and vascular health? Pregnancy Hypertension 2017;10:83-89.	No relevant results
Mone F, McAuliffe FM. Preconception low-dose aspirin and pregnancy outcomes: Results from the EAGeR randomized trial. Irish Medical Journal 2015;108.	Not a relevant study or publication type
Mone F, Mulcahy C, McParland P, et al. An open-label randomized-controlled trial of low dose aspirin with an early screening test for pre-eclampsia and growth restriction (TEST): Trial protocol. Contemporary Clinical Trials 2016;49:143-148.	Not a relevant study or publication type
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Monteith C, McSweeney L, Breatnach CR, et al. Non-invasive cardiac output monitoring (NICOM) can predict the evolution of uteroplacental disease-Results of the prospective HANDLE study. European Journal of Obstetrics Gynecology and Reproductive Biology 2017;216:116-124.	No relevant results
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Morris K, Bilagi A, Devani P. et al. Association of serum PAPP-A levels in first trimester with small for gestational age and adverse pregnancy outcomes: systematic review and meta-analysis. Prenatal Diagnosis 2017;37:253-265	Not a relevant study or publication type
Morton S, and Thangaratinam S. Statins in pregnancy. Current Opinion in Obstetrics and Gynecology 2013;25:433-440	Not a relevant study or publication type
Mosimann B, Amylidi-Mohr S, Holand K, et al. Importance of Timing First-Trimester Placental Growth Factor and Use of Serial First-Trimester Placental Growth Factor Measurements in Screening for Preeclampsia. Fetal Diagnosis and Therapy 2017;42:111-116.	No relevant results
*Moura, N. S., et al. Clinical Procedures for the Prevention of Preeclampsia in Pregnant Women: A Systematic Review. Revista Brasileira de Ginecologia e Obstetricia 2020;42(10): 659-668	Not a relevant study or publication type
Mulrooney J. Uterine artery doppler of the gravid uterus as a predictor identifying at-risk pregnancies: A meta-analysis. Journal of Diagnostic Medical Sonography 2015;31:64-69	Not a relevant study or publication type
Mutlu I, Mutlu MF, Biri A, et al. Effects of anticoagulant therapy on pregnancy outcomes in patients with thrombophilia and previous poor obstetric history. Blood Coagulation & Fibrinolysis 2015;26:267-73.	Not in a relevant population
Nabhan, A. F. and Elsedawy M. Tight control of mild-moderate pre-existing or non-proteinuric gestational hypertension. Cochrane Database of Systematic Reviews 2011	Not a relevant study or publication type
Napolitano R, Melchiorre K, Arcangeli T, et al. Screening for pre-eclampsia by using changes in uterine artery Doppler indices with advancing gestation. Prenatal Diagnosis 2012;32:180-184.	No relevant results
Napolitano R, Rajakulasingam R, Memmo A, et al. Uterine artery Doppler screening for pre-eclampsia: comparison of the lower, mean and higher first-trimester pulsatility indices. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2011;37:534-537.	No relevant results
*Nascimento IBD, Dienstmann G, de Souza MLR, et al. Evaluation of Preeclampsia Results after Use of Metformin in Gestation: Systematic Review and Meta-analysis. Revista Brasileira de Ginecologia e Obstetricia 2018;40:713-721.	Not a relevant setting
Navaratnam K, Alfirevic A, Jorgensen A, et al. Aspirin non-responsiveness in pregnant women at high-risk of pre-eclampsia. European Journal of Obstetrics Gynecology and Reproductive Biology 2018;221:144-150.	Not a relevant intervention
Nuriyeva G, Kose S, Tuna G, et al. A prospective study on first trimester prediction of ischemic placental diseases. Prenatal Diagnosis 2017;37:341-349.	Not a relevant intervention
Odibo AO, Patel KR, Spitalnik A, et al. Placental pathology, first-trimester biomarkers and adverse pregnancy outcomes. Journal of Perinatology 2014;34:186-191.	No relevant results
Ohkuchi A, Hirashima C, Matsubara S, et al. Threshold of soluble fms-like tyrosine kinase 1/placental growth factor ratio for the imminent onset of preeclampsia. Hypertension 2011;58:859-866.	Not a relevant intervention
Ohkuchi A, Hirashima C, Takahashi K, et al. Prediction and prevention of hypertensive disorders of pregnancy. Hypertension Research 2017;40:5-14.	Not a relevant study or publication type
Oliveira N, Doyle LE, Atlas RO, et al. External validity of first-trimester algorithms in the prediction of pre-eclampsia disease severity. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2014;44:286-292.	Not a relevant intervention
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Oliveira N, Poon LC, Nicolaides KH, et al. First trimester prediction of HELLP syndrome. Prenatal Diagnosis 2016;36:29-33.	No relevant results
Ong GSY, Hadlow NC, Brown SJ, et al. Does the thyroid-stimulating hormone measured concurrently with first trimester biochemical screening tests predict adverse pregnancy outcomes occurring after 20 weeks gestation? Journal of Clinical Endocrinology and Metabolism 2014;99:E2668-E2672.	No relevant results
Otero Gonzalez A, Uribe Moya S, Arenas Moncaleano IG, et al. Hyperbaric index in the primary prevention of hypertensive complications in high-risk pregnancy. Nefrologia : publicacion oficial de la Sociedad Espanola Nefrologia 2015;35:572-577.	Not a relevant intervention

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Ozat M, Kanat-Pektas M, Yenicesu O, et al. Serum concentrations of CA-125 in normal and preeclamptic pregnancies. Archives of Gynecology and Obstetrics 2011;284:607-612.	Not a relevant intervention
Pagani G, D'Antonio F, Khalil A, et al. Association between reduced fetal movements at term and abnormal uterine artery Doppler indices. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2014;43:548-552.	Not a relevant intervention
Palatnik A, Grobman WA, Miller ES. Is a history of preeclampsia associated with an increased risk of a small for gestational age infant in a future pregnancy? American Journal of Obstetrics and Gynecology 2016;215:355.e1-355.e6.	Not in a relevant population
Palmer KR, Kaitu'u-Lino TJ, Cannon P, et al. Maternal plasma concentrations of the placental specific sFLT-1 variant, sFLT-1 e15a, in fetal growth restriction and preeclampsia. Journal of Maternal-Fetal and Neonatal Medicine 2017;30:635-639.	No relevant results
Panaitescu AM, Akolekar R, Kametas N, et al. Impaired placentation in women with chronic hypertension who develop pre-eclampsia. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2017;50:496-500.	No relevant results
Park F, Russo K, Williams P, et al. Prediction and Prevention of Early-Onset Preeclampsia: Impact of Aspirin after First-Trimester Screening. Obstetrical and Gynecological Survey 2016;71:11-13.	Not a relevant study or publication type
Parra-Cordero M, Sepulveda-Martinez A, Preisler J, et al. Role of the glucose tolerance test as a predictor of preeclampsia. Gynecologic and Obstetric Investigation 2014;78:130-135.	Not a relevant intervention
Patrelli TS, Dall'Asta A, Gizzo S, et al. Calcium supplementation and prevention of preeclampsia: A meta-analysis. Journal of Maternal-Fetal and Neonatal Medicine 2012;25:2570-2574.	Not a relevant study or publication type
Pedrosa AC, Matias A. Screening for pre-eclampsia: A systematic review of tests combining uterine artery Doppler with other markers. Journal of Perinatal Medicine 2011;39:619-635.	Published pre-2011
Pedroso MA, Palmer KR, Hodges RJ, et al. Uterine Artery Doppler in Screening for Preeclampsia and Fetal Growth Restriction. Revista Brasileira de Ginecologia e Obstetricia 2018;40:287-293.	Not a relevant study or publication type
Pergialiotis V, Koutaki D, Christopoulos-Timogiannakis E, et al. Anti-Mullerian hormone levels in preeclampsia: A systematic review of the literature. Journal of Family and Reproductive Health 2017;11:179-184	Not a relevant study or publication type
Pergialiotis, V, Prodromidou A, Pappa E, et al. An evaluation of calprotectin as serum marker of preeclampsia: a systematic review of observational studies. Inflammation Research 2016;65:95-102	Not a relevant study or publication type
Pihl K, Sorensen S, Nystad M, et al. Maternal serum laeverin (aminopeptidase Q) measured in the first trimester of pregnancy does not predict preeclampsia. Journal of maternal-fetal & neonatal medicine 2018:1-4.	No relevant results
Pinheiro Mde B, Junqueira R, Coelho F, et al. D-dimer in preeclampsia: systematic review and meta-analysis. Clinica Chimica Acta 2012;414:166-70	Not a relevant study or publication type
Poon LC, Rolnik DL, Tan MY, et al. ASPRE Trial: Incidence of Pre-term Preeclampsia in Patients Fulfilling ACOG and NICE Criteria According to Risk by FMF Algorithm. Obstetrical and Gynecological Survey 2018;73:623-625.	Not a relevant study or publication type
Poon LC, Rolnik DL, Tan MY, et al. ASPRE trial: incidence of pre-term pre-eclampsia in patients fulfilling ACOG and NICE criteria according to risk by FMF algorithm. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2018;51:738-742.	No relevant results
Praciano De Sousa PC, Gurgel Alves JA, Bezerra Maia EHMS, et al. Brachial artery flow mediated dilation and pulsatility index change as independent predictors for hypertensive disorders in the second trimester of pregnancy. European Journal of Obstetrics Gynecology and Reproductive Biology 2016;200:94-97.	Not a relevant setting
Quant HS, Sammel MD, Parry S, et al. Second-Trimester 3-Dimensional Placental Sonography as a Predictor of Small-for-Gestational-Age Birth Weight. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine 2016;35:1693-1702.	No relevant results
*Rahnemaei, F. A., et al. Factors effective in the prevention of Preeclampsia:A systematic review. Taiwanese Journal of Obstetrics and Gynecology 2020;59(2): 173-182	Not a relevant study or publication type

Reference	Reason for exclusion
Rasanen J, Quinn MJ, Laurie A, et al. Maternal serum glycosylated fibronectin as a point-of-care biomarker for assessment of preeclampsia. American Journal of Obstetrics and Gynecology 2015;212:82.e1-82e9.	Not a relevant intervention
Rehfeldt M, Eklund E, Struck J, et al. Relaxin-2 connecting peptide (pro-RLX2) levels in second trimester serum samples to predict preeclampsia. Pregnancy Hypertension 2018;11:124-128.	No relevant results
Rey E, Rivard GE. Is testing for aspirin response worthwhile in high-risk pregnancy? European Journal of Obstetrics Gynecology and Reproductive Biology 2011;157:38-42.	Not a relevant intervention
Rizos D, Eleftheriades M, Karampas G, et al. Placental growth factor and soluble fms-like tyrosine kinase-1 are useful markers for the prediction of preeclampsia but not for small for gestational age neonates: A longitudinal study. European Journal of Obstetrics Gynecology and Reproductive Biology 2013;171:225-230.	No relevant results
Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of pre-term and term preeclampsia: systematic review and metaanalysis. American journal of obstetrics and gynecology 2018;218:287-293.	Not a relevant study or publication type
Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of pre-term and term preeclampsia: Systematic review and meta-analysis. Obstetrical and Gynecological Survey 2018;73:437-438.	Not a relevant study or publication type
Roberge S, Bujold E, Nicolaides KH. Meta-analysis on the effect of aspirin use for prevention of preeclampsia on placental abruption and antepartum hemorrhage. American Journal of Obstetrics and Gynecology 2018;218:483-489.	Not a relevant study or publication type
Roberge S, Bujold E, Nicolaides KH. Meta-analysis on the Effect of Aspirin Use for Prevention of Preeclampsia on Placental Abruption and Antepartum Hemorrhage. Obstetrical and Gynecological Survey 2018;73:553-555.	Not a relevant study or publication type
Roberge S, Demers S, Nicolaides KH, et al. Prevention of pre-eclampsia by low-molecular-weight heparin in addition to aspirin: a meta-analysis. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2016;47:548-553.	Not a relevant study or publication type
Roberge S, Giguere Y, Villa P, et al. Early administration of low-dose aspirin for the prevention of severe and mild preeclampsia: A systematic review and meta-analysis. American Journal of Perinatology 2012;29:551-556.	Published pre-2011
Roberge S, Giguere Y, Villa P, et al. Erratum: Early administration of low-dose aspirin for the prevention of severe and mild preeclampsia: A systematic review and meta-analysis (American Journal of Perinatology (2014) 31 (e3)). American Journal of Perinatology 2014;31:e3.	Not a relevant study or publication type
Roberge S, Nicolaides K, Demers S, et al. The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. American Journal of Obstetrics and Gynecology 2017;216:110-120.e6.	Not a relevant study or publication type
Roberge S, Nicolaides KH, Demers S, et al. Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2013;41:491-499.	Not a relevant study or publication type
Roberge S, Sibai B, McCaw-Binns A, et al. Low-Dose Aspirin in Early Gestation for Prevention of Preeclampsia and Small-for-Gestational-Age Neonates: Meta-analysis of Large Randomized Trials. American Journal of Perinatology 2016;33:781-785	Not a relevant study or publication type
Roberge S, Villa P, Nicolaides K, et al. Early administration of low-dose aspirin for the prevention of pre-term and term preeclampsia: A systematic review and meta-analysis. Fetal Diagnosis and Therapy 2012;31:141-146.	Not a relevant study or publication type
Roberge S, Villa P, Nicolaides K, et al. Early administration of low-dose aspirin for the prevention of pre-term and term preeclampsia: A systematic review and meta-analysis. Obstetrical and Gynecological Survey 2012;67:537-539.	Not a relevant study or publication type
Rodger A, Carrier M, Le Gal G, et al. Meta-analysis of low-molecular-weight heparin to prevent recurrent placenta-mediated pregnancy complications. Blood 2014;123:822-828	Not a relevant study or publication type
Rodger A, Gris C, De Vries J, et al. Low-molecular-weight heparin and recurrent placenta-mediated pregnancy complications: a meta-analysis of individual patient data from randomised controlled trials. The Lancet 2016;388:2629-2641	Not a relevant study or publication type
Rodger A, Gris C, Rey E, et al. Low molecular weight heparin for the secondary prevention of placental-mediated pregnancy complications: A systematic review and meta-analysis. Journal of Thrombosis and Haemostasis 2011;2):751	Not a relevant study or publication type

Reference	Reason for exclusion
Rodger A, Langlois J, De Vries P, et al. Molecular-weight heparin for prevention of placenta-mediated pregnancy complications: Protocol for a systematic review and individual patient data meta-analysis (AFFIRM). Systematic Reviews 2015;3	Not a relevant study or publication type
Rodger M, De Vries P, Rey E, et al. Low molecular weight heparin for prevention of placenta-mediated pregnancy complications: An individual patient data meta-analysis. Blood 2015;126 (23):890	Not a relevant study or publication type
Rolnik DL, Wright D, Poon LC, et al. Aspirin Versus Placebo in Pregnancies at High Risk for Pre-term Preeclampsia. Obstetrical & gynecological survey 2018;73:11-12.	Not a relevant study or publication type
Ronsmans C, and Campbell O. Quantifying the fall in mortality associated with interventions related to hypertensive diseases of pregnancy. BMC Public Health 2011;11 Suppl 3:S8	Not a relevant study or publication type
Rossi C, and Mullin M. Prevention of pre-eclampsia with low-dose aspirin or vitamins C and e in women at high or low risk: A systematic review with meta-analysis. European Journal of Obstetrics Gynecology and Reproductive Biology 2011;158:42614	Not a relevant study or publication type
Rumbold A, Ota E, Hori H, et al. Vitamin E supplementation in pregnancy. Cochrane Database of Systematic Reviews 2015;2016	Not a relevant study or publication type
Rumbold A, Ota E, Nagata C, et al. Vitamin C supplementation in pregnancy. Cochrane Database of Systematic Reviews 2015	Not a relevant study or publication type
Salles AMR, Galvao TF, Silva MT, et al. Antioxidants for preventing preeclampsia: A systematic review. The Scientific World Journal 2012;2012 (no pagination).	Published pre-2011
Salvianti F, Inversetti A, Smid M, et al. Prospective evaluation of RASSF1A cell-free DNA as a biomarker of pre-eclampsia. Placenta 2015;36:996-1001.	No relevant results
Sanchez-Ramos L, Roeckner J, et al. Small studies in meta-analyses overestimate treatment effects of aspirin for the prevention of preeclampsia: A systematic review and metaepidemiological study. American Journal of Obstetrics and Gynecology 2018;218(Supplement 1):S189-S190	Not a relevant study or publication type
Sanchez-Ramos L, Roeckner J, Knupp R, et al. Timing and dose of aspirin for the prevention of pre-eclampsia: A systematic review and network meta-analysis. American Journal of Obstetrics and Gynecology 2018;218(Supplement 1):S190	Not a relevant study or publication type
Saxena AR, Seely EW, Rich-Edwards JW, et al. First trimester PAPP-A levels correlate with sFlt-1 levels longitudinally in pregnant women with and without preeclampsia. BMC Pregnancy and Childbirth 2013;13 (no pagination).	No relevant results
Schneuer FJ, Nassar N, Tasevski V, et al. Association and predictive accuracy of high TSH serum levels in first trimester and adverse pregnancy outcomes. Journal of Clinical Endocrinology & Metabolism 2012;97:3115-22.	No relevant results
Schneuer FJ, Roberts CL, Ashton AW, et al. Angiopoietin 1 and 2 serum concentrations in first trimester of pregnancy as biomarkers of adverse pregnancy outcomes. American Journal of Obstetrics and Gynecology 2014;210:345.e1-345.e9.	No relevant results
Schwartz N, Pessel C, Coletta J, et al. Early biometric lag in the prediction of small for gestational age neonates and preeclampsia. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine 2011;30:55-60.	No relevant results
Shokrani S. Effects of vitamins B6, B12 and C in pregnancy. Iranian Journal of Reproductive Medicine 2014;124	Not a relevant study or publication type
Sibai BM, Koch MA, Freire S, et al. The impact of prior preeclampsia on the risk of superimposed preeclampsia and other adverse pregnancy outcomes in patients with chronic hypertension. American Journal of Obstetrics & Gynecology 2011;204:345.e1-6.	Not a relevant setting
Soliman AA, Csorba R, Yilmaz A, et al. Rheologic results and their correlation to hemostatic changes in patients with moderate and severe preeclampsia: An observational cross-sectional study. Clinical Hemorheology and Microcirculation 2015;59:1-15.	Not a relevant intervention
Sovio U, Gaccioli F, Cook E, et al. Prediction of Preeclampsia Using the Soluble fms-Like Tyrosine Kinase 1 to Placental Growth Factor Ratio: A Prospective Cohort Study of Unselected Nulliparous Women. Hypertension 2017;69:731-738.	No relevant results

Reference	Reason for exclusion
Spyroulis C. Pre-eclampsia. Can we predict or prevent it? literature review. International Journal of Gynecology and Obstetrics 2015;5:E185-E186	Not a relevant study or publication type
Stepan H, Hund M, Gencay M, et al. A comparison of the diagnostic utility of the sFlt-1/PlGF ratio versus PlGF alone for the detection of preeclampsia/HELLP syndrome. Hypertension in Pregnancy 2016;35:295-305.	Not a relevant intervention
Stewart B, Altman G, Askie M. Statistical Analysis of Individual Participant Data Meta-Analyses: A Comparison of Methods and Recommendations for Practice. PLoS ONE 2012;7	Not a relevant study or publication type
Stott D, Bolten M, Salman M, et al. A prediction model for the response to oral labetalol for the treatment of antenatal hypertension. Journal of Human Hypertension 2017;31:126-131.	Not in a relevant population
Stout J, Conner N, Colditz A, et al. The utility of 12-hour urine collection for the diagnosis of preeclampsia: A systematic review and meta-analysis. Obstetrics and Gynecology 2015;126:731-736	Not a relevant study or publication type
Stubert J, Kleber T, Bolz M, et al. Acute-phase proteins in prediction of preeclampsia in patients with abnormal midtrimester uterine Doppler velocimetry. Archives of Gynecology and Obstetrics 2016;294:1151-1160.	Not a relevant intervention
Stubert J, Ullmann S, Bolz M, et al. Prediction of preeclampsia and induced delivery at <34 weeks gestation by sFLT-1 and PlGF in patients with abnormal midtrimester uterine Doppler velocimetry: A prospective cohort analysis. BMC Pregnancy and Childbirth 2014;14 (1) (no pagination).	Not a relevant intervention
Suri S, Muttukrishna S, Jauniaux E. 2D-Ultrasound and endocrinologic evaluation of placentation in early pregnancy and its relationship to fetal birthweight in normal pregnancies and pre-eclampsia. Placenta 2013;34:745-50.	No relevant results
Tang R, Tang IC, Henry A, et al. Limited evidence for calcium supplementation in preeclampsia prevention: A meta-analysis and systematic review. Hypertension in Pregnancy 2015;34:181-203.	Not a relevant study or publication type
Tardif C, Dumontet E, Caillon H, et al. Angiogenic factors sFlt-1 and PlGF in preeclampsia: Prediction of risk and prognosis in a high-risk obstetric population. Journal of Gynecology Obstetrics and Human Reproduction 2018;47:17-21.	Not in a relevant population
*Tarry-Adkins, J. L., et al. Impact of metformin treatment during pregnancy on maternal outcomes: a systematic review/meta-analysis. Scientific reports 2021;11(1): 9240	Not a relevant study or publication type
Tenorio B, Ferreira C, Moura A, et al. Oral antioxidant therapy for prevention and treatment of preeclampsia: Meta-analysis of randomized controlled trials. Nutrition, Metabolism and Cardiovascular Diseases 2018;28:865-876	Not a relevant study or publication type
Thangaratinam S, Rogozinska E, Jolly K, et al. Effects of interventions in pregnancy on maternal weight and obstetric outcomes: Meta-analysis of randomised evidence. Obstetrical and Gynecological Survey 2012;67:603-604	Not a relevant study or publication type
Thomsen LCV, Klungsoyr K, Roten LT, et al. Validity of the diagnosis of pre-eclampsia in the Medical Birth Registry of Norway. Acta Obstetricia et Gynecologica Scandinavica 2013;92:943-950.	Not in a relevant population
*Townsend R, Khalil A, Premakumar Y, et al. Prediction of pre-eclampsia: review of reviews. Ultrasound in Obstetrics & Gynecology 2018;28:28.	Not a relevant study or publication type
*Turner, J. M., et al. Impact of low-dose aspirin on adverse perinatal outcome: meta-analysis and meta-regression. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2020;55(2): 157-169	Not a relevant study or publication type
Ukah V, Hutcheon A, Payne B, et al. Placental growth factor as a prognostic tool in women with hypertensive disorders of pregnancy a systematic review. Hypertension 2017;70:1228-1237	Not a relevant study or publication type
Uusi-Rasi, K, Karkkainen U, and Lamberg-Allardt J. Calcium intake in health maintenance - a systematic review. Food & Nutrition Research 2013;57:	Not a relevant study or publication type
Van den Hof MC, Smithies M, Nevo O, et al. No. XXX-Clinical Practice Guideline on the Use of First Trimester Ultrasound. Journal of Obstetrics and Gynaecology Canada. 2018.	Not a relevant study or publication type
Van Hoorn ME, Hague WM, Van Pampus MG, et al. Low-molecular-weight heparin and aspirin in the prevention of recurrent early-onset pre-eclampsia in women with antiphospholipid antibodies: The FRUIT-RCT. European Journal of Obstetrics Gynecology and Reproductive Biology 2016;197:168-173.	Not in a relevant population

Reference	Reason for exclusion
Vandenberghe G, Mensink I, Twisk JWR, et al. First trimester screening for intra-uterine growth restriction and early-onset pre-eclampsia. Prenatal Diagnosis 2011;31:955-961.	No relevant results
*van Doorn, R., et al. Dose of aspirin to prevent preterm preeclampsia in women with moderate or high-risk factors: A systematic review and meta-analysis. PLoS ONE 2021;16(3 March) (no pagination)	Not a relevant study or publication type
Vasapollo B, Novelli GP, Gagliardi G, et al. Medical treatment of early-onset mild gestational hypertension reduces total peripheral vascular resistance and influences maternal and fetal complications. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2012;40:325-331.	Not a relevant intervention
Vatten LJ, Asvold BO, Eskild A. Angiogenic factors in maternal circulation and preeclampsia with or without fetal growth restriction. Acta Obstetricia et Gynecologica Scandinavica 2012;91:1388-94.	No relevant results
Velauthar L, Plana N, Kalidindi M, et al. First-trimester uterine artery Doppler and adverse pregnancy outcome: a meta-analysis involving 55,974 women. Ultrasound in Obstetrics and Gynecology 2014;43:500-507	Not a relevant study or publication type
Verlohren S, Herraiz I, Lapaire O, et al. New gestational phase-specific cutoff values for the use of the soluble fms-like tyrosine kinase-1/placental growth factor ratio as a diagnostic test for preeclampsia. Hypertension (dallas, tex. : 1979) 2014;63:346-352.	No relevant results
Verlohren S, Melchiorre K, Khalil A, et al. Uterine artery Doppler, birth weight and timing of onset of pre-eclampsia: providing insights into the dual etiology of late-onset pre-eclampsia. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2014;44:293-298.	No relevant results
Verlohren S, Perschel FH, Thilaganathan B, et al. Angiogenic Markers and Cardiovascular Indices in the Prediction of Hypertensive Disorders of Pregnancy. Hypertension 2017;69:1192-1197.	Not a relevant intervention
Viguiliouk E, Park AL, Berger H, et al. A simple clinical method to identify women at higher risk of preeclampsia. Pregnancy Hypertension 2017;10:10-13.	No relevant results
Wang X, Gao H. Prevention of preeclampsia in high-risk patients with low-molecular-weight heparin: a meta-analysis. Journal of Maternal Fetal and Neonatal Medicine. 2018.	Not a relevant study or publication type
Webster LM, Conti-Ramsden F, Seed PT, et al. Impact of antihypertensive treatment on maternal and perinatal outcomes in pregnancy complicated by chronic hypertension: A systematic review and meta-analysis. Journal of the American Heart Association 2017;6 (5) (no pagination).	Published pre-2011
Weed S, Bastek JA, Anton L, et al. Examining the correlation between placental and serum placenta growth factor in preeclampsia. American Journal of Obstetrics and Gynecology 2012;207:140.e1-140.e6.	Not a relevant intervention
Weissgerber TL, Gandley RE, Roberts JM, et al. Haptoglobin phenotype, pre-eclampsia, and response to supplementation with vitamins C and e in pregnant women with type-1 diabetes. BJOG: An International Journal of Obstetrics and Gynaecology 2013;120:1192-1199.	Not in a relevant population
Wen SW, Champagne J, Rennicks White R, et al. Effect of folic acid supplementation in pregnancy on preeclampsia: the folic acid clinical trial study. Journal of pregnancy 2013;2013:294312.	Not a relevant intervention
Wen SW, White RR, Rybak N, et al. Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (FACT): double blind, phase III, randomised controlled, international, multicentre trial. BMJ (online) 2018;362.	Not a relevant intervention
Widmer M, Cuesta C, Khan KS, et al. Accuracy of angiogenic biomarkers at <=20 weeks' gestation in predicting the risk of pre-eclampsia: A WHO multicentre study. Pregnancy Hypertension 2015;5:330-338.	Not a relevant setting
Williamson RD, McCarthy FP, Khashan AS, et al. Exploring the role of mitochondrial dysfunction in the pathophysiology of pre-eclampsia. Pregnancy Hypertension 2018;13:248-253.	No relevant results
Woodham PC, Brittain JE, Baker AM, et al. Midgestation maternal serum 25-hydroxyvitamin D level and soluble fms-like tyrosine kinase 1/placental growth factor ratio as predictors of severe preeclampsia. Hypertension 2011;58:1120-5.	No relevant results
Wright D, Papadopoulos S, Silva M, et al. Serum free beta-human chorionic gonadotropin in the three trimesters of pregnancy: effects of maternal characteristics and medical history. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2015;46:51-59.	No relevant results

Reference	Reason for exclusion
Wu P, Van Den Berg C, Alfirevic Z, et al. Early pregnancy biomarkers in pre-eclampsia: A systematic review and meta-analysis. International Journal of Molecular Sciences 2015;16:23035-23056.	Not a relevant study or publication type
Xu M, Guo D, Gu H, et al. Selenium and Preeclampsia: a Systematic Review and Meta-analysis. Biological Trace Element Research 2016;171:283-292.	Not a relevant study or publication type
Xu TT, Zhou F, Deng CY, et al. Low-Dose Aspirin for Preventing Preeclampsia and Its Complications: A Meta-Analysis. Journal of Clinical Hypertension 2015;17:567-573.	Not a relevant study or publication type
Yuan J, Wang X, Xie Y, et al. Circulating asymmetric dimethylarginine and the risk of preeclampsia: A meta-analysis based on 1338 participants. Oncotarget 2017;8:43944-43952	Not a relevant study or publication type
Yucel B and Ustun B. Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, mean platelet volume, red cell distribution width and plateletcrit in preeclampsia. Pregnancy Hypertension 2017; 7:29-32	No relevant results
Yusuf, A. M., Kahane, A. and Ray, J. G..First and Second Trimester Serum sFlt-1/PlGF Ratio and Subsequent Preeclampsia: A Systematic Review. Journal of Obstetrics and Gynaecology Canada 2018;40:618-626	Not a relevant study or publication type
Zerfu, A, and Ayele T. Micronutrients and pregnancy; Effect of supplementation on pregnancy and pregnancy outcomes: A systematic review. Nutrition Journal 2013;12	Not a relevant study or publication type
Zeybek B, Costantine M, Kilic S, et al. Therapeutic Roles of Statins in Gynecology and Obstetrics: The Current Evidence. Reproductive Sciences 2018;25:802-817	Not a relevant study or publication type
Zhai T, Furuta I, Nakagawa K, et al. Second-trimester urine nephrin:creatinine ratio versus soluble fms-like tyrosine kinase-1:placental growth factor ratio for prediction of preeclampsia among asymptomatic women. Scientific reports 2016;6:37442.	Not a relevant intervention
Zhao M, Zhu Z, Liu C, et al. Dual-cutoff of sFlt-1/PlGF ratio in the stratification of preeclampsia: a systematic review and meta-analysis. Archives of Gynecology and Obstetrics 2017;295:1079-1087.	Not in a relevant population
Zhong Y, Zhu F, Ding Y. Serum screening in first trimester to predict pre-eclampsia, small for gestational age and pre-term delivery: Systematic review and meta-analysis. BMC Pregnancy and Childbirth 2015;15.	Not a relevant study or publication type

*Denotes an SLR or meta-analysis publication that was hand-searched but not included in its own right (due to more than 50% of studies within it not fulfilling eligibility criteria)

Appendix 3 — Summary and appraisal of individual studies

Data Extraction

Table 27. Studies relevant to criterion 4 (question 1)

Table 25a: Al-Amin 2018

Study Reference	Al-Amin 2018
Study Design	Design Prospective cohort study Objective To compare the performance of 3 different screening methods (National Institute for Health and Care Excellence [NICE] guidelines, American College of Obstetricians and Gynecologists [ACOG] recommendations and Fetal Medicine Foundation [FMF] algorithm for second trimester prediction of pre-eclampsia (PE). Dates June 2012 to January 2015 Country Australia Setting The Royal Women's Hospital, Melbourne
Population Characteristics	Patient recruitment and eligibility Women attending for their second trimester morphology ultrasound during the study period at the study hospital were offered participation in the study. Exclusion criteria were NR. Data collection Maternal demographic characteristics and history were recorded, as well as meant arterial pressure (MAP) after 2 measurements in each arm (following a previously published technique). A standardised colour Doppler technique was used to measure the left and right uterine arteries pulsatility index (PI) by transabdominal ultrasound and the average value was recorded. Duration of follow-up NR (assumed to be until delivery) Prevalence of PE in the study

Study Reference	Al-Amin 2018

There were 27 (4.9%) cases of PE, including 3 cases (0.5%) of PE before 34 weeks, 8 cases (1.4%) of preterm PE and 19 cases of term PE (3.4%).

Sample size
N screened/invited = NR
N eligible = NR
N enrolled = NR
N excluded (with reason) = NR
N lost to follow-up = NR
N completed = 543 (complete outcome data)
N excluded from analysis = 0
N included in analysis = 543

Demographics

Characteristic	No PE (n=516)	PE <34 weeks (n=3)	PE <37 weeks (n=8)	PE >37 weeks (n=19)
Median maternal age, years (IQR)	35 (28 to 42)	36 (32 to 40)	34 (27 to 41)	32 (26 to 38)
Median gestational age, weeks (IQR)	20.3 (19.3 to 21.3)	20.7 (20.0 to 21.4)	20.3 (19.3 to 21.3)	20.4 (19.4 to 21.4)
Median weight, kg (IQR)	69 (53 to 85)	88.6 (72.4 to 102.8)*	85.5 (57.5 to 113.5)*	69.9 (38.9 to 100.9)
Median height, cm (IQR)	165 (156 to 174)	164 (157 to 171)	163.2 (151.2 to 175.2)	164 (158 to 170)
Median BMI (IQR)	25.3 (19.3 to 31.3)	33.7 (27.4 to 40.0)	32 (24 to 40)	28.4 (17.4 to 39.4)
Racial origin, n (%)				
Caucasian	389 (75.4)	2 (66.7)	5 (62.5)	17 (89.5)
Afro-Caribbean	19 (3.7)	0	1 (12.5)	0
East Asian	42 (8.1)	1 (33.3)	1 (12.5)	2 (10.5)
South Asian	43 (8.3)	0	1 (12.5)	0
Mixed	23 (4.5)	0	0	0
Medical history, n (%)				
Chronic hypertension	18 (3.5)	1 (33.3)	3 (37.5)*	0
Diabetes	23 (4.4)	1 (33.3)	2 (25.0)	3 (15.8)
SLE or APS	5 (0.9)	0	0	1 (5.3)
Cigarette smoking, n (%)	33 (6.4)	0	1 (12.5)	2 (10.5)
Family history of PE, n (%)	28 (5.4)	0	0	0
Conception, n (%)				
Spontaneous	483 (93.6)	2 (66.7)	7 (87.5)	16 (84.2)
Ovulation drugs	6 (1.2)	0	0	0
IVF	27 (5.2)	1 (33.3)	1 (12.5)	3 (15.8)
Parity, n (%)				
Nulliparous	222 (43.0)	1 (33.3)	1 (12.5)	13 (68.4)*
Parous: no previous PE	260 (50.4)	2 (66.7)	4 (50.0)	4 (21.1)*
Parous: previous PE	34 (6.6)	0	3 (37.5)*	2 (10.5)

Study Reference	**Al-Amin 2018**
	*P<0.05 when compared to the unaffected group
Screening Method	Index test Each woman was classified as high or low risk for PE according to NICE guidelines and ACOG recommendations. • NICE guidelines: considers pregnant women to be at high risk of developing PE if they have any one high-risk factor (history of hypertensive disease in previous pregnancy, chronic kidney disease, autoimmune disease, diabetes mellitus, chronic hypertension) or any two moderate-risk factors (first pregnancy, age >40 years, inter-pregnancy interval >10 years, BMI at first visit >35 kg/m2 or family history of PE) • ACOG guidelines: risk factors are nulliparity, age >40 years, BMI >30 kg/m2, conception by in vitro fertilisation (IVF), history of previous pregnancy with PE, family history of PE, chronic hypertension, chronic renal disease, diabetes mellitus, systemic lupus erythematosus (SLE) or thrombophilia • The individual risk for preterm PE according to the FMF algorithm (based on maternal factors, MAP and UtA-PI) was retrospectively calculated at the end of the study by one of the authors who was blinded to the outcomes using the FMF algorithm. Detection rates, false positive rates and positive likelihood ratios for detection of PE requiring delivery before 34 weeks, before 37 weeks and after 37 weeks were calculated and receiver operating characteristic (ROC) curves were produced with the statistical software package IBM SPSS for each method of screening. Reference standard Outcomes of the pregnancies were determined and the occurrence of PE was confirmed or ruled out by review of medical records. The main outcome measure was preterm PE, as defined by the International Society for the Study of Hypertension in Pregnancy.
Test Accuracy	Sensitivity of screening for PE

Method of screening	PE < 34 weeks		PE < 37 weeks		PE >37 weeks		FPR (%)
	DR, % (95% CI)	LR+, % (95% CI)	DR, % (95% CI)	LR+, % (95% CI)	DR, % (95% CI)	LR+, % (95% CI)	
NICE guidelines	33.3 (0.8–90.5)	1.38 (0.28–6.91)	75.0 (34.9–96.8)	3.21 (2.09–4.93)	47.3 (24.4–71.1)	2.03 (1.24–3.35)	22.4
ACOG recommendations	66.6 (9.4–99.1)	0.97 (0.43–2.16)	87.5 (47.3–9.6)	1.28 (0.98–1.67)	89.4 (66.8–98.7)	1.31 (1.11–1.55)	67.8
FMF (cut-off 1:100)	100.0 (29.2–100.0)	4.82 (4.0–5.6)	100.0 (63.0–100.0)	5.00 (4.22–5.92)	42.1 (20.2–66.5)	2.06 (1.19–3.59)	19.1
FMF (cut-off 1:60)	100.0 (29.2–100.0)	7.11 (5.7–8.7)	100.0 (63.0–100.0)	7.54 (6.07–9.36)	26.3 (9.1–51.2)	1.86 (0.85–4.07)	12.7

Authors' Conclusions	Screening for preterm PE in the second trimester by individual risk calculation using maternal factors, MAP and uterine artery Doppler pulsatility index (FMF algorithm) performs better than screening by maternal factors alone using the NICE guidelines and the ACOG recommendations.

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; APS, antiphospholipid syndrome; AUC, area under the curve; BMI, body mass index; DR, detection rate; FMF, Fetal Medicine Foundation; FPR, false positive rate; IQR, interquartile range; IVF, *in vitro* fertilisation; LR, likelihood ratio; MAP, mean arterial pressure; NICE, National Institute for Health and Care Excellence; NPV, negative predictive value; NR, not reported; PAPP-A, pregnancy associated

plasma protein A; PE, pre-eclampsia; PI, pulsatility index; PlGF, placental growth factor; PPV, positive predictive value; RI, resistance index; ROC, receiver operating characteristic; SGA, small-for-gestational age; SLE, systemic lupus erythematosus; UtA, uterine artery.

Table 25b: Allen 2018

Study Reference	Allen 2018
Study Design	Design Prospective cohort study Objective To assess the role of AFP in the first trimester in combination with PlGF, uterine artery Dopplers and arteriography as a predictive test for detecting pregnancies at high risk of developing PE and other adverse outcomes. Additionally, to assess PAPP-A and β-hCG in those women who had the combined screening test for trisomy 21. Dates January 2013 to July 2014 Country UK Setting Royal London Hospital
Population Characteristics	Patient recruitment and eligibility An unselected population of pregnant women attending the hospital for their first-trimester scan (11 to 14-week gestation) were recruited. Data collection Maternal characteristics and medical history, including information on age, ethnicity, method of conception, parity, smoking, alcohol and drug use, past medical and obstetric history, family history, and drug history were recorded. Maternal weight and height were measured and BMI was calculated. Arteriography, uterine artery Doppler measurements and maternal serum samples were taken. In the serum blood samples, the following biomarkers were measured: PlGF, AFP, PAPP-A, and β-hCG. Duration of follow-up Delivery (assumed based on outcomes reported). Prevalence of PE in the study 14 (1.3%) developed PE Sample size N screened/invited = NR N eligible = NR N enrolled = 1250 N excluded (with reason) = NR N lost to follow-up = NR N completed = NR N excluded from analysis = 205 total including: no haemodynamics (n=47), no uterine artery Doppler (n=4), miscarriages (n=8), TOPs (n=6), fetal anomalies (n=2), outcome data not available (n=106), blood results not available (n=32)

Study Reference **Allen 2018**

N included in analysis = 1045 (2186 when the second cohort of 1141 women were added for additional PE data from previous research)

Demographics

Characteristic	Control (n=855, 81.8%)	PE (n=14, 1.34%)
Maternal age (years, median [range])	30 (15–45)	31.5 (24–39)
BMI	23 (15–51)	23 (19–41)
Ethnicity, n (%)		
Caucasian	342 (45)	5 (35.7)
Afro-Caribbean	83 (9.7)	6 (42.8)
South Asian	304 (35.5)	3 (21.4)
Oriental	89 (10.4)	0
Mixed/other	37 (4.33)	0
Parity, n (%)		
Nulliparous	482 (56.4)	8 (57)
Parous - no previous PE	365 (42.7)	3 (21.4)
Parous – previous PE	8 (0.93)	3 (21.4)*
Family history of PE (mother/sister), n (%)	24 (2.8)	1 (7.14)
Smoker, n (%)	27 (3.16)	1 (7.14)
Medical history, n (%)		
Essential hypertension	5 (0.58)	1 (7.14)
Lupus/antiphospholipid syndrome	4 (0.47)	0
Renal disease	0	1 (7.14)
Sickle cell disease	0	0
Medication during pregnancy, n (%)		
Aspirin	19 (2.2)	1 (7.14)
Antithrombotics	4 (0.47)	0
Antihypertensives	4 (0.47)	0
Immunosuppressants	4 (0.47)	1 (7.14)
Steroids	1 (0.12)	0

*critical significance level p<0.008

Screening Method

Index test

Haemodynamic parameters, maternal serum biomarkers, UAD mean PI and MAP were converted into MoM. PlGF, AFP, PAPP-A, β-hCG and MAP MoMs were adjusted for gestational age, weight and ethnicity. The biomarkers were also adjusted for smoking status. In addition, PAPP-A and β-hCG were adjusted for IVF. Mean UAD PI MoMs were adjusted by the crown-rump measurement and maternal height in meters. SBPAO, Aix50 and pulse wave velocity MoMs were adjusted for weight, parity and maternal age. Aix50 and SBPAO were also adjusted for ethnicity. Aix50 was further adjusted by maternal height. Univariate analysis was initially performed to determine variables with a significant association with the outcomes. Logistic regression with stepwise selection was then performed to determine multivariate models in the prediction of PE. Variables were included in the models based on a significant p value (p<0.05) on multivariate analysis only. Final models were used to construct DRs for specified FPRs.

<table>
<tr><td><u>Study Reference</u></td><td>Allen 2018</td></tr>
<tr><td></td><td><u>Reference standard</u>
The diagnosis of PE was made according to the International Society for the Study of Hypertension in Pregnancy criteria.</td></tr>
<tr><td>Test Accuracy</td><td>SBP_{AO} (p=0.002) was the only parameter significantly associated with the development of PE, and therefore the only variable included in the model; the DR for PE was 72% for a FPR of 15%. When an additional cohort of 1141 women, who were recruited prospectively for research in the first trimester of pregnancy (2010 to 2012) for the prediction of PE, had their PlGF and AFP data added, creating a larger sample size of 2186 participants, of whom 56 developed PE, the results remained unchanged.
<table>
<tr><th>Outcome</th><th colspan="4">PE</th></tr>
<tr><td>FPR</td><td>5</td><td>10</td><td>15</td><td>20</td></tr>
<tr><td>Sensitivity</td><td>28</td><td>50</td><td>72</td><td>72</td></tr>
</table></td></tr>
<tr><td>Authors’ Conclusions</td><td>This study did not show AFP to have a role in first-trimester screening for hypertensive disease, however findings do suggest a role for arteriography in the prediction of women at risk of PE. Overall, findings do not support a role for the routine use of first-trimester biomarkers for predicting risk of PE.</td></tr>
</table>

Abbreviations: AFP, alpha-fetoprotein; Aix, augmentation index; β-hCG, beta-human chorionic gonadotrophin; BMI, body mass index; DR, detection rate; IVF, [abbreviation not provided]; FPR, false-positive rate; MAP, mean arterial pressure; MoM, multiples of the median; PE, pre-eclampsia; PAPP-A, pregnancy-associated plasma protein-A; PI, pulsatility index; PlGF, placental growth factor; SBP_{AO}, systolic blood pressure in the aorta; TOPs, [abbreviation not provided]; UAD, uterine artery Doppler; UK, United Kingdom.

Table 25c: Baweja 2011

Study Reference	Baweja 2011
Study Design	Design Prospective cohort study Objective To establish whether a spot urinary albumin: creatinine ratio (ACR) measured before 20 weeks of gestation can predict subsequent pre-eclampsia when urinary albumin is measured by high-performance liquid chromatography (HPLC). Dates March 2006–December 2007 (recruitment) Country Australia Setting Antenatal clinic at a tertiary teaching hospital in Victoria, Australia
Population Characteristics	Patient recruitment and eligibility All women with singleton pregnancies attending antenatal clinics who consented to participate in the study (between 12 and 20 weeks of gestation) were recruited. Inclusion criteria were women over 18 years of age, singleton pregnancy, ≤20 weeks of gestation at the time of recruitment, and nil proteinuria upon measurement with a dipstick. Women with haematuria, dipstick-positive proteinuria, ongoing urinary tract infection, multiple pregnancy, acute renal failure, CKD, assisted reproduction, or a poor obstetric history were excluded. However, women with a past history of urinary tract infection, renal failure, haematuria, or proteinuria were included if there was no evidence of current disease, if the urine was dipstick-negative for proteinuria, and if the serum creatinine level was within the normal range. Data collection Data regarding demographic profile, blood pressure, BMI, and medical and family history (history of CHT, diabetes mellitus, and/or CKD) were recorded. Obstetric history documented gravidity, parity, past history of pre-eclampsia, prematurity, SGA, miscarriage, and family history of PE. Urine collection and dipstick examination was conducted between 17 and 20 weeks of gestation. Duration of follow-up Until delivery Prevalence of PE in the study 6 (2.3%) developed PE Sample size N screened/invited = NR N eligible = NR N enrolled = 295 N excluded (with reason) = NR N lost to follow-up = NR N completed = NR N excluded from analysis = 30 (miscarriage, transferral to another facility, withdrawal of consent, or misplaced urine sample during transport) N included in analysis = 265

Study Reference | **Baweja 2011**

Demographics

Characteristic	Entire sample (n=265)	PE (n=6)
Maternal age, years (mean ± SD)	29.5 ± 4.7	26.3 ± 4.9
BMI, kg/m2 (mean ± SD)	26.9 ± 6.2	30.3 ± 10.2
Ethnicity, n (%)		
Australian	NR (44.5)	3 (50.0)
European	NR (33.2)	0 (0)
Asian	NR	2 (33.3)
African	NR	1 (16.7)
Australian Torres Strait islanders (ATSI)	NR	0 (0)
Others	NR	0 (0)
Obstetric history, n (%)		
Primigravida	91 (34.3)	4 (66.7)
Medical history, n (%)		
Gestational diabetes mellitus	21 (7.9)	0 (0)
Pre-gestational diabetes	15 (5.75)	NR
Chronic hypertension	23 (8.7)	2 (33.3)
History of renal disease	23 (8.7)	0 (0)
History of renal or urinary tract disease	10 (3.8)	0 (0)
History of pre-eclampsia	NR	0 (0)
Gestational age at delivery (mean ± SD)	NR	36.7±2.4

Screening Method

Index test

- Median spot urinary ACR

Urine collection and dipstick examination were conducted between 17 and 20 weeks of gestation, assessing total intact urinary albumin and urine creatine. Intact urinary albumin was determined by HPLC, creatine was measured by modified Jaffe's method.

Reference standard

- Diagnosis of pre-eclampsia, as defined by the standard clinical criteria laid out by the American College of Obstetricians Gynaecologists practice bulletin (Number 33, January 2002).

Test Accuracy

- The optimum spot urinary ACR to predict pre-eclampsia was 35.5 mg/mmol, which had a test sensitivity of 83.3%, specificity of 61.2%, positive predictive value 63.0%, and negative predictive value of 78.6%.

Authors' Conclusions

When urinary albumin is measured by HPLC, spot urinary ACR values are higher in uncomplicated pregnancy in comparison with conventional methods. A spot urinary ACR value of ≥35.5 mg/mmol (measured by HPLC between 17 and 20 weeks of gestation) predicted future pre-eclampsia with a sensitivity and specificity of 83.3% and 61.2%, respectively. Additional studies and a cost-benefit analysis are required to confirm these findings before recommending this test for screening purposes.

Abbreviations: ACR, albumin: creatinine ratio; ATSI, Australian Torres Strait islanders; BMI, body mass index; CHT, chronic hypertension; CKD, chronic kidney disease; HPLC, high-performance liquid chromatography; NR, not reported; PE, pre-eclampsia; SGA, small for gestational age.

Table 25d: Boucoiran 2013a

Study Reference	Boucoiran 2013a
Study Design	Design Prospective cohort study Objective To determine the screening accuracy of PlGF, PP13, and ADAM12 for the detection of subsequent PE using statistical modelling for cross-trimester repeated measurements. Dates November 2006 and June 2008 Country Canada Setting Sainte-Justine hospital (Montreal, Quebec, Canada)
Population Characteristics	Patient recruitment and eligibility 1,000 pregnant women were consecutively recruited. Inclusion criteria were nulliparous women with singleton pregnancies without major fetal chromosomal or structural anomaly. Data collection At the time of screening for Down syndrome at 11^{+0} to 13^{+6} weeks of gestation (visit 1), maternal characteristics and medical history were recorded, an ultrasound examination was performed to determine the gestational age based on CRL evaluation and blood samples were collected. PlGF, PP13 and ADAM12 were measured in maternal serum. Duration of follow-up Until delivery (assumed based on outcomes reported) Prevalence of PE in the study 40 women developed PE (4.5%) Sample size N screened/invited = 1,000 N eligible = 893 N enrolled = 893 N excluded (with reason) = NR N lost to follow-up = NR N completed = NR N excluded from analysis = 93 – Second-trimester data were missing in 93 women. As the distributions of biomarkers with missing and complete data were not significantly different, the subjects with missing values were omitted in further correlation and risk modelling analyses N included in analysis = NR

Study Reference — **Boucoiran 2013a**

Demographics

Characteristic	Unaffected (n = 833)	Pre-eclampsia (n = 40)	Early onset pre-eclampsia (n = 9)
Age (year), median (IQR)	29.0 (27.0–32.7)	30 (27.2–32.0)	32.0 (28.5–34.5)
BMI (kg/m^2), median (IQR)	22.5 (20.8–24.9)	27.8 (22.4–30.3)	28.9 (21.8–35.1)[a]
Ethnicity, n (%)			
Caucasian	671 (80.6)	30 (75.0)	6 (66.7)
Afro-Caribbean	58 (7.0)	7 (17.5)[a]	3 (33.3)[a]
Other	104 (12.5)	3 (7.5)	0
One or more medical history, n (%)[b]	30 (3.6)	4 (10.0)[a]	3 (33.3)[a]
Smoking during pregnancy, n (%)	56 (6.7)	2 (5.0)	1 (11.1)
Medication during pregnancy, n (%)			
Heparin	10 (1.2)	3 (7.5)	0
Low-dose aspirin	17 (2.0)	3 (7.5)	2 (22.2)
Gestational age at delivery (week), median (IQR)	39.8 (38.9–40.7)	38.3 (36.0–39.4)	34.9 (33.9–36.4)[a]
Birth weight (g), median (IQR)	3400 (3045–3665)	2937 (2197–3327)[a]	2000 (1465–2400)[a]

[a]Comparison with the unaffected group by chi-square test or Mann-Whitney test when appropriate, p <0.05
[b]Medical history: chronic hypertension, diabetes, autoimmune disease, thrombophilia, hyperthyroidism, renal disease

Screening Method

Index test
Maternal characteristics and PlGF at 11^{+0} to 13^{+6} weeks of gestation (the maternal characteristics used in the model are NR in this paper).

Reference standard
The definition of PE used came from the International Society for the Study of Hypertension in Pregnancy. PE was defined as GH (a diastolic BP of 90 mmHg or more or systolic BP of 140 mmHg or more on at least 2 occasions 4 hours apart developing after 20 weeks of gestation in previously normotensive women in the absence of significant proteinuria) with significant proteinuria (≥0.3 g/d in a 24-hour collection or urinary protein-to-creatinine ratio ≥0.03 g/mmol in a spot random urine sample. Early onset PE was defined as PE diagnosed before 34 weeks (first elevated BP or urinary protein measurement leading to the diagnosis), based on American College of Obstetricians and Gynaecologist Committee Opinion for corticoid therapy in situations of anticipated preterm delivery.

Test Accuracy

	Maternal characteristics + PlGF at visit 1[a]
Detection rate (%)	35.3
Positive predictive value (%)	13.5
Negative predictive value (%)	96.9
Positive likelihood ratio	3.51
Negative likelihood ratio	0.72

[a]11^{+0} to 13^{+6} weeks of gestation
10% FPR

Authors' Conclusions

In this study, first-trimester PlGF assay is a promising screening tool for PE in an unselected population. The disappointing results of ADAM12 as a screening tool for PE in this study are consistent with those previously reported. The predictive accuracy of PP13 was not confirmed in this study, possibly due to the absence of adjustment on maternal characteristics or difference in assay technique in previous studies. First-trimester measurement of PlGF is a promising marker of PE, but its screening accuracy is limited for clinical usefulness as a

Study Reference	Boucoiran 2013a
	single test, even with repeated measures. External validation of the models in other similar population is recommended to confirm the absence of benefit of repeated measures of PlGF.

Abbreviations: ADAM12, A disintegrin and metalloprotease 12; BMI, body mass index; BP, blood pressure; CRL, crown-rump length; GH, gestational hypertension; IQR, interquartile range; MoM, multiples of the expected median; NR, not reported; PE, pre-eclampsia; PlGF, placental growth factor; PP13, placental protein 13.

Table 25e: Boucoiran 2013b

Study Reference	Boucoiran 2013b
Study Design	Design Prospective cohort study Objective To determine the predictive accuracy of PlGF, sFlt-1, and inhibin A plasma concentrations in multiple compared with singleton pregnancies as a prenatal screening for PE and SGA birth and to elaborate prediction models based on their combinations. Dates January 2004 to March 2006 Country Canada Setting 17 research centres
Population Characteristics	Patient recruitment and eligibility Women between 12 and 18 completed weeks of pregnancy were eligible for the trial. The exclusion criteria were: regular consumption of vitamin C and/or vitamin E supplements, history of major medical complications, major fetal defects, repeated spontaneous abortion, and/or use of an illicit drug or warfarin treatment during the current pregnancy. Data collection Maternal blood samples were collected between 12 and 18 weeks gestation (visit 1). Duration of follow-up NR Prevalence of PE in the study 34 (4.4%) developed PE Sample size N screened/invited = NR N eligible = NR N enrolled = 798 N excluded (with reason) = NR N lost to follow-up = NR N completed = NR N excluded from analysis = 26 (no outcome data) N included in analysis = 772 Demographics

Characteristic	Unaffected (n=584)	PE (n=34)
Age (years), median (IQR)[a]	30.0 (27.0–34.0)	31.5 (26.0–35.0)
Caucasian, n (%)	526 (90.1)	30 (88.2)
Weight (kg), median (IQR)[a]	63.6 (58.2–75.0)	69.5 (61.3–84.1)[b]
BMI (kg/m^2), median (IQR)[a]	23.4 (21.0–27.0)	25.4 (22.5–31.6)[b]

Study Reference	**Boucoiran 2013b**

Smoking, n (%)	124 (21.2)	6 (17.6)
Chronic hypertension, n (%)	25 (4.3)	7 (20.6)[b]
Pregestational diabetes, n (%)	54 (9.2)	7 (20.6)
Multiple-gestation pregnancy, n (%)	51 (8.7)	5 (14.7)
History of PE, n (%)	55 (9.4)	9 (26.5)[b]
IVF, n (%)	35 (6.0)	3 (8.8)
Antioxidant supplementation, n (%)	286 (49.0)	17 (50.0)
Aspirin started at first trimester, n (%)	28 (5.4)	5 (19.2)[b]

[a]Interquartile range, 25th to 75th percentile; [b]Comparison to the unaffected group with Wilcoxon or chi-square test, $p < 0.05$.

Screening Method

Index test

- **PlGF, sFlt-1, and inhibin A plasma concentrations**

Maternal non-fasting blood samples were collected between 12 and 18 weeks gestation (visit 1). Inhibin-A and sFlt-1 were measured by immunometric assay, and PlGF was measured by DELFIA kit. Adjustments were made for the observed potential confounding factors (maternal weight and age, type of gestation, smoking, and gestational age).

Reference standard

- **PE was defined as gestational hypertension (blood pressure higher or equal to 140/90 mm Hg on 2 readings at least 4 hours apart after 20 weeks of gestation) with proteinuria higher or equal to 0.3 g in 24 hours urine collection, 2+ or higher in urine dipstick test, or >30 mg/mmol creatinine (International Society for the Study of Hypertension in Pregnancy)**

Test Accuracy

	Biomarker	DR for 10% FP rate of biomarkers for predicting PE, %
Singleton pregnancies, visit 1[a]	**PlGF**	**21.4**
	Slft1:PlGF ratio	**25.0**
	Inhibin A	**21.4**

[a]Between 12 and 18 weeks gestation

Authors' Conclusions	In singleton pregnancies, PlGF showed the best predictions of PE.

Abbreviations: BMI, body mass index; DR, detection rate; FP, false positive; IVF, in vitro fertilisation; PE, preeclampsia; PIFG, placental growth factor; SGA, small for gestational age; sFlt-1, soluble fmslike tyrosine kinase-1

Table 25f: Caradeux 2013

Study Reference	Caradeux 2013
Study Design	Design Prospective cohort study Objective To evaluate and validate a clinical model for prediction of early-onset pre-eclampsia (PE), gestational hypertension (GH) and late PE by combining maternal history, biometric variables and biophysical factors at 11–14 weeks of pregnancy. Dates NR Country Chile Setting Three hospitals (Hospital Regional de Valdivia, Hospital Parroquial de San Bernado, Clínica Dávila)
Population Characteristics	Patient recruitment and eligibility Participants were recruited when attending for an 11–14 weeks ultrasound evaluation. Inclusion and exclusion criteria not specified. Data collection *At enrolment* • Personal and family history: age, weight, height, race, smoking status, parity, gravidity, previous PE, hypertension, diabetes mellitus, family history of PE in participant's mother • Biophysical variables: systolic blood pressure (SBP)*, diastolic blood pressure (DBP)*, body mass index (BMI), uterine artery pulsatility index (UtA-PI)** *Measurements of SBP and DBP were conducted with electronic sphygmomanometer devices, certified by the Chilean Cardiologic Society. **Measurement of bilateral Doppler UtA-PI was conducted by trained physicians with transvaginal colour Doppler with an Applio Toshiba ultrasound *During pregnancy* • Women were managed according to the normal protocols of the different centres and followed until postpartum period • Normal pregnancies followed every 4 weeks; those with chronic hypertension were followed every 2 weeks; cases that developed mild PE were followed every 1 week; women with early-onset PE or with PE which developed ≥1 of the severity criteria (proposed by American College of Obstetricians and Gynecologists [ACOG]) were classified as severe and hospitalised until delivery *After delivery* • Outcome information recorded: GH, PE, gestational age at delivery, weight of newborn, mode of deliverybirth Duration of follow-up Until postpartum period Prevalence of PE in the study PE developed in 29 (4.6%) pregnancies, 9 (1.5%) of which were early PE (defined as delivery ≤34 weeks) Sample size N screened/invited = NR N eligible = 627

Study Reference **Caradeux 2013**

N enrolled = 627
N excluded (with reason) = NR
N lost to follow-up = NR
N completed = NR
N excluded from analysis = NR
N included in analysis = NR*

*Predictive models generated by multivariate logistic regression were informed by maternal variables taken at baseline, but not exactly clear if all eligible women were included

Demographics
Maternal variables, medical history and characteristics presented separately for early PE, GH, late PE and normotensive pregnancy.

Variable	Early PE	GH	Late PE	Normotensive
Maternal variables, Mean (SD)				
Age, years	28.3 (8.53)	29.1 (6.5)	28 (6.8)	28.9 (6.3)
Weight, kg	61.6 (14.1)	74 (15.8)	79 (17.7)	66 (11.7)
Height, cm	157 (4.9)	160 (5.2)	160 (4.1)	160 (6.9)
BMI, kg/m^2	24.9 (5.94)	29.1 (6.4)	30.9 (7.1)	25.8 (4.4)
SBP, mmHg	118 (13.8)	122 (13.5)	124 (12.5)	116 (11.1)
DBP, mmHg	74.1 (14.7)	73.9 (12.4)	75.2 (13.1)	69.5 (9.6)
Mean arterial pressure (MAP), mmHg	88.9 (14.1)	89.4 (12.8)	91.4 (11.9)	84.9 (8.9)
UtA-PI	1.87 (0.472)	1.67 (0.5)	1.75 (0.6)	1.6 (0.5)
Maternal medical history and characteristics (%)				
Smoking	0.0	9.4	10.5	3.2
Multiparous	77.8	67.7	55.0	79.9
Preterm labour	25	10.3	5.3	3.2
Previous PE	11.1	9.2	5.0	1.6
Hypertension	11.1	10.8	10.0	1.1
Diabetes mellitus	11.1	1.5	0.0	1.6
Thrombophilia	0.0	0.0	0.0	0.2
Women with PE	0.0	9.2	15.0	4.1

Screening Method

Index test
Different predictive models generated from multivariate logistic regression. Different combinations of maternal and sonographic variables were used (variables included in the model were identified by backward stepwise logistic regression). Full models NR, variables include:

- Maternal variables (at enrolment): age, weight, SBP, DBP, MAP
- Maternal medical history and characteristics: parity, history of PE, hypertension, diabetes mellitus, log UtA-PI, history of preterm labour

Reference standard
PE was defined as GH associated with proteinuria greater than 300 mg in 24 h urine or more than a trace of proteinuria on dipstick testing, in 2 evaluations, after 20 weeks of pregnancy.

If PE was detected before 34^{+0} weeks, it was considered early PE and if detected after 34^{+0} weeks as late PE.

Test Accuracy Detection rate, specificity and likelihood ratios (LHR) with 5% false positive rate (FPR) for prediction of PE at 11–14 weeks

Study Reference **Caradeux 2013**

Model variables	Early-onset PE				Late-onset PE			
	Detection rate	Specificity	Positive LHR	Negative LHR	Detection rate	Specificity	Positive LHR	Negative LHR
Age, weight, SBP, DBP, MAP, parity, history of PE, hypertension, diabetes mellitus, log UtA-PI, history of preterm labour	62.5%	95.5%	13.9	0.39	31.6%	NR	6.3	0.7

Authors' Conclusions

The results confirm that the multiparameter approach used was able to identify those cases at higher risk to develop early PE.

Even without serum markers, the detection rate of 62.5% with 5% false positive and a positive LHR of 13.9, make this model a potentially helpful tool to identify the highest risk group of women that may develop early PE and that can be important in some health care systems, where serum markers may initially be too expensive.

It is important to note that the World Health Organization (WHO) considers that an adequate screening test needs a positive LHR higher of at least ten, allowing a focalised follow-up of the at-risk women.

The positive and negative LHRs given by demographic, clinical, and sonographic data in the first trimester will enable clinicians to identify high-risk women in a low-risk population, allowing recommendations for commencing prophylactic aspirin for prevention of PE.

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; BMI, body mass index; DBP, diastolic blood pressure; FPR, false positive rate; GH, gestational hypertension, LHR, likelihood ratio; MAP, mean arterial pressure; NR, not reported; PE, pre-eclampsia; SBP, systolic blood pressure; UtA-PI, uterine artery pulsatility index; WHO, World Health Organization

Table 25g: Carter 2015

Study Reference	Carter 2015
Study Design	Design Prospective cohort study Objective To compare the ability of previously reported uterine artery Doppler indices, including the pulsatility index (PI), resistive index (RI), and bilateral notching, to predict pre-eclampsia (PE), preterm birth, or small for gestational age (SGA), and to determine the most discriminatory definition of abnormal uterine artery Doppler parameters in the first trimester to predict adverse pregnancy outcomes. Dates December 2009 to April 2012 Country United States Setting Tertiary care centre
Population Characteristics	Patient recruitment and eligibility A prospective cohort of women with singleton gestations between 11 and 14 weeks gestation who underwent first-trimester sonographic screening for aneuploidy and consented to uterine artery Doppler measurements during the study period. Excluded: pregnancies with major fetal anomalies, chromosomal abnormalities, and those that did not continue past 20 weeks gestation. Data collection • Gestational age was defined by the last menstrual period if the first-trimester sonography agreed with the due date within 7 days. If there was a greater than 7-day discrepancy, the pregnancy was re-dated to the due date calculated from the earliest available sonographic examination. • Doppler examination of the uterine arteries was performed by dedicated obstetric and gynaecologic sonographers who were certified by the Nuchal Translucency Quality Review program for first-trimester screening. The mean PI and RI from the left and right sides were calculated and averaged. A single investigator finalised all Doppler measurements and evaluated for the presence of bilateral notching. • Perinatal research coordinators obtained obstetric outcomes for each pregnancy prospectively. Duration of follow-up NR, assumed to be until delivery. Prevalence of PE in the study Of 1,192 pregnancies, 98 (8.4%) had PE, 20 (1.8%) had early PE. Sample size N screened/invited = NR N eligible = 1,200 N enrolled = 1,200 N excluded (with reason) = NR N lost to follow-up = 8 N completed = 1,192 N excluded from analysis = 0

Study Reference | **Carter 2015**

N included in analysis = 1,192

Demographics

Characteristic	Value
Mean maternal age (range), years	31.5 (17 to 49)
Mean BMI (range), kg/m2	26.4 (15.50 to 67.67)
Race, %	
White	61.3
African American	27.1
Asian	7.8
Latino	1.9
Native American	0.1
Multiethnic	1.9
Median parity (IQR)	1 (0 to 2)
Nulliparous, n (%)	517 (43.6)
High risk, n (%)[a] (n=1,200)	265 (22.1)

[a]History of chronic hypertension, PE, preterm birth, or type 1/type 2 diabetes

Screening Method

Index test

UtA-PI, UtA-RI and bilateral notch at 11 to 14 weeks gestation.

The association between published indices for abnormal uterine artery Doppler parameters and adverse outcomes were calculated using relative risks and 95% CIs. A receiver operating characteristic (ROC) analysis was used to define the best cut-off points for the mean PI and RI for adverse outcomes. These identified cut-offs were also compared with definitions of abnormal uterine artery Doppler parameters reported in the literature. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic odds ratios (OR) were then calculated for various definitions of abnormal uterine artery Doppler indices.

Reference standard

Perinatal research coordinators obtained obstetric outcomes for each pregnancy prospectively; PE was defined using the guidelines of the American College of Obstetricians and Gynecologists (ACOG). Early PE was defined as PE necessitating delivery before 34 weeks gestation.

Test Accuracy

Mean PI >75th percentile for early PE: Sensitivity 40%, specificity 77%*
Mean PI >75th percentile for 'overall' early PE: Sensitivity 45%, specificity 75.5%, PPV 3.3%, NPV 98.7%*

*It is not clear which screening test/population/cut-off these measures of test accuracy relate to

Sensitivity of screening for early PE in high-versus low-risk women with a PI above the 75th percentile

Group	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
High risk	57.1	75.6	13.8	96.3
Low risk	16.7	75.3	0.5	99.2

Study Reference	**Carter 2015**
Authors' Conclusions	A mean uterine PI above the 75th percentile is the most discriminative abnormal uterine artery Doppler parameter for predicting both early preeclampsia and early preterm birth. The results of this study suggest that, although there are associations between uterine artery Doppler indices and early preeclampsia and preterm birth, none of these parameters is optimal for predicting these adverse pregnancy outcomes, except in a high-risk group of women. Our results suggest that none of the uterine artery Doppler thresholds assessed in this study are robust screening tools in the first trimester.

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; BMI, body mass index; FPR, false positive rate; IQR, interquartile range; NPV, negative predictive value; OR, odds ratio; PE, pre-eclampsia; PI, pulsatility index; PPV, positive predictive value; RI, resistance index; ROC, receiver operating characteristic; SGA, small-for-gestational age; UtA, uterine artery.

Table 25h: Di Lorenzo 2012

Study Reference	Di Lorenzo 2012
Study Design	Design Prospective cohort study Objective To evaluate the detection of pregnancy hypertensive disorders by integrating maternal history, serum biomarkers and uterine artery Doppler in the first trimester. Dates October 2007 to April 2009 Country Italy Setting Prenatal Diagnosis and Gynaecologic Unit of a third level hospital in Trieste (Institute for Maternal and Child Health)
Population Characteristics	Patient recruitment and eligibility All women were recruited consecutively and were followed from first trimester ultrasound aneuploidy screening to delivery. Singleton pregnancies between 11^{+0} and 13^{+6} weeks of gestation. All pregnancies were dated by last menstrual period if consistent with crown-rump length measurements (+/-7 days), or by the crown-rump length (CRL) measurement if it was not consistent with menstrual dating. The exclusion criteria were major fetal abnormalities (such as aneuploidy and multiple congenital abnormality syndromes), miscarriage and termination of pregnancy. Data collection During the first visit a written informed consent was collected and enrolled women were interviewed. Maternal history was recorded (women were asked to provide information on age, height and weight to calculate body mass index [BMI], ethnicity, method of conception, cigarette smoking during pregnancy, history of chronic hypertension and diabetes, parity and previous pregnancy with pre-eclampsia [PE] or gestational diabetes mellitus), blood samplings were collected and an ultrasound examination was performed measuring CRL, nuchal translucency (NT) and uterine artery (UtA) Doppler velocimetry. Duration of follow-up Women were followed from the first trimester ultrasound until delivery. Prevalence of PE in the study Of 2,118 pregnancies, 25 women developed PE (1.2%), including 12 early-onset PE (0.6%) and 13 late-onset PE (0.6%). Sample size N screened/invited = 2,328 N eligible = NR N enrolled = 2,170 N excluded (with reason) = Declined to participate (before enrolment) n=158, miscarriage n=22, termination of pregnancy n=16 N lost to follow-up = 14 N completed = NR N excluded from analysis = NR

Study Reference **Di Lorenzo 2012**

N included in analysis = 2,118

Demographics

Comparing women in the unaffected group with those affected by gestational hypertension (GH), PE, early-onset PE and late-onset PE, maternal characteristics did not differ significantly, with the exception of BMI at enrolment and chronic hypertension.

Characteristic	Unaffected (n=2,047)	GH (n=46)	PE (n=25)	Early-onset PE (n=12)	Late-onset PE (n=13)
Mean age, years (95% CI)	33.05 (32.84–33.26)	33.63 (32.17–35.83)	33.92 (32.01–35.82)	33.63 (31.21–36.06)	34.18 (30.92–37.44)
Mean BMI, kg/m^2 (95% CI)	22.34 (22.18–22.51)	25.85 (24.49–27.21)*	23.85 (22.21– 25.48)**	24.68 (21.88–27.47)**	23.08 (20.97–25.19)
Ethnicity, n (%)					
Caucasian	1,975 (96.77)	43 (93.48)	23 (92.00)	11 (91.67)	12 (92.31)
Other	50 (2.53)	1 (1.87)	1 (4.00)	0 (0)	1 (7.69)
Black	19 (0.70)	2 (4.65)	1 (4.00)	1 (8.33)	0 (0)
Parity, n (%)					
Nulliparous	1,178 (57.55)	31 (67.39)	18 (72.00)	9 (75.00)	6 (69.23)
Multiparous	869 (42.45)	15 (32.61)	7 (28.00)	3 (25.00)	4 (30.77)
Conception, n (%)					
Spontaneous	1,990 (97.22)	43 (93.48)	25 (100)	12 (100)	13 (100)
Other	57 (2.78)	3 (6.52)	0 (0)	0 (0)	0 (0)
Smoking during pregnancy, n (%)					
No	1,798 (89.28)	39 (84.78)	24 (96.00)	12 (100)	12 (92.31)
Yes	216 (10.72)	7 (15.22)	1 (4.00)	0 (0)	1 (7.69)
Diabetes mellitus, n (%)					
No	2,025 (98.93)	45 (97.83)	25 (100)	12 (100)	13 (100)
Yes	22 (1.07)	1 (2.17)	0 (0)	0 (0)	0 (0)
Gestational diabetes mellitus (GDM), n (%)					
No	1,990 (97.22)	44 (95.65)	23 (92.00)	11 (91.67)	12 (92.31)
Yes	57 (2.78)	2 (4.35)	2 (8.00)	1 (8.33)	1 (7.69)
Chronic hypertension					
No	2,039 (97.84)	45 (97.83)	23 (92.00)	10 (83.00)	13 (100)
Yes	8 (2.16)	1 (2.17)	2 (8.00)**	2 (17.00)**	0 (0)
Mean infant birth weight, g (95% CI)	3,365 (3,344–3,386)	3,295 (3,126–3,464)	2,290 (1,979–2,600)*	1,799 (1,451–2,146)*	2,743 (2,364–3,123)*
Infants born small for gestational age (SGA), n (%)					
No	1,948 (95.16)	44 (95.65)	20 (80.00)	11 (91.67)	9 (69.23)
Yes	99 (4.84)	2 (4.35)	5 (20.00)*	1 (8.33)	4 (30.77)*

* p<0.001; ** p<0.05

Screening Method

Index test

Model A: Maternal factors (age, BMI, black vs. others, parity, conception, smoking during pregnancy, diabetes mellitus, GDM, sex of child, chronic hypertension), biomarkers (log free beta-human chorionic gonadotropin [fβhCG], log pregnancy associated plasma protein A [PAPP-

Study Reference — **Di Lorenzo 2012**

A], log placental growth factor [PlGF], log placental protein-13 [PP-13]) and UtA variables (bilateral notch, uterine artery pulsatility index [UtA-PI]) at 11–13 weeks gestation

Model B: Maternal factors (BMI, black vs. others, parity, chronic hypertension), biomarkers (log free B-HCG, log PAPP-A, log PlGF) and UtA-PI at 11–13 weeks gestation

In the first trimester UtA Doppler was evaluated using trans-abdominal ultrasound with colour flow mapping. According to Fetal Medicine Foundation guidelines, bilateral UtA Doppler impedance indices were recorded: UtA PI, uterine artery resistance index (UtA-RI) and bilateral Notch. PP-13, fβhCG, PAPP-A and PlGF were quantified by DELFIA Xpress. Concentrations of PP-13, PlGF, PAPP-A and fβhCG were then transformed as multiples of the median (MoM) and adjusted for gestational age and maternal BMI. The samples were analysed by an examiner blinded to the clinical outcomes.

Reference standard

GH, early-onset PE, late-PE and PE. American College of Obstetricians and Gynecologists (ACOG) definitions were used. GH was defined as de novo hypertension (>140/90 mmHg) developing after 20 weeks of gestation in a woman with previously normal blood pressure; if associated by co-existing significant proteinuria (>0.3 g in a 24-h urine specimen), it was defined as PE. PE was further subdivided into early-onset PE and late-onset PE, when diagnosed, respectively, before or after 34 weeks of gestation.

Test Accuracy

Sensitivity of screening for PE, early PE, late PE and GH using maternal characteristics and biomarkers

Outcome	GH, %				PE, %				Early PE, %				Late PE, %			
Model A Multivariate regression of saturated model (both maternal characteristics and biomarkers)																
FPR	5	10	15	20	5	10	15	20	5	10	15	20	5	10	15	20
Sensitivity	24	39	57	63	36	52	60	60	58	67	67	92	23	31	38	46
Model B Sensitivity rates from multivariate regression with step-down procedure (maternal characteristics and biomarkers with p<0.05)																
FPR	5	10	15	20	5	10	15	20	5	10	15	20	5	10	15	20
Sensitivity	22	41	48	59	32	40	48	60	67	75	75	75	23	31	31	46

Authors' Conclusions — An integration of maternal characteristics and first trimester maternal serum biomarkers (fβhCG and PlGF) provided a possible screening for early-onset PE. The detection rates of women who developed early-onset PE are respectively 67% and 75% with 5% and 10% of FPR, comparable with other studies. In the overall PE model, UtA-PI turned out to be statistically significant but did not improve the detection rate.

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; BMI, body mass index; CRL, crown-lump length; fβhCG, free beta-human chorionic gonadotropin; FPR, false positive rate; GDM, gestational diabetes mellitus; GH, gestational hypertension; MoM, multiple of the median; NR, not reported; NT, nuchal translucency PAPP-A, pregnancy associated plasma protein-A; PE, pre-eclampsia; PlGF, placental growth factor; PP-13, placental protein-13; SGA, small-for-gestational age; UtA, uterine artery, UtA-PI, uterine artery pulsatility index; UtA-RI, uterine artery resistance index.

Table 25i: Di Martino 2019

Study Reference	Di Martino 2019
Study Design	Design Prospective cohort (multicentre) Objective To compare the predictive performance of 2 models for the “a priori” risk calculation of early and late PE in a Northern Italian population: the 2012 Fetal Medicine Foundation (FMF) algorithm and the 2013 BCNatal algorithm. In the “a priori” risk estimation, the biophysical and biochemical markers which play an essential role in improving and determining the screening performance of both algorithms were excluded. Dates January 2014 to May 2017 Country Italy Setting 4 centres in Northern Italy
Population Characteristics	Patient recruitment and eligibility Women who underwent a routine first trimester admission visit and/or routine first trimester screening at 11 to 13 weeks gestation in the hospitals which participated in the study were recruited. The eligibility criteria were: a singleton pregnancy, maternal age >18 years, live fetus at 11–13 weeks gestation and written informed consent. The participants were selected if a complete follow-up of the pregnancy (stored in the electronic database) was available. The exclusion criteria were: a lack of follow-up recorded in the electronic database, multiple gestation, fetal congenital anomalies and miscarriage at <24 weeks gestation. Data collection The gestational age was confirmed by ultrasound measurement of the crown-rump length. Maternal characteristics/medical history were collected via questionnaire. Maternal weight and height at the time of enrolment were also measured. No information about the use of aspirin was taken at the time of enrolment. All women were screened for PE in the first trimester. Duration of follow-up Delivery (assumed based on outcomes reported) Prevalence of PE in the study 67 (0.6%) developed early PE (delivery <34 weeks); 211 (1.8%) developed late PE (delivery at 34 to 42 weeks) Sample size N screened/invited = 12,284 N eligible = 11,632 N enrolled = 11,632 N excluded (with reason) = NR N lost to follow-up = NR (5.3%; major reason: not delivering in one of the participating hospitals) N completed = NR N excluded from analysis = NR but for comparison purposes, the PE cases delivering at <34 weeks were excluded from the ROC curve generated for evaluating the DRs for late PE (211 women developed late PE)

Study Reference

Di Martino 2019

N included in analysis = 11,632 (can assume 211 fewer included from ROC curve generated for evaluating the DRs for late PE)

Demographics

Characteristic	No PE (n=11,354)	PE (n=278)	p value
Maternal age, years, mean (SD)	32.4 (4.68)	34.3 (4.70)	<0.001
Maternal BMI, mean (SD)	22.61 (3.92)	24.88 (4.88)	<0.001
Racial origin, n (%)			
Caucasian	97.2 (11,036)	87.4 (243)	<0.01
Afro-Caribbean	0.9 (102)	2.2 (6)	<0.01
South-East Asian	2 (227)	4 (11)	<0.05
Other	2.2 (250)	0	<0.05
Nulliparous, n (%)	65.7 (7460)	70.9 (197)	0.073
Parous with previous PE, n (%)	2.9 (329)	35.3 (98)	<0.01
Family history of PE, n (%)	2.6 (295)	3.9 (11)	<0.01
Family history of hypertension, n (%)	29.8 (3383)	35.4 (98)	<0.05
Conception, n (%)			
Spontaneous	96.5 (10,957)	87.1 (242)	<0.01
Assisted	3.5 (397)	12.9 (36)	<0.01
History of chronic hypertension, n (%)	0.5 (57)	14.4 (40)	<0.01
History of type 1/type 2 diabetes mellitus	3.1 (352)	6.1 (17)	<0.01
History of SLR or APLS autoimmune disease, n (%)	0.4 (45)	1.4 (4)	<0.01
Renal disease, n (%)	1.4 (159)	3.6 (10)	<0.01
Known congenital thrombophilia, n (%)	2.4 (272)	2.9 (8)	0.0536

Screening Method

Index test

Comparison of 2 algorithms: FMF and BCNatal. To assess the agreement between the predicted risk and the prevalence of PE, the population screened was ranked according to the predicted risk of PE with the FMF and the BCNAtal algorithms, and was then divided into groups with a roughly similar number of cases of PE. For each group, the expected number of cases of PE was calculated as the sum of each pregnancy's individual risk. The observed prevalence of PE was also calculated for each group. For each group, the predicted and observed prevalences were compared (using a z test).

Reference standard

The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy: systolic blood pressure of >140 mm Hg and/or the diastolic blood pressure of >90 mm Hg on at least 2 occasions 4 hours apart developing after 20 weeks of gestation in previously normotensive women, and proteinuria of >300 mg in 24 hours or 2 readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection is available. In PE superimposed on chronic hypertension, significant proteinuria (as defined above) developed after 20 weeks of gestation in women with known chronic hypertension.

Test Accuracy

The DRs (95% CI) for early and late PE were 58.2% (45.5–70.2) vs. 41.8% (29.6–54.5) (p value <0.05) and 44.1% (37.3–51.1) vs. 38% (31.3–44.8) (p value <0.05) for the FMF and the BCNatal algorithms, respectively (at a 10% FPR). A similar difference between the 2 algorithms' performance (+17% for early PE and +7% about for late PE) was found at 5% and 10% FPR. Both algorithms underestimated the early PE risk; late PE risk estimation resulted in a better performance for both the algorithms.

Study Reference Di Martino 2019

	Algorithm	DR (95% CI) at 5% FPR	DR (95% CI) at 10% FPR	p value
Early PE <34 weeks	FMF	47.8 (35.4–60.3)	58.2 (45.5–70.2)	<0.001
	BCNatal	30.0 (19.3–42.3)	41.8 (29.6–54.5)	<0.001
Late PE 34 to 42 weeks	FMF	37.0 (30.4–43.9)	44.1 (37.3–51.1)	<0.001
	BCNatal	30.0 (22.4–38.6)	38.0 (31.3–44.8)	<0.001

Risk category		DR for FMF	FPR for FMF	DR for BCNatal	FPR for BCNatal
Early PE <34 weeks	>1:20	17.9	0.5	6.0	1.7
	>1:50	20.9	1.2	19.4	2.8
	>1:100	34.3	2.5	26.9	3.7
	>1:300	65.7	18.4	62.7	34.9
Late PE 34 to 42 weeks	>1:10	30.8	2.7	18.0	1.8
	>1:20	52.1	16.6	30.8	5.5
	>1:50	90.5	76.9	56.9	22.9
	>1:100	99.5	98.2	95.7	86.1

Authors' Conclusions

In this study population, the FMF algorithm had a better performance for early PE detection (+17% at both 5% and 10% FPR); Also for late PE the FMF resulted in a slight better performances (+7% at both 5% and 10% FPR) when compared with BCNAtal algorithm. As for calibration, both the FMF and the BCNAtal algorithms underestimated the risk of early PE, the number of observed PE cases being higher than that predicted. It must, however, be pointed out that prediction with "a priori risk" alone is still not sufficient, and the addition of biophysical and biochemical markers could improve the DRs of both algorithms, up to 80% for early PE, and lower the FPRs. In conclusion, in this study, the FMF and BCNatal algorithms yielded the expected DRs and furnished a reliable calculation of the "a priori" risk for early and late PE.

Caution should be used, however, in the comparison with the FMF algorithm as the high-risk group has been defined with slightly different criteria

Abbreviations: APLS, antiphospholipid antibody syndrome; BMI, body mass index; CI, confidence interval; DR, detection rate; FMF, fetal medicine foundation; FPR, false positive rate; NR, not reported; PE, preeclampsia; ROC, receiver operating characteristic; SD, standard deviation; SLR, systemic lupus erythematosus.

Table 25j: Erkamp 2020

Study Reference	Generation R Study (Erkamp 2020)
Study Design	Design Prospective cohort study Objective To determine screening performance of maternal, fetal and placental characteristics for selecting pregnancies at risk of gestational hypertension and pre-eclampsia in a low-risk multi-ethnic population. Dates 2001 to 2006 (pregnant women enrolled) Country The Netherlands Setting NR
Population Characteristics	Patient recruitment and eligibility: Included: low-risk pregnant women. Excluded: non-singleton live-births, women with pre-existing hypertension and women without information on GHD. Data collection: Maternal: Maternal age, height and weight were assessed/measured at enrolment and BMI was calculated. Information about ethnicity, parity and smoking status was obtained at enrolment by questionnaire. Blood pressure was measured at a median 13.8 (IQR 12.4–16.1) weeks gestation; the mean value of 2 blood pressure readings over a 60-second interval was documented. PlGF was measured in maternal venous blood samples at a median of 13.2 (IQR 12.2–14.9) weeks gestation. Fetal: Ultrasound examinations were carried out in first trimester (median 13.2 [IQR 12.2–14.7] weeks). Gestational age was established from the first ultrasound examination. Duration of follow-up: Delivery (inferred from 'response rate at birth was 61%') Prevalence of PE in the study: 149 (2.1%) women Sample size [some info from supplementary figure S1]: N screened/invited = NR N eligible = 7,617 N enrolled = NR N excluded (with reason) = twin birth (n=82), induced abortion (n=29), intra-uterine fetal demise (n=72), no information on hypertensive disorders available (n=200), pre-existing hypertension (n=75) N lost to follow-up = 35 N completed = NR N excluded from analysis = 0 N included in analysis = 7,124 Demographics: Characteristics of mothers and their children

Study Reference **Generation R Study (Erkamp 2020)**

Maternal characteristics	No gestational hypertensive disorders (n=6,702)	Pre-eclampsia (n=149)	p value
Age (years)			
<25, n (%)	1,364 (20.4)	30 (20.1)	0.07
25–35, n (%)	4,364 (65.1)	102 (68.5)	-
>35, n (%)	974 (14.5)	17 (11.4)	-
BMI			
Normal, n (%)	4,298 (64.1)	70 (47.0)	<0.01
Overweight, n (%)	1,661 (24.8)	47 (31.5)	-
Obese, n (%)	698 (10.4)	30 (20.1)	-
Race/ethnicity			
Dutch or European, n (%)	3,232 (58.2)	75 (53.6)	0.18
Surinamese, n (%)	561 (8.8)	19 (13.6)	-
Turkish, n (%)	575 (9.0)	11 (7.9)	-
Moroccan, n (%)	431 (6.7)	5 (3.6)	-
Cape Verdean or Dutch Antilles, n (%)	469 (7.3)	17 (12.2)	-
Parity, n nulliparous (%)	3,667 (55.2)	117 (79.1)	<0.01
Smoking, n (%)			
None, n (%)	4,265 (72.1)	97 (74.0)	0.09
Early-pregnancy only, n (%)	531 (9.0)	17 (13.0)	-
Continued, n (%)	1,121 (18.9)	17 (13.0)	-
Mean systolic blood pressure, median (IQR), mmHg	114 (107–122)	120 (112–128)	<0.01
Mean diastolic blood pressure, median (IQR), mmHg	67 (61–73)	73 (66–80)	<0.01
Mean arterial pressure, median (IQR), mmHg	82.7 (77.0–88.7)	88.3 (81.4–95.3)	<0.01
Placental growth factor			
First trimester, median (IQR) MOM	1.01 (0.76–1.35)	0.80 (0.59–1.13)	<0.01
First trimester, median (IQR), ng/ml	43.5 (29.2–73.0)	35.5 (23.2–57.58)	-

Screening Method

Index test

A baseline model, consisting of maternal characteristics known in early-pregnancy and associated with GHD, including maternal age, BMI, ethnicity, parity and smoking, was used to assess the screening potential of a simple maternal characteristics model. To evaluate the additional effect of first trimester blood pressure, first trimester MAP, per 10 mmHg, was added to the baseline model.

Reference standard

Pre-eclampsia was defined as de novo hypertension (blood pressure ≥140/90 mmHg) after 20 weeks gestation with concurrent proteinuria. Early-onset pre-eclampsia was defined as pre-eclampsia with a delivery <34 weeks gestational age based on available data. Any GHD was defined as either gestational hypertension or pre-eclampsia.

Test Accuracy

Screening performance for Pre-eclampsia

Models	Sensitivity at specificity:		
	70%	80%	90%
Maternal characteristics[a]	55%	45%	28%

Study Reference	**Generation R Study (Erkamp 2020)**

Blood pressure[b]	58%	49%	33%

[a]Maternal characteristics model: maternal age, BMI, ethnicity, parity, and smoking
[b]Blood pressure model: maternal characteristics model + first trimester MAP per 10 mmHg

For the secondary outcome early-onset pre-eclampsia, maternal characteristics with blood pressure achieved a good performance, with a sensitivity 57% at 90% specificity, which was better than screening for pre-eclampsia at any gestational age.

Authors' Conclusions	Routinely measured maternal characteristics including age, BMI, ethnicity, parity, smoking and blood pressure known in early-pregnancy have a moderate screening performance for pregnancies at risk of pre-eclampsia in a contemporary, multi-ethnic, low-risk population. This study adds to existing evidence that maternal characteristics, routinely measured in clinical practice, known early in pregnancy, can be used in screening for risk of pre-eclampsia in low-risk multi-ethnic populations. This study shows that maternal characteristics in early-pregnancy contain valuable information for assessment of risk of GHD and should be considered in routine care.

Abbreviations: BMI, body mass index; GHD, gestational hypertensive disorders; IQR, interquartile range; MAP, mean arterial pressure; MoM, multiple of the median; NR, not reported; PlGF, placental growth factor.

Table 25k: Gabbay-Benziv 2016

Study Reference	Gabbay-Benziv 2016
Study Design	Design Prospective observational study Objective To compare performance of a multimarker algorithm, risk profiles and their sequential application in prediction of preeclampsia and determining potential intervention targets Dates NR Country NR Setting NR
Population Characteristics	Patient recruitment and eligibility Women presenting with singleton gestation at 9–14 weeks were enrolled by informed written consent. Excluded: Patients who received aspirin prior to 16 weeks gestation and patients with prothrombotic risk profiles receiving heparin for prevention of PE as they were already recognised at risk and treated accordingly. Data collection A questionnaire was utilised to ascertain relevant medical history, and a standardised trans-abdominal ultrasound examination was performed to confirm gestational age, measure the fetal crown-rump length and perform uterine artery Dopplers to measure the Pulsatility Index. On maternal examination the weight (in kg), height (in cm) and body mass index (BMI, kg/m^2) were measured on regularly calibrated equipment. Blood pressure measurements (BP, mmHg) were taken using the Dinamap Pro 1000 automated sphygmomanometer. Maternal blood samples obtained by occlusive venipuncture were analysed for serum concentration of pregnancy-associated protein-A (PAPP-A), free beta human chorionic gonadotrophin (free β-HCG) and placental growth factor (PlGF). Pregnancy outcome was ascertained by study personnel and verified by source documentation. Duration of follow-up NR but at least until delivery (inferred based on outcomes reported) Prevalence of PE in the study PE developed in 108 (4.4%) of 2,433 women meeting the inclusion criteria, 18 of these were early-onset PE. Sample size N screened/invited = NR N eligible = 2,433 N enrolled = 2,433 N excluded (with reason) = NR N lost to follow-up = 0 N completed = 2433 N excluded from analysis = 0

Study Reference | **Gabbay-Benziv 2016**

N included in analysis = 2,433 – the first trimester multimarker algorithm for prediction of PE was derived from 1,258 women with available placental biomarkers results

Demographics

Characteristic	Value (n=2,433)
Mean maternal age, mean	29.5 ± 6.5 years (range 18–55)
Nulliparity, n (%)	1063 (43.7)
Caucasian	43.3%
African-Americans	49.8%
Prior history	
Chronic hypertension	156 (6.4%)
Diabetes mellitus	86 (3.5%)
Thrombophilia	3 (0.1%)
Prior PE	69 (2.8%)
Prior gestational diabetes	44 (1.8%)
Mean BMI	28.4 kg/m^2
Mean arterial BP at enrolment	83 mmHg
Getational age at delivery, mean	38.8 ± 2.3 weeks (range 20.6–42.6)
Mean birth weight	3218±601 g
Women delivered infants with birth weight >90th percentile	173 (7.1%)
Women delivered infants with birth weight <10th percentile	221 (9.1%)

Screening Method

Index test

- PAPP-A
- Free β-HCG
- PlGF

Univariate analysis was performed to identify statistically significant individual factors that were associated with subsequent development of PE. Relevant key factors that were found statistically significant on the univariate analysis were subsequently stratified as cardiovascular or metabolic or personal risk modifiers. Continuous variables were transformed to categorical ones using receiver operator characteristics (ROC) statistics with Youden's Index as cut off values. Women were then assigned as positive (1) or negative (0) for every risk profile based on the relevant key factors. All significant key variables were utilised together in logistic regression analysis to determine the best multimarker prediction algorithm for first trimester prediction of PE. The optimal probability score cut-off was determined using ROC curve with sensitivity set at 90%. Women were assigned as screen positive or screen negative according to above prediction algorithm. Finally, the predictive performance of each risk profile individually, the constructed multimarker algorithm and the sequential application of the 2 strategies was compared.

Chronic hypertension (listed as pre-pregnancy maternal diagnosis) and a BP over 120/71.5 mmHg at first trimester (values calculated by ROC statistics) were identified as the significant factors defining cardiovascular risk profile. Maternal diabetes, maternal BMI >28.7 kg/m^2 or ovulation induction defined the metabolic risk profile. Finally, logistic regression analysis identified nulliparity and prior PE as the significant personal risk modifiers. The first trimester multimarker algorithm was derived from 1258 women with available placental biomarkers results. All variables identified as significant in the univariate analysis were entered into logistic regression analysis to construct a prediction rule for PE.

Study Reference	**Gabbay-Benziv 2016**
	Reference standard Pregnancy outcome was ascertained by study personnel and verified by source documentation
Test Accuracy	The final model included nulliparity, prior PE, BMI, diastolic BP and PlGF A probability score of 0.021 cut-off value corresponded to 90% sensitivity, 40% specificity, 7% positive predictive value (PPV) and 99% negative predictive value (NPV) The prediction performance of the multimarker algorithm and risk profiles for subsequent development of pre-eclampsia is detailed below:

	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	TP	TN	FP	FN
Cardiovascular risk profile (N=2,433)	80.6 (71.8–87.5)	59.2 (57.2–61.2)	8.4 (6.8–10.3)	99 (97.7–99.1)	87	1,376	949	21
Metabolic risk profile (N=2,433)	60.6 (50.7–69.8)	61.9 (59.9–63.9)	6.9 (5.4–8.4)	97.1 (96.1–97.9)	66	1,439	886	42
Personal risk profile (N=2,433)	71.3 (61.8–79.6)	54.7 (52.7–56.8)	6.8 (5.4–8.4)	97.6 (96.6–98.4)	77	1,272	1,053	31
Multimarker algorithm (N=2,433)	90 (79.5–96.2)	40.2 (37.4–43.0)	7 (5.3–9)	98.8 (97.3–99.5)	54	481	717	6
Second stage sequential analysis[a] (N=771)	90.7 (79.7–96.9)	26.2 (23–29.6)	8.5 (6.3–11.1)	97.4 (94.1–99.1)	49	188	529	5

[a]Sequential approach – this line refers to applying cardiovascular or metabolic risk profiles (treatable) only on women screened positive by the multimarker algorithm

Authors' Conclusions	The study demonstrates that sequential application of a multimarker algorithm followed by risk profile categorisation in screen positive women numerically provides the best prediction of PE. A new sequential approach was presented for first trimester prediction of PE using a multimarker algorithm followed by application of risk profiles. This approach correctly predicts the highest proportion of women that develop PE and has the advantage of identifying potential treatment targets to prevent PE. This sequential screening approach may prove beneficial to determine women who should receive management for metabolic risks and to clarify appropriate management of cardiovascular risks.

Abbreviations: BMI, body mass index; BP, blood pressure; FN, false negatives; FP, false positives; HCG, human chorionic gonadotropin; PAPP-A, pregnancy-associated plasma protein A; PE, pre-eclampsia; PlGF, placental growth factor; NR, not reported; TN, true negatives; TP, true positives.

Table 25l: Goetzinger 2013 (Goetzinger 2013, Goetzinger 2014)

Study Reference	Goetzing 2013, Goetzinger 2014
Study Design	Design Prospective cohort study Objective To estimate the efficiency of first-trimester uterine artery Doppler, A-disintegrin and metalloprotease 12 (ADAM12), pregnancy associated plasma protein A (PAPP-A), and maternal characteristics in the prediction of pre-eclampsia (PE) and to develop a simplified multi-parameter risk-based scoring system for first-trimester prediction of PE for practical use in clinical practice, and to validate this scoring system in a patient population. Dates Goetzinger 2013: 2008 to 2010 Goetzinger 2014: 2008 to 2012 Country United States Setting Washington University Medical Centre
Population Characteristics	Patient recruitment and eligibility Women with singleton pregnancies between 11 and 14 weeks gestation. All consecutive eligible patients were approached for participation in the study at the time of their sonographic examinations. Exclusion: known chromosomal abnormalities, major congenital malformations. Data collection *Standard of care for first-trimester aneuploidy screening* Fetal crown rump length measurement to confirm pregnancy dating (within ±7 days of menstrual dating), nuchal translucency measurement, and serum PAPP-A and free β-human chorionic gonadotropin (β-hCG) measurements. Maternal demographics, medical histories, and obstetric histories were obtained from a detailed questionnaire routinely administered at the time of all initial sonographic examinations. *Additional data collection for study participants* • Patients provided an additional 10 mL of blood, which was used to measure the ADAM12 concentration • Bilateral uterine artery Doppler assessment (performed by transabdominal approach with colour flow mapping) • Delivery outcome information obtained from an electronic medical record review by a dedicated nurse coordinator. Patients who delivered outside the study institution signed a consent for release of medical records at the time of study enrolment Duration of follow-up Assumed until delivery, based on outcomes Prevalence of PE in the study Among 578 patients with complete data, PE developed in 54 pregnancies (9.3%), and early PE developed in 13 pregnancies (2.2%) Sample size N screened/invited = NR

Study Reference	**Goetzing 2013, Goetzinger 2014**

N eligible = NR
N enrolled = 1,225
N excluded (with reason) = withdrew (n=6), diagnosed with Trisomy 18 postnatally (n=1)
N lost to follow-up = 18
N completed = NR
N excluded from analysis = NR
N included in analysis = 578 (as study cohort, used to generate a PE prediction model); 622 (as validation cohort)

Demographics

Baseline maternal characteristics and obstetric history

Characteristic	PE (n=49)	No PE (n=529)	p value
Mean maternal age, years, mean (SD)	30.5 (6.2)	31.4 (5.7)	0.36
Nulliparous, n (%)	23 (46.9)	212 (40.1)	0.43
African American, n (%)	23 (46.9)	144 (27.2)	<0.001
Tobacco use, n (%)	7 (14.6)	43 (8.1)	0.15
BMI ≥30 kg/m^2, n (%)	31 (64.6)	150 (28.3)	<0.001
History of PE, n (%)	8 (16.3)	25 (4.7)	0.001
Chronic hypertension, n (%)	18 (36.7)	35 (6.6)	<0.001
Pre-gestational diabetes, n (%)	10 (20.4)	30 (5.7)	<0.001
Mean GA at delivery, weeks, mean (SD)	35.6 (3.9)	38.2 (3.6)	<0.001
PAPP-A MoM <10th percentile, n (%)	9 (18.4)	53 (10.0)	0.08
Mean uterine artery PI MoM, mean (SD)	1.03 (0.28)	1.04 (0.36)	0.79
Bilateral uterine artery notching, n (%)	7 (14.3)	64 (12.1)	0.63

Screening Method

Index test

- Maternal characteristics alone
- ADAM12 alone
- PAPP-A alone
- Uterine artery Doppler (pulsatility index [PI]) alone
- Various combinations of maternal characteristics, ADAM12, PAPP-A, uterine artery Doppler (PI)

Baseline maternal characteristics as well as ADAM12, PAPP-A, and uterine artery PI MoM values were compared between patients who developed PE and those who did not. Logistic regression was used to model the prediction of PE, incorporating various combinations of first-trimester parameters as well as maternal factors identified as significant in the univariate analysis. Sensitivity and specificity values at both 10% and 20% fixed false-positive rates were also calculated for each model.

Individual risk-based scoring

Maternal characteristics (chronic hypertension, history of PE, pre-gestational diabetes, BMI ⩾30 kg/m^2), serum markers (PAPP-A MoM <10th percentile), and ultrasound parameters (bilateral uterine artery notching) were used to develop individual risk-based scores

A weighted score was assigned by rounding the raw adjusted odds ratio to the nearest whole number. The total score for an individual patient was calculated by adding together the individual component scores. The prediction model and scoring system were then validated in the validation cohort.

Study Reference **Goetzing 2013, Goetzinger 2014**

Variable	aOR (95% CI)	p value	Weighted score
Chronic hypertension	4.5 (2.1–9.9)	<0.001	4
Past history of PE	2.8 (1.0–7.5)	0.04	3
Pre-gestational diabetes	2.2 (0.9–5.5)	0.09	2
BMI ≥30 kg/m2	2.2 (1.3–5.4)	0.006	2
PAPP-A MoM <10th percentile	1.5 (0.6–3.7)	0.33	1
Bilateral Uterine Artery Notching	0.8 (0.3–2.0)	0.63	1

Reference standard

- PE, defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg on at least 2 occasions, separated by at least 4 hours in the presence of proteinuria (≥0.3 g in a 24-hour specimen or ≥1+ protein on a urine dipstick) after 20 weeks gestation.
- Early onset PE, defined as PE requiring delivery before 34 weeks gestation.

Test Accuracy

Predictive efficiency of first-trimester markers for early PE

Marker	Sensitivity (10% FPR), %	Sensitivity (20% FPR), %
Maternal characteristics alone	55	58
ADAM12 alone	22	30
PAPP-A alone	16	22
Uterine artery Doppler alone	10	38
ADAM12 + PAPP-A + uterine artery Doppler	35	46
Maternal characteristics + ADAM12	54	62
Maternal characteristics + PAPP-A	54	54
Maternal characteristics + uterine artery Doppler	54	62
Maternal characteristics + ADAM12 + PAPP-A	54	62
Maternal characteristics + ADAM12 + uterine artery Doppler	54	62
Maternal characteristics + ADAM12 + PAPP-A + uterine artery Doppler	54	62

*Maternal characteristics include African American race and history of chronic hypertension.

Test performance characteristics for the prediction of pre-eclampsia at individual risk-based scores

Appendix 1 Score	**Appendix 2** Sensitivity (95% CI)	**Appendix 3** Specificity (95% CI)	**Appendix 4** PPV (95% CI)	**Appendix 5** NPV (95% CI)
Appendix 6 ≥4 (n = 80)	46.9% (32.5–61.7) **Appendix 7**	89.1% (86.1–91.7) **Appendix 8**	29.1% (19.4–40.4) **Appendix 9**	94.6% (92.2–96.5) **Appendix 10**
Appendix 11 ≥5 (n = 67)	40.8% (27.0–55.8) **Appendix 12**	91.1% (88.3–93.4) **Appendix 13**	30.3% (19.6–42.9) **Appendix 14**	94.2% (91.7–96.1) **Appendix 15**
Appendix 16 ≥6 (n = 53)	36.7% (23.4–51.7) **Appendix 17**	93.2% (90.7–95.2) **Appendix 18**	34.0% (21.5–48.3) **Appendix 19**	93.9% (91.5–95.8) **Appendix 20**
Appendix 21 ≥7 (n = 30)	24.5% (13.3–38.9) **Appendix 22**	96.5% (94.5–97.9) **Appendix 23**	40.0% (22.7–59.4) **Appendix 24**	93.1% (90.6–95.1) **Appendix 25**
Appendix 26 ≥8				

Study Reference	**Goetzing 2013, Goetzinger 2014**

(n=16)	14.3% (5.9–27.2) **Appendix 27**	98.3% (96.7–99.2) **Appendix 28**	43.8% (19.8–70.1) **Appendix 29**	92.3% (89.9–94.4) **Appendix 30**

Test performance characteristics for the prediction of pre-eclampsia using the risk factor-based scoring system compared between study cohort and validation cohort

		Study cohort (n=578)	Validation cohort (n=622)
Appendix 31	Sensitivity (95% CI)	36.7% (23.4–51.7) **Appendix 32**	25.6% (13.0–42.1) **Appendix 33**
Appendix 34	Specificity (95% CI)	93.2% (90.7–95.2) **Appendix 35**	94.9% (92.3–96.8) **Appendix 36**
Appendix 37	PPV (95% CI)	34.0% (21.5–48.3) **Appendix 38**	32.3% (16.7–51.4) **Appendix 39**
Appendix 40	NPV (95% CI)	93.9% (91.5–95.8) **Appendix 41**	93.1% (90.3–95.3) **Appendix 42**
Appendix 43	Positive likelihood ration (95% CI)	5.4 (3.3–8.8) **Appendix 44**	5.0 (2.6–9.9) **Appendix 45**
Appendix 46	Negative likelihood ration (95% CI)	0.7 (0.5–0.8) **Appendix 47**	0.8 (0.6–0.9) **Appendix 48**

Authors' Conclusions

First-trimester ADAM12, PAPP-A, and uterine artery Doppler characteristics are not sufficiently predictive of preeclampsia. Combinations of these parameters do not further improve their screening efficiency.

Findings from our prospective cohort study demonstrate that both ADAM12 and PAPP-A levels are significantly reduced in patients who develop PE. However, despite these associations, the predictive efficiency of ADAM12 and PAPP-A was overall modest and not sufficient for clinical use.

Maternal characteristics alone actually have superior test performance for the prediction of PE, which are not enhanced by the addition of these first-trimester markers, either individually or in combination.

The risk factor-based scoring system for the first-trimester prediction of pre-eclampsia demonstrates both acceptable accuracy (overall predictive accuracy of 80%) and excellent reproducibility. Combining maternal characteristics, serum markers, and ultrasound parameters, this scoring system provides a user-friendly tool with both clinical application as well as research opportunity for future pre-eclampsia intervention studies.

Abbreviations: ADAM12, A-disintegrin and metalloprotease 12; BMI, body mass index; EMR, electronic medical record; FPR, false positive rate; GA, gestational age; β-hCG, β-human chorionic gonadotropin; MoM, multiples of the median; NPV, negative predictive value; NR, not reported; PAPP-A, pregnancy associated plasma protein A; PE, pre-eclampsia; PI; pulsatility index; PPV, positive predictive value; SD, standard deviation.

Table 25m: GOS Study

Study Reference	GOS study (Gasse 2018, Boutin 2018a, Boutin 2018b, Boutin 2018c, Demers 2018, Boutin 2021a, Boutin 2021b)
Study Design	Design Prospective cohort study Objective **Gasse 2018:** To estimate the value of first-trimester mean arterial pressure (MAP), alone or in combination with other maternal characteristics, for the prediction of the hypertensive disorders of pregnancy, including gestational hypertension (GH), PE, preterm PE and early-onset PE. **Boutin 2018a**: To estimate the predictive value of first trimester pregnancy-associated plasma protein A (PAPP-A) for PE, small for gestational age (SGA), and fetal death in a Canadian population of nulliparous women. **Boutin 2018b:** To evaluate the role of maternal characteristics for the prediction of PE in a large cohort of Canadian nulliparous women with singleton pregnancies. **Boutin 2018c:** To evaluate the performance of first-trimester placental growth factor (PlGF) concentration in the prediction of PE in nulliparous women. **Demers 2018:** To estimate the performance of first-trimester uterine artery pulsatility index (UtA-PI) for the prediction of PE. **Boutin 2021a:** To estimate the ability of a combination of first-trimester markers to predict preterm pre-eclampsia in nulliparous women. **Boutin 2021b:** To estimate the rate of placenta-mediated pregnancy complications in nulliparous women with a positive first-trimester Fetal Medicine Foundation preterm pre-eclampsia screening test. Dates March 2011 to December 2014 Country Canada Setting Two academic centres in Quebec City (Centre Hospitalier Universitaire de Québec and Université Laval, Québec)
Population Characteristics	Patient recruitment and eligibility Prospective nulliparous women with singleton pregnancies attending their 11 0/7–13 6/7 weeks ultrasound comprised the cohort. Eligible women were at least 18 years old and at 11 0/7–13 6/7 weeks of gestation. Gestational age was determined by the fetal crown-rump length (CRL). Only pregnancies without major fetal abnormalities were included. Multiple pregnancy, miscarriages diagnosed at recruitment, and chromosomal abnormality or lethal anomaly leading to medical termination of pregnancy were excluded. Participants who received daily aspirin for medical reasons at any time during their pregnancy were also excluded. **Boutin 2021a:** Women willing to participate were instructed to contact the research team for an initial visit between 11 0/7 and 13 6/7 weeks gestation. Included: nulliparous women with singleton, living fetuses. Women with fetal demise at the initial visit or before 14 weeks gestation and multiparous women were excluded. Women who subsequently underwent medical termination of pregnancy for fetal anomalies or reported taking aspirin on a regular basis at any point during their pregnancy were excluded. Participants with CRL below 45 mm or over 85 mm at the time of blood pressure measurement, blood sampling, or ultrasound examination were excluded from the analysis. **Boutin 2021b:** Nulliparous women with singleton living fetuses were recruited at 11 0/7 to 13 6/7 weeks of gestation. Multifetal pregnancies, fetal lethal abnormalities and fetal chromosomal abnormalities leading to medical termination of pregnancy and fetal demise before 14 weeks of gestation were excluded. Women who had reported taking daily aspirin over the course of their pregnancies (any indication) were also excluded. Complete follow-ups were required for inclusion in the study.

Data collection

Gasse 2018:

- Maternal weight and height were measured to calculate body mass index (BMI).
- Crown-rump length was measured as part of the initial ultrasound visit.
- Participants were followed until delivery and medical charts were reviewed.
- Trained research nurses took maternal blood pressure with validated automated devices for pregnant women that were calibrated at regular intervals during this study. Automated devices were taking a series of recordings (minimum of 2) until the difference between 2 consecutive readings was least than 10 mmHg in systolic or 6 mmHg in diastolic blood pressure to obtain the best validity of the measurement as recommended by previous studies, a single measurement being associated to be a common error in blood pressure measurement.

Boutin 2018a:

- Maternal venous blood was collected, centrifuged, aliquoted, and stored at −80°C.
- Pregnancy outcomes, including PE and preterm PE (definition according to the Society of Obstetricians and Gynaecologists of Canada [SOGC] guidelines), birth weight, and fetal death at 16 weeks of gestation or later, were collected from medical records by a nurse blinded to all first trimester data.

Boutin 2018b:

- A nurse interviewed the participant at the initial visit to collect data on maternal age, declared ethnicity, smoking habit, use of assisted reproductive technology, and medical and obstetrical history.
- A nurse reviewed medical charts after delivery for perinatal outcomes including PE and gestational age at delivery.

Boutin 2018c:

- A nurse collected maternal venous blood for measurement of PlGF and PAPP-A concentration. Data from the medical record were retrieved by a nurse blinded to all first-trimester data after the expected date of delivery.

Demers 2018:

- At recruitment, a research nurse evaluated eligibility, collected data on maternal characteristics (age, ethnicity, smoking status, history of chronic disease, and use of assisted reproductive technologies [ART]), and measured the participant's weight and height for the calculation of BMI.
- Transabdominal ultrasound was conducted by technicians certified from the Fetal Medicine Foundation (FMF). CRL was measured and UtA-Doppler's was performed on both uterine sides to measure and to calculate mean UtA-PI according to the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) criteria.

Boutin 2021a:

- During the initial visit, a research nurse collected information on maternal age, ethnicity, weight and height, fertility treatment (use of ovulation agents, insemination, and/or assisted reproductive techniques), and chronic diseases (diabetes, hypertension, renal disease, antiphospholipid syndrome). Systolic and diastolic arterial pressures were measured. Maternal venous blood was collected. The initial visit also included a trans-abdominal ultrasound examination to measure CRL and UtA-PI.
- After the end of the recruitment period, concentrations of PlGF, SFlt-1,, PAPP-A, β-hCG, and AFP were measured.
- Within 3 months after the expected end of pregnancy, medical records were reviewed to collect data on fetal congenital or chromosomal abnormalities, gestational diabetes, gestational hypertension, pre-eclampsia, intrauterine death, medical termination of pregnancy, gestational age at any collected diagnosis and gestational age at birth, fetal sex and birth weight.

Boutin 2021b:

- During baseline visits, data on maternal age, ethnicity, smoking, methods of conception and history of chronic diseases (e.g. hypertension, diabetes and antiphospholipid syndrome). Maternal height and weight were measured to calculate the BMI. Mean arterial blood pressure was also measured. A blood sample was collected for the measurement of maternal serum biomarkers. PAPP-A, PlGF and SFlt-1 concentrations were measured. Crown-rump length and mean UtA-PI were both measured. All medical records were reviewed

Study Reference	GOS study (Gasse 2018, Boutin 2018a, Boutin 2018b, Boutin 2018c, Demers 2018, Boutin 2021a, Boutin 2021b)

within 3 months of the expected delivery date. Information on medical terminations of pregnancy and congenital and chromosomal anomalies were collected to confirm eligibility. Diagnoses of gestational diabetes and gestational hypertension, fetal sex, and gestational age and weight at delivery were collected.

Duration of follow-up
Until delivery

Prevalence of PE in the study
Of 4,700 women, 491 (10.3%) developed a hypertensive disorders of pregnancy (HDP), including 250 (5.3%) GH without PE; 241 (5.1%) PE; 33 (0.7%) preterm PE and 10 (0.2%) early-onset PE.

Boutin 2021a:
- 225 (4.9%) cases of PE were observed; 29 (0.6%) cases of preterm PE were observed.

Boutin 2021b:
- 223 (4.9%) cases of PE were observed including 29 (0.6%) cases of preterm PE.

Sample size
N screened/invited = 5,005
N eligible = 4,749
N enrolled = 4,749
N excluded (with reason) = <18 years old (n=2), multiple gestations (n=29), medical termination of pregnancy (n=46) and baseline visit outside the targeted gestational age window (n=179)
N lost to follow-up = 49
N completed = 4,700
N excluded from analysis = 0
N included in analysis = 4,700

Boutin 2021a:
- 4,659 participants were recruited
- Follow-up data were unavailable for 49 women (1%)
- Complete data for all predictors considered were available for 4,531 (97%) participants
- In 11 (0.2%) women, the pregnancy ended before 20 weeks gestation

Boutin 2021b:
- 4,738 participants were eligible for the study
- 50 (1.1%) were lost to follow up
- At least 1 of the predictors' value was missing in 113 participants (2.4%)
- 4,575 participants (96.6%) with complete observations were included in the analyses

Demographics

Characteristic	No GH or PE	GH	PE	p value
Mean maternal age, years (SD)	28.9 (4.1)	28.3 (4.4)	29.3 (3.9)	0.009

Study Reference **GOS study (Gasse 2018, Boutin 2018a, Boutin 2018b, Boutin 2018c, Demers 2018, Boutin 2021a, Boutin 2021b)**

Mean baseline gestational age, weeks (SD)	13.0 (0.6)	13.0 (0.7)	13.0 (0.6)	0.54
Mean baseline crown-rump length, mm (SD)	67 (9)	67 (9)	67 (8)	0.58
Mean BMI, kg/m^2 (SD)	24.7 (4.7)	28.3 (4.4)	29.3 (3.9)	<0.0001
Mean gestational age at delivery, weeks (SD)	39.5 (2.0)	39.4 (1.5)	38.3 (2.5)	<0.0001
Ethnicity, n (%)				
Caucasian	4,038 (96.0)	245 (97.2)	232 (96.3)	0.72
Afro-American	57 (1.4)	1 (0.4)	1 (0.4)	
Asian	33 (0.8)	2 (0.8)	2 (0.8)	
First Nations, mixed or others	69 (1.6)	4 (1.6)	6 (2.5)	
Missing	10 (0.2)	0 (0)	0 (0)	
Smoking, n (%)	306 (7.4)	17 (6.8)	13 (5.5)	0.27
History of chronic disease, n (%)				
Diabetes	8 (0.2)	0	1 (0.4)	0.58
Hypertensive disorder	13 (0.3)	4 (1.6)	6 (2.5)	<0.0001
Renal disease	92 (2.2)	7 (2.8)	5 (2.1)	0.88
Rheumatoid arthritis/other inflammatory diseases	69 (1.6)	2 (0.8)	1 (0.4)	0.07

Boutin 2021a:

	Group; n (%) or median (IQR)		
Variables	Overall (n=4,659)	Unaffected (n=3,764)	Preterm PE (n=29)
Maternal age, years	28.7 (26.1–31.3)	28.7 (26.1–31.3)	29.0 (26.0–31.2)
Ethnicity/race			
Caucasian/white	4,408 (94.6)	3,564 (94.7)	28 (96.6)
Afro-American/Black	59 (1.3)	48 (1.3)	-
Latin Hispanic	65 (1.4)	51 (1.4)	-
Asian	38 (0.8)	31 (0.8)	1 (3.5)
Native American	6 (0.1)	5 (0.1)	-
Mixed/other	73 (1.7)	55 (1.5)	-
Smoking	339 (7.3)	256 (6.8)	1 (3.5)
Fertility treatment	395 (8.5)	309 (8.2)	4 (13.8)
Assisted reproductive techniques	81 (1.7)	61 (1.6)	-
Ovulation agents	226 (4.9)	175 (4.7)	3 (10.3)
Insemination	169 (3.6)	136 (3.6)	2 (6.9)
Chronic diseases			
Hypertension	12 (0.3)	8 (0.2)	-
Diabetes mellitus	7 (0.2)	7 (0.2)	-
Renal diseases	102 (2.2)	85 (2.3)	-

Study Reference	**GOS study (Gasse 2018, Boutin 2018a, Boutin 2018b, Boutin 2018c, Demers 2018, Boutin 2021a, Boutin 2021b)**

Antiphospholipid syndrome	4 (0.1)	3 (0.1)	-
Biometrics			
BMI, kg/m²	23.8 (21.6–27.0)	23.8 (21.6–26.9)	26.4 (23.0–30.9)
MAP, mmHg	82.5 (78.5–87.5)	82.3 (78.5–87.0)	90.0 (85.7–94.8)
Biomarkers			
PAPP-A, mU/L	3,638 (2,284–5,544)	3,742 (2,355–5,653)	2,235 (1,856–3,233)
PlGF, pg/mL	34.7 (26.6–45.7)	35.5 (27.3–46.3)	21.6 (15.0–31.0)
sFlt-1, pg/mL	998.6 (754.7–1,341.9)	1,021.8 (771.0–1,370.7)	851.6 (657.9–1,095.1)
AFP, ng/mL	15.6 (11.3–20.7)	15.3 (11.0–20.3)	16.8 (11.1–23.4)
Free β-hCG, ng/mL	31.4 (20.9, 48.8)	31.5 (21.0–48.9)	34.5 (25.9–52.1)
Ultrasound			
UtA-PI	1.64 (1.33–2.03)	1.63 (1.32–1.99)	2.21 (1.81–2.58)

Boutin 2021b:

Variables	Overall (n=4,575)	No placenta-mediated complications (n=3,705)	Preterm PE (n=29)	Term PE (n=194)
Maternal age, years	28.7 (26.1–31.3)	28.7 (26.1–31.3)	29.0 (26.0–31.2)	29.3 (26.5–32.0)
Body mass index, kg/m²[a]	23.8 (21.6–26.9)	23.8 (21.6–26.9)	26.4 (23.0–30.9)	25.5 (22.5–30.3)
Ethnicity[a]				
White	4,341 (94.9)	3,519 (95.0)	28 (96.6)	183 (94.3)
Black	57 (1.3)	47 (1.3)	0 (0)	1 (0.5)
Asian	37 (0.8)	31 (0.8)	1 (3.5)	1 (0.5)
Mixed or other	140 (3.1)	108 (2.9)	0	9 (4.6)
History of hypertension	12 (0.3)	8 (0.2)	0	2 (1.0)
Diabetes mellitus, type I[a]	1 (0.02)	1 (0.03)	0	0
Diabetes mellitus, type II[a]	6 (0.10)	6 (0.20)	0	0
Antiphospholipid syndrome[a]	4 (0.1)	3 (0.1)	0	0
Ovulation stimulation	206 (4.5)	161 (4.4)	3 (10.3)	10 (5.2)
In vitro fertilisation	81 (8.1)	61 (1.7)	0 (0)	8 (4.1)
MAP, mmHg	82.5 (78.5–87.5)	82.3 (78.5–87.0)	90.0 (85.7–94.8)	87.9 (84.2–93.0)
UtA-PI	1.64 (1.33–2.03)	1.63 (1.32–1.99)	2.21 (1.81–2.58)	1.57 (1.27–2.04)
PlGF (pg/mL)	34.7 (26.5–45.7)	35.5 (27.3–46.3)	21.6 (15.0–31.0)	31.7 (23.0–42.0)
sFlt-1 (pg/mL)	998 (754–1341)	1,023 (771–1373)	852 (658–1,095)	933 (726–1,221)
PAPP-A, mU/L	3,640 (2,281–5,534)	3,751 (2,355–5,640)	2,235 (1,856–3,233)	2,996 (2,144–48,34)

Data are presented as number (percentage) and median (Q1–Q3)
[a]Participants who identified as Latin Hispanic and participants who identified as Indigenous were classified in mixed or other

Screening Method	Index test **Gasse 2018: First-trimester MAP:** • Trained research nurses took maternal blood pressure with validated automated devices for pregnant women that were calibrated at regular intervals during this study. The MAP was the average of both arms' computation of the addition of the systolic blood pressure and

the double of diastolic blood pressure, divided by 3. Measures of blood pressure taken in the research setting were not revealed to the participants or to their healthcare providers. Multiples of the median (MoM) of MAP adjusted for gestational age were computed, and a graphical display of the relationship between CRL and MAP was produced. Receiver operating characteristic (ROC) curves analyses were performed, and screening performance of MAP for HDP were estimated by calculating the area under the curve (AUC).

Boutin 2018a: PAPP-A:

- Maternal venous blood was collected, centrifuged, aliquoted, and stored at −80°C. At the end of the recruitment period, a technician blinded to all clinical outcomes measured the concentrations of PAPP-A in all serum samples by using an automated immunofluorescent assay. The automated assay can detect concentrations of PAPP-A ranging from 4 to 90,000 mU/L. In samples where PAPP-A was below detectable threshold, a value of one half the minimal detection limit (2 mU/L) was used. PAPP-A concentrations were reported in MoMs adjusted for gestational age (on the basis of CRL) at sampling date. ROC curves analyses with their area under the curve were used to evaluate the performance of PAPP-A for the prediction of PE. Detection rates (DR), false-positive rates (FPR), and positive predictive values (PPV) were calculated for PAPP-A <0.4 MoM, which was reported as approximately the 5th percentile.

Boutin 2018b: Maternal characteristics:

- Maternal characteristics for the prediction of all PE and preterm PE, including maternal age, BMI, history of hypertension, chronic inflammatory disease, ovulation induction, and in vitro fertilisation (IVF). Using ROC curve analyses and AUC, the screening performances of each marker and of the final model for the prediction of all PE and for preterm PE specifically were calculated. DRs at specific FPRs of 10% were reported.

Boutin 2018c: PlGF:

- At the end of recruitment, a technician blinded to all clinical outcomes measured concentrations of PlGF and PAPP-A in all serum samples. As the PlGF concentration was not normally distributed, it was log transformed to obtain a centered distribution. The MoM adjusted for gestational age (on the basis of CRL) at serum sampling date was calculated for the log10 concentrations of PlGF and PAPP-A. Using ROC curve analyses, the screening performance of log10 PlGF MoMs for the prediction of PE, term PE and preterm PE, as well as detection rates at a FPR of 10%, were calculated.

Demers 2018:

- Mean UtA-PI was log-transformed to obtain normal distribution and reported in MoM adjusted for gestational age. ROC curves were constructed based on cumulative incidences computed through proportional hazard models. The screening performance of log10 UtA-PI MoMs was calculated using AUC for the prediction of PE, term PE, and preterm PE (<7 weeks), as well as DR with 10% FPR. Additionally, ROC curves combining UtA-PI and maternal characteristics (age, BMI, ethnicity, smoking, history of diabetes, chronic hypertension, chronic renal disease, inflammatory disease, antiphospholipid syndrome [APS], and use of ART) were used. Family history of PE was not collected and therefore was not included.

Boutin 2021a:

- Biomarkers were log-transformed to obtain a symmetrical distribution
- BMI and MAP were computed as well as MoM of the MAP, $\log_{10}$PlGF, $\log_{10}$free β-hCG, $\log_{10}$AFP and $\log_{10}$UtA-PI, all adjusted for CRL.
- First-trimester variables were first assessed individually for their association with preterm pre-eclampsia. A multivariable proportional hazard model predicting preterm pre-eclampsia was constructed. Predictors were selected using a backward elimination approach based on the change in the Akaike information criterion.
- A receiver operating characteristic curve was created with the predicted risk from the final model. The AUC and its 95% CI and the detection rate of preterm pre-eclampsia for a 10% false-positive rate were calculated. The proportion of participants identified by the model as having a high or low risk of preterm pre-eclampsia who developed any great obstetrical syndrome (composite outcome including term pre-eclampsia, birth weight below the 10^{th} centile for the gestational age, intrauterine death or prematurity) was also estimated.
- The final model included 4 variables, 3 of which were strong predictors: MAP MoM ($p<0.001$), $\log_{10}$PlGF MoM ($p<0.001$), $\log_{10}$AFP MoM ($p=0.106$) and $\log_{10}$UtA-PI MoM ($p=0.002$).

Boutin 2021b:

Study Reference	**GOS study (Gasse 2018, Boutin 2018a, Boutin 2018b, Boutin 2018c, Demers 2018, Boutin 2021a, Boutin 2021b)**

- The online FMF algorithm batch assessment tool was used for the calculation of risk of all women in the cohort using the combination of maternal characteristics, mean arterial blood pressure, serum biomarkers and UtA-PI.
- The individual risks estimated by the FMF algorithm were dichotomised into positive or negative screening tests using risk cut-offs of 1 in 70 or 1 in 100. The chosen cut-offs were based on previous reports on the algorithm corresponding to the estimated risk cut-offs for a 10% to 15% false positive rate.

Reference standard

Gasse 2018:

- Outcomes included all HDP including PE as the primary outcome.
- A standard definition based on the American College of Obstetricians and Gynecologists (ACOG) and the SOGC guidelines was used. The diagnosis of PE was based on the presence of GH occurring at or after 20 weeks gestation in previously normotensive women with the presence of significant proteinuria and/or one or more adverse conditions and/or one or more severe complications.
- GH is defined as a systolic blood pressure of 140 mmHg or more and/or a diastolic blood pressure of 90 mmHg or more on at least 2 occasions 4 h apart. Proteinuria is defined as ≥0.3 g/d in a complete 24-h urine collection or ≥30 mg/Mmol urinary creatinine in a spot (random) urine sample or ≥1+ proteinuria on a urinary dipstick.
- Adverse conditions and severe complications include headache and visual symptoms, epigastric pain, fetal death, intra-uterine growth restriction, placental abruption, elevated liver enzyme, thrombocytopenia, and severe hypertension (>160 mmHg of systolic blood pressure or >105 mmHg of diastolic blood pressure).
- Gestational age at delivery was used to divide cases of PE into term (≥37 weeks), preterm (<37 weeks) and early-onset (<34 weeks) PE.
- A maternal-fetal medicine subspecialist blinded to all other research data reviewed all cases with an adverse pregnancy outcome to confirm the diagnosis.

Demers 2018 and Boutin 2018a, b and c:

A maternal fetal medicine specialist, also blinded to first trimester data, reviewed all cases of hypertensive disorder to confirm the diagnoses. Boutin 2021a: Pre-eclampsia was defined as hypertension observed after the 20th week of pregnancy in the presence of proteinuria or an adverse condition or severe complication (e.g., headache; chest pain; dyspnea; oxygen saturation <97%; high white blood cell count; high international normalised ratio; activated partial thromboplastin time, or low platelet count; high serum creatinine or uric acid; nausea; epigastric pain) and classified as preterm when delivered before 37 weeks gestation.

Boutin 2021a and 2021b:

- PE was defined as hypertension observed after 20 weeks of gestation in the presence of proteinuria or an adverse condition or a severe complication (such as headache, chest pain, dyspnoea, oxygen saturation of <97%, high white blood cell count, high international normalised ratio or activated partial thromboplastin time or low platelet count, high serum creatinine or uric acid, nausea, and epigastric pain).
- Preterm PE was defined as PE with delivery before 37 weeks of gestation.
- Early-onset PE referred to cases with delivery before 34 weeks of gestation.

Test Accuracy

Gasse 2018: First-trimester MAP for prediction of HDP

HDP	Detection rate (%)		
	FPR 5%	FPR 10%	FPR 25%
GH, no PE	21	39	66
All PE	19	36	58
Term PE	17	34	57

Study Reference **GOS study (Gasse 2018, Boutin 2018a, Boutin 2018b, Boutin 2018c, Demers 2018, Boutin 2021a, Boutin 2021b)**

Preterm PE	33	48	70
Early-onset PE	40	60	70

Boutin 2018b: First-trimester low PAPP-A (<0.4 MoM) for the prediction of placenta-mediated outcomes

Outcomes	DR (%)	FPR (%)	PPV (%)	NPV (%)	LR+ (95% CI)	LR− (95% CI)
PE	9.8	7.4	6.3	95.2	1.32 (0.87–1.99)	0.97 (0.93–1.02)
Preterm PE	17.2	7.5	1.4	99.4	2.31 (1.03–5.15)	0.89 (0.76–1.06)

Boutin 2018a: Maternal characteristics

For an FPR of 10%, a combination of maternal characteristics could have predicted 23% of PE and 19% of preterm PE. The discriminative ability of such model was not significantly different from that of BMI alone (both with p>0.10).

Boutin 2018c: First-trimester log_{10}PlGF MoM and log_{10}PlGF MoM plus maternal characteristics for prediction of term and pre-term PE at 10% FPR

Outcome	DR (%)	PPV
Log_{10}PlGF MoM <0.8537		
Preterm PE	40	NR
Term PE	21	NR
Log_{10}PlGF MoM + maternal characteristics[a]		
Preterm PE	55	NR
Term PE	26	NR
PlGF <10th percentile (0.59 MoM)		
PE	NR	9.7
Preterm PE	NR	7.2
Term PE	NR	2.5

[a] Maternal age, BMI, ethnicity, smoking, chronic diseases and fertility treatment

Demers 2018: First trimester UtA-PI and UtA-PI plus maternal characteristics for the prediction of term and pre-term PE at 10% FPR

Outcome	DR (%)
UtA-PI	
Preterm PE	40
Term PE	16
UtA-PI + maternal characteristics	
Preterm PE	45
Term PE	25

Boutin 2021a:

- For a 10% false-positive rate, the model would have detected 55.2% (95% CI 37.1–73.3% of preterm PE cases. The removal of AFP from the model gave similar results (detection rate 51.7% [95% CI 33.5%–69.9%] at a 10% false positive rate), but with a slightly higher Akaike information criterion. The addition of maternal age, body mass index and PAPP-A did not improve the statistical model and increased the uncertainty.
- Among participants identified at high risk of preterm PE by the final model, 9.8% (95% CI 7.3%–12.8%) developed PE at term).

Study Reference	**GOS study (Gasse 2018, Boutin 2018a, Boutin 2018b, Boutin 2018c, Demers 2018, Boutin 2021a, Boutin 2021b)**

- Overall 32.8% (95% CI 28.6%–37.2%) of women considered at high risk for preterm pre-eclampsia developed at least one complication of the composite outcome, compared with 16.6% (95% CI 15.5%–17.8%) among those with negative screening (p<0.001).

Boutin 2021b:

- A risk cut-off of 1 in 70 could have correctly predicted up to 27.4% of PE, 55.2% of preterm PE, 70.0% of early-onset PE at a 10% false-positive rate.
- A risk cut-off of 1 in 100 could have correctly predicted up to 35.4% of PE, 69.0% of preterm PE, 70.0% of early-onset PE at a 15% false-positive rate.

	FMF risk cutoff of 1 in 70							FMF risk cutoff of 1 in 100						
Variables	DR (%)	FPR (%)	PPV (%)	NPV (%)	LR+	LR-	ACC	DR (%)	FPR (%)	PPV (%)	NPV (%)	LR+	LR-	ACC
PE	27.4	9.9	12.3	96.0	2.75	0.81	0.87	35.4	14.9	10.9	96.3	2.38	0.76	0.83
Preterm PE	55.2	10.5	3.2	99.7	5.25	0.50	0.89	69.0	15.6	2.7	99.8	4.43	0.37	0.84
Early-onset PE	70.0	10.7	1.4	99.9	6.56	0.34	0.89	70.0	15.8	1.0	99.9	4.43	0.36	0.84

Authors' Conclusions

Gasse 2018: The study confirms that MAP measured with an automated device between $11^{0/7}$ and $13^{6/7}$ weeks of gestation is useful in the early identification of nulliparous women at high-risk of GH, term and preterm PE.

Boutin 2018a: Low first trimester PAPP-A is of limited predictive value for PE, preterm PE, SGA, and fetal death. The study concludes that that low PAPP-A should not be used alone for the prediction of these outcomes, and it does not constitute an indication for low-dose aspirin or additional fetal well-being monitoring during pregnancy.

Boutin 2018b: The performance of maternal risk factors in the discrimination between PE and unaffected pregnancies is moderate. Therefore, these risk factors should not be used alone in clinical practice for the identification of pregnancies at high risk of PE.

Boutin 2018c: Maternal serum PlGF concentrations in the first trimester can be used to discriminate between nulliparous women at low and those at high risk of PE and especially preterm PE. However, its predictive value alone remains moderate, and it should be used in combination with other markers and maternal characteristics in order to determine the benefits of targeted aspirin prophylaxis.

Demers 2018: Mean UtA-PI should not be used alone but remains a useful factor in the first-trimester prediction of preterm PE. It should be adjusted for gestational age (or CRL) at the time of measurement and combined with other markers (maternal characteristics and biochemical markers such as PAPP-A and PlGF) to reach optimal benefits.

Boutin 2021a: In this cohort of nulliparous women mainly of Caucasian ethnicity, it was demonstrated that the combination of MAP, serum levels of PlGF and AFP, and Uta-PI measured at 11–13 weeks gestation could identify 55% of women who developed preterm pre-eclampsia at a false-positive rate of 10%. Furthermore, the prediction of high risk of preterm pre-eclampsia by the model was also associated with greater risk of other complications. Almost a third of women identified as high risk by the model developed one of the great obstetrical syndromes, namely pre-eclampsia, SGA, intrauterine fetal death, or preterm delivery. This cohort study demonstrates the potential of a multivariable algorithm for the prediction of high risk of preterm pre-eclampsia in a population of nulliparous women. Moreover, we observed that the combination of first-trimester MAP, maternal serum PlGF and AFP and UtA-PI could be used for the prediction of any of the great obstetrical syndromes.

Boutin 2021b: This study shows the potential benefit of introducing the FMF algorithm in obstetrical practices in Canada as part of the placenta-mediated complication prevention. Although placenta-mediated complications of pregnancy encompass a wide range of pathophysiological processes, the FMF algorithm identified up to 32% of women at a high risk of such complications. Furthermore, approximately 1 in 10 women with a positive test (estimated risk of ≥1 in 70) developed a severe complication. In addition to the benefits observed in the prevention of PE, the use of a screening algorithm with introduction of low-dose aspirin prophylaxis could help reduce the

Study Reference	GOS study (Gasse 2018, Boutin 2018a, Boutin 2018b, Boutin 2018c, Demers 2018, Boutin 2021a, Boutin 2021b)
	frequency of other placenta-mediated pregnancy complications and improve the health of mothers and fetuses. The results are supportive of the use of the FMF algorithm in the Canadian population.

Abbreviations: β-hCG, beta-human chorionic gonadotrophin; ACC, accuracy; ACOG, American College of Obstetricians and Gynecologists; AFP, alpha-fetoprotein; APS, antiphospholipid syndrome; ART, assisted reproductive technologies; AUC, area under the curve; BMI, body mass index; CRL, crown-lump length; DR, detection rate; FMF, Fetal Medicine Foundation; FPR, false positive rate; GH, gestational hypertension; HDP, hypertensive disorder of pregnancy; IQR, interquartile range; LR, likelihood ratio; MAP, mean arterial pressure; MoM, Multiples of the median; NPV, negative predictive value; PAPP-A, pregnancy associated plasma protein A; PE, pre-eclampsia; PlGF, placental growth factor; PPV, positive predictive value; ROC, receiver operating characteristic; SD, standard deviation; SFlt-1, soluble fms-like tyrosine kinase-1; SGA, small-for-gestational age; SOGC, Society of Obstetricians and Gynaecologists of Canada; UtA-PI, uterine artery pulsatility index.

Table 25n: Goto 2021

Study Reference	Goto 2021
Study Design	Design Prospective cohort study Objective To assess the screening performance of the FMF Bayes theorem-based model in the Japanese population at 11–13 weeks of gestation. Dates June 2017–December 2019 (all enrolled subjected followed up and delivered) Country Japan Setting Showa University Hospital in Tokyo
Population Characteristics	Patient recruitment and eligibility: Eligibility: maternal age ≥18 years; no serious mental illness or learning disabilities; singleton pregnancy with a live fetus with no major abnormality identified at 11–13 weeks of gestation. Data collection: All pregnant women at 11–13 weeks of gestation underwent ultrasonography for the measurement of CRL and assessment of fetal morphological abnormalities. At the same time, the measurement of UtA-PI was performed. Maternal characteristics and medical history, which consisted of gestational age, maternal age, weight, height, ethnic origin, method of conception, smoking, chronic hypertension, pre-existing diabetes mellitus, systemic lupus erythematosus/antiphospholipid syndrome, parity, history of PE and family history of PE were recorded. Gestational age was determined by the fetal CRL at 11–13 weeks. The MAP was measured. Maternal serum concentrations of PlGF were measured. Duration of follow-up: June 2017–December 2019 (all enrolled subjected followed up and delivered) Prevalence of PE in the study: 26 (2.8%) women developed PE including 11 (1.2%) developed preterm PE Sample size: N screened/invited = 2,655 N eligible = 1,036 N enrolled = 913 N excluded (with reason) = serious maternal disorder (n=11), major fetal anomaly (n=5), multiple pregnancies (n=32), disagreed (n=1,571), miscarriage (n=3), missing outcome and incomplete data (n=120) N lost to follow-up = NR N completed = NR N excluded from analysis = 0 N included in analysis = 913 Demographics:

Study Reference **Goto 2021**

Variable	Preterm PE (n=11)[a]	Term PE (n=15)[a]	Unaffected (n=887)[a]	p value
Maternal age (years)	40 (34–47)	35 (27–40)	34 (22–45)	<0.05
BMI (kg/m^2)	21.7 (19.8–30.5)	20.5 (17.3–30.8)	20.4 (13.7–36.2)	<0.05
Primipara	73% (8)	73% (11)	53% (469)	0.12
In vitro fertilisation	55% (6)	40% (6)	23% (201)	<0.05
Smoking	18% (2)	0% (0)	6% (49)	0.37
Chronic hypertension	36% (4)	13% (2)	0.2% (2)	<0.05
Diabetes mellitus	9% (1)	0% (0)	0.3% (3)	0.10
Family history of PE	0% (0)	7% (1)	4% (34)	0.57
Parous with previous PE	0% (0)	0% (0)	0.6% (6)	0.84
UtA-PI	2.0 (0.9–3.2)	1.3 (0.6–2.6)	1.8 (0.5–3.5)	0.06
UtA-PI MoM	1.26 (0.63–2.06)	0.84 (0.32–1.58)	1.09 (0.34–2.44)	0.13
MAP (mmHg)	91 (78–125)	97 (71–115)	80 (55–110)	<0.05
MAP MoM	1.09 (0.96–1.28)	1.08 (0.87–1.28)	0.97 (0.70–1.31)	<0.05
PlGF (pg/mL)	19.1 (1.1–63.6)	38.7 (15.5–134.8)	36.5 (5.1–124.2)	<0.05
PlGF MoM	0.43 (0.02–0.98)	0.82 (0.31–2.19)	0.72 (0.09–2.38)	<0.05

[a]The results are expressed as either median (range) or % (n)

Screening Method

Index test

The FMF Bayes theorem-based model, which uses a combination of maternal characteristics, medical history, MAP, UtA-PI, and serum PlGF. According to the risk calculation with the use of this combined prediction algorithm, women are classified into high- and low-risk groups. This model combines the a priori risk from maternal characteristics and medical history (maternal factors) with the results of various combinations of biophysical and biochemical measurements.

The measured values of MAP, UtA-PI, and PlGF were converted into multiple of the median (MoM) values using the application, and then the risks were calculated using the prediction model in individual cases. The cutoff values for high-risk status were set to 1/100 for preterm PE and 1/50 for term PE.

Reference standard

PEwas defined as gestational hypertension accompanied by proteinuria or other maternal organ dysfunctions at or after 20 weeks of gestation with all symptoms normalising by 12 weeks postpartum, according to the Japan Society for the Study of Hypertension in Pregnancy. Proteinuria is not mandatory for the diagnosis of pre-eclampsia. Rather, pre-eclampsia is diagnosed by the presence of de novo hypertension after 20 weeks of gestation accompanied by proteinuria and/or evidence of maternal acute kidney injury, liver dysfunction, neurological features, haemolysis or thrombocytopenia, or fetal growth restriction.
Proteinuria was defined as protein excretion of ≥300 mg/day in a 24-h urine collection.

Superimposed PE was defined as CH (systolic blood pressure ≥150mmHg and/or diastolic blood pressure ≥90 mmHg on at least 2 occasions 4 hours apart) diagnosed before 20 weeks of gestation, with proteinuria emerging afterward. Superimposed PE was included as PE in this study.

Researchers reconfirmed the clinical diagnosis determined by the clinicians to enhance accuracy. Preterm and term PE were defined as PE with delivery <37 and ≥37 weeks of gestation, respectively.

Test Accuracy

Predictive performance (i.e. detection rates) of screening for preterm and term pre-eclampsia

Parameters	FPR5%	FPR10%	FPR20%

Study Reference	**Goto 2021**			
	Preterm PE	-	-	-
	Maternal characteristics + MAP + UtA-PI + PlGF	73%	91%	91%
	Maternal characteristics + MAP + UtA-PI	64%	64%	82%
	Maternal characteristics + MAP + PlGF	73%	91%	100%
	Maternal characteristics + MAP	64%	82%	82%
	Term PE	-	-	-
	Maternal characteristics + MAP + UtA-PI + PlGF	21%	47%	47%
	Maternal characteristics + MAP + UtA-PI	33%	40%	53%
	Maternal characteristics + MAP + PlGF	27%	47%	53%
	Maternal characteristics + MAP	47%	60%	60%
Authors' Conclusions	This study has demonstrated that the FMF Bayes theorem-based model could be used to predict preterm and term pre-eclampsia in the Japanese population at 11–13 weeks of gestation with a detection rate for preterm pre-eclampsia as high as 91% at a 10% false positive rate and can be implemented as part of routine prenatal care in Japan. This study demonstrated that the combination of maternal characteristics, MAPP and PlGF is sufficient for the prediction of preterm pre-eclampsia in Japanese women. UtA-PI has a limited effect on predicting preterm PE compared to other parameters in this population. In the prediction of term pre-eclampsia, higher performance was observed with the combination of maternal characteristics and MAP than with the combination of all parameters.			

Abbreviations: BMI, body mass index; CH, chronic hypertension; CRL, crown-rump length; FMF, fetal medicine foundation; FPR, false positive rate; MAP, mean arterial pressure; MoM, multiple of the median; PE, pre-eclampsia; PlGF, placental growth factor; UtA-PI, uterine artery pulsatility index.

Table 25o: Hafner 2013

Study Reference	Hafner 2013
Study Design	Design Prospective cohort study Objective To evaluate the performance of placental bed vascularization in a low-risk population to predict severe pregnancy risks. Vascularization was measured in the first trimester, using 3D power-Doppler vascularisation index. Dates Women enrolled during a period of 3 years. Actual dates not reported. Country Austria Setting Single hospital
Population Characteristics	Patient recruitment and eligibility All women with singleton pregnancies in the first trimester who booked for delivery in the hospital were included in the study. Women with fetal aneuploidy or malformations were excluded (N.B. this was after the recruitment stage) Data collection *Before birth* • Fetal and placental crown data: crown-rump length (CRL), placental volume (PV), placental quotient (PQ), pregnancy-associated plasma protein-A (PAPP-A)* • Maternal data: age, gravidity, parity, body mass index (BMI), history of high blood pressure, length in cm, cigarette smoking, vascularisation index of the placental bed (PBVI), mean pulsatility index (PI) at 12 weeks, mean notch at 12 weeks, mean PI at 22 weeks, mean notch at 22 weeks *After birth* • Birth-weight in g, birth weight centile (both new-borns <10th and <3rd centile of birth-weight were assessed as small for gestational age [SGA] and evaluated), gestational week at delivery, occurrence of pregnancy-induced hypertension (PIH) or pre-eclampsia (PE), mode of delivery *Values for PAPP-A determined using the BRAHMS Kryptor Immunoassay, blood samples were collected and processed on the same day Duration of follow-up Until delivery (assumed based on outcomes reported) Prevalence of PE in the study PE developed in 62 (1.4%) pregnancies, 25 (0.6%) of which were severe PE (defined as delivery ≤34 weeks) Sample size N screened/invited = NR N eligible = NR N enrolled = 5,098 N excluded (with reason) = fetal aneuploidy or malformations [n=89], miscarriage between 12 and 22 weeks [n=43], did not attend fetal anomaly scan at scheduled time for unknown reasons or could not be followed up [n=641] N lost to follow-up = NR

Study Reference **Hafner 2013**

N completed = NR
N excluded from analysis = NR
N included in analysis = 4,325

Demographics

Characteristic	N*	Median	Minimum	Maximum
Age (years)	4,325	29.4	13.6	47.5
BMI (kg/m^2)	4,319	22.7	14.1	52.7
Gravidity	4,325	2	1	15
Parity	4,325	1	0	13
Cigarettes (n)	702	5	1	40
PBVI (%)	4,325	34.014	0.766	82.831
PV (cm^3)	4,325	54.17	15.17	198.36
PQ	4,325	0.892	0.140	3.27
MOM PAPP-A	4,277	1.040	0.17	5.94
Uterina12**	4,325	3.905	1.545	9.77
Uterina22***	4,325	1.89	1.28	5.99
Birth weight (g)	4,325	3,390	320	5,270
Percentile	4,325	42	1	99
Week at delivery	4,325	39	22	43

*Data was not available for the full analysis sample (N=4,325) for all characteristics
**Uterina12 = addition of mean uterine PI and mean notch measured at 12 weeks
***Uterina22 = addition of mean uterine PI and mean notch measured at 22 weeks

Screening Method

Index test
- PBVI
- PQ
- Uterina12
- Uterina22
- PAPP-A

Reference standard
The International Society for the Study of Hypertension in Pregnancy (ISSHP) guidelines provided the basis for our classification of complications, i.e. proteinuria, PIH and PE. Proteinuria was determined on 2 consecutive occasions on the basis of +2 or more proteinuria on the reagent strip urinalysis, or proteinuria of over 30 mg/24 h. PIH was judged as >140/90 mmHg if recorded on 2 or more occasions during pregnancy, more than 155/105 on one occasion or the need for antihypertensive therapy during the pregnancy. PE was defined as a condition of PIH and proteinuria.

A total of 7 outcome groups were assessed:
- Uncomplicated pregnancy
- Birthweight ≤3rd centile
- Delivery ≤34 weeks
- PIH
- All PE

Study Reference **Hafner 2013**

- Severe PE: delivery ≤34 weeks
- Severe pregnancy problems (SPP): PIH or PE plus birthweight ≤10th centile or delivery ≤34 weeks*

*This group takes into consideration that reduced uteroplacental blood flow does not only lead to maternal hypertensive disorders like PE, but to a range of obstetrical disorders, such as intrauterine growth restriction (IUGR), preterm birth and their combinations

Test Accuracy

Sensitivity to pregnancy associated problems at a 10% cut-off (90%)

Marker	Cut-off	PE		Severe PE	
		Sensitivity	Specificity	Sensitivity	Specificity
PBVI	≤18.05	51.6	90.6	60.0	90.3
PQ	≤0.63	12.9	90.9	16.0	90.9
Uterina12	≥5.18	22.6	90.1	24.0	90.0
Uterina22	≥3.11	43.5	90.5	72.0	90.4
PAPP-A	≤0.51	19.4	90.4	20.0	90.3

Authors' Conclusions

The most important findings in this study are that the 3D power Doppler vascularisation of the placental bed measured at the end of the first trimester can give important information for assessing the risk for pregnancy associated problems including PE. It is superior to other first trimester sonographic or biochemical markers and performs approximately equal to second trimester uterine artery measurement.

In conclusion it appears that the 3D measurement of the placental bed vascularisation gives a valuable first trimester information on a woman's risk of developing severe pregnancy problems. It will be interesting to find out whether its predictive strength can be additionally improved by combining it with other first trimester markers.

Abbreviations: BMI, body mass index; CRL, crown rump length; ISSHP, International Society for the Study of Hypertension in Pregnancy; IUGR, Intrauterine growth restriction; MoM, multiple of median; NR, not reported; PAPP-A, pregnancy-associated plasma protein-A; PBVI, Power Doppler vascularisation index of the placental bed; PE, pre-eclampsia; PI, pulsatility index; PIH, pregnancy-induced hypertension; PQ, placental quotient (placental volume/crown rump length); PV, placental volume; SGA, small for gestational age; SPP, severe pregnancy problems.

Table 25p: Honigberg 2016

Study Reference	Honigberg 2016, McElrath 2012 (Only methodology was extracted from McElrath 2012 as results were only presented for overall PE)
Study Design	Design Prospective cohort study Objective To assess whether changes in maternal angiogenic factors throughout pregnancy predict the development of pre-eclampsia (PE). Dates October 2007 to June 2009 Country United States Setting Three tertiary care academic centres (Brigham and Women's Hospital and Beth Israel Deaconess Medical Center, Boston; Hospital of the University of Pennsylvania, Philadelphia)
Population Characteristics	Patient recruitment and eligibility Women aged >18 years presenting for prenatal care prior to 15 weeks gestation were eligible for enrolment. The only initial cohort exclusion criterion was higher-order multiple gestations (triplets or greater). The cohort included women at both low and high risk of developing PE. Data collection Information on the index pregnancy and neonate was abstracted from the medical record and supplemented with data that were collected specifically for the study. Maternal blood pressure and urine protein dip measurements were recorded at each study visit. The dates and times of the highest recorded blood pressures in the pregnancy also were noted. When applicable, the dates and times of the results of 24-hour urine protein collections were recorded. Height and weight were recorded at the first study visit. Gestational age was confirmed by ultrasound scanning at <15 weeks gestation. Date and time of delivery, birthweight, gender, Apgar score, mode of delivery, diagnoses of any pregnancy complications, medication use, and conception by assisted reproductive technologies (ART) were abstracted from records. The participants completed a brief questionnaire that ascertained information about race/ethnicity, tobacco use before and during the index pregnancy, medical history, and history of PE in a previous pregnancy. Duration of follow-up Study visits occurred at, median (IQR): 10.0 (4.4 to 16.7), 17.8 (12.6 to 22.7), 26.0 (19.6 to 30.9), and 35.3 (31.3 to 39.4) weeks of gestation. Prevalence of PE in the study Of 2,355 women, 137 (5.8%) developed PE and delivered after 37 weeks gestation, 47 (2.0%) developed PE and delivered between 34 and 37 weeks gestation and 18 (0.8%) developed 'early' PE with delivery before 34 weeks gestation. Sample size N screened/invited = NR N eligible = NR N enrolled = 2,355 N excluded (with reason) = NR N lost to follow-up = NR N completed = 2,355 N excluded from analysis = 0

Study Reference

Honigberg 2016, McElrath 2012 (Only methodology was extracted from McElrath 2012 as results were only presented for overall PE)

N included in analysis = 2,355

Demographics

Characteristic	No PE (n=2,153)	PE, delivery ≥37 weeks (n=137)	PE, delivery ≥34 and <37 weeks (n=47)	PE delivery <34 weeks (n=18)
Mean maternal age, years (SD)	31.0 (5.7)	30.6 (6.1)	32.1 (6.3)	32.0 (4.8)
Nulliparous, n (%)	909 (42.2)	61 (44.5)	25 (53.2)	11 (61.1)
Mean body mass index (BMI), kg/m2 (SD)	25.7 (5.9)	31.0 (8.2)	30.4 (9.1)	32.0 (7.4)
Race/ethnicity, n (%)				
Caucasian	1,275 (59.2)	61 (44.5)	24 (51.1)	7 (38.9)
Hispanic	200 (9.3)	13 (9.5)	4 (8.5)	2 (11.1)
African-American	454 (21.1)	59 (43.0)	16 (34.0)	5 (27.8)
Asian	145 (6.7)	2 (1.5)	1 (2.1)	2 (11.1)
Other	79 (3.7)	2 (1.5)	2 (4.3)	2 (11.1)
Smoking status, n (%)				
Never smoked	1,332 (61.8)	89 (65.0)	32 (68.1)	8 (44.4)
Former smoker	482 (22.4)	20 (14.6)	7 (14.9)	7 (38.9)
Current smoker	68 (3.2)	4 (2.9)	5 (10.6)	0 (0)
Missing	271 (12.6)	24 (17.5)	3 (6.4)	3 (16.7)
Chronic hypertension, n (%)	74 (3.4)	20 (14.6)**	9 (19.2)**	6 (33.3)**
Pre-gestational diabetes, n (%)	31 (1.1)	11 (8.0)**	8 (17.0)**	2 (11.1)*
Family history of PE, n (%)	105 (4.9)	8 (5.8)	8 (17.0)*	3 (16.7)
Personal history of PE, n (%)	60 (2.8)	17 (12.4)**	11 (23.4)**	5 (27.8)**
Mean blood pressure at enrolment (systolic/diastolic), mm Hg (SD)	109.4 (10.8)/66.8 (7.8)	115.9 (11.5)/71.1 (8.8)**	121.7 (15.3)/73.7 (8.9)**	124.9 (16.9)/78.6 (12.0)**
Gestational diabetes, n (%)	81 (3.8)	18 (13.1)**	5 (10.6)*	1 (5.6)
Use of ART, n (%)	131 (6.1)	13 (9.5)	7 (14.9)*	1 (5.6)

* p<0.05 compared to the no PE group; p< 0.0001 compared to the no PE group.

Screening Method

Index test

- Placental growth factor (PlGF)
- Soluble fms-like tyrosine kinase 1 (sFlt-1)

Maternal blood and urine samples were obtained at the 4 visits during the pregnancy, and PlGF and soluble fms-like tyrosine kinase 1 (sFlt-1) were measured by immunoassay. Median rate of change of angiogenic factor concentrations between adjacent study visits were compared using Wilcoxon rank-sum tests based on PE diagnosis. Receiver operating characteristic analysis was used to calculate the optimal cut-offs for the angiogenic analytes. Linear mixed-effect models were used to generate slopes and intercepts for PlGF and sFlt-1 over time. These intercepts and slopes were then used as predictors in the adjusted logistic regression models. In the adjusted models, covariates were included on the basis of biological plausibility or those previously shown to be associated with PE. Included covariates were: maternal BMI, race/ethnicity, parity, prior history of PE, current diagnosis of chronic hypertension or gestational diabetes and use of ART.

<table>
<tr><td><u>Study Reference</u></td><td>Honigberg 2016, McElrath 2012 (Only methodology was extracted from McElrath 2012 as results were only presented for overall PE)</td></tr>
<tr><td></td><td><u>Reference standard</u>
PE was defined as systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 at study visits 2 to 4 with either urine protein/creatinine >0.20 or 24-h urine collection with >300 mg proteinuria. Each case of hypertensive disease was de-identified and reviewed by a panel of investigators before a diagnosis of PE was applied.</td></tr>
<tr><td>Test Accuracy</td><td>Sensitivity of screening for early PE
<table>
<tr><th>Method of screening</th><th>Cut-off</th><th>Value (pg mL^{-1} week^{-1})</th><th>Sensitivity (%)</th><th>Specificity (%)</th><th>PPV (%)</th><th>NPV (%)</th></tr>
<tr><td rowspan="2">PlGF at 10–18 weeks gestation</td><td>Empirical</td><td>≤10.73</td><td>70.6</td><td>70.6</td><td>2.0</td><td>99.6</td></tr>
<tr><td>25th percentile</td><td>≤9.85</td><td>70.6</td><td>75.4</td><td>2.4</td><td>99.7</td></tr>
<tr><td rowspan="2">sFlt-1 at 10–18 weeks gestation</td><td>Empirical</td><td>≥0.26</td><td>64.7</td><td>64.8</td><td>1.6</td><td>99.5</td></tr>
<tr><td>75th percentile</td><td>≥0.41</td><td>29.4</td><td>75.0</td><td>1.0</td><td>99.2</td></tr>
</table></td></tr>
<tr><td>Authors' Conclusions</td><td>Given the rarity of early PE, PPV was low (<2.5%), and NPV was >99.5% for all the cut-offs examined. With NPV >99.5% even as early as 10 to 18 weeks, changes in PlGF and sFlt-1 may enable clinicians to 'rule out' the subsequent development of early PE. The sensitivity and specificity of PlGF at 10 to 18 weeks gestation were both 70.6%, and for sFlt-1 the values were 64.7% and 64.8%, respectively (empirical values).</td></tr>
</table>

Abbreviations: ART, assisted reproductive technology; BMI, body mass index; IQR, interquartile range; NPV, negative predictive value; NR, not reported; PE, pre-eclampsia; PlGF, placental growth factor; PPV, positive predictive value; SD: standard deviation; sFlt-1; Soluble fms-like tyrosine kinase-1.

Table 25q: Kanat-Pektas 2014

Study Reference	Kanat-Pektas 2014
Study Design	Design Prospective cohort study Objective To determine whether mean platelet volume (MPV) specified in the late first trimester of pregnancy (between 11th and 14th gestational week) can be used to predict adverse perinatal outcomes including PE and IUGR. Dates January 2012-June 2012 Country Turkey (inferred from author affiliations) Setting Obstetric outpatient clinic
Population Characteristics	Patient recruitment and eligibility 200 healthy women with late first trimester pregnancies (11th to 14th gestational week) who were consecutively admitted to the obstetric outpatient clinic of the study centre were included in the study. Women with systemic diseases (hypertension, diabetes mellitus, collagen tissue disease, heart disease, renal disease, hepatic disease), poor obstetric history requiring medication during gestation (recurrent pregnancy loss, previous occurrence of preeclampsia, preterm labour, IUGR or intrauterine demise) and pregnancies with fetal chromosomal abnormalities and congenital defects were excluded. Data collection At initial visit [between 11th and 14th gestational week], maternal blood pressure was recorded, transabdominal ultrasonography was performed and 2 samples of blood were drawn. The first sample was kept for the evaluation of red blood cell count, haemoglobin, haematocrit, mean corpuscular volume (MCV), platelet count and MPV. The second sample was preserved to determine maternal serum concentrations of free hCG and pregnancy associated plasma protein-A (PAPP-A). Duration of follow-up All of the participants were put on routine obstetric follow-up which consisted of monthly visits until the 32nd gestational week, bimonthly visits between the 32nd and 36th gestational week, and weekly thereafter. Prevalence of PE in the study 15 (7.5%) developed PE Sample size N screened/invited = NR N eligible = NR N enrolled = 200 N excluded (with reason) = NR N lost to follow-up = NR N completed = NR N excluded from analysis = 4 [intrauterine fetal demise] N included in analysis = 196

Study Reference	**Kanat-Pektas 2014**

Demographics

Characteristic	Uncomplicated (n=164)	IUGR (n=17)	PE (n=15)	p value
Age (years)	26.2 (5.3)	26.2 (4.0)	25.2 (4.1)	0.770
Gestational age at admission (weeks)	12.6 (0.8)	12.8 (0.7)	12.6 (0.7)	0.685
Gestational age at delivery (weeks)	37.8 (4.0)	38.8 (0.7)	36.0 (4.1)	0.001*‡
Gravidity	2.1 (1.0)	1.7 (0.5)	1.5 (0.7)	0.388
Parity	1.2 (0.8)	1.2 (0.4)	1.1 (0.6)	0.211
SBP (mmHg)	94.5 (11.0)	91.8 (14.2)	96.7 (9.8)	0.663
DBP (mmHg)	60.0 (25.8)	58.8 (11.7)	60.7 (4.6)	0.997
Haemoglobin (g/dL)	12.7 (0.7)	13.0 (1.4)	12.9 (1.0)	0.487
MCV (fl)	83.0 (8.4)	81.9 (6.2)	85.0 (3.6)	0.646
Leukocyte count (/mm^3)	9,120.5 (2,064.1)	9,930.0 (2,960.8)	8,328.7 (1,869.2)	0.172
Platelet count (x10^3/mm^3)	286.9 (55.4)	240.0 (48.5)	225.5 (87.7)	0.001*†
MPV (fl)	10.2 (0.9)	10.8 (1.1)	11.0 (1.2)	0.001*†
Crown-rump length (mm)	61.5 (9.6)	63.0 (9.9)	59.0 (9.4)	0.279
Nuchal translucency (mm)	1.4 (0.4)	1.4 (0.2)	1.4 (0.2)	0.689
PAPP-A (MoM)	1.1 (0.7)	0.7 (0.3)	0.6 (0.4)	0.002*†
Free β-hCG (MoM)	1.1 (0.6)	0.8 (0.4)	1.2 (0.5)	0.036*‡

*p<0.05 accepted to be statistically significant; †statistical significance between uncomplicated and PE pregnancies; ‡statistical significance between uncomplicated pregnancies and pregnancies with IUGR
[assumed values are mean (SD) or n (%), as applicable; not stated]

Screening Method	Index test • Mean platelet volume (MPV) value alone • MPV and PAPP-A MoM values in combination Measured in a blood sample collected between the 11th to 14th gestational week Reference standard Preeclampsia was defined as the onset of hypertension (blood pressure ≥140/90 mmHg measured ≥6 hours apart) and consistent proteinuria (≥300 mg/day or dipstick ++) after 20th week of pregnancy.
Test Accuracy	• MPV values of ≥10.5 fl can predict PE with 66.7% sensitivity and 63.8% specificity • MPV values of ≥10.5 fl in combination with PAPP-A MoM values of ≤0.33 can predict PE with 75.0% sensitivity and 70.0% specificity
Authors' Conclusions	In this study, MPV values of 10.5 fl or more could predict pre-eclampsia with 66.7% sensitivity and 63.8% specificity.

Abbreviations: DBP, diastolic blood pressure; IUGR, intrauterine growth restriction; MCV, Mean corpuscular volume; MPV, mean platelet volume; MoM, multiples of the median; PE, preeclampsia; PAPP-A, pregnancy associated plasma protein-A; SBP, systolic blood pressure

Table 25r: Khalil 2012

Study Reference	Khalil 2012
Study Design	Design Prospective cohort study Objective The aim of this screening study was to examine the potential value of assessment of arterial stiffness and central aortic systolic blood pressure (SBP_{Ao}) at 11–13 weeks gestation in identifying women who subsequently develop PE, and to examine the association between the markers of arterial stiffness and UtA-PI and serum PAPP-A. Dates December 2009-February 2011 Country UK (England) Setting University College Hospital and King's College Hospital
Population Characteristics	Patient recruitment and eligibility Women attending their routine first-trimester (11^{+0} to 13^{+6} weeks gestation) ultrasound scan were recruited to the study. The inclusion criteria for this study were women with a singleton pregnancy and a live fetus identified at the 11^{+0} to 13^{+6}-week scan. Pregnancies with major fetal abnormalities and those ending in termination, miscarriage or fetal death before 24 weeks gestation were excluded. Data collection Maternal characteristics and medical history were recorded at the routine first-trimester ultrasound scan. The women were asked to complete a questionnaire on their age, racial origin, method of conception, cigarette smoking status during pregnancy, history of chronic hypertension, family history of PE in the mother of the patient and obstetric history including parity and previous pregnancy with PE. The questionnaire was then reviewed by a doctor together with each woman. Maternal weight and height were measured and BMI calculated. Combined screening for aneuploidies were performed by measurement of fetal crown–rump length, nuchal translucency thickness and maternal serum PAPP-A and free β-human chorionic gonadotropin levels. Doppler ultrasonography was used to visualize the left and right UtAs, measure the PI in each vessel and calculate the mean PI. The Arteriograph was used to measure the AIx, PWV and SBPAo. Data on pregnancy outcomes were collected from the hospital maternity records or the women's general practitioners. The obstetric records of all women with pre-existing or pregnancy-induced hypertension were examined to determine if the condition was chronic hypertension, PE or GH. Duration of follow-up Delivery [assumed based on results reporting gestational age at delivery] Prevalence of PE in the study 181 (2.6%) developed PE Sample size N screened/invited = NR N eligible = NR N enrolled = 7,653 N excluded (with reason) = NR N lost to follow-up = NR

Study Reference — **Khalil 2012**

N completed = NR
N excluded from analysis = 569 including: missing outcome data (n=449), fetal death or miscarriage before 24 weeks gestation n=60), pregnancy terminated for fetal abnormalities or social reasons n=60)
N included in analysis = 7,084

Demographics

Characteristic	Unaffected group (n=6,766)	PE group (n=181)	GH group (n=137)
Age (years)	32.0 (28.0–35.4)	32.8 (27.9–37.1)	31.7 (28.5–35.5)
BMI (kg/m^2)	23.5 (21.3–26.5)	26.4 (23.5–29.7)*	26.5 (23.2–29.8)*
Ethnicity			
Caucasian	4,898 (72.4)	94 (51.9)*	84 (61.3)
African	1,005 (14.9)	67 (37.0)*	37 (27.0)*
South Asian	416 (6.1)	13 (7.2)	10 (7.3)
East Asian	271 (4.0)	3 (1.7)	4 (2.9)
Mixed	176 (2.6)	4 (2.2)	2 (1.5)
Parity			
Nulliparous	3,665 (54.2)	109 (60.2)	84 (61.3)
Parous: no previous PE	2,933 (43.3)	42 (23.2)*	34 (24.8)*
Parous: previous PE	168 (2.5)	30 (16.6)*	19 (13.9)*
Cigarette smoker	413 (6.1)	11 (6.1)	3 (2.2)
Family history of PE	310 (4.6)	23 (12.7)*	5 (3.6)
Conception			
Spontaneous	6,486 (95.9)	166 (91.7)	129 (94.2)
Ovulation drugs	280 (4.1)	15 (8.3)*	8 (5.8)
Chronic hypertension	47 (0.7)	21 (11.6)*	0 (0.0)

Data are given as median (interquartile range) or n (%). *p<0.025

Screening Method

Index test
- History alone
- History plus vascular-derived risk (AIx-75, PWV, SBP_{AO})
- History plus vascular-derived risk (AIx-75, PWV, SBP_{AO}) plus UtA-PI and PAPP-A

Measured at 11-13 weeks gestation

Reference standard
- PE was diagnosed according to the criteria of the International Society for the Study of Hypertension in Pregnancy; PE was defined as GH (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least 2 occasions 4 h apart developing after 20 weeks gestation in previously normotensive women in the absence of significant proteinuria) with proteinuria of ≥300 mg in 24 h, or 2 readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-h collection available. PE superimposed on chronic hypertension was defined as significant proteinuria (as defined above) developing after 20 weeks gestation in women with known chronic hypertension (a history of hypertension before conception or the presence of hypertension at the booking visit before 20 weeks in the absence of trophoblastic disease).

Test Accuracy

Screening test for PE	Detection rate (95% CI) for:	p value

Study Reference	**Khalil 2012**

	5% FPR	10% FPR	
History	33.7 (26.9-41.1)	47.0 (39.5-54.5)	-
History plus vascular-derived risk (AIx-75, PWV, SBPAO)	43.7 (36.3–51.2)	56.9 (49.4–64.2)	0.005*
History plus vascular-derived risk (AIx-75, PWV, SBPAO), UtA-PI and PAPP-A	46.4 (38.7–54.3)	61.9 (54.1–69.3)	0.001*

*comparison with performance of screening based on maternal history only

- The estimated detection rate of *early PE* at an FPR of 10% was 56.5% using history plus vascular-derived risk (AIx-75, PWV, SBPAO), and 71.4% using history plus vascular-derived risk (AIx-75, PWV, SBPAO), UtA-PI and PAPP-A
- The estimated detection rate of *late PE* was 60.5% at an FPR of 10% [history plus vascular-derived risk]

Authors' Conclusions	In this study it was found that such a maternal factor-based method of screening identifies around 45% of cases that develop PE, at a FPR of 10%. The detection rate was improved by combining maternal factors with the vascular parameters at 11–13 weeks gestation. The extent to which such combined testing, undertaken before conception and thus allowing for earlier administration of aspirin, could result in further reduction in the prevalence of PE merits further investigation.

Abbreviations: BMI, body mass index; AIx, augmentation index; FPR, false positive rate; GH, gestational hypertension; PE, preeclampsia; PAPP-A, pregnancy associated plasma protein-A; PI, pulsatility index; PWV, pulse wave velocity; SBPAo, central aortic systolic blood pressure; UtA-PI, uterine artery pulsatility index; UtAs, uterine arteries.

Table 25s: London Cohorts

Study Reference	London Cohorts (Tan 2018c [Francisco 2017, Gallo 2014, Gallo 2016, Mazer Zumaeta 2020, O'Gorman 2016a, O'Gorman 2016b, O'Gorman 2017a, O'Gorman 2017b, Poon 2012, Poon 2020, Tan 2017, Tan 2018a, Tsiakkas 2016a, Wright 2012, Wright 2015, Wright 2016])
Study Design	Design Prospective cohort study Objective To examine the performance of screening for early, preterm and term pre-eclampsia (PE) at 11–13 weeks gestation by maternal factors (MF) and combinations of mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum placental growth factor (PlGF) and serum pregnancy-associated plasma protein-A (PAPP-A). **Mazer Zumaeta 2020:** To examine the additive value of PlGF and PAPP-A in first-trimester screening for preterm PE by maternal factors, MAP and Uta-PI and the potential impact on the performance of screening if serum PAPP-A and/or PlGF are included or excluded from the method of screening. **Poon 2020:**To compare the performance of first trimester screening for pre-eclampsia by the competing risk model with that of the current NICE guidelines. **Poon 2012:** To identify the simplest protocol for measurement of MAP at 11–13 weeks gestation that could achieve a comparable performance in the prediction of PE to that obtained using the National Health Foundation of Australia (NHFA) protocol. Dates **Tan 2018a** (SPREE): April 2016 to December 2016 **Tan 2018c**: January 2006 to December 2015 **Mazer Zumaeta 2020:** Between March 2006 and July 2012 and between August 2013 and March 2017 at King's College Hospital; between April 2010 and July 2012 and between August 2013 and March 2017 at Medway Maritime Hospital. (PlGF measured using a DELFIA Xpress system) Between August 2012 and July 2013 in both hospitals (PlGF measured using a Cobas e411 system). (PAPP-A was measured during the whole study period in both hospitals). **Poon 2012:** February 2007 and February 2011 Country UK **O'Gorman 2017a, O'Gorman 2017b:** UK, Spain, Belgium, Greece, Italy Setting Multiple ≤7 NHS maternity hospitals in England, including King's College Hospital, University College London Hospital, and Medway Maritime Hospital **Mazer-Zumaeta 2020:** King's College Hospital, London and Medway Maritime Hospital, Gillingham, UK. **Poon 2012:** King's College Hospital, University College Hospital and Medway Maritime Hospital

Study Reference	**London Cohorts (Tan 2018c [Francisco 2017, Gallo 2014, Gallo 2016, Mazer Zumaeta 2020, O'Gorman 2016a, O'Gorman 2016b, O'Gorman 2017a, O'Gorman 2017b, Poon 2012, Poon 2020, Tan 2017, Tan 2018a, Tsiakkas 2016a, Wright 2012, Wright 2015, Wright 2016])**
Population Characteristics	Patient recruitment and eligibility Singleton pregnancy undergoing first-trimester combined screening for aneuploidy and subsequently delivering a phenotypically normal live birth or stillbirth at ≥24 weeks gestation. **Excluded**: pregnancies with aneuploidy and major fetal abnormalities and those ending in termination, miscarriage or fetal death before 24 weeks. **Tan 2018a and Poon 2020:** Additionally excluded women who were unconscious or severely ill, suffered from learning difficulties or serious mental illness. **Poon 2012:** Additionally excluded women with missing outcome data. Data collection Maternal characteristics and medical history were recorded. Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to determine the diagnosis of PE. The following measurements were also recorded at the routine examination at 11 to 13 weeks gestation: • Measurement of the left and right uterine artery PI by transabdominal colour Doppler ultrasound scanning and calculation of the mean • Measurement of MAP by validated automated devices and standardized protocol • Measurement of serum concentration of PlGF and PAPP-A **Tan 2018a and Poon 2020:** All data on participant characteristics, biomarker values and outcome from each site were reported to the University College London Comprehensive Clinical Trials Unit (UCL-CCTU). The data, blinded to outcome, were then provided to the study statistician who (1) defined the screen-positive group according to NICE criteria, (2) computed risks for all-PE and preterm PE for the prespecified combinations of biomarkers using the Bayes' theorem-based method, (3) identified the group that was treated with aspirin (≥75 mg/day, starting at <14 weeks gestation and ending at ≥36 weeks or at the time of earlier birth) and (4) examined associations between aspirin treatment and baseline covariates, including the components of NICE guidelines and biomarkers, before updating the statistical analysis plan (SAP). When the SAP was finalized and UCL-CCTU received and approved the file with fields of risks, NICE criteria and aspirin treatment, they provided data on pregnancy outcome for linking before the unblinded analysis. **Poon 2020:** Additionally, serum inhibin A was measured in all 5,245 stored samples from patients who participated in the SPREE study at King's College Hospital. These included 140 patients who developed PE. The competing risk model was used to calculate risks for various combinations of biomarkers so that the performance of screening could be assessed based on the inclusion of inhibin A. Duration of follow-up Until delivery (assumed based on outcomes reported) Prevalence of PE in the study PE developed in 1,770/61,174 (2.9%) pregnancies. Early-onset PE (<32 weeks) developed in 116 pregnancies, preterm PE (<37 weeks) developed in 493 pregnancies, term PE (≥37 weeks) developed in 1,277 pregnancies. **Mazer Zumaeta 2020:** During the study period, serum PAPP-A and PlGF were measured in 60,875 pregnancies, including 1736 (2.9%) that developed PE; in 57,131 of the pregnancies, including 1590 (2.8%) that developed PE, MAP and UtA-PI were also measured. **Poon 2020:** PE developed in 473/16,747 (2.8%) pregnancies. In 142 (0.8%) of cases, this was preterm PE. **Poon 2012:** PE developed in 587 (2.4%) of pregnancies.

| Study Reference | London Cohorts (Tan 2018c [Francisco 2017, Gallo 2014, Gallo 2016, Mazer Zumaeta 2020, O'Gorman 2016a, O'Gorman 2016b, O'Gorman 2017a, O'Gorman 2017b, Poon 2012, Poon 2020, Tan 2017, Tan 2018a, Tsiakkas 2016a, Wright 2012, Wright 2015, Wright 2016])

Sample size
N screened/invited = NR
N eligible = NR
N enrolled = NR
N excluded (with reason) = NR
N lost to follow-up = NR
N completed = NR
N excluded from analysis = NR
N included in analysis = 61,174

A breakdown of subgroup sample sizes is provided in Tan 2018c and Tan 2017.

Mazer Zumaeta 2020: overall population with PAPP-A and PlGF measured, n = 60,875; population with PAPP-A, PlGF, MAP and UtA-PI measured, n = 57,131

Poon 2020:
N screened/invited = 20,168
N eligible = NR
N enrolled = 17,051
N excluded (with reason) = <18 years, severely ill, learning difficulties, multiple pregnancy (n=389), declined participation (n=1,690), fetal death, multiple pregnancy, major defects, crown-rump length <45 mm or <84 mm (n=1,034), withdrawal of consent (n=3)
N lost to follow-up = 304
N completed = NR
N excluded from analysis = NR
N included in analysis = 16,747

Poon 2012:
N screened/invited = 25,505
N eligible = 24,142
N enrolled = 24,142
N excluded (with reason) = 1,363 including missing outcome data (n = 873), major fetal defect (n = 51), aneuploidy (n = 96), the pregnancies resulted in fetal death or miscarriage before 24 weeks of gestation (n = 238), the women underwent termination of pregnancy (n = 105)
N lost to follow-up = 0
N completed = 24,142
N excluded from analysis = 0
N included in analysis = 24,142

Demographics

Characteristic	No PE (n=59,404)	PE<32 weeks (n=116)	PE<37 weeks (n=493)	PE≥37 weeks (n=1,277)
Median maternal age, years (IQR)	31.3 (27.1–35.0)	30.2 (25.8–35.1)	32.1 (27.5–36.0)	31.2 (26.9–35.2)

Study Reference **London Cohorts (Tan 2018c [Francisco 2017, Gallo 2014, Gallo 2016, Mazer Zumaeta 2020, O'Gorman 2016a, O'Gorman 2016b, O'Gorman 2017a, O'Gorman 2017b, Poon 2012, Poon 2020, Tan 2017, Tan 2018a, Tsiakkas 2016a, Wright 2012, Wright 2015, Wright 2016])**

Median gestational age at screening, weeks (IQR)	12.7 (12.3–13.1)	12.6 (12.2–13.1)	12.7 (12.3–13.1)	12.7 (12.3–13.1)
Median gestational age at delivery, weeks (IQR)	40.0 (39.0–40.9)	29.4 (28.0–30.8)	34.4 (32.1–35.9)	39.1 (38.1–40.3)
Median weight, kg (IQR)	66.6 (59.0–77.0)	74.8 (65.0–89.6)	74.0 (63.4–86.7)	73.0 (63.0–87.0)
Median height, cm (IQR)	165 (160–169)	163 (159–167)	163 (158–168)	164 (160–168)
Racial origin, n (%)				
Caucasian	43,663 (73.5)	48 (41.4)	256 (51.9)	765 (59.9)
Afro-Caribbean	9,539 (16.1)	56 (48.3)	183 (37.1)	386 (30.2)
South Asian	3,332 (5.6)	9 (7.8)	38 (7.7)	76 (6.0)
East Asian	1,383 (2.3)	0 (0)	4 (0.8)	20 (1.6)
Mixed	1,487 (2.5)	3 (2.6)	12 (2.4)	30 (2.3)
Conception, n (%)				
Spontaneous	57,315 (96.5)	112 (96.6)	459 (93.1)	1,218 (95.4)
Assisted	2,089 (3.5)	4 (3.4)	34 (6.9)	59 (4.6)
Cigarette smoker, n (%)	5,000 (8.4)	6 (5.2)	30 (6.1)	70 (5.5)
Family history of PE, n (%)	2,256 (3.8)	10 (8.6)	56 (11.4)	90 (7.0)
Medical history, n (%)				
Chronic hypertension	590 (1.0)	19 (16.4)	78 (15.8)	130 (10.2)
SLE/APS	117 (0.2)	0 (0)	5 (1.0)	2 (0.2)
Diabetes mellitus	470 (0.8)	4 (3.4)	17 (3.4)	23 (1.8)
Obstetric history, n (%)				
Nulliparous	28,014 (47.2)	61 (52.6)	271 (55.0)	790 (61.9)
Parous without previous PE	29,771 (50.1)	33 (28.4)	146 (29.6)	336 (26.3)
Parous with previous PE	1,619 (2.7)	22 (19.0)	76 (15.4)	151 (11.8)
Median interval from last pregnancy, years (IQR)	2.9 (1.8–4.8)	4.4 (2.3–7.4)	4.6 (2.6–7.6)	3.6 (2.2–6.3)

Mazer Zumaeta 2020:

	Overall population with PAPP-A and PlGF (n=60,875)			Population with PAPP-A, PlGF, MAP and UtA-PI (n=57,131)		
Characteristic	Normal (n=59,139)	PE (n=1,736)	p value	Normal (n=55,541)	PE (n=1,590)	p value
Maternal age (years)	31.0 (26.6–34.8)	31.2 (26.7–35.2)	0.112	31.1 (26.7–34.8)	31.2 (26.8–35.2)	0.086
Body mass index (kg/m^2)	24.7 (22.0–28.6)	27.6 (23.8–32.8)	<0.0001)	24.7 (22.0–28.6)	27.6 (23.8–32.7)	<0.0001
Racial origin			<0.0001			<0.0001
White	43,963 (74.3)	993 (57.2)	-	41,030 (73.9)	923 (58.1)	-
Black	9,790 (16.6)	599 (34.5)	-	9,415 (17.0)	536 (33.7)	-
South Asian	2,641 (4.5)	83 (4.8)	-	2,486 (4.5)	75 (4.7)	-

Study Reference **London Cohorts (Tan 2018c [Francisco 2017, Gallo 2014, Gallo 2016, Mazer Zumaeta 2020, O'Gorman 2016a, O'Gorman 2016b, O'Gorman 2017a, O'Gorman 2017b, Poon 2012, Poon 2020, Tan 2017, Tan 2018a, Tsiakkas 2016a, Wright 2012, Wright 2015, Wright 2016])**

East Asian	1,230 (2.1)	24 (1.4)	-	1,159 (2.1)	22 (1.4)	-
Mixed	1,515 (2.6)	37 (2.1)	-	1,451 (2.6)	34 (2.1)	-
Medical history						
Chronic hypertension	630 (1.1)	215 (12.4)	<0.0001	598 (1.1)	195 (12.3)	<0.0001
Diabetes mellitus type I	228 (0.4)	12 (0.7)	<0.0001	209 (0.4)	12 (0.8)	<0.0001
Diabetes mellitus type II	294 (0.5)	26 (1.5)	<0.0001	274 (0.5)	23 (1.4)	<0.0001
SLE/APS	113 (0.2)	9 (0.5)	0.006	105 (0.2)	6 (0.4)	0.164
Smoker	5,667 (9.6)	101 (5.8)	<0.0001	5,116 (9.2)	92 (5.8)	<0.0001
Family history of PE	2,257 (3.8)	136 (7.8)	<0.0001	2,109 (3.8)	126 (7.9)	<0.0001
Method of conception			<0.0001			<0.0001
Spontaneous	57,258 (96.8)	1,644 (94.7)	-	53,760 (96.8)	1,504 (94.6)	-
In vitro fertilisation	1,408 (2.4)	72 (4.1)	-	1,339 (2.4)	67 (4.2)	-
Ovulation drugs	473 (0.8)	20 (1.2)	-	442 (0.8)	19 (1.2)	-
Parity			<0.0001			<0.0001
Nulliparous	27,303 (46.2)	1,008 (58.1)	-	25,784 (46.4)	923 (58.1)	-
Parous, no previous PE	30,179 (51.0)	494 (28.5)	-	28,233 (50.8)	455 (28.6)	-
Parous, previous PE	1,657 (2.8)	234 (13.5)	-	1,524 (2.7)	212 (13.3)	-

Poon 2020:

Characteristic	Total (n=16,746)
Gestational age at screening, weeks, median (IQR)	12.8 (12.4–13.2)
Age, years, median (IQR)	31.5 (27.4–35.1)
BMI, kg/m^2, median (IQR)	24.7 (22.0–28.7)
Race, n (%)	-
White	12,112 (72.3)
Black	2404 (14.4)
South Asian	1384 (8.3)
East Asian	414 (2.5)
Mixed	433 (2.6)
Conception, n (%)	-
Natural	16,046 (95.8)
Assisted by ovulation drugs	126 (0.8)
In vitro fertilisation	575 (3.4)
Smoker, n (%)	1132 (6.8)
Mother had PE, n (%)	543 (3.2)
Medical history, n (%)	-
Chronic hypertension	143 (0.85)
Systemic lupus erythematosus/antiphospholipid syndrome	40 (0.24)

Study Reference **London Cohorts (Tan 2018c [Francisco 2017, Gallo 2014, Gallo 2016, Mazer Zumaeta 2020, O'Gorman 2016a, O'Gorman 2016b, O'Gorman 2017a, O'Gorman 2017b, Poon 2012, Poon 2020, Tan 2017, Tan 2018a, Tsiakkas 2016a, Wright 2012, Wright 2015, Wright 2016])**

Diabetes	119 (0.71)
Renal disease	29 (0.17)
Obstetrical history, n (%)	-
Nulliparous	7714 (46.1)
Multiparous without PE	8641 (51.6)
Multiparous with PE	392 (2.3)
Screen positive by NICE guidelines, n (%)	1727 (10.3)
Aspirin intake during pregnancy, n (%)	749 (4.5)
NICE screen positive group	400 (23.2)
NICE screen negative group	349 (2.3)

Comparisons of the maternal characteristics of the 3 study populations AJOG, ASPRE, and SPREE is provided in Poon 2020.

Poon 2012:

Characteristic	Control[a] (n=22,900)	PE (n=587)	p value
Maternal age, years	26.6 (26.6–34.9)	31.8 (26.4–36.3)	0.003*
Weight, kg	65.3 (58.6–75.4)	72.2 (63.9–85.0)	<0.0001*
Height, m	1.64 (1.60–1.69)	1.64 (1.60–1.68)	0.042*
Racial origin	-	-	-
Caucasian	16,449 (71.8)	304 (51.8)	0.0001*
Afro-Caribbean	4,074 (17.8)	226 (38.3)	0.0001*
South Asian	1,143 (5.0)	38 (6.5)	0.127
East Asian	650 (2.8)	8 (1.4)	0.044*
Mixed	584 (2.6)	12 (2.0)	0.524
Parity	-	-	-
Nulliparous	11,446 (50.0)	348 (59.3)	<0.0001*
Parous – no previous PE	10,851 (47.4)	146 (24.9)	<0.0001*
Parous – previous PE	603 (2.6)	93 (15.8)	<0.0001*
Cigarette smoker	2,145 (9.4)	37 (6.3)	0.014*
Family history of PE – mother	1,035 (4.5)	60 (10.2)	<0.0001*
Conception	-	-	-
Spontaneous	22,185 (96.9)	552 (94.0)	0.0002*
Ovulation drugs	220 (1.0)	8 (1.4)	0.442
In vitro fertilisation	495 (2.2)	27 (4.6)	<0.0001*
Chronic hypertension	266 (1.2)	68 (11.6)	<0.0001*
Diabetes mellitus	154 (0.7)	14 (2.4)	<0.0001*

[a]Control cases were women unaffected by PE or GH; Values are median (range) or n (%).*p<0.05

Screening Method

Index test

- MF
- MAP
- UtA-PI
- PAPP-A

Study Reference	**London Cohorts (Tan 2018c [Francisco 2017, Gallo 2014, Gallo 2016, Mazer Zumaeta 2020, O'Gorman 2016a, O'Gorman 2016b, O'Gorman 2017a, O'Gorman 2017b, Poon 2012, Poon 2020, Tan 2017, Tan 2018a, Tsiakkas 2016a, Wright 2012, Wright 2015, Wright 2016])**
	• PlGF MAP measurements were carried out by healthcare assistants or research sonographers and UtA-PI measurements were performed by research sonographers, according to standardised protocols. Maternal serum concentrations of PAPP-A and serum PlGF were measured using one of two automated devices. Patient-specific risks of delivery with PE at 37 weeks gestation were calculated using the competing-risks model to combine the prior distribution of gestational age at delivery with PE, obtained from maternal characteristics and medical history, with multiples of the median (MoM) values of MAP, UtA-PI, PlGF and PAPP-A. **Mazer Zumaeta 2020:** Patient-specific risks of delivery with PE at <37 weeks gestation were calculated using the competing-risks model to combine the prior distribution of gestational age at delivery with PE, obtained from maternal characteristics and medical history, with multiples of the median values of MAP, UtA-PI, PlGF and PAPP-A. **Poon 2020: Additionally assessed inhibin-A as an added biomarker.** **Poon 2012:** Screening was performed at 11^{+0}–13^{+6} weeks gestation. Based on NHFA protocol, the MAP of each arm was calculated as the average of the last 2 stable measurements and the arm with the highest final MAP was taken for subsequent analysis of results. Based on the first 4 recordings from both arms, 50 possible combinations of MAP were generated. The performance of screening for each of these 50 combinations was determined by the AUROC and this was compared to the AUROC of the NHFA protocol. Reference standard PE, defined as hypertension (systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg on at least 2 occasions 4 h apart, developing after 20 weeks gestation in previously normotensive women) and at least one of the following: proteinuria (≥300 mg/24h or protein to creatinine ratio ≥30 mg/mmol or ≥2+ on dipstick testing), renal insufficiency (serum creatinine >1.1 mg/dL or two-fold increase in serum creatinine in the absence of underlying renal disease), liver involvement (blood concentration of transaminases to twice the normal level), neurological complications (e.g. cerebral or visual symptoms), thrombocytopenia (platelet count <100 000/μL), or pulmonary oedema. **Mazer Zumaeta 2020:** PE was defined by the American College of Obstetricians and Gynecologists (ACOG). According to this definition, diagnosis of PE requires the presence of new-onset hypertension (blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic) at ≥20 weeks gestation and either proteinuria (≥300 mg/24h or protein-to-creatinine ratio >30 mg/mmol or ≥2+ on dipstick testing) or evidence of renal dysfunction (serum creatinine >97 μmol/L), hepatic dysfunction (transaminases ≥65 IU/L) or hematological dysfunction (platelet count < 100,000/μL). **Poon 2012:** The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy. PE: GH (diastolic BP ≥90 mmHg on at least 2 occasions 4 hours apart developing after 20 weeks of gestation in previously normotensive women) with proteinuria of 300 mg or more in 24 hours or 2 readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection available. In PE superimposed on chronic hypertension, significant proteinuria (as defined above) should develop after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or the presence of hypertension at the booking visit before 20 weeks of gestation in the absence of trophoblastic disease).
Test Accuracy	**Tan 2018c: Sensitivity with 95% CI, at screen-positive rate of 10%, in screening for PE by various combinations of MF with biomarkers**

Method of screening	Risk cut-off for PE <37 weeks	n (sensitivity %; 95% CI)		
		PE<32 weeks (N=116)	PE<37 weeks (N=493)	PE≥37 weeks (N=1,277)
MF	1 in 62	61 (52.6; 43.6–61.4)	221 (44.8; 40.5–49.2)	428 (33.5; 31.0–36.2)

Study Reference **London Cohorts (Tan 2018c [Francisco 2017, Gallo 2014, Gallo 2016, Mazer Zumaeta 2020, O'Gorman 2016a, O'Gorman 2016b, O'Gorman 2017a, O'Gorman 2017b, Poon 2012, Poon 2020, Tan 2017, Tan 2018a, Tsiakkas 2016a, Wright 2012, Wright 2015, Wright 2016])**

MF + MAP	1 in 61	71 (61.2; 52.1–69.6)	249 (50.5; 46.1–54.9)	488 (38.2; 35.6–40.9)
MF + UtA-PI	1 in 60	81 (69.8; 61.0–77.4)	288 (58.4; 54.0–62.7)	449 (35.2; 32.6–37.8)
MF + PAPP-A	1 in 61	64 (55.2; 46.1–63.9)	239 (48.5; 44.1–52.9)	450 (35.2; 32.7–37.9)
MF + PlGF	1 in 62	84 (72.4; 63.7–79.3)	299 (60.6; 56.3–64.9)	441 (34.5; 32.0–37.2)
MF + MAP + UtA-PI	1 in 61	96 (82.8; 74.9–88.6)	337 (68.4; 64.1–72.3)	529 (41.4; 38.8–44.2)
MF + MAP + PAPP-A	1 in 60	76 (65.5; 56.5–73.5)	275 (55.8; 51.4–60.1)	499 (39.1; 36.4–41.8)
MF + MAP + PlGF	1 in 65	92 (79.3; 71.1–85.7)	326 (66.1; 61.8–70.2)	502 (39.3; 36.7–42.0)
MF + UtA-PI + PAPP-A	1 in 60	81 (69.8; 61.0–77.4)	292 (59.2; 54.8–63.5)	464 (36.3; 33.7–39.0)
MF + UtA-PI + PlGF	1 in 62	94 (81.0; 73.0–87.1)	330 (66.9; 62.7–70.9)	471 (36.9; 34.3–39.6)
MF + PlGF + PAPP-A	1 in 62	86 (74.1; 65.5–81.2)	313 (63.5; 59.2–67.6)	456 (35.7; 33.1–38.4)
MF + MAP + UtA-PI + PAPP-A	1 in 61	96 (82.8; 74.9–88.6)	336 (68.2; 63.9–72.1)	518 (40.6; 37.9–43.3)
MF + MAP + UtA-PI + PlGF	1 in 66	104 (89.7; 82.8–94.0)	369 (74.8; 70.8–78.5)	523 (41.0; 38.3–43.7)
MF + MAP + PAPP-A + PlGF	1 in 65	94 (81.0; 73.0–87.1)	332 (67.3; 63.1–71.3)	502 (39.3; 36.7–42.0)
MF + UtA-PI + PAPP-A + PlGF	1 in 63	94 (81.0; 73.0–87.1)	336 (68.2; 63.9–72.1)	471 (36.9; 34.3–39.6)
MF + MAP + UtA-PI + PAPP-A + PlGF	1 in 66	104 (89.7; 82.8–94.0)	369 (74.8; 70.8–78.5)	528 (41.3; 38.7–44.1)

Tan 2018c: Screen-positive rate (SPR), false-positive rate (FPR) sensitivity of PE at <32, <37 and ≥37 weeks gestation, in screening by MF and biomarkers at risk cut-offs of ≥1 in 70 and ≥1 in 100 for PE at <37 weeks

Risk of PE<37 weeks/ method of screening		PE<32 weeks		PE<37 weeks		PE≥37 weeks	
	SPR (N=61,174), n (%)	Sensitivity (N=116), n (%, 95% CI)	FPR (N=61,058), n (%)	Sensitivity (N=493), n (%, 95% CI)	FPR (N=60,681), n (%)	Sensitivity (N=1,277), n (%, 95% CI)	FPR (N=59,897), n (%)
Risk ≥1 in 70							
MF	7,206 (11.8)	62 (53.4, 44.4–62.3)	7,144 (11.7)	238 (48.3, 43.9–52.7)	6,968 (11.5)	470 (41.3; 38.7–44.1	6,736 (11.2)
MF + MAP	7,342 (12.0)	78 (67.2, 58.3–75.1)	7,264 (11.9)	275 (55.8, 51.4–60.1	7,067 (11.6)	547 (42.8, 40.2–45.6)	6,795 (11.3)
MF + UtA-PI	7,456 (12.2)	83 (71.6, 62.8–79.0)	7,373 (12.1)	312 (63.3, 58.9–67.4)	7,144 (11.8)	502 (39.3, 36.7–42.0)	6,954 (11.6)
MF + PAPP-A	7,312 (12.0)	71 (61.2, 52.1–69.6)	7,241 (11.9)	262 (53.1, 48.7–57.5)	7,050 (11.6)	493 (38.6, 36.0–41.3)	6,819 (11.4)
MF + PlGF	6,910 (11.3)	86 (74.1, 65.5–81.2)	6,824 (11.2)	321 (65.1, 60.8–69.2)	6,589 (10.9)	480 (37.6, 35.0–40.3)	6,430 (10.7)
MF + MAP + UtA-PI	7,140 (11.7)	98 (84.5, 76.8–90.0)	7,042 (11.5)	348 (70.6, 66.4–74.4)	6,792 (11.2)	570 (44.6, 41.9–47.4)	6,570 (11.0)
MF + MAP + PAPP-A	7,303 (11.9)	82 (70.7, 61.9–78.2)	7,221 (11.8)	289 (58.6, 54.2–62.9)	7,014 (11.6)	557 (43.6, 40.9–46.4)	6,746 (11.3)
MF + MAP + PlGF	6,604 (10.8)	95 (81.9, 73.9–87.8)	6,509 (10.7)	338 (68.6, 64.3–72.5)	6,266 (10.3)	520 (40.7, 38.1–43.4)	6,084 (10.2)

Study Reference	London Cohorts (Tan 2018c [Francisco 2017, Gallo 2014, Gallo 2016, Mazer Zumaeta 2020, O'Gorman 2016a, O'Gorman 2016b, O'Gorman 2017a, O'Gorman 2017b, Poon 2012, Poon 2020, Tan 2017, Tan 2018a, Tsiakkas 2016a, Wright 2012, Wright 2015, Wright 2016])							
	MF + UtA-PI + PAPP-A	7,390 (12.1)	85 (73.3, 64.6–80.5)	7,305 (12.0)	314 (63.7, 59.4–67.8)	7,076 (11.7)	503 (39.4, 36.7–42.1)	6,887 (11.5)
	MF + UtA-PI + PlGF	6,837 (11.2)	95 (81.9, 73.9–87.8)	6,742 (11.0)	346 (70.2, 66.0–74.1)	6,491 (10.7)	499 (39.1, 36.4–41.8)	6,338 (10.6)
	MF + PAPP-A + PlGF	6,955 (11.4)	88 (75.9, 67.3–82.7)	6,867 (11.2)	331 (67.1, 62.9–71.1)	6,624 (10.9)	482 (37.7, 35.1–40.4)	6,473 (10.8)
	MF + MAP + UtA-PI + PAPP-A	7,065 (11.5)	98 (84.5, 76.8–90.0)	6,967 (11.4)	353 (71.6, 67.5–75.4)	6,712 (11.1)	569 (44.6, 41.9–47.3)	6,496 (10.8)
	MF + MAP + PAPP-A + PlGF	6,599 (10.8)	94 (81.0, 73.0–87.1)	6,505 (10.7)	337 (68.4, 64.1–72.3)	6,262 (10.3)	524 (41.0, 38.4–43.8)	6,075 (10.1)
	MF + MAP + UtA-PI + PlGF	6,458 (10.6)	104 (89.7, 82.8–94.0)	6,354 (10.4)	372 (75.5, 71.5–79.1)	6,086 (10.0)	540 (42.3, 39.6–45.0)	5,918 (9.9)
	MF + UtA-PI + PAPP-A + PlGF	6,856 (11.2)	95 (81.9, 73.9–87.8)	6,761 (11.1)	345 (70.0, 65.8–73.9)	6,511 (10.7)	498 (39.0, 36.4–41.7)	6,358 (10.6)
	MF + MAP + UtA-PI + PAPP-A + PlGF	6,473 (10.6)	106 (91.4, 84.9–95.3)	6,367 (10.4)	375 (76.1, 72.1–79.6)	6,098 (10.0)	541 (42.4, 39.7–45.1)	5,932 (9.9)
	MF	11,713 (19.1)	73 (62.9, 53.9–71.2)	11,640 (19.1)	293 (59.4, 55.0–63.7)	11,420 (18.8)	619 (48.5, 45.7–51.2)	11,094 (18.5)
	MF + MAP	11,184 (18.3)	87 (75.0, 66.4–82.0)	11,097 (18.2)	329 (66.7, 62.5–70.8)	10,855 (17.9)	703 (55.1, 52.3–57.8)	10,481 (17.5)
	MF + UtA-PI	11,355 (18.6)	93 (80.2, 72.0–86.4)	11,262 (18.4)	355 (72.0, 67.9–75.8)	11,000 (18.1)	651 (51.0, 48.2–53.7)	10,704 (17.9)
	MF + PAPP-A	11,704 (19.1)	78 (67.2, 58.3–75.1)	11,626 (19.0)	310 (62.9, 58.5–67.0)	11,394 (18.8)	635 (49.7, 47.0–52.5)	11,069 (18.5)
	MF + PlGF	9,973 (16.3)	93 (80.2, 72.0–86.4)	9,880 (16.2)	353 (71.6, 67.5–75.4)	9,620 (15.9)	594 (46.5, 43.8–49.3)	9,379 (15.7)
	MF + MAP + UtA-PI	10,336 (16.9)	104 (89.7, 82.8–94.0)	10,232 (16.8)	383 (77.7, 73.8–81.1)	9,953 (16.4)	689 (54.0, 51.2–56.7)	9,647 (16.1)
	MF + MAP + PAPP-A	10,837 (17.7)	93 (80.2, 72.0–86.4)	10,744 (17.6)	340 (69.0, 64.8–72.9)	10,497 (17.3)	676 (52.9, 50.2–55.7)	10,161 (17.0)
	MF + MAP + PlGF	9,372 (15.3)	101 (87.1, 79.8–92.0)	9,271 (15.2)	384 (77.9, 74.0–81.3)	8,988 (14.8)	633 (49.6, 46.8–52.3)	8,739 (14.6)
	MF + UtA-PI + PAPP-A	11,161 (18.2)	95 (81.9, 73.9–87.8)	11,066 (18.1)	360 (73.0, 68.9–76.8)	10,801 (17.8)	630 (49.3, 46.6–52.1)	10,531 (17.6)
	MF + UtA-PI + PlGF	9,576 (15.7)	102 (87.9, 80.8–92.7)	9,474 (15.5)	378 (76.7, 72.7–80.2)	9,198 (15.2)	601 (47.1, 44.3–49.8)	8,975 (15.0)
	MF + PAPP-A + PlGF	9,915 (16.2)	96 (82.8, 74.9–88.6)	9,819 (16.1)	362 (73.4, 69.4–77.1)	9,553 (15.7)	604 (47.3, 44.6–50.0)	9,311 (15.5)
	MF + MAP + UtA-PI + PAPP-A	10,211 (16.7)	104 (89.7, 82.8-94.0)	10,107 (16.6)	393 (79.7, 75.9–83.0)	9,818 (16.2)	682 (53.4, 50.7–56.1)	9,529 (15.9)

Study Reference **London Cohorts (Tan 2018c [Francisco 2017, Gallo 2014, Gallo 2016, Mazer Zumaeta 2020, O'Gorman 2016a, O'Gorman 2016b, O'Gorman 2017a, O'Gorman 2017b, Poon 2012, Poon 2020, Tan 2017, Tan 2018a, Tsiakkas 2016a, Wright 2012, Wright 2015, Wright 2016])**

MF + MAP + PAPP-A + PlGF	9,296 (15.2)	102 (87.9, 80.8–92.7)	9,194 (15.1)	382 (77.5, 73.6–81.0)	8,914 (14.7)	624 (48.9, 46.1–51.6)	8,672 (14.5)
MF + MAP + UtA-PI + PlGF	8,970 (14.7)	109 (94.0, 88.1–97.1)	8,861 (14.5)	394 (79.9, 76.2–83.2)	8,576 (14.1)	655 (51.3, 48.6–54.0)	8,315 (13.9)
MF + UtA-PI + PAPP-A + PlGF	9,599 (15.7)	103 (88.8, 81.8–93.3)	9,496 (15.6)	380 (77.1, 73.2–80.6)	9,219 (15.2)	604 (47.3, 44.6–50.0)	8,995 (15.0)
MF + MAP + UtA-PI + PAPP-A + PlGF	8,980 (14.7)	109 (94.0, 88.1–97.1)	8,871 (14.5)	398 (80.7, 77.0–84.0)	8,582 (14.1)	651 (51.0, 48.2–53.7)	8,329 (13.9)

Tan 2018a: Sensitivity of screening recommended by the NICE guidelines vs mini-combined test (a Bayes' theorem-based method involving MF, MAP, PlGF, UtA-PI and PAPP-A) in the prediction of PE (n=16,747)

Method of screening	Sensitivity, n (%, 95% CI)
All-pre-eclampsia (N=473)	
NICE guidelines	144 (30.4, 26.3–34.6)
MF + MAP + PAPP-A	201 (42.5, 38.0–46.9)
Preterm pre-eclampsia (N=142)	
NICE guidelines	58 (40.8, 32.8–48.9)
MF + MAP + PAPP-A	76 (53.5, 45.3–61.7)
MF + MAP + PlGF	98 (69.0, 61.4–76.6)
MF + MAP + PlGF + UtA-PI	117 (82.4, 76.1–88.7)

Tan 2018a: Incremental benefit in sensitivity of preterm PE, at screen-positive rate of 10%, when a single biomarker is added to a specific combination of one or more biomarkers (n=16,747)

Method of screening	Sensitivity (%)			p value
	Before	After	Difference (95% CI)	
MF *vs* MF + MAP	41.55	49.30	7.75 (1.6–14.6)	0.0291
MF *vs* MF + UtA-PI	41.55	61.97	20.42 (12.9–28.5)	<0.0001
MF *vs* MF + PlGF	41.55	59.15	17.61 (10.1–25.7)	<0.0001
MF *vs* MF + PAPP-A	41.55	45.07	3.52 (–1.7–9.2)	0.2673
MAP *vs* MF + MAP + PlGF	49.30	68.31	19.01 (11.7–27.0)	<0.0001
MF+ MAP *vs* MF + MAP + UtA-PI	49.30	73.94	24.65 (16.7–33.0)	<0.0001
MF+ MAP + UtA-PI *vs* MF + MAP + UtA-PI + PlGF	73.94	81.69	7.75 (2.3–14.1)	0.0153
MF+ MAP + PlGF *vs* MF + MAP + PlGF + UtA-PI	68.31	81.69	13.38 (8.0–20.2)	<0.0001
MF+ UtA-PI + PlGF *vs* MF + UtA-PI + PlGF + MAP	70.42	81.69	11.27 (5.3–18.2)	0.0014

Poon 2020: Performance of risk assessment for PE by NICE guidelines and screening by the competing risk model with screen-positive and FPRs fixed according to NICE guidelines

	No adjustment for aspirin		Adjusted for aspirin	
	DR, % (95% CI)	Difference from NICE, % (95% CI)	DR, % (95% CI)	Difference from NICE, % (95% CI)
All pregnancies				

Study Reference	London Cohorts (Tan 2018c [Francisco 2017, Gallo 2014, Gallo 2016, Mazer Zumaeta 2020, O'Gorman 2016a, O'Gorman 2016b, O'Gorman 2017a, O'Gorman 2017b, Poon 2012, Poon 2020, Tan 2017, Tan 2018a, Tsiakkas 2016a, Wright 2012, Wright 2015, Wright 2016])					
	(SPR = 10.3%)					
	All PE (n = 473)	NICE guidelines	30.4 (26.3 to 34.6)	-	31.6 (27.3 to 35.9)	-
		MF + MAP + PAPP-A	42.7 (38.2 to 47.2)	12.3 (8.1 to 16.4)	42.8 (38.4 to 47.3)	11.2 (6.9 to 15.6)
	Preterm PE (n = 142)	NICE guidelines	40.8 (32.8 to 48.9)	-	44.1 (35.7 to 52.6)	-
		MF + MAP + PAPP-A	53.5 (45.3 to 61.7)	12.7 (4.7 to 20.7)	53.5 (45.5 to 61.6)	9.4 (0.1 to 18.2)
		MF + MAP + PlGF	69.0 (61.4 to 76.6)	28.2 (19.4 to 37.0)	67.3 (59.7 to 75.0)	23.2 (13.2 to 33.3)
		MF + MAP + UtA-PI + PlGF	82.4 (76.1 to 88.7)	41.6 (33.2 to 49.9)	79.6 (72.7 to 86.5)	35.5 (25.2 to 45.8)
	Nulliparous (SPR = 12.7%)					
	All PE (n = 284)	NICE guidelines	21.5 (16.7 to 26.3)	-	22.3 (17.4 to 27.2)	-
		MF + MAP + PAPP-A	35.9 (30.3 to 41.5)	14.4 (9.0 to 19.8)	36.1 (30.6 to 41.7)	13.8 (8.4 to 19.3)
	Preterm PE (n = 75)	NICE guidelines	29.3 (19.0 to 39.6)	-	31.6 (21.1 to 42.2)	-
		MF + MAP + PAPP-A	48.0 (36.7 to 59.3)	18.7 (6.0 to 31.3)	48.6 (37.3 to 60.0)	17.0 (4.2 to 29.8)
		MF + MAP + PlGF	65.3 (54.6 to 76.1)	36.0 (23.4 to 48.6)	64.5 (53.5 to 75.5)	32.8 (19.3 to 46.4)
		MF + MAP + UtA-PI + PlGF	77.3 (67.9 to 86.8)	48.0 (36.1 to 59.9)	75.7 (65.7 to 85.7)	44.0 (30.9 to 57.2)
	Parous (SPR = 8.3%)					
	All PE (n = 189)	NICE guidelines	43.9 (36.8 to 51.0)	-	45.2 (37.9 to 52.6)	-
		MF + MAP + PAPP-A	51.9 (44.7 to 59.0)	7.9 (1.7 to 14.2)	51.7 (44.6 to 58.7)	6.4 (–0.3 to 13.1)
	Preterm PE (n = 67)	NICE guidelines	53.7 (41.8 to 65.7)	-	57.1 (44.9 to 69.3)	-
		MF + MAP + PAPP-A	61.2 (49.5 to 72.9)	7.5 (–2.1 to 17.0)	60.3 (48.9 to 71.6)	3.2 (–8.5 to 14.9)
		MF + MAP + PlGF	80.6 (71.1 to 90.1)	26.9 (16.3 to 37.5)	77.4 (67.3 to 87.4)	20.2 (6.9 to 33.5)
		MF + MAP + UtA-PI + PlGF	85.1 (76.5 to 93.6)	31.3 (20.2 to 42.5)	81.0 (71.3 to 90.6)	23.8 (9.6 to 38.1)

Poon 2020: DR with 95% CI for a SPR of 10% in screening for PE by various combinations of biomarkers using the competing risk model

Method of screening	PE at <34 weeks		PE at <37 weeks		PE at ≥37 weeks	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
MF	29/60	48.3 (35.2 to 61.6)	59/142	41.5 (33.3 to 50.1)	100/331	30.2 (25.3 to 35.5)
MF + MAP	39/60	65.0 (51.6 to 76.9)	70/142	49.3 (40.8 to 57.8)	128/331	38.7 (33.4 to 44.2)
MF + UtA-PI	44/60	73.3 (60.3 to 83.9)	88/142	62.0 (53.5 to 70.0)	105/331	31.7 (26.7 to 37.0)
MF + PAPP-A	33/60	55.0 (41.6 to 67.9)	64/142	45.1 (36.7 to 53.6)	100/331	30.2 (25.3 to 35.5)
MF + PlGF	40/60	66.7 (53.3 to 78.3)	84/142	59.2 (50.6 to 67.3)	113/331	34.1 (29.0 to 39.5)
MF + MAP + UtA-PI	53/60	88.3 (77.4 to 95.2)	105/142	73.9 (65.9 to 80.9)	144/331	43.5 (38.1 to 49.0)
MF + MAP + PAPP-A	39/60	65.0 (51.6 to 76.9)	75/142	52.8 (44.3 to 61.2)	125/331	37.8 (32.5 to 43.2)
MF + MAP + PlGF	44/60	73.3 (60.3 to 83.9)	97/142	68.3 (60.0 to 75.9)	131/331	39.6 (34.3 to 45.1)
MF + UtA-PI + PAPP-A	44/60	73.3 (60.3 to 83.9)	90/142	63.4 (54.9 to 71.3)	107/331	32.3 (27.3 to 37.7)
MF + UtA-PI + PlGF	45/60	75.0 (62.1 to 85.3)	100/142	70.4 (62.2 to 77.8)	126/331	38.1 (32.8 to 43.5)
MF + PAPP-A + PlGF	41/60	68.3 (55.0 to 79.7)	87/142	61.3 (52.7 to 69.3)	113/331	34.1 (29.0 to 39.5)
MF + MAP + UtA-PI + PAPP-A	52/60	86.7 (75.4 to 94.1)	108/142	76.1 (68.2 to 82.8)	141/331	42.6 (37.2 to 48.1)
MF + MAP + UtA-PI + PlGF	54/60	90.0 (79.5 to 96.2)	116/142	81.7 (74.3 to 87.7)	141/331	42.6 (37.2 to 48.1)
MF + MAP + PAPP-A + PlGF	46/60	76.7 (64.0 to 86.6)	96/142	67.6 (59.2 to 75.2)	130/331	39.3 (34.0 to 44.8)
MF + UtA-PI + PAPP-A + PlGF	47/60	78.3 (65.8 to 87.9)	102/142	71.8 (63.7 to 79.1)	119/331	36.0 (30.8 to 41.4)
MF + MAP + UtA-PI + PAPP-A + PlGF	54/60	90.0 (79.5 to 96.2)	115/142	81.0 (73.6 to 87.1)	144/331	43.5 (38.1 to 49.0)

Poon 2020: Incremental benefit in DR of preterm PE (with 95% CI) for a SPR of 10% when one biomarker is added to a specific combination of one or more biomarkers

Comparison of methods of screening	DR (%)			
	Before	After	Difference (95% CI)	p value
MF vs. addition of MAP	41.55	49.30	7.75 (1.6 to 14.6)	0.0291
MF vs. addition of UTA-PI	41.55	61.97	20.42 (12.9 to 28.5)	<0.0001

Study Reference **London Cohorts (Tan 2018c [Francisco 2017, Gallo 2014, Gallo 2016, Mazer Zumaeta 2020, O'Gorman 2016a, O'Gorman 2016b, O'Gorman 2017a, O'Gorman 2017b, Poon 2012, Poon 2020, Tan 2017, Tan 2018a, Tsiakkas 2016a, Wright 2012, Wright 2015, Wright 2016])**

MF vs. addition of PLGF	41.55	59.15	17.61 (10.1 to 25.7)	<0.0001
MF vs. addition of PAPP-A	41.55	45.07	3.52 (–1.7 to 9.2)	0.2673
MF and MAP vs. addition of PLGF	49.30	68.31	19.01 (11.7 to 27.0)	<0.0001
MF and MAP vs. addition of UTA-PI	49.30	73.94	24.65 (16.7 to 33.0)	<0.0001
MF, MAP and UTA-PI vs. addition of PLGF	73.94	81.69	7.75 (2.3 to 14.1)	0.0153
MF, MAP and PLGF vs. addition of UTA-PI	68.31	81.69	13.38 (8.0 to 20.2)	<0.0001
MF, UTA-PI and PLGF vs. addition of MAP	70.42	81.69	11.27 (5.3 to 18.2)	0.0014

A comparison of the DRs for PE at <32 <37 and ≥37 weeks gestation and all PE at a fixed SPR of 10% by various combinations of biomarkers for the 3 datasets AJOG, ASPRE and SPREE are provided in Poon 2020.

Poon 2020: Empirical DR at a 10% FPR in screening for all PE; incorporation of Inhibin-A

Method of screening	DR (95% CI)		
	All PE	PE with delivery <37 weeks gestation	PE with delivery <32 weeks gestation
MF	37 (29 to 46)	49 (34 to 64)	60 (26 to 88)
MF + inhibin-A	41 (32 to 49)	60 (44 to 74)	80 (44 to 97)
MF + PlGF	48 (39 to 56)	60 (44 to 74)	80 (44 to 97)
MF + PlGF + inhibin-A	48 (39 to 56)	64 (49 to 78)	80 (44 to 97)
MF + MAP + PlGF	54 (45 to 62)	67 (51 to 80)	80 (44 to 97)
MF + MAP + PlFG + inhibin-A	51 (42 to 59)	67 (51 to 80)	70 (35 to 93)
MF + MAP + UtA-PI + PlGF	61 (52 to 69)	80 (65 to 90)	100 (69 to 100)
MF + MAP + UtA-PI + PlGF + inhibin-A	61 (52 to 69)	80 (65 to 90)	100 (69 to 100)

Poon 2012:

Blood pressure method	DR (95% CI) for 10% FPR	DR (95% CI) for 5% FPR
NHFA	42.3 (38.2–46.4)	29.6 (26.0–33.5)
Left arm		
MAP-1	38.2 (34.2–42.2)	26.4 (22.9–30.2)
MAP-2	40.7 (36.7–44.8)	28.3 (24.7–32.1)
MAP-3	39.4 (35.9–44.0)	28.1 (24.5–31.9)
MAP-4	38.0 (34.0–42.1)	27.1 (23.5–30.9)
MAP-1+2	41.2 (37.2–45.3)	28.8 (25.2–32.6)
MAP-2+3	40.4 (36.4–44.5)	30.7 (27.0–34.6)
MAP-3+4	40.4 (36.4–44.5)	29.1 (25.5–33.0)
MAP-1+2+3	42.4 (38.4–46.5)	29.5 (25.8–33.3)
MAP-2+3+4	42.1 (38.0–46.2)	29.6 (26.0–33.5)
MAP-1+2+3+4	43.1 (39.1–47.2)	29.5 (26.1–33.7)
Right arm		
MAP-1	39.0 (35.0–43.1)	24.7 (23.1–28.4)

Study Reference	London Cohorts (Tan 2018c [Francisco 2017, Gallo 2014, Gallo 2016, Mazer Zumaeta 2020, O'Gorman 2016a, O'Gorman 2016b, O'Gorman 2017a, O'Gorman 2017b, Poon 2012, Poon 2020, Tan 2017, Tan 2018a, Tsiakkas 2016a, Wright 2012, Wright 2015, Wright 2016])		
	MAP-2	40.2 (36.2–44.3)	28.6 (25.0–32.5)
	MAP-3	41.9 (37.9–46.0)	26.1 (22.6–29.8)
	MAP-4	38.5 (34.5–42.6)	26.6 (23.0–30.3)
	MAP-1+2	41.1 (37.0–45.2)	27.8 (24.2–31.6)
	MAP-2+3	42.9 (38.9–47.0)	29.0 (25.3–32.8)
	MAP-3+4	42.1 (38.0–46.2)	28.5 (24.8–32.3)
	MAP-1+2+3	42.3 (38.2–46.4)	28.3 (24.7–32.1)
	MAP-2+3+4	43.3 (39.2–47.4)	29.3 (25.6–33.2)
	MAP-1+2+3+4	42.8 (38.7–46.9)	28.8 (25.2–32.6)
	Highest		
	MAP-1	39.5 (35.5–43.6)	27.3 (23.7–31.1)
	MAP-2	41.9 (37.9–46.0)	28.1 (24.5–31.9)
	MAP-3	41.6 (37.5–45.7)	27.8 (24.2–31.6)
	MAP-4	38.8 (34.9–42.9)	27.3 (23.7–31.1)
	MAP-1+2	43.6 (39.6–47.7)	29.0 (25.3–32.8)
	MAP-2+3	43.6 (39.6–47.7)	29.6 (26.0–33.5)
	MAP-3+4	40.7 (36.7–44.8)	29.1 (25.5–33.0)
	MAP-1+2+3	44.6 (40.6–48.8)	29.1 (25.5–33.0)
	MAP-2+3+4	42.9 (38.9–47.0)	29.1 (25.5–33.0)
	MAP-1+2+3+4	42.8 (38.7–46.9)	28.6 (25.0–32.5)
	Lowest		
	MAP-1	40.9 (36.9–45.0)	26.6 (23.0–30.3)
	MAP-2	42.1 (38.0–46.2)	29.1 (25.5–33.0)
	MAP-3	39.0 (35.0–43.1)	28.3 (24.7–32.1)
	MAP-4	38.7 (34.7–42.7)	27.1 (24.0–31.4)
	MAP-1+2	42.9 (38.9–47.0)	29.1 (25.5–33.0)
	MAP-2+3	42.9 (38.9–47.0)	30.2 (26.5–34.0)
	MAP-3+4	41.9 (37.9–46.0)	28.5 (24.8–32.3)
	MAP-1+2+3	42.9 (38.9–47.0)	30.7 (27.0–34.6)
	MAP-2+3+4	43.3 (39.2–47.4)	31.0 (27.3–34.9)
	MAP-1+2+3+4	43.3 (39.2–47.4)	30.8 (27.1–34.7)
	Average of left and right		
	MAP-1	41.1 (37.0–45.2)	27.6 (24.0–31.4)
	MAP-2	43.6 (39.6–47.7)	29.5 (25.8–33.3)
	MAP-3	41.2 (37.2–45.3)	30.0 (26.3–33.9)
	MAP-4	40.2 (36.2–45.0)	27.9 (24.3–31.8)
	MAP-1+2	42.8 (38.7–46.9)	28.6 (25.0–32.5)
	MAP-2+3	43.1 (39.1–47.2)	30.5 (26.8–34.4)
	MAP-3+4	42.8 (38.7–46.9)	29.5 (25.8–33.3)

Study Reference	**London Cohorts (Tan 2018c [Francisco 2017, Gallo 2014, Gallo 2016, Mazer Zumaeta 2020, O'Gorman 2016a, O'Gorman 2016b, O'Gorman 2017a, O'Gorman 2017b, Poon 2012, Poon 2020, Tan 2017, Tan 2018a, Tsiakkas 2016a, Wright 2012, Wright 2015, Wright 2016])**		
	MAP-1+2+3	43.4 (39.4–47.6)	29.3 (25.6–33.2)
	MAP-2+3+4	44.1 (40.1–48.2)	29.3 (25.6–33.2)
	MAP-1+2+3+4	44.3 (40.2–48.4)	30.0 (26.3–33.9)
Authors' Conclusions	The study concluded that screening by maternal factors and biomarkers at 11–13 weeks gestation can identify a high proportion of pregnancies that develop early and preterm PE. Combined screening by maternal factors, UtA-PI, MAP and PlGF predicted 90% of early PE, 75% of preterm PE and 41% of term PE, at a screen-positive rate of 10%; inclusion of PAPP-A did not improve the performance of screening. When the risk cut-off for PE at <37 weeks was fixed at 1 in 70 or 1 in 100, the SPR, DR and FPR varied with the combination of biomarkers used for screening. **Tan 2018a:** The SPREE study has demonstrated that the performance of first-trimester screening for PE by a combination of maternal factors and biomarkers is superior to that achieved by the method recommended by the current NICE guidelines, which identifies only about 30% of pregnancies that would develop PE and about 40% of those that will develop severe PE leading to preterm birth, at a screen-positive rate of 10%. The difference in sensitivity between using a combination of maternal factors, MAP and PAPP-A and the NICE guidelines methods was 12.1%. In screening for preterm PE by a combination of maternal factors, MAP and PlGF, the sensitivity was 69.0%, which was superior to that of the NICE method by 28.2% and with the addition of UtA-PI the sensitivity was 82.4%, which was higher than that of the NICE method by 41.6%. **Mazer Zumaeta 2020:** The performance of first-trimester screening for PE by a combination of maternal factors, MAP, UtA-PI and PlGF is superior to that of screening by maternal factors, MAP, UtA-PI and PAPP-A. The addition of serum PAPP-A does not improve the prediction of PE provided by maternal factors, MAP, UtA-PI and PlGF. The risk cut-off and screen-positive rate to achieve a desired detection rate of PE vary according to the racial composition of the study population and whether the biomarkers used for screening are MAP, UtA-PI and PlGF or MAP, UtA-PI and PAPP-A. Replacing PlGF by PAPP-A can achieve the same high detection rate but at a higher screen-positive rate. The best first-trimester biomarkers of PE are UtA-PI, MAP and PlGF and that combined screening by maternal factors and these 3 biomarkers can predict about 85% and 75% of deliveries with PE <34 and <37 weeks gestation, respectively, at a screen-positive rate of 10%. The performance of screening depends on the racial origin of the women. For a given risk cut-off, the screen-positive rate in black women is about three-times higher than in white women and, invariably, the detection rate is also higher. In first-trimester screening for PE, the preferred biochemical marker is PlGF rather than PAPP-A. However, if PAPP-A is used rather than PlGF, the same detection rate can be achieved but at a higher screen-positive rate. **Poon 2020:** There is little evidence of substantive differences in DRs across the 3 data sets AJOG, ASPRE and SPREE at a SPR of 10% (equivalent to that of NICE guidelines). The combined results demonstrate that (1) the performance of screening is substantially better for early PE and preterm PE than for term pre-eclampsia (DR by the triple test at a 10% SPR of 90% and 75% vs. 41%, respectively); (2) in preterm PE screening by MF is sequentially improved by the addition of 1, 2 and 3 biomarkers; and (3) addition of PAPP-A to any combination of biomarkers that includes PlGF has little benefit. Inhibin A improved the prediction provided by maternal factors alone, but it did not improve the prediction provided by biomarkers that included PlGF. The findings suggest that although inhibin A is a biomarker of PE, it is unlikely to improve the prediction provided by a combination of MAP and PlGF or MAP, UtA-PI and PlGF. Overall, there was considerable uncertainty concerning the additional value of inhibin A in improving the performance of screening achieved by the other biomarkers. The results of the screening demonstrated that inhibin A is unlikely to be a useful first trimester biomarker of PE. **Poon 2012:** The findings of this study demonstrate that in first-trimester screening for PE by MAP, the best performance is provided by following the NHFA protocol. However, in order to achieve the necessary point of stability in BP according to this protocol it was necessary		

Study Reference	London Cohorts (Tan 2018c [Francisco 2017, Gallo 2014, Gallo 2016, Mazer Zumaeta 2020, O'Gorman 2016a, O'Gorman 2016b, O'Gorman 2017a, O'Gorman 2017b, Poon 2012, Poon 2020, Tan 2017, Tan 2018a, Tsiakkas 2016a, Wright 2012, Wright 2015, Wright 2016])
	to perform a minimum of 2 measurements from both arms in about 50% of cases, 3 measurements in 25% of cases, and 4 measurements in 25% of cases. The results of this study suggest that similarly good results to those achieved with the NHFA protocol can be obtained by a simpler protocol using the average of 3, 2 or even 1 measurement from each arm. Measurement of MAP at 11–13 weeks gestation is an important component of effective first-trimester screening for PE by a combination of maternal history and measurement of MAP, uterine artery pulsatility index and serum placental growth factor. This study established that the high performance of screening for PE by MAP using the complex NHFA protocol can be achieved by the simpler approach of using the average of 2 recordings from each arm.

Abbreviations: ACOG, American College of Obstetricians and Gynaecologists; APS, antiphospholipid syndrome; AUROC, area under the receiver operating characteristic curve; BMI, body mass index; BP, blood pressure; CI, confidence interval; DR, detection rate; FPR, false-positive rate; GH, gestational hypertension; IQR, interquartile range; MAP, mean arterial pressure; MF, maternal factors; NHFA, National Heart Foundation of Australia; NICE, National Institute for Health and Care Excellence; NPV, negative predictive value; NR, not reported; PAPP-A, pregnancy-associated plasma protein-A; PE, pre-eclampsia; PlGF, placental growth factor; PPV, positive predictive value; SLE, systemic lupus erythematosus; SPR, screen-positive rate; UCL-CCTU, University College London Comprehensive Clinical Trials Unit; UK, United Kingdom; UtA-PI, uterine artery pulsatility index.

Table 25t: Maymon 2017

Study Reference	Maymon 2017
Study Design	Design Prospective cohort study Objective To construct a new PE predicting algorithm in twins [only data on singleton pregnancies extracted] Dates September 2011 to December 2013 Country Israel Setting NR
Population Characteristics	Patient recruitment and eligibility In parallel with enrolment of twin pregnancies, a cohort of singleton pregnancies in women ≥18 years were recruited. Gestational age at enrolment was 11-14 weeks. Exclusion criteria: ultrasound examination indicating a major fetal anomaly or nuchal translucency above 3.5 mm; a fetal reduction of high order multiplicity; known chromosomal abnormalities; any maternal disease that could affect fetal growth (i.e. diabetes, autoimmune disorders); and those who were under treatment with aspirin or low molecular weight heparin due to known thrombophilia. Data collection Demographic, medical and pregnancy history, including all the maternal prior risk factors that are used in the FMF algorithm for singleton, were collected including: maternal age (MA), parity, BMI, smoking, current hypertensive disease and previous hypertensive disorders in pregnancy, and method of conception. Blood samples were obtained at the enrolment visit and at 16–20 weeks. Trans-abdominal Doppler UTPI and MAP were collected in both visits according to the FMF method. After delivery, pregnancy outcomes were extracted from the hospital medical records and verified through telephone interviews with the patients. Duration of follow-up Delivery (assumed based on outcomes reported) Prevalence of PE in the study NR for singleton pregnancies Sample size N screened/invited = NR for singleton pregnancies N eligible = NR for singleton pregnancies N enrolled = 467 (singletons) N excluded (with reason) = NR for singleton pregnancies N lost to follow-up = NR for singleton pregnancies N completed = NR for singleton pregnancies N excluded from analysis = NR for singleton pregnancies N included in analysis = 467 (singletons) Demographics

Study Reference	**Maymon 2017**			
	NR for singleton pregnancies			
Screening Method	Index test • Screening based on maternal prior risk factors, MAP, UTPI, PlGF, PAPP-A and PP13. Reference standard PE was diagnosed according to the criteria of the International Society for the Study of Hypertension in Pregnancy. The criteria were: systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg on at least 2 occasions 4 hours apart, developed after 20 weeks of gestation in previously normotensive women, combined with proteinuria of ≥300 mg in 24 hours, or 2 readings of at least 2+ on dipstick analysis of midstream or catheter urine specimens if a 24 hour collection was available.			
Test Accuracy		Number of fetuses	Detection rate (%)	FPR (%)
	Appendix 49	Singletons 467	79	10
Authors' Conclusions	The study's model was as effective as the model developed by Wright et al. and the FMF for predicting PE in singleton.			

Abbreviations: AFP, alpha feto protein; BMI, body mass index; FPR, false positive rate; FMF, fetal medicine foundation; HCG, Human chorionic gonadotropin; MA, maternal age; MAP, mean arterial pressure; PE, pre-eclampsia; PAPP-A, pregnancy associated placental protein A; PlGF, placental growth factor; PP13, placental protein 13; UTPI, uterine artery Doppler pulsatility index.

Table 25u: Meiri 2014

Study Reference	Meiri 2014
Study Design	Design Prospective cohort study Objective To evaluate PP13 and risk factors (RFs) as markers for predicting PE. Dates July 2007 to February 2011 Country Israel Setting Doctors' offices and community clinics
Population Characteristics	Patient recruitment and eligibility Pregnant women who attended doctors' offices or community clinics for first trimester evaluation of pregnancy were enrolled in the study. Exclusion criteria: women <18 years, women with non-viable fetuses identified by the absence of a fetal heartbeat, twin pregnancies (including twin pregnancies in which one fetus vanished), women with pregnancy loss before 22 weeks, and women with pregnancy termination due to fetal malformation. Women undergoing in vitro fertilisation, including women with oocyte donation, were enrolled by only after discontinuing treatment for hormonal support of placentation. Data collection Blood was drawn from pregnant women between 8 and 14 weeks of gestation. PP13 test was performed within 2 to 12 days of blood collection. Gestational age was determined by the last menstrual period and confirmed by first trimester crown rump length measurements. Demographics, medical and pregnancy history were obtained at enrolment. Pregnancy outcome after delivery was obtained either from the patients' medical records and hospital discharge form (85%) or a detailed telephone interview was conducted with a) patients who had delivered at home (13 cases), b) delivered abroad (when contact information was available), and 3) patients who did not keep their hospital discharge form as well as with the patient's physician. Duration of follow-up Post-delivery (assumed based on outcomes reported) Prevalence of PE in the study 63 (7.7%) developed PE; of these, 6 had early PE (delivery <34 weeks), 21 had preterm PE (delivery at 34 weeks-36 weeks and 6 days), and 36 had term PE (delivery ≥37 weeks). Sample size N screened/invited = NR N eligible = NR N enrolled = 947 N excluded (with reason) = NR N lost to follow-up = 15 (address change or move to another country) N completed = NR

Study Reference **Meiri 2014**

N excluded from analysis = 34 (twin pregnancies, including n = 7 twin pregnancies in which one fetus vanished) [results of twin pregnancies analysed elsewhere]; 36 (pregnancy loss before 22 weeks); 6 (pregnancy termination due to fetal malformation); 36 (multiple gestation pregnancies)
N included in analysis = 820

Demographics

Characteristic	Unaffected singleton (n = 757)	PE (n = 63)	p value
Characteristic at enrolment	-	-	-
Maternal age, years, median (range)	30 (18–54)	32 (21–47)	NS
Gestational age, weeks, median (range)	12 (6–14)	11 (7–13)	NS
Nullipara, n (%)	405 (54)	24 (38)	<0.001
Caucasian, n (%)	717 (95)	61 (97)	NS
Smoking, n (%)	27 (3.6)	2 (3.2)	NS
BMI, kg/m^2, median (range)	22.3 (17–47)	24.5 (18–40)	NS
MAP, mmHg, median (range)	77 (57–113)	89 (66–103)	<0.001
In vitro fertilisation, n (%)	55 (7.3)	11 (17.5)	<0.001
All risk factors, n (%)	262 (34.6)	33 (52.4)	<0.001
PP13 MoM	0.83 (0.08–2.5)	0.27 (0.0–1.5)	<0.0001
Chronic hypertension in current pregnancy, %	3.2	0	0.09
Pre-gestational diabetes, %	0.6	0	0.17
Nephropathy, %	0.1	7.9	<0.001
Antiphospholipid antibodies syndrome, %	0.6	0	0.13
Thrombophilia, %	1.7	0	0.11
Lupus, %	0.1	0	0.19
Others, %	0.4	0	0.15
Total with maternal disease in current pregnancy, %	10.3	11.1	0.17
Maternal age >40 years, %	6.2	3.2	0.07
BMI >35, %	3.8	7.9	0.09
Total maternal demography RFs, %	9.0	10.2	0.13
PE or GH or IUGR in previous pregnancy, %	20.5	34.9	<0.001
In vitro fertilisation, %	7.3	17.5	<0.001
Total with significant risk factor/s, %	34.6	52.4	<0.005

Screening Method

Index test
First-trimester pregnancy screening was based on having PP13 level ≤0.4 MoM and/or at least one major risk factor (RF) for PE. PP13 MoM above or below the cutoff of 0.4 MoM or major RFs for PE. The definition of being at risk for PE was based on having PP13 ≤0.4 MoM or having major RFs or both. Major RFs included: 1) maternal disease (chronic hypertension or diabetes or kidney disorders) or cardiovascular

Study Reference | **Meiri 2014**

diseases, phospholipid syndrome, thrombophilia, and lupus erythromatosus; 2) history of PE; 3) a BMI >35 or maternal age >40; and 4) conception by assisted fertility (IVF or intra-cytoplasmic sperm injection).

Reference standard

PE was diagnosed according to the criteria of the International Society for the Study of Hypertension in Pregnancy (ISSHP). The criteria were as follows: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least 2 occasions 4 hours apart developed after 20 weeks of gestation in previously normotensive women combined with proteinuria of ≥300 mg in 24 hours, or 2 readings of at least 2+ on dipstick analysis of midstream or catheter urine specimens, if no 24 hour collection was available. Severe PE was defined according to systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg, proteinuria ≥3 g in 24-hour urine specimen or ≥3+ on dipstick as above. Preterm PE cases and Early PE were all delivered before 37 and 34 weeks, respectively.

Test Accuracy

Screening for PE by PP13 alone predicted 80% of cases at 20% and at 13% FPR when aspirin treated patients were excluded. For RFs alone, screening for PE by any RF identified 55% of cases at 45% FPR. For PP13 plus RFs, prediction by combining PP13 with all of the RFs yielded a detection rate of 85% at 15% FPR. Using only nephropathy, previous PE or in vitro fertilisation, the detection rate increased to 87% at 12% FPR. The detection rate for MAP alone was 43% at 15% FPR; exclusion of the aspirin-treated pregnancies yielded a detection rate of 49%. However, combining MPA with PP13 and all RFs increased the detection rate to 93% at 10% FPR, and to 94% at 9% FPR when those treated with aspirin were omitted. Detection rate at 10% FPR was 52% for PP13 alone, 18% for RFs alone, and 59% for PP13 plus RFs. Combining PP13 with RFs and MAP increased the detection rate to 93%.

Marker	Detection rate (%)	FPR (%)
PP13	80	21.5
RFs	55	45
PP13 + RF	85	15
PP13 + RF + MAP	93	10

	Sensitivity, % (95% CI)		
Marker	10% FPR	15% FPR	20% FPR
PP13	52 (44–55)	76 (72–81)	81 (76–57)
RFs	18 (16–20)	55 (49–61)	5 (49–61)
PP13 + RF	59 (89–93)	91 (89–93)	100
PP13 + RF + MAP	93 (87–100)	100	-

Authors' Conclusions

RFs were weak predictors of PE compared with PP13 and MAP but combining these 3 parameters increased their prediction power to good clinical performance by WHO criteria. The use of RFs in combination with PP13 and MAP for predicting PE risk yielded better performance compared with each individual parameter alone.

Abbreviations: BMI, body mass index; CI, confidence interval; FPR, false positive rate; GH, gestational hypertension; IUGR, intrauterine growth restriction; MAP, mean arterial pressure; MoM, multiples of the median; NS, not significant; PE, pre-eclampsia; PP13, placental protein 13; RF, risk factor

Table 25v: Metcalfe 2014

Study Reference	Metcalfe 2014
Study Design	Design Prospective cohort study Objective To identify whether the combination of obstetrical risk factors and maternal serum markers collected during aneuploidy screening could be used to develop prediction models with sufficient accuracy for clinical use. Dates April 2010 to March 2012 Country Canada Setting British Columbia Perinatal Services BC captured data on deliveries of live and stillborn infants born at ≥20 weeks of gestation or with a birth weight of ≥50 g who were born in an acute care hospital or at home in the presence of a registered midwife.
Population Characteristics	Patient recruitment and eligibility All women with singleton pregnancies who met all eligibility criteria for this study and had an estimated delivery date between 1 April 2010 and 31 March 2012 who had data from the BC Prenatal Genetic Screening Program were included; since 2009, all pregnant women in British Columbia have been offered full-funded aneuploidy screening through this program. Pregnancy terminations and pregnancies that involved chromosomal or congenital anomalies were excluded. Data collection Two blood samples were collected; the first between 9 weeks and 13 weeks and 6 days of gestation to measure PAPP-A, and the second between 15 weeks and 20 weeks and 6 days of gestation to measure AFP, total HCG, Inhibin A, uE_3. Data were collected on ethnicity, maternal age, current weight, smoking status, use of in vitro fertilisation, and gestational age (by last menstrual period and/or ultrasound). Maternal serum concentrations of PAPP-A, AFP, hCG, Inhibin A, and uE_3 were measured. Data on clinical risk factors and pregnancy outcomes were obtained from Perinatal Services British Columbia. Duration of follow-up Delivery (assumed based on outcomes reported) Prevalence of PE in the study 0.8% developed severe PE (PE with preterm birth <34 weeks [0.2%] or an SGA infant <10^{th} percentile birth weight [0.6%]) Sample size N screened/invited = NR N eligible = 45,287 N enrolled = 45,287 N excluded (with reason) = 0

Study Reference	**Metcalfe 2014**

N lost to follow-up = NR
N completed = 45,287
N excluded from analysis = 0
N included in analysis = 45,287

Demographics

Characteristic	Overall sample, n (%)
Obstetrical history	
Multiparous with no history of adverse events[a]	19,919 (44.0)
Multiparous with history of adverse events[a]	3,271 (7.2)
Primiparous	22,097 (48.8)
Smoking status	
Non-smoker	14,974 (67.6)
Former smoker	4,231 (19.1)
Current smoker	2,940 (13.3)
Ethnicity	
White	25,427 (56.9)
Black	1,939 (4.3)
East Asian	9,375 (21.0)
South Asian	6,143 (13.7)
First Nations	1,435 (3.2)
Other	377 (0.8)
Pre-pregnancy BMI	
Normal (18.5 to 24.9)	20,558 (61.6)
Underweight (<18.5)	1,846 (5.5)
Overweight (25.0 to 29.9)	7,042 (21.1)
Obese (≥30.0)	3,920 (11.7)
Used some form of assisted reproductive technology to conceive current pregnancy	1,364 (3.0)
Maternal age, mean (SD)	31.2 (5.3)

[a]History of adverse events included at least one of the following in a previous pregnancy: congenital anomaly, low birth weight, macrosomia, preterm birth <37 weeks, neonatal death, rh isoimmunization, and stillbirth.

Screening Method

Index test

- Obstetrical risk factors, PAPP-A, total hCG, AFP, Inhibin A, and uE_3
- Multivariable logistic regression models were derived and validated in 2 independent samples to assess the impact of serum markers and clinical variables on adverse pregnancy outcomes
- Models were based on maternal serum markers and clinical risk factors

Serum concentrations were expressed as multiples of the median for gestational age and subsequently corrected for weight, ethnicity, smoking status, and use of in vitro fertilisation

Study Reference **Metcalfe 2014**

Reference standard

- Severe PE is defined as PE with SGA infant <10th percentile or preterm birth <34 weeks; PE not defined

Test Accuracy

			Severe PE (PE with SGA <10th percentile or preterm birth <34 weeks)		
Serum marker	Cut-point	Screen positive women, n (%)	Detection rate, % (95% CI)	Likelihood ratio + (LR+, 95% CI)	Post-test probability, % (95% CI)
AFP	≥2.5 MoM	228 (0.5)	3.9 (2.1–6.6)	8.1 (4.7–14.0)	5.7 (3.1–9.6)
	≥3.0 MoM	85 (0.2)	2.4 (1.1–4.7)	13.9 (6.8–28.6)	9.4 (4.2–17.7)
	≥3.5 MoM	44 (0.1)	2.1 (0.9–4.3)	25.3 (11.4–56.4)	15.9 (6.6–30.1)
hCG	≥3.0 MoM	700 (1.6)	9.7 (6.7–13.4)	6.4 (4.5–8.9)	4.6 (3.2–6.4)
	≥3.5 MoM	314 (0.7)	5.1 (3.0–8.1)	7.6 (4.7–12.3)	5.4 (3.2–8.5)
	≥4.0 MoM	164 (0.4)	3.6 (1.9–6.3)	10.5 (5.9–18.7)	7.3 (3.8–12.4)
	≥4.5 MoM	87 (0.2)	3.0 (1.5–5.5)	17.3 (9.0–33.1)	11.5 (5.6–20.1)
Inhibin A	≥3.0 MoM	495 (1.1)	11.8 (8.5–15.8)	11.4 (8.4–15.5)	7.9 (5.7–10.6)
	≥3.5 MoM	271 (0.6)	8.2 (5.4–11.6)	14.7 (10.0–21.6)	10.0 (6.7–14.2)
	≥4.0 MoM	146 (0.3)	6.3 (4.0–9.5)	22.3 (14.3–35.0)	14.4 (9.2–21.1)
	≥4.5 MoM	99 (0.2)	5.7 (3.5–8.8)	31.6 (19.4–51.5)	19.2 (12.0–28.3)
uE_3	≤0.40 MoM	72 (0.2)	0.9 (0.2–2.6)	5.8 (1.8–18.4)	4.2 (0.9–11.7)
	≤0.30 MoM	26 (0.1)	0	0	No true positives
	≤0.25 MoM	19 (0.04)	0	0	No true positives
PAPP-A	≤0.40 MoM	2336 (7.3)	21.8 (16.7–27.5)	3.0 (2.4–3.8)	2.2 (1.8–2.9)
	≤0.35 MoM	1524 (4.8)	15.9 (11.5–21.2)	3.4 (2.5–4.6)	2.5 (1.8–3.4)
	≤0.30 MoM	918 (2.9)	13.8 (9.7–18.8)	4.9 (3.6–6.8)	3.6 (2.5–5.0)
	≤0.25 MoM	483 (1.5)	9.2 (5.9–13.6)	6.3 (4.2–9.5)	4.6 (2.9–6.8)
	≤0.20 MoM	217 (0.7)	4.6 (2.3–8.1)	7.1 (3.9–12.8)	5.1 (2.6–8.9)
	≤0.15 MoM	85 (0.3)	2.1 (0.7–4.8)	8.3 (3.4–20.2)	5.9 (1.9–13.2)

Outcome	Predicted probability	Detection rate [sensitivity] (%)	False positive rate (%)
Severe PE (PE with SGA <10th percentile or preterm birth <34 weeks)	<0.1%	-	-
	≥0.1–0.5%	99.1	95.0
	≥0.5–3%	81.0	41.4
	≥3–5%	19.8	2.2
	≥5–10%	9.5	0.8
	≥10–20%	4.3	0.2
	≥20%	3.4	0.05

Detection rate (sensitivity) and false positive rate (one-specificity) were calculated using cumulative row values as different cut-offs to define high risk, for example, if all women with a model predicted probability of severe PE of 0.5% or higher are considered to have a positive test, this test would have a sensitivity of 81.0% and a false positive rate of 41.4%.

Study Reference	Metcalfe 2014
	• Model discrimination based on clinical risk factors and serum markers for predicting severe PE was substantially improved compared to a model based on clinical factors alone and slightly improved compared to a model based on serum markers alone. Model calibration and stratification capacity for predicting severe PE was adequate and identified women at increased and decreased risk of developing severe PE. For both the models predicting serious prenatal events and severe PE, detection rates at higher cut-off levels were low; however, false positive rates were also low thereby supporting the increased risk in these groups.
Authors' Conclusions	This study showed that models, based on maternal serum markers and obstetrical history, have poor detection rates and a modest risk stratification and calibration ability for identifying severe PE. In spite of overall poor performance of maternal serum markers to predict obstetrical risk, the combination of maternal serum markers and clinical risk factors results in an improved ability to identify women with the highest risk for severe preeclampsia. Although the predictive performance of maternal serum markers and clinical risk factors is less than optimal, the model provides accurate prediction for a small number of women with extreme values. Identifying these women early in pregnancy may permit appropriate triage into a higher risk stream of prenatal care and improved fetal outcomes.

Abbreviations: AFP, alpha fetoprotein; BMI, body mass index; CI, confidence interval; hCG, human chorionic gonadotropin; PE, pre-eclampsia; PAPP-A, pregnancy associated plasma protein A; SGA, small for gestational age; uE_3, unconjugated estriol

Table 25w: Myatt 2012

Study Reference	Myatt 2012
Study Design	Design Prospective cohort study Objective To address the hypothesis that uterine artery doppler measurements made in the early second trimester would predict the subsequent development of PE Dates April 2004 to February 2008 Country USA (inferred based on study authors) Setting The Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) Network; 16 clinical centres
Population Characteristics	Patient recruitment and eligibility Women who participated in an earlier RCT, which was evaluating whether antioxidant supplementation prevented PE in nulliparous women at low risk of developing PE, were eligible to participate in this study if their gestational age at enrolment was between 9 weeks 0 days and 12 weeks 6 days. Exclusion criteria were: a prior pregnancy lasting beyond 19 weeks 6 days, an elevated blood pressure (systolic pressure ≥ 135 mmHg or diastolic blood pressure ≥ 85 mmHg), proteinuria (24 hour urine collection of ≥ 300 mg protein or a dipstick value more than trace), use of antihypertensive medication, pre-gestational diabetes, regular use or use within 7 days of platelet active drugs or non-steroidal anti-inflammatory agents, known fetal abnormalities or demise at the time of enrolment, or a history of medical complications.

Study Reference	**Myatt 2012**

Data collection
Clinical information including demographics, medical, obstetrical, family, social, and sexual history was obtained at the time of enrolment by personal interview and chart review. BMI and body fat by the waist-to-hip ratio at enrolment were measured. Four measures of blood pressure were assessed: 1) systolic blood pressure, 2) diastolic blood pressure, 3) mean arterial pressure, and 4) pulse pressure. A complete blood count was performed and additional blood was collected and stored for future evaluation of biochemical assays. Six biochemical markers, ADAM-12, PAPP-A, PP-13, sFlt-1, endoglin, and PlGF were measured. All women had an initial uterine artery Doppler at 16 weeks gestation. If a notch was present at the time of the initial ultrasound, a second ultrasound was scheduled for 24 weeks gestation to determine if a notch was still present. The earlier the Doppler was to be performed was 14 weeks, 0 days of gestation and the latest was 26 weeks, 6 days of gestation; this analysis only included initial Dopplers performed prior to 21 weeks of gestation. To determine the diagnosis of PE, de-identified medical charts of all women with pregnancy-associated hypertension were reviewed.

Duration of follow-up
NR

Prevalence of PE in the study
165 of 2,188 women developed PE; of these, 18 had early onset PE (<34 weeks) and 66 had severe PE

Sample size
N screened/invited = 10,154
N eligible = NR
N enrolled = 2,434
N excluded (with reason) = NR
N lost to follow-up = 40
N completed = 2,394
N excluded from analysis = 40 (uterine artery Doppler not performed before 21 weeks of gestation)
N included in analysis = 2,188

Demographics

Characteristic	PE (n=165)	No PE (n=2,023)	p value
Gestational age at enrolment, median (IQR)	11.6 (10.6–12.3)	11.6 (10.7–12.3)	0.78
Maternal age, median (IQR)	22 (19–25)	23 (20–27)	0.02
Race, n (%)	-	-	<0.001
African American	59 (35.8)	454 (22.4)	-
Hispanic	49 (29.7)	496 (24.5)	-
Caucasian or other	57 (34.5)	1,073 (53.0)	-
Previous pregnancy (before 20 weeks), n (%)	34 (20.6)	454 (22.4)	0.59
Family history of PE, n (%)	24 (14.5)	266 (13.1)	0.61
Smoked during pregnancy, n (%)	27 (16.4)	334 (16.5)	0.96
BMI at enrolment, median (IQR)	27.1 (23.0–31.6)	24.6 (21.8–28.7)	<0.001
Systolic blood pressure, median (IQR)	112 (106–118)	110 (102–118)	0.007
Diastolic blood pressure, median (IQR)	66 (60–70)	66 (60–70)	0.78

Screening Method	Index test • Uterine artery Doppler performed <21 weeks of gestation; presence of a notch, RI, PI

Study Reference	Myatt 2012
	Reference standard Mild PE was defined as mild pregnancy-associated hypertension with documentation of proteinuria within 72 hours before or after an elevated blood-pressure measurement. Proteinuria was defined as total protein excretion of 300mg or more in a 24-hour urine sample of 2+ or higher on dipstick testing, or a protein-to-creatinine ratio of 0.35 or more if a 24-hour urine sample was not available. Severe PE was defined as PE with either severe pregnancy-associated hypertension with oliguria (<500 ml in a 24-hour urine sample), pulmonary oedema (confirmed by radiography), or thrombocytopenia (platelet count of <100,000 per cubic millimetre. PE included mild and severe PE, HELLP syndrome and eclampsia. For this analysis, severe PE, HELLP syndrome and eclampsia were combined as severe PE. The time of onset of PE (early onset defined as <34 weeks or late onset defined as ≥34 weeks gestation) was determine at the time at which individuals first met the criteria for diagnosis of PE given above. To determine the diagnosis of PE, de-identified medical charts of all women with pregnancy-associated hypertension were reviewed centrally by at least 3 reviewers.
Test Accuracy	The diagnostic utility for PE was not great for notch, RI or PI; notch or RI MoM at or above the 75th percentile had a sensitivity of 43% (95% CI 35–51), specificity of 67% (95% CI 65–69), positive predictive value of 10% (95% CI 8–12), negative predictive value of 93%, (95% CI 92–95) positive likelihood ratio 1.29 (95% CI 1.07–1.55) and negative likelihood ratio 0.86 (95% CI 0.75–0.98). However, for predicting the development of early onset PE, the presence of a notch or an RI MoM at or above the 75th percentile had a sensitivity of 78% (95% CI 52–94), specificity of 66% (95% CI 64–68), positive predictive value of 1.9% (95% CI 1.0–3.1), negative predictive value of 99.7% (95% CI 99.3–99.9), positive likelihood ratio of 2.30 (95% CI 1.79–2.97) and negative likelihood ratio of 0.34 (95% CI 0.14–0.80). For predicting the development of severe PE, the presence of a notch or an RI MoM at or above the 75th percentile had a sensitivity of 53% (95% CI 40–65), specificity of 66% (95% CI 64–68), positive predictive value of 5% (95% CI 3–6), negative predictive value of 98% (95% CI 97–99), positive likelihood ratio of 1.58 (95% CI 1.25–2.00) and negative likelihood ratio of 0.71 (95% CI 0.55–0.91).
Authors' Conclusions	Whereas the presence of a notch or bilateral notch in the waveform was not associated with preeclampsia this study found a significant relationship of RI and PI MoM to PE; however, selection of a notch or RI or PI MoM at or above the 75th percentile as a positive predictor did not yield clinically useful sensitivity (43%) and specificity (67%) for predicting PE. Addition of the pulsatility index from this Doppler data to the best biomarkers identified of the original study [Myatt 2012a] (ADAM12, PlGF and PAPP-A) only yielded a sensitivity of 43% (95% CI 35–51) reinforcing the limited utility of Doppler measurements in predicting PE.

Abbreviations: ADAM-12, a disintegrin and metalloprotease 12; BMI, body mass index; CI, confidence interval; IQR, interquartile range; MoM, multiples of the median; MPV, mean platelet volume; PAPP-A, pregnancy-associated plasma protein-A; PE, pre-eclampsia; PI, pulsatility index; PlGF, placental growth factor; PP-13, placental protein-13; RCT, randomised controlled trial; RI, resistance index; sFlt-1, soluble fmslike tyrosine kinase-1; USA, United States of America.

Table 25x: Odibo 2011a

Study Reference	Odibo 2011a
Study Design	Design Prospective cohort study Objective To estimate the utility of first-trimester 3D placental volume and vascular flow indices in the prediction of adverse pregnancy outcomes. Dates NR but participants were enrolled over an 18 month period.

Study Reference	Odibo 2011a
	Country US Setting The Washington University Division of Ultrasound and Genetics
Population Characteristics	Patient recruitment and eligibility Women with singleton pregnancies seen between 11–14 weeks of gestation at the Washington University Division of Ultrasound and Genetics as part of a screening programme for aneuploidy. Any cases with fetal anomalies or chromosomal anomalies were excluded. Data collection Acquisition of the images used for the determination of placental volume and vascularisation indices were obtained at the time of the first-trimester visit. Placental volume and vascularisation indices were obtained using 3D power Doppler imaging and the VOCAL technique. PV was calculated and VI, FI and VFI were obtained from 4-D power Doppler histograms. Duration of follow-up Until delivery (assumed based on outcomes reported) Prevalence of PE in the study PE was seen in 30 women (7.7%). Sample size N screened/invited = NR N eligible = NR N enrolled = 405 N excluded (with reason) = NR N lost to follow-up = 6 N completed = 388 (2 women experienced a spontaneous miscarriage and in 9 women the 3D Doppler evaluation could not be performed due to technical reasons) N excluded from analysis = NR N included in analysis = 388 Demographics

Characteristic	Value (n=388)
Mean age (±SD)	31.6 (±5.6)
Gravidity, median (range)	2 (1–10)
Parity, median (range)	1 (0–5)
Race, n (%)	-
White	226 (58.2)
African American	103 (26.6)
Asian	37 (9.5)
Hispanic	8 (2.1)
Others	14 (3.6)
Smoking, n (%)	34 (8.8)

Study Reference	Odibo 2011a	
	Current BMI, mean (±SD)	28.4 (±7.5)
	Chronic hypertension	34 (8.8)
	Pregestational diabetes	28 (7.2)
	Gestational age at delivery in weeks, mean (±SD)	38.0(±3.8)
	Birth weight (grams), mean (±SD)	3247.1 (±654.8)
	PE, n (%)	30 (7.7)
	GH, n (%)	37 (9.5)
	SGA, n(%)	318.0 (8.0)
Screening Method	Index test Logistic regression analysis was used to determine if the placenta volume and vascularisation indices had a significant contribution to the prediction of PE The women were seen and measurements taken between 11–14 weeks of pregnancy. Reference standard PE was defined using guidelines of the American College of Obstetricians and Gynaecology and by the criteria proposed by the National High Blood Pressure Education Programme Working Group in Pregnancy. Mild PE was defined as: BP>140/90 after 20 weeks gestation in a woman with a previously normal BP and proteinuria of ≥300 mg in a 24-hour urine sample or at least 1+ on urine dipstick. Severe PE was defined using the presence of any of the following criteria in patients with PE: BP≥160/110 on 2 or more occasions at least 6 hours apart; proteinuria of at least 5g or 3+ on urine dipstick on 2 samples randomly taken at least 4 hours apart; elevated liver enzymes; visual disturbance, headache or other neurological disturbances; persistent right upper quadrant or epigastric pain; oliguria with <500 ml of urine in 25 hours; oligohydramnios and fetal growth restriction.	
Test Accuracy	The detection rates and false positive rates for PE using VI and VFI are: 44.8% and 22.6%; and 44.8% and 22.1%, respectively. For a fixed false positive rate of 10%, the detection rate using either VI or VFI is 22%.	
Authors' Conclusions	The prediction model using vascular indices were associated with only modest discriminatory ability. The detection rates for PE using VI, FI and VFI were poor and the false positive rates high. This finding suggests these indices may need to be combined with other reliable maternal characteristics; biochemical markers and biophysical properties become reliable predictors or PE. The screening efficacy of vascular flow indices obtained using 3D power Doppler in the first-trimester was, modest.	

Abbreviations: BMI, body mass index; BP, blood pressure; FI, flow index; GH, gestational hypertension; NR, not recorded; PE, pre-eclampsia; PV, placental volume; SD, standard deviation; SGA, small for gestational age; US, United States; VFI, vascularisation flow index; VI, vascularisation index.

Table 25y: Odibo 2011b

Study Reference	Odibo 2011b
Study Design	Design Prospective cohort study Objective To test the hypothesis that a combination of PP13, PAPP-A and first-trimester uterine artery Doppler would improve the prediction of pre-eclampsia Dates

Study Reference	Odibo 2011b
	December 2009 to March 2011 (when potential participants were approached) Country USA (inferred based on author affiliations) Setting NR
Population Characteristics	Patient recruitment and eligibility Women with singleton pregnancies between 11–14 weeks gestation attending first-trimester aneuploidy screening were included in the study. Women who suffered spontaneous miscarriage prior to 20 weeks, were lost to follow-up or had fetal anomalies diagnosed in the second trimester were all later excluded. Data collection Patients provided approximately 10 cc of maternal blood which was used to measure PP13 concentration. PAPP-A levels were measured as part of routine first-trimester aneuploidy screening. Doppler examination of the uterine arteries was performed; the uterine artery was isolated and the pulsatility index (PI) was measured. Duration of follow-up To delivery Prevalence of PE in the study PE was diagnosed in 42 patients. There were 12 cases with early onset PE. Sample size N screened/invited = 477 N eligible = 452 N enrolled = 452 N excluded (with reason) = 25 (spontaneous miscarriage prior to 20 weeks, loss to follow-up or fetal anomalies diagnosed in the second trimester) N lost to follow-up = NR – included in the n = 25 above N completed = 452 N excluded from analysis = 0 N included in analysis = 452 Demographics

Characteristic	Control (n=410)	PE (n=42)	p value
Mean age (SD)	31.6 (5.6)	30.2 (6.4)	0.18
Race			
White, n (%)	237 (57.8)	17 (40.4)	-
Black, n (%)	113 (27.6)	21 (50.0)	0.03
Hispanic, n (%)	10 (2.4)	0 (0)	-
Asian, n (%)	37 (9.0)	2 (4.8)	-
Others, n (%)	13 (3.2)	2 (4.8)	-
Smoking, n (%)	32 (7.8)	7 (16.7)	0.05
Mean BMI (SD)	28.0 (7.2)	34.0 (8.9)	<0.001
Nulliparous, n (%)	163 (39.8)	20 (47.6)	0.32

Study Reference	**Odibo 2011b**			
	Chronic hypertension, n (%)	27 (6.6)	15 (35.7)	<0.001
	Pre-gestational diabetes, n (%)	25 (6.1)	10 (23.8)	<0.001

Screening Method

Index test

Logistic regression analysis was used to model the prediction of PE using PP13, PAPP-A and the mean uterine artery PI MoM individually or in combination. PP13 concentrations were expressed as MoM for gestational age and adjusted for maternal BMI. PAPP-A levels were also converted to MoM and were adjusted for maternal weight, ethnicity, smoking status, and for pregnancies conceived using assisted reproductive technologies. The mean uterine artery PI was also converted to MoM for the gestational age.

Reference standard

PE was defined using guidelines of the American College of Obstetricians and Gynaecology and other hypertensive disorders by the criteria proposed by the National High Blood Pressure Education Programme Working Group Report in Pregnancy. Ealy PE was defined as those requiring delivery prior to 34 weeks gestation.

Test Accuracy

At a 20% FPR, PP13 could identify 49% of all PE and 79% of early onset PE. When combined with uterine artery Doppler, the detection rate for all or early PE did not significantly change (50% and 78%, respectively). The sensitivity for predicting all or early PE using PAPP-A alone was 58% and 68%, respectively. When PAPP-A is combined with uterine artery PI, the sensitivity for all PE improved to 64%, but was unchanged for early onset PE, at 68%. When PP13 and PAPP-A were combined, then sensitivity was 50% and 79% for all and early PE, respectively. The sensitivity when all markers are combined was 60% and 79% for all and early PE, respectively.

Screening performance of PP13, PAPP-A and uterine artery Doppler for all cases of PE

Marker	Sensitivity for fixed false positive rates (FPR)		
	5%	10%	20%
PP13	0.30	0.45	0.49
PAPP-A	0.21	0.50	0.58
Mean uterine artery PI	0.21	0.51	0.62
PP13 + Mean uterine artery PI	0.30	0.45	0.50
PAPP-A + Mean uterine artery PI	0.25	0.45	0.64
PP13 + PAPP-A	0.30	0.42	0.50
PP13 + PAPP-A + Mean uterine artery PI	0.35	0.48	0.60

Screening performance of PP13, PAPP-A and uterine artery Doppler for all cases of preeclampsia delivered at <34 weeks

Marker	Sensitivity for fixed false positive rates (FPR)		
	5%	10%	20%
PP13	0.56	0.68	0.79
PAPP-A	0.50	0.59	0.68
Mean uterine artery PI	0.59	0.59	0.68
PP13 + Mean uterine artery PI	0.55	0.68	0.78
PAPP-A + Mean uterine artery PI	0.50	0.58	0.68
PP13 + PAPP-A	0.68	0.68	0.79

Study Reference	Odibo 2011b			
	PP13 + PAPP-A + Mean uterine artery PI	0.68	0.68	0.79
Authors' Conclusions	PP13 and PAPP-A as first trimester serum markers of placental mal-development identify pregnancies at an increased risk for development of PE in the second half of pregnancy, compared to a control population who subsequently exhibit an uncomplicated pregnancy outcome. Increased uterine artery resistance in the first trimester, reflected by a high mean PI, also predicts and increased risk for later development of PE. Combinations of 2 or more of the first trimester assessments failed to yield an improvement in risk identification for the prediction of PE. The study confirms the potential role of PP13, PAPP-1 and uterine artery PI as predictors of PE.			

Abbreviations: BMI, body mass index; FPR, false positive rate; MoM, multiple of the median; PAPP-A, pregnancy associated plasma protein A; PE, pre-eclampsia; PI, pulsatility index; PP13, placental protein 13; ROC, receiver-operating characteristic curves; SD, standard deviation.

Table 25z: POP Study (Sovio 2019a)

Study Reference	POP study (Sovio 2019a)
Study Design	Design Prospective cohort study Objective To derive a simple risk score for preterm PE based on the model used in the ASPRE trial, and to compare it (i) with the original ASPRE algorithm, (ii) with the NICE Guideline score, and (iii) with and without biochemical and ultrasonic predictors. Dates January 2008 to July 2012 Country UK Setting Rosie Hospital
Population Characteristics	Patient recruitment and eligibility The risk score was derived from the ASPRE model, which was developed in a screening study of 59,947 nulliparous and 60,545 multiparous women with a singleton pregnancy at 11-13 weeks gestation. The performance of the total risk score was tested in the Pregnancy Outcome Prediction (POP) study, which included unselected nulliparous women with a singleton pregnancy. Women who completed the POP study and had information on PE status were eligible for the analysis. Women who reported use of aspirin in the questionnaire administered at 20 weeks of gestation were excluded. Data collection The risk score was derived from the ASPRE trial's regression coefficients from a fitted competing risks model. The performance of the total risk score was tested in the POP study, in which participants had phlebotomy and fetal biometry at 12, 20, 28 and 36 weeks of gestational age (wkGA). Doppler flow velocimetry was performed at 20, 28 and 36wkGA. Outcome data were retrieved through individual review of each patient's case record and by linkage to electronic databases of imaging, blood tests, delivery episode and neonatal care. MAP was calculated from the blood pressure recorded at each woman's booking antenatal visit. UtA-PI was analysed as a log-transformed z score adjusted for the exact gestational age at measurement. Maternal serum levels of PAPP-A and PlGF were measured on stored serum samples

Study Reference	POP study (Sovio 2019a)
	Duration of follow-up Delivery (inferred based on outcomes reported) Prevalence of PE in the study 28 out of 4,184 (0.7%) had PE leading to preterm birth Sample size N screened/invited = NR N eligible = NR N enrolled = NR N excluded (with reason) = NR N lost to follow-up = NR N completed = 4,212 N excluded from analysis = 5 no information on PE (n=5), reported use of aspirin (n=24, one of whom had no information on PE) N included in analysis = 4,184 Demographics NR
Screening Method	Index test A simple risk score was derived from the ASPRE trial's prior history model, which employed a maternal history algorithm (PGAPE) developed by the FMF. In nulliparous women, the prior history model utilises information on maternal age, height, ethnicity, chronic hypertension, systemic lupus erythematosus, antiphospholipid syndrome, conception by IVF, maternal weight, family history of PE, and diabetes mellitus. In parous women, the model additionally includes gestational age at birth from the previous pregnancy and the inter-pregnancy interval. Otherwise, the regression coefficients are exactly the same in nulliparous and in multiparous women. A simple scoring system was developed for nulliparous women. The age-related risk score was set to 0 for women aged 35 years and below, similarly to the prior history model. The published coefficient was rounded to -0.2. From age 36 and above, a one year increase in age was set to increase the age-related risk score by 1. Since very few nulliparous women get pregnant after the age of 45, risk score 10 was given to all women aged 45 or over. The relative weight of every other variable was determined against the coefficient for age. The coefficient for a 1cm increase in height was 0.1. Therefore, a 2 cm decrease in height was equivalent to one year increase in age. Height was stratified into 2 cm categories and the height-related risk score was one point lower by every 2 cm increase in height. Women who were ≥184 cm were grouped to a single category (height-related risk score = 0) and women who were <148 cm were also grouped to a single category (height-related risk score = 19) so that both categories would contain <0.5% of the women. Similarly, the coefficient for a 1kg increase in weight was -0.0694. Therefore, a 3kg increase in weight was equivalent to a one year increase in age. Hence, weight was grouped into 3-kg categories and a one category increase in weight was equivalent to one year increase in age. The lower tail (<45 kg) and the upper tail (≥120 kg) of the distribution were grouped to single categories so that each of them would contain <0.5% of the women. For categorical variables, the risk score was determined as the ratio of the coefficient in question and the coefficient of age, e.g. for chronic hypertension, risk score was -7.2897/-0.2069 = 35. The risk scores for each component are rounded to the nearest integer and their sum gives a total risk score. The last 3 items are added only if the woman does not have chronic hypertension. An individual's risk score was calculated for each woman in the POP study and its screening performance was assessed in relation to PE leading to preterm birth Reference standard PE was defined and classified using the 2013 ACOG Guideline.
Test Accuracy	Diagnostic effectiveness of the NICE guidelines, the simple risk score, and the maternal history algorithm in screening for preterm preeclampsia at 12wkGA

Study Reference **POP study (Sovio 2019a)**

Screening test	TP/ FP	TN/ FN	Positive LR (95% CI)	Negative LR (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	FPR (95% CI)	PPV (95% CI)	NPV (95% CI)
NICE guidelines	15/442	3714/13	5.0 (3.5–7.2)	0.52 (0.35–0.77)	53.6 (34.3–71.8)	89.4 (88.4–90.3)	10.6 (9.7–11.6)	3.3 (2.0–5.4)	99.7 (99.4–99.8)
Risk score derived from maternal history algorithm	16/366	3790/12	6.5 (4.6–9.1)	0.47 (0.31–0.72)	57.1 (37.5–74.8)	91.2 (90.3–92.0)	8.8 (8.0–9.7)	4.2 (2.6–6.7)	99.7 (99.4–99.8)
Maternal history algorithm (PGAPE)	17/397	3759/11	6.4 (4.7–8.7)	0.43 (0.27–0.69)	60.7 (40.8–77.6)	90.4 (89.5–91.3)	9.6 (8.7–10.5)	4.1 (2.6–6.5)	99.7 (99.5–99.8)

The cut-off points for the risk score and PGAPE were determined using a 10% screen positive rate. A risk score of ≥30 and PGAPE of ≤52.3 were categorised as screen positives.

Analysis of the addition of 12 week measurements of MAP, PAPP-A and PlGF and 20 week measurement of UtA-PI into the logistic regression models using the likelihood ratio test

Model	LR-test p value
PGAPE	-
PGAPE + MAP	0.034
PGAPE + PAPP-A	0.053
PGAPE + PlGF	0.34
PGAPE + UtA-PI	<0.0001
Risk score	-
Risk score + MAP	0.033
Risk score + PAPP-A	0.045
Risk score + PlGF	0.28
Risk score + UtA-PI	<0.0001

Authors' Conclusions

The main finding of this study is that a simple risk score based on maternal characteristics, derived from the ASPRE trial predictive model, provided clinically useful prediction of risk in a cohort of nulliparous women with a singleton pregnancy.

In conclusion, (1) employing the simple risk score may be useful as a means of targeting the use of aspirin in nulliparous pregnant women, (2) adding first trimester MAP, PAPP-A and PlGF did not significantly improve prediction in this study, and (3) resolving the contribution of first trimester uterine artery Doppler and verifying the higher specificity of the simple risk score will require further research.

Abbreviations: ACOG, American College of Obstetricians and Gynaecologists; CI, confidence interval; FMF, fetal medicine foundation; FN, false negative; FP, false positive; FPR, false positive rate; IVF, in vitro fertilisation; LR, likelihood ratio; MAP, mean arterial pressure; NICE, National Institute for Health and Care Excellence; NPV, negative predictive value; NR, not reported; PAPP-A, pregnancy-associated plasma protein-A; PE, pre-eclampsia; PGAPE, predicted gestational age at preeclampsia; PlGF, placental growth factor; POP, Pregnancy Outcome Prediction; PPV, positive predictive value; TN, true negative; TP, true positive; UK, United Kingdom; UtA-PI, uterine artery pulsatility index; wkGa, weeks of gestational age.

Table 25aa: Sandström 2019

Study Reference	Sandström 2019
Study Design	Design Prospective cohort study Objective To create multivariable predictive models using 3different methodological approaches (a logistic regression model with pre-specified variables similar to the FMF model including maternal variables and MAP, a backward selection model starting from the full suite of variables, and a Random forest model) and the NICE guidelines to identify nulliparous women at increased risk of PE, using detailed routinely collected information from early pregnancy. Dates January 2008 to December 2013 Country Sweden Setting Stockholm-Gotland counties in Sweden
Population Characteristics	Patient recruitment and eligibility Live-born births between 1 January 2008 and 31 December 2013 were included in the cohort of singleton pregnancies. The population was restricted to pregnancies of nulliparous women delivered from gestational week 22. Pregnancies of women without information on gestational length or without notation of blood pressure before 15 weeks gestation were excluded. For sensitivity analysis, pregnancies with major fetal malformations or maternal use of aspirin during pregnancy were excluded. Data collection Data were derived from the Stockholm-Gotland Obstetric Cohort, a population-based database with information automatically retrieved from the computerised medical record system in the Stockholm-Gotland counties in Sweden. The database contains detailed, prospectively collected demographic, medical, obstetrical and neonatal data from all antenatal, delivery and postnatal care units in the region. The pregnancies in the Stockholm-Gotland Obstetric Cohort were individually linked using the person-unique national registration numbers with the National Patient Register and the Swedish Prescribed Drug Register. The National Patient Register includes International Classification of Diseases (ICD) diagnoses on inpatient admissions and outpatient visits. The Swedish Prescribed Drug Register holds data on all prescribed substances, ATC-code (Anatomical Therapeutic Chemical classification) and date of purchase for all dispensed drugs in the outpatient population. At the first visit to antenatal care, around gestational week 10, the woman is interviewed about her social, reproductive and medical background, and medical examinations are performed. The routinely collected information from this visit were included in this study as 36 candidate predictors for PE in the predictive models. Gestational length is determined using the following hierarchy: a) date of embryo transfer, b) early first or early second trimester ultrasound, c) date of last menstrual period, and d) from postnatal assessment. Information on social factors (family situation and country of birth), smoking, snuff and alcohol habits as well as reproductive history (parity, previous miscarriage or ectopic pregnancy, assisted reproduction and infertility duration) is self-reported. Women are interviewed about their medical history (including pre-existing chronic diseases). The collected information is registered in a standardised way either as tick boxes, pre-specified options, or as numbers. Family history of hypertension or PE is however registered as free text and 2 dichotomous variables (family history of hypertension and family history of PE) were constructed. Maternal BMI (kg/m^2) was calculated from self-reported height and measured or self-reported weight. The first recorded blood pressure <15 weeks was collected. Mean arterial pressure (MAP) was calculated and used in the predictive models. Capillary blood

Study Reference	Sandström 2019

sampling for plasma glucose and haemoglobin, venous sampling for blood group and urine dipstick test for protein is collected. All the candidate predictors were treated as continuous or categorised.

Duration of follow-up
Delivery (inferred based on outcomes reported)

Prevalence of PE in the study
2,773 out of 65,562 women developed PE (4.4%)

216 (0.3%) developed early-onset PE, 497 (0.8%) developed preterm PE, and 2,276 (3.6%) developed term PE.

Sample size
N screened/invited = 149,298
N eligible = 62,562
N enrolled = 62,562
N excluded (with reason) = 80,370 (parous), 5 (missing information on gestational length), 6,361 (no registered blood pressure ≤14^{+6} weeks gestation)
N lost to follow-up = NR
N completed = NR
N excluded from analysis = main analysis, 0; restricted analysis, 3,663 (fetal major malformations) and 623 (aspirin use in pregnancy)
N included in analysis = 62,562 (58,276 included in restricted analysis)

Demographics

Characteristic	No PE (n=59,789) 95.6%	Overall PE (n=2,773) 4.4%	p value*	Preterm(<37 weeks) PE (n=497) 0.8%	p value**
Maternal age, years[a]	29.3 (5.0)	29.9 (5.3)	<0.001	30.3 (5.8)	<0.001
BMI, kg/m^2 [a]	23.4 (4.0)	25.1 (4.9)	<0.001	24.7 (5.1)	<0.001
Missing (n)	2,066	92	-	11	-
MAP, mmHg[a]	81.5 (8.0)	86.3 (9.1)	<0.001	86.7 (9.6)	<0.001
Previous miscarriage[a]	0.23 (0,57)	0.26 (0.60)	0.017	0.25 (0.62)	0.537
Previous ectopic pregnancy[a]	0.012 (0.12)	0.013 (0.13)	0.529	0.014 (0.13)	0.635
Smoking 3 months before pregnancy, n (%)			0.867		0.054
<10	5,173 (8.65)	237 (8.55)	-	27 (5.43)	-
≥10	4,333 (7.25)	190 (6.85)	-	32 (6.44)	-
Missing (n)	361 (0.60)	16 (0.58)		4 (0.80)	-
Smoking at registration, n (%)			0.128		0.213
<10	2,071 (3.46)	76 (2.74)	-	14 (2.82)	-
≥10	371 (0.62)	21 (0.76)	-	5 (1.01)	-

Study Reference	**Sandström 2019**				
Missing (n)	332 (0.56)	12 (0.43)		0 (0)	-
Family history of PE, n (%)	150 (0.25)	18 (0.65)	<0.001	5 (1.01)	0.001
Family history of hypertension, n (%)	10,034 (16.78)	634 (22.86)	<0.001	116 (23.34)	<0.001
Infertility, n (%)			0.006		0.870
Without treatment	3,997 (6.69)	201 (7.25)	-	7.24	-
Ovary stimulation	885 (1.48)	48 (1.73)	-	1.81	-
IVF	3,979 (6.66)	225 (8.11)	-	7.04	-
Pre-existing diabetes, n (%)	264 (0.44)	62 (2.24)	<0.001	21 (4.23)	<0.001
Chronic hypertension, n (%)	260 (0.43)	43 (1.55)	<0.001	12 (2.41)	<0.001
Chronic kidney disease, n (%)	276 (0.46)	27 (0.97)	<0.001	10 (2.01)	<0.001

[a]mean at registration (SD)
*PE overall compared to no PE
**Preterm PE compared to no preterm PE (no PE and term PE)

Screening Method

Index test
The routinely collected information from a woman's first visit to antenatal care, around gestational week 10, which included social, reproductive and medical background information as well as information from a medical examination, were included in this study as 36 candidate predictors for PE in the predictive models.

In order to maximise the predictive power of the models, 3different multivariable statistical methods were used:

- Pre-specified variables model: Multivariable regression model for nulliparous women using similar variables as in the FMF maternal factors and MAP model, which included: family history of PE, country of birth, method of conception, gestational length at registration, maternal age, height, weight, smoking habits in early pregnancy, pre-existing type I and type II diabetes, chronic hypertension, systemic lupus erythematosus, and MAP.
- Backward selection model: Backward selection was used on a multivariable logistic regression with an exclusion criterion of p-value more than 0.2. The 36 candidate predictors were submitted to this model-selection procedure. The variables ultimately included, in different combinations for the different outcomes (early onset, preterm, and term PE), were: maternal age, BMI, MAP, protein in urine, infertility treatment, diabetes, blood group, alcohol consumption at registration, gestational length at registration, capillary glucose, haemoglobin, infertility duration, family history of PE, family history of hypertension, alcohol consumptions 3 months before registration, chronic kidney disease, family situation, smoking 3 months before pregnancy, snuff 3 months before pregnancy, snuff at registration, region of birth, hepatitis, morbus chron/ulcerous colitis, and psychiatric disease [supplementary materials].
- Random forest model: a machine learning, ensemble method making use of multiple decision trees was used. The same 36 candidate predictors used in the backward selection model were used in this model. For each tree, a bootstrap sample was drawn, from which the tree was built. In order to get an unbiased estimate of the area under the receiver operating characteristic curve (AUC), the Out-of-Bag samples were used when predicting the probabilities of the outcomes.

In addition to the 3 models, a risk classification system was created based on the NICE-guidelines binary (high-risk: yes or no) clinical decision rule. Having a high-risk for PE for nulliparous women in early pregnancy according to the NICE guidelines includes any of the

Study Reference **Sandström 2019**

following risk factors: chronic kidney disease, systemic lupus erythematosus, type 1 or type 2 diabetes, chronic hypertension, age 40 or older, BMI 35 or more at registration, and family history of PE.

Reference standard

PE was defined as hypertension (blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg 2 times with an interval of at least 4 hours), combined with proteinuria (≥0.3 g/24 hours or 2+ on a dipstick test) occurring after 20 weeks gestation. In order to fulfil the definition of PE, there had to be one diagnosis in the inpatient register or two in the outpatient register, where the data of the first diagnosis was used. Early onset PE was defined with delivery <34 weeks, preterm PE with delivery <37 weeks, and term PE with delivery ≥37 weeks.

Test Accuracy

The sensitivity at a FPR of 10% for PE <34 and <37 weeks were superior in the groups of pre-specified variables. For detection of PE with delivery ≥37 weeks, the best performing models were the pre-specified variables and the backward selection, compared to the Random forest model.

Predictive method		Total study population (n = 62,562)		Restricted study population[a] (n = 58,276)	
		Sensitivity for 10% FPR	95% CI	Sensitivity for 10% FPR	95% CI
Prediction of PE <34 weeks	Pre-specified variables	30.6	(24.5–37.2)	28.8	(22.1–36.3)
	Backward selection	26.9	(21.1–33.3)	28.8	(22.1–36.3)
	Random forest	18.5	(13.6–24.4)	17.6	(12.2–24.2)
Prediction of PE <37 weeks	Pre-specified variables	29.2	(25.2–33.4)	29.3	(25.0–34.0)
	Backward selection	25.8	(22.0–29.8)	27.9	(23.6–32.5)
	Random forest	24.3	(20.6–28.4)	21.4	(17.5–25.7)
Prediction of PE ≥37 weeks	Pre-specified variables	28.1	(26.3–30.0)	27.6	(25.7–29.5)
	Backward selection	28.2	(26.4–30.1)	27.5	(25.6–29.5)
	Random forest	22.4	(20.7–24.2)	22.7	(20.9–24.5)

[a]Pregnancies without major malformations or treatment with aspirin

When using the binary NICE-guidelines risk classification system for identifying women at risk of PE, 5.8% of all nulliparous women would be classified as high risk (screen positive). The DR for PE with delivery <34 weeks would be 22.2% (95% CI 16.8–28.4), PE with delivery <37 weeks 19.5% (95% CI 16.1–23.3) and PE with delivery ≥37 weeks 12.2% (95% CI 10.9–13.7), all with a fixed FPR of about 5.5%. In the best performing models with a chosen FPR of 10%, the DR is higher for preterm and term PE, but with an overlapping CI for early onset PE, compared to the NICE-guidelines.

Authors' Conclusions

Using routinely collected information on well-known and less established or unknown risk factors from first visit to antenatal care as predictive variables generated a modest predictive capacity for PE, irrespective of type of multivariable statistical method used. The logistic regression models performed better than models using Random forest. The prediction of PE with delivery <34, <37 or ≥37 weeks with the 3different methods was similar. The sensitivities at a fixed 10% FPR varied between 18.5–30.6%. The performance of the customisable multivariable risk prediction approach at the FPR of 10% was however significantly better than using the binary NICE guidelines for PE with delivery <37 weeks and ≥37 weeks.

Abbreviations: ATC, Anatomical Therapeutic Chemical; BMI, body mass index; CI, confidence interval; DR, detection rate; FMF, Fetal Medicine Foundation; FPR, false positive rate; ICD, International Classification of Diseases; IVF, in vitro fertilisation; MAP, mean arterial pressure; NICE, National Institute for Health and Care Excellence; PE, pre-eclampsia; SD, standard deviation.

Table 25ab: Scazzocchio 2013, Scazzocchio 2017a (validation cohort)

Study Reference	**Scazzocchio 2013, Scazzocchio 2017a (validation cohort)**
Study Design	Design Prospective cohort study Objective To evaluate the effectiveness of an integrated first-trimester screening test to predict pre-eclampsia (PE). Dates May 2009 to October 2011 Country Spain Setting Hospital Clinic Barcelona
Population Characteristics	Patient recruitment and eligibility Prospective cohort composed of singleton pregnancies underwent routine first-trimester screening at the study hospital. Each participant provided written confirmed consent. Data collection Maternal characteristics and medical history were prospectively recorded at the time of first-trimester ultrasound (11.0 to 13.6 weeks) via a patient questionnaire. Medical and obstetric history, maternal age, ethnicity, smoking status, parity, height, and weight were recorded. Duration of follow-up NR Prevalence of PE in the study Of 5,170 included women, 136 (2.6%) developed PE, including 110 (2.1%) cases of late PE and 26 (0.5%) cases of early PE. Sample size N screened/invited = 5,759 N eligible = NR N enrolled = 5,170 N excluded (with reason) = 589 (missing outcome data [n=525], major fetal defects or chromosomopathies [n=25], miscarriage or fetal death <24 weeks [n=80], and termination of pregnancy in the absence of medical indication [n=21]). N lost to follow-up = NR N completed = 5,710 N excluded from analysis = 0 N included in analysis = 5,170 Demographics

Study Reference **Scazzocchio 2013, Scazzocchio 2017a (validation cohort)**

Characteristic	Unaffected (N=5,034)	Late PE (N=110)	Early PE (N=26)
Median age, years (IQR)	32 (28 to 35.4)	33.2 (29 to 36.3)	31.3 (29.9 to 36.5)
Median body mass index (BMI), kg/m^2 (IQR)	24 (22.7 to 24.7)	24.6 (23.5 to 26.4)	24.4 (22.7 to 28)
Ethnicity, n (%)			
White European	3,757 (74.6)	73 (66.4)	15 (57.7)
Black	22 (0.4)	1 (0.9)	1 (3.8)
South American	784 (15.6)	28 (5.5)	6 (23.1)
Other	471 (9.4)	8 (7.3)	4 (15.4)
Smoking status, cigarettes per day, n (%)			
0	4,637 (92.1)	100 (90.9)	24 (92.3)
<10	107 (2.1)	4 (3.6)	0 (0)
10–20	245 (4.9)	4 (3.6)	1 (3.8)
>20	45 (0.9)	2 (1.8)	1 (3.8)
Medical history, n (%)			
Chronic hypertension	48 (1)	10 (9.1)[a]	4 (15.4)[b]
Diabetes mellitus	88 (1.7)	7 (6.4)[a]	0 (0)
Renal disease	6 (0.1)	0	3 (11.5)[b,c]
Autoimmune disease	68 (1.4)	4 (3.6)	1 (3.8)
Coagulation disease	40 (0.8)	4 (3.6)[a]	0 (0)
Obstetrical history, n (%)			
Nulliparous	2,971 (59)	70 (63.6)	14 (53.8)
Previous PE	28 (0.6)	10 (9.1)[a]	5 (19.2)[b]
Previous intrauterine growth restriction (IUGR)[d]	28 (0.6)	1 (0.9)	3 (11.5)[b,c]
Mean arterial pressure (MAP), mmHg (IQR)	78.5 (74.1 to 83.1)	79.4 (74.9 to 84.1)	85.7 (80 to 89.7)
Mean uterine artery pulsatility index (UtA-PI) (IQR)[e]	1.67 (0.53 to 1.25)	1.68 (1.54 to 1.84)	2.23 (1.75 to 3.0)[b,c]
Median maternal serum biochemistry, multiple of the median (MoM) (IQR)			
Pregnancy associated plasma protein A (PAPP-A)	1.06 (0.53 to 1.25)	0.55 (0.28 to 1.05)[a]	0.87 (0.44 to 1.24)
Free beta human chorionic gonadotrophin (fβhCG)	1 (0.63 to 1.16)	0.96 (0.55 to 1.15)	0.92 (0.5 to 1.04)

[a] Significant comparison between unaffected and late PE; [b] Significant comparison between unaffected and early PE; [c] Significant comparison between late and early PE; [d] Birthweight <10th centile that required delivery <37 weeks gestation [e] Assumed to be mean of left and right UtA-PI

Screening Method

Index test

Maternal characteristics, PAPP-A, fβhCG at 8–12 weeks, and MAP and UtA-PI at 11.0 to 13.6 weeks gestation

- A nurse measured blood pressure (BP) automatically with a calibrated device in the outpatient clinics according to standard procedure. BP was measured in one arm (right or left) without distinction while women were seated and after a 5-minute rest. MAP was calculated as: diastolic BP + (systolic – diastolic) divided by 3.

Study Reference **Scazzocchio 2013, Scazzocchio 2017a (validation cohort)**

- UtA evaluation was performed transvaginally during the first-trimester ultrasound. Both UtA-PIs were automatically measured and mean UtA-PI was calculated. Maternal serum PAPP-A and fβhCG were measured using the DELFIA Xpress analyser between 8–12 weeks of gestation. Thereafter, these levels were converted to multiples of the expected normal median (MoM), which were corrected for crown-rump length (CRL), maternal age, BMI, smoking and diabetes status, and ethnicity according to local references.

Logistic regression analysis was performed to estimate the individual risks for early and late PE with respect to the following covariables: a priori risk (log transformed), log MoM mean UtA-PI, log MoM MAP, log MoM PAPP-A, and log MoM fβhCG. Receiver operating characteristic (ROC) curves were performed to analyse model performance, which was expressed as DR for different cut-offs of false-positive rates (FPRs).

Reference standard
PE was defined as systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg on at least 2 occasions 4 hours apart, developing >20 weeks of gestation in previously normotensive women, and proteinuria >300 mg in a 24-hour urine specimen. Early PE was defined as PE requiring delivery <34 weeks. Doctors who made the diagnosis were blinded to the study parameters obtained during the first trimester.

Test Accuracy

Sensitivity of screening for late and early PE using maternal characteristics, PAPP-A, fβhCG at 8–12 weeks, and MAP and UtA-PI at 11.0 to 13.6 weeks gestation

PE	Risk cut-off	Prevalence of positives %	Detection rate (DR), %	FPR, %	Positive likelihood ratio	Negative likelihood ratio
Late PE	>1/14	5.5	29.4	5	5.88	0.74
	>1/18	10.6	39.6	10	3.96	0.67
	>1/22	15.6	42.2	15	2.81	0.68
Early PE	>1/73	5.1	69.2	5	13.84	0.32
	>1/178	10.1	80.0	10	8.08	0.21
	>1/278	15.1	96.2	15	6.41	0.04

Sensitivity of screening for early PE of each individual predictor and their combinations

Variable	Sensitivity, %	
	5% FPR	10% FPR
A priori risk	25	31.4
MAP	38.5	61.5
Mean UtA-PI	46.2	57.7
A priori risk + MAP	46.3	69.2
A priori risk + mean UtA-PI	65	73.3

Sensitivity of screening for early- and late-PE in construction and validation cohorts for fixed FPRs (N=4,621; Scazzocchio 2017a)

Screening	FPR (%)	DR, % (95% CI)	Positive predictive value (PPV), % (95% CI)	Negative predictive value (NPV), % (95% CI)
Construction cohort (Maternal characteristics, MAP, UtA Doppler, PAPP-A)				
Late-onset PE	5	39.7 (28.2 to 53.8)	11.3 (8.3 to 14.7)	99.0 (98.8 to 99.2)
	10	52.6 (42.3 to 62.9)	7.8 (6.4 to 9.2)	99.2 (99.0 to 99.3)

Study Reference	Scazzocchio 2013, Scazzocchio 2017a (validation cohort)				
	Early-onset PE	5	62.5 (45.0 to 80.0)	4.9 (3.6 to 6.2)	99.8 (99.8 to 99.9)
		10	75.0 (59.8 to 85.3)	3.0 (2.4 to 3.4)	99.9 (99.8 to 99.9)
	Validation cohort (Maternal characteristics, MAP, UtA Doppler, PAPP-A)				
	Late-onset PE	5	31.2 (22.7 to 36.9)	17.9 (13.7 to 20.5)	97.5 (97.2 to 97.7)
		10	43.4 (37.6 to 51.1)	13.1 (11.6 to 15.2)	97.8 (97.6 to 98.1)
	Early-onset PE	5	78.6 (64.1 to 89.5)	9.8 (8.2 to 11.0)	99.8 (99.7 to 99.9)
		10	85.7 (71.3 to 96.4)	5.6 (4.7 to 6.3)	99.9 (99.8 to 100)
Authors' Conclusions	To conclude, the study suggests that first-trimester screening combining maternal factors with UtA Doppler, BP, and PAPP-A is useful to predict PE in a routine care setting, with sensitivities of 69.2% and 80.8% for early PE and 29.4% and 39.6% for late PE at 5% and 10% FPRs respectively.				

Abbreviations: BMI, body mass index; BP: blood pressure; CRL, crown-rump length; DR, detection rate; FPR, false positive rate; fβHCG, free beta-human chorionic gonadotropin; IQR, interquartile range; IUGR, intrauterine growth restriction; MAP, mean arterial pressure; MoM, multiple of the median; NPV, negative predictive value; NR, not reported; PAPP-A, pregnancy associated plasma protein A; PE, pre-eclampsia; PlGF, placental growth factor; PPV, positive predictive value; ROC, receiver operating characteristic; UtA-PI, uterine artery pulsatility index.

Table 25ac: Schneuer 2012 (Schneuer 2012 and Schneuer 2013)

Study Reference	Schneuer 2012 (Schneuer 2012 and Schneuer 2013)
Study Design	Design Prospective cohort study Objective To describe normative levels of placental protein 13 (PP13) in first-trimester of pregnancy and determine the accuracy of PP13 in predicting PE and small-for-gestational age (SGA) infants. Schneuer 2013: To assess the accuracy of first trimester sFlt-1 and PlGF, both alone and in combination, in predicting pregnancy hypertension and PE; and compare with the accuracy of routinely collected maternal and clinical risk factors. Dates July 2006 to October 2006 Country Australia Setting Single-centre in New South Wales Schneuer 2013: New South Wales (NSW); data obtained from Down syndrome screening service laboratory database
Population Characteristics	Patient recruitment and eligibility Unselected cohort of women with a singleton pregnancy attended first trimester Down syndrome screening. Inclusion criteria not specified.

Study Reference	Schneuer 2012 (Schneuer 2012 and Schneuer 2013)
	Schneuer: The study population included pregnant women attending first trimester Down syndrome screening. Excluded women included those whose blood sample was taken before 10 or after 14 weeks of gestation, or those who had a medical abortion, had a twin pregnancy or had an infant with a major congenital anomaly. Data collection Serum samples collected by Pacific Laboratory Medicine Services (aneuploidy screening service), then archived and stored at -80℃. Samples were thawed and PP13 levels measured using automated immunoassay system. Maternal information and first trimester screening results derived from the laboratory database were combined via record linkage with women's health records from routinely collected birth and hospital databases to obtain information on pregnancy and infant outcomes. Birth information was obtained from Perinatal Data Collection (PDC). Hospital data were obtained from The Admitted Patient Data Collection (APDC). Probabilistic record linkage of data was conducted independently by the New South Wales Centre for Health Record Linkage Schneuer 2013: Serum samples for this study were thawed and serum levels of sFlt-1 were measured. The laboratory database contained maternal information for those with archived serum samples and women's corresponding pregnancy and birth outcomes were ascertained from the PDC (a statutory surveillance system of all births in NSW of at least 400 grams birth weight, or at least 20 week gestation) and the APDC (a census of all patient hospital admissions from NSW public and private hospitals, with records for both mothers and liveborn infants) and all 3sources were then combined via record linkage Duration of follow-up Until delivery (assumed based on outcomes reported) Prevalence of PE in the study PE developed in 71 pregnancies (2.7% of the total population), 5 (0.2% of the total population) of which were early PE (defined as delivery ≤34 weeks) Schneuer 2013: 68 cases (2.5%) Sample size N screened/invited = 2,989 (samples tested) N eligible = 2,784 (had linked health information available) N enrolled = NR N excluded (with reason) = 106 (blood samples taken before 10 or after 14 weeks gestation, had a medical abortion, twin pregnancy, infant with major congenital anomalies) N lost to follow-up = NR N completed = NR N excluded from analysis = NR N included in analysis = NR Schneuer 2013: N screened/invited = 2,973 N eligible = 2,782 N enrolled = 2,681 N excluded (with reason) = 101 (women whose blood sample was taken before 10 or after 14 weeks gestation, had a medical abortion, had a twin pregnancy or had an infant with major congenital anomaly)

Study Reference	**Schneuer 2012 (Schneuer 2012 and Schneuer 2013)**

N lost to follow-up = 0
N completed = 2,681
N excluded from analysis = 0
N included in analysis =2,681

Demographics

Demographic characteristics of in-house study population

Maternal characteristics	Unaffected N=2,423	Early PE N=5	All PE N=71	SGA (<3rd) N=41	SGA (<10th) N=191
Mean maternal age, years (SD)	32.8 (4.6)	32.0 (3.4)	32.0 (4.2)	32.7 (5.7)	32.8 (5.3)
Nulliparous (n [%])	1,057 (43.6)	1 (20.0)	46 (64.8)	27 (65.0)	118 (61.8)
Smoking (n [%])	134 (5.5)	0	1 (1.5)	9 (22.0)	24 (12.6)
Maternal weight, kg (mean [SD])	67.4 (14.5)	68.4 (6.8)	73.5 (16.6)	59.9 (11.1)	61.1 (12.0)
Preterm birth, <37 weeks (n [%])	110 (4.5)	5 (100)	16 (22.9)	2 (4.9)	12 (6.3)
Previous hypertension (n [%])	160 (6.6)	1 (20)	10 (14.1)	4 (9.8)	8 (4.2)
Infant birthweight, g (mean [SD])	3,582 (492)	1,264 (482)	3,100 (779)	2,487 (269)	2,686 (365)
PP13, pg/mL (median [IQR])	53.5 (37.7–71.8)	44.0 (20.8–52.2)	44.0 (32.4–65.8)*	40.5 (30.0– 58.1)*	42.8 (32.9–58.2)*
PP13 MoM (median [IQR])	1.00 (0.74–1.33)	0.87 (0.42–1.03)	0.87 (0.70–1.27)	0.80 (0.54–0.93)*	0.77 (0.59–1.06)*

*P-value <0.05 compared with unaffected pregnancies

Schneuer 2013:

Characteristic	Unaffected women (n = 2468)	Pregnancy hypertension (n = 213)	Pre-eclampsia (n = 68)
Age (SD)	32.8 (4.7)	32.6 (4.3)	32.1 (4.1)
Maternal weight (SD)	66.3 (13.7)	74.4 (18.0)[b]	72.8 (16.8)[b]
Smoking (%)	150 (6.2)	12 (5.6)	1 (1.5)
Nulliparous (%)	1064 (43.9)	118 (55.7)[b]	44 (65.7)[b]
Country of birth (%)	-	-	-
Australia and New Zealand	1641 (66.5)	180 (84.5)[b]	50 (73.5)
Asian countries	322 (13.1)	11 (5.2)[b]	6 (8.8)
Other countries	505 (20.5)	22 (10.3)[b]	12 (17.7)
Previously diagnosed hypertension (%)	139 (15.6)	40 (18.8)[b]	11 (16.2)[b]
Previously diagnosed diabetes (%)	61 (2.5)	11 (5.2)[a]	4 (5.9)
PIGF pg/ml (IQR)	24.1 (18.3, 31.7)	21.3 (16.9, 28.0)[b]	20.7 (17.2, 32.6)
sFlt-1 pg/ml (IQR)	286.8 (167.1, 472.1)	272 (169.6, 441.7)	268.1 (164.8, 390.5)
PAPP-A pg/ml (IQR)	1.71 (1.06, 2.79)	1.41 (0.80, 2.14)[b]	1.34 (0.76, 2.4)[a]
PlGF MoM (IQR)	1.01 (0.77, 1.31)	0.92 (0.71, 1.24)[b]	0.92 (0.73, 1.31)
sFlt-1 MoM (IQR)	1.01 (0.60, 1.67)	1.01 (0.62, 1.56)	0.82 (0.53, 1.46)

Study Reference	**Schneuer 2012 (Schneuer 2012 and Schneuer 2013)**			
	PAPP-A MoM (IQR)	0.98 (0.66, 1.46)	0.94 (0.62, 1.37)	0.83 (0.57, 1.32)

[a] p<0.05
[b] p<0.001

Screening Method

Index test
PP13 concentrations to predict early-onset PE and overall PE
Exploratory variables included:

- Maternal characteristics: maternal age, parity (nulliparous/multiparous), smoking during pregnancy, maternal weight (kg), previous history of PE or gestational hypertension (GH)
- Down syndrome screening biomarkers: free beta human chorionic gonadotropin (β-hCG), pregnancy associated plasma protein-A (PAPP-A)

PP13 levels were standardized by gestational age, weight and smoking status, using multiple of the median (MoM). A logarithmic transformation was used to normalize the distribution of PP13 MoM and multivariate logistic regression analysis was conducted to assess the association between log PP13 MoM with each pregnancy outcome adjusting for significant explanatory variables and other relevant biomarkers. The area under the receiver operating characteristic curve (AUC) was assessed by a traditional academic point system with an AUC result of 1 representing a perfect test, 0.9-<1 an excellent test, 0.8-<0.9 a good test, 0.7-<0.8 a moderate test, 0.6-<0.7 a poor test and 0.5-<0.6 a test with no discriminatory value. For each outcome, women's specific risk was dichotomized using 7 probability cut-points corresponding to 5% and 10% fixed false positive rates (FPRs). The predicted outcome was then compared with the observed outcome for all women in the study and estimates of sensitivity, specificity, positive (PPV) and negative predictive value (NPV), likelihood ratios (LR) and diagnostic odds ratios were calculated.

Schneuer 2013: Separate models were conducted, firstly evaluating just serum biomarkers alone, and then serum biomarkers combined, then maternal and clinical factors only (excluding biomarkers) and finally a combined model including both serum biomarkers and maternal risk factors. Serum biomarkers included PlGF, sFlt-1, and PAPP-A. Maternal clinical information included in the models were maternal weight, smoking during pregnancy, parity, previously diagnosed hypertension, previously diagnosed diabetes, high blood pressure recorded during pregnancy and country of birth. Each of these models were compared to determine whether serum biomarker levels provided any additional information to maternal and clinical risk factors in predicting PE.

Reference standard
Information on PE was obtained from the hospital data, based on a diagnosis by the attending clinician. PE was defined as the onset of hypertension (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg) from 20 weeks gestation onwards accompanied by proteinuria. Early-onset PE was defined as women with preeclampsia requiring delivery at ≤34 weeks gestation.

Schneuer 2013: PE (regardless of severity) and any pregnancy hypertension (PE or GH) were determined either if 'yes' was recorded in response to the relevant questions (proteinuric or non proteinuric hypertension with onset >20 week) in the PDC record, or if any APDC record had a diagnosis of GH, PE or eclampsia.

Test Accuracy

Accuracy of models using PP13 concentrations in early pregnancy to predict subsequent adverse pregnancy outcomes based on a 5% false positive rate

Model type	AUC (95% CI)	Detected cases, n	Sensitivity (95% CI)	PPV (95% CI)	NPV (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)	Diagnostic odds ratio
All PE								
Univariate	0.55	4	5.6	3.0	97.4	1.1	1.0	1.1

Study Reference	**Schneuer 2012 (Schneuer 2012 and Schneuer 2013)**

	(0.48–0.62)		(1.6–13.8)	(0.8–7.4)	(96.7–98.0)			(0.4–3.1)
Adjusted*	0.72 (0.66–0.78)	11	15.5 (8–26)	7.7 (3.9–13.4)	97.6 (97.0–98.2)	3.1	0.9	3.5 (1.8–6.7)
Early-onset PE								
Univariate	0.61 (0.26–0.96)	2	40.0 (5.3–85.3)	1.5 (0.2–5.3)	99.9 (99.6–100)	8.0	0.6	12.6 (2.1–76.1)
Adjusted*	0.82 (0.63–0.99)	1	20.0 (0.5–71.6)	0.7 (0–3.6)	99.8 (99.6–100)	3.4	0.8	4.0 (0.4–36.3)

*Adjusted for parity, weight, age, previous hypertension and β-hCG

Schneuer 2013:

In analyses for all and for nulliparous women, the positive likelihood ratio results for maternal and clinical risk factors were superior

Accuracy of models using serum biomarker levels and maternal and clinical information in early pregnancy to predict PE based on a 5% false positive rate in all women.

Variable (n = 68)	Sensitivity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI	LR (+)
PlGF MoM	7.4 (2.4, 17.3)	3.7 (1.2, 8.4)	97.5 (96.8, 98.1)	1.47
sFlt-1 MoM	5.9 (1.6, 14.4)	3.0 (0.8, 7.6)	97.5 (96.8, 98.0)	1.18
PAPP-A MoM	8.8 (3.3, 18.2)	4.4 (1.6, 9.4)	97.6 (96.9, 98.1)	1.77
Serum biomarkers only	7.4 (2.4, 16.3)	3.8 (1.2, 8.6)	97.5 (96.8, 98.1)	1.77
Previously diagnosed hypertension + parity	16.2 (8.4, 27.1)	6.4 (3.2, 11.2)	97.6 (97.0, 98.2)	2.53
All maternal and clinical information[a]	25.0 (15.3, 37.0)	12.0 (7.1, 18.5)	97.9 (97.3, 98.4)	5.03
Combined – biomarkers + maternal and clinical information	25.0 (15.3, 37.0)	12.0 (7.1, 18.5)	97.9 (97.3, 98.4)	5.03

[a]Including: maternal weight, smoking during pregnancy, parity, previously diagnosed hypertension, previously diagnosed diabetes, high blood pressure recorded during pregnancy and country of birth.

Authors' Conclusions

Lower serum levels of PP13 in early pregnancy are associated with increased risks of women developing PE and having an SGA infant.

The diagnostic performance of PP13 for PE and SGA >10th centile, including information on maternal factors and other serum biomarkers was only fair, based on AUC analysis. Results improved for the more severe adverse pregnancy outcomes of early-onset preeclampsia and SGA <3rd centile.

Overall results (including those from the MA) revealed that for a given 5% false positive rate, a test including PP13, maternal characteristics and other biomarkers would identify around 25% of pregnancies that will develop PE and SGA and 45% of early-onset PE.

Schneuer 2013:
The predictive accuracies of first trimester serum concentrations of sFlt-1 and PlGF were insufficient in predicting PE. Clinical and maternal risk factors had fair predictive accuracy and outperformed a combination of these first trimester serum biomarkers. Adding serum sFlt-1, PlGF and PAPP-A levels to risk factors did not improve the accuracy of models in predicting PE. Compared with serum biomarker information alone, it was found maternal and clinical risk factors, specifically parity, previously diagnosed hypertension and maternal weight provide greater predictive value. When sFlt-1 or PlGF information is added to these combined, neither biomarker provided any additional predictive information. Overall, the results highlight that complete maternal risk factor information compared with any serum biomarker tested in early pregnancy would potentially provide much better information in predicting hypertensive disorders in pregnancy. In conclusion, the

Study Reference	Schneuer 2012 (Schneuer 2012 and Schneuer 2013)
	findings suggest that maternal first trimester serum concentrations of sFlt-1 and PlGF do not predict PE any better than routinely assessed clinical and maternal risk factor information. Screening for sFlt-1 and PlGF levels in early pregnancy would not predict those pregnancies at risk.

Abbreviations: APDC, Admitted Patient Data Collection; AUC, area under the curve; β-hCG, beta human chorionic gonadotropin; CI, confidence interval; FPR, false positive rate; GH, gestational hypertension; IQR, interquartile range; LR, likelihood ratio; MoM, multiple of the median; NPV, negative predictive value; NR: not reported; NSW, New South Wales; PAPP-A, pregnancy associated plasma protein A; PDC, perinatal data collection; PE, pre-eclampsia; PlGF, placental growth factor; PPV, positive predictive value; SD, standard deviation; sFlt-1, soluble fms-like tyrosine kinase-1; SGA, small for gestational age.

Table 25ad: SCOPE (Kenny 2014, Myers 2013a, Myers 2013b, North 2011)

Study Reference	SCOPE (Kenny 2014, Myers 2013a, Myers 2013b, North 2011)
Study Design	Design Prospective cohort study Objective To develop a method to predict those at risk of pre-eclampsia (PE) by combining clinical factors and measurements of biomarkers in women recruited to the Screening for Pregnancy Endpoints (SCOPE) study of low-risk nulliparous women. **Myers 2013b:** Identify, verify and validate panels of biomarkers which are predictive of PE and to develop a test with ≥50% sensitivity for a positive predictive value (PPV) of 20%. Dates November 2004 to February 2011 Country New Zealand, Australia, UK, Ireland Setting Five centres (hospitals) **Myers 2013b:** Biomarker discovery – women recruited at Ninewells Hospital, Dundee, UK at a routine clinical visit; Biomarker verification and validation – research midwife interviewed participants recruited in Australia, New Zealand, UK and Ireland; Training set – women recruited in Australia and New Zealand ; Validation set – women recruited to European centres (London, Manchester, Leeds, and Cork)
Population Characteristics	Patient recruitment and eligibility Nulliparous women with singleton pregnancies attending hospital antenatal clinics, obstetricians, general practitioners, or community midwives before 15 weeks gestation were invited to participate. Exclusion criteria included being recognised as high risk of PE, small for gestational age (SGA) baby or spontaneous preterm birth because of underlying medical conditions (chronic hypertension requiring antihypertensive drugs, diabetes, renal disease, systemic lupus erythematosus [SLE], antiphospholipid syndrome [APS], sickle cell disease, human immunodeficiency virus [HIV]), previous cervical knife cone biopsy, ≥3 abortions or miscarriages, current ruptured membranes; known major fetal anomaly or abnormal karyotype; or intervention that could modify the outcome of pregnancy (such as aspirin, cervical suture). **Myers 2013b:** For biomarker discovery, healthy, normotensive, nulliparous and multiparous women were recruited. For biomarker verification and validation, women who were recruited into the SCOPE study, a prospective screening study of low-risk nulliparous women,

Study Reference	SCOPE (Kenny 2014, Myers 2013a, Myers 2013b, North 2011)

participated in this study. For the training set, 100 women who developed PE and 200 controls were randomly selected from the 3182 women recruited in Australia and New Zealand. Controls were selected 2:1 from those who did not have PE at the same centre and included women with uncomplicated pregnancies and those with complications. For the validation set, 50 cases of PE and 5:1 controls (no PE), stratified by centre, were randomly selected form women recruited to the European centres

Data collection

- A research midwife interviewed and examined women at 14–16 and 19–21 weeks gestation. Women underwent an ultrasound scan at 19–21 weeks. At the time of interview, data were entered on an internet accessed central database with a complete audit trail (MedSciNet).
- At 14–16 weeks gestation data on the following were collected: demographic information; woman's birth weight, gestation at delivery and whether it was a singleton/multiple pregnancy; previous miscarriages, abortions, or ectopic pregnancies and **whether these** pregnancies were with the same partner as the current pregnancy or not; history of infertility, use of assisted reproductive technologies (ART), duration of sexual relationship, and exposure to partner's sperm; gynaecological history (including polycystic ovarian syndrome [PCOS]) and medical history, including hypertension while taking combined oral contraception, asthma, urinary tract infection, inflammatory bowel disease, thyroid disease, and thromboembolism; and family history of obstetric complications and medical conditions.
- Information was collected on vaginal bleeding early in pregnancy, hyperemesis, and infections during pregnancy.
- Vegetarian status and dietary information before conception and during pregnancy was obtained from food frequency questions for fruit, green leafy vegetables, oily and other fish, and fast foods. Use of folate and multivitamins, cigarettes, alcohol, and recreational drugs was recorded for before conception, first trimester, and at 15 weeks.
- A lifestyle questionnaire was completed on work, exercise and sedentary activities, snoring, domestic violence, and social supports.
- Psychological scales were completed to measure perceived stress, depression, anxiety, and behavioural responses to pregnancy.
- Two consecutive manual blood pressure measurements were recorded. Other maternal measurements included maternal height and weight and waist, hip, arm, and head circumference. Proteinuria in a midstream urine specimen was measured by dipstick or a protein:creatinine ratio. Random whole blood glucose and serum lipid concentrations were also measured.

Myers 2013b: Biomarker discovery – assessment of uterine artery Doppler waveform at a routine clinical visit and an EDTA plasma was obtained at 22 and 26 weeks of gestation. Pregnancy outcome data were available in all women. Biomarker verification and validation – a research midwife interviewed participants at 14 to 16 weeks and 19 to 21 weeks gestation, and pregnancy outcomes were prospectively tracked. At the time of interview, data were entered on the Internet-accessed central database (MedSciNet). Two consecutive manual BP measurements were recorded. Blood samples were collected on EDTA at 14 to 16 and 19 to 21 weeks. An N-terminomics platform was used to identify candidate biomarkers in the 22- and 26-week discovery samples. The candidate proteins were quantified in the training sample set with targeted mass spectrometry assays based on a selection reaction monitoring (SRM) peptide quantification method, using custom-built assays. PlGF was measured in all samples. In the validation samples, only IGFALS was also measured.

Duration of follow-up

Participants were followed prospectively, and research midwives collected data on pregnancy out come and measurements of the baby. Assumed to be post-delivery, but extent of follow-up unclear.

Prevalence of PE in the study

Preeclampsia developed in 278 (4.9%), of whom 209 had term PE (3.7%), 69 (1.2%) had preterm PE, and 28 (0.5%) had early-onset PE.

Myers 2013b: Biomarker discovery sample – 26 women (12%); Training set – 100 women who developed PE were randomly selected from 3,182 women; Validation set – 50 cases of PE were randomly selected from 2,423 women; In training and validation sample subsets – women recruited in Australia and New Zealand = 5.8% (178); women recruited in Europe = 4.1% (100)

Study Reference

SCOPE (Kenny 2014, Myers 2013a, Myers 2013b, North 2011)

Sample size

N screened/invited = 8,531 invited, 5,989 initially agreed to participate
N eligible = NR
N enrolled = 5,690
N excluded (with reason) = of 5,989 invited, miscarriage/terminations before 15 weeks n=193, ineligible n=64, did not consent n=25, closure of recruitment n=17; after recruitment, protocol violation n=14, no outcome data n=53
N lost to follow-up = NR
N completed = 5,623
N excluded from analysis = NR
N included in analysis = 5,623

Demographics

Characteristic	PE (N=278)	No PE (N=5,345)	P value*
Mean maternal age, years (SD)	27.7 (5.7)	28.7 (5.5)	0.002
Ethnicity, n (%)			
White	247 (89)	4,811 (90)	0.67
Maori or Polynesian	9 (3)	107 (2)	
Asian	7 (2.5)	163 (3)	
Indian	7 (2.5)	127 (2)	
Other	8 (3)	137 (3)	
Primigravida, n (%)	66 (24)	1,231 (23)	0.84
Previous miscarriage	37 (13)	738 (14)	0.88
Previous termination	28 (10)	569 (11)	0.84
Smoking status, n (%)			
Non-smoker	212 (76)	4,047 (76)	0.82
Stopped during pregnancy	39 (14)	718 (13)	
Current smokers	27 (10)	580 (11)	
Body Mass Index (BMI), kg/m^2, n (%)			
<20.0	10 (4)	393 (7)	<0.0001
20.0 to 24.9	96 (34)	2,705 (51)	
25.0 t0 29.9	94 (34)	1481 (28)	
≥30	78 (28)	766 (14)	
Mean blood pressure, mm Hg (SD)			
Systolic	112 (11)	107 (10)	<0.0001
Diastolic	69 (8)	65 (8)	<0.0001

* For comparison between groups with Chi-square or Student's *t* test

Screening Method

Index test

Kenny 2014: Predictive models were constructed for PE, term PE, preterm PE, and early-onset PE, using biomarkers, clinical risk factors, clinical risk factors with biomarkers, and the combination of clinical risk factors, biomarkers, and uterine scan variables.

- A nurse examined women at 14–16 weeks and 19–21 weeks gestation. Blood pressure (2 consecutive measurements with a mercury or aneroid sphygmomanometer), BMI, maternal anthropometry, random blood glucose and proteinuria (assessed by semi-quantitative automated dip-stick reading) were measured and blood specimens collected.

Study Reference	**SCOPE (Kenny 2014, Myers 2013a, Myers 2013b, North 2011)**

- Serum and plasma (collected on ethylenediaminetetraacetic acid [EDTA]) was stored at -80°C within 4 hours of collection.
- Ultrasound measurements at 19-21 weeks included uterine and umbilical Doppler waveforms and fetal anthropometry (biparietal diameter, head circumference, abdominal circumference and femur length).
- Women were tracked prospectively and information about pregnancy outcome obtained. Fetal measurements were adjusted for gestational age by calculating the multiple of the median (MoM) for each gestational week.
- Mean uterine artery resistance index (UT-RI) was calculated from the left and right uterine RI. If only a left or right uterine RI was available, this was used as 'mean RI' (n=98). An abnormal uterine artery Doppler result was defined as a mean RI >90th centile (RI >0.695).

The cohort was randomly divided (2:1) into training and validation cohorts. The training cohort was used for clinical variables and biomarker investigation and selection and was used to develop models for each end point. The validation cohort was used to evaluate the predictive performance of the model.

Myers 2013a: Clinical risk factors, uterine Doppler and biomarkers (plasma placental growth factor [PlGF], soluble fms-like tyrosine kinase 1 [sFlt-1] and soluble endoglin [sENG])

- Biomarkers were quantified in EDTA plasma samples at 15 weeks and 20 weeks gestation.

Myers 2013b: Logistic regression was used to develop multivariable models. The clinical parameters (maternal age and MAP; no missing values) obtained at 20 weeks, protein assays (log transformed) with <20% missing values, and a <25% CV were used for the multivariable analysis. The modelling aimed to discover all marker combinations predictive of PE using a maximum of 6 covariates to limit the risk of overfitting the data. For each combination, a logistic regression model was fitted on the participants with complete data; observations with outlying values were discarded. A conservative stepwise approach was used to select the models. First, that statistical significance of all coefficients was estimated using the Wald test. A model was ignored when the Wald test for one of the coefficients associated with a covariate was p>0.05. For the retained models, the discriminatory power was then estimated using the AUC. Models with an AUC below 0.70 were ignored (this AUC corresponds to the AUC of the best univariate predictor; IGFALS). Finally, the sensitivity at 20% PPV was computed for the remaining models, and those with a sensitivity of ≥50%, the preset threshold, were retained for external validation.

The selected models were evaluated in the European samples (validation set). The performance was computed in the validation set using the models developed in the training set without any refitting.

Reference standard

Participants were followed prospectively, and research midwives collected data on pregnancy outcome and measurements of the baby. PE was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90mmHg on at least 2 occasions 4 hours apart after 20 weeks of gestation but before the onset of labour, or postpartum, with either proteinuria (24-hour urinary protein >300 mg or spot urine protein:creatinine ratio ≥30 mg/mmol creatinine or urine dipstick protein ≥2+) or any multi-system complication of PE. Preterm PE was PE resulting in delivery before 37^{+0} week's gestation. Early-onset PE was delivery <34 weeks.

Test Accuracy

Kenny 2014: Screening test characteristics at 95% specificity for PE and term, preterm and early-onset PE based on biomarkers, clinical risk factors and ultrasound scan

Clinical Group	Sensitivity (95% CI)	PPV (95% CI)	NPV (95% CI)	Positive LR
PE: Calculated based on high fruit intake, BMI, mean arterial pressure (MAP), mean UT-RI, PlGF				
Training	22 (17–29)	20 (15–26)	95 (95–96)	4.5
Validation	17 (10–27)	13 (8–21)	96 (95–97)	3.3
Term PE: Calculated based on high fruit intake, MAP, BMI, tissue inhibitor of metalloproteinase 1				
Training	19 (13–26)	14 (10–20)	96 (96–97)	3.8

Study Reference **SCOPE (Kenny 2014, Myers 2013a, Myers 2013b, North 2011)**

Validation	6 (2–16)	3 (1–9)	97 (96–98)	1.1
Preterm PE: MAP, mean UT-RI, interleukin receptor antagonist/PlGF				
Training	41 (28–57)	9 (6–14)	99 (99–100)	8.3
Validation	42 (24–61)	10 (5–17)	99 (99–99)	7.9
Early-onset PE: MAP, mean UT-RI, cystatin C/PlGF				
Training	67 (41–85)	5 (3–10)	100 (100–100)	13.4
Validation	44 (19–74)	4 (2–11)	100 (99–100)	8.9

Myers 2013a: Screening for clinical risk factors, angiogenic biomarkers and uterine artery Doppler to predict pre-term PE

Test	Sensitivity (95% CI)*	Positive LR (95% CI)
PlGF 15 weeks	0.22 (0.12–0.35)	4.3 (1.8–9.9)
sEng 20 weeks	0.28 (0.17–0.43)	5.7 (2.6–12.5)
Clinical risk	0.34 (0.22–0.48)	6.8 (3.2–14.5)
Clinical risk + 15 weeks PlGF	0.45 (0.31–0.59)	9.0 (4.4–18.3)
Clinical risk + 20 weeks uterine Doppler	0.49 (0.35–0.63)	8.9 (4.5–17.3)
Clinical risk +15 weeks PlGF + 20 weeks uterine Doppler	0.47 (0.33–0.61)	9.4 (4.6–9.1)
Clinical risk + 15 weeks PlGF + 20 weeks uterine Doppler + 20 weeks sEng	0.52 (0.38–0.66)	10.5 (5.2–21.0)

* At 95% specificity

Myers 2013b:

IGFALS had the highest performance as a single marker with 48% (95% CI, 37% to 59%) sensitivity at 80% specificity. PlGF, sEng, ADAM12, and 20-week MAP also significantly discriminated women destined to develop preterm PE from control pregnancies ($p<0.001$). 44 models had a prediction performance higher than the predefined cutoff (sensitivity ≥50% at 20% PPV). There was significant overlap of protein biomarkers in these prediction models, with a small number of biomarkers (PlGF, IGFALS, MCAM, sEng, ADAM12 and SPINT1) appearing in the majority of algorithms.

Of the 44 models, 8 reached the target performance of 50% sensitivity at 20% PPV for a 5% prevalence in the validation set. These validated models included combinations of the proteins IGFALS, sEng, ADAM12, SPINT1, MCAM, selenoprotein P, multimerin-2, extracellular matrix protein 1, microtubule-associated protein RP/EB family member 1 or 3, fructose-biphosphate adolase A, PlGF and BP (MAP). The 8 validated models all showed very similar performance for overall PE prediction. With the exception of 1 model, these models combine IGFALS and sEng and a selection of 3 or 4 markers out of SPINT1, PlGF, MCAM, selenoprotein P, and MAP.

Using the model that combines the 6 most frequently occurring covariates, a risk index (relative risk to develop PE) was computed for each patient. A risk index cutoff corresponding to 20% PPV was computed on the training set. The cutoff corresponds to a detection rate (sensitivity) of 54% (95% CI, 37% to 66%) in the training set and 50% (95% CI, 36% to 68%) in the validation set. Using the model for all PE and the same risk index cutoff, the detection of preterm PE was 72% (95% CI, 48% to 88%) in the training set and 80% (95% CI, 50% to 100%) in the validation set.

		Sensitivity at 20% PPV*		Sensitivity at 80% specificity	
Training model no.		Sens	95% CI	Sens	95% CI
1	MAP, sEng, SPINT1, IGFALS, MCAM, PlGF	54	36%–66%	67	54%–80%

Study Reference	**SCOPE (Kenny 2014, Myers 2013a, Myers 2013b, North 2011)**

2	MAP, ADAM12, ECM1, MCAM, PIGF	53	37%–63%	62	51%–73%
3	MAP, MMRN2, sEng, MAPRE1/3, IGFALS, ALDOA	51	34%–61%	59	47%–72%
4	MAP, sEng, SEPP1, IGFALS, MCAM, PlGF	50	37%–64%	64	53%–74%
5	MAP, MMRN2, sEng, SPINT1, SEPP1, IGFALS	56	39%–67%	64	52%–74%
6	MAP, sEng, SPINT1, SEPP1, IGFALS, PlGF	53	35%–65%	64	54%–76%
7	sEng, SPINT1, SEPP1, IGFALS, MCAM, PlGF	54	39%–67%	64	52%–75%
8	sEng, SPINT1, IGFALS, MCAM, PlGF	53	38%–65%	64	52%–76%
Validation model no.					
1	MAP, sEng, SPINT1, IGFALS, MCAM, PlGF	50	36%–68%	59	45%–73%
2	MAP, ADAM12, ECM1, MCAM, PIGF	51	32%–64%	57	43%–74%
3	MAP, MMRN2, sEng, MAPRE1/3, IGFALS, ALDOA	53	35%–68%	60	43%–75%
4	MAP, sEng, SEPP1, IGFALS, MCAM, PlGF	54	35%–67%	56	42%–71%
5	MAP, MMRN2, sEng, SPINT1, SEPP1, IGFALS	53	38%–69%	53	40%–71%
6	MAP, sEng, SPINT1, SEPP1, IGFALS, PlGF	53	38%–67%	58	44%–73%
7	sEng, SPINT1, SEPP1, IGFALS, MCAM, PlGF	50	32%–64%	59	43%–73%
8	sEng, SPINT1, IGFALS, MCAM, PlGF	50	32%–64%	59	41%–73%

*Calculated for 5% prevalence

Authors' Conclusions

In nulliparous women, combining multiple biomarkers and clinical data provided modest prediction of PE. The modest prediction of all cases of PE precludes translation of the algorithm into clinical practice. Our data suggest that prediction of early-onset disease may be attainable. However, early-onset disease accounts for a minority of cases and the burden of disease lies within PE presenting at or close to term. Early pregnancy prediction of term PE remains too poor to be of clinical use and, on the basis of these data, we support the concept of two-stage screening with screening in early pregnancy for early-onset disease and screening for term PE in the third trimester.

Myers 2013a suggests that the addition of PlGF testing at 15 weeks of gestation to clinical risk factor screening could improve the ability to predict preterm PE in this low-risk group. Given the rarity of preterm PE, the number needed to treat with low-dose aspirin to prevent one case of preterm pre-eclampsia was 54. Before clinical implementation, the addition of novel biochemical markers to combinations of clinical risk factors and PlGF will be required to improve screening performance such that the necessary health and economic benefits are achieved.

Myers 2013b: The study identified a number of novel biomarkers associated with the later development of PE in low-risk nulliparous women. During the development of predictive models, 4 of these novel biomarkers, IGFALS, MCAM, selenoprotein P and SPINT1, were highly recurrent. In combination with known biomarkers (PlGF and sEng) and MAP, these markers achieved predictive performances with the potential to identify a subgroup of healthy nulliparous women who could receive specialist prenatal care. Novel biomarkers relevant to the prediction of PE were confirmed in 2 independent sample sets in this study, and IGFALS has emerged as a novel marker, predictive of term and preterm PE.

Abbreviations: ADAM12 indicates disintegrin and metalloproteinase domain-containing protein 12; ALDOA, fructose-biphosphate aldolase A; APS, antiphospholipid syndrome; ART, assisted reproductive technologies; AUC, area under the receiver-operator curve; BMI, body mass index; BP, blood pressure; CI, confidence interval; CV, coefficients of variation; ECM1, extracellular matrix protein 1; EDTA, ethylenediamine tetraacetic acid; HIV, human immunodeficiency virus; IGFALS, insulin-like growth factor acid labile subunit; LR, likelihood ratio; MAP, mean arterial pressure; MAPRE1/3, microtubule-associated protein RP/EB family member 1 or 3; MCAM, melanoma cell adhesion molecule; MMRN2, multimerin-2; MoM, multiple of the median; NPV, negative predictive value; PCOS, polycystic ovarian syndrome; PE, pre-eclampsia; PlGF, placental growth factor; PPV, positive predictive value; SCOPE, Screening for Pregnancy Endpoints; SD,

standard deviation; sEng, soluble endoglin; SEPP1, selenoproetin; sFlt-1, soluble fms-like tyrosine kinase 1; SGA, small-for-gestational age; SLE, systemic lupus erythematosus; SPINT1, serine peptidase inhibitor Kunitz type 1; SRM, selective reaction monitoring; UK, United Kingdom; UT-RI, uterine artery resistance index

Table 25ae: Serra 2020 (Mendoza 2021a; Mendoza 2021b)

Study Reference	Serra 2020 [Mendoza 2021a; Mendoza 2021b]
Study Design	Design Prospective cohort; secondary analysis of a prospective cohort Objective To evaluate the performance for the screening of early-onset PE of a multivariate Gaussian distribution model that includes maternal variables and history plus biophysical and biochemical biomarkers assessed during the first trimester of pregnancy in singleton pregnancies being referred for aneuploidy screening. The aim of a secondary analysis [Mendoza 2021a] was to evaluate the performance of the FMF and the Gaussian algorithms in predicting early-onset and preterm PE when PAPP-A and PlGF were assessed before, compared with after, 11 weeks. This analysis was conducted using data from the Vall d'Hebron cohort. The aim of a secondary analysis [Mendoza 2021b] was to offer cut-off values for all possible combinations of markers involved in the Gaussian algorithm that can be used in clinical practice in settings willing to offer universal first-trimester screening for early-onset PE, but where prospective validation of this algorithm is not feasible, prior to its implementation. Dates March 2014 to May 2016 (Dexeus University hospital) and October 2015 to September 2017 (Vall d'Hebron University Hospital) Country Spain Setting Dexeus University Hospital (Barcelona) and Vall d'Hebron University Hospital (Barcelona) [Mendoza 2021a and 2021b only used data from the Vall d'Hebron cohort]
Population Characteristics	Patient recruitment and eligibility Eligible participants were women of the general population, ≥18 years of age, with singleton pregnancies attending their routine first-trimester aneuploidy screening (8 weeks 0/7 days to 13 weeks 6/7 days weeks of gestation) at either of the 2participating centres. Pregnancies with aneuploidies, major fetal abnormalities, or ending in termination, miscarriage or fetal death before 24 weeks of gestation were excluded. Women receiving low-dose aspirin according to current clinical guidelines during the study period were not excluded from the primary study. Women that had received aspirin at any time before the first-trimester scan were not included in the secondary analysis [Mendoza 2021b]. Data collection The gestational age of all pregnancies was calculated based on the crown-rump length at 8 weeks 0/7 days to 13 weeks 6/7 days. All procedures (measurements, data recording) were made according to the routine clinical practice. Maternal characteristics and medical and obstetric history were recorded at the early first-trimester ultrasound via a patient questionnaire. Blood pressure (BP) was measured at 11 weeks 0/7 days to 13 weeks 6/7 days, and MAP was calculated. Uterine artery (UtA) Doppler evaluation was performed transvaginally in the Dexeus cohort and transabdominally in the Vall d'Hebron cohort at 11 weeks 0/7 days to 13 weeks 6/7 days of gestation. Bilateral uterine pulsatility indices (PIs) were measured and mean UtA-PI was calculated. Blood samples for biochemical

Study Reference	Serra 2020 [Mendoza 2021a; Mendoza 2021b]

markers were drawn between 8 weeks 0/7 days to 13 weeks 6/7 days of gestation. Maternal serum PAPP-A PlGF were measured.

Duration of follow-up
Delivery (inferred based on outcomes reported)

Prevalence of PE in the study

161 (2.3%) developed PE; 17 (0.2%) developed early-onset PE

Mendoza 2021a: 90 (3.4%) developed PE including 30 (1.1%) who developed preterm PE and 11 (0.4%) who developed early-onset PE. 5 (45.5%) cases of early-onset and 16 (53.3%) of preterm PE were identified in the group in which serum biomarkers were assessed at 8^{+0} to 10^{+6} weeks and 6 (54.5%) cases of early-onset and 14 (46.7%) of preterm PE in the group in which serum biomarkers were assessed at 11^{+0} to 13^{+6} weeks

Mendoza 2021b: 90 (3.41%) developed PE; 79 (2.99%) developed late-onset and 11 (0.42%) developed early-onset PE

Sample size
N screened/invited = 7,908
N eligible = NR
N enrolled = NR
N excluded (with reason) = NR
N lost to follow-up = NR
N completed = NR
N excluded from analysis = 1,015 (missing outcome, 932 [mainly those who after having the screening procedure done decided to have the follow up of their pregnancies and/or delivery in other hospitals]; major fetal defects or chromosomopathies, 39; miscarriage or fetal death before 24 weeks, 42; termination of pregnancy for any other reason, 2)
N included in analysis = 6,893

[Sample size for Mendoza 2021a and 2021b]:
N screened/invited = 3,898 assessed for eligibility at first-trimester scan; 3,777 invited
N eligible = NR
N enrolled = 2,946
N excluded (with reason) = 121 including multiple pregnancies n=48), current aspirin treatment (n=31), age <18 years (n=42), declined to participate (n=831)
N lost to follow-up = NR
N completed = NR
N excluded from analysis = 305 including missing outcome data (n=86), major fetal defects or chromosomopathies (n=13), miscarriage or fetal death before 24 weeks (n=15), insufficient remaining blood sample to measure PlGF (n=191)
N included in analysis = 2,641

Demographics

Characteristic	Early-onset PE (n=17)	Late-onset PE (n=144)	No PE (n=6732)
Age, year, median (IQR)	34.0 (32.5–37.0)	35.0 (32.0–38.0)	33.9 (30.4–37.0)
BMI, kg/m^2, median (IQR)	23.1 (222.5–27.5)	24.8 (22.7–30.5)	22.9 (20.9–25.8)
Ethnicity, n (%)			
White European	15 (88.2)	127 (88.2)	6133 (91.1)
South American	2 (11.8)	11 (7.6)	331 (4.9)
Black	0 (0)	2 (1.4)	84 (1.2)

Study Reference **Serra 2020 [Mendoza 2021a; Mendoza 2021b]**

Asian	0 (0)	3 (2.1)	150 (2.2)
North African	0 (0)	0 (0)	7 (0.1)
Other	0 (0)	1 (0.7)	27 (0.4)
Smoking habit, n (%)	1 (5.9)	18 (12.5)	628 (9.3)
Assisted reproductive technologies, n (%)	1 (5.9)	21 (14.6)	544 (8.1)
Medical history, n (%)			
Chronic hypertension	3 (17.6)	8 (5.6)	42 (0.6)
Diabetes mellitus	0 (0)	4 (2.8)	47 (0.7)
Renal disease	0 (0)	1 (0.7)	7 (0.1)
Autoimmune disease	0 (0)	6 (4.2)	236 (3.5)
Coagulation disorders	0 (0)	2 (1.4)	89 (1.3)
Obstetric history, n (%)			
Nulliparous	8 (47.1)	93 (64.6)	3630 (53.9)
Previous PE	2 (11.8)	13 (9.0)	56 (0.8)
Biophysical variables, median (IQR)			
MAP, mm Hg[a]	94.3 (85.0–99.7)	89.0 (81.7–95.3)	80.0 (75.0–86.0)
Mean UtA-PI[a]	2.1 (1.9–2.5)	1.6 (1.3–2.1)	1.5 (1.3–1.9)
Biochemical variables, MoM, median (IQR)			
PAPP-A, mU/L[a]	0.71 890.0 (602–1,669)	0.91 890 (482–1464)	1.03 830 (472–1,470)
PlGF, pg/mL[a]	0.62 19.5 (15.5–24.1)	0.91 26.5 (20.6–34.5)	1.0 28.1 (21.5–37.3)

[a]Indicates significant difference (p<0.001)

[Mendoza 2021a]

Parameter	PE before 34+^{0} weeks (n = 11)		p value	PE before 37^{+0} weeks (n = 30)		p value	No PE before 37^{+0} weeks (n = 2,611)		p value
	Biochemical markers measured at:			Biochemical markers measured at:			Biochemical markers measured at:		
	8^{+0} to 10^{+6} weeks (n = 5)	11^{+0} to 13^{+6} weeks (n = 6)		8^{+0} to 10^{+6} weeks (n = 16)	11^{+0} to 13^{+6} weeks (n = 14)		8^{+0} to 10^{+6} weeks (n = 1,659)	11^{+0} to 13^{+6} weeks (n = 952)	
Age, year, median (IQR)	34.0 (34.0–37.0)	34.5 (31.3–37.0)	0.642	34.0 (28.8–37.0)	37.0 (32.8–38.0)	0.143	32.0 (28.0–36.0)	32.0 (28.0–36.0)	0.222
BMI, kg/m^2, median (IQR)	23.2 (22.7–32.1)	23.1 (22.2–25.5)	0.537	25.1 (23.2–28.7)	23.1 (21.8–26.0)	0.096	23.9 (21.4–27.4)	23.8 (21.2–27.5)	0.521
Ethnicity, n (%)			0.455			0.734			<0.001

Study Reference	Serra 2020 [Mendoza 2021a; Mendoza 2021b]								
	White	4 (80.0)	6 (100)	-	13 (81.3)	12 (85.7)	-	1,441 (86.9)	768 (80.7)	<0.001
	Black	0 (0)	0 (0)	-	0 (0)	1 (7.1)	-	34 (2.0)	37 (3.9)	0.008
	Mixed	1 (20.0)	0 (0)	-	2 (12.5)	0 (0)	-	109 (6.6)	100 (10.5)	<0.001
	Asian	0 (0)	0 (0)	-	1 (6.3)	1 (7.1)	-	40 (2.4)	23 (2.4)	1.0
	South-East Asian	0 (0)	0 (0)	-	0 (0)	0 (0)	-	35 (2.1)	24 (2.5)	0.497
	Smoker, n (%)	1 (20.0)	0 (0)	0.455	1 (6.3)	2 (14.3)	0.586	214 (12.9)	95 (10.0)	0.028
	Assisted reproductive technologies, n (%)	0 (0)	1 (16.7)	1.0	0 (0)	2 (14.3)	0.209	60 (3.6)	33 (3.5)	0.731
	Medical history, n (%)			1.0			1.0			0.695
	Chronic hypertension	2 (40.0)	1 (16.7)	-	3 (18.8)	2 (14.3)	-	15 (0.9)	9 (0.9)	-
	Diabetes mellitus	0 (0)	0 (0)	-	1 (6.3)	0 (0)	-	25 (1.5)	10 (1.1)	-
	Autoimmune disease	0 (0)	0 (0)	-	1 (6.3)	2 (14.3)	-	63 (3.8)	42 (4.4)	-
	Antiphospholipid syndrome	0 (0)	0 (0)	-	1 (6.3)	0 (0)	-	4 (0.2)	4 (0.4)	-
	Obstetric history, n (%)			0.250			0.484			0.002
	Nulliparous	0 (0)	2 (33.3)	-	6 (37.5)	7 (50.0)	-	813 (49.0)	406 (42.6)	0.002
	Previous PE	1 (20.0)	1 (16.7)	-	4 (25.0)	1 (7.1)	-	16 (1.0)	14 (1.5)	0.256
	Previous FGR	0 (0)	0 (0)	-	0 (0)	1 (7.1)	-	18 (1.1)	5 (0.5)	0.191
	Biophysical variables, median (IQR)									
	MAP, mm Hg	94.3 (91.0–101.7)	96.3 (89.5–104.9)	0.931	90.5 (87.9–93.8)	94.5 (83.0–104.1)	0.693	84.0 (78.7–90.3)	84.7 (78.3–90.7)	0.829
	MAP MoM	1.14 (1.10–1.37)	1.22 (1.14–1.22)	0.931	1.14 (1.10–1.21)	1.16 (1.05–1.30)	0.866	1.05 (0.97–1.14)	1.06 (0.97–1.14)	0.844
	Mean UtA-PI	2.54 (2.25–2.80)	1.89 (1.88–2.76)	0.247	2.15 (1.71–2.32)	1.89 (1.71–2.21)	0.618	1.69 (1.36–2.08)	1.65 (1.31–2.00)	0.002
	Mean UtA-PI MoM	1.67 (1.19–1.81)	1.18 (1.12–1.91)	0.537	1.24 (1.06–1.46)	1.12 (1.00–1.33)	0.552	1.03 (0.84–1.26)	1.03 (0.83–1.26)	0.834

Study Reference **Serra 2020 [Mendoza 2021a; Mendoza 2021b]**

Biochemical variables, MoM, median (IQR)									
PAPP-A, mU/L	607.3 (602.3–1,119.0)	1,801.0 (1,447.0–2,201.5)	0.177	604.8 (307.8–1,071.0)	1,869.5 (1,387.0–3,513.5)	<0.001	1,033.0 (655.9–1,575.5)	2,395.5 (1,499.0–3,832.3)	<0.001
PAPP-A MoM	0.93 (0.71–1.09)	0.69 (0.61–0.74)	0.314	0.68 (0.53–1.06)	0.73 (0.61–0.85)	0.574	1.05 (0.74–1.50)	1.06 (0.72–1.51)	0.769
PlGF, pg/mL	19.77 (19.03–22.35)	27.00 (20.69–40.15)	0.329	22.67 (19.00–26.24)	30.60 (25.10–47.48)	0.017	28.23 (22.0–35.89)	41.36 (31.92–54.40)	<0.001
PlGF MoM	0.65 (0.62–0.86)	0.71 (0.45–0.97)	1.0	0.85 (0.70–0.96)	0.69 (0.52–1.00)	0.257	0.96 (0.77–1.19)	0.95 (0.74–1.19)	0.256

[Mendoza 2021b]

	Unaffected (n = 2,551)	PE ≥34^{+0} (n = 79)	PE <34^{+0} (n = 11)
Age, year, median (IQR)	32.0 (28.0–36.0)	33.0 (29.0–37.0)	34.0 (33.0–37.0)
BMI, kg/m^2, median (IQR)	23.8 (21.3–27.3)[a]	25.5 (22.9–29.6)[b]	23.1 (22.6–29.2)
Ethnicity, n (%)			
White	2158 (84.6%)	65 (83.3%)	11 (91.7%)
Black	70 (2.7%)	2 (2.6%)	0
Mixed	202 (7.9%)	8 (10.2%)	1 (8.3%)
Asian	63 (2.5%)	2 (2.6%)	0
South-East Asian	58 (2.3%)	1 (1.3%)	0
Smoker, n (%)	300 (11.8%)	10 (12.8%)	1 (8.3%)
Assisted reproductive technologies, n (%)			
Insemination	15 (0.6%)[a]	1 (1.3%)[b]	1 (8.3%)
In vitro fertilisation	51 (2.0%)	2 (2.6%)	0
In vitro fertilisation with egg donation	22 (0.9%)[a]	4 (5.1%)[b]	0
Medical history, n (%)			
Chronic hypertension	22 (0.9%)[ac]	4 (5.1%)[b]	3 (25.0%)[b]
Diabetes mellitus	34 (1.3%)	2 (2.6%)	0
Autoimmune disease	103 (4.0%)	5 (6.4%)	1 (8.3%)
Antiphospholipid syndrome	8 (0.3%)	1 (1.3%)	0
Obstetric history, n (%)			
Nulliparous	1183 (52.6%)	47 (60.3%)	3 (25.0%)
Previous PE	24 (0.9%)[ac]	8 (10.3%)[b]	3 (25.0%)[b]
Previous FGR	21 (0.8%)	3 (3.8%)	0

Study Reference	Serra 2020 [Mendoza 2021a; Mendoza 2021b]			
	Biophysical variables, median (IQR)			
	MAP, mm Hg	84.0 (78.3–90.3)[ac]	91.2 (82.8–96.0)[b]	95.1 (89.7–103.0)[b]
	Mean UtA-PI	1.68 (1.34–2.04)[c]	1.72 (1.31–2.15)[c]	2.25 (1.89–2.92)[ab]
	Biochemical variables, MoM, median (IQR)			
	PAPP-A, mU/L	1,361.0 (826.6–2,387.5)	1,255.5 (721.6–1,844.0)	1,373 (748.7–2,112.0)
	PAPP-A MoM	1.05 (0.73–1.50)	0.91 (0.63–1.25)	0.72 (0.62–0.84)
	PlGF, pg/mL	32.3 (24.4–43.0)	28.8 (21.0–39.0)	23.2 (19.3–27.9)
	PlGF MoM	0.96 (0.76–1.19)[c]	0.91 (0.67–1.11)	0.69 (0.57–0.96)[b]

[a]significant difference compared to late-onset PE; [b]significant difference compared to unaffected women; [c]significant difference compared to early-onset PE

Screening Method

Index test

A multivariate Gaussian distribution model for PE screening consisting of prior risk definition, MoM calculation, and posterior risk definition was constructed. A priori risk was estimated using the incidence of early-onset PE and material characteristics. As no information about the distributions of PE risk factors in the population was known, these were deducted from a wide MA. The a priori risk, determined by the incidence in the study population and expressed as an odds, was then adjusted to maternal age, ethnicity, parity, chronic hypertension and a personal history of PE. Values of markers were, as is routine practice for screenings, transformed to MoM. Gaussian modelling to derive LRs was performed according to the formula published by Reynolds and Penney in 1990. Posterior risk was then obtained modifying the a priori odds by the LR of a multimarker profile and transforming the resulting odds to a risk.

In a secondary analysis of the Vall d'Hebron cohort [Mendoza 2021a], women were classified into 2 groups according to whether the blood sample for biomarker assessment was drawn before or after 11 weeks gestation. The variables required for the prediction formulae according to the description provided in the articles were then coded and the probability score for early-onset PE was calculated using 2 different algorithms: the multivariate Gaussian-distribution model and the FMF competing-risks model. DRs at fixed 5% and 10% FPRs were computed for all combinations of markers involved in the risk assessment, to compare the performance of the 2 algorithms for predicting early-onset and preterm PE when PAPP-A and PlGF were measured before and after 11 weeks.

In a secondary analysis of the Vall d'Hebron cohort [Mendoza 2021b], DRs and cut-off values for fixed 5%, 10%, 15%, 20%, 25%, and 30% FPR were calculated for all combinations of markers.

Reference standard

PE was defined in accordance with the American College of Obstetricians and Gynaecologists as systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg on at least 2 occasions 4 hours apart, developing from 20 weeks of gestation onward in previously normotensive women and proteinuria ≥300 mg in a 24 hour urine specimen. In the absence of proteinuria, it was considered the new onset of hypertension with new onset of any of the following: thrombocytopenia: platelet count <100,000/mL; renal insufficiency: serum creatinine concentration greater than 1.1 g/dL or doubling the serum creatinine concentration in the absence of other renal disease; impaired liver function: elevated concentrations of liver transaminases to twice normal concentration; pulmonary oedema; cerebral or visual symptoms.

PE superimposed on chronic hypertension was defined as significant proteinuria after 20 weeks of gestation in women with known chronic hypertension diagnosed before pregnancy or before 20 weeks of gestation.

Early-onset PE, the focus of this study, was defined as PE requiring delivery <34 weeks, which is the severe subtype of PE. Preterm PE (<37 weeks of pregnancy) can be prevented by administering low-dose aspirin to women classified as high risk by multiparametric algorithms. The obstetric records of women with pre-existing or pregnancy-associated hypertension were examined to determine whether the condition was chronic hypertension, PE, or gestational hypertension.

Study Reference **Serra 2020 [Mendoza 2021a; Mendoza 2021b]**

[Mendoza 2021a and 2021b] PE was defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy as systolic BP ≥140mmHg and/or diastolic BP ≥90mmHg confirmed by repeat measurements over a few hours, developing after 20 weeks gestation in a previously normotensive woman, accompanied by proteinuria of ≥300 mg per 24 h or a spot urine protein-to-creatinine ratio ≥0.3mg/mg or dipstick urinalysis ≥1+ when a quantitative method was not available. Early-onset and preterm PE were defined as PE necessitating delivery before 34 weeks and before 37 weeks, respectively.

Test Accuracy

Detection rates, positive and negative predictive values, and positive and negative likelihood ratios for early-onset PE of each individual predictor and their combinations

Screening variables, a priori risk plus the following factors:	DR (95% CI) for a FPR of the following:		PPV (95% CI) for a FPR of the following:		NPV (95% CI) for a FPR of the following:		PLR for a FPR of the following:		NLR for a FPR of the following:	
	5%	10%	5%	10%	5%	10%	5%	10%	5%	10%
PAPP-A	23.5%	35.3%	1.15%	0.86%	99.8%	99.82%	4.72	3.53	0.8	0.72
MAP	41.2%	47.1%	1.98%	1.15%	99.85%	99.85%	8.18	4.72	0.62	0.59
PlGF	41.2%	41.2%	2%	1.01%	99.85%	99.84%	8.25	4.11	0.62	0.65
Mean UtA-PI	47.1%	58.8%	2.29%	1.43%	99.86%	99.89%	9.46	5.87	0.56	0.46
MAP + PAPP-A	52.3%	58.8%	2.52%	1.43%	99.88%	99.89%	10.46	5.89	0.5	0.46
Mean UtA-PI + PAPP-A	47.1%	58.8%	2.26%	1.43%	99.86%	99.89%	9.35	5.86	0.56	0.46
Mean UtA-PI + PlGF	52.9%	70.6%	2.53%	1.72%	99.88%	99.92%	10.49	7.06	0.5	0.33
MAP + PlGF	52.9%	70.6%	2.56%	1.71%	99.88%	99.92%	10.61	7.04	0.5	0.33
MAP + mean UtA-PI	58.8%	58.8%	2.82%	1.43%	99.89%	99.89%	11.72	5.87	0.43	0.46
MAP + mean UtA-PI + PAPP-A	58.8%	64.7%	2.82%	1.57%	99.89%	99.9%	11.76	6.46	0.43	0.39
MAP + mean UtA-PI + PlGF	58.8%	94.1%	2.82%	2.27%	99.89%	99.98%	11.76	9.41	0.43	0.07
MAP + mean UtA-PI + PlGF + PAPP-A	58.8%	94.1%	2.81%	2.27%	99.89%	99.98%	11.69	9.41	0.43	0.07

Highest DR at 5% and 10% FPR for a priori risk adding a single biomarker was found with UtA-PI (47.1% and 58.8%, respectively). The

Study Reference **Serra 2020 [Mendoza 2021a; Mendoza 2021b]**

addition of PAPP-A to the combination of a priori risk plus biophysical markers (MAP plus mean UtA-PI) did not improve test performance, while the addition of PlGF did it significantly, increasing the DR for a 10% FPR from 58.8% to 94.1%.

Detection rate and positive and negative predictive values for early onset PE prediction of the combination of MAP + mean UtA-PI + PlGF + PAPP-A with their 95% CIs

Variables	Estimate	Lower bound	Upper bound
DR	94.12%	71.31%	99.85%
PPV	2.27%	1.31%	3.67%
NPV	99.98%	99.91%	100%

The 95% CI for the DR, PPV, and NPV corresponds to a 10% FPR cutoff.

[Mendoza 2021a]:

DR for prediction of PE before 34 weeks gestation by Gaussian model, according to whether PAPP-A and PlGF were measured before or after 11 weeks

Method of screening: a priori risk plus:	8^{+0} to 10^{+6} weeks (n=5)		11^{+0} to 13^{+6} weeks (n=6)	
	DR (% (95% CI)) at:		DR (% (95% CI)) at:	
	5% FPR	10% FPR	5% FPR	10% FPR
MAP	40.0 (0–80.0)	40.0 (0–80.0)	33.3 (0–66.7)	50.0 (0–83.3)
UtA-PI	60.0 (20.0–100)	60.0 (20.0–100)	33.3 (0–66.7)	50.0 (16.7–83.3)
PAPP-A	20.0 (0–60.0)	40.0 (0–80.0)	33.3 (0–66.7)	50.0 (0–83.3)
PlGF	40.0 (0–80.0)	40.0 (0–80.0)	33.3 (0–66.7)	33.3 (0–66.7)
PlGF + UtA-PI	60.0 (20.0–100)	60.0 (20.0–100)	50.0 (16.7–83.3)	50.0 (16.7–83.3)
MAP + PlGF	40.0 (0–80.0)	40.0 (0–80.0)	33.3 (0–66.7)	66.7 (33.3–100)
MAP + UtA-PI	60.0 (20.0–100)	60.0 (20.0–100)	66.7 (33.3–100)	66.7 (33.3–100)
PAPP-A + PlGF	20.0 (0–60.0)	40.0 (0–80.0)	33.3 (0–66.7)	50.0 (16.7–83.3)
MAP + PAPP-A	40.0 (0–80.0)	40.0 (0–80.0)	33.3 (0–66.7)	66.7 (16.7–100)
UtA-PI + PAPP-A	60.0 (20.0–100)	60.0 (20.0–100)	50.0 (16.7–83.3)	50.0 (16.7–83.3)
MAP + UtA-PI + PAPP-A	60.0 (20.0–100)	60.0 (20.0–100)	66.7 (33.3–100)	66.7 (33.3–100)
MAP + UtA-PI + PlGF	60.0 (20.0–100)	80.0 (20.0–100)	50.0 (16.7–83.3)	83.3 (50.0–100)
MAP + PAPP-A + PlGF	40.0 (0–80.0)	40.0 (0–80.0)	33.3 (0–73.9)	66.7 (16.7–100)
UtA-PI + PlGF + PAPP-A	60.0 (20.0–100)	60.0 (20.0–100)	50.0 (16.7–83.3)	50.0 (16.7–83.3)
MAP + UtA-PI + PlGF + PAPP-A	60.0 (20.0–100)	80.0 (20.0–100)	50.0 (16.7–83.3)	83.3 (50.0–100)

DR for prediction of PE before 37 weeks gestation by Gaussian model, according to whether PAPP-A and PlGF were measured before or after 11 weeks

Study Reference **Serra 2020 [Mendoza 2021a; Mendoza 2021b]**

Method of screening: a priori risk plus:	8^{+0} to 10^{+6} weeks (n=16)		11^{+0} to 13^{+6} weeks (n=14)	
	DR (% (95% CI)) at:		DR (% (95% CI)) at:	
	5% FPR	10% FPR	5% FPR	10% FPR
MAP	25.0 (6.3–43.8)	37.5 (18.8–68.8)	28.6 (7.1–50.0)	35.7 (7.1–64.3)
UtA-PI	43.8 (18.8–68.8)	50.0 (25.0–75.0)	28.6 (7.1–50.0)	35.7 (14.3–64.3)
PAPP-A	25.0 (6.3–50.0)	43.8 (18.8–68.8)	14.3 (0–35.7)	35.7 (7.1–64.3)
PlGF	25.0 (6.3–43.8)	25.0 (6.3–43.8)	35.7 (14.3–64.3)	35.7 (14.3–64.3)
PlGF + UtA-PI	37.5 (12.5–62.5)	43.8 (18.8–68.8)	42.9 (14.3–71.4)	42.9 (14.3–71.4)
MAP + PlGF	25.0 (6.3–50.0)	31.3 (12.5–56.3)	28.6 (7.1–57.1)	57.1 (28.6–85.7)
MAP + UtA-PI	31.3 (12.5–56.3)	31.3 (12.5–56.3)	42.9 (14.3–71.4)	50.0 (21.4–78.6)
PAPP-A + PlGF	25.0 (6.3–43.8)	25.0 (6.3–50.0)	35.7 (14.3–64.3)	42.9 (21.4–71.4)
MAP + PAPP-A	37.5 (18.8–62.5)	43.8 (18.8–68.8)	28.6 (7.1–50.0)	42.9 (14.3–71.4)
UtA-PI + PAPP-A	43.8 (18.8–68.8)	50.0 (25.0–75.0)	21.4 (7.1–50.0)	35.7 (14.3–64.3)
MAP + UtA-PI + PAPP-A	31.3 (12.5–56.3)	37.5 (12.5–62.5)	42.9 (21.4–71.4)	50.0 (28.4–78.6)
MAP + UtA-PI + PlGF	31.3 (12.5–56.3)	37.5 (12.5–62.5)	42.9 (21.4–71.4)	50.0 (21.4–78.6)
MAP + PAPP-A + PlGF	31.3 (12.5–62.5)	37.5 (12.5–62.5)	28.6 (7.1–57.1)	50.0 (21.4–78.6)
UtA-PI + PlGF + PAPP-A	37.5 (12.5–62.5)	43.8 (18.8–68.8)	42.9 (14.3–71.4)	42.9 (14.3–71.4)
MAP + UtA-PI + PlGF + PAPP-A	31.3 (12.5–56.3)	50.0 (25.0–75.0)	35.7 (14.3–64.3)	64.3 (35.7–85.7)

DR for prediction of PE before 34 weeks gestation by FMF competing risks model, according to whether PAPP-A and PlGF were measured before or after 11 weeks

Method of screening: a priori risk plus:	8^{+0} to 10^{+6} weeks (n=5)		11^{+0} to 13^{+6} weeks (n=6)	
	DR (% (95% CI)) at:		DR (% (95% CI)) at:	
	5% FPR	10% FPR	5% FPR	10% FPR
MAP	40.0 (0–80.0)	40.0 (0–80.0)	16.7 (0–50.0)	16.7 (0–50.0)
UtA-PI	40.0 (0–80.0)	40.0 (0–80.0)	33.3 (0–66.7)	66.7 (33.3–100)
PAPP-A	40.0 (0–80.0)	40.0 (0–80.0)	33.3 (0–66.7)	33.3 (0–66.7)
PlGF	20.0 (0–60.0)	40.0 (0–80.0)	33.3 (0–66.7)	33.3 (0–66.7)
PlGF + UtA-PI	40.0 (0–80.0)	60.0 (20.0–100)	50.0 (16.3–83.3)	66.7 (16.7–100)
MAP + PlGF	40.0 (0–80.0)	40.0 (0–80.0)	33.3 (0–83.3)	50.0 (16.7–83.3)
MAP + UtA-PI	40.0 (0–80.0)	40.0 (0–80.0)	50.0 (16.7–83.3)	66.7 (16.7–100)

Study Reference **Serra 2020 [Mendoza 2021a; Mendoza 2021b]**

PAPP-A + PlGF	20.0 (0–60.0)	40.0 (0–80.0)	33.3 (0–66.7)	33.3 (0–83.3)
MAP + PAPP-A	40.0 (0–80.0)	40.0 (0–80.0)	16.7 (0–50.0)	50.0 (16.7–83.3)
UtA-PI + PAPP-A	40.0 (0–80.0)	60.0 (20.0–100)	50.0 (0–83.3)	66.7 (33.3–100)
MAP + UtA-PI + PAPP-A	40.0 (0–80.0)	40.0 (0–80.0)	50.0 (16.7–83.3)	66.7 (33.3–100)
MAP + UtA-PI + PlGF	40.0 (0–80.0)	60.0 (20.0–100)	83.3 (33.3–100)	83.3 (50.0–100)
MAP + PAPP-A + PlGF	40.0 (0–80.0)	40.0 (0–80.0)	50.0 (0–83.3)	50.0 (16.7–100)
UtA-PI + PlGF + PAPP-A	40.0 (0–80.0)	60.0 (20.0–100)	50.0 (16.7–83.3)	66.7 (16.7–100)
MAP + UtA-PI + PlGF + PAPP-A	60.0 (20.0–100)	80.0 (40.0–100)	66.7 (33.3–100)	100 (100–100)

DR for prediction of PE before 37 weeks gestation by FMF competing risks model, according to whether PAPP-A and PlGF were measured before or after 11 weeks

Method of screening: a priori risk plus:	8^{+0} to 10^{+6} weeks (n=16)		11^{+0} to 13^{+6} weeks (n=14)	
	DR (% (95% CI)) at:		DR (% (95% CI)) at:	
	5% FPR	10% FPR	5% FPR	10% FPR
MAP	31.3 (12.5–56.3)	31.3 (12.5–56.3)	21.4 (0–42.9)	28.6 (7.1–50.0)
UtA-PI	18.8 (0–37.7)	43.8 (25.0–68.8)	21.4 (0–42.9)	50.0 (28.4–78.6)
PAPP-A	12.5 (0–37.5)	31.3 (12.5–56.3)	21.4 (0–42.9)	35.7 (14.3–57.1)
PlGF	12.5 (0–37.5)	31.3 (12.5–56.3)	35.7 (14.3–57.1)	35.7 (14.3–57.1)
PlGF + UtA-PI	18.8 (0–43.8)	37.5 (18.8–62.5)	42.9 (21.4–71.4)	50.0 (21.4–78.6)
MAP + PlGF	31.3 (6.3–50.0)	37.5 (18.8–62.5)	35.7 (14.3–64.3)	42.9 (21.4–71.4)
MAP + UtA-PI	25.0 (6.3–50.0)	37.5 (18.8–62.5)	35.7 (14.3–64.3)	50.0 (21.4–78.6)
PAPP-A + PlGF	12.5 (0–43.8)	43.8 (18.8–68.8)	35.7 (14.3–64.3)	35.7 (14.3–64.3)
MAP + PAPP-A	31.3 (6.3–56.3)	43.8 (18.8–68.8)	14.3 (0–42.9)	28.6 (7.1–57.1)
UtA-PI + PAPP-A	37.5 (12.5–68.8)	56.3 (31.3–81.3)	28.6 (7.1–57.1)	50.0 (29.9–78.6)
MAP + UtA-PI + PAPP-A	31.3 (12.5–56.3)	43.8 (18.8–68.8)	35.7 (14.3–57.1)	57.1 (28.6–85.7)
MAP + UtA-PI + PlGF	18.8 (0–37.7)	43.8 (18.8–68.8)	42.9 (14.3–71.4)	57.1 (28.6–85.7)
MAP + PAPP-A + PlGF	31.3 (12.5–56.3)	43.8 (18.8–68.8)	35.7 (14.3–64.3)	50.0 (21.4–78.6)
UtA-PI + PlGF + PAPP-A	25.0 (6.3–43.8)	37.5 (12.5–62.5)	42.9 (14.3–71.4)	50.0 (29.9–78.6)
MAP + UtA-PI + PlGF + PAPP-A	31.3 (6.3–50.0)	50.0 (25.0–81.3)	42.9 (14.3–71.4)	57.1 (28.6–85.7)

Study Reference **Serra 2020 [Mendoza 2021a; Mendoza 2021b]**

In the prediction of early-onset PE and preterm PE using either the Gaussian algorithm or the FMF algorithm, no substantial differences were observed in the detection rates at fixed 5% and 10% FPRs for any of the combinations of markers evaluated when the biochemical markers were assessed at 8^{+0} to 10^{+6} weeks compared with 11^{+0} to 13^{+6} weeks.

[Mendoza 2021b]:
Performance for predicting early-onset PE of each individual marker and their combinations (FPR 5%, 10%. And 15%)

A priori risk plus:	PE <34^{+0} (n=11)					
	DR % (95% CI) at 5% FPR	Cut-off for 5% FPR ≤	DR % (95% CI) at 10% FPR	Cut-off for 10% FPR ≤	DR % (95% CI) at 15% FPR	Cut-off for 15% FPR ≤
MAP	36.4 (9.1–63.6)	1/21	45.5 (18.2–72.7)	1/39	54.5 (27.3–81.8)	1/66
UtA-PI	45.5 (18.2–72.7)	1/94	54.5 (27.3–81.8)	1/155	54.5 (27.3–81.8)	1/250
PAPP-A	27.3 (0–54.5)	1/205	45.5 (18.2–72.7)	1/281	54.5 (27.3–81.8)	1/345
PlGF	27.3 (0–54.5)	1/116	27.3 (0–54.5)	1/184	45.5 (18.2–72.7)	1/257
PlGF + UtA-PI	54.5 (27.3–81.8)	1/80	54.5 (27.3–81.8)	1/170	63.6 (27.3–90.9)	1/291
MAP + PlGF	36.4 (9.1–63.6)	1/28	63.6 (27.3–90.9)	1/57	81.8 (54.6–100)	1/95
MAP + UtA-PI	63.6 (27.3–90.9)	1/31	63.6 (27.3–90.9)	1/71	63.6 (27.3–90.9)	1/162
PAPP-A + PlGF	27.3 (0–54.6)	1/133	27.3 (0–54.5)	1/211	36.4 (9.1–63.6)	1/287
MAP + PAPP-A	36.4 (9.1–63.6)	1/24	54.5 (27.3–81.8)	1/47	54.5 (27.3–81.8)	1/82
UtA-PI + PAPP-A	54.5 (27.3–81.8)	1/107	54.5 (27.3–81.8)	1/210	54.5 (27.3–81.8)	1/302
MAP + UtA-PI + PAPP-A	63.6 (36.4–90.9)	1/36	63.6 (27.3–90.9)	1/91	72.7 (45.5–100)	1/192
MAP + UtA-PI + PlGF	54.5 (27.3–81.8)	1/37	81.8 (54.6–100)	1/115	90.9 (72.7–100)	1/226
MAP + PAPP-A + PlGF	36.4 (9.1–63.6)	1/29	54.5 (27.3–81.8)	1/61	72.7 (45.5–100)	1/102
UtA-PI + PlGF + PAPP-A	54.5 (27.3–81.8)	1/88	54.5 (27.3–81.8)	1/180	63.6 (27.3–90.9)	1/315
MAP + UtA-PI + PlGF + PAPP-A	54.5 (27.3–81.8)	1/38	81.8 (54.6–100)	1/118	90.9 (72.7–100)	1/258

(Table above continued for FPR 20%, 25%, and 30%)

A priori risk plus:	PE <34^{+0} (n=11)					
	DR % (95% CI) at 20% FPR	Cut-off for 20% FPR ≤	DR % (95% CI) at 25% FPR	Cut-off for 25% FPR ≤	DR % (95% CI) at 30% FPR	Cut-off for 30% FPR ≤
MAP	63.6 (27.3–90.9)	1/104	72.7 (45.5–100)	1/146	72.7 (45.5–100)	1/192
UtA-PI	54.5 (27.3–81.8)	1/341	63.6 (27.3–90.9)	1/473	72.7 (45.5–100)	1/642
PAPP-A	54.5 (27.3–81.8)	1/402	54.5 (27.3–81.8)	1/461	54.5 (27.3–81.8)	1/516
PlGF	45.5 (18.2–72.7)	1/324	63.6 (27.3–90.9)	1/401	72.7 (45.5–100)	1/476
PlGF + UtA-PI	81.8 (54.6–100)	1/451	81.8 (54.6–100)	1/704	81.8 (54.6–100)	1/1070
MAP + PlGF	81.8 (54.6–100)	1/161	81.8 (54.6–100)	1/230	90.9 (72.7–100)	1/314
MAP + UtA-PI	72.7 (45.5–100)	1/279	81.8 (54.6–100)	1/485	90.9 (72.7–100)	1/764

Study Reference	**Serra 2020 [Mendoza 2021a; Mendoza 2021b]**						
	PAPP-A + PlGF	36.4 (9.1–63.6)	1/361	45.5 (18.2–72.7)	1/453	63.6 (27.3–90.9)	1/542
	MAP + PAPP-A	72.7 (45.5–100)	1/130	72.7 (45.5–100)	1/195	72.7 (45.5–100)	1/284
	UtA-PI + PAPP-A	63.6 (27.3–90.9)	1/408	63.6 (27.3–90.9)	1/582	81.8 (54.6–100)	1/822
	MAP + UtA-PI + PAPP-A	72.7 (45.5–100)	1/350	90.9 (72.7–100)	1/620	100 (100–100)	1/1117
	MAP + UtA-PI + PlGF	100 (100–100)	1/445	100 (100–100)	1/810	100 (100–100)	1/1420
	MAP + PAPP-A + PlGF	72.7 (45.5–100)	1/165	81.8 (54.6–100)	1/249	90.9 (72.7–100)	1/355
	UtA-PI + PlGF + PAPP-A	72.7 (45.5–100)	1/476	81.8 (54.6–100)	1/718	81.8 (54.6–100)	1/1118
	MAP + UtA-PI + PlGF + PAPP-A	100 (100–100)	1/488	100 (100–100)	1/892	100 (100–100)	1/1625
Authors' Conclusions	The results of this prospective study support the effectiveness of a multivariate Gaussian distribution model combining maternal characteristics and history with biophysical (MAP and mean UtA-PI) and biochemical markers for the prediction of early-onset PE in a Mediterranean population, characterised by having a low a priori risk in a routine clinical care. With regard to the tested biochemical markers, (PlGF and PAPP-A), only the addition of PlGF improved the performance of the model. In conclusion, this model is a feasible tool for early-onset PE screening in the routine care setting, even in low risk populations. Performance of this model should be validated in different populations. **Mendoza 2021a:** This secondary analysis study provides evidence that the Gaussian and the FMF multimarker algorithms have a similar performance in predicting early-onset and preterm PE when PlGF and PAPP-A are measured before or after 11 weeks, allowing the use of a two-step risk assessment for PE. This approach allows immediate PE risk calculation at the time of the first-trimester scan. **Mendoza 2021b:** This secondary analysis study provides cut-off values that may serve as reference in clinical practice for a routine Gaussian first-trimester PE screening regardless of the approach used to measure UtA-PI, demographic characteristics of the population or the time biochemical markers were obtained (between 8^{+0} and 13^{+6} weeks).						

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; DR, detection rate; FGR, fetal growth restriction; FMF, fetal medicine foundation; FPR, false positive rate; IQR, interquartile range; LR, likelihood ratio; MAP, mean arterial pressure; MoM, multiples of the median; NLR, negative likelihood ratio; NPV, negative predictive value; NR, not recorded; PAPP-A, pregnancy-associated plasma protein-A; PE, pre-eclampsia; PLR, positive likelihood ratio; PlGF, placental growth factor; PPV, positive predictive value; UtA-PI, uterine artery pulsatility index.

Table 25af: Skrastad 2015

Study Reference	Skrastad 2015
Study Design	Design Prospective cohort study Objective To evaluate and compare 2 risk calculation algorithms for prediction of pre-eclampsia (PE) at 11–13^{+6} weeks gestational age in a population of nulliparous women in Norway. Dates September 2010 to March 2012 Country Norway Setting National Centre for Fetal Medicine, Trondheim
Population Characteristics	Patient recruitment and eligibility Norwegian women are offered one routine ultrasound free of charge at around 18 weeks of gestation; a letter with information about the study was sent to women referred to routine ultrasound at the study hospital department, and the study was also advertised through the Internet at the hospital homepage and via Google AdWords. Both nulliparous women (no previous pregnancies at or after 22 weeks gestation) and high-risk parous women (with one or more previous preeclamptic pregnancies) were recruited to the study, however the article deals with nulliparous women only. Exclusion criteria: Women using any anticoagulant medication or acetylsalicylic acid in pregnancy. Participants received oral and written information before they gave their written consent. Delayed miscarriages, multiple pregnancies or suspected congenital anomalies were also excluded. Data collection Participants attended a study visit between gestational weeks 11^{+0} and 13^{+6} and were interviewed about chronic disease, medication, ethnic origin, method of conception (any kind of assisted reproduction), family history of PE, smoking status and current height. Data on pregnancy outcomes were collected from hospital records. A total of 33 women gave birth at another hospital, and information about outcome of pregnancy and labour was obtained from the respective hospital's records. Duration of follow-up NR, assumed until delivery Prevalence of PE in the study 21 women (3.9%) developed PE. Delivery <34 weeks (n=1), delivery between 34 and 37 weeks (n=4), delivery between 37 and 42 weeks (n=15), delivery >42 weeks (n=1). Sample size N screened/invited = 585 N eligible = NR N enrolled = 560

Study Reference	**Skrastad 2015**

N excluded (with reason) = 19 (pregnancy terminated at 19 weeks due to a central nervous system [CNS] anomaly [n=1], miscarriage [n=1], impossible to draw blood or calculate multiple of the median [MoM] values for pregnancy-associated plasma protein-A [PAPP-A] and placental growth factor [PlGF] [n=17]).
N lost to follow-up = 0
N completed = 541
N excluded from analysis = 0
N included in analysis = 541

Demographics

Characteristic	Cases of PE (n=21)	Controls (n=520)	P-value
Mean maternal age, years (SD)	25.2 (4.8)	27.4 (3.9)	0.02
Mean body mass index (BMI), kg/m^2 (SD)	25.4 (5.2)	24.4 (4.4)	0.3
Smoking in pregnancy, n (%)	4 (19)	57 (11)	0.3
Ethnicity/Race, n (%)			
European, Middle Eastern or North African	21 (100)	511 (98.3)	1.0
South Asian (Indian, Pakistani, from Bangladesh)	0 (0)	1 (0.2)	
East Asian (Chinese, Korean, Japanese)	0 (0)	3 (0.6)	1.0
African or African American	0 (0)	0 (0)	1.0
Hispanic	0 (0)	1 (0.2)	1.0
Any mixed ethnicity	0 (0)	4 (0.8)	1.0
Chronic hypertension, n (%)	0 (0)	1 (0.2)	1.0
Family history of women with PE, n (%)	1 (4.8)	36 (6.5)	1.0

Screening Method

Index test
Blood pressure was measured and mean arterial pressure (MAP) was calculated. Ultrasound examinations were performed. Crown-rump length (CRL) was used to estimate gestational age and this estimate was used in the calculation of MoM values and in the calculation of risk for PE. The uterine artery pulsatility index (UtA-PI) was measured with transabdominal ultrasound as recommended by Khalil and Nicolaides. The UtA-PI was measured 3times on each side, and the average of 3measurements was used. All scans were carried out by specialised trained midwifes who were certified by the Fetal Medicine Foundation (FMF). Venous blood was drawn in order to measure PlGF and PAPP-A. The samples were analysed using one kit lot of each assay over a total of 14 runs on 2 instruments.

FMF algorithm: Calculates risks based on maternal characteristics, and the MoM-values of the mean of left and right UtA-PI, mean MAP and PAPP-A and PlGF. The FMF risk estimates were calculated by a researcher at the Fetal Medicine Foundation with the 2.8 version of the FMF algorithm, blinded for the outcome of pregnancies. Fetal Medicine Foundation calculated their own MoM values based on medians from their own population and the PlGF and PAPP-A MoM values were adjusted for gestational age, maternal weight, ethnicity, smoking status and method of conception, and PlGF was also corrected for maternal age. The FMF algorithm also includes maternal risk factors such as diabetes mellitus, antiphospholipid syndrome and systematic lupus erythematosus, but no women in the study suffered from those conditions.

PREDICTOR algorithm: Calculates a ‘prior risk’ based on BMI, ethnicity, parity, family history of PE, chronic hypertension and MAP, and a ‘posterior risk’ based on prior risk and MoMs of MAP, UtA-PI, PlGF and PAPP-A. The algorithm uses the highest MAP value and the PI

Study Reference	Skrastad 2015
	value from the UtA with the lowest PI. The risk can only be calculated if UtA-PI is between 0.4 and 4.0. Statisticians at Perkin Elmer blinded for the outcome of pregnancies calculated risks with the PREDICTOR algorithm. An employee at Perkin Elmer blinded to the outcome of the pregnancies did the analysis and calculated the MoM values applied in PREDICTOR based on medians from their population. The PlGF and PAPP-A MoM values in PREDICTOR were adjusted for BMI, ethnicity and smoking status. Perkin Elmer was paid for doing the serum analyses and had no influence on study design or interpretation of results. Reference standard PE was defined as systolic blood pressure over 140 mmHg and/or diastolic blood pressure over 90 mmHg and proteinuria ≥0.3 g/24 hours measured more than once at 4 to 6-hour intervals occurring after gestational week 20. Preterm PE was defined as delivery before 37^{+0} weeks, whether or not labour was induced due to PE or started spontaneously in women with PE. Data on pregnancy outcomes were collected from hospital records. The first author reviewed all diagnoses and if there was any doubt about classification of a woman, the hospital record was also evaluated by the last author.
Test Accuracy	**Sensitivity of screening at 10% FPR (false-positive rate)**

Method of screening	Sensitivity, % (95% CI)	Positive predictive value (PPV), % (95% CI)	Negative predictive value (NPV), % (95% CI)	Positive likelihood ratio, % (95% CI)	Negative likelihood ratio, % (95% CI)
Prediction of preterm PE (n=5)					
FMF37 Screening Algorithm	80.0 (28.4 to 99.5)	6.8 (1.9 to 16.5)	99.8 (98.8 to 100)	7.8 (4.7 to 12.9)	0.2 (0.04 to 1.3)
Prediction of PE <42 weeks (n=20)					
FMF	40.0 (19.1 to 63.9)	12.1 (5.4 to 22.5)	97.5 (95.6 to 98.7)	3.6 (2.0 to 6.5)	0.7 (0.5 to 1.0)
PREDICTOR prior	15.0 (3.2 to 37.9)	5.6 (1.2 to 15.4)	96.5 (94.5 to 98)	1.5 (0.5 to 4.5)	0.9 (0.8 to 1.1)
PREDICTOR posterior	30.0 (11.9 to 54.3)	10.3 (3.9 to 21.2)	97.1 (95.2 to 98.4)	3.01 (1.5 to 6.2)	0.8 (0.6 to 1.04)
Prediction of PE ≥34 weeks (n=20)					
FMF	30.0 (11.9 to 54.3)	10.3 (3.9 to 21.2)	97.1 (95.2 to 98.4)	3.01 (1.5 to 6.2)	0.8 (0.6 to 1.04)
PREDICTOR prior	15.0 (3.2 to 37.9)	5.6 (1.2 to 15.4)	96.5 (94.5 to 98)	1.5 (0.5 to 4.5)	0.9 (0.8 to 1.2)
PREDICTOR posterior	30.0 (11.9 to 54.3)	10.3 (3.9 to 21.2)	97.1 (95.2 to 98.4)	3.01 (1.5 to 6.2)	0.8 (0.6 to 1.04)

Authors' Conclusions	This study shows that the FMF and PREDICTOR algorithms have similar and only modest performance in detecting PE. The results indicate that the FMF algorithm could be useful for predicting preterm PE in Scandinavian nulliparous women, but these results should be interpreted with caution. Due to the severity of the disease, well-tolerated screening procedures and promising results of prophylactic treatment, a first trimester screening for preterm PE combined with prophylaxis should be further evaluated in a sufficiently large randomised controlled trial.

Abbreviations: BMI, body mass index; CI, confidence interval; CNS, central nervous system; CRL, crown-rump length; FMF, Fetal Medicine Foundation; MAP, mean arterial pressure; MoM, multiple of the median; NPV, negative predictive value; NR, not reported; PAPP-A, pregnancy-associated plasma protein-A; PE, pre-eclampsia; PI, pulsatility index; PlGF, placental growth factor; PPV, positive predictive value; SD, standard deviation; UtA, uterine artery; UtA-PI, uterine artery pulsatility index.

Table 25ag: Sonek 2018

Study Reference	Sonek 2018
Study Design	Design Prospective cohort study Objective To evaluate the feasibility of screening for pre-eclampsia (PE) in the first trimester based on maternal characteristics, medical history, biomarkers, and placental volume. Dates 2013 to 2016 Country United States Setting One maternity centre (Maternal-Fetal Medicine, Ultrasound, and Genetics Center at Miami Valley Hospital) in Dayton, Ohio
Population Characteristics	Patient recruitment and eligibility Women referred to the study hospital for first-trimester combined screening at 11^{+0} to 13^{+6} weeks gestation were offered participation in the study. Upon agreeing to participate, participants signed an informed consent. The gestational age was confirmed by measuring the crown-rump length (CRL). Only those participants with CRL measurements of 45–84 mm were enrolled. Exclusion criteria: Women with multiple gestations, with fetal congenital anomalies, and those who delivered <20 weeks gestation. Data collection Each participant was weighed and historical data were obtained and recorded. Participant outcome data were obtained from electronic medical records in 896 women and from birth certificates in 172 women. Duration of follow-up NR (assumed to be until delivery) Prevalence of PE in the study 46 (4.31%) developed PE. Late-onset PE (≥34 weeks) was seen in 33 (3.09%) of women and 13 (1.22%) developed early-onset PE (<34 weeks). Sample size N screened/invited = 1,288 N eligible = 1,288 N enrolled = 1,288 N excluded (with reason) = 220 (lost to follow-up or incomplete data) N lost to follow-up = see 'N excluded' N completed = 1,068 N excluded from analysis = 0 N included in analysis = 1,068 Demographics

Characteristic	Value		p-value
	All PE (N=46)	No PE (N=1,022)	

Study Reference	**Sonek 2018**			
	Median maternal age, years (IQR)	29 (25 to 32.9)	27.7 (23.5 to 32.3)	0.33
	Median body mass index (BMI) (IQR)	35.3 (25.5 to 40.0)	27.2 (23.5 to 32.3)	<0.001
	Ethnicity, n (%)			0.51
	Caucasian	28 (61)	679 (66)	-
	African American	16 (35)	276 (27)	-
	Other	2 (4)	67 (7)	-
	Chronic hypertension, n (%)	17 (37)	88 (9)	<0.001
	Insulin-dependent diabetes mellitus, n (%)	5 (11)	36 (4)	0.03
	Smoker, n (%)	4 (9)	154 (15)	0.29
	Nulliparous, n (%)	19 (41)	356 (35)	0.43
	Parous (with a history of PE), n (%)	16 (35)	78 (8)	<0.001
	Parous (with no history of PE), n (%)	11 (24)	588 (58)	<0.001
	Family history of PE, n (%)	7 (15)	83 (8)	0.1
	Conception, n (%)			0.99
	Spontaneous	45 (98)	986 (96)	-
	Ovulation drugs	1 (2)	21 (2)	-
	Intrauterine insemination (IUI)/in vitro fertilization (IVF)/egg donor	0 (0)	15 (1)	-
	Median gestational age at draw, days (IQR)	88 (85 to 90)	88 (85 to 90)	0.79

Screening Method

Index test

- Single test or combination test of maternal characteristics
- Maternal biomarkers (pregnancy-associated plasma protein-A [PAPP-A], placental growth factor [PlGF], maternal serum alpha-fetoprotein [MSAFP])
- Uterine artery pulsatility index (UtA-PI)
- Mean arterial pressure (MAP)
- Estimated placental volume (EPV)

Ultrasound measurements included transabdominal Doppler measurement of the UtA-PI (done in accordance with the Fetal Medicine Foundation [FMF] protocol) and EPV. UtA-PI was measured in both the left and right uterine artery (UtA), and all sonographers had a current FMF accreditation for this procedure. Each Doppler measurement was reviewed for compliance with the FMF criteria by one of the authors after the completion of the study, and each EPV measurement was reviewed for compliance with established criteria by one of the authors, who was unaware of the pregnancy outcome, after the completion of the study. Maternal blood pressure was obtained using an automated device with the participant in a seated position. Serum specimens were analysed for PAPP-A, PlGF and MSAFP.

Multiples of the median (MoM) were determined (adjusted for independent predictors). Using a methodology similar to that of aneuploidy screening, log-Gaussian distributions for early onset PE (<34 weeks gestation) and unaffected pregnancies were developed based on the adjusted MoM values. A likelihood ratio was calculated and posterior risk was determined by multiplying the likelihood ratio by the a priori risk. A priori risk of PE <34 weeks was determined based on a previous study (Wright et al). The detection rate for PE specimens >34 weeks was based on the incidental detection using their risk of PE <34 weeks.

Study Reference	**Sonek 2018**
	Reference standard The diagnosis of PE was made based on American Congress of Obstetricians and Gynecologists (ACOG) criteria. It was defined by the onset of hypertension (blood pressure >140/90 mm Hg) and proteinuria (≥0.3 g of protein in the urine within a 24-hour period) during the second half of pregnancy (>20 weeks). In the absence of proteinuria, the diagnosis of PE was made based on hypertension with any of the following: thrombocytopenia, impaired liver function, renal insufficiency, pulmonary oedema, or cerebral or visual disturbances. Outcome data were gathered using either electronic medical records or through birth certificates. Early-PE was defined as PE <34 weeks, and late-onset PE was defined as PE ≥34 weeks.
Test Accuracy	Sensitivity of screening for PE at <34, ≥34, <37 and ≥37 weeks and for all PE at a 5% false positive rate (FPR)

Method of screening	Sensitivity, % (95% CI)				
	<34 weeks (n=13)	≥34 weeks (n=33)	<37 weeks (n=25)	≥37 weeks (n=21)	All PE (n=46)
Maternal characteristics	54	15	28	24	26
Maternal characteristics + biochemical markers (PlGF, PAPP-A, AFP)	69	15	48	10	30
Maternal characteristics + biochemical markers (PlGF, PAPP-A, AFP) + UtA-PI	85	15	52	14	35
Maternal characteristics + biochemical markers (PlGF, PAPP-A, AFP) + MAP	69	15	48	10	30
Maternal characteristics + biochemical markers (PlGF, PAPP-A, AFP) + MAP + UtA-PI	85	18	56	14	37
Maternal characteristics + biochemical markers (PlGF, PAPP-A, AFP) + MAP + UtA-PI + EPV	85	18	56	14	37

Sensitivity of screening for PE at <34, ≥34, <37 and ≥37 weeks and for all PE at a 10% FPR

Method of screening	Sensitivity, % (95% CI)				
	<34 weeks (n=13)	≥34 weeks (n=33)	<37 weeks (n=25)	≥37 weeks (n=21)	All PE (n=46)
Maternal characteristics	62	48	60	43	52
Maternal biochemical markers (PlGF, PAPP-A, AFP)	85	24	60	19	41
Maternal biochemical markers + UtA-PI	85	27	60	24	43
Maternal biochemical markers + MAP	77	24	60	14	39
Maternal biochemical markers + MAP + UtA-PI	85	24	64	14	41
Maternal biochemical markers + MAP + UtA-PI + EPV	85	36	68	29	50

Authors' Conclusions	Screening for PE at 11–13 weeks gestation using maternal characteristics and biomarkers is associated with a high sensitivity for a low FPR. Using maternal characteristics, serum biomarkers, and uterine artery pulsatility index, the detection rate of early-onset PE for either 5% or 10% false-positive rate was 85%. Screening for late-onset PE yields a much poorer performance; based on maternal characteristics, the sensitivities for late-onset PE were 15% and 48% for 5% and 10%. These sensitivities for late-onset PE were not improved by the

Study Reference	Sonek 2018
	addition of biomarkers. In this study, the utility of EPV and MAP was limited but larger studies are needed to ultimately determine the effectiveness of these markers.

Abbreviations: ACOG, American Congress of Obstetricians and Gynecologists; BMI, body mass index; CRL, crown-rump length; EPV, estimated placental volume; FMF, Fetal Medicine Foundation; FPR, false-positive rate; IQR, interquartile range; IUI, intrauterine insemination; IVF, in vitro fertilisation; MAP, mean arterial pressure; MoM, multiple of the median; MSAFP, maternal serum alpha-fetoprotein; NR, not reported; PAPP-A, pregnancy-associated plasma protein-A; PE, pre-eclampsia; PlGF, placental growth factor; UtA-PI, uterine artery pulsatility index.

Table 25ah: Takahashi 2012

Study Reference	Takahashi 2012
Study Design	Design Prospective cohort study Objective To determine the reference values of indices of impedance to flow in uterine arteries at 16–23 weeks, and to evaluate the effects of these indices for predicting early-onset pre-eclampsia (PE), which was defined as PE with onset at <32 weeks. Dates April 2004 to October 2008 Country Japan Setting Single-centre
Population Characteristics	Patient recruitment and eligibility Pregnant women with a singleton pregnancy who sought an antepartum maternal check-up before 24 weeks gestation. Inclusion and exclusion criteria not specified. Data collection • Planned prediction model of PE using maternal characteristics, blood pressure levels, uterine artery flow velocity waveforms (measured once or twice at 16–23 weeks) and blood markers • Colour-pulsed Doppler ultrasound examinations to measure waveforms: mean pulsatility index (mPI), mean notch depth index (mNDI), mean resistance index (mRI), calculated for both uterine arteries (averaged values in 2 consecutive waveforms) Duration of follow-up Assumed until delivery, based on outcomes (until 12th week postpartum, based on definition of PE) Prevalence of PE in the study PE developed in 47 pregnancies, 16 (1.0% of the total population) of which 16 were early PE (defined as delivery <32 weeks) Sample size N screened/invited = 1,724 N eligible = NR

Study Reference **Takahashi 2012**

N enrolled = 1,536
N excluded (with reason) = 188 (uterine artery indices measured at <16 or ≥24 weeks gestation [n=70], delivered at another hospital and details of clinical outcome were not available [n=118])
N lost to follow-up = NR
N completed = NR
N excluded from analysis = NR, but women with previous history of PE or gestational hypertension (GH) were excluded from the model construction
N included in analysis = 1,266

Demographics
Maternal variables, medical history and characteristics presented separately for early PE, GH, late PE and normotensive pregnancy.

Variable	Normal pregnant women (Group A) N=1,266	Women with PE (Group B) N=47	Women with early-onset PE (Group C) N=16	Numbers of missing values	P-value (Group A vs. Group B)	P-value (Group A vs. Group C)
Age, years (mean ± SD)	32.7 ± 5.1	33.7 ± 5.6	35.6 ± 3.4	–	NS	0.025
Nulliparous women, n (%)	615 (49)	27 (57)	12 (75)	–	NS	0.044
Multiparous women without past history of PE/GH, n (%)	651 (51)	11 (23)	2 (13)	–	–	–
Women with family history of PE/GH, n (%)	0 (0)	9 (19)	2 (13)	–	–	–
Women with family history of hypertension, n (%)	322 (26)	22 (47)	11 (69)	Group A: 4	0.002	<0.001
Current smoker, n (%)	63 (5.3)	4 (8.7)	1 (6.7)	Group A: 70 Group B: 1	NS	NS
Pre-pregnancy body mass index (BMI), kg/m^2 (mean ± SD)	22.2 ± 4.2	24.6 ± 5.7	24.6 ± 6.4	Group A: 2	0.005	0.022
Obesity, n (%)	230 (18)	18 (38)	7 (44)	Group A: 2	0.002	0.017
Chronic hypertension (%)	13 (1.0)	12 (26)	6 (38)	–	<0.001	<0.001
Systolic blood pressure (SBP) at 16–23 weeks gestation, mmHg (mean ± SD)	116 ± 13	134 ± 18	136 ± 14	Group A: 3 Group B: 1	<0.001	<0.001
Diastolic blood pressure (DBP) at 16–23 weeks gestation, mmHg (mean ± SD)	67 ± 9	81 ± 12	83 ± 11	Group A: 3 Group B: 1	<0.001	<0.001
Gestational age at delivery, weeks gestation (mean ± SD)	38.8 ± 2.2	35.7 ± 4.6	31.0 ± 4.6	–	<0.001	<0.001
Birthweight, g (mean ± SD)	3,003 ± 442	2,245 ± 901	1,259 ± 578	–	<0.001	<0.001
Small for gestational age (SGA), n (%)	0 (0)	18 (38)	10 (63)	–	–	–
Onset of PE, weeks gestation (mean ± SD)	–	33.7 ± 5.2	27.6 ± 3.8	–	–	–

– p values were not calculated

Study Reference **Takahashi 2012**

Screening Method

Index test

Indices of impedance to flow in uterine arteries:

- mNDI
- mPI
- mRI

Study planned to make a prediction model of PE using maternal characteristics, blood pressure levels, uterine artery flow velocity waveforms* and blood markers.

*Measured once or twice at 16–23 weeks

Construction of predictive model

- Calculated standard deviation scores (SDS) of log10mPI and log10mRI
- Fitted curve estimation performed using SPSS software (area under the receiver operation characteristics curve [AROC] and 95% confidence intervals [CIs] also calculated using SPSS)
- mNDI were classified into 5 classes: <80th, 80–89th, 90–94th, 95–97.4th, ≥97.5th centiles (by estimating the 'fittest' lines or curves through the points at each week using SPSS curve estimation function)
- Values of mPI and mRI converted to mPI-SDS and mRI-SDS (in which effects of gestational age were adjusted) using statistical distributions
- Optimal cut-off values of mNDI, mPI and mRI for predicting early-onset PE were sought:
  - Numbers of true positive, false positive, false negative and true negative results for all PE and early-onset PE were counted

Reference standard

PE and GH defined according to definition and classification of pregnancy-induced hypertension (PIH) (2004) of the Japan Society for the Study of Hypertension in Pregnancy

- PE: hypertension with proteinuria occurring after the 20th week of gestation but resolving by the 12th week postpartum
  - Hypertension: SBP ≥140 mmHg and/or DBP ≥90 mmHg on 2 occasions at least 4 hours apart
  - Proteinuria: ≥300 mg/day from 24 hour urine collection or (if only available test was test tape or dipstick), results of ≥1+ protein on 2 occasions at least one day apart
- Early-onset PE: PE with onset at <32 weeks gestation
- Late-onset PE: PE with onset at ≥32 weeks gestation
- Severe PE: SBP ≥160 mmHg, DBP ≥110 mmHg, or proteinuria ≥2 g/day or semi-quantitative (tape or dipstick) result of 3+

Test Accuracy

Prediction of all PE and early-onset PE using best cut-off values for mNDI, mPI, mRI and bilateral notching (BN)[a]

Cut-off value		True positive	False positive	False negative	True negative	Sensitivity	Specificity	PPV	NPV	Positive LR (95% CI)	Negative LR (95% CI)
All PE											
mNDI	90th percentile	23	24	162	1,327	0.124	0.982	0.489	0.891	4.5 (3.2–6.2)	0.57 (0.43–0.76)
mPI-SDS	SDS = 1.38	22	25	158	1,331	0.122	0.982	0.468	0.894	4.4 (3.1–6.2)	0.60 (0.46–0.78)
mRI-SDS	SDS = 0.98	23	24	280	1,209	0.076	0.981	0.489	0.812	2.6 (1.9–3.6)	0.63 (0.48–0.83)
BN	Positive	23	24	224	1,265	0.093	0.981	0.498	0.850	3.3 (2.4–4.5)	0.60 (0.45–0.80)
Early-onset PE											

Study Reference	Takahashi 2012											
	mNDI	90th percentile	11	5	174	1,346	0.059	0.996	0.688	0.886	6.0 (4.2–8.6)	0.35 (0.17–0.73)
	mPI-SDS	SDS = 1.38	12	4	168	1,352	0.067	0.997	0.750	0.889	6.8 (4.9–9.3)	0.28 (0.12–0.66)
	mRI-SDS	SDS = 0.98	13	3	290	1,230	0.043	0.998	0.813	0.809	4.3 (3.3–5.5)	0.23 (0.08–0.64)
	BN	Positive	12	4	235	1,285	0.049	0.997	0.750	0.845	4.9 (3.6–6.6)	0.30 (0.13–0.69)

Authors' Conclusions	The positive LRs for predicting early-onset PE using mNDI or mPI-SDS were superior to those using mRI-SDS or BN, indicating the usefulness of mNDI and mPI for predicting early-onset PE. For the occurrence of early-onset PE, the incidence of early-onset PE in women with only high mNDI was significantly higher than in those with both a low mNDI and a low mPI, and the incidence of early-onset PE in women with both a high mNDI and a high mPI was the highest among 4 groups, suggesting the importance of the mNDI on the occurrence of early-onset PE. The LR+ of the mNDI and mPI for predicting early-onset PE showed moderate screening performances, indicating that establishment of the mNDI or mPI in the second trimester could assist in identifying high-risk women with the subsequent onset of early-onset PE. Finally, the mNDI and mPI showed synergic effects on the occurrence of all PE, early-onset PE, GH and SGA infants, indicating the importance of evaluating not only the mPI, but also the mNDI for predicting pregnancy diseases related to placental dysfunction.

[a] Authors of this review believe that the values reported in the publication for sensitivity and PPV were switched; the authors believe that the way the values are presented here is correct

Abbreviations: AROC, area under receiver operating curve; BMI, body mass index; BN, bilateral notching; DBP, diastolic blood pressure; GH, gestational hypertension, LR, likelihood ratio; mNDI, mean notch depth index; mPI, mean pulsatility index; mRI, mean resistance index; NR, not reported; NS, not significant; PE, pre-eclampsia; PIH, pregnancy-induced hypertension; SBP, systolic blood pressure; SD, standard deviation; SDS, standard deviation score; SGA, small for gestational age.

Table 25ai: Tsiakkas 2016b

Study Reference	Tsiakkas 2016b (the study population in this cohort likely overlaps with those included in Tan 2018c [London Cohorts])
Study Design	Design Prospective cohort study Objective To examine the distribution of maternal serum placental growth factor (PlGF) at 12, 22, 32 and 36 weeks gestation in singleton pregnancies which develop pre-eclampsia (PE) and examine the performance of this biomarker in screening for PE. Dates November 2011 to December 2014 Country UK

Study Reference	**Tsiakkas 2016b (the study population in this cohort likely overlaps with those included in Tan 2018c [London Cohorts])**

Population Characteristics

Setting
King's College Hospital, University College London Hospital and Medway Maritime Hospital.

Patient recruitment and eligibility
Singleton pregnancies delivering a phenotypically normal live birth or stillbirth at ≥24 weeks gestation were included. Excluded: Pregnancies with aneuploidies or major fetal abnormalities, and those ending in termination, miscarriage or fetal death before 24 weeks.

Data collection

Maternal characteristics and medical history were recorded. Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to determine the diagnosis of PE. Maternal serum soluble fms-like tyrosine kinase-1 (sFlt-1) was measured at the 11–13 weeks visit.

Bayes' theorem was used to combine the a-priori risk from maternal characteristics and medical history with serum levels of sFlt-1. Patient-specific risks of delivery with PE were calculated using the competing-risks model to combine the prior distribution of gestational age at delivery with PE, obtained from maternal characteristics and medical history, with multiple of the median (MoM) values of sFlt-1.

Duration of follow-up
Until delivery (assumed based on outcomes reported)

Prevalence of PE in the study

PE developed in 157/7,066 pregnancies who were screened at 11 to 13 weeks gestation.

Sample size
N screened/invited = NR
N eligible = NR
N enrolled = NR
N excluded (with reason) = NR
N lost to follow-up = NR
N completed = NR
N excluded from analysis = NR
N included in analysis = 7,066

Demographics (11–13 weeks)

Characteristic	No PE (N=6,909)	PE (N=157)
Median maternal age, years (IQR)	31.0 (26.4–34.7)	31.3 (26.7–34.8)
Median gestational age at screening, weeks (IQR):	12.7 (12.3–13.1)	12.6 (12.3–13.1)
Median weight, kg (IQR)	67.8 (59.6–78.0)	71.0 (63.0–86.9)*
Median height, cm (IQR)	165 (160–169)	164 (160–168)
BMI (kg/m2)	24.8 (22.1–28.8)	26.5 (23.3–32.1)*
Racial origin, n (%)		
Caucasian	5,161 (74.7)	86 (54.8)
Afro-Caribbean	1,181 (17.1)	63 (40.1)
South Asian	286 (4.1)	6 (3.8)

Study Reference	**Tsiakkas 2016b (the study population in this cohort likely overlaps with those included in Tan 2018c [London Cohorts])**

East Asian	121 (1.8)	1 (0.6)
Mixed	160 (2.3)	1 (0.6)
Cigarette smoker, n (%)	686 (9.9)	11 (7.0)
Family history of PE, n (%)	204 (3.0)	10 (6.4)**
Medical history, n (%)		
Chronic hypertension	80 (1.2)	21 (13.4)*
SLE/APS	9 (0.1)	0 (0)
Diabetes mellitus	63 (0.9)	5 (3.2)*
Obstetric history, n (%)		
Nulliparous	3,154 (45.7)	87 (55.4)
Parous without previous PE	3,500 (50.7)	46 (29.3)
Parous with previous PE	255 (3.7)	24 (15.3)
Median interval from last pregnancy, years (IQR)	3.0 (2.0–5.0)	4.1 (2.3–7.2)*

*p<0.05

Screening Method

Index test

- Maternal factors (MF)
- sFlt-1

Of the participants included in the study, maternal serum sFlt-1 was measured at each visit by an automated biochemical analyser within 10 minutes of blood sampling.

Computed risks model: A dataset of 123,406 singleton pregnancies, including 2,748 (2.2%) with PE, which were previously used to develop a model for PE based on maternal demographic characteristics and medical history was obtained. For each of the records, sFlt-1 MoM values were simulated from the fitted multivariate Gaussian distribution for log10 transformed MoM values. Risks were obtained using the competing-risks model from the simulated MoM values and pregnancy characteristics. These 3steps were applied to pregnancies within the normal group with no restriction on the time of delivery. For a given false-positive rate, risks from the normal group were used to define a risk cut-off. The proportion of PE risks was then used to obtain an estimate of the associated detection rate. The area under the receiver–operating characteristics curve (AUC) was also calculated.

Reference standard

Hypertension (systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg on at least 2 occasions 4 h apart, developing after 20 weeks gestation in previously normotensive women) and at least one of the following: proteinuria (≥300 mg/24h or protein to creatinine ratio ≥30 mg/mmol or ≥2+ on dipstick testing), renal insufficiency (serum creatinine >1.1 mg/dL or two-fold increase in serum creatinine in the absence of underlying renal disease), liver involvement (blood concentration of transaminases to twice the normal level), neurological complications (e.g. cerebral or visual symptoms), thrombocytopenia (platelet count <100 000/μL), or pulmonary oedema.

Test Accuracy	**Empirical and model-based sensitivity of PE by screening with MF and a combination of MF and serum sFlt-1 at 11–13 weeks gestation**

Study Reference	**Tsiakkas 2016b (the study population in this cohort likely overlaps with those included in Tan 2018c [London Cohorts])**

Method of screening	Sensitivity of PE							
	PE<32 weeks		PE 32^{+0} to 36^{+6} weeks		PE<37 weeks		PE≥37 weeks	
	Empirical (95% CI) (%) (n/N)	Model (%)	Empirical (95% CI) (%) (n/N)	Model (%)	Empirical (95% CI) (%) (n/N)	Model (%)	Empirical (95% CI) (%) (n/N)	Model (%)
MF								
5% FPR	40 (12–74) 4/10	41	35 (21–52) 14/40	31	36 (23–51) 18/50	34	26 (18–36) 28/107	26
10% FPR	60 (26–88) 6/10	52	53 (36–68) 21/40	45	54 (39–68) 27/50	47	35 (26–44) 37/107	37
Combination of MF + serum sFlt-1 at 11 to 13 weeks gestation								
5% FPR	40 (12–74) 4/10	41	35 (21–52) 14/40	31	36 (23–51) 18/50	34	26 (18–36) 28/107	27
10% FPR	60 (26–88) 6/10	52	53 (36–68) 21/40	44	54 (39–68) 27/50	46	35 (26–44) 37/107	37

Authors' Conclusions	Measurement of sFlt-1 at 11–13 weeks did not improve the prediction of PE achieved by maternal factors alone.

Abbreviations: AUC, area under the curve; CI, confidence interval; FPR, false positive rate; IQR, interquartile range; MF, maternal factors; MoM, multiple of the median; NR, not reported; PE, pre-eclampsia; sFlt-1, soluble fms-like tyrosine kinase-1.

Table 25aj: Youssef 2011

Study Reference	**Youssef 2011**
Study Design	Design Prospective cohort study Objective To evaluate the screening accuracy of late PE by some maternal characteristics, the highest UtA pulsatility index (hUtA PI) and a combination of biochemical markers, namely pregnancy-associated plasma protein A (PAPP-A), placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1), P-selectin and neutrophil gelatinase-associated lipocalin (NGAL). Dates September 2009 to June 2010 Country Italy (inferred based on author affiliations) Setting A tertiary level centre
Population Characteristics	Patient recruitment and eligibility Pregnant women at the time of screening for Down syndrome at 11 to 13^{+6} weeks of gestation who decided to deliver in the centre with a complete follow-up were enrolled. As thecentre was a tertiary-level centre, complicated pregnancies, including those affected by PE were more common, creating possible bias in the selection process. Exclusion criteria: multiple gestations, pregnancies with

Study Reference	Youssef 2011

fetal chromosomal or major structural anomaly, gestational age as determined by CRL outside the inclusion criteria and miscarriage before 20 weeks. Cases of early PE were also excluded.

Data collection
Maternal characteristics, detailed medical and obstetrical history, and family history of hypertension were recorded. An ultrasound examination was carried out for diagnosis of major fetal defects, measurement of NT and CRL, used to determine gestational age. At the same visit, both uterine arteries were examined; the uterine artery PI was measured and hUtA PI of the left and right arteries was determined and used. A blood sample was taken from each woman; maternal serum PAPP-A, PIGF, P-selectin and NGAL were measured.

Duration of follow-up
Until delivery (assumed based on outcomes reported)

Prevalence of PE in the study
The rate of late PE was 13 (2.5%). 4 (30.8%) of these had severe PE.

Sample size
N screened/invited = around 630
N eligible = 528
N enrolled = 528
N excluded (with reason) = NR
N lost to follow-up = NR
N completed = 528
N excluded from analysis = 0
N included in analysis = 528

Demographics

Characteristic	PE Cases (n=13)	Controls (n=515)	p value
Gestation at recruitment (days)	88±5.2	88±4.5	0.732
Maternal age (years)	30±3.5	31±3.9	0.493
BMI	25.4±3.1	22.3±2.4	0.143
Neonatal weight (g)	2131±408	3219±303	<0.001
% of nulliparae	84.6	55.3	0.042
% smoking	7.7	7.7	1.000
Previous hypertension (%)	15.4	11.6	0.500
Family history for hypertension (%)	7.7	1.94	0.642
hUtA PI MoM	1.26±0.61	1.00±0.34	0.023
PAPP-A MoM	0.84±0.38	1.00±0.56	0.082
PlGF MoM	0.85±0.43	1.00±0.30	0.026
sFlt-1 MoM	2.52±0.79	1.00±0.60	0.035
P-selectin MoM	1.68±1.25	1.00±0.46	<0.001
NGAL MoM	1.39±0.57	1.00±0.27	<0.001

Continuous variables are presented as mean ± SD.

Study Reference	Youssef 2011
Screening Method	Index test The DR and FPR were calculated for each available marker using a univariable ROC curve. Logistic regression was used to calculate the a posterior risk for each patient to determine classification as a control or PE case by using the panel of available markers expressed in MoM and parity as predictors of the disease. Each available marker included hUtAPI, PAPP-A, sFlt-1, endoglin, PlGF and NGAL. Reference standard PE was defined as gestational hypertension (defined as systolic blood pressure of at least 140 mm Hg and/or a diastolic bloody pressure of at least 90 mm Hg on at least 2 occasions at least 6 hours apart after the 20th week of gestation in women known to be normotensive before pregnancy and before 20 weeks gestation) plus proteinuria (300 mg or more per 24 hour period). If 24 hour urine collection was not available then proteinuria was defined as a concentration of at least 30 mg/dL (at least 1+ on a dipstick) in at least 2 random urine samples collected at least 6 hours apart. Late onset PE was defined as PE diagnosed at or after 34 weeks and severe PE was defined as described as Tuffnell et al. in 2006.
Test Accuracy	A combined model including PlGF, NGAL and sFlt1 yielded a DR of 77% at 10% FPR. It was decided just to use the 3variables with the highest DR because of the relatively small number of affected cases in the series of data. The corresponding cut-off risk was 4.3%. This result is significant and can potentially aid patient counselling with regard to early screening for PE.
Authors' Conclusions	This model for late PE prediction yielded a sufficient DR to allow prospective extensive use of the parameters considered. Only biochemical variables have been used in building up the model. The risk estimation for the control group is in line with the expected values for the general population, while the risks quotes for PE cases correlate with the severity. Both these estimations assign a reliable value to the results obtained.

Variable	DR at 10% FPR	p value
hUtA PI MoM	30.8	0.256
PAPP-A MoM	15.4	0.163
PlGF MoM	61.5	0.012
sFlt-1 MoM	30.8	0.002
P-selectin MoM	30.8	0.052
NGAL MoM	38.5	0.001
PlGF+sFlt-1+NGAL	77.0	<0.001

Abbreviations: BMI, body mass index; CRL, crown-rump length; DR, detection rate; FPR, false positive rate; hUtA, highest UtA; MoM, multiple of the median; NGAL, neutrophil gelatinase-associated lipochalin; NT, nuchal translucency thickness; PAPP-A, pregnancy associated plasma protein A; PE, pre-eclampsia; PI, pulsatility index; PlGF, placental growth factor; ROC, receiver operating characteristic; sFlt-1, soluble fms-like tyrosine kinase-1.

Table 25ak: Yucel 2016

Study Reference	Yucel 2016
Study Design	Design Prospective cohort study Objective To evaluate the detection of PE by integrating uterine artery Doppler, placental volume and PAPP-A level in the first trimester. Dates NR Country

Study Reference	Yucel 2016
	Turkey (inferred from author affiliations) Setting Gynaecologic and Prenatal Diagnosis Unit of a third level reference hospital
Population Characteristics	Patient recruitment and eligibility Women with singleton pregnancies between 11 and 14 weeks gestation attending for first-trimester aneuploidy screening of the routine antenatal care were invited to participate in the study. Participants were recruited consecutively. Exclusion criteria were late miscarriages (miscarriages between 14 and 24 weeks of pregnancy) and major fetal abnormalities (such as aneuploidy and multiple congenital abnormality syndromes) Data collection Maternal history was recorded (women were asked to provide information on age, weight and height, previous pregnancies, history of chronic hypertension, diabetes, previous pregnancy with PE, and cigarette smoking during pregnancy. Last menstrual period was used to calculate gestational age and it was confirmed by crown-rump length measurement. Doppler ultrasound scan of uterine arteries, volumetry of placenta were performed and blood samples were collected. The PI was calculated; the average PI of the left and the right uterine arteries were recorded. The placenta was examined. The placental volume was calculated. Each patient provided a blood sample for first trimester screening. Concentrations of PAPP-A were transformed as MoM. Duration of follow-up To delivery Prevalence of PE in the study 41 women (8.37%) Sample size N screened/invited = 602 N eligible = 602 N enrolled = 543 N excluded (with reason) = miscarriage (n = 13), aneuploidy or congenital abnormality (n = 5) N lost to follow-up = 35 N completed = 490 N excluded from analysis = 0 N included in analysis = 490 Demographics

Characteristic	Preeclampsia group (n=41)	Control group (non-affected) (n=449)	p value
Age, years, median (range)	28 (18–42)	28 (18–45)	0.819
BMI, kg/m^2, median (range)	23.24 (17.78–38.2)	23.83 (17.07–42.15)	0.989
Number of parity, median (range)	1 (0–5)	1 (1–7)	0.472
Nulliparous, n (%)	15 (36.59)	97 (21.6)	0.034
Smokers, n (%)	9 (21.95)	62 (13.81)	0.16
History of preeclampsia, n (%)	5 (12.2)	13 (2.9)	0.012
PAPP-A, MoM, median (range)	0.26 (0.06–1.47)	0.75 (0.22–3.42)	<000.1
Placental volume, ml, median (range)	34 (16.40–74.63)	62 (15–131)	<000.1
Uterine artery PI, median (range)	2.74 (0.8–5.12)	1.24 (0.02–6.39)	<000.1
Delivery week, median (range)	36 (28–38)	38 (28–41)	<000.1

Study Reference	**Yucel 2016**			
	Fetal weight, grams, median (range)	2400 (740–3700)	3110 (1080–4720)	<000.1
Screening Method	Index test Demographic characteristics, ultrasound findings and the results of biochemical testing were entered into a computerised database. Patients' individual medical records at delivery were reviewed to obtain the data on pregnancy outcomes. The 10th and 90th percentiles of uterine artery mean PI, placental volume and PAPP-A levels were calculated. These cut offs were used for prediction of PE. Specificity, sensitivity, NPV and PPV results for each measurement were examined to the diagnostic test performances. These were calculated for PE screening characteristics of uterine artery PI >90th centile, placental volume <10th centile and MoM of PAPP-A levels <10th centile used alone or in combination. Reference standard The American College of Obstetricians and Gynaecologists definition was used for the diagnosis of PE: hypertension, defined as a BP >140/90 mmHg, measured on 2 separate occasions, >6 hours apart developing after 20 weeks of gestation in a pregnancy with previously normal BP and co-existing significant proteinuria, defined as >0.3 grams in a 24-hour urine specimen.			
Test Accuracy	An abnormal PI in uterine arteries or PAPP-A levels had similar sensitivities and specificities in predicting PE but the sensitivities and specificities for placental volume below the 10th centile was lower for predicting PE. The higher sensitivity values were reached when uterine arteries PI, placental volume and PAPP-A levels were used in combination considering the result of the test positive such as at least one or two of the parameters was abnormal.			
		Sensitivity	Specificity	PPV	NPV
	Uterine PI >90th centile	70.73% (54.46–83.87%)	95.32% (92.94–97.08%)	58.00% (43.21–71.81%)	97.27% (95.28–98.58%)
	Placental volume <10th centile	53.66% (37.42–69.34%)	93.99% (91.37–96.00%)	44.90% (30.67–59.77%)	95.69% (93.35–97.39%)
	PAPP-A measurement <10th centile	63.41% (46.94–77.88%)	94.88% (92.41–96.73%)	53.06% (38.27%–67.47%)	96.60% (94.45–98.08%)
	At least one parameter is abnormal	92.68% (80.08–98.46%)	85.20% (81.56–88.37%)	36.54% (27.31–46.55%)	99.22 (97.73–99.84%)
	At least two parameters are abnormal	85.37% (70.83–94.43%)	98.89% (97.42–99.64%)	87.50% (73.20–95.81%)	98.67% (97.12–99.51%)
Authors' Conclusions	This study revealed that pregnancies complicated by PE are associated with increased uterine artery PI and decreased placental volume and PAPP-A levels in first trimester. Certainly, use of parameters in the combination improves prediction over the use of parameters alone.			

Abbreviations: BMI, body mass index; BP, blood pressure; MoM, multiple of the median; NPV, negative predictive value; NR, not reported; PAPP-A, pregnancy associated plasma protein A; PE, pre-eclampsia; PI, pulsatility index; PPV, positive predictive value.

Table 28. Studies relevant to criterion 9 (question 2)

Table 26a: ASPRE Trial

Study Reference	ASPRE trial (Roknik 2017a, Rolnik 2017b [intervention component], Wright 2019)
Study Design	Design RCT Objective To test the hypothesis that, among women who are identified as being at high risk for preterm pre-eclampsia (PE) (on the basis of factors including maternal characteristics, features of medical/obstetric history, history of PE in >1 pregnancy or history of PE that resulted in delivery before 34 weeks of gestation), aspirin at a dose of 150 mg per day, taken from 11 to 14 weeks of gestation until 36 weeks of gestation, would result in an incidence of preterm preeclampsia that was half the incidence observed with placebo. The objective of an unplanned secondary analysis of the data from the primary study was to explore the hypothesis that in women at high risk of PE, use of aspirin delays the gestational age at delivery in women who have PE (Wright 2019). Dates April 2014–June 2014, July 2015–April 2016 (recruitment; trial was stopped temporarily due to administrative problems) Country UK, Spain, Italy, Belgium, Greece and Israel Setting 13 maternity hospitals
Population Characteristics	Patient recruitment/eligibility All women who had a routine prenatal visit at 11^{+0} weeks of gestation through 13^{+6} weeks of gestation in the participating hospitals were offered screening for PE by means of an algorithm that combines maternal factors, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), and maternal serum pregnancy-associated plasma protein A (PAPP-A) and placental growth factor (PlGF). Included: maternal age ≥18 years, no serious mental illness or learning difficulty and singleton pregnancy with live fetus with no major abnormality demonstrated on the 11–13-week scan, high risk (>1 in 100) for pre-term PE according to the screening algorithm. Excluded: unconscious or severely ill status, learning difficulties or serious mental illness, major fetal abnormality identified at the time that scanning was performed at 11–13 weeks of gestation, regular treatment with aspirin within 28 days before screening, bleeding disorder such as von Willebrand's disease, peptic ulceration, hypersensitivity to aspirin, long-term use of non-steroidal anti-inflammatory medication, and participation in another drug trial within 28 days before screening. Randomisation methods Eligible women were randomly assigned, in a 1:1 ratio, with the use of a Web-based system (Sealed Envelope), to receive either aspirin or placebo, and in the random-sequence generation there was stratification according to participating centre. Blinding Researchers and participants (including principle investigator, participating research doctors, pharmacists, project managers and others involved in the trial). The protocol reported that treatment allocation was only to be revealed to the researchers after completion of the study or where clinically essential. The placebo tablets were identical to the aspirin tablets with respect to variables such as size, thickness, physical properties and appearance. Data collection • Gestational age was determined from the measurement of the fetal crown–rump length (CRL).

Study Reference	ASPRE trial (Roknik 2017a, Rolnik 2017b [intervention component], Wright 2019)

- Maternal characteristics and medical and obstetrical histories were recorded, and the maternal weight and height were measured.
- The MAP was measured by validated automated devices with the use of a standardised protocol.
- Transabdominal colour Doppler ultrasonography was used to measure the left and right UtA-PI, and the average value was recorded.
- Serum concentrations of PAPP-A and PlGF were measured by an automated device.
- Quality control was applied to achieve consistency of the measurement of biomarkers across trial centres. Quality control of screening and verification of adherence to the protocol were performed by the University College London Comprehensive Clinical Trials Unit.
- Participants were encouraged to record any side effects or adverse events in a diary that was reviewed at each trial visit, and they were specifically asked about such events during 3telephone interviews (primarily conducted to gather information on safety and adherence).

Duration of follow-up
NR, assumed until delivery based on primary outcome

Follow-up clinical visits to record safety and adherence data were at 19 to 24 weeks of gestation, 32 to 34 weeks of gestation, and 36 weeks of gestation and during 3telephone interviews, which occurred at 16 weeks and 28 weeks of gestation and 30 days after the last tablet was taken (for safety and adherence).

Definition of PE
PE: defined according to the International Society for the Study of Hypertension in Pregnancy, as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least 2 occasions 4 hours apart developing after 20 weeks of gestation in previously normotensive women, plus proteinuria (appearance of ≥300 mg in 24 hours or 2 readings of at least ++ on dipstick analysis of midstream catheter urine specimens if no 24 hour collection was available).

Pre-term PE: PE at <37 weeks gestation (primary outcome)

Secondary outcomes were PE at <34 weeks gestation and at ≥37 weeks gestation.

Sample size
N screened/invited = 26,941 screened, 2,971 (11.0%) at risk of PE
N eligible = 2,641
N enrolled = 1,776
N excluded (with reason) = 332 excluded due to ineligibility (receiving aspirin [n=253], hypersensitivity to aspirin [n=47], peptic ulcer or bleeding disorder [n=17], participated in another drug trial [n=10], miscarriage before randomisation [n=2], termination of pregnancy
before randomisation [n=3]), 865 declined to participate, 152 withdrew consent after randomisation (aspirin arm [n=78], placebo arm [n=74])
N lost to follow-up = 4 (aspirin arm n=2, placebo arm n=2)
N completed = 1,620
N excluded from analysis = 0
N included in analysis = 1,620 (aspirin arm n=798, placebo arm n=822)

Power
Enrolment of 1,600 participants was expected to give 90% power to show a treatment effect at a two-sided alpha level of 5%. The target recruitment number was inflated to 1776 to account for attrition.

Maternal characteristics
There were no significant between-group differences with regard to the characteristics at baseline.

Characteristic	Aspirin (N=798)	Placebo (N=822)

Study Reference	ASPRE trial (Roknik 2017a, Rolnik 2017b [intervention component], Wright 2019)		
	Median gestational age at randomisation, week (IQR)	12.7 (12.3 to 13.1)	12.6 (12.3 to 13.0)
	Median age, years (IQR)	31.5 (27.3 to 35.8)	31.4 (26.9 to 35.8)
	Median BMI, kg/m^2 (IQR)	26.7 (23.3 to 31.1)	26.5 (23.0 to 31.5)
	Race or ethnic group, n (%)		
	White	528 (66.2)	559 (68.0)
	Black	208 (26.1)	201 (24.5)
	South Asian	37 (4.6)	37 (4.5)
	East Asian	13 (1.6)	16 (1.9)
	Mixed race	12 (1.5)	9 (1.1)
	Method of conception, n (%)		
	Natural	747 (93.6)	779 (94.8)
	Assisted by use of ovulation drugs	6 (0.8)	7 (0.9)
	In vitro fertilisation	45 (5.6)	36 (4.4)
	Cigarette smoking, n (%)	57 (7.1)	59 (7.2)
	Mother had pre-eclampsia, n (%)	66 (8.3)	74 (9.0)
	Medical history, n (%)		
	Chronic hypertension	49 (6.1)	61 (7.4)
	Systemic lupus erythematosus	3 (0.4)	1 (0.1)
	Antiphospholipid syndrome	2 (0.3)	2 (0.2)
	Diabetes mellitus type 1	7 (0.9)	2 (0.2)
	Diabetes mellitus type 2	8 (1.0)	8 (1.0)
	Obstetrical history, n (%)		
	Nulliparous	547 (68.5)	543 (66.1)
	Multiparous without pre-eclampsia	164 (20.6)	195 (23.7)
	Multiparous with pre-eclampsia	87 (10.9)	84 (10.2)
	Median interval from last pregnancy, years (IQR)	4.2 (2.5 to 7.0)	4.6 (2.9 to 7.5)
	Median gestational age at delivery of last pregnancy, weeks (IQR)[a]	39 (37 to 40)	39 (36 to 40)
	Risk of pre-term pre-eclampsia as assessed at screening at 11 to 13 weeks, % (95% CI)	2.3 (1.4 to 4.8)	2.6 (1.5 to 4.8)

[a]Units NR in publication, assumed to be median (IQR)

Intervention	Aspirin at a dose of 150 mg per day was compared with matching placebo, administered from 11 to 14 weeks of gestation until 36 weeks of gestation or, in the event of early delivery, at the onset of labour Participants received instructions to take one tablet every night throughout the trial **Secondary analysis (Wright 2019):** Development of a statistical model in which the effect of aspirin is to delay the gestational age of delivery was fitted to the primary study data in order to demonstrate the consistency of the predictions from the model with the observed incidence.

Study Reference	**ASPRE trial (Roknik 2017a, Rolnik 2017b [intervention component], Wright 2019)**
Outcomes Measured	Primary endpoint Delivery with PE before 37 weeks of gestation. Secondary endpoints Adverse outcomes of pregnancy before 34 weeks of gestation, before 37 weeks of gestation, and at or after 37 weeks of gestation; stillbirth or neonatal death; death and neonatal complications; neonatal therapy; and poor fetal growth (birth weight <3rd, 5th or 10th percentile). Endpoint for secondary analysis (Wright 2019) Incidence of term PE in those treated with aspirin stratified according to the risk of preterm PE at randomisation (given that women were included in the study with risks of preterm PE >1 in 100, a risk cutoff of 1 in 50 was used to define higher risk and lower risk strata).
Effectiveness of the Intervention	Efficacy There was a significant between-group difference in preterm pre-eclampsia at <37 weeks gestation (p=0.004). There was no significant between-group difference in the incidence of any secondary outcomes, but the trial was not powered for these outcomes.

Outcome	Aspirin Group (N=798)	Placebo Group (N=822)	Odds Ratio (95% or 99% CI)
Maternal outcomes, n (%)			
Preterm PE at <37 weeks gestation	13 (1.6)	35 (4.3)	0.38 (0.20 to 0.74)*
Adverse outcomes at <34 weeks gestation			
Any	32 (4.0)	53 (6.4)	0.62 (0.34 to 1.14)
PE	3 (0.4)	15 (1.8)	0.18 (0.03 to 1.03)
Gestational hypertension	2 (0.3)	2 (0.2)	1.02 (0.08 to 13.49)
SGA status without pre-eclampsia, n/N (%)	7/785 (0.9)	14/807 (1.7)	0.53 (0.16 to 1.77)
Miscarriage or stillbirth without pre-eclampsia	14 (1.8)	19 (2.3)	0.78 (0.31 to 1.95)
Abruption without pre-eclampsia	1 (0.1)	3 (0.4)	0.36 (0.02 to 7.14)
Spontaneous delivery without pre-eclampsia	12 (1.5)	12 (1.5)	1.07 (0.37 to 3.10)
Adverse outcomes at <37 weeks gestation			
Any	79 (9.9)	116 (14.1)	0.69 (0.46 to 1.03)
Gestational hypertension	8 (1.0)	7 (0.9)	1.19 (0.31 to 4.56)
SGA status without pre-eclampsia, n/N (%)	17/785 (2.2)	18/807 (2.2)	1.01 (0.42 to 2.46)
Miscarriage or stillbirth without pre-eclampsia	14 (1.8)	19 (2.3)	0.78 (0.31 to 1.95)
Abruption without pre-eclampsia	2 (0.3)	4 (0.5)	0.52 (0.06 to 4.91)
Spontaneous delivery without pre-eclampsia	40 (5.0)	49 (6.0)	0.83 (0.47 to 1.47)
Adverse outcomes at ≥37 weeks gestation,			
Any	178 (22.3)	171 (20.8)	1.12 (0.82 to 1.54)
Pre-eclampsia	53 (6.6)	59 (7.2)	0.95 (0.57 to 1.57)
Gestational hypertension	72 (9.0)	62 (7.5)	1.24 (0.78 to 1.98)

Study Reference	ASPRE trial (Roknik 2017a, Rolnik 2017b [intervention component], Wright 2019)			
	SGA status without pre-eclampsia, n/N (%)	54/785 (6.9)	56/807 (6.9)	1.00 (0.60–1.66)
	Stillbirth without pre-eclampsia	2 (0.3)	2 (0.2)	1.01 (0.08 to 13.40)
	Abruption without pre-eclampsia	2 (0.3)	2 (0.2)	1.05 (0.08 to 13.92)
	Neonatal outcomes, n (%)			
	Stillbirth or death	8 (1.0)	14 (1.7)	0.59 (0.19 to 1.85)
	All stillbirths or deaths	5 (0.6)	8 (1.0)	0.65 (0.15 to 2.90)
	With PE or status of being SGA	3 (0.4)	6 (0.7)	0.51 (0.08 to 3.19)
	With placental abruption or bleeding	0	2 (2.02)	0.00 (0.00 to ∞)
	Without placental abruption or bleeding	8 (1.0)	12 (1.5)	0.69 (0.21 to 2.28)
	Death or complications			
	Any	32 (4.0)	48 (5.8)	0.69 (0.37 to 1.27)
	Miscarriage, stillbirth or death	19 (2.4)	26 (3.2)	0.76 (0.35 to 1.68)
	Intraventricular haemorrhage of grade ≥II	2 (0.3)	1 (0.1)	2.23 (0.09 to 52.70)
	Sepsis with confirmed bacteraemia in cultures	3 (0.4)	6 (0.7)	0.52 (0.08 to 3.32)
	Anaemia resulting in blood transfusion	5 (0.6)	11 (1.3)	0.47 (0.11 to 1.92)
	Respiratory distress syndrome treated with surfactant and ventilation	11 (1.4)	22 (2.7)	0.53 (0.20 to 1.40)
	Necrotising enterocolitis resulting in surgery	2 (0.3)	1 (0.1)	2.10 (0.09 to 49.54)
	Poor fetal growth			
	Birth weight <3rd percentile	57/785 (7.3)	63/807 (7.8)	0.92 (0.57 to 1.51)
	Birth weight <5th percentile	82/785 (10.4)	96/807 (11.9)	0.86 (0.57 to 1.30)
	Birth weight <10th percentile	148/785 (18.9)	187/807 (23.2)	0.77 (0.56 to 1.06)

*Significant difference p=0.004The ASPRE trial demonstrated that administration of aspirin, compared with placebo, resulted in a 62% reduction in the incidence of preterm PE but had no significant effect on the incidence of term PE.

Secondary analysis (Wright 2019):
In the subgroup analysis in which participants were divided into high-risk (risk of preterm PE ≥ 1 in 50) and low-risk (risk of preterm PE <1 in 50), the higher risk placebo group had a ratio of term PE to preterm PE of 41 to 31 (1.3 to 1) compared with a ratio of 18 to 4 (4.5 to 1) in the lower risk group, demonstrating that in the higher-risk group, there were relatively more cases of preterm PE that could, with aspirin, convert to term PE than in the lower-risk group.

Risk of preterm PE	Treatment group	PE < 37 weeks, n (%)	PE ≥ 37 weeks, n (%)	No PE, n (%)	Total
≥ 1 in 50	Aspirin	11 (2.7)	41 (8.8)	412 (88.8)	464
	Placebo	31 (7.1)	41 (8.1)	435 (85.8)	507
<1 in 50	Aspirin	2 (0.6)	12 (3.6)	320 (95.8)	334

Study Reference **ASPRE trial (Roknik 2017a, Rolnik 2017b [intervention component], Wright 2019)**

	Placebo	4 (1.4)	18 (5.7)	293 (93.0)	315
All	Aspirin	13 (1.8)	53 (6.6)	732 (91.7)	798
	Placebo	35 (4.8)	59 (7.2)	728 (88.6)	822

There was a larger reduction in incidence of term PE in the lower risk group (odds ratio, 0.62, 95% confidence interval, 0.29 to 1.30) compared to in the higher-risk group, in which there was a small by insignificant increase in the incidence of term PE (odds ratio, 1.11, 95% confidence interval, 0.71 to 1.75).

The effect of aspirin treatment was to delay the gestational age at delivery with PE by an estimated 4.4 weeks (95% credibility interval, 1.4 to 7.1 weeks) for those in the placebo group would be delivered at 24 weeks. The effect decreased by an estimated 0.23 weeks (95% credibility interval, 0.02 to 0.40 weeks) for each week of gestation, and at 40^{+0} weeks, the estimated effect was a delay by 0.8 weeks (95% credibility interval, -0.03 to 1.7 weeks).

		Number of cases delivering with PE			
Groups		<34 weeks	34^{+0} to 36^{+6} weeks	≥37 weeks	None
Aspirin group (n = 798)	Observed	3	10	53	732
	Predicted model	4.9 (1, 11)	16.4 (8, 26)	44.1 (29, 62)	732.5 (711, 752)
Placebo group (n = 822)	Observed	15	20	59	728
	Predicted Model	16.9 (8, 26)	27.6 (17, 39)	49.3 (34, 67)	728.3 (703, 751)

Safety

In the aspirin group, ≥1 serious adverse event (SAE) occurred in 13 patients (1.6%) and ≥1 AE occurred in 207 patients (25.9%). In the placebo group, ≥1 SAE occurred in 26 patients (3.2%) and ≥1 AE occurred in 210 patients (25.5%). There was no significant between-group difference in the incidence of AEs.

Adherence

Good: 1,294/1,620 (79.9%) [defined as reported intake of tablets ≥85% of total number that participants were expected to have taken between date of randomisation and visit at 36 weeks (or date of delivery if this occurred first)]

Moderate: 241 (14.9%) [defined as reported intake 50–84.9%]

Poor: 85 (5.2%) [defined as reported intake <50%]

Authors' Conclusions

The randomised trial showed that among women with singleton pregnancies who were identified by first-trimester screening as being at high risk for preterm PE, the administration of aspirin at a dose of 150 mg per day from 11 to 14 weeks of gestation until 36 weeks of gestation resulted in a significantly lower incidence of preterm PE than that with placebo.

In this trial, aspirin did not reduce the incidence of term PE.

In a secondary analysis, a statistical model found that aspirin prevents both preterm and term PE and the reduction of term PE is by about 40%. However, much of term PE prevented is replaced by term PE that results from the effect of aspirin in delaying the need for preterm delivery with PE. This model therefore explains the findings from the trial that treatment with aspirin leads to a substantial reduction in the incidence of preterm PE but has little effect on the incidence of term PE. As such, the model demonstrates that the data from the trial are consistent with the hypothesis that aspirin delays the gestational age at delivery with PE in a way that has a larger effect for deliveries that would, without treatment, occur at earlier gestations. Within the context of this model, the incidence of deliveries with PE at term is increased by the effects of delays to preterm PE. In interpretation of this trial data, it is important to recognise that reductions in preterm PE might counter or even reverse any effects on the incidence of term PE (Wright 2019).

There was no significant between-group difference in the incidence of other pregnancy complications or of adverse fetal or neonatal outcomes. However, this trial was not adequately powered for the secondary outcomes.

Abbreviations: AE, adverse event; BMI, Body Mass Index; CRL, crown rump length; IQR, interquartile range; MAP, mean arterial pressure; NR, not reported; PAPP-A, pregnancy associated plasma protein-A; PE, pre-eclampsia; PlGF, placental growth factor; RCT, randomised controlled trial; SAE, serious adverse event; SGA, small for gestational age; UK, United Kingdom; UtA-PI, uterine artery pulsatility index.

Table 26b: Ayala 2013

Study Reference	Ayala 2013
Study Design	Design RCT, single-centre Objective To report the administration-time-dependent effects of low-dose aspirin (ASA) (100 mg/d) in ambulatory BP and pregnancy outcome on women enrolled in the ASEM trial (a trial which investigated whether bedtime treatment with low-dose ASA exerts significantly better BP control during gestation and reduction of the risk of preeclampsia, IUGR, and preterm delivery than ASA upon awakening or placebo in high-risk pregnant women who entered the study protocol at ≤16 weeks of gestation) who were systematically studied by 48h hour ABPM from the first obstetric consultation at the hospital until delivery, which marked the termination of treatment with either ASA or placebo, as well as at 6–8 weeks after delivery. Dates NR Country Spain Setting The Obstetric Physiopathology Service (high-risk unit) of a hospital. Reasons for receiving medical care at this unit include familial or personal history of either gestational hypertension or pre-eclampsia; chronic hypertension; cardiovascular, endocrine, bleeding, or metabolic disease; personal history of spontaneous abortion; multiple pregnancy; obesity; and adolescent or middle-aged nulliparous pregnancy (<18 or >35 years). The relative risk of gestational hypertension and pre-eclampsia in this unit is approximately 3.5-fold higher than in the general obstetric population in the Spanish setting.
Population Characteristics	Patient recruitment/eligibility Spanish pregnant women with higher risk for gestational hypertension or pre-eclampsia than the general obstetric population and who were receiving medical care at a high-risk pregnancy unit of a hospital were eligible. Additional inclusion criteria for this trial were gestational age ≤16 weeks at randomisation and maternal age ≥18 yrs. Exclusion criteria were multiple pregnancy, chronic hypertension or any other condition requiring the use of BP-lowering medication, cardiovascular disorders, chronic liver disease, any disease requiring the use of anti-inflammatory medication, diabetes or any other endocrine disease such as hyperthyroidism, history of drug/alcohol abuse, night/shiftwork employment, acquired immunodeficiency syndrome (AIDS), intolerance to ABPM, and inability to communicate and comply with all of the study requirements. Randomisation methods Participants were randomly assigned at the time of their first visit to the hospital to one of six groups, defined according to treatment (placebo or ASA, 100 mg/d) and to the timing of daily administration of ASA or placebo: upon awakening (Time 1), 8 hours after awakening (Time 2), or at bedtime (Time 3). Randomisation followed an allocation table constructed by a computerised random-number generator. Concealed assignment of participants to the six treatment-time regimens was done according to the order of recruitment. Blinding Double-blind; Placebo and ASA (100 mg uncoated tablets) were prepared in identical presentation and provided monthly to the participants in a box containing 3 blister packs, each with 10 tablets. Treatment of each box (placebo or ASA) was enclosed in serially numbered, opaque, sealed envelopes. Envelopes were open only after conclusion of the trial for every participant.

Data collection
Adherence to the time-of-day (awakening, 8 hours after awakening, or bedtime) treatment schedule and prescribed medication (ASA or placebo) was enforced at each follow-up visit. Compliance was measured on the basis of tablet count at the time of each visit to the hospital. Before commencing each 48-hour ambulatory blood pressure monitoring (ABPM) session, the same midwife nurse, to avoid examiner bias, obtained 3 to 6 consecutive clinic BP measurements after the woman had rested in a seated position for ≥10 min. During each ABPM session, the SBP and DBP of each pregnant woman were automatically measured every 20 minutes between 7:00 and 23:00 h and every 30 minutes during the night for 48 consecutive hours.

Duration of follow-up
NR

Definition of PE
Pre-eclampsia was defined as gestational hypertension (hyperbaric index [HBI]—total area of BP excess summed over the 24-hour period above the upper limit of the time-varying tolerance interval calculated as a function of gestational age—consistently above the threshold for diagnosis of hypertension in pregnancy after the 20th week of gestation) and proteinuria, ≥300 mg/24 hour urine, diagnosed after the 20th week of gestation in a previously normotensive woman.

Sample size
N screened/invited = NR
N eligible = NR
N enrolled = 350
N excluded (with reason) = NR
N lost to follow-up = NR
N completed = NR
N excluded from analysis = 0
N included in analysis = 350

Power
The minimum sample size for this trial, 55 women for each of the 6 treatment-time groups, was calculated to show as statistically significant at the two-sided α level of 5% and with a power of 95% a BP difference between ASA and placebo ≥4 mm Hg in the 24-hour BP mean at the time of delivery, according to the estimation of interindividual variability provided by previous studies.

Maternal characteristics

Characteristic	Placebo				ASA				p value (placebo vs ASA)
	Time 1 (n=59)	Time 2 (n=57)	Time 3 (n=58)	All (n=174)	Time 1 (n=58)	Time 2 (n=59)	Time 3 (n=59)	All (n=176)	
Gestational age at randomisation, weeks, mean ± SD	13.6 ± 1.6	13.6 ± 1.4	13.6 ± 1.4	13.6 ± 1.5	13.6 ± 1.4	13.4 ± 1.5	13.4 ± 1.4	13.5 ± 1.4	0.411
Age, years, mean ± SD	31.5 ± 5.8	32.0 ± 4.5	30.0 ± 5.2	31.1 ± 5.2	31.0 ±5.8	30.4 ± 5.3	29.7 ± 4.8	30.3 ± 5.3	0.175
BMI, kg/m^2, mean ± SD	24.8 ± 3.9	25.5 ± 4.3	26.3 ± 4.4	25.5 ± 4.2	25.8 ± 3.9	24.9 ± 4.6	25.4 ± 4.3	25.4 ± 4.3	0.714
Nulliparous, %	59.3	52.6	53.4	55.1	41.4	59.3	47.5	49.4	0.282
Previous abortion, %	32.2	28.1	25.9	30.5	29.3	32.2	32.2	31.3	0.873

Study Reference **Ayala 2013**

Clinic SBP[a], mm Hg, mean ± SD	120.5 ± 9.7	119.2 ± 9.2	120.2 ± 9.8	120.0 ± 9.6	121.4 ± 8.8	122.5 ± 10.1	121.8 ± 9.8	121.9 ± 9.5	0.130
Clinic DBP[a], mm Hg, mean ± SD	66.6 ± 8.7	66.6 ± 7.2	67.1 ± 9.0	66.8 ± 8.3	67.7 ± 8.4	68.5 ± 8.5	67.7 ± 8.1	68.0 ± 8.3	0.182

[a]Clinic BP corresponds to the average of 3 to 6 measurements obtained by a midwife nurse for each woman at the time of their visit to the hospital at the time of randomisation

Intervention

Placebo or ASA, 100 mg/d upon awakening (Time 1), 8 hours after awakening (Time 2), or at bedtime (Time 3

	Participants assigned to each group, n		
Intervention	Time 1	Time 2	Time 3
Aspirin (100 mg/d) (n=176)	58	59	59
Placebo (n=174)	59	57	58

Outcomes Measured

Primary endpoint

The primary outcome study endpoint was total serious adverse events, which included pre-eclampsia, preterm delivery, IUGR, and stillbirth.

Secondary endpoints

The composite of these serious adverse events plus gestational hypertension.

Effectiveness of the Intervention

Efficacy

Characteristic	Placebo				ASA				p value (placebo vs ASA)
	Time 1 (n=59)	Time 2 (n=57)	Time 3 (n=58)	All (n=174)	Time 1 (n=58)	Time 2 (n=59)	Time 3 (n=59)	All (n= 76)	
Gestational age at delivery, weeks, mean ± SD	39.2 ± 1.5	39.1 ± 2.0	39.1 ± 2.2	39.2 ±1.9	39.1 ± 2.1	39.8 ± 1.1	39.6 ± 1.1	39.5 ± 1.6	0.067
Newborn weight, g, mean ± SD	3140 ± 517	3183 ± 599	3162 ± 624	3162 ± 580	3156 ± 568	3375 ± 453	3330 ± 511	3286 ± 519	0.040
Pre-eclampsia[a], (95% CI)	11.9 (3.6, 20.1)	10.5 (2.6, 18.5)	15.5 (6.1, 24.8)	12.6 (7.7, 17.6)	15.5 (6.1, 24.8)	1.7 (−1.6, 5.0)	1.7 (−1.6, 5.0)	6.3 (2.7, 9.8)	0.041
Preterm delivery[ab], (95% CI)	6.8 (0.4, 13.2)	10.5 (2.6, 18.5)	17.2 (7.5, 27.0)	11.5 (6.8, 16.2)	12.1 (3.7, 20.5)	0	0	4.0 (1.1, 6.8)	0.008
IUGR[a], (95% CI)	20.3 (10.1, 30.6)	17.5 (7.7, 27.4)	17.2 (7.5, 27.0)	18.4 (12.6, 24.2)	17.2 (7.5, 27.0)	6.8 (.4, 13.2)	3.4 (−1.2, 8.0)	9.1 (4.8, 13.3)	0.011
Stillbirth[a], (95% CI)	5.1 (−0.5, 10.7)	3.5 (−1.3, 8.3)	0	2.9 (0.4, 5.4)	1.7 (−1.6, 5.1)	1.7 (−1.6, 5.0)	0	1.1 (−0.4, 2.7)	0.246

Study Reference	Ayala 2013									
	Gestational hypertension[a], (95% CI)	27.1 (15.8, 38.5)	29.8 (17.9, 41.7)	27.6 (16.1, 39.1)	28.2 (21.5, 34.8)	25.9 (14.6, 37.1)	11.9 (3.6, 20.1)	6.8 (0.4, 13.2)	14.8 (9.5, 20.0)	0.002
	Serious adverse outcomes [ac], (95% CI)	30.5 (18.8, 42.3)	35.1 (22.7, 47.5)	31.0 (19.1, 42.9)	32.2 (25.2, 39.1)	29.3 (17.6, 41.0)	10.2 (2.5, 17.9)	5.1 (−0.5, 10.7)	14.8 (9.5, 20.0)	<0.001
	Antepartum haemorrhage[a], (95% CI)	6.8 (0.4, 13.2)	3.5 (−1.3, 8.3)	5.2 (−0.5, 10.9)	5.2 (1.9, 8.4)	3.5 (−1.2, 8.1)	3.4 (−1.2, 8.0)	3.4 (−1.2, 8.0)	3.4 (0.7, 6.1)	0.415
	Postpartum haemorrhage[a], (95% CI)	3.4 (−1.2, 8.0)	3.5 (−1.3, 8.3)	3.5 (−1.2, 8.1)	3.5 (0.7, 6.2)	1.7 (−1.6, 5.1)	1.7 (−1.6, 5.0)	1.7 (−1.6, 5.0)	1.7 (−0.2, 3.6)	0.303
	[a]Percent ratio of observed number of events to total number of women per group; [b]Delivery at <37 weeks of gestation; [c] Composite endpoint including preeclampsia, preterm delivery, IUGR, and stillbirth. Safety There was no increased risk of haemorrhage, either before or after delivery, with low dose ASA at 8h after awakening or at bedtime compared with ASA upon awakening or placebo (HR: 0.62, 95% CI:.25–1.59; p = 0.321).									
Authors' Conclusions	Results from this study document highly significant benefits of low-dose ASA on BP regulation and pregnancy outcome in high-risk pregnant women. These beneficial effects are markedly dependent on the circadian time of ASA administration, being negligible when ASA is ingested upon awakening The results indicate that (i) 100 mg/d ASA should be the recommended minimum dose to be used for prevention of complications in pregnancy; (ii) ingestion of low-dose ASA for prevention of complications in pregnancy should start at ≤16 weeks of gestation; and (iii) low-dose ASA ingested at bedtime, but not upon awakening, significantly lowers ambulatory BP and reduces the incidence of preeclampsia, gestational hypertension, preterm delivery, and IUGR.									

Abbreviations: ABPM, ambulatory blood pressure monitoring; ASA, aspirin; BP, blood pressure; DBP, diastolic blood pressure; HBI, hyperbaric index; IUGR, intrauterine growth retardation; RCT, randomised controlled trial; SBP, systolic blood pressure.

Table 26c: Bella 2020

Study Reference	Bella 2020
Study Design	Design RCT (multicentre) Objective To assess the effectiveness of LMWH in the prevention of PE, IUGR, fetal death, and abruptio placentae in women classified as high risk based on their medical history and in women selected by first trimester screening of PE. Dates 13 March 2012 to 30 November 2015 (randomisation) Country Spain

Study Reference	Bella 2020
	Setting 4 tertiary centres, placental insufficiency unit
Population Characteristics	Patient recruitment/eligibility All women attending their first trimester scan or outpatient visit for high-risk patients were screened for eligibility. Women between 6.0 and 15.6 weeks of gestation were asked to participate if they met the following inclusion criteria: severe PE resulting in delivery before 34 weeks of gestation, newborn weight <3rd percentile or <10th percentile with documented abnormal Doppler in the umbilical artery (PI >95th centile) during pregnancy before 34 weeks of gestation, and/or abruptio placentae or unexplained intrauterine death after 20 weeks of gestation in a previous pregnancy, and uterine artery mean PI Doppler >95th percentile at 12–13.6 weeks. After June 2014, first trimester screening of PE was done according to a validated algorithm available online, with a cutoff point for high-risk women of 1/175 with a PE detection rate at <34 weeks of gestation of 80.8% (positive predictive value: 8.08%; false-positive rate: 10%). Exclusion criteria included positive thrombophilia status, multiple pregnancy, alcohol or illicit drug use, type 1 diabetes, hyperthyroidism, renal disease, severe maternal illness, cytomegalovirus or toxoplasmosis infection, maternal HIV infection, known major fetal anomaly or chromosomal abnormality at randomisation, previous venous or arterial thrombotic event, known allergy to heparin or LMWH, contraindication to LMWH, an absolute indication for anticoagulant therapy and denial of written informed consent. Randomisation methods Pregnant women were randomly assigned according to a computer-generated allocation sequence (1:1 ratio). Blinding Open-label; no blinding Data collection Women were followed at the placental insufficiency unit of each of the participating centres. Visits were scheduled every 4 weeks until 34 weeks of gestation and thereafter every 2 weeks until delivery. At each visit, blood pressure, urine dipstick analysis for proteinuria, and adverse events were recorded. Fetal well-being was assessed by ultrasound with the measurement of fetal growth parameters and uterine, umbilical, and middle cerebral artery Doppler waveforms from 20 weeks of gestation onward. Women with prior early-onset PE received 100 mg of aspirin daily. A first trimester scan was performed on all patients, and crown-rump length measurement was used to date the pregnancy. Uterine artery Doppler velocimetry was evaluated at 11.0–13.6 weeks of gestation by abdominal ultrasound at the time of the first trimester scan. The PI of both uterine arteries was automatically measured and the mean uterine artery PI was calculated. A logistic regression-based predictive model for early- and late-onset PE was used according to a validated algorithm based on maternal characteristics, levels of pregnancy-associated plasma protein-A and free β-human chorionic gonadotropin at 8–12 weeks, and blood pressure and uterine artery Doppler at 11.0–13.6 weeks. Maternal history risk factors were obtained prospectively via a patient-completed questionnaire on maternal age, race, height, weight, smoking status, obstetric history (previous PE, IUGR, abruptio placentae, or stillbirth), and medical history including chronic hypertension or diabetes. Demographic characteristics and Doppler findings were recorded in a computer database at the time of Doppler studies at each participating centre. Data on pregnancy outcomes were obtained from examination of each patient's clinical history and labour ward records. Duration of follow-up Post-birth (inferred from outcomes reported, including days spend in NICU where maximum duration was 21 days) Definition of PE Criteria for the definition of PE were those of the International Society for the Study of Hypertension in Pregnancy. Sample size N screened/invited = NR N eligible = NR N enrolled = 283

Study Reference — **Bella 2020**

N excluded (with reason) = miscarriage <16 weeks (control group n=3; treatment group n=2)
N lost to follow-up = 9 (control group), 8 (treatment group)
N completed = NR
N excluded from analysis = control group: declined to continue (n=1), violation of protocol (n=5), maternal request for other reasons (n=3); treatment group: discontinued intervention (n=7), violation of protocol (n=12), withdrawal medication (n=8), maternal request for other reason (n=1)
N included in analysis = 224 (116 control, 108 treatment)

Power
In order to achieve 80% power at a 2-sided significance level of 0.05, to detect a difference between 25 and 12.5%, a sample size of 266 participants was estimated (133 women in each group, including a 21% dropout/early miscarriage rate)

Maternal characteristics

Characteristic	Standard high-risk care only (n=134)	Standard high-risk care + enoxaparin (n=144)	p value
Maternal age, years, median (IQR)	33 (29–36)	33 (28–35)	0.22
Caucasian/European ethnicity, n (%)	93 (72.1)	99 (73.3)	0.78
Gestational age at the inclusion, years, median (IQR)	12.86 (12.14–13.57)	12.86 (12.29–13.57)	0.99
Spontaneous conception, n (%)	121 (93.1)	129 (95.5)	0.38
Obstetric history[a], n (%)	35 (26.12)	39 (27.08)	0.85
BMI, kg/m^2, median (IQR)	24.3 (19–47)	25.4 (18–41)	0.62
Smoking status at trial entry, n (%)	17 (12.9)	20 (14.8)	0.79
Aspirin use in pregnancy (100 mg/24 hours), n (%)	26 (19.5)	20 (13.9)	0.04

[a]Previous pregnancy affected by severe PE resulting in delivery before 34 weeks of gestation; newborn weight <3rd percentile or <10th percentile with documented abnormal Doppler in the umbilical artery during pregnancy before 34 weeks of gestation; and abruptio placentae or unexplained intrauterine death after 20 weeks of gestation.

Intervention

No intervention (standard high-risk care): n = 137

Standard high-risk care + Enoxaparin (LMWH) 40 mg (4,000 IU) self-administered subcutaneous injection once a day until the 36th week of gestation (dose adjusted to 60 mg if maternal weight was above 90 kg): n = 146

Outcomes Measured

Primary endpoint
The primary composite outcome consisted of 1 or more of the following: development of PE; newborn weight ≤10th percentile and abnormal Doppler in the umbilical artery; abruptio placentae; and intrauterine fetal death.

Secondary endpoints
Secondary outcomes included maternal complications (HELLP syndrome, eclampsia, admission to ICU, severe maternal complications [maternal death, pulmonary oedema, cerebral haemorrhage, and renal insufficiency]), and severe neonatal complications (1 or several of the following: severe respiratory distress, intraventricular haemorrhage grade III–IV, treated ductus arteriosus persistence, renal dysfunction, necrotising enterocolitis, intestinal perforation, vertical sepsis, nosocomial sepsis, retinopathy of prematurity treated with laser, bronchopulmonary dysplasia, periventricular leukomalacia, postnatal administration of corticosteroids or inotropic drugs and death). Potential

Study Reference	Bella 2020

differences in perinatal outcome according to 2 inclusion criteria were also assessed: adverse obstetric history and positive screening at the first trimester of pregnancy.

Effectiveness of the Intervention

Efficacy

Overall, 93 (33%) women experienced placental insufficiency complications, with no significant differences between the 2 arms: 50/144 (34.7%) in the LMWH arm and 43/134 (32%) in the control arm (p = 0.64, OR: 1.13, 95% CI: 0.68–1.85). No differences were found in secondary composite outcomes for maternal or neonatal complications.

Placental complications and composite pregnancy outcomes

	Standard high-risk care only (n=134)	Standard high-risk care + enoxaparin (n=144)	OR (95% CI)
PE, n (%)	13 (9.7)	11 (7.6)	0.77 (0.33–1.78)
IUGR, n (%)	15 (11.2)	18 (12.5)	1.13 (0.55–2.35)
SGA, n (%)	15 (11.2)	15 (10.4)	0.92 (0.43–1.97)
Antepartum fetal death, n (%)	2 (1.5)	1 (0.7)	2.83 (0.29–27.54)
Antepartum haemorrhage/abruption, n (%)	7 (5.2)	17 (11.8)	2.43 (0.97–6.06)
Composite placental insufficiency outcome, n (%)	43 (32)	50 (34.7)	1.13 (0.68–1.85)
Severe maternal complications, n (%)	3 (2.2)	2 (1.3)	0.93 (0.06–15.02)
Severe neonatal complications, n (%)	21 (15.67)	20 (13.89)	0.87 (0.45–1.68)

No differences found in secondary composite outcomes for maternal or neonatal complications.

	Standard high-risk care only (n=134)	Standard high-risk care + enoxaparin (n=144)	OR (CI 95%)
Delivery outcomes	-	-	-
Spontaneous delivery, n (%)	64 (56.1)	58 (49.1)	0.28
Gestational age at delivery, years, median (IQR)	38.24 (37.4–41)	38.4 (37.8–40)	0.23
Birth weight, grams, median (IQR)	2,934 (2,660–3,310)	3,030 (2,655–3,460)	0.72
Secondary outcomes: maternal complications, n (%)	-	-	-
HELLP syndrome	3 (2.2)	0	0.11
Eclampsia	0	0	N/A
Acute oedema	1 (0.7)	1 (0.7)	0.48
Intracranial haemorrhage	1 (0.7)	0	0.48
ICU admission	1 (0.7)	0	0.48
Gestational thromboembolism	0	1 (0.7)	0.48
Secondary outcomes: neonatal complications	-	-	-
Preterm birth <37 weeks, n (%)	19 (14.2)	15 (10.4)	0.34
Preterm birth <34 weeks, n (%)	9 (6.7)	7 (4.8)	0.50
NICU admission, n (%)	8 (5.9)	8 (5.5)	0.88

Study Reference **Bella 2020**

Duration of NICU admission, days, median (IQR)	10.0 (4–21)	3.5 (2.5–5.5)	0.06
Intraventricular haemorrhage, n (%)	1 (0.97)	0	1
Bronchopulmonary dysplasia, n (%)	0	0	NA
Necrotising enterocolitis, n (%)	0	1 (0.7)	0.33

No statistically significant differences

Pregnancy outcomes in women included due to previous obstetric complications

	Standard high-risk care only (n=35)	Standard high-risk care + enoxaparin (n=39)	OR (95% CI)
PE, n (%)	6 (17.1)	4 (10.2)	0.55 (0.14–2.15)
IUGR, n (%)	4 (11.4)	9 (23.1)	2.32 (0.65–8.36)
SGA, n (%)	3 (8.5)	3 (7.7)	0.89 (0.17–4.72)
Antepartum fetal death, n (%)	1 (2.8)	3 (7.7)	2.83 (0.28–28.58)
Abruptio, n (%)	4 (11.4)	8 (20.5)	0.53 (0.09–2.94)
Preterm birth <37 weeks, n (%)	9 (25.7)	8 (20.5)	0.75 (0.25–2.21)
Preterm birth <34 weeks, n (%)	4 (11.4)	6 (15.4)	1.41 (0.36–5.47)
Placental insufficient, n (%)	18 (51.4)	20 (51.3)	0.99 (0.40–2.48)
Composite maternal complications, n (%)	1 (2.8)	1 (2.5)	0.89 (0.05–14.86)
Composite neonatal complications, n (%)	9 (25.7)	10 (25.6)	0.99 (0.35–2.83)

In a subgroup analyses of women with an adverse obstetric history, the use of enoxaparin had no effect on the rates of placental insufficiency complications.

There were also no statistically significant differences found in any of the pregnancy outcomes in the subgroup analysis of women included due to first trimester screening (raw data not available for extraction).

Safety

For women in the standard high-risk care and enoxaparin treatment group, 8 patients (1.98%) reported epistaxis and 4 patients reported irritation (n = 2, 0.49%) or bruising (n = 2, 0.49%) at the puncture site. Two women (0.49%) had thrombocytopenia (<100,000 platelets) while on LMWH therapy, and the treatment was discontinued. There were 3 cases of fetal death, 1 in the LMWH arm and 2 in the non-LMWH arm. These 3 women were included due to first trimester screening of PE.

Authors' Conclusions

LMWH in women without thrombophilia, but with a history of severe pregnancy complications, showed no benefit in decreasing the risk of PE or any adverse maternal or fetal event. Perinatal outcomes were not improved after treatment with LMWH in women included due to abnormal uterine artery Doppler evaluation, not in women who were determined to be at high risk according to PE screening at 12 to 14 weeks of gestation. In conclusion, LMWH did not reduce the incidence of placenta-mediated complications either in women with previous adverse obstetric history without thrombophilia or in women selected by first trimester screening for PE. In this population, only the concomitant use of a prophylactic low-dose aspirin and LMWH showed a benefit in women selected based on previous risk factors.

Abbreviations: BMI, body mass index; CI, confidence interval; HELLP, haemolysis, elevated liver enzymes, and low platelet count; HIV, human immunodeficiency virus; ICU, intensive care unit; IU, international unit; IUGR, intrauterine growth restriction; IQR, interquartile range; LMWH, low-molecular-weight heparin; NICU, neonatal intensive care unit; NR, not reported; OR, odds ratio; PE, pre-eclampsia; PI, pulsatility index; RCT, randomised controlled trial; SGA, small for gestational age.

Table 26d: Chiswick 2015

Study Reference	Chiswick 2015
Study Design	Design Multicentre RCT Objective To establish whether the insulin sensitising drug metformin improves maternal and fetal outcomes in obese pregnant women without diabetes Dates Between Feb 3, 2011 and Jan 16, 2014 (inclusive) Country UK Setting 15 National Health Service Hospitals in the UK
Population Characteristics	Patient recruitment/eligibility Eligible women were aged 16 years or older, had a BMI or 30 kg/m^2 or more, and were between 12 and 16 weeks gestation. Excluded: non-white women and those with pre-existing diabetes; gestational diabetes in a previous pregnancy; gestational diabetes diagnosed in the index pregnancy before randomisation; systemic disease at the time of trial entry (requiring either regular drugs or treatment with systemic corticosteroids in the past 3 months); previous delivery of a baby smaller than the 3rd percentile for weight; previous pregnancy with pre-eclampsia prompting delivery before 32 weeks gestation; known hypersensitivity to metformin hydrochloride or any of the excipients; known liver failure; known renal failure; acute disorders at the time of trial entry with the potential to change renal function, such as dehydration sufficient to require intravenous infusion, severe infection, shock, intravascular administration of iodinated contrast agents, or acute or chronic diseases that might case tissue hypoxia (e.g. cardiac or respiratory failure, recent myocardial infarction, hepatic insufficiency, acute alcohol intoxication, or alcoholism); lactating women and women with multiple pregnancy. Also excluded participants with impaired renal function (urea >6.6 mmol/L, creatinine >85 µmol/L, sodium >145 mmol/L, potassium >5.0 mmol/L) or liver function (bilirubin >16 µmol/L, alanine transferase >60 IU/L), or with abnormal lactate (according to local laboratory reference range) or gestational diabetes defined by WHO criteria (fasting glucose ≥7.0 mmol/L and 2 h glucose ≥7.8 mmol/L), or any other local hospital criteria (e.g. International Association of Diabetes and Pregnancy Study Groups [IADPSG]). Randomisation methods Participants were randomly assigned (1:1) via a web-based computer-generated block randomisation procedure (block size of 2 to 4). Randomisation was stratified by study site and BMI band (30–39 vs ≥40 kg/m^2). Blinding Participants, caregivers and study personnel were masked to treatment assignment. Members of the independent Data Monitoring Committee had access to unmasked data reports but had no contact with study participants. Data collection Demographics, medical history and maternal anthropometry were recorded at baseline. Randomised participants were reviewed face to face or by telephone at 18–20, 28, 36 and 40 weeks gestation: around the time of delivery and 3 months postnatally. Pregnancy complications were recorded and women were asked to complete a side-effect questionnaire at each review visit until delivery. Maternal anthropometry was repeated at 36 weeks gestation and 3 months postnatally. A formal 75 g oral glucose tolerance test was done in addition to screening for liver and renal function and was repeated at 28 and 36 weeks gestation. Blood was stored for measurement of inflammatory and metabolic indices. The baby's weight and anthropometry were recorded at delivery and at the 3 month postnatal visit. Duration of follow-up 3 months postnatally

Study Reference **Chiswick 2015**

Definition of PE

NR

Sample size
N screened/invited = 4,867
N eligible = NR
N enrolled = 449
N excluded (with reason) = declined (n=2,872), ineligible (n=730), uncontactable (n=752), other reasons (n=56, including change in eligibility from screening of notes to recruitment visit: unable to arrange recruitment visit before 16 weeks [26], recruitment stopped before screening appointment [14], miscarriage [2], moved out of area [1], unable to provide informed consent because of difficulties with spoken English [5], own doctor or midwife advised against participation [4], duplicate note screening number issued in error [4]), did not attend appointments (n=8)
N lost to follow-up = 92 PBO and 82 metformin
N completed = 128 PBO reached last follow-up and 132 metformin reached last follow up
N excluded from analysis = 2 PBO and 11 metformin.
N included in analysis = 220 PBO included in intention-to-treat analysis and 214 metformin included in intention-to-treat analysis

Power
Calculated that a sample size of 143 women in each group would provide 80% power, and a sample size of 163 women in each group would provide 85% power to detect a difference in mean birthweight percentile of SD 0.33 (equivalent to the difference between a placebo mean of 4.0 kg and a metformin mean of 3.8 kg) at a two-sided 5% significance level with a two-group *t* test.

Maternal characteristics

	Placebo		Metformin	
Demographics and lifestyle	Mean (SD) or n (%)	N	Mean (SD) or n (%)	N
Age (years)	28.9 (5.1)	223	28.7 (5.8)	226
Currently smokes	31 (14%)	223	40 (18%)	226
Currently drinks alcohol	9 (4%)	223	3 (1%)	226
Illicit drug use	1 (<1%)	223	0	226
At least one previous pregnancy ≥12 weeks gestation	161 (73%)	220	147 (65%)	226
Systolic blood pressure (mm Hg)	119.4 (10.4)	223	117.6 (10.8)	226
Diastolic blood pressure (mm Hg)	68.9 (7.3)	223	68.0 (7.8)	226
Medical history				
Pre-eclampsia or pregnancy induced hypertension	7 (3%)	223	10 (4%)	226
Pre-pregnancy hypertension requiring treatment	2 (1%)	223	1 (<1%)	226
Polycystic ovary syndrome	21 (9%)	223	28 (12%)	226
Family history				

Study Reference	**Chiswick 2015**				
	Cardiovascular disease	69 (31%)	223	71 (31%)	226
	Pre-eclampsia	22 (10%)	223	19 (8%)	226
	Diabetes	101 (45%)	223	99 (44%)	226
	Other	96 (43%)	223	109 (48%)	226
	Anthropometry				
	Weight	102.9 (17.0)	223	103.6 (15.5)	226
	BMI (kg/m^2)	37.7 (5.6)	223	37.8 (4.9)	226
	Maternal fat (%)*	46.8 (5.6)	48	48.2 (5.2)	53
	*Measured only in Edinburgh participants				
Intervention	Metformin Participants received oral metformin 500 mg, in a dose of up to 5 tablets daily in 2 or 3 divided doses. Treatment was initiated at 12–16 weeks gestation and continued until the delivery of the baby. Treatment started at one 500 mg tablet once a day at Week 1 and escalated by one tablet a day each week over 5 weeks, to reach either the maximum tolerable dose or the maximum permitted dose of 2500 mg, whichever was lower. The local investigator was allowed to change the treatment regimen at their discretion, as long as the maximum daily dose did not exceed 2500 mg in 3 divided doses. Placebo Participants received matched placebo tablets, in a dose of up to 5 tablets daily in 2 or 3 divided doses.				
Outcomes Measured	Primary endpoint The primary outcome was Z score corresponding to the gestational age, parity and sex-standardised birthweight percentile of liveborn babies delivered at 24 or more weeks gestation. Secondary endpoints The main secondary outcome was maternal insulin resistance at 36 weeks gestation. Other secondary outcomes included maternal fasting glucose and insulin and 2 h glucose at 36 week; maternal anthropometry and body composition, baby anthropometry and body composition; maternal inflammatory and metabolic outcomes at 36 weeks, including C-reactive protein (CRP), cholesterol, HDL, LDL, triglycerides, interleukin (IL)-6, leptin, serum cortisol, non-esterified fatty acids, and the ratio of plasminogen activator inhibitor 1 to 2; incidence of low birthweight percentile (<3rd and <10th); incidence of other adverse maternal and neonatal outcomes, including maternal symptoms; maternal plasma metformin concentration to explore tablet taking in the metformin group; and the maternal metabolic (fasting glucose and insulin and 2 h glucose) and inflammatory markers at 28 weeks.				
Effectiveness of the Intervention	Efficacy				
		Placebo	Metformin	OR (95% CI)	p value
	Maternal delivery and postnatal				
	Preterm birth	14/220 (6%)	18/214 (8%)	1.345 (0.651–2.777)	0.47
	Development of gestational diabetes	36/153 (24%)	26/142 (18%)	0.728 (0.414–1.283)	0.27
	Pregnancy induced hypertension	14/222 (6%)	21/221 (10%)	1.56 (0.772–3.152)	0.22
	Pre-eclampsia	3/222 (1%)	7/221 (3%)	2.39 (0.61–9.36)	0.21
	Fetal and neonatal outcomes				
	Admission to neonatal unit	29/219 (13%)	14/213 (7%)	0.461 (0.236–0.899)*	0.02

Study Reference	Chiswick 2015

Neonatal death in the delivery room	0/220	0/214	NR	NR
Neonatal death at a later stage	2/220 (1%)	1/214 (<1%)	NR	1.00*§
Incidence of low birthweight <10th percentile	11/220 (5%)	14/214 (7%)	1.330 (0.590–2.999)	0.49

*Post-hoc analysis. §Fisher's exact test reported

Safety
Maternal symptoms of diarrhoea and vomiting were more common in women in the metformin group. Incidence of other adverse outcomes, including preterm birth and low birthweight, caesarean section, and postpartum haemorrhage were similar in the 2 groups. No adverse effects of metformin were recorded in post-hoc safety analyses comparing the proportion of women with a recordable serious adverse event between the 2 groups. The increase in the combined adverse outcome of miscarriage, termination of pregnancy, stillbirth or neonatal death in women in the metformin group was not significant. Admission to the neonatal unit was less common in the metformin group than the placebo group. No differences were noted in outcomes at other timepoints between the 2 groups, with the exception of fasting glucose and HOMA-IR score.

Authors' Conclusions

Primary conclusions of the study, as stated by the authors.
Metformin does not have a role in reducing the birthweight of offspring of obese women. Metformin had its expected pharmacodynamic effects. Metformin had no effect on the primary outcome but the metformin-associated reduction in inflammatory markers CRP and IL-6 might be beneficial as these markers have been associated with adverse outcomes such as preterm birth and pre-eclampsia. The present study provides the first experimental evidence that factors other than maternal glucose are important in fetal overgrowth. Metformin should not be used to improve pregnancy outcomes in obese women.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein; HOMA-IR: homeostatic model assessment of insulin resistance; IADPSG, International Association of Diabetes and Pregnancy Study Groups; IL, interleukin; LDL, low-density lipoprotein; NR, not reported; PBO, placebo; PE, pre-eclampsia; SD, standard deviation.

Table 28e: Costantine 2016 [Costantine 2016 and Costantine 2021]

Study Reference	Costantine 2016 [Costantine 2016 and Costantine 2021]
Study Design	Design RCT, multicentre Objective To determine pravastatin safety and pharmacokinetic parameters when used in pregnant women at high risk of PE. Costantine 2021: Determine the maternal-fetal safety and pharmacokinetic parameters of a higher dose (20 mg) of pravastatin in a similar cohort of high-risk pregnant patients. Dates August 2012 to February 2014 Costantine 2021: NR Country USA

Study Reference	Costantine 2016 [Costantine 2016 and Costantine 2021]
	Setting Five clinical centre sites of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Obstetric-Fetal Pharmacology Research Units Network **Costantine 2021:** 3 clinical centre sites
Population Characteristics	Patient recruitment/eligibility Eligible women were 18 years or older, with singleton, non-anomalous pregnancy between $12^{0/7}$ weeks and $16^{6/7}$ weeks gestation (confirmed with an ultrasound examination), and with a history of severe pre-eclampsia in a prior pregnancy that required delivery prior to 34 weeks gestation (documented by chart review). Excluded: women with known fetal genetic or major malformations, fetal demise, multifetal gestation, contraindications for statin therapy (e.g., hypersensitivity to pravastatin, recent or active liver disease), concomitant therapy with fibrates, niacin, cyclosporine, clarithromycin, or erythromycin, pre-gestational diabetes mellitus, HIV infection, history of solid organ transplant, chronic renal disease, epilepsy, uterine malformations, cancer, familial hypercholesterolemia, or inability to tolerate oral medications secondary to severe nausea and vomiting of pregnancy. **Costantine 2021:** Eligible patients were 18 years or older, with singleton, non-anomalous pregnancies between 12^{+0} weeks and 16^{+6} weeks gestation (confirmed with an ultrasound gestation) and who had a history of PE with severe features in a pregnancy that required delivery before 34^{+6} weeks of gestation (documented by chart review). Excluded: patients with a current pregnancy with known fetal genetic or major malformations; those with contraindications for statin therapy (e.g. hypersensitivity to pravastatin or recent active liver disease); statin use in current pregnancy; concomitant therapy with fibrates, niacin, cyclosporine, clarithromycin or erythromycin; HIV infection; history of solid organ transplant; chronic renal disease; uterine malformations; cancer; or participation in another intervention study that could influence the outcomes of the study. Randomisation methods Randomisation was performed through a central process that was prepared and maintained by the data coordinating centre. Initial stratification was by clinical site. **Costantine 2021:** Randomisation was performed through a central process that was prepared and maintained centrally at the University of Texas Medical Branch's Investigational Drug Services. Initial stratification was by clinical site. Blinding Double blind study; patients, investigators and outcome assessors were blind to treatment allocation. **Costanine 2021:** Pravastatin and placebo capsules were packaged in identical capsules. Patients, care providers, investigators, and outcome assessors were blinded during the trial and analysis. Data collection After randomisation, research personnel followed subjects at scheduled intervals. At each study visit, medication's side effects were assessed using a checklist, adverse events (AEs) were determined and assessed, and pill count performed. All data were collected or abstracted by research coordinators at the clinical centres and uploaded to a central database that was managed by the data coordinating centre, which was responsible for data analysis. Steady-state pharmacokinetic studies were conducted at 18 to 24 weeks gestation and 30 to 34 weeks gestation, as well as 4 to 6 weeks postpartum; each subject served as their own control. Subjects recorded the time of pravastatin dosing for the 4 days prior to each study day, and pill counts were conducted to determine adherence. Serial blood samples were collected for measurement of pravastatin and a pravastatin metabolite. Urine was collected periodically. Maternal, umbilical cord venous and umbilical cord arterial blood samples were collected at delivery. **Costantine 2021:** Data were collected or abstracted by research coordinators at the clinical centres. Steady-state pravastatin pharmacokinetic studies were conducted in the second trimester (18–24 weeks gestation) of pregnancy, third trimester (30–34 weeks gestation) of pregnancy and

Study Reference	Costantine 2016 [Costantine 2016 and Costantine 2021]
	during the postpartum period (4–6 months post delivery). Subjects recorded the time of pravastatin dosing for the 4 days before each study day and pill counts were conducted to determine adherence. Serial blood samples (6 mL each) were collected for measurement of pravastatin concentrations in plasma at the following times: predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours after the dose on each pharmacokinetic study day. Urine was collected predose and then all urine over 1 dosing interval was collected as follows: 0–4, 4–8, 8–12 and 12–24 hours following dosing on each pharmacokinetic study day. Urine collected in each interval was combined, mixed and the total volume measured. An aliquot from each interval was assayed for pravastatin concentrations. Cumulative amount of drug excreted in urine was calculated as sum of the amount in urine from 0 to 24 hours. Maternal, venous umbilical cord and arterial umbilical cord blood samples were collected at the time of delivery for measurement of pravastatin concentrations in plasma. Duration of follow-up NR, but assumed at least up to 7 days postpartum based on reported outcomes **Costantine 2021:** NR but assumed at least to 4 to 6 months postpartum based on reported outcomes Definition of PE Pre-eclampsia was diagnosed according to criteria set by the American College of Obstetricians and Gynecologists; defined as the presence of either a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on 2 occasions at least 4 hours (but less than 7 days) apart, with proteinuria (either ≥1+ on urine dipstick 4 hours apart or ≥300 mg in an adequately collected, timed urine sample) after the 20th week of gestation. The diagnosis (or absence) was confirmed by a panel of 3 maternal-fetal medicine physicians, blinded to treatment assignment, who reviewed the de-identified medical records of all enrolled women. Sample size N screened/invited = NR N eligible = NR N enrolled = 22 N excluded (with reason) = 'social reasons' (n=1) N lost to follow-up = 0 N completed = 21 N excluded from analysis = 0 N included in analysis = 21 **Costantine 2021:** N screened/invited = 432 N eligible = NR N enrolled = 21 [20 randomised] N excluded (with reason) = 378 prior to enrolment (prior PE >34 6/7 weeks or not in 2 preceding pregnancies [n=302]; gestational age >16 6/7 weeks [n=29]; multifetal gestation [n=15]; selected maternal conditions [n=13]; fetal malformations, demise or plan to terminate [n=11]; contraindications to statins or medications interactions with statins [n=8]; not willing to do a PK study [n=8]; plan to deliver at non-network site [n=5]) and 1 after enrolment (other reasons) N lost to follow-up = 0 N completed = 10 in placebo arm and 10 in pravastatin arm N excluded from analysis = 0 N included in analysis = 10 in placebo arm and 10 in pravastatin arm 1 patient [pravastatin arm] had study drug discontinued

Power

Power calculations not reported. However, authors state that the 'study does not have the power to detect differences in individual outcomes such as congenital anomalies or other clinical or safety outcomes of low prevalence.'

Costantine 2021: Sample size was not intended to achieve power to detect differences in primary or secondary clinical outcomes or other laboratory values; study did not have power to detect differences in individual clinical or safety outcomes of low prevalence.

Maternal characteristics

None of the comparisons between the 2 groups was statistically significant (p>0.05 for all).

Characteristic	Pravastatin (n=11)	Placebo (n=10)
Median gestational age at randomisation, weeks (IQR)	13.9 (13.3–16.1)	14.9 (13.4–16.4)
Median gestational age at delivery in prior pregnancy, weeks (IQR)	32.0 (30.7–33.0)	30.7 (29.4–32.0)
Median maternal age, years (IQR)	27 (21–34)	30 (27–34)
Median BMI, kg/m^2 (IQR)	36 (26–38.2)	29.6 (27–32.3)
Race/ethnicity, n		
White	10	9
African American	0	1
Asian	0	0
American Indian	1	0
Hispanic	5	7
Non-Hispanic	6	3
Obesity[a] n (%)	8 (72.7)	4 (40)
Median systolic blood pressure at entry to care, mmHg (IQR)	109 (107–131)	115 (110–122)
Median diastolic blood pressure at entry to care, mmHg (IQR)	64 (55–77)	68 (64–72)
Chronic hypertension, n (%)	5 (50)	3 (30)
Median parity (IQR)	1 (1–2)	2 (2–3)
Use of low-dose aspirin, n (%)	2 (18)	3 (30)

[a]Defined as BMI≥30 kg/m^2 using pre-pregnancy weight.

Costantine 2021:

Characteristics	Placebo[a] (n=10)	Pravastatin[a] (n=10)
Race		
White	6 (60)	7 (70)
Black	4 (40)	2 (20)
Asian	0 (0)	1 (10)
Ethnicity		
Hispanic	4 (40)	2 (20)
Non-Hispanic	6 (60)	8 (80)
Marital status		
Married	6 (60)	7 (70)

Study Reference	**Costantine 2016 [Costantine 2016 and Costantine 2021]**

Divorced	1 (10)	0 (0)
Single	3 (30)	3 (30)
Age (years)	31.5 (24–33)	31.5 (29–33)
Body mass index (kg/m^2)[a]	36.3 (32.8–42.6)	25.4 (20.9–27.9)
Systolic blood pressure at entry to care (mm Hg)	124.5 (114–132)	113.5 (98–125)
Diastolic blood pressure at entry to care (mm Hg)	71.0 (65–78)	68.0 (64–75)
Gestational age at randomisation (week)	13.9 (13.4–14.6)	15.1 (14.0–16.3)
Diabetes mellitus	0 (0)	1 (10)
Chronic hypertension	4 (40)	2 (20)
Parity	3 (2–5)	3 (2–4)
Gestational age at delivery in previous index pregnancy (week)	29.8 (26–33.1)	32.5 (30.3–33.4)
Use of low dose aspirin	6 (60)	8 (80)

Data are reported as median (interquartile range), or number (percentage). Prepregnancy weight was used to determine body mass index. Race and ethnicity were self-reported by patients. Blood pressure at entry to care, measured in clinic after a 10-minute rest period, was measured in seating position with the right arm in a roughly horizontal position at heart level and supported on a desk. Parity is any pregnancy that lasted >20 weeks gestation.

[a]None of the comparisons between the 2 groups is statistically significant (p>0.05) except for body mass index and gestational age at randomisation

Obesity: placebo 9 (90%), pravastatin 2 (20%)

Intervention

Women's pregnancy management (including antenatal testing, ultrasounds, management of preeclampsia, use of low dose aspirin, and others) was left to the discretion of the treating physician and performed as recommended by standard prenatal care as defined by the respective participating institution. Women's care and that of their infants was according to standard practice.

Pravastatin (n = 11)
Women randomised to pravastatin took 1 capsule containing 10 mg pravastatin orally daily, and treatment continued until delivery or until a condition developed that required discontinuation of the study drug.

Placebo (n = 10)
Women randomised to placebo took 1 capsule containing placebo orally daily, and treatment continued until delivery or until a condition developed that required discontinuation of the study drug.

Costantine 2021: Patients were randomised to a daily dose of 20 mg pravastatin (n=10) or placebo (n=10). Patients were asked to take 1 capsule orally daily and treatment continued until delivery or until a condition developed that required discontinuation of the study drug.

Outcomes Measured

Primary endpoint
The primary outcomes were maternal-fetal safety and pravastatin pharmacokinetic parameters during pregnancy. Safety outcomes included evaluation of medication side effects, maternal AEs and serious AEs, as well as fetal or perinatal death, and congenital malformations.

Secondary endpoints
Maternal and fetal/neonatal outcomes including rate and severity of pre-eclampsia, gestational age at delivery, rate of preterm delivery, maternal lipid profile, and the concentrations of PlGF, sFlt-1 and sEng in the maternal circulation.

Costantine 2021:

Study Reference | **Costantine 2016 [Costantine 2016 and Costantine 2021]**

Primary endpoints included maternal-fetal safety (medication side effects, maternal adverse events and serious adverse events, fetal or perinatal death, congenital malformations, and others) and pharmacokinetic parameters (maximum concentration, time to maximum concentration, area under the concentration time curve, apparent oral clearance, half-life, and renal clearance) of pravastatin during pregnancy.

Secondary endpoints included maternal and umbilical cord blood chemistries and maternal and neonatal outcomes, including rates and severity of PE and preterm delivery, gestational age at delivery and birthweight.

Effectiveness of the Intervention

Efficacy

None of the comparisons between the 2 groups was statistically significant (p>0.05 for all).

Outcome	Pravastatin (n=10)	Placebo (n=10)
Maternal outcomes		
Pre-eclampsia, n (%)	0 (0)	4 (40)
Severe features, *n*	0	3
Postpartum pre-eclampsia, n (%)	0 (0)	1 (10)[a]
Gestational hypertension, n (%)	1 (10)	1(10)
Gestational age at delivery, weeks, mean (SD)	37.7 (0.9)	36.7 (2.1)
Indicated preterm delivery less than 37 weeks, n (%)	1 (10)[b]	5 (50)[c]
Indicated preterm delivery less than 34 weeks, n (%)	0 (0)	1(10)
Neonatal outcomes		
Respiratory Distress Syndrome, n (%)	1 (10)	2 (20)

[a]This woman developed pre-eclampsia and was delivered at $35^{3/7}$ weeks because of spontaneous preterm labour and history of prior classical caesarean delivery. She received magnesium sulphate and on discharge had normal blood pressure. She then presented 7 days after delivery with elevated blood pressure and was diagnosed with postpartum pre-eclampsia.

[b]One woman was delivered at $35^{5/7}$ weeks for worsening chronic hypertension

[c]Three women were delivered at $33^{6/7}$, $34^{3/7}$, and $35^{2/7}$ for preeclampsia with severe features, one woman was delivered at 361/7 for worsening gestational hypertension and history of classical caesarean delivery, and one woman was delivered at 354/7 for placenta previa.

Costantine 2021:

Maternal and neonatal outcomes of subjects who participated in the study

Characteristic	Placebo (n=10)	Pravastatin (n=10)
Maternal outcomes		
Pre-eclampsia	5 (50)	2 (20)
[a]Pre-eclampsia with severe features	5 (50)	0 (0)
Highest BP		
Systolic blood pressure (mmg Hg)	151.5 (135–186)	144.5 (133–149)
Diastolic blood pressure (mm Hg)	96.0 (89–109)	92.5 (87–104)
Gestational age at delivery (week)	36.5 (30.4–37) 34.5 (10, 4.1)	37.2 (34.9–38.7) 36.4 (10, 3.2)
Indicated PTD <37 week[b]	6 (60)	3 (30)
Indicated PTD <34 week	3 (30)	1 (10)
Length of hospital stay (day)[c]	3 (3–5)	3 (2–3)
Intrauterine growth restriction	2 (20)	1 (10)
Mode of delivery		
Vaginal delivery	2 (20)	2 (20)

Study Reference **Costantine 2016 [Costantine 2016 and Costantine 2021]**

Caesarean delivery	8 (80)	8 (80)
Breastfeeding	8 (80)	6 (75)
Neonatal outcomes		
Birthweight, median (IQR) (g)	2627.5 (1255–2810)	2870 (2445–3395)
Birthweight, mean (SD) (g)	2355.5 (10. 1023.9)	2811.9 (10, 1016.3)
Highest level of care	-	-
Well baby	4 (40)	6 (60)
Intermediate (level 2) or NICU	6 (60)	4 (40)
Length of stay on NICU admission (d)	22.2 (4.1–42.9)	16.2 (6.0–50.9)
Respiratory distress syndrome	4 (40)	3 (30)
[a]Duration oxygen support (day)	26 (15.5–56.5)	3 (2.5–4.0)
Passed ABR or OAE	10 (100)	10 (100)

Data are reported as median (IQR), mean (number, standard deviation) or number (percentage).
[a]p=0.03 for the difference in the rates of PE with severe features and in the duration of oxygen support. None of the other comparisons between the 2 groups is statistically significant (p>0.05)
[b]PE with severe features was an indication for the preterm deliveries in 5 patients of the placebo group and none in the pravastatin group. The overall rates of preterm delivery (irrespective of type) were 60% in the placebo group and 40% in the pravastatin group
[c]For the admission/hospitalisation resulting in delivery

Safety

There were no statistically significant differences between the 2 groups in rates of study drug side effects, congenital anomalies, or other adverse or serious adverse events. The most common side effects reported by women who received pravastatin were musculoskeletal pain and heartburn. There were no reports of myopathy/rhabdomyolysis or liver injury.

Costantine 2021:

Adverse and serious adverse events experienced by patients

Condition	Placebo group[a] (n=10)	Pravastatin group[a] (n=10)
Adverse events		
Headache	3 (30)	5 (50)
Heartburn	1 (10)	4 (40)
Musculoskeletal pain	4 (40)	4 (40)
Muscle weakness	0 (0)	2 (20)
Dizziness	1 (10)	2 (20)
Chest pain	0 (0)	1 (10)
Diarrhoea	2 (20)	2 (20)
Cough	1 (10)	0 (0)
Swelling	0 (0)	2 (20)
Flatulence	1 (10)	1 (10)
Vomiting	1 (10)	0 (0)
Influenza-like symptoms	0 (0)	1 (10)
Constipation	3 (30)	0 (0)
Rash	0 (0)	1 (10)
Anxiety or nervousness	2 (20)	1 (10)

Study Reference	Costantine 2016 [Costantine 2016 and Costantine 2021]

Serious adverse events		
Maternal, fetal or infant death	0 (0)	0 (0)
Rhabdomyolysis[b]	0 (0)	0 (0)
Livery injury[b]	0 (0)	0 (0)
Congenital anomalies	2 (20)	0 (0)
Myopathy[c]	0 (0)	1 (10)
Hospitalisation >24 hour	3 (30)	2 (20)
Pre-eclampsia workup/BP	3 (30)	1 (10)
Fetal growth restriction	0 (0)	1 (10)
Preterm contractions	0 (0)	1 (10)

Data are reported as number (percentage).
[a]None of the comparisons between the 2 groups are statistically significant ($p<0.05$).
[b]Rhabdomyolysis was defined as muscle pain or muscle weakness in conjunction with an increase in CK values to greater than 10-fold the upper limit of normal. Liver injury was diagnosed based on elevation of transaminase (AST or ALT) levels greater than 3-fold the upper limit of normal. Myopathy was considered in any patient with diffuse myalgias, muscle tenderness, or weakness and/or marked elevation of CK.
[c]This patient as randomised to pravastatin and developed muscles weakness. Workup was negative with CK below the upper limit of normal. The study drug was discontinued 18 days after it was started and the patient symptoms resolved completely 5 days later. Patient presented at 28^{+6} weeks gestation with placental abruption and delivered. There was no evidence of pre-eclampsia. The patient's **obstetrical history was significant for** abruption and neonatal demise at 30 weeks gestation in her first pregnancy. This patient was considered to have myopathy, per protocol definition.

Authors' Conclusions	Although the data are preliminary, no identifiable safety risks were associated with pravastatin use in this cohort. This favourable risk-benefit analysis justifies continued research with dose escalation in a future larger clinical trial to evaluate pravastatin's effectiveness in preventing PE. **Costantine 2021:** This study confirms the safety data regarding the use of pravastatin (20 mg) for the prevention of pre-eclampsia in high-risk pregnant patients. Although data are preliminary, no identifiable safety risks were associated with pravastatin risk in this cohort and a trend towards improved maternal and neonatal outcomes was demonstrated (potential signal for benefit [lower rates of pre-eclampsia and indicated preterm delivery]). However, these serious safety outcomes are rare, and the study was not powered to detect any significant differences. This overall favourable risk-benefit analysis justifies a larger clinical trial to evaluate pravastatin's effectiveness in preventing pre-eclampsia.

Abbreviations: ABR, auditory brainstem response; AE, adverse event; ALT, alanine aminotransferase; ASD, atrial septal defect; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CK, creatinine kinase; HIV, human immunodeficiency virus; IQR, interquartile range; NICU, neonatal intensive care unit; NR, not reported; OAE, otoacoustic emissions; PE, pre-eclampsia; PlGF, placental growth factor; PK, pharmacokinetic; PTD, preterm delivery; RCT, randomised controlled trial; SD, standard deviation; sEng, soluble endoglin; sFlt-1, soluble fms-like tyrosine kinase

Table 26f: Cruz-Lemini 2021

Study Reference	Cruz-Lemini 2021
Study Design	Design SLR and MA Objective To assess the effectiveness of LMWH in the prevention of PE and other placenta-related complications. As secondary objectives, analyses of the effect of combined treatment of LMWH and LDA, presence of thrombophilia, moment of initiation of treatment, type of heparin administered, and number of study centres were performed. The risk of haemorrhagic complications or secondary effects of LMWH were also evaluated. Finally, a sub analysis was performed to ascertain differences among types of heparin administered.

Study Reference	Cruz-Lemini 2021
	Dates 1945 to June 25, 2020 (search limits for studies) Country Italy, Egypt, Canada, France, the Netherlands, Germany, New Zealand, Turkey, Spain Setting NR
Population Characteristics	Patient recruitment/eligibility An electronic search was made from PubMed and Cochrane Central Register of Controlled Trials to identify studies. Abstracts of congresses and scientific meetings, reference lists of retrieved articles, published study protocols, previously published systematic reviews, and review articles for any additional relevant studies were reviewed. No language restriction was imposed. RCTs comparing treatment with LMWH or unfractionated heparin (with or without LDA) with no treatment or LDA alone in women who had any known risk factors for developing PE, such as adverse obstetrical history (previous PE, FGR, PA, or stillbirth), and medical history including thrombophilia, autoimmune diseases, and chronic hypertension were included. Trials were excluded if they (1) were not randomised, (2) assessed the effect of heparin on diagnosed PE, or (3) did not report PE as an outcome. Studies were also excluded if additional information on methodological issues or complete results could not be obtained. If cointerventions were present, the studies were considered eligible for inclusion provided they were present equally for each trial arm. Randomisation methods All included studies were randomised Blinding Blinding was not possible in most trials because of the intervention, i.e., subcutaneous injection of LMWH) Data collection Abstract screening was performed independently by 2 of the authors. The final selection, with full article review and data extraction to a specifically developed form, was performed independently by 3 reviewers and any discrepancies were resolved by discussion. Information was extracted on study characteristics (randomisation procedure, uni- or multicentric), participants (inclusion and exclusion criteria, number of women per group, presence and type of risk factors, maternal age, GA at inclusion), details of interventions (heparin type, daily dose, presence of cointervention with aspirin, use of placebo), and outcomes (number of outcome events, adverse effects reported). Risk of bias of the final included studies was also performed. Duration of follow-up N/A Definition of PE The criteria for the definition of PE were those of the International Society for the Study of Hypertension in Pregnancy or those of the American College of Obstetricians and Gynaecologists. Considering the variations in the definition of PE worldwide, similar definitions were accepted. Sample size N records identified through database searches and screened = 556 N excluded based on title and abstract = 520 N full-text articles assessed for eligibility = 36 N excluded (with reason) = 21 (some duplicates, other reasons for exclusions NR) N included in MA = 15 (which included 2,795 women) Power N/A

Study Reference	Cruz-Lemini 2021
	Maternal characteristics Women with any known risk factors for developing PE, such as adverse obstetrical history (previous PE, FGR, PA or stillbirth) and medical history including thrombophilia, autoimmune diseases and chronic hypertension. Otherwise N/A
Intervention	Treatment with LMWH or unfractionated heparin (with or without LDA) compared with no treatment or LDA alone
Outcomes Measured	Primary endpoint The primary outcome was the development of PE (mild or severe, term, or preterm) Secondary endpoints Secondary outcomes included FGR or small for gestational age (SGA); stillbirth; perinatal death; miscarriage; PA; preterm delivery; HELLP syndrome; eclampsia; and maternal death. The presence of adverse events was also analysed such as bleeding or haemorrhage, treatment-related allergies, and thrombocytopenia. In addition, sub analyses of the studies based on 5 important points for clinical practice were performed: combination of LMWH with LDA, moment of initiating treatment, presence of thrombophilia, and type of heparin administered.
Effectiveness of the Intervention	Efficacy Primary outcomes (PE) • The MA with data from the 15 trials included (2795 women) showed that patients treated with LMWH presented significantly fewer PE than those not treated with LMWH (OR, 0.62; 95% CI, 0.43–0.90; p=0.010; I^2=36%; NNT=26). Calculation using these data yielded a prediction interval of 0.24 to 1.63. • Subgroup analyses for the timing of treatment excluded 2 studies where LMWH administration began after 16 weeks gestation; the impact of LMWH on PE was stronger than in the global MA (13 RCTs, 2474 participants; OR, 0.55; 95% CI, 0.39–0.76; p=0.0004; I^2=17%). • Analysis according to concomitant LDA use showed that this association was also significant for the 6 studies (920 participants) where LMWH was combined with LDA as an intervention or in the overall population (OR, 0.62; 95% CI, 0.41–0.95; p=0.030; I^2=6%). When the analysis was performed with the other 9 RCTs including 1875 participants, in whom LDA was not systematically administered, no significant differences were found (OR, 0.65; 95% CI, 0.36–1.16; p=0.140; I^2=52%). However, if studies beginning treatment after 16 weeks gestation were excluded, it showed a reduction of PE (7 RCTs, 1554 participants; OR, 0.48; 95% CI, 0.29–0.82; p=0.006; I^2=29%). • Analysis for previous PE as inclusion criteria before 16 weeks gestation (9 studies, 1405 participants) showed a 40% reduction on the incidence of recurrent PE (OR, 0.60; 95% CI, 0.39–0.93; P=0.020; I^2=31%). • When studies were divided by inclusion (4 studies, 580 participants) or exclusion (8 studies, 1482 participants) of patients with thrombophilia, the effect of LMWH on occurrence of PE was nonsignificant in thrombophilic patients versus patients without thrombophilia (p=0.470). • Analysis for studies with miscarriage as inclusion criteria (3 studies, 809 participants) showed no significant effect of LMWH on the incidence of PE (OR, 0.60; 95% CI, 0.29–1.23, P=0.160; I^2=0%). • When analyses by type of LMWH were performed, both enoxaparin and dalteparin were each associated with a significant reduction in PE, with no statistical differences between them (enoxaparin, 7 RCTs, 1532 participants; OR, 0.58; 95% CI, 0.39–0.87; p=0.008; I^2=20%; dalteparin, 6 RCTs, 1103 participants; OR, 0.50; 95% CI, 0.25–0.97; p=0.040; I^2=36%). Secondary outcomes • Data from the 15 trials included showed that patients treated with LMWH presented significantly fewer SGA than those not treated with LMWH (15 RCTs, 2799 participants; OR, 0.61; 95% CI, 0.44–0.83; p=0.002; I^2=39%; NNT=21). • Subgroup analysis by type of heparin showed that dalteparin was associated with a significant reduction in the development of SGA, whereas in patients treated with enoxaparin, such reduction did not reach statistical significance (enoxaparin, 7 RCTs, 1532 participants; OR, 0.75; 95% CI, 0.50–1.11; p=0.150; I^2=42%; dalteparin, 6 RCTs, 1103 participants; OR, 0.48; 95% CI, 0.28–0.82; p=0.007; I^2=29%); the test for subgroup differences was not significant (p=0.190).

Study Reference	Cruz-Lemini 2021
	• No statistically significant differences were found in the occurrence of stillbirth between LMWH-treated and nontreated patients (11 RCTs, 2315 participants; OR, 0.72; 95% CI, 0.40–1.30; p=0.280; I^2=0%). • Significantly fewer perinatal deaths occurred among the offspring of LMWH-treated patients than nontreated patients (7 RCTs, 1393 participants; OR, 0.49; 95% CI, 0.25–0.94; p=0.030; I^2=4%). • Notably, 8 RCTs (1566 women) reported the outcome of miscarriage. Patients treated with LMWH showed no significant benefit compared with nontreated patients with regard to miscarriage (OR, 0.78; 95% CI, 0.46–1.33; p=0.360; I^2=0%). • No statistically significant difference in the occurrence of PA was found between LMWH-treated and nontreated patients, regardless of combination with LDA (14 RCTs, 2877 participants; OR, 1.12; 95% CI, 0.69–1.82; p=0.650; I^2=0%). • Patients treated with LMWH showed no differences compared with nontreated patients with regard to preterm delivery (14 RCTs, 2719 participants; OR, 0.93; 95% CI, 0.76–1.13; p=0.460; I^2=2%). • No statistically significant differences were found in terms of the occurrence of HELLP syndrome between LMWH-treated and nontreated patients (8 RCTs, 1243 participants; OR, 0.65; 95% CI, 0.27–1.56; p=0.340; I^2=0%). • 7 RCTs recorded the outcome eclampsia, although 4 of them reported no events in any of the groups. 1 study reported 3 episodes of eclampsia, 1 in the LMWH group and 2 in the nontreated group; 3 studies reported maternal mortality as an outcome, with no events in either group. • Subgroup analysis by uni- vs multicentre studies showed single-centre studies associated with a significant reduction in the development of PE, whereas in multicentre studies, such reduction did not reach statistical significance (unicentre, 6 RCTs, 956 participants; OR, 0.44; 95% CI, 0.23–0.85; p=0.020; I^2=45%; multicentre, 9 RCTs, 1839 participants; OR, 0.78; 95% CI, 0.55–1.12; p=0.180; I^2=2%); the test for subgroup differences was not significant (p=0.130). Finally, both types of studies showed significant associations with reduction of SGA. Overall, methodological quality ranged from moderate to very low owing to concerns about the risk of bias (e.g. lack of blinding), the small number of events for many outcomes, lack of details about important methodological issues in some studies, substantial heterogeneity detected in the analyses, and wide CIs indicating imprecision in the results. All trials, except 2, were considered as high risk of bias owing to lack of blinding, but even for these with unclear risk of bias, it was unlikely to have occurred. Safety • No statistically significant difference in bleeding was found between LMWH-treated and nontreated patients, regardless of whether or not LMWH was combined with LDA (10 RCTs, 2109 participants; OR, 1.14; 95% CI, 0.75–1.71; p=0.540; I^2=8%). • Significantly more episodes of allergies and skin reactions occurred in patients treated with LMWH than nontreated patients (6 RCTs, 1106 participants; OR, 4.86; 95% CI, 2.04–11.62; p=0.0004; I^2=0%). However, the number of events was small, and the 95% CIs were too wide to be certain about these results. • With the exception of bleeding and allergies, other adverse effects reported were very rare. Thrombocytopenia was reported in 3 studies, with a range between 0 and 6 events; thrombosis was reported in 3 studies, with a range between 0 and 4 events, and finally, another study reported similar numbers of transfusion events in both groups.
Authors' Conclusions	The results of this systematic review and MA suggest that in high-risk women, LMWH prophylaxis may decrease the risk of PE, delivery of an SGA neonate, and perinatal death. The observed benefit seems to be conditioned by beginning treatment before 16 weeks gestation, especially to prevent PE and SGA, and in women with previous placental complications. These effects seem to be maintained, regardless of the presence of thrombophilia or the type of heparin administered. Sub analysis of 6 studies that included LDA as intervention in both study groups showed that the combination of LMWH and LDA performed better than LDA alone in the prevention of PE. In addition, no major side effects such as PA or haemorrhage were observed in women treated with LMWH (alone or in combination with LDA). In conclusion, LMWH reduces the incidence of PE and placenta-mediated complications in high-risk women with previous adverse obstetrical history, especially in those included for previous placental complications and when treatment is started before 16 weeks gestation. Combined treatment with LDA was associated with a substantial reduction in the risk of PE compared with LDA alone. However, this MA gives rise to concerns regarding the low quality of evidence available, and therefore, although pooled effect estimates were associated with marked PE reduction, heterogeneity (clinical and statistical)

Study Reference	Cruz-Lemini 2021
	questions the validity of this conclusion. Future trials examining the prevention of placental complications by LMWH in addition to LDA are warranted before any clinical application is adopted.

Abbreviations: CI, confidence interval; FGR, fetal growth restriction; GA, gestational age; HELLP, haemolysis, elevated liver enzymes, and low platelet count; LDA, low-dose aspirin; LMWH, low-molecular-weight heparin; N/A, not applicable; NNT, number needed to treat; OR, odds ratio; PA, placental abruption; PE, pre-eclampsia; RCT, randomised controlled trial; SGA, small for gestational age; SLR, systematic literature review.

Table 26g: Dobert 2021

Study Reference	Dobert 2021
Study Design	Design RCT, multicentre Objective To test the hypothesis that, among women identified as high risk for term PE, pravastatin at a dose of 20 mg/d from 35^{+0} to 36^{+6} weeks of gestation until delivery, compared with placebo, would result in halving of the incidence of delivery with PE. Dates August 2018 to November 2019 Country England, Spain and Belgium Setting 10 maternity hospitals
Population Characteristics	Patient recruitment/eligibility Inclusion criteria for the trial were age of ≥18 years, singleton pregnancy, live fetus at the 35- to 37-week scan, and high risk (≥1 in 20) for term preeclampsia determined via a screening at 35 to 36 weeks which used an algorithm that combined maternal demographic characteristics and medical history, MAP, and maternal serum PlGF and sFlt-1. Women who were unconscious or severely ill; those with learning difficulties or serious mental illness; women with major fetal abnormality; women with planned delivery within 7 days of the randomisation date; women with established PE; those with statin use within 28 days before randomisation; women participating in another intervention study that influences the outcomes of this study; and those with contraindications for statin therapy were excluded. Randomisation methods Eligible women were randomly assigned in a 1:1 ratio with the use of a web-based system to receive either pravastatin or placebo. In the random-sequence generation, there was stratification according to participating centre. Blinding Double-blind; The placebo capsules were identical to the pravastatin capsules in parameters such as size, thickness, physical properties, and appearance. Data collection There was a central adjudication process to establish the diagnosis of PE; all anonymised data in cases of suspected PE reported to the Fundación para la Formación e Investigación Sanitaria and by the Fetal Medicine Foundation were examined by 1 researcher to determine whether the diagnosis was correct. Gestational age was determined by the measurement of the fetal CRL at 11 to 13 weeks or fetal head circumference at 19 to 24 weeks. Maternal characteristics, medical history and obstetric history were recorded and maternal weight and height were measured. Race and ethnic group were self-reported The effect of pravastatin on serum PlGF and sFlt-1 concentrations 1 and 3 weeks after the onset of treatment and the safety of pravastatin were

Study Reference	Dobert 2021

assessed by creatine kinase concentrations in women with adverse muscle symptoms. Adherence and adverse events were assessed and recorded at follow up clinical visits at 36 to 38 and 39 to 40 weeks of gestation, at 6 weeks after delivery, and in 1 telephone interview at 37 to 39 weeks of gestation. Participants were encouraged to record any side effects or adverse events in a diary that was reviewed at each trial visit, and they were specifically asked about such events at the telephone interview. Researchers assessed adherence by counting the capsules returned by participants at each visit and by the participants themselves at the telephone interview. The total number of capsules taken was calculated by subtracting the number of capsules returned from the number of capsules prescribed. Adherence was considered to be good if the reported intake of capsules was ≥80% of the total number that the participants should have taken between the date of randomisation and the date of the 41 weeks gestation or delivery if it occurred before 41 weeks.

Duration of follow-up
6 weeks after delivery

Definition of PE
Defined as per the American College of Obstetrics and Gynaecology

Sample size
N screened/invited = 29,816 women were screened for term PE; 3,490 deemed high-risk for term PE via screening at 35 to 36 weeks
N eligible = 3,105
N enrolled = 1,120 (1,985 of those eligible declined to participate in the trial)
N excluded (with reason) = 385 excluded including: expected delivery within 1 week (n=143), PE already established (n=125), delivered before randomisation (n=24), high liver enzymes (n=52), high creatinine kinase (n=5), major fetal defect (n=8), chronic renal disease (n=4), severe heart condition (n=3), muscular dystrophy (n=1), lactose intolerance (n=3), concurrent or previous cancer (n=3), concurrent medication (n=7), participating in another trial (n=2), moved away (n=4), breastfeeding (n=1)
N lost to follow-up = NR
N completed = NR
N excluded from analysis = 19 from pravastatin group, 10 from placebo group (withdrew consent)
N included in analysis = 548 (pravastatin) and 543 (placebo)

Of the 29,818 pregnancies screened, 108 women were lost to follow-up, 29 women withdrew consent and 2 pregnancies were terminated

Power
It was calculated that enrolment of 1020 participants would give the study a power of 90% to show a treatment effect at a 2-sided α level of 5%. The target recruitment figure was inflated to 1120 to account for attrition. The trial was not adequately powered for the secondary outcomes.

Maternal characteristics

- The pravastatin and placebo groups were similar in baseline characteristics; there was balance in baseline variables between the 2 groups

Characteristic	Pravastatin group (n=548)	Placebo group (n=543)
Gestation at randomisation, median (IQR), week	35.9 (35.4–36.1)	35.9 (35.4–36.1)
Age, median (IQR), years	32.9 (28.6–36.9)	32.5 (28.0–36.8)
BMI, median (IQR), kg/m^2	30.5 (27.3–34.8)	30.9 (27.2–34.9)
Race or ethnic group, n (%)	-	-
White	392 (71.5)	402 (74.0)
Black	67 (12.2)	68 (12.5)
South Asian	68 (12.4)	47 (8.7)
East Asian	4 (0.7)	11 (2.0)

Study Reference	Dobert 2021		
	Mixed	17 (3.1)	15 (2.8)
	Conception, n (%)	-	-
	Natural conception, n (%)	513 (93.6)	509 (93.7)
	In vitro fertilisation, n (%)	35 (6.4)	34 (6.3)
	Cigarette smoker, n (%)	26 (4.7)	24 (4.4)
	Mother had PE, n (%)	36 (6.6)	43 (7.9)
	Medical history, n (%)	-	-
	Chronic hypertension	28 (5.1)	20 (3.7)
	Systemic lupus erythematosus	3 (0.5)	2 (0.4)
	Antiphospholipid syndrome	1 (0.2)	7 (1.3)
	Diabetes type 1	3 (0.5)	2 (0.4)
	Diabetes type 2	11 (2.0)	11 (2.0)
	Obstetric history	-	-
	Nulliparous, n (%)	311 (56.8)	319 (58.7)
	Multiparous without preeclampsia, n (%)	209 (38.1)	191 (35.2)
	Multiparous with preeclampsia, n (%)	28 (5.1)	33 (6.1)
	Interval from last pregnancy, median (IQR), years	3.9 (2.1–6.6)	3.1 (1.8–5.5)
	Gestation at delivery of last pregnancy, week	39.0 (38.0–40.0)	39.0 (38.0–40.0)
	Treatment with aspirin 150 mg/d, n (%)	92 (16.8)	76 (14.0)
	Screening for preeclampsia at 35–36 weeks	-	-
	MAP, median (IQR), mm Hg	95.6 (91.3–100.2)	96 (91.8–100.2)
	MAP MoM	1.1 (1.0–1.1)	1.1 (1.0–1.1)
	Serum PlGF, median (IQR), pg/mL	87.61 (58.53–131.03)	85.7 (54.8–133.8)
	Serum PlGF MoM	0.3 (0.2–0.5)	0.3 (0.2–0.5)
	Serum sFlt-1, median (IQR), pg/mL	4921 (3614–6831)	4929 (3677–6658)
	sFlt-1 MoM	2.2 (1.7–3.0)	2.2 (1.7–2.9)
	Risk of preeclampsia, median (IQR)	1 in 8 (1 in 14–1 in 4)	1 in 9 (1 in 14–1 in 5)
Intervention	Pravastatin 20 mg once per day from 35 to 37 weeks until 41 weeks of gestation or delivery, onset of labour, or 1 day before planned caesarean section (n=548 included in analysis) Placebo (n=543 included in analysis)		
Outcomes Measured	Primary endpoint Delivery with PE (any time after randomisation) Secondary endpoints Adverse outcomes of pregnancy at any gestation and at or after 37 weeks of gestation, stillbirth or neonatal death, neonatal morbidity, neonatal therapy, and low birth weight. The effect of pravastatin on serum PlGF and sFlt-1 concentrations 1 and 3 weeks after the onset of treatment and the safety of pravastatin were also assessed.		
Effectiveness of the Intervention	Efficacy Primary outcome: Allowing for the effect of risk at the time of screening and participating centre, the mixed-effects Cox regression showed no evidence of an effect of pravastatin (hazard ratio for statin/placebo, 1.08 [95% CI, 0.78–1.49]; p=0.65). There was no evidence of interaction among the effect of pravastatin, estimated risk of preeclampsia, pregnancy history, adherence, and aspirin treatment.		

Study Reference **Dobert 2021**

Secondary outcomes: There was no significant between-group difference in the incidence of any secondary outcomes

Outcome	Pravastatin group	Placebo group	Relative Risk (95% CI)	p value
Group total, n	548	543	-	-
PE, n (%)	80 (14.6)	74 (13.6)	1.08 (0.78–1.49)*	0.65
Secondary outcomes				
Adverse outcomes at any gestation n (%)				
GH	99 (18.1)	89 (16.4)	1.08 (0.83–1.40)	0.57
PE or GH	179 (32.7)	163 (30)	1.05 (0.89–1.23)	0.60
SGA <5th percentile	86 (15.7)	77 (14.2)	1.08 (0.81–1.43)	0.61
Stillbirth	0	0	-	-
Abruption	1 (0.2)	2 (0.4)	-	-
Composite of all above	238 (43.4)	221 (40.7)	1.03 (0.90–1.17)	0.67
Group total, n	536	530	-	-
Adverse outcomes at ≥37 week, n (%)				
PE	79 (14.7)	74 (14.0)	1.01 (0.76–1.33)	0.96
GH	99 (18.5)	86 (16.2)	1.12 (0.86–1.45)	0.41
PE or GH	178 (33.2)	160 (30.2)	1.06 (0.90–1.25)	0.48
SGA <5th percentile	83 (15.5)	76 (14.3)	1.06 (0.79–1.40)	0.71
Stillbirth	0	0	-	-
Abruption	1 (0.2)	2 (0.4)	-	-
Composite of all above	234 (43.7)	218 (41.1)	1.03 (0.90–1.17)	0.70
Group total, n	548	543	-	-
Neonatal outcomes, n (%)				
SGA <3rd percentile	65 (11.9)	55 (10.1)	1.00 (0.72–1.40)	1.00
SGA <10th percentile	118 (21.5)	116 (21.4)	0.99 (0.79–1.24)	0.93
Neonatal therapy, n (%)	-	-	-	-
ICU admission	10 (1.8)	16 (2.9)	0.62 (0.28–1.35)	0.23
Ventilation with positive airway pressure or intubation	7 (1.3)	15 (2.8)	0.46 (0.19–1.13)	0.09
Composite of all above	12 (2.2)	21 (3.9)	0.57 (0.28–1.14)	0.11
Neonatal morbidity, n (%)				
Respiratory distress syndrome	7 (1.3)	15 (2.8)	0.46 (0.19–1.13)	0.09
Intraventricular haemorrhage	0	1 (0.2)	-	-
Anaemia	0	1 (0.2)	-	-
Necrotising enterocolitis	0	0	-	-
Sepsis	1 (0.2)	1 (0.2)	-	-

Study Reference **Dobert 2021**

Composite of all above	8 (1.5)	15 (2.8)	0.53 (0.23–1.24)	0.14

*Hazard Ratio (95% CI)

Safety

In the pravastatin group, there was at least 1 serious adverse event in 2 cases (0.4%) and at least 1 adverse event in 112 (20.4%); respective frequencies for the placebo group were 6 (1.1%) and 103 (19.0%). There was no significant between-group difference in the incidence of these events. Muscle pains or cramps developed in 6 patients in the pravastatin group and in 7 in the placebo group; creatine kinase concentrations were normal in all 13 cases.

Serious adverse events among trial participants

Serious adverse event	Pravastatin group (n=548)	Placebo group (n=543)
Maternal serious adverse events, n	-	-
Rupture of uterus and bladder	0	1
Fetal structure defects, n	-	-
Cleft palate and lip	1	0
Ventricular septal defect	1	0
Ventricular septal defect and atrial septal defect	0	1
Hip dysplasia	0	1
Hypospadias	0	2
Talipes equinovarus unilateral	0	1
At least 1 serious adverse event, n (%)	2 (0.4)	6 (1.1)
No serious adverse event, n (%)	546 (99.6)	537 (98.9)

*None of these serious adverse events were considered by the investigators to be associated with pravastatin or placebo

Supplemental table IV – adverse events according to trial group

Adverse event	Pravastatin group (n = 548)	Placebo group (n = 543)	p value
Headache and/or dizziness, n (%)	52 (9.5)	45 (8.3)	0.52
Nausea and/or vomiting, n (%)	34 (6.2)	26 (4.8)	0.35
Abdominal and/or pelvic pain, n (%)	9 (1.6)	6 (1.1)	0.60
Dyspepsia and/or heartburn	6 (1.1)	6 (1.1)	1.00
Nasal bleeding, n (%)	2 (0.4)	1 (0.2)	1.00
Pain in chest, back or limbs, n (%)	5 (0.9)	5 (0.9)	1.00
Skin rash, n (%)	2 (0.4)	4 (0.7)	0.45
Pruritus, n (%)	9 (1.6)	8 (1.5)	1.00
Diarrhoea, n (%)	14 (2.6)	18 (3.3)	0.48
Constipation, n (%)	4 (0.7)	1 (0.2)	0.37
Peripheral oedema, n (%)	6 (1.1)	3 (0.6)	0.51
Shortness of breath, n (%)	1 (0.2)	2 (0.4)	0.62
Visual disturbance, n (%)	3 (0.6)	9 (1.7)	0.09
Palpitations, n (%)	1 (0.2)	1 (0.2)	1.00
Paraesthesia, n (%)	4 (0.7)	5 (0.9)	0.75
Fatigue or weakness, n (%)	5 (0.9)	10 (1.8)	0.21

Study Reference	Dobert 2021			
	Muscle pain/cramps, n (%)	6 (1.1)	7 (1.3)	0.79
	Anxiety/depression, n (%)	1 (0.2)	2 (0.4)	0.62
	Sweating, n (%)	3 (0.6)	1 (0.2)	0.62
	Dry mouth, n (%)	1 (0.2)	2 (0.4)	0.62
	Sleep disturbance, n (%)	2 (0.4)	6 (1.1)	0.18
	Other adverse event, (%)[a]	6 (1.1)	3 (0.6)	0.51
	At least one adverse event, n (%)	112 (20.4)	103 (19.0)	0.54
	No adverse event, n (%)	436 (79.6)	440 (81.0)	0.54
	[a]The group of other adverse events includes 1 case of groin pain, 1 case of dark urine and hip pain, 1 case of tachycardia, 1 case of tinnitus, 2 cases of impaired liver function, 1 case of pyrexia, 1 case of rib pain and 1 case of sore throat			
Authors' Conclusions	There was no evidence of interaction among the effect of pravastatin, estimated risk for PE, pregnancy history, adherence and aspirin consumption. There was no significant between-group difference in the incidence of pregnancy complications or of adverse fetal or neonatal outcomes. In women with singleton pregnancies at high risk of term preeclampsia, the administration of pravastatin at a dose of 20 mg/d from 35 to 37 weeks of gestation until delivery did not reduce the incidence of delivery with preeclampsia.			

Abbreviations: BMI, body mass index; CI, confidence interval; CRL, crown rump length; GH, gestational hypertension; ICU, intensive care unit; IQR, interquartile range; MAP, mean arterial pressure; MoM, multiple of the median; NR, not reported; PE, pre-eclampsia; PlGF, placental growth factor; RCT, randomised controlled trial; sFlt-1, soluble fms-like tyrosine kinase-1; SGA, small for gestational age

Table 26h: McLaughlin 2021

Study Reference	McLaughlin 2021
Study Design	Design Single centre pilot observational study Objective Explore the potential of daily LMWH administration to restore deficient circulating levels of PlGF in clinically high-risk patients, beginning in the second trimester. Dates July 2017 to March 2021 (follow-up period) Country Canada Setting Speciality high-risk clinic in Toronto at Mount Sinai Hospital; maternal-fetal medicine placenta clinic programme of care focused on placental dysfunction disorders
Population Characteristics	Patient recruitment/eligibility Eligible patients included those at the age of >18 years with a live singleton fetus. Patients were not eligible if they were already on LMWH therapy for a maternal indication or if previously diagnosed with a major thrombophilia disorder or antiphospholipid syndrome.

Study Reference **McLaughlin 2021**

12 pregnant patients with a circulating PlGF at the <10th centile in the early second trimester (between 16 and 20 weeks gestation) were identified for study inclusion.

Randomisation methods
NR

Blinding
NR but after delivery the placenta was sent for histopathology testing by a dedicated perinatal pathologist blinded to treatment during pregnancy

Data collection
At the 16-week assessment, each patient completed an early placental health assessment comprising fetal biometry, amniotic fluid and mean uterine artery Doppler ultrasound. Same-day PlGF testing was included. Circulating maternal PlGF levels in response to LMWH were measured every 2 to 4 weeks in the placenta clinic appointments.

Duration of follow-up
Delivery

Definition of PE

Systolic blood pressure of ≥140 mm Hg or diastolic blood pressure of ≥90 mm Hg on 2 occasions at least 4 hours apart after 20^{+0} weeks gestation, with evidence of related organ injury: proteinuria (urine protein to creatinine ratio of ≥30 mg/mol), thrombocytopenia (platelets of <100x109/L), renal compromise (serum creatinine of ≥1.1 mg/dL), or impaired liver function (aspartate aminotransferase of ≥70 U/L or alanine aminotransferase of ≥70 U/L).

Sample size
N screened/invited = NR
N eligible = NR
N enrolled = 12
N excluded (with reason) = 0
N lost to follow-up = 0
N completed = 12
N excluded from analysis = 0
N included in analysis = 12

Power
NR

Maternal characteristics

Maternal characteristics	Early-second-trimester low PlGF, LMWH (n=7)	Early-second-trimester low PlGF, no LMWH (n=5)
Demographic characteristics		
Age, years	35 (34–38)	39 (35–40)
Ethnicity		
White	5 (71)	1 (20)
Black	0 (0)	0 (0)

Study Reference	McLaughlin 2021		
	East Asian	1 (14)	1 (20)
	South Asian	1 (14)	3 (60)
	BMI, kg/m^2	27 (24–31)	26 (21–29)
	Chronic hypertension	0 (0)	1 (20)
	Preexisting diabetes	0 (0)	0 (0)
	Initial assessment, week gestation	12 (11–13)	16 (16–18)
	Systolic blood pressure at initial assessment, mm Hg[a]	118 (92–120)	112 (105–143)
	Diastolic blood pressure at initial assessment, mm Hg[a]	66 (59–72)	80 (63–89)
	Obstetrical history		
	History of placental complications	5 (71)	2 (40)
	Previous pre-eclampsia	2 (29)	2 (40)
	Early-onset pre-eclampsia <34 week gestation	2	2
	Late-onset pre-eclampsia ≥34 wk gestation	0	0
	Previous fetal death at ≥20 week gestation	3 (43)	2 (40)
	Obstetrical characteristics		
	Nulliparous	2 (29)	2 (40)
	First trimester aneuploidy screening		
	Not performed	1 (14)	1 (20)
	PAPP-A, MoM	0.63 (0.39–0.91)	0.16 (0.12–0.39)
	hCG, MoM	1.00 (0.98–1.32)	2.17 (1.28–3.01)
	Mean uterine artery PI		
	14–20 week gestation	1.99 (1.38–2.49)	1.54 (1.42–1.66)
	20–24 week gestation	1.57 (1.36–1.82)	1.53 (1.45–1.60)
	24–28 week gestation	1.54 (1.16–1.78)	-
	28–36 week gestation	1.21 (0.90–1.38)	-

Data are presented as median (interquartile range) or number (percentage of column)

[a]Blood pressure data missing from 1 patient in the LMWH group

Intervention	LMWH + aspirin (n = 7): received daily prophylactic low-molecular-weight heparin (enoxaparin; 40 mg/day subcutaneously) in addition to aspirin No LMWH; aspirin alone (n = 5) Patients at high risk of severe placental dysfunction in the current pregnancy, based on pre-pregnancy health and obstetrical history, received low-dose (162 mg nightly) aspirin prophylaxis for preeclampsia from 12 weeks gestation as part of standard clinical management.

Study Reference	McLaughlin 2021
	All patients continued to receive standardised high-risk maternal-fetal medicine obstetrical care at the placenta clinic, with appointments every 2 to 4 weeks.
Outcomes Measured	Primary endpoint Primary outcome: change in circulating maternal PlGF levels in response to LMWH Secondary endpoints Secondary outcomes: change in mean uterine artery Doppler PI, gestational age at delivery, maternal and perinatal outcomes and placental pathology diagnosis
Effectiveness of the Intervention	Efficacy Pregnancy outcomes and placental pathology of pregnant patients at risk of severe placental dysfunction

Outcomes	Early-second-trimester low PlGF, LMWH (n=7)	Early-second-trimester low PlGF, no LMWH (n=5)
Pregnancy outcome characteristics	-	-
Gestational age at delivery, week	36 (33–37)	23 (22–26)
Maternal outcome	-	-
Pre-eclampsia	4 (57)	0 (0)
Fetal outcome	-	-
Live birth	6 (86)	1 (20)
Stillbirth	1 (14)	4 (80)
Antihypertension medication use	3 (43)	2 (40)
Birthweight, kg	1.93 (1.1–2.7)	0.32 (0.19–0.39)
Placental pathology[a]	-	-
Principal placental pathology	-	-
Maternal vascular malperfusion	3 (43)	2 (40)
Fetal thrombotic vasculopathy	0 (0)	2 (40)
Fetal vascular malperfusion	1 (14)	0 (0)
Chronic histiocytic intervillositis	1 (14)	0 (0)
Perivillous fibrin deposition	1 (14)	0 (0)
Villitis of known etiology	1 (14)	0 (0)
Massive perivillous fibrin deposition	1 (14)	0 (0)
Additional pathology features	-	-
Maternal vascular malperfusion	2 (29)	1 (20)
Chronic histiocytic intervillositis	0 (0)	1 (20)
Fetal thrombotic vasculopathy	1 (14)	0 (0)
Weight at the <third centile	1 (14)	0 (0)
Fetal thrombotic vasculopathy	0 (0)	0 (0)

Data are presented as median (interquartile range) or number (percentage of column)
[a]Placental pathology data missing from 1 patient in the no LMWH group

5 of 7 patients in the LMWH group exhibited increases in circulating PlGF following initiation of LMWH, which ultimately decreased as gestational age advanced. In contrast, no patients in group 2 demonstrated a notable rise in circulating PlGF.

Study Reference	McLaughlin 2021
	Patients in the LMWH group exhibited a later gestational age at delivery, had babies with higher birth weights, and had lower incidence of stillbirth compared to patients in the no LMWH group. In the LMWH group, both patients with normal mean uterine artery Doppler were found to each have a rare placental pathology diagnosis (perivillous fibrin deposition and chronic histiocytic intervillositis), whereas the remaining 5 with abnormal mean uterine artery Doppler expressed features of MVM pathology. Safety NR
Authors' Conclusions	**The findings do not support the clinical use of LMWH to prevent placenta-mediated complications, but they may inform the design** of new pilot randomised control trials confined to a subgroup of high-risk patients already on aspirin prophylaxis. At present, it is not known whether any of the observed in vitro effects of LMWH could exert clinically meaningful actions on the placental such as restoring PlGF release into the maternal circulation, directly acting on the systemic maternal endothelium or on improving the typically restricted uteroplacental circulation that is found in women at the highest risk of severe pre-eclampsia. Therefore, future baseline trial data could incorporate serine urine analysis of the stable C5b fragment that reflects complement activation, together with serial maternal blood angiogenic growth factors and incorporate specialist placental pathology blinded to trial allocation. A continuous reference range for maternal circulating PlGF was established between 12 and 36 weeks gestation for high-risk pregnancy clinicians to assess the ongoing risk of preterm delivery owing to severe placental dysfunction. Among a small subgroup of pregnancies considered high-risk in this context with low maternal circulating PlGF at 16 to 20 weeks gestation, the addition of prophylactic LMWH to aspirin prophylaxis induced a rise in circulating PlGF that was sustained in most patients over several weeks before delivery. Given that the most relevant evidence obtained from systematic reviews of relevant trials support the limited use of LMWH in this context, this data may inform future efforts to conduct a pilot randomised trial to further explore the relevant biologic actions of LMWH in this context, which if favourable could inform a subsequent definitive randomised trial with entry criteria that focus on the assessment of placental function in vivo.

Abbreviations: BMI, body mass index; hCG, human chorionic gonadotrophin; LMWH, low molecular weight heparin; MoM, multiples of the median; MVM, maternal vascular malperfusion; NR, not reported, PAPP-A, pregnancy-associated plasma protein A; PE, pre-eclampsia; PI, pulsatility index; PlGF, placental growth factor.

Table 26i: Meiri 2014

Study Reference	Meiri 2014
Study Design	Design Prospective cohort study, multicentre Objective Evaluation of the use of aspirin for PE prevention. Dates July 2007 to February 2011 Country Israel Setting Doctors' offices and community clinics
Population Characteristics	Patient recruitment/eligibility Pregnant women who attended doctors' offices or community clinics for first trimester evaluation of pregnancy were enrolled in the study. Exclusion criteria: women <18 years, women with non-viable fetuses identified by the absence of a fetal heartbeat, twin pregnancies (including twin pregnancies in

Study Reference	Meiri 2014

which one fetus vanished), women with pregnancy loss before 22 weeks, and women with pregnancy termination due to fetal malformation. Women undergoing in vitro fertilisation, including women with oocyte donation, were enrolled by only after discontinuing treatment for hormonal support of placentation.

Randomisation methods
No randomisation

Blinding
NR – can infer likely no blinding as it remained the physician's decision to prescribe aspirin based on major RFs alone

Data collection
Blood was drawn from pregnant women between 8 and 14 weeks of gestation. PP13 test was performed within 2 to 12 days of blood collection. Gestational age was determined by the last menstrual period and confirmed by first trimester crown rump length measurements. Demographics, medical and pregnancy history were obtained at enrolment. Pregnancy outcome after delivery was obtained either from the patients' medical records and hospital discharge form (85%) or a detailed telephone interview was conducted with a) patients who had delivered at home (13 cases), b) delivered abroad (when contact information was available), and 3) patients who did not keep their hospital discharge form as well as with the patient's physician.

Duration of follow-up
Post-delivery (assumed based on outcomes reported)

Definition of PE
PE was diagnosed according to the criteria of the International Society for the Study of Hypertension in Pregnancy (ISSHP). The criteria were as follows: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least 2 occasions 4 hours apart developed after 20 weeks of gestation in previously normotensive women combined with proteinuria of ≥300 mg in 24 hours, or 2 readings of at least 2+ on dipstick analysis of midstream or catheter urine specimens, if no 24 hour collection was available. Severe PE was defined according to systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg, proteinuria ≥3 g in 24-hour urine specimen or ≥3+ on dipstick as above. Preterm PE cases and Early PE were all delivered before 37 and 34 weeks, respectively.

Sample size
N screened/invited = NR
N eligible = NR
N enrolled = 947
N excluded (with reason) = NR
N lost to follow-up = 15 (address change or move to another country)
N completed = NR
N excluded from analysis = twin pregnancies (n=34, including n = 7 twin pregnancies in which one fetus vanished [results of twin pregnancies analysed elsewhere]); pregnancy loss before 22 weeks (n=36); pregnancy termination due to fetal malformation (n=6); 36 multiple gestation pregnancies (n=36)
N included in analysis = 820

Power
NR

Maternal characteristics

Characteristic	Unaffected singleton (n=757)	PE (n=63)	p value
Characteristic at enrolment	-	-	-

Study Reference	Meiri 2014			
	Maternal age, years, median (range)	30 (18–54)	32 (21–47)	NS
	Gestational age, weeks, median (range)	12 (6–14)	11 (7–13)	NS
	Nullipara, n (%)	405 (54)	24 (38)	<0.001
	Caucasian, n (%)	717 (95)	61 (97)	NS
	Smoking, n (%)	27 (3.6)	2 (3.2)	NS
	BMI, kg/m^2, median (range)	22.3 (17–47)	24.5 (18–40)	NS
	MAP, mmHg, median (range)	77 (57–113)	89 (66–103)	<0.001
	In vitro fertilisation, n (%)	55 (7.3)	11 (17.5)	<0.001
	All risk factors, n (%)	262 (34.6)	33 (52.4)	<0.001
	PP13 MoM	0.83 (0.08–2.5)	0.27 (0.0–1.5)	<0.0001
	Chronic hypertension in current pregnancy, %	3.2	0	0.09
	Pre-gestational diabetes, %	0.6	0	0.17
	Nephropathy, %	0.1	7.9	<0.001
	Antiphospholipid antibodies syndrome, %	0.6	0	0.13
	Thrombophilia, %	1.7	0	0.11
	Lupus, %	0.1	0	0.19
	Others, %	0.4	0	0.15
	Total with maternal disease in current pregnancy, %	10.3	11.1	0.17
	Maternal age >40 years, %	6.2	3.2	0.07
	BMI >35, %	3.8	7.9	0.09
	Total maternal demography RFs, %	9.0	10.2	0.13
	PE or GH or IUGR in previous pregnancy, %	20.5	34.9	<0.001
	In vitro fertilisation, %	7.3	17.5	<0.001
	Total with significant risk factor/s, %	34.6	52.4	<0.005
	Characteristic at delivery	-	-	-
	Gestational age, weeks, median (range)	39.3 (37–42)	38 (27–42)	NS
	Caesarean section, n (%)	209 (27.6)	38 (60.3)	<0.001
	MAP, mmHg, median (range)	80 (65.7–95)	119 (109–168)	<0.001
	Urine protein, g/dL, median (range)	0 (0–0.4)	1.050 (0.4–9.0)	<0.001
	Maternal hospitalisation, days, median (range)	3 (0–7)	5 (2–14)	<0.005
	Newborn birth weight, grams, median (range)	3220 (2220–4200)	2775 (1120–4000)	<0.005
	Newborn hospitalisation, days, median (range)	3 (0–28)	5 (2–54)	<0.001
Intervention	Physicians decided whether to prescribe aspirin to patients based on major RFs alone, based on PP13 test results alone (PP13 M0.4 MoM considered low), or based on both. Major RFs included: 1) maternal disease (chronic hypertension or diabetes or kidney disorders) or cardiovascular diseases, phospholipid syndrome, thrombophilia, and lupus erythromatosus; 2) history of PE; 3) a BMI >35 or maternal age >40; and 4) conception by assisted fertility (IVF or intra-cytoplasmic sperm injection). Aspirin was prescribed for daily use prior to 16 weeks of gestation at 75 mg/day between gestational weeks 14 to 35; otherwise, the high risk were managed by close surveillance. There were 377 women with PP13 levels within normal range who did not have any prior RFs, and none were treated with aspirin. The group of first trimester PP13 <0.4 MoM and no RFs included 127 women. Of this group, 31 were treated with aspirin. The group with only RFs (but PP13 >0.4 MoM) included 219 women. Of this group, 39 were treated with aspirin. The group with both low PP13 levels and RFs included 97 women. Of this group, 45 were treated with aspirin.			

Study Reference **Meiri 2014**

Outcomes Measured

Primary endpoint
PE

Secondary endpoints
NR

Effectiveness of the Intervention

Efficacy

- Of the 31 women with a first trimester PP13≤0.4 MoM and no RFs treated with aspirin, 1 (3.2%) developed PE; this was compared to 26 cases of PE (27.08%) among the 96 women with first trimester PP13≤0.4 MoM and no RFs who were not treated with aspirin.
- Of the 39 women who had only RFs (but PP13 >0.4 MoM) who were treated with aspirin, 5 (12.8%) developed PE; this was compared to 5 cases of PE (2.77) among the 180 women who had only RFs who were not treated.
- Of the 45 women who had both low PP13 levels and RFs who were treated with aspirin, 8 (17.78%) developed PE; this was compared to 16 cases of PE (30.77%) among the 52 women with both low PP13 and RFs who were not treated.

Effect on aspirin on PE by risk group

Group	Treated/untreated	PE (%)
Low PP13	Treated	3.2
	Untreated	27.0
RF	Treated	12.8
	Untreated	2.7
Low PP13 and RFs	Treated	17.7
	Untreated	30.7

Treatment effectiveness by risk group

Aspirin effect	Only low PP13	Only RF	low PP13 and RFs
Relative ratio	8.43	0.21	1.73

Frequency of PE by risk group

Group	PE/unaffected	Patient number (n)
Low PP13	PE	27
	unaffected	100
RF	PE	10
	unaffected	209
Low PP13 and RFs	PE	24
	unaffected	72
No risk	PE	2
	unaffected	375

PE frequency by risk group

Group	Only low PP13 (n=127)	Only RF (n=219)	PP13 + RF (n=96)	No risk (n=377)
PE, n (%)	27 (42.8)	10 (15.9)	24 (38.1)	2 (3.2)

Safety
NR

Study Reference	Meiri 2014
Authors' Conclusions	Aspirin appeared to be more effective when the risk was determined by low PP13 levels alone compared with a risk predicted based on PP13 combined with RFs (PE frequency of the aspirin treated groups was 3.2% in the low PP13 alone group compared with 17.78% in the RFs combined with low PP13 group). This indicates that aspirin efficacy may be related to the cause underlying the risks for developing PE. Low aspirin indicates a placental derived risk, whereas RFs are mainly derived on maternal factors. Thus, aspirin may not be a sufficient prevention agent when the risk for PE is multifactorial.

Abbreviations: BMI, body mass index; CI, confidence interval; FPR, false positive rate; GH, gestational hypertension; IUGR, intrauterine growth restriction; MAP, mean arterial pressure; MoM, multiples of the median; NS, not significant; PE, pre-eclampsia; PP13, placental protein 13; RF, risk factor

Table 26j. Odibo 2015

Study Reference	Odibo 2015
Study Design	Design RCT Objective To estimate the efficacy of low-dose aspirin for preventing PE in women identified as high risk. Dates April 2012 to March 2014 (participants screened) Country US (inferred from author affiliations) Setting Women who were presenting for first-trimester ultrasound examination
Population Characteristics	Patient recruitment/eligibility All eligible women who presented for first-trimester ultrasound examination were approached for consent to participate in the study. The inclusion criteria were singleton pregnancy undergoing ultrasound examination at 11^{+0} to 13^{+6} weeks and deemed high risk for PE by the criteria in the following table:

Risk Factor	Score
Chronic hypertension	4
History of prior pre-eclampsia	3
Diabetes mellitus	2
Obesity (BMI > 30)	2
Bilateral uterine artery notches	1
Low PAPP-A (<0.52 MoM)	1

Excluded: pregnancies with multiple gestation, fetal aneuploidy, major fetal structural anomaly and bleeding disorder, and women with allergy to aspirin or already on aspirin or heparin.

A total score of at least 6 based on the risk factor scoring system was initially needed to be eligible for randomisation. However, due to slow recruitment 2 years into the study (with only 23 women enrolled) and following the recommendation form the data safety monitoring committee, the Institutional Review Board was asked for permission to revise the inclusion criteria to the presence of any of the risk factors listed in the table.

Randomisation methods
Randomisation was 1:1 using a computerised randomisation programme by the pharmacist who was otherwise uninvolved in the study.

Blinding
Double-blind. The study team and the patients were blinded to the intervention the patient was receiving.

Data collection
Consenting women had the following assessments between 9^{+0} and 13^{+6} weeks: history for risk factors, uterine artery Doppler, and measurement of pregnancy associated plasma protein-A (PAPP-A). Compliance was assessed by having the women complete a pill diary, which they were asked to return along with any unused pills, which were counted and returned to pharmacy. Demographic, previous medical and obstetric history and current obstetric information were collected from patient questionnaires and chart abstraction. Also collected included: pre-eclampsia, small-for-gestational age neonate; early pre-eclampsia; severe pre-eclampsia; gestational hypertension; preterm birth; stillbirth; antepartum haemorrhage; neonatal death; neonatal intensive care unit admission and miscarriage.

Duration of follow-up
Until delivery (assumed based on outcomes reported)

Definition of PE
PE was diagnosed per ACOG criteria

Early PE: delivery <34 weeks

Severe PE: BP >160/110 or symptoms including persistent headaches, visual disturbance, or evidence of abnormal renal failure, abnormal liver enzymes or thrombocytopenia

Sample size
N screened/invited = 1,470
N eligible = 138
N enrolled = 53
N excluded (with reason) = 79 screen positive declined randomisation, 16 found ineligible (10 women met both criteria)
N lost to follow-up = 2 (treatment group)
N completed = 30 – 16 treatment group and 14 placebo
N excluded from analysis = 10 treatment group including: on patient request (n=7), termination (n=1), 1 LTF (n=1); 13 placebo group including on patient request (n=10), rash/hives (n=3)
N included in analysis = 30

Power
Based on the anticipated baseline rate of 36% in the placebo group, a total of 186 women would be needed for 80% power to detect a 50% reduction in the risk of PE (two-tailed α of 0.048; incorporating one interim analysis and using the O'Brien-Fleming stopping rule). To account for an estimated 15% dropout rate, estimated that 220 screen-positive women would need to be randomised. Following the revised inclusion criteria, a revised sample of 684 women needed to be randomised to detect the same 50% reduction of pre-eclampsia with 80% power and 15% anticipated dropout rate; this was based on the revised accuracy of the model of 65%. However, the trial was terminated prematurely due to slow recruitment and lack of equipoise given a change to national guidelines to administer aspirin to high-risk women.

Maternal characteristics

	Placebo (n=14)	Aspirin (n=16)	p value
Maternal age (years), mean (SD)	31.6 ± 6.1	30.0 ± 5.0	0.45
Body mass index (kg/m^2), mean (SD)	36.6 ± 6.9	37.4 ± 8.9	0.78
Nulliparous, n (%)	3 (21.4)	5 (31.2)	0.54
Race/ethnicity, n (%)			0.013
Black	11 (78.6)	4 (25)	-

Study Reference	**Odibo 2015**			
	White	3 (21.4)	1 (6.2)	-
	Other	0 (0)	11 (68.8)	-
	Risk score, mean (SD)	5.9 ± 3.2	5.0 ± 2.9	0.40
	GA at randomisation (weeks), mean (SD)	12.1 ± 1.0	11.7 ± 1.3	0.35
	Mean UtA-PI (SD)	1.68 ± 0.4	1.57 ± 0.8	0.69
	Chronic hypertension, n (%)	10 (71.4)	6 (37.5)	0.06
	Pregestational diabetes, n (%)	2 (14.3)	4 (25.0)	0.46
Intervention	Daily 81 mg aspirin or placebo pill from 11^{+0} to 13^{+6} weeks until 37 weeks or delivery, whichever occurred first.			
Outcomes Measured	Primary endpoint PE diagnosed per ACOG criteria at the onset of the study Secondary endpoints Small-for-gestational-age neonate (birth weight <10th percentile for gestational age on the Alexander growth standard); early PE (delivery <34 weeks); severe PE (BP >160/110 or symptoms including persistent headaches, visual disturbance, or evidence of abnormal renal failure, abnormal liver enzymes or thrombocytopenia); gestational hypertension (elevated BP occurring after 20 weeks gestation with no evidence of PE); preterm birth (delivery <37 weeks); stillbirth; antepartum haemorrhage (haemorrhage after 20 weeks gestation); neonatal death, neonatal intensive care unit admission; and miscarriage.			
Effectiveness of the Intervention	Efficacy PE was seen in 6 of the 30 women (20%) with complete follow-up, 3 in the aspirin group and 3 in the placebo group (RR 0.88, 95% CI 0.21–3.66). All cases with PE occurred and were delivered before 34 week's gestation. Gestational hypertension was seen in 2 women, both in the aspirin group Small-for-gestational age was seen in 2 of the randomised women (6.7%), one in the aspirin and one in the placebo group (RR 0.88, 95% CI 0.06–12.72). The mean (SD) risk score was significantly higher (9.2±1.2) in the 6 women who developed early PE vs 4.5±0.4 in the other 24 women enrolled in the study with complete follow-up (p=0.0001) Safety With the exception of the 3 women reporting rash/hives (all in the placebo group), no other adverse effect was reported in either of the groups			
Authors' Conclusions	The findings, which should be interpreted with caution given that the study was underpowered to test the original hypothesis, are, however, consistent with the majority of trials using low-dose aspirin for preventing pre-eclampsia prior to 16 weeks. The failure to detect a difference in this study should be interpreted with caution due to the difficulties encountered with the trial and the study being underpowered to show a difference.			

Abbreviations: ACOG, American College of Obstetricians and Gynaecologists; BMI, body mass index; BP, blood pressure; GA, gestational age; LTF, lost to follow up; MoM, multiple of the median; PAPP-A. pregnancy associated plasma protein-A; PE, pre-eclampsia; RR, relative risk; US, United States

Table 26k: Park 2021 (Park 2021, El-Achi 2021)

Study Reference	Park 2021
Study Design	Design Prospective cohort **El-Achi 2021:** retrospective analysis of data from a prospective cohort Objective To determine whether prophylactic use of aspirin intended to prevent pre-term PE also reduced the prevalence of SGA in 2consecutive cohorts. **El-Achi 2021:** To investigate whether aspirin had any risk or benefit in context of PPRoM by analysing its effect on the prevalence of PPRoM. Dates April 2010 to March 2012 (observational cohort); April 2012 to December 2017 (2 separate cohorts were combined to form the interventional cohort) **El-Achi 2021:** April 2010 to March 2012 (observational cohort); April 2012 to October 2016 (interventional cohort). Country Australia Setting Large university hospital in Sydney **El-Achi 2021:** Royal Prince Alfred Hospital
Population Characteristics	Patient recruitment/eligibility Women were referred by their GP from the local community for first-trimester screening. For the observational cohort, the primary intention of screening was to establish a risk for aneuploidy. The intervention cohort were screened with the intention of defining risk for both aneuploidy and pre-term PE. The pre-term PE screening algorithm used a combination of maternal characteristics, MAP, uterine artery Doppler PI and maternal serum PAPP-A. Three consecutive cohorts of women, screened for pre-term PE with the FMF screening algorithm at 11 to 13^{+6} weeks of pregnancy, were included in this analysis. The first observational cohort was used to validate the pre-term PE algorithm in a local Australian population. The second cohort was screened prospectively and high-risk women were prescribed aspirin as prophylaxis against PE. The same process of prediction and prevention was used for the third cohort. Cohorts 2 and 3 were managed in an identical fashion and were merged to form the intervention cohort in this analysis. **El-Achi 2021:** Data were collected for women presenting to the hospital for combined first trimester screening at 11 to 13^{+6} weeks gestation. All women were included in this study with multiple pregnancies as the only exclusion criteria. At presentation for first trimester screening, the risk for pre-term PE was calculated using the validated FMF pre-term PE algorithm. The first cohort was observed and no therapeutic intervention with aspirin occurred. The subsequent cohort was screened using the same algorithm. Women who were defined as high risk for pre-term PE were treated with aspirin up to 36 weeks gestation. Randomisation methods No randomisation Blinding No blinding Data collection Data related to screening were collated with pregnancy outcome data. Individual medical records were reviewed for all women delivering <37 weeks gestation and in circumstances where the computerised data were incomplete. Data for pregnancy outcome included gestation at the time of delivery, infant gender and birthweight. Local contemporary birthweight reference charts were used to calculate a birthweight percentile for each infant. A newborn infant was defined as SGA when birthweight was calculated to be $<5^{th}$ percentile.

Study Reference **Park 2021**

El-Achi 2021: Data for patient demographics, pregnancy, and neonatal outcome were collated from the FMF database and the hospital patient information system. The formal hard copy medical record was also reviewed in all cases of delivery <37 weeks gestation or when the electronic record was incomplete.

Duration of follow-up
Delivery (inferred based on outcomes reported)

Definition of PE
NR

Sample size
N screened/invited = 3066 (observational cohort), 8572 (interventional cohort)
N eligible = NR
N enrolled = 3066 (observational, cohort 1) 8572 (interventional cohort)
N excluded (with reason) = NR
N lost to follow-up = NR
N completed = NR
N excluded from analysis = observational cohort n=53 including due to delivery before 24 weeks (n=1), termination of pregnancy (n=27), fetal death in utero (n=23), or missing birth weight data (n=2); interventional cohort n=144 including due to delivery before 24 weeks (cohort 2 n=14, cohort 3 n=6), termination of pregnancy (cohort 2 n=58, cohort 3 n=2), fetal death in utero (cohort 2 n=9, cohort 3 n=9), or missing PE risk (cohort 3 n=46).
N included in analysis = 3013 (observational cohort), 8428 (interventional cohort)

El-Achi 2021:
N screened/invited = 3066 (observational cohort), 7343 (interventional cohort)
N eligible = NR
N enrolled = 3066 (observational, cohort 1) 7343 (interventional cohort)
N excluded (with reason) = NR
N lost to follow-up = NR
N completed = NR
N excluded from analysis = observational cohort including due to no follow-up data (n=12) and n =due to termination of pregnancy (n=27); interventional cohort including due to no follow-up data (n=15) and due to termination of pregnancy (n=48)
N included in analysis = 3027 (observational cohort), 7280 (interventional cohort)

Power
The sample size was underpowered to examine the effect of aspirin on SGA neonates in the preterm setting

El-Achi 2021: The study was not powered to demonstrate a small reduction in the prevalence of PPRoM

Maternal characteristics

Characteristics	Observational cohort (n=3013)	Interventional cohort (n=8428)	p value
Age, years			
≤34	1718 (64.32)	5276 (65.40)	0.018
35–39	822 (30.77)	2305 (28.57)	-
≥40	131 (4.90)	486 (6.02)	-
Nulliparous	1581 (52.47)	4850 (57.55)	<0.001
Caucasian	2036 (67.57)	5259 (63.76)	<0.001

Study Reference	**Park 2021**

BMI, kg/m^2			
Underweight	89 (2.98)	198 (2.38)	0.025
Healthy	1874 (62.80)	5058 (60.69)	-
Overweight	694 (23.26)	2104 (25.25)	-
Obese	327 (10.96)	974 (11.69)	-
Smoking	91 (3.02)	188 (2.23)	0.016
Mean uterine artery PI	1.64 (0.51)	1.73 (0.51)	<0.001
MAP	81.20 (0.14)	88.97 (0.10)	<0.001
PAPP-A, MoM	1.21 (0.71)	1.28 (0.76)	<0.001
Gestation at delivery, days	276.63 (12.40)	275.31 (12.22)	<0.001
Birthweight, grams	3391.62 (533)	3345.56 (525)	<0.001

Mean (SD) or n (%)

El-Achi 2021:

Characteristics	Observational cohort (n=3027)	Interventional cohort (n=7280)	p value
Maternal age, years, mean (SD)	33.1 (4.5)	32.5 (4.4)	<0.0001
Parity, n (%)			
Nulliparous	1590 (52.5)	4405 (6.5)	<0.0001
Parous	1437 (47.5)	2875 (39.5)	-
Ethnicity, n (%)			
Caucasian	2041 (67.4)	4744 (65.2)	0.16
Asian	936 (30.9)	2411 (33.1)	-
African	32 (1.1)	75 (1.0)	-
Mixed	18 (0.6)	50 (0.7)	-
BMI, kg/m^2, mean (SD)	24.5 (4.7)	24.6 (4.7)	0.33
Smoking, n (%)	92 (3.0)	172 (2.4)	0.06
Gestation age, weeks, mean (SD)	39.41 (2.6)	39.3 (2.1)	0.02
Birthweight, grams, mean (SD)	3287.9 (635.5)	3350.4 (542.9)	<0.0001

Intervention

Observational cohort: screened for risk of pre-term PE, no treatment

Interventional cohort: screened for risk of pre-term PE, women identified as high-risk prescribed 150 mg aspirin to be taken before bed every night until 34 weeks

El-Achi 2021:
Observational cohort: screened for risk of pre-term PE, no treatment

Interventional cohort: screened for risk of pre-term PE, women identified as high-risk treated with 150 mg aspirin at night up to 36 weeks gestation

Outcomes Measured

Primary endpoint
The effect of aspirin on the prevalence of SGA infants in women who screened positive for pre-term at the time of combined first-trimester screening.

El-Achi 2021: The prevalence of PPRoM, defined as births occurring before 37 weeks gestation with rupture of membranes before the onset of contractions, in the observational and interventional cohort.

Study Reference **Park 2021**

Secondary endpoints

El-Achi 2021: Pregnancy outcomes, including termination of pregnancy, intrauterine death, neonatal death, and late miscarriage.

Effectiveness of the Intervention

Efficacy

After adjusting for confounders, there was no effect from aspirin therapy given to women who screened high risk on the prevalence of preterm or term infants being classified as SGA. For infants classified as birthweight <3rd centile, the OR was 0.37 (0.11–1.26, p=0.112), <5th centile the OR was 0.55 (0.25–1.22, p=0.14) and for the <10th centile, the OR was 0.75 (0.45–1.24, p =0.26).

Prevalence of SGA in women who screen high risk for PE in both cohorts, comparing the observational cohort and the interventional cohort who were given aspirin from 12 weeks

Cohort	Observational Screened high risk		Interventional Screened high risk		Adjusted OR (95% CI)	p value
	Total, n	SGA, n (%)	Total, n	SGA, n (%)		
<3rd centile						
Preterm <37 weeks	41	3 (7.3)	113	12 (10.6)	0.37 (0.11–1.26)	0.112
Term ≥37 weeks	310	10 (3.2)	878	21 (2.4)	-	-
Total births	351	13 (3.7)	991	33 (3.3)	0.92 (0.45–1.87)	0.819
<5th centile						
Preterm <37 weeks	41	6 (14.6)	113	18 (15.9)	0.55 (0.25–1.22)	0.140
Term ≥37 weeks	310	18 (5.8)	878	41 (4.7)	-	-
Total births	351	24 (6.8)	991	59 (5.9)	0.84 (0.50–1.42)	0.511
<10th centile						
Preterm <37 weeks	41	8 (19.5)	113	33 (29.2)	0.75 (0.45–1.24)	0.263
Term ≥37 weeks	310	41 (13.2)	878	131 (14.9)	-	-
Total births	351	49 (13.96)	991	164 (16.5)	1.13 (0.78–1.64)	0.505

Adjusted for age categories, BMI, nulliparous, ethnicity and smoking

El-Achi 2021:

There was no statistically significant difference in the prevalence of PPRoM between the 2 cohorts or between the high-risk subgroups that were observed and treated with low dose aspirin (p=0.31).

Cohort	Screening outcome and treatment	PPRoM, n (%)	p value
Observational	High risk, no treatment (n=128)	4 (3.1)	0.04
	Low risk, no treatment (n=2899)	28 (1.0)	-

Study Reference	Park 2021			
	Interventional	High risk, treated with aspirin (n=766)	14 (1.8)	0.54
		Low risk, no treatment (n=6516)	100 (1.5)	-
	Observational	High risk, no treatment (n=128)	4 (3.1)	0.31
	Interventional	High risk, treated with aspirin (n=766)	14 (1.8)	-
	Safety **El-Achi 2021:** Aspirin did not increase the prevalence of PPRoM			
Authors' Conclusions	This study confirmed that in an Australian population who underwent screening for preterm PE between 11 and 13^{+6} weeks gestation, aspirin given to women who screened high risk did not affect the rate of SGA infants born before or after 37 weeks. When aspirin was prescribed to women who screened high risk for preterm PE in the first trimester, a reduction in the prevalence of SGA did not reach clinical significance. El-Achi 2021: Aspirin does not increase the prevalence of PPRoM; routine treatment of women at high risk for preterm PE are not being exposed to an increase risk of harm, and doing so is safe, in the context of PPRoM, but does not significantly reduce the prevalence of PPRoM.			

Abbreviations: BMI, body mass index; CI, confidence interval; FMF, fetal medicine foundation; GP, general practitioner; MAP, mean arterial pressure; MoM, multiples of the median; NR, not reported; OR, odds ratio; PAPP-A, pregnancy-associated plasma protein A; PE, pre-eclampsia; PI, pulsatility index; PPRoM, preterm prelabour rupture of membranes; SD, standard deviation; SGA, small for gestational age.

Table 26l: PREDO trial (Villa 2013, Murtoniemi 2018)

Study Reference	PREDO trial (Prediction and prevention of preeclampsia and intrauterine growth restriction) (Villa 2013, Murtoniemi 2018)
Study Design	Design Randomised, double-blind, placebo-controlled trial Objective To study the effect of aspirin started at 12^{+0} to 13^{+6} (weeks + days) of gestation on prevention of pre-eclampsia (PE) and intrauterine growth restriction (IUGR) in high-risk women identified by abnormal uterine artery flow. Dates September 2005 to December 2009 Country Finland Setting Maternity clinics in ten Finnish hospitals participating in the PREDO Project.
Population Characteristics	Patient recruitment/eligibility Women with risk factors for PE and those without known risk factors (comparison group) were recruited. Women with one or more risk factors for PE were invited in arrival order to participate unless any of the exclusion criteria was present. Women who had bilateral second-degree notch were allocated to medication group. Included: age under 20 years; age over 40 years; obesity (BMI >30 kg/m^2); chronic hypertension (≥140/90 mmHg or medication for hypertension before 20 weeks of gestation); Sjögren's syndrome; a history of gestational diabetes or PE (blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic and

proteinuria ≥0.3 g/day or dipstick equivalent in 2 consecutive measurements); SGA (birthweight <–2SD); fetus mortus (fetal death after 22 weeks of gestation or >500 g weight in a previous pregnancy); systemic lupus erythematosus.

Excluded: allergy to aspirin; tobacco smoking (during this pregnancy); multiple pregnancy; and a history of asthma, peptic ulcer, placental ablation, inflammatory bowel diseases (Crohn's disease, colitis ulcerosa), rheumatoid arthritis, haemophilia or thrombophilia (previous venous or pulmonary thrombosis or coagulation abnormality).

Randomisation methods
The Tampere University Hospital Pharmacy performed the randomisation. The randomisation was made in blocks of ten by the pharmacists not otherwise involved in the study. The randomisation code of each participant was sealed in an envelope and was opened after the outcome diagnoses of all participants had been set by the jury (2 physicians and a study nurse).

Blinding
Double-blinded study. As a paid service, the aspirin and placebo tablets were prepared by a pharmaceutical company (Orion, Espoo, Finland) to appear identical.

Data collection
Uterine artery blood flow was measured by colour Doppler ultrasound transvaginally from all participants of the PREDO trial at 12^{+0} to 13^{+6} weeks of gestation. Women who had bilateral second-degree notch were allocated to the medication group. Aspirin or placebo was continued until 35^{+0} weeks of gestation or delivery, whichever occurred first.

Each individual outcome diagnosis was set by a jury, which consisted of 2 physicians and a study nurse.

Duration of follow-up
NR

Definition of PE
Overall: blood pressure ≥140 systolic and/or 90 mmHg diastolic in 2 consecutive measurements and proteinuria ≥0.3 g/24 hours.

Early-onset PE: PE diagnosed before 34^{+0} weeks of gestation.

Severe PE: blood pressure ≥160 systolic and or/ ≥110 mmHg diastolic and/or proteinuria ≥5 g/24 hours).

Preterm PE: PE diagnosed before 37^{+0} weeks of gestation.

Sample size
N screened/invited = 947
N eligible = 152 (16.0%)
N enrolled = 152
N excluded (with reason) = 31 (miscarriage [n=4], lost to follow-u p [n=11], discontinued due to medical condition [n=5], noncompliance with the study protocol [n=11])
N lost to follow-up = 11 (aspirin group n=7, placebo group n=4)
N completed = 121
N excluded from analysis = 0
N included in analysis = 121

Power

It was estimated that with a power of 0.80 and an α of 0.05 it would be possible to confirm or exclude a reduction in incidence to 10%, in groups of 80 participants each. For groups of 60 and 61 participants, which was the number included in analysis, the corresponding power is 0.62.

Study Reference **PREDO trial (Prediction and prevention of preeclampsia and intrauterine growth restriction) (Villa 2013, Murtoniemi 2018)**

Maternal characteristics

None of the comparisons between the 2 groups was statistically significant (p>0.05 for all).

Characteristic	Aspirin (N=61)	Placebo (N=60)
Baseline characteristics		
Mean age, years (SD)	30.8 (5.3)	31.0 (5.1)
Mean BMI before pregnancy, kg/m^2 (SD)	27.9 (6.6)	29.7 (7.8)
Mean height, cm (SD)	165.7 (5.3)	165.1 (5.2)
Primiparous, n (%)	19 (26.2)	9 (15.0)
Educational attainment, n (%)		
Elementary or less	3 (7.5)	1 (2.4)
High school or vocational school	7 (17.5)	15 (35.7)
Intermediate	13 (32.5)	13 (31.0)
University	17 (42.5)	13 (31.0)
Pregnancy characteristics[a]		
Antihypertensive medication, n (%)		
Before 20 weeks of gestation	4 (6.6)	3 (5.0)
After 20 weeks of gestation	7 (11.5)	9 (15.0)
Mean weight gain during pregnancy, kg (SD)	11.7 (4.7)	12.1 (4.9)
Gestational diabetes, n (%)		
Diet	10 (16.4)	9 (15.0)
Insulin	1 (1.6)	3 (5.0)
Oral glucose tolerance test not performed, n (%)	6 (9.8)	5 (8.3)
Mean highest systolic blood pressure, mmHg (SD)	142.5 (19.6)	146.2 (21.9)
Mean highest diastolic blood pressure, mmHg (SD)	92.1 (11.8)	95.1 (12.5)
Highest proteinuria, g/day*	3.3	1.3
Mode of delivery, n (%)		
Vaginal	47 (77.0)	43 (71.7)
Elective caesarean section	3 (4.9)	3 (5.0)
Caesarean section during labour	11 (18.0)	14 (23.3)
Mean Apgar score at 5 min (SD)	9.0 (0.8)	8.9 (0.8)
Umbilical artery pH below 7.5,** n (%)	7 (12.5)	4 (7.4)
Mean newborn birthweight, g (SD)	3,413 (630)	3,321 (871)
Mean placental weight, g (SD)	602 (131)	585 (150)

[a]None of the pregnancy characteristics were significantly different (all p values >0.05), p values were NR for baseline characteristics

*Geometric mean

**No umbilical artery pH was below 7.00

Intervention

Aspirin (N=61)

Tablets of 100 mg/day, continued to 35^{+0} weeks of gestation or delivery.

<table>
<tr><td><u>Study Reference</u></td><td>PREDO trial (Prediction and prevention of preeclampsia and intrauterine growth restriction) (Villa 2013, Murtoniemi 2018)</td></tr>
<tr><td></td><td><u>Placebo (N=60)</u>
Matching placebo (tablets prepared by a pharmaceutical company (Orion®, Espoo, Finland) to appear identical to the aspirin tablets, continued to 35^{+0} weeks of gestation or delivery)</td></tr>
<tr><td>Outcomes Measured</td><td><u>Primary endpoint</u>
PE, gestational hypertension (new onset hypertension after 20 weeks of gestation), and birthweight SD score as continuous variable calculated according to Finnish standards.
<u>Secondary endpoints</u>
Early-onset PE, severe PE, preterm PE, SGA (birthweight <–2 SD), length of gestation (continuous variable).</td></tr>
<tr><td>Effectiveness of the Intervention</td><td><u>Efficacy</u>
<table>
<tr><th>Outcome</th><th>Aspirin (N=61)</th><th>Placebo (N=60)</th><th>RR</th><th>95% CI</th></tr>
<tr><td>Primary outcomes, n (%)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>PE</td><td>8 (13.1)</td><td>11 (18.3)</td><td>0.7</td><td>0.3–1.7</td></tr>
<tr><td>Gestational hypertension</td><td>10 (16.4)</td><td>6 (10.0)</td><td>1.6</td><td>0.6–4.2</td></tr>
<tr><td>Secondary outcomes</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Early PE*</td><td>1 (1.6)</td><td>4 (6.7)</td><td>0.2</td><td>0.03–2.1</td></tr>
<tr><td>Preterm PE**</td><td>3 (4.9)</td><td>5 (8.3)</td><td>0.6</td><td>0.2–2.4</td></tr>
<tr><td>Severe PE***</td><td>3 (4.9)</td><td>8 (13.3)</td><td>0.4</td><td>0.1–1.3</td></tr>
<tr><td>SGA****</td><td>2 (3.3)</td><td>6 (10.0)</td><td>0.3</td><td>0.1–1.6</td></tr>
<tr><td>Severe diagnosis*****</td><td>4 (6.6)</td><td>10 (16.7)</td><td>0.4</td><td>0.1–1.2</td></tr>
</table>
*Diagnosed before h34^{+0}.
**Diagnosed before h37^{+0}.
***Blood pressure ≥160 systolic and/or ≥110 diastolic and/or proteinuria ≥5 g/24 hr.
****Birthweight <–2SD.
*****Early PE and/or severe PE and/or small for gestational age.
<u>Safety</u>
One participant reported sudden deafness in one ear at 24 weeks of gestation. The medication was discontinued and the randomisation code was opened: this participant had received placebo. No other adverse effects were reported.</td></tr>
<tr><td>Authors' Conclusions</td><td>We did not find statistically significant benefit for the effect of low-dose aspirin in preventing pre-eclampsia or related traits in women identified by clinical risk factors and bilateral uterine artery second-degree notch in early pregnancy.</td></tr>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; GH, gestational hypertension; IUGR, intrauterine growth restriction; NR, not reported; PE, pre-eclampsia; PREDO, Prediction and Prevention of Pre-eclampsia; SD, standard deviation; SGA, small for gestational age.

Table 26m: Scazzocchio 2017

Study Reference	Scazzocchio 2017
Study Design	Design Phase II multicentre RCT Objective To explore whether administration of low-dose aspirin from the first trimester improves trophoblastic invasion in women defined as high risk by abnormal UtA Doppler in the first trimester. Dates September 2012 to July 2015 Country Spain Setting Three university hospitals (Hospital Clinic, Barcelona University, Barcelona; Dexeus University Hospital, Barcelona; Lozano Blesa University Hospital, Zaragoza)
Population Characteristics	Patient recruitment/eligibility Eligible women were attending routine ultrasound examination at 11 to 14 weeks of gestation at one of three university hospitals who met the following inclusion criteria: maternal age ≥18 years, singleton pregnancy, crown rump length of 45 to 84 mm, and a mean UtA PI >95th percentile. Exclusion criteria included: pre-existing hypertensive, immune, renal, or cardiovascular disease, history of PE in a previous pregnancy, history of gastric ulcer, known allergy or hypersensitivity to aspirin, haemorrhagic disease, fetal malformation (including chromosomopathy), or active treatment with heparin or aspirin before recruitment. Randomisation methods An online service was used to generate randomised sequences in blocks of 10 subjects, stratified by participating centre, to ensure balanced distributions within the study arms. Blinding The study was triple-blinded with respect to subject, caregiver and investigator Duration of follow-up Delivery (assumed based on outcomes) Definition of PE PE: systolic BP ≥140mmHg or diastolic BP ≥90mmHg on 2 readings at least 4 hours apart in previously normotensive women after 20 weeks of gestation, and proteinuria >300 mg/24 hours); early-onset PE: PE requiring delivery before 34 weeks of gestation; severe PE: BP ≥160/110mmHg on 2 or more occasions, proteinuria ≥5 g/24 hour, or the presence of maternal complications including: (i) eclampsia; (ii) haemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, (iii) acute renal failure, (iv) subcapsular hepatic hematoma; (v) pulmonary oedema, (vi) placental abruption; or (vii) the presence of disseminated intravascular disease. Sample size N screened/invited = 8,012 N eligible = 244 N enrolled = 186 N excluded (with reason) = 58 (declined to participate) N lost to follow-up = 7 (placebo), 6 (aspirin) N completed = NR

Study Reference	Scazzocchio 2017

N excluded from analysis = 31 including placebo: 7 lost to follow up (n=7), voluntary withdrawal (n=6), preterm birth before 28 weeks (n=1), congenital malformation (n=1), miscarriage (n=2); aspirin: lost to follow up (n=6), voluntary withdrawal (n=5), preterm birth before 28 weeks (n=1), congenital malformation (n=1), asthma attack n=1)
N included in analysis = 75 (placebo), 80 (aspirin)

Power
It was calculated that 120 experimental subjects and 120 control subjects were needed to be able to reject the null hypothesis, so that the rates for experimental and control subjects are equal with a probability (power) of 80%. To compensate for a 10% rate of loss to follow-up, investigators aimed to recruit a total of 133 patients per arm. The probability of Type-1 error associated with this test of the null hypothesis was set at 5%. This study was underpowered to detect potential small effects. This study did not contain sufficient power to assess the effect of aspirin in reducing the development of placenta-related diseases.

Maternal characteristics

Characteristic	Placebo (n=75)	Aspirin (n=80)	p value
Maternal age, years, mean (SD)	33.4 (4.5)	32.3 (4.2)	0.13
BMI, mean (SD)	23.5 (3.4)	23.5 (2.8)	0.99
Parity, n (%)			0.85
0	48 (64.0)	50 (62.5)	-
1	25 (33.3)	27 (33.8)	-
2	1 (1.3)	3 (3.8)	-
≥3	1 (1.3)	0 (0)	-
Ethnic origin, n (%)			0.17
European	63 (84.0)	60 (75.0)	-
South American	10 (13.3)	13 (16.3)	-
North African	1 (1.3)	2 (2.5)	-
Other	1 (1.3)	2 (2.5)	-
Previous FGR, n (%)	3 (4.0)	2 (2.5)	0.67
Smoker, n (%)	9 (12.0)	9 (11.3)	0.88
Gestational age, weeks, mean (SD)	12.8 (0.7)	13.0 (0.6)	0.15
Systolic BP, mmHg, mean (SD)	109.7 (11.1)	108.2 (12.5)	0.42
Diastolic BP, mmHg, mean (SD)	66.5 (7.8)	65.9 (9.4)	0.67
UtA-PI, mean (SD)	2.6 (0.3)	2.7 (0.3)	0.26
UtA-PI Z-score, mean (SD)	2.4 (0.5)	2.6 (0.6)	0.10

Intervention

Treatment (n=80): 150mg daily extended-release aspirin

Control (n=75): placebo

Outcomes Measured

Primary endpoint
The main outcome variable was mean UtA-PI at 28^{+0} weeks ± 2 days.

Secondary endpoints
Secondary perinatal outcomes were: (1) development of PE (2) early-onset PE (3) severe PE (4) FGR and SGA, defined as birth weight <3rd and <10th customised percentiles, respectively, according to local standards (5) non-reassuring fetal status during labour, determined by a pathological fetal heart

<table>
<tr><td>Study Reference</td><td>Scazzocchio 2017</td></tr>
<tr><td></td><td>rate or a suspicious tracing with fetal scalp blood pH <7.15 or <7.20 in 2 samples 30 minutes apart; (6) neonatal metabolic acidosis at birth, defined as umbilical arterial pH <10th percentile (pH 7.15) and base excess >90th percentile (12mEq/L).</td></tr>
<tr><td>Effectiveness of the Intervention</td><td>Efficacy
<table><tr><th>Outcome</th><th>Placebo (n=75)</th><th>Aspirin (n=80)</th><th>p value</th></tr><tr><td>PE, n (%)</td><td>3 (4.0)</td><td>4 (5.0)</td><td>0.76</td></tr><tr><td>Severe PE, n (%)</td><td>1 (1.3)</td><td>1 (1.3)</td><td>1</td></tr><tr><td>FGR, n (%)</td><td>24 (32.0)</td><td>19 (23.8)</td><td>0.25</td></tr><tr><td>SGA, n (%)</td><td>13 (17.3)</td><td>7 (8.8)</td><td>0.11</td></tr><tr><td>Caesarean delivery for non-reassuring fetal status during labour, n (%)</td><td>2 (2.7)</td><td>6 (7.5)</td><td>0.28</td></tr><tr><td>Significant neonatal morbidity, n (%)</td><td>1 (1.3)</td><td>0 (0)</td><td>0.48</td></tr><tr><td>Postpartum haemorrhage</td><td>5 (6.7)</td><td>2 (2.5)</td><td>0.21</td></tr><tr><td>Uterine bleeding during follow-up, n (%)</td><td>11 (14.7)</td><td>9 (11.3)</td><td>0.53</td></tr></table>
Safety
Of the outcomes assessed, there was no statistically significant difference between placebo and treatment groups, including for incidence of postpartum haemorrhage, uterine bleeding during follow-up, and caesarean delivery.</td></tr>
<tr><td>Authors' Conclusions</td><td>This study failed to observe a significant effect of aspirin on trophoblastic flow resistance in women with evidence of defective invasion in the first trimester, as determined by abnormal UtA Doppler; however the study was underpowered to detect potential small effects. This finding also does not necessarily conflict with a benefit of aspirin in reducing the incidence of PE. This study did not contain sufficient power to assess the effect of aspirin in reducing the development of placenta-related diseases. However, a trend toward lower incidence of SGA in women treated with aspirin was identified. In conclusion, for women with abnormal trophoblastic invasion (as reflected by abnormal UtA Doppler), low-dose aspirin started in the first trimester does not have a significant effect on UtA Doppler resistance as pregnancy progresses; however, the study was underpowered to detect potential small effects.</td></tr>
</table>

Abbreviations: BMI, body mass index; FGR, fetal growth restriction; PE, pre-eclampsia; PI, pulsatility index; SGA, small for gestational age; UtA, uterine artery.

Table 26n: Stanescu 2018

<table>
<tr><td>Study Reference</td><td>Stanescu 2018</td></tr>
<tr><td>Study Design</td><td>Design
RCT (single- or multi-centre NR)

Objective
To investigate when in pregnancy to stop the administration of low dose aspirin (150 mg/daily) so as to prevent fetal growth restriction (FGR)

Dates
NR

Country
Romania (inferred from author affiliations)

Setting
NR</td></tr>
</table>

Study Reference	Stanescu 2018

Patient recruitment/eligibility
Inclusion criteria: singleton pregnancies; all patients were screened positive using the FMF early pregnancy screening test for PE and FGR prediction.
Exclusion criteria: constitutionally small fetuses, screened positive for infections, fetal chromosomal or structural abnormalities, gestational diabetes or multiple pregnancies.

Randomisation methods
Randomisation was done using the sealed envelope method.

Blinding
The patient was assigned to one of the three groups but the patient was never allowed to discuss their treatment with any of the scanning doctors (who were not allowed to ask about patient's treatment). The doctors who did the scanning were blinded. The patients were informed about their treatment. The statistician was informed that there were 3 groups (A, B and C), butdid not have any information regarding the patient's treatment.

Data collection
Patients were all screened positive using the FMF early pregnancy screening test for PE and FGR prediction which involved screening by a combination of maternal medical history and characteristics, maternal serum PAPP-A, MAP and uterine artery PI, with an estimated risk for IUGR of more than 1 in 100. The growth curves, fetal and maternal Doppler measurements and AFI were monitored every 4 weeks. The outcome of the pregnancy was noted and all results were compared between groups. IUGR was defined as a fetal weight below the 10th centile for gestational age. Constitutionally small babies were defined as having an EFW <10th centile and anormal Doppler.

Duration of follow-up
Until delivery (assumed based on outcomes reported)

Population Characteristics

Definition of PE
NR

Sample size
N screened/invited = NR
N eligible = NR
N enrolled = 150
N excluded (with reason) = NR
N lost to follow-up = NR
N completed = NR
N excluded from analysis = 0
N included in analysis = 150

Power
NR

Maternal characteristics

Maternal characteristics	Control (n=50)	Aspirin until 32 weeks (n=50)	Aspirin until 36 weeks (n=50)
Maternal age [years, median (range)]	32.74 (20–45)	31.27 (20–40)	33.63 (23–44)
Weight [kg, median (range)]	67.21 (43–102)	66.55 (49–94)	65.42 (58–100)
Racial origin [n (%)]			
Caucasian	50 (100)	50 (100)	50 (100)
Parity [n (%)]			
Nulliparous	30 (60)	24 (48)	36 (72)

Study Reference	**Stanescu 2018**			
	Parous – no previous IUGR	20 (40)	24 (48)	13 (26)
	Parous – previous IUGR	–	2 (4)	1 (2)
	Cigarette smoker [n (%)]	8 (16)	3 (6)	3 (6)
	Conception [n (%)]			
	Spontaneous	48 (96)	50 (100)	49 (98)
	Ovulation drugs	1 (2)	-	1 (2)
	In vitro fertilisation	1 (2)	–	–
	Gestational age at delivery [weeks, median (range)]	38.6 (35.7–40.3)	39.2 (37.0–40.6)	39.0 (36.0–40.4)
	Neonatal birth weight [grams, median (range)]	2760 (1700–3250)	2950 (2300–3460)	3180 (2480–3780)

Intervention

Placebo (Group A; control)
150 mg aspirin daily until 32 weeks of gestation (Group B)
150 mg aspirin daily until 36 weeks of gestation (Group C)

Outcomes Measured

Primary endpoint
NR

Secondary endpoints
NR

Effectiveness of the Intervention

Efficacy
In group C, there were fewer cases of FGR compared with other groups: 6% vs. 10% in group B vs. 24% in controls. There was a significant birth weight improvement in this group with a median of 3180 grams compared with 2950 grams in group B and 2760 g in group A (p=0.01). The gestational age at delivery was similar in all groups (39 weeks in group C, 39.2 weeks in group B, 38.6 weeks in group A). There were 3cases of PE in the control group and no case of PE in the aspirin groups. The incidence of FGR in group A was 6 cases, in group B was 3cases (there were late IUGR cases after 34 weeks) and in group C was one case. There was a significant reduction in the incidence of FGR among the patients who took aspirin until 36 weeks.

EFW centiles	Control (n=50)	Aspirin until 32 weeks (n=50)	Aspirin until 36 weeks (n=50)
<10	17 (0.34%)	6 (0.12%)	2 (0.04%)
<5	6 (0.12%)	3 (0.06%)	1 (0.02%)
<3	3 (0.06%)	1 (0.02%)	0

Mean PI values of uterine arteries			
Gestational age (weeks)	Control (n=50)	Aspirin until 32 weeks (n=50)	Aspirin until 36 weeks (n=50)
32	0.78 (0.6–1)	0.6 (0.43–0.82)	0.61 (0.41–0.84)
36	0.68 (0.57–0.82)	0.5 (0.45–0.69)	0.42 (0.3–0.6)

Regarding PI of uterine arteries for groups A, B and C there was a stagnation in the curve in group B after 32 weeks of gestation – results show a drop in the fetal estimated growth curve in the group that took aspirin until 32 weeks. Regarding growth curves for groups A, B and C, there was a slight drop in growth in group B after 32 weeks of gestation.

Safety
No case of ductus arteriosus constriction was noted

Study Reference	Stanescu 2018
Authors' Conclusions	There is good evidence that in women at high risk for PE and FGR, it is safe to take 80-150 mg aspirin daily at bedtime and the treatment should be initiated at 8-16 weeks of gestation. Low dose aspirin improves the outcome in the selected population and should be offered for prevention of FGR until 36 weeks, when it should be stopped to avoid potential adverse neonatal effects.

- **Abbreviations:** AFI, amniotic fluid index; EFW, estimated fetal weight; FMF, fetal medicine foundation; FGR, fetal growth restriction; IUGR, intrauterine growth restriction; MAP, mean arterial pressure; NR, not recorded; PAPP-A, pregnancy associated plasma protein A; PE, pre-eclampsia; PI, pulsatility index; RCT, randomised controlled trial.

Table 26o: Syngelaki 2016

Study Reference	Syngelaki 2016
Study Design	Design RCT, multicentre Objective To test the hypothesis that metformin, as compared with placebo, would be associated with a lower median neonatal birth-weight z score when administered to pregnant women without diabetes who had a BMI of more than 35. Dates October 2010 to June 2015 (study period at Epsom and St. Helier University Hospitals) June 2013 to June 2015 (study period at King's College Hospital) September 2013 to June 2015 (study period at Medway Maritime Hospital) Country UK Setting Three NHS maternity hospitals
Population Characteristics	Patient recruitment/eligibility Patients were recruited from 3NHS maternity hospitals in the UK. Women without diabetes who had a BMI of more than 35 and a singleton pregnancy were assessed for eligibility. Exclusion criteria were a maternal age of less than 18 years; a major fetal defect observed on the scan performed at 11 to 13 weeks of gestation; a history of gestational diabetes mellitus; kidney, liver or heart failure; a serious medical condition; hyperemesis gravidarum; treatment with metformin at the time of screening; known sensitivity to metformin; and miscarriage before randomisation. Randomisation methods Eligible women were randomly assigned, in a 1:1 ratio, with the use of computer-generated random numbers, to receive either metformin or placebo. In the random-sequence generation there were no restrictions, such as block size or stratification according to study site. Blinding Double-blind. The appearance, size, weight and taste of the placebo tablets were identical to those of the metformin tablets; both were purchased at full cost. Data collection Pregnancy dating was based on the measurement of the fetal crown-rump length at the ultrasonographic examination/scan at 11 to 13 weeks of gestation. The demographic characteristics of the mothers and the medical history were recorded in a database. Follow-up visits were scheduled at intervals of 4 to 6 weeks. Maternal assessment was performed, including measurement of weight and BP and urinalysis for proteins and ketones.

Study Reference **Syngelaki 2016**

Adherence to taking metformin or placebo was assessed by counting the tablets returned by the patients each visit; if during a given visit a patient forgot to return the tablets a verbal report as well as the results of the previous and subsequent visits were used. All the women underwent a 75 gram OGTT at 28 weeks of gestation; women with abnormal results were advised to continue the assigned study regimen as before and to commence home glucose monitoring. The clinical data of the participants were recorded in the study database at each visit. Details regarding delivery and neonatal outcomes were added as soon as they became available. If adverse event occurred, patients were advised to contact their local investigator, and the nature, time of onset, and severity of the event, the treatment needed, and any relation to the assigned study regimen were recorded.

Duration of follow-up
Until delivery (assumed based on outcomes reported)

Definition of PE
PE in the paper referenced to the classification and diagnosis of the hypertensive disorders statement from ISSHP

Sample size
N screened/invited = 1,071
N eligible = 844
N enrolled = 450 (225 metformin, 225 placebo)
N excluded (with reason) = 227 including <18 years (n=6), fetus with fetal defect (n=17), history of gestational diabetes mellitus (n=66), medical problems (n=18), gastric bypass (n=6), hyperemesis (n=68), receiving metformin (n=25), could not take metformin (n=8), miscarriage (1n=3)]; declined to participate (n=394)
N lost to follow-up = 0
N completed = 202 metformin and 198 placebo
N excluded from analysis = 23 metformin (withdrew consent), 27 placebo (withdrew consent)
N included in analysis = 202 metformin, 225 placebo

Power
Estimated that 400 patients would need to undergo randomisation to give the study 80% power to detect a reduction in mean neonatal birth weight by 0.3 SD – down to the value observed in neonates born to women with a BMI of 35 or less – at a 5% significance level; after allowing for an expected withdrawal of 20%, it was calculated that 450 patients would need to be recruited. The study was not adequately powered for the secondary outcomes; for a randomised trial to have 80% power to detect a reduction in the incidence of PE from 5.5% to the observed 3.0% in the metformin group, at a 5% significance level, 2050 patients would need to be recruited. Using a cutoff point of a BMI of 35 enabled the study to have adequate power with a smaller sample size.

Maternal characteristics

Characteristic	Metformin (n=202)	Placebo (n=198)
Median maternal age (IQR) – year	32.9 (27.3–36.2)	30.8 (26.6–34.4)
Median BMI at 12 to 18 weeks of gestation (IQR)	38.6 (36.5–41.5)	38.4 (36.3–41.9)
Median gestational age at randomisation (IQR) – week	15.1 (13.7–17.0)	14.9 (13.6–17.3)
Race or ethnic group – n (%)		
White	142 (70.3)	128 (64.6)
Black	50 (24.8)	55 (27.8)
South Asian	7 (3.5)	12 (6.1)
East Asian	1 (0.5)	0
Mixed	2 (1.0)	3 (1.5)
Medical history – n (%)		

Study Reference	**Syngelaki 2016**		
	Chronic hypertension	13 (6.4)	17 (8.6)
	Polycystic ovary syndrome	26 (12.9)	18 (9.1)
	Cigarette smoking	15 (7.4)	21 (10.6)
	Conception – n (%)		
	Spontaneous	197 (97.5)	194 (98.0)
	Ovulation induction	2 (1.0)	3 (1.5)
	In vitro fertilisation	3 (1.5)	1 (0.5)
	Parity – n (%)		
	Nulliparous	55 (27.2)	68 (34.3)
	Parous with previous PE	14 (6.9)	13 (6.6)
	Parous with previous large-for-gestational-age neonate	39 (19.3)	31 (15.7)
	There were no significant (p<0.05) between-group differences in the characteristics at baseline apart from maternal age, which was higher in the metformin group than the placebo group (p=0.02).		
Intervention	Metformin 1.0 grams per day in week 1, increasing by 0.5 grams each week to a maximum dose of 3.0 grams per day in week 5 (n=225) Placebo (n=225)		
Outcomes Measured	Primary endpoint The median neonatal birth-weight z score (difference between observed and expected birth weight, with adjustment for gestational age, divided by the fitted standard deviation). The expected birth weight, corrected for gestational age, was derived from the population of phenotypically normal neonates born alive at 24 weeks of gestation or later. Secondary endpoints Maternal secondary outcome measures included gestational weight gain (difference in maternal weight between day of randomisation and last antenatal visit), gestational diabetes mellitus, PE, pregnancy-induced hypertension, delivery by caesarean section, and postpartum haemorrhage (blood loss of 1 litre or more). Key secondary outcomes for the fetus/neonate included death before 24 weeks gestation or later, preterm birth before 37 weeks of gestation, status of being large for gestational age (birth weight >90th percentile with adjustment for gestational age), birth trauma (shoulder dystocia, or brachial plexus injury or fracture), an Apgar score of less than 7 at 5 minutes, admission to a level 2 or 3 neonatal unit, hypoglycaemia (plasma glucose levels <46.8 mg per decilitre [2.6 mmol per litre] on 2 occasions ≥30 minutes apart), hyperbilirubinemia requiring phototherapy, and respiratory distress (need for more than 4 hours of respiratory support or supplemental oxygen).		
Effectiveness of the Intervention	Efficacy There were no significant differences between the metformin group and the placebo group in the median neonatal birth-weight z score, the incidence of large-for-gestational-age neonates, or the incidence of adverse fetal or neonatal outcomes. The median gestational weight gain in the mother and the incidence of PE were lower in the metformin group then in the placebo group, but there were no significant between-group differences in the other secondary outcomes.		

Outcome	Metformin (n=202)	Placebo (n=198)	Odds Ratio (95% CI)	p value
Primary outcome				
Median birth-weight z score (IQR)	0.05 (-0.71 to 0.92)	0.17 (-0.62 to 0.89)	-	0.66
Fetal or neonatal outcomes	-	-	-	-
Miscarriage – n (%)	0	3 (1.5)	-	0.12
Stillbirth – n (%)	1 (0.5)	2 (1.0)	0.49 (0.04 to 5.42)	0.62

Study Reference	Syngelaki 2016				
	Neonatal death – n (%)	0	1 (0.5)	-	0.49
	Live birth – n (%)	201 (99.5)	192 (97.0)	6.28 (0.78 to 52.66)	0.12
	Delivery at <37 weeks of gestation – n/total n (%)	13/202 (6.4)	21/195 (10.8)	0.57 (0.28 to 1.17)	0.12
	Median birth-weight percentile (IQR)	51.8 (23.9 to 82.1)	56.6 (26.8 to 81.4)	-	0.66
	Large for gestational age (weight higher than the 90th percentile) – n/total n (%)	34/202 (16.8)	30/195 (15.4)	1.11 (0.65 to 1.90)	0.79
	Birth trauma – n (%)	3/202 (1.5)	3/195 (1.5)	0.96 (0.19 to 4.84)	1.00
	Apgar score at 5 min <7 – n (%)	1/202 (0.5)	3/195 (1.5)	0.32 (0.03 to 3.09)	0.36
	Admission to NICU – no./total n (%)	11/202 (5.4)	14/195 (7.2)	0.74 (0.33 to 1.68)	0.47
	Hypoglycaemia – n/total n (%)	9/202 (4.5)	11/195 (5.7)	0.78 (0.32 to 1.93)	0.58
	Hyperbilirubinemia – n/total n (%)	11/202 (5.4)	15/195 (7.7)	0.69 (0.31 to 1.54)	0.36
	Respiratory distress syndrome – n/total n (%)	9/202 (4.5)	13/195 (6.7)	0.65 (0.27 to 1.56)	0.33
	Maternal outcomes				
	Median weight gain (IQR) – kg	4.6 (1.3 to 7.2)	6.3 (2.9 to 9.2)	-	<0.001
	Gestational diabetes mellitus – n/total n (%)	25/202 (12.4)	22/195 (11.3)	1.11 (0.60 to 2.04)	0.74
	Preeclampsia – n/total n (%)	**6/202 (3.0)**	**22/195 (11.3)**	**0.24 (0.10 to 0.61)**	**0.001**
	Pregnancy-induced hypertension – n/total n (%)	13/202 (6.4)	13/195 (6.7)	0.96 (0.43 to 2.13)	0.93
	Delivery by caesarean section – n/total n (%)	80/202 (39.6)	82/195 (42.1)	0.93 (0.62 to 1.38)	0.79
	Postpartum haemorrhage – n/total n (%)	19/202 (9.4)	16/195 (8.2)	1.16 (0.58 to 2.33)	0.67
	The percentages for delivery before 37 weeks of gestation, birth trauma, Apgar score less than 7 at 5 minutes, admission to the NICU, hypoglycaemia, hyperbilirubinemia, and the respiratory distress syndrome and all secondary maternal outcomes were calculated after the exclusion of 3patients with miscarriage in the placebo group. Data on median birth-weight z score and percentile were missing for 3neonates in the placebo group.				
	Safety There was no significant between-group difference in the incidence of serious adverse events, but the incidence of side effects was significantly higher in the metformin group than in the placebo groups. In response to side effects, 17.6% of the women stopped taking their tablets, 41.8% reduced the dose and 40.6% continued with the full dose; there were no significant between-group differences with regard to these decisions. In 7 patients (2 patients in the metformin group and 5 in the placebo group), the study regimen was stopped because of fetal growth restriction, as evidenced by an estimated fetal weight below the 5th percentile and abnormal fetal Doppler studies.				
Authors' Conclusions	In pregnant women without diabetes who had a BMI of more than 35, the daily administration of metformin from 12 to 18 weeks of gestation until delivery did not reduce the median neonatal birth-weight z score or the incidence of large-for-gestational-age neonates. Metformin was associated with less maternal gestational weight gain and a lower incidence of PE than were seen with placebo. Less gestational weight gain was associated with a lower prevalence of PE. There was no significant difference between the groups in the incidence of other pregnancy complications or of adverse fetal or neonatal outcomes.				

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; IQR, interquartile range; ISSHP, International Society for the Study of Hypertension in Pregnancy; NICU, neonatal intensive care unit; NHS, national health service; OGTT, oral glucose-tolerance test; PE, pre-eclampsia; RCT, randomised controlled trial; SD, standard deviation; UK, United Kingdom.

Table 26p: Tapp 2020

Study Reference	Tapp 2020
Study Design	Design (Pilot) RCT, single centre

Study Reference	Tapp 2020
	Objective To compare the effects of 80 mg and 160 mg of aspirin, initiated in the first trimester of pregnancy, on mid-trimester UtA-PI in women with a history of PE. Dates NR Country Canada Setting CHU de Québec
Population Characteristics	Patient recruitment/eligibility Pregnant women with singleton pregnancy at 10^{+0}–13^{+6} weeks gestation with a history of PE were included. Eligible participants were referred by their doctor to a research nurse at the time of first-trimester ultrasound, usually scheduled between 10^{+0} and 13^{+6} weeks. Reasons for exclusion were any contraindication to aspirin (previous anaphylactic reaction, previous or present peptic ulcer, or documented coagulopathy), ongoing anticoagulant therapy, multiple pregnancy, or major fetal abnormality. Randomisation methods Women were randomly assigned to 80 mg or 160 mg of aspirin via computer-generated randomisation by blocks of 10 numbers. A unique identifier was assigned to each participant. Blinding Allocation remained unknown to the participants and all collaborators (investigator, nurses, coordinator, ultrasound technician, and laboratory assistants) until the recruitment, data collection, and laboratory analyses were completed and approved by the principal investigator. Additionally, all ultrasound images were double-checked by an independent observer at the end of the study; this observer was blinded to the pregnancy outcomes. Data collection Medical charts were reviewed before randomisation to confirm the diagnosis of PE in a previous pregnancy. Sonographers measured mean UtA-PI via ultrasound prior to randomisation and at each visit. Ultrasound was also performed to determine exact gestational age prior to randomisation. Once women were randomised and began treatment, they were seen 3times thereafter (at 16−18, 22−24, and 32−34 weeks). At each visit, participants were asked to complete a short questionnaire, which verified any changes, complications, or potential side effects. At each visit, blood pressure was measured and UtA Doppler was performed to calculate mean UtA-PI. One month after delivery, every participant completed a phone questionnaire about postpartum complications. Compliance with treatment was verified by a count of capsules at each visit. Information regarding any concomitant medication use or potential adverse reactions was also collected. Duration of follow-up One month post delivery Definition of PE Hypertension >140/90 measured at least twice 4 hours apart, with proteinuria or one or more adverse conditions Sample size N screened/invited = 119 N eligible = 107 N enrolled = 107 (53 in 80 mg group, 54 in 160 mg group) N excluded (with reason) = 12 (non-eligible; specific reasons NR) N lost to follow-up = 1 (moved; 160 mg group)

Study Reference — **Tapp 2020**

N completed = 50 (80 mg group), 50 (160 mg group)
N excluded from analysis = 0
N included in analysis = 53 (80 mg group), 54 (160 mg group)

Power

Considering a probable rate of attrition of 3%, a sample size of 52 women in each group was required to detect a clinically meaningful difference of 0.2 in UtA-PI (α= 0.05; β= 0.20). The study was not sufficiently powered to detect an impact of treatment on clinical outcomes.

Maternal characteristics

Characteristic	80 mg group (n=53)	160 mg group (n=54)
Maternal age, years, median (IQR)	32 (30−34)	30 (28−32)
Gestational age, week^{day}, median (IQR)	$12^{6}(12^{1}–13^{1})$	$12^{7}(12^{4}–13^{1})$
BMI, kg/m^2, median (IQR)	29 (24−34)	26 (23−30)
Ethnicity, n (%)		
Caucasian	49 (92)	53 (98)
Asian	-	1 (2)
Hispanic/Latino	4 (8)	-
Pre-existing diabetes, n (%)	2 (4)	1 (2)
Aspirin before randomisation, n (%)	26 (49)	33 (61)
Daily folic acid supplement, n (%)	51 (96)	50 (93)
UtA-PI, median (IQR)	1.7 (1.3−2.3)	1.6 (1.4−2.2)
UtA-PI, MoM (IQR)	1.0 (0.8−1.5)	1.1 (0.9−1.4)
Gestational age at previous PE diagnosis, n (%)		
Term (≥ 37 weeks)	30 (57)	36 (67)
Preterm (<37 weeks)	23 (43)	18 (33)
Early onset (<34 weeks)	8 (15)	8 (15)

Intervention

80 mg enteric-coated acetylsalicylic acid (aspirin) each evening at bedtime from the time of randomisation to 35^{+6} weeks of pregnancy (n = 53)

160 mg enteric-coated acetylsalicylic acid (aspirin) each evening at bedtime from the time of randomisation to 35^{+6} weeks of pregnancy (n = 54)

Outcomes Measured

Primary endpoint
Placental function as assessed by Doppler ultrasound (UtA-PI)

Secondary endpoints
Pregnancy complications associated with placental insufficiency, including preterm birth (<37 weeks), PE, preterm PE (before 37 weeks of gestation), early-onset PE (before 34 weeks), FGR (≤10th percentile), and stillbirth.

Effectiveness of the Intervention

Efficacy
There was no significant difference in UtA-PI between the 2 groups at 22 to 24 weeks of pregnancy, with a mean UtA-PI of 0.97 (95% CI 0.88−1.05) in the 80-mg group versus 0.97 (95% CI 0.88−1.07) in the 160-mg group (p=0.9). The mean difference was 0.01 (95% CI -0.12−0.13).

There was no difference between groups in terms of PE, FGR, or preterm birth. No stillbirth occurred. There was no difference between the 2 groups in MAP variation during pregnancy.

Of the women who had previously experience PE at earlier than 34 weeks of pregnancy (8 in each group), none had recurrent early-onset PE.

Study Reference **Tapp 2020**

Outcome		Group; n (%) 160 mg group (n=53)	80 mg group (n=51)	RR (95% CI)	p value
PE	All PE	8 (15)	6 (12)	1.3 (0.49−3.58)	0.775
	Term PE (>37 weeks)	7 (13)	4 (8)	1.8 (0.54−5.53)	0.526
	Preterm PE (<37 weeks)	1 (2)	2 (4)	0.5 (0.04−5.25)	0.556
	Early-onset PE (<34 weeks)	1 (2)	0 (0)	2.8 (0.12−68.08)	0.520
FGR	All FGR (<10th centile)	1 (2)	4 (8)	0.2 (0.03−2.08)	0.195
	Mild FGR (3rd− 9th centile)	1 (2)	3 (6)	0.3 (0.03−2.28)	0.318
	Severe FGR (<3rd centile)	0 (0)	1 (2)	0.3 (0.01−7.70)	0.483
PTB	All PTB (<37 weeks)	4 (8)	8 (16)	0.5 (0.15−1.49)	0.207
	Mild PTB (34−36 weeks)	2 (4)	6 (12)	0.3 (0.07−1.52)	0.161
	Severe PTB (<34 weeks)	2 (4)	2 (4)	1.0 (0.14−6.58)	0.969

There was no significant difference in primary or secondary outcomes between women who started aspirin before 11 weeks and those who started after 11 weeks.

Safety

No serious adverse events associated with or potentially attributable to the study treatment were observed.

Authors' Conclusions

No significant impact of 80 mg or 160 mg of aspirin taken at bedtime and initiated before 14 weeks gestation was observed on mid trimester UtA-PI in pregnant women with a history of PE. There was also no significant impact observed on clinical outcomes, but this pilot study did not have the power to explore this. The results suggest that the difference in clinical impact observed according to aspirin dose is mildly related to placental function evaluated by UtA-PI measurement. On the other hand, no early-onset PE recurrence among 16 participants with such history was observed, and a low incidence of FGR in a high-risk population was found, emphasising the efficacy of aspirin at 80 and 160 mg taken daily at bedtime.

When taken regularly at bedtime beginning in the first trimester of pregnancy, 80 and 160 mg doses of aspirin are associated with similar mid trimester UtA-PI in women with previous PE. Aspirin has a major beneficial impact on the prevention of PE and FGR. Based on the results of this study results and the current literature, authors concluded that (1) the impact of aspirin on the prevention of preterm PE is not directly related to improvement of deep placentation alone; (2) no single factor or marker (history, biophysical, ultrasound, or biochemical markers) should be used to identify pregnant women who could benefit from aspirin; and (3) a minimum of 100 mg daily at bedtime should be prescribed to high-risk women accurately identified as at risk of preterm PE.

Abbreviations: BMI, body mass index; CI, confidence interval; FGR, fetal growth restriction; IQR, interquartile range; MAP, mean arterial pressure; MoM, multiple of median; NR, not reported; PE, pre-eclampsia; PTB, preterm birth; RCT, randomised controlled trial; RR, risk ratio; UtA-PI, uterine artery pulsatility index.

Appraisal for quality and risk of bias

Quality assessments of included studies are reported below.

Table 29. Guidance for QUADAS-2 Quality Assessment of Studies Extracted for Question 1

Question		
PARTICIPANT SELECTION		
Was a consecutive or random sample of pregnancies enrolled?	A study should ideally enrol all consecutive, or a random sample of, eligible patients – otherwise there is potential for bias. Studies that make inappropriate exclusions, e.g. excluding "difficult to diagnose" patients, may result in overoptimistic estimates of diagnostic accuracy	**Yes** if all pregnancies (or a random sample of patients) within the study period were included **No** if patients were selected in a different way, e.g. by referral or convenience sample **Unclear** if all screened pregnancies are enrolled but it is not specified if the screening test is routinely administered at the study site
Was a case-control design avoided?	Studies enrolling patients with known disease and a control group without the condition may exaggerate diagnostic accuracy	**Yes** if the study was a prospective or retrospective cohort study **No** if cases (pre-eclampsia, gestational hypertension, or hypertensive disorders of pregnancy) were matched to controls
Did the study avoid inappropriate exclusions?	Exclusion of patients with "red flags" for the target condition, who may be easier to diagnose, may lead to underestimation of diagnostic accuracy	**Yes** if all pregnancies were included, or if exclusions were appropriate and unlikely to lead to bias **No** if any group within the screening population was systematically excluded
Could the selection of pregnancies have introduced bias?	If all signalling questions for a domain are answered "yes" then risk of bias can be judged "low". If any signalling question is answered "no" this flags the potential for bias	Answered based on the previous questions in this domain
Is there concern that the included pregnancies do not match the review question?	There may be concerns regarding applicability if patients included in the study differ, compared to those targeted by the review question, in terms of severity of the target condition, demographic features, presence of differential diagnosis or co-morbidity, setting of the study and previous testing protocols	**Low** if patients overall are low-risk pregnancies representative of the screening population (i.e. similar to the pregnant population in the UK) **High** if patients overall are not representative of the screening population, such as pregnancies with at least one moderate risk factor as specified in UK guidelines or demographically dissimilar to the UK population
INDEX TESTS		
Were the index test results interpreted without knowledge of the reference standard?	This item is similar to "blinding" in intervention studies. Interpretation of index test results may be influenced by knowledge of the reference standard	**Yes** if screening results were interpreted before the diagnosis was confirmed **No** if screening results were only examined after the diagnosis was confirmed
If a threshold was used, was it pre-specified?	Selecting the test threshold to optimise sensitivity and/or specificity may lead to overoptimistic estimates of test performance, which is likely to be poorer in an independent sample of patients in whom the same threshold is used	**Yes** if the criteria used to diagnose pre-eclampsia or gestational hypertension were explicitly stated, well-defined, and specified before the study **No** if criteria were not stated, were insufficiently well-defined, or were specified retrospectively

Could the conduct or interpretation of the index test have introduced bias?	If all signalling questions for a domain are answered "yes" then risk of bias can be judged "low". If any signalling question is answered "no" this flags the potential for bias	Answered based on the previous questions in this domain. Consider whether the staff conducting the index test could have had foreknowledge of who was at risk by presence of major factors.
Is there concern that the index test, its conduct, or interpretation differ from the review question?	Variations in test technology, execution, or interpretation may affect estimates of its diagnostic accuracy. If index tests methods vary from those specified in the review question there may be concerns regarding applicability	**Low** if the screening test is similar to tests or screening tests administered as part of UK clinical practice **High** if any aspect of the index test, including its conduct or interpretation, is substantially different from clinical practice in a UK setting (as outlined in the CG 107 NICE guidance)
REFERENCE STANDARD		
Is the reference standard likely to correctly classify the test condition?	Estimates of test accuracy are based on the assumption that the reference standard is 100% sensitive and specific. Disagreements between the reference standard and index test are assumed to result from incorrect classification by the index test	**Yes** if pre-eclampsia was confirmed consistently at ≥20 completed weeks of gestation based on accepted definition (see below) **No** if diagnosis was performed inconsistently, or if the methods used are likely to be unreliable
Were the reference standard results interpreted without knowledge of the results of the index test?	Potential for bias is related to the potential influence of prior knowledge on the interpretation of the reference standard	**Yes** if the final diagnosis of pre-eclampsia (or GH or HDP) were made by an investigator blinded to the index test results **No** if the screening results were known by the investigator making the final diagnosis **Unclear** if it is not clear whether the investigator was aware of the test result when making the final diagnosis
Could the reference standard, its conduct, or its interpretation have introduced bias?	If all signalling questions for a domain are answered "yes" then risk of bias can be judged "low". If any signalling question is answered "no" this flags the potential for bias	Answered based on the previous questions in this domain
Is there concern that the target condition as defined by the reference standard does not match the review question?	The reference standard may be free of bias but the target condition that it defines may differ from the target condition specified in the review question. For example, when defining urinary tract infection, the reference standard is generally based on specimen culture but the threshold above which a result is considered positive may vary	**Low** if the definition of pre-eclampsia or gestational hypertension used was the standard UK definition or similar: **PE**: GH with significant proteinuria [Persistent systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg with proteinuria ≥0.3 g/24 h or ≥1+ dipstick (=30 mg/dL in a single urine sample), after 20 weeks of gestation] OR **PE**: GH and either of high protein in the urine, or the new development of decreased blood platelets, trouble with the kidney or liver, fluid in the lungs, or signs of brain trouble such as seizures and/or visual disturbances **GH**: new hypertension presenting after 20 weeks of pregnancy without significant proteinuria **High** if the reference standard defined pre-eclampsia in any other way
PARTICIPANT FLOW		
Was there an appropriate interval between the index test(s) and the reference standard?	Ideally results of the index test and reference standard are collected on the same patients at the same time. If there is a delay or if treatment is started between index test and reference standard, misclassification may occur due to recovery or deterioration of the condition. The length of interval	**Yes** if all women gave birth spontaneously or were induced for reasons other than to prevent pre-eclampsia **No** if some women were induced to deliver to avoid developing pre-eclampsia

	leading to a high risk of bias will vary between conditions. A delay of a few days may not be a problem for chronic conditions, while for acute infectious diseases a short delay may be important	
Did all participants receive a reference standard? **Did participants receive the same reference standard?**	Verification bias occurs when not all of the study group receive confirmation of the diagnosis by the same reference standard. If the results of the index test influence the decision on whether to perform the reference standard or which reference standard is used, estimated diagnostic accuracy may be biased	**Yes** if all screened patients had confirmation of their diagnosis, and all were diagnosed in the same manner (using the same reference standard by similarly trained staff) **No** if patients received different reference standards **Unclear** if there was a high variability in staff diagnosing and recording pre-eclampsia, or the staff may not have received the same training
Were all pregnancies included in the analysis?	All patients who were recruited into the study should be included in the analysis. There is a potential for bias if the number of patients enrolled differs from the number of patients included in the 2x2 table of results, for example because patients lost to follow-up differ systematically from those who remain	**Yes** if all screened women were included in the final analysis **No** if any screened women were not included in the final analysis
Could the participant flow have introduced bias?	If all signalling questions for a domain are answered "yes" then risk of bias can be judged "low". If any signalling question is answered "no" this flags the potential for bias	**No** if women who underwent the index test were all equally likely to develop and be diagnosed with pre-eclampsia in the same manner **Yes** if some women could have been prevented from developing pre-eclampsia (e.g. by labour induction) or if women received different reference standards or a significant proportion were removed from the analysis

Table 30. Quality assessment of studies included for question 1

Question	Al-Amin 2018	Allen 2018	ASPRE (Rolnik 2017)	Baweja 2011	Boucoiran 2013a	Boucoiran 2013b	Caradeux 2013	Carter 2015	Di Lorenzo 2012	Di Martino 2019	Erkamp 2020	Gabbay-Benziv 2016	Goetzinger 2013
PARTICIPANT SELECTION													
Was a consecutive or random sample of pregnancies enrolled?	Yes	Unclear but likely	Yes	Yes	Yes	Unclear but likely	Yes	Yes	Yes	Unclear but likely	Unclear but likely	Yes	Yes
Was a case-control design avoided?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the study avoid inappropriate exclusions?	Unclear	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	Yes	No	No	Yes
Could the selection of pregnancies have introduced bias?	High	Low	Low	High	Low	Low	Unclear	Low	Low	Low	High	High	No
Is there concern that the included pregnancies do	High	Low	Low	Low	Low	Low	High	High	Low	Low	Low	Low	Low

Question	Al-Amin 2018	Allen 2018	ASPRE (Rolnik 2017)	Baweja 2011	Boucoiran 2013a	Boucoiran 2013b	Caradeux 2013	Carter 2015	Di Lorenzo 2012	Di Martino 2019	Erkamp 2020	Gabbay-Benziv 2016	Goetzinger 2013
not match the review question?													
INDEX TESTS													
Were the index test results interpreted without knowledge of the reference standard?	Yes	No	Yes	Unclear	Yes	Unclear	No	No	Yes	Unclear	Yes	No	No
If a threshold was used, was it pre-specified?	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low	High	Low	Unclear	Low	Unclear	High	High	Low	Unclear	Low	High	Low
Is there concern that the index test, its conduct, or interpretation differ from the review question?	High	Low	Low	Low	Low	Low	High	Low	High	Low	Low	Low	High
REFERENCE STANDARD													
Is the reference standard likely to correctly classify the test condition?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High	Unclear	Unclear	High	Unclear	Low	Unclear
Is there concern that the target condition as defined by the reference standard does not match the review question?	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
PARTICIPANT FLOW													
Was there an appropriate interval between the index test(s) and the reference standard?	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	No	Unclear
Did all participants receive a reference standard?	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes

Question	Al-Amin 2018	Allen 2018	ASPRE (Rolnik 2017)	Baweja 2011	Boucoiran 2013a	Boucoiran 2013b	Caradeux 2013	Carter 2015	Di Lorenzo 2012	Di Martino 2019	Erkamp 2020	Gabbay-Benziv 2016	Goetzinger 2013
Did participants receive the same reference standard?													
Were all pregnancies included in the analysis?	No	No	No	No	No	Yes	Unclear	No	No	No	No	No	No
Could the participant flow have introduced bias?	High	High	High	High	Yes	Low	High	High	High	High	High	Yes	No

Table 31. Quality assessment of studies included for question 1 (continued)

Question	GOS study	Goto 2021	Hafner 2013	Honigberg 2016	Kanat-Pektas 2014	Khalil 2012	Maymon 2017	Meiri 2014	Metcalfe 2014	Myatt 2012	Odibo 2011a	Odibo 2011b
PARTICIPANT SELECTION												
Was a consecutive or random sample of pregnancies enrolled?	Yes	Unclear but likely	Yes	Yes	Yes	Unclear but likely	Unclear but likely	Unclear but likely	Unclear but likely	Unclear but likely	Unclear but likely	Unclear but likely
Was a case-control design avoided?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the study avoid inappropriate exclusions?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Could the selection of pregnancies have introduced bias?	Low	Low	Low	Low	High	Low	Low	Low	Low	High	Low	Low
Is there concern that the included pregnancies do not match the review question?	Low	Low	Low	High	Low	Low	Unclear	Low	Low	Low	Low	Low
INDEX TESTS												
Were the index test results interpreted without knowledge of the reference standard?	Unclear	Yes	Unclear	No	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes
If a threshold was used, was it pre-specified?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear	Low	Unclear	High	Low	Unclear	Unclear	Low	High	Low	Low	Low
Is there concern that the index test, its conduct, or interpretation differ from the review question?	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low

Question	GOS study	Goto 2021	Hafner 2013	Honigberg 2016	Kanat-Pektas 2014	Khalil 2012	Maymon 2017	Meiri 2014	Metcalfe 2014	Myatt 2012	Odibo 2011a	Odibo 2011b
REFERENCE STANDARD												
Is the reference standard likely to correctly classify the test condition?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Is there concern that the target condition as defined by the reference standard does not match the review question?	Low	Low	Low	Low	Low	Low	Low	Low	Unclear	Low	Low	Unclear
PARTICIPANT FLOW												
Was there an appropriate interval between the index test(s) and the reference standard?	Unclear	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Did all participants receive a reference standard? **Did participants receive the same reference standard?**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Were all pregnancies included in the analysis?	No	No	No	Unclear	Yes	No	Yes	Yes	Yes	Yes	No	No
Could the participant flow have introduced bias?	Low	High	High	High	Low	High	No	No	Yes	No	High	High

Table 32. Quality assessment of studies included for question 1 (continued)

Question	POP study	Sandström 2019	Scazzocchio 2013	SCOPE study	Schneuer 2012	Serra 2020	Skrastad 2015	Sonek 2018	Takahashi 2012	Tan 2018a	Tsiakkas 2016	Youssef 2011	Yucel 2016
PARTICIPANT SELECTION													
Was a consecutive or random sample of pregnancies enrolled?	Unclear but likely	Unclear but likely	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	

Question	POP study	Sandström 2019	Scazzocchio 2013	SCOPE study	Schneuer 2012	Serra 2020	Skrastad 2015	Sonek 2018	Takahashi 2012	Tan 2018a	Tsiakkas 2016	Youssef 2011	Yucel 2016
Was a case-control design avoided?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Did the study avoid inappropriate exclusions?	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	
Could the selection of pregnancies have introduced bias?	Low	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	High	
Is there concern that the included pregnancies do not match the review question?	Low	Low	High	Low	Low	Low	High	High	High	Low	High	High	
INDEX TESTS													
Were the index test results interpreted without knowledge of the reference standard?	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	No	Yes	Unclear	Yes	
If a threshold was used, was it pre-specified?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	
Could the conduct or interpretation of the index test have introduced bias?	Unclear	Low	High	Low	Low	Unclear	Low	Low	High	Low	Unclear	Low	
Is there concern that the index test, its conduct, or interpretation differ from the review question?	Low	Low	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	
REFERENCE STANDARD													
Is the reference standard likely to correctly classify the test condition?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	
Is there concern that the target condition as defined by the reference standard does not match the review question?	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	

Question	POP study	Sandström 2019	Scazzocchio 2013	SCOPE study	Schneuer 2012	Serra 2020	Skrastad 2015	Sonek 2018	Takahashi 2012	Tan 2018a	Tsiakkas 2016	Youssef 2011	Yucel 2016
PARTICIPANT FLOW													
Was there an appropriate interval between the index test(s) and the reference standard?	No	No	Unclear	Unclear	Unclear	Yes	No	Unclear	Unclear	Unclear	Unclear	Yes	
Did all participants receive a reference standard? **Did participants receive the same reference standard?**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Unclear	Unclear	Yes	
Were all pregnancies included in the analysis?	No	Yes	No	No	No	No	Yes	No	No	No	No	No	
Could the participant flow have introduced bias?	High	High	High	Low	Low	Yes	Low	High	Low	High	High	Yes	

Table 33. Guidance for Downs and Black Quality Assessment of Studies Extracted for Question 2

Question	
REPORTING	
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	**Yes** when maternal age and at least 3 baseline characteristics are reported from: parity, any general or specific previous pregnancy complications, hypertension, diabetes, BMI, smoking history **Partly** when only maternal age and/or between 1-3 baseline characteristics are reported **No** when maternal age was not reported and few or none other relevant baseline characteristics are reported
Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Answer should relate to the outcome measures of interest to this review
EXTERNAL VALIDITY	
Modified question: Were the subjects asked to participate in the study representative of the population of interest for this review? **Original question: Were the subjects asked to participate in the study representative of the entire population from which they were recruited?**	**Yes** only when pregnant women were identified as being at risk of PE through screening and the population they were identified from was representative of the expected screening population, that is, women who would be part of the normal antenatal care pathway (NICE CG 62) **No** if pregnant women were at risk of PE as determined by risk factors or tests
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Question removed – majority of interventions expected to be self-administered
INTERNAL VALIDITY - BIAS	
Was an attempt made to blind study subjects to the intervention they have received?	**Yes** if women were blind to treatment allocation, and if methods of blinding were appropriate, such as use of matching placebos **No** if any women were aware of treatment allocation

	NA if observational study
Was an attempt made to blind those measuring the main outcomes of the intervention?	**Yes** if outcome assessors were blind to treatment allocation, and if methods of blinding were appropriate, such as data analysis taking place at a separate site using blinded datasets **No** if any outcome assessors were aware of treatment allocation **NA** if observational study
If any of the results of the study were based on "data dredging", was this made clear?	**No dredging** if all outcomes of relevance to this review were pre-specified, and all outcomes listed in the methods section are fully reported **Dredging** if the authors report that any analyses were post hoc, or if some analyses were not pre-specified **Unclear** if the methods section or protocol do not specify a list of primary and secondary outcomes, and it is not clear whether outcomes were pre-specified
Were the statistical tests used to assess the main outcomes appropriate?	**Yes** if treatment groups were compared appropriately using risk difference, risk ratios, odds ratios, unpaired t-tests or similar; for single-arm trials a paired t-test may be appropriate; other methods may also be appropriate if justified in the publication **No** if the statistical tests were not appropriate – to be determined on a case-by-case basis **Unclear** if the statistical methods were not specified **NA** if no statistical tests were performed
Was compliance with the intervention/s reliable?	**Yes** if compliance or adherence were reported and were above 80% **No** if compliance or adherence were below 80% **Unclear** if compliance or adherence were not reported
Were the main outcome measures used accurate (valid and reliable)?	Answer should relate to the outcome measures of interest to this review **Yes** when the definitions of PE and SGA were pre-specified appropriately and there is no reason to suppose that staff were inadequately trained to diagnose these; or the only relevant outcomes reported were mortality **No** if the definition was not pre-specified, the criteria were unclear, outcomes were not routinely and consistently recorded, or there is reason to believe staff were not adequately trained to make measurements
Question added: Were the main outcome measures defined using definitions relevant to the UK?	**Yes** if the study used the NICE or ACOG definition of PE and if SGA (if reported) was defined as an infant born with a birth weight less than the 10th centile based on local or national charts from the UK **No** if the study defined PE or SGA in any other way
NTERNAL VALIDITY - SELECTION BIAS	
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	**Yes** if women from all intervention groups were recruited from the same population **No** if different intervention groups were recruited from different populations, such as different geographical location, different baseline characteristics, or patients selected using a different screening test
Question added: Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	**Yes** if baseline characteristics were similar between treatment groups, particularly maternal age, parity, BMI, pre-existing disorders, smoking or other narcotic use etc. **No** if there were significant differences between the groups in any of the characteristics

	listed above **Unclear** if relevant baseline characteristics were not reported or it is not clear if the differences between these are significant
Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	**Yes** if women from all intervention groups were recruited over the same period of time **No** if women from different intervention groups were recruited at different times, such as historical control groups
Were study subjects randomised to intervention groups?	**Yes** if randomisation was performed using computer-generated random numbers or random number tables **Inadequate** if alternation, case record numbers, birth dates or week days were used to allocate patients to treatment arms **No** if no attempt was made at randomisation or the study is non-interventional (observational)
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	**Yes** if the allocation sequence was protected before and until assignment, using methods such as: centralised or pharmacy-controlled randomisation, serially-numbered identical containers, on-site computer-based system with a randomisation sequence that is not readable until allocation, or other approaches with robust methods to prevent foreknowledge of the allocation sequence **No** if inadequate methods of randomisation were used, or if random number lists could have been viewed before allocation, such as open random number lists or serially numbered envelopes **NA** in non-randomised studies
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Answer should relate to the outcome measures of interest to this review **Yes** if analyses were adjusted for differences in key baseline characteristics (maternal age, BMI, pre-existing disorders, smoking or other narcotic use), or if adjustment was not necessary **No** if adjustment was necessary but was not performed
Were losses of patients to follow-up taken into account?	Answer should relate to the outcome measures of interest to this review **Yes** if there were no imbalances in drop-outs between groups, or if there was an imbalance in drop-outs but this was discussed and accounted for in the statistical analyses; for RCTs, check whether an intention-to-treat (ITT) analysis was used and whether this was appropriate (generally appropriate for superiority studies, not appropriate for non-inferiority studies) **No** if drop-out rates were unbalanced and this was not explained or adjusted for or when ITT analysis was used incorrectly or inappropriately
POWER	
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	**Yes** if power calculations are reported and an adequate sample size was used **No** if power calculations are reported and an adequate sample size was not reached or the study was not powered to detect a difference for the outcomes of interest **Unclear** if power calculations are not reported (adequate sample sizes may be calculated for each outcome when a clinically important difference has been determined)

Table 34. Quality assessment of studies relevant to question 2

Question	ASPRE Rolnik 2017	Ayala 2013	Bella 2020	Costantine 2016 Costaintine 2016	Chiswick 2015	Dobert 2021
REPORTING						
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
Have actual probability values been reported for the main outcomes except where the probability value is less than 0.001?	Yes	Yes	Yes	No	Yes	Yes
EXTERNAL VALIDITY						
Were the subjects asked to participate in the study representative of the population of interest for this review?	Yes	No	Partially	No	No	Yes
INTERNAL VALIDITY - BIAS						
Was an attempt made to blind study subjects to the intervention they have received?	Yes	Yes	No	Yes	Yes	Yes
Was an attempt made to blind those measuring the main outcomes of the intervention?	Yes	Yes	No	Yes	Yes	Yes
If any of the results of the study were based on "data dredging", was this made clear?	No dredging	Unclear	No dredging	No dredging	Dredging	No dredging
Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes	Yes	Yes	Yes	Yes
Was compliance with the intervention/s reliable?	Yes	Yes	Unclear	Yes	No	Yes
Were the main outcome measures used accurate (valid and reliable)?	Yes	Unclear	Yes	Yes	No	Yes
Were the main outcome measures defined using UK definitions?	Yes	No	Yes	Yes	No	Yes
INTERNAL VALIDITY – SELECTION BIAS						
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	No	Yes	Yes	Yes	Yes	Yes

Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Yes	No	Yes	Yes	Yes
Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	Yes	Unclear	Yes	Unclear	Yes	Yes
Were study subjects randomised to intervention groups?	Yes	Yes	Yes	Yes	Yes	Yes
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	Yes	Yes	Unclear	Yes	Yes	Yes
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Yes	Yes	No	Yes	Yes	Yes
Were losses of patients to follow-up taken into account?	Yes	Yes	Yes	Yes	Yes	Yes
POWER						
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Yes	Yes	Partially	No	No	Partially

Table 35. Quality assessment of studies relevant to question 2 (continued)

Question	McLaughlin 2021	Odibo 2015	Park 2021 Park 2021	PREDO Villa 2013	Scazzocchio 2017	Stanescu 2018	Syngelaki 2016	Tapp 2020
REPORTING								
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Have actual probability values been reported for the main outcomes except where the probability value is less than 0.001?	No	No	Yes	No	Yes	No	Yes	Yes
EXTERNAL VALIDITY								

Were the subjects asked to participate in the study representative of the population of interest for this review?	Yes	No	Yes	No	Yes	Yes	No	No
INTERNAL VALIDITY - BIAS								
Was an attempt made to blind study subjects to the intervention they have received?	No	Yes	No	Yes	Yes	No	Yes	Yes
Was an attempt made to blind those measuring the main outcomes of the intervention?	No	Yes	No	Yes	Yes	Yes	Yes	Yes
If any of the results of the study were based on "data dredging", was this made clear?	No dredging	Dredging	No dredging	No dredging	No dredging	Unclear	No dredging	No dredging
Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Was compliance with the intervention/s reliable?	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes
Were the main outcome measures used accurate (valid and reliable)?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Were the main outcome measures defined using UK definitions?	Yes	Yes	Unclear	No	Yes	Unclear	Unclear	Unclear
INTERNAL VALIDITY – SELECTION BIAS								
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	No	Partly	No	Yes	Yes	Unclear	No	Unclear
Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes

(case-control studies) recruited over the same period of time?								
Were study subjects randomised to intervention groups?	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	No	Unclear	Partially	Yes	Yes	Unclear	No	No
Were losses of patients to follow-up taken into account?	Yes	No	No	Yes	No	Unclear	Unclear	Yes
POWER								
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Unclear	No	Unclear	No	No	Unclear	Partly	Partially

Table 36. Quality assessment of studies relevant to question 2 (continued)

Question	**Cruz-Lemini**
Was an 'a priori' design provided?	Yes – the study protocol was registered with PROSPERO (number CRD42020191148)
Was there duplicate study selection and data extraction?	Yes – abstract screening was performed independently by 2 authors and full-text review and data extraction was performed independently by 3 reviewers
Was a comprehensive literature search performed?	Yes – 2 databases were searched, dates are provided, key words/MeSH terms are reported, the search strategy is provided in supplementary materials; database searches were supplemented with reviews of congress abstracts and meetings, reference lists of articles, published protocols, and other reviews; no language restriction was imposed
Was the status of publication (i.e. grey literature) used as an inclusion criterion?	No
Was a list of studies (included and excluded) provided?	No – while a list of included studies is provided, a list of studies excluded, and the reasons for excluding these studies at full-text stage, is not provided
Were the characteristics of the	Yes

included studies provided?	
Was the scientific quality of the included studies assessed and documented?	Yes – risk of bias assessed for all included studies, with clear documentation
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes – discussion of the potential bias of included studies in included in the results section and as a qualification of the conclusions
Were the methods used to combine the findings of studies appropriate?	Yes
Was the likelihood of publication bias assessed?	Yes – assessed via funnel plot, which suggested no publication bias
Was the conflict of interest included?	Yes – conflicts of interest declared

Appendix 4 — UK NSC reporting checklist for evidence summaries

All items on the UK NSC Reporting Checklist for Evidence Summaries have been addressed in this report. A summary of the checklist, along with the page or pages where each item can be found in this report, is presented in Table 37.

Table 37. UK NSC reporting checklist for evidence summaries

	Section	Item	Page no.
1.	TITLE AND SUMMARIES		
1.1	Title sheet	Identify the review as a UK NSC evidence summary.	Title page
1.2	Plain English summary	Plain English description of the executive summary.	5-6
1.3	Executive summary	Structured overview of the whole report. To include: the purpose/aim of the review; background; previous recommendations; findings and gaps in the evidence; recommendations on the screening that can or cannot be made on the basis of the review.	7-12
2.	INTRODUCTION AND APPROACH		
2.1	Background and objectives	Background – Current policy context and rationale for the current review – for example, reference to details of previous reviews, basis for current recommendation, recommendations made, gaps identified, drivers for new reviews Objectives – What are the questions the current evidence summary intends to answer? – statement of the key questions for the current evidence summary, criteria they address, and number of studies included per question, description of the overall results of the literature search. Method – briefly outline the rapid review methods used.	13-19
2.2	Eligibility for inclusion in the review	State all criteria for inclusion and exclusion of studies to the review clearly (PICO, dates, language, study type, publication type, publication status etc.) To be decided *a priori*.	23-25
2.3	Appraisal for quality/risk of bias tool	Details of tool/checklist used to assess quality, e.g. QUADAS 2, CASP, SIGN, AMSTAR.	26
3.	SEARCH STRATEGY AND STUDY SELECTION (FOR EACH KEY QUESTION)		

3.1	Databases/ sources searched	Give details of all databases searched (including platform/interface and coverage dates) and date of final search.	26
3.2	Search strategy and results	Present the full search strategy for at least one database (usually a version of Medline), including limits and search filters if used. Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion.	90-99
3.3	Study selection	State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out.	21
4.	STUDY LEVEL REPORTING OF RESULTS (FOR EACH KEY QUESTION)		
4.1	Study level reporting, results and risk of bias assessment	For each study, produce a table that includes the full citation and a summary of the data relevant to the question (for example, study size, PICO, follow-up period, outcomes reported, statistical analyses etc.). Provide a simple summary of key measures, effect estimates and confidence intervals for each study where available. For each study, present the results of any assessment of quality/risk of bias.	Study level reporting: 123-326 Quality assessment: 329-341
5.	QUESTION LEVEL SYNTHESIS		
5.1	Description of the evidence	For each question, give numbers of studies screened, assessed for eligibility, and included in the review, with summary reasons for exclusion.	100-122
5.2	Combining and presenting the findings	Provide a balanced discussion of the body of evidence which avoids over reliance on one study or set of studies. Consideration of four components should inform the reviewer's judgement on whether the criterion is 'met', 'not met' or 'uncertain': quantity; quality; applicability and consistency.	28-36 65-70
5.3	Summary of findings	Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion. Summarise the main findings including the quality/risk of bias issues for each question. Have the criteria addressed been 'met', 'not met' or 'uncertain'?	36-64 71-85
6.	REVIEW SUMMARY		
6.1	Conclusions and implications for policy	Do findings indicate whether screening should be recommended? Is further work warranted? Are there gaps in the evidence highlighted by the review?	85-88
6.2	Limitations	Discuss limitations of the available evidence and of the review methodology if relevant.	88-89

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