Hypertensive disorders of pregnancy

Pensée Wu,[1,2,3] Marcus Green,[4] Jenny E Myers[5]

[1]School of Medicine, Keele University, Newcastle-under-Lyme, UK
[2]Academic Department of Obstetrics and Gynaecology, University Hospital of North Midlands, Stoke-on-Trent, UK
[3]Department of Obstetrics and Gynecology, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[4]Action on Pre-eclampsia, Evesham, UK
[5]Maternal and Fetal Health Research Centre, University of Manchester, Manchester, UK
Correspondence to: P Wu
p.wu@keele.ac.uk

Cite this as: *BMJ* 2023;381:e071653
http://dx.doi.org/10.1136/bmj-2022-071653

Series explanation: State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason they are written predominantly by US authors

Abstract

Hypertensive disorders of pregnancy (HDP) are one of the most commonly occurring complications of pregnancy and include chronic hypertension, gestational hypertension, and pre-eclampsia. New developments in early pregnancy screening to identify women at high risk for pre-eclampsia combined with targeted aspirin prophylaxis could greatly reduce the number of affected pregnancies. Furthermore, recent advances in the diagnosis of pre-eclampsia, such as placental growth factor based testing, have been shown to improve the identification of those pregnancies at highest risk of severe complications. Evidence from trials has refined the target blood pressure and timing of delivery to manage chronic hypertension and pre-eclampsia with non-severe features, respectively. Importantly, a wealth of epidemiological data now links HDP to future cardiovascular disease and diabetes decades after an affected pregnancy. This review discusses the current guidelines and research data on the prevention, diagnosis, management, and postnatal follow-up of HDP. It also discusses the gap in knowledge regarding the long term risks for cardiovascular disease following HDP and illustrates the importance of improving adherence to postnatal guidelines to monitor hypertension and the need for more research focused on primary prevention of future cardiovascular disease in women identified as being at high risk because of HDP.

Introduction

Hypertensive disorders of pregnancy (HDP) are the leading causes of maternal morbidity and mortality worldwide.[1] The International Society for the Study of Hypertension in Pregnancy (ISSHP) has updated the definition of HDP: chronic hypertension, white coat hypertension, masked hypertension, gestational hypertension, and pre-eclampsia.[2] This review is aimed at specialists providing maternity services and gives an overview of the prevention, diagnosis, management, postnatal sequelae, and follow-up of HDP. We highlight the latest evidence on screening for and diagnosis of pre-eclampsia and the long term consequences of HDP.

Sources and selection criteria

We searched Medline and Embase databases for studies published between January 2013 and December 2022, using synonyms of hypertensive disorders of pregnancy ("hypertensive pregnancy disorders" or "hypertension in pregnancy") or pre-eclampsia ("preeclampsia" or "pre-eclampsia" or "EPH" or "pregnancy toxemia" or "edema-proteinuria-hypertension gestos") or pregnancy induced hypertension ("pregnancy-induced hypertension" or "gestational hypertension") or "chronic hypertension in pregnancy" or "eclampsia" or "HELLP syndrome". We predefined the priority of the studies to be included on the basis of quality (systematic reviews and meta-analyses, randomised controlled trials (RCTs), large size of study), direct relevance to the topic, and year of publication, with preference given to more recent publications. We also assessed relevant international professional guidelines and conducted hand searching for relevant articles in the bibliography of the studies found by the search criteria. We included earlier references if a strong case existed for their inclusion owing to their relevance.

Epidemiology

The prevalence of HDP varies according to region, with a global prevalence of 116 per 100 000 women of childbearing age.[3] Regionally, Africa had the highest prevalence of HDP (335 per 100 000 women of childbearing age), followed by Southeast Asia and the Middle East, whereas the Western Pacific region had the lowest prevalence of HDP (16 per 100 000 women of childbearing age).[3] Worldwide, 18.1 million incident cases of HDP were estimated for 2019, with HDP thought to be responsible for 27 800 deaths in women of childbearing age, a reduction of 30% since 1990.[4] Moreover, HDP is estimated to be present in 200 000 pregnancies ending in stillbirths every year worldwide.[5]

Classification of HDP

The ISSHP defines hypertension in pregnancy as a systolic blood pressure (sBP) ≥140 mm Hg and/or

Box 1: ISSHP classification of hypertensive disorders of pregnancy

Pre-pregnancy or <20 weeks' gestation

Chronic hypertension:
- Hypertension pre-pregnancy or <20 weeks' gestation

White coat hypertension:
- BP ≥140/90 mm Hg in clinic, but BP <135/85 mm Hg with home or ambulatory BP monitoring

Masked hypertension:
- BP <140/90 mm Hg in clinic, but BP ≥135/85 mm Hg outside clinic

≥20 weeks' gestation

Gestational hypertension:
- Hypertension de novo ≥20 weeks' gestation without proteinuria or other features suggestive of pre-eclampsia

Pre-eclampsia:
- Gestational hypertension with ≥1 new onset conditions of organ or uteroplacental dysfunction:
  - Proteinuria
  - Other maternal end organ dysfunction, including:
    - Neurological complications (eg, eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, or persistent visual scotomata)
    - Pulmonary oedema
    - Haematological complications (eg, platelet count <150 000/µL, disseminated intravascular coagulation, haemolysis)
    - Acute kidney injury (such as creatinine ≥90 µmol/L or 1 mg/dL)
    - Liver involvement (eg, elevated transaminases such as ALT or AST >40 IU/L) with or without right upper quadrant or epigastric abdominal pain)
    - Uteroplacental dysfunction (eg, placental abruption, angiogenic imbalance, fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or intrauterine fetal death)
  - With severe features (according to ACOG):
    - Systolic BP ≥160 mm Hg or diastolic BP ≥110 mm Hg on two occasions at least 4 hours apart
    - Thrombocytopenia
    - Impaired liver function
    - Renal insufficiency
    - Pulmonary oedema
    - New onset headache unresponsive to medication and not accounted for by alternative diagnoses and visual disturbances

Superimposed pre-eclampsia on chronic hypertension:
- Chronic hypertension with development of new proteinuria and/or organ or uteroplacental dysfunction(s) with the conditions listed above

Adapted from ISSHP 2021 guideline.[2]

ACOG=American College of Obstetrics and Gynecology; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BP=blood pressure; ISSHP=International Society for the Study of Hypertension in Pregnancy.

a diastolic blood pressure (dBP) ≥90 mm Hg, with sBP ≥160 mm Hg and/or a dBP ≥110 mm Hg defined as severe hypertension.[2] The use of an automated device validated in pregnancy and pre-eclampsia is preferable for the measurement of blood pressure; a list of suitable devices is available online.[6] It is good practice to confirm the diagnosis with repeated measures of blood pressure, ideally over several hours or days. Ideally, the diagnosis would be confirmed by ambulatory monitoring, which is the gold standard outside of pregnancy, but for logistical reasons the diagnosis in pregnancy is usually confirmed by repeated hospital or clinic based measurements. Self-monitoring of blood pressure is now increasingly common in the management of HDP. The BUMP trials confirmed that this practice was acceptable to women and not associated with increased risk of adverse outcomes.[7 8]

The ISSHP has refined the classification of HDP over the years (box 1).[2] Chronic hypertension is defined as hypertension present before pregnancy or diagnosed before 20 weeks' gestation. The modified definitions include white coat hypertension and masked hypertension. White coat hypertension should be monitored with regular blood pressure surveillance and/or home or 24 hour ambulatory blood pressure monitoring, as it is associated with an increased risk of pre-eclampsia.[9 10] For masked hypertension, as the blood pressure seems to be normal in clinic, the diagnosis is usually sought only when unexplained features of organ damage from hypertension are present. Diagnosis is confirmed by home or 24 hour ambulatory blood pressure monitoring.[11]

Gestational hypertension (often previously referred to as pregnancy induced hypertension) is defined as de novo hypertension after 20 weeks' gestation. Pre-eclampsia is a multisystem disease characterised by widespread endothelial dysfunction, and the definition requires at least two features of the syndrome to be present (see box 1). In addition to hypertension (de novo or chronic), proteinuria is the most frequent additional sign of endothelial dysfunction and therefore most often used to make the diagnosis. The clinical diagnosis is based on the presence of signs/symptoms including vasoconstriction (hypertension), increased capillary permeability

Box 2: Major and moderate risk factors for pre-eclampsia in National Institute for Health and Care Excellence guideline[30]

Major
- HDP during previous pregnancy
- Chronic kidney disease
- Autoimmune disease—eg, SLE or APS
- Diabetes—type 1, type 2
- Chronic hypertension

Moderate
- Nulliparity
- Age ≥40 years
- Pregnancy interval >10 years
- BMI ≥35 at first clinic visit
- Family history of pre-eclampsia
- Multi-fetal pregnancy

APS=antiphospholipid syndrome; BMI=body mass index; HDP=hypertensive disorders of pregnancy; SLE=systemic lupus erythematosus

(proteinuria, peripheral oedema, cerebral oedema, liver congestion, pulmonary oedema), and abnormal endothelial/platelet interactions (thrombocytopenia, disseminated intravascular coagulation).

Pre-eclampsia is strongly associated with placental dysfunction; placental damage and/or stress is thought to precede the development of the maternal condition.[12] Recognising the strong association between chronic placental insufficiency and particularly preterm pre-eclampsia, the presence of objective features of placental dysfunction, including fetal growth restriction, oligohydramnios, abnormal umbilical artery, or maternal uterine artery Doppler, are also accepted features of the pre-eclampsia syndrome (box 1). The combination of placental dysfunction and hypertension is therefore usually considered to satisfy a clinical diagnosis of pre-eclampsia although this combination is not included in the American College of Obstetricians and Gynecologists (ACOG) guideline definition.[13]

The importance of distinguishing pre-eclampsia from other HDP is very important in clinical practice. Left unchecked, pre-eclampsia leads to severe adverse maternal outcomes including cerebrovascular haemorrhage, pulmonary oedema, acute kidney injury, hepatic rupture, placental abruption, and eclampsia.[14-19] Prevention of these severe, life threatening outcomes relies on early diagnosis and intervention; early delivery is the only current treatment. The consequences of inaccurate classification of HDP therefore include missed diagnoses and avoidable adverse outcomes, as well as inappropriate iatrogenic preterm births leading to significant neonatal morbidity.

Risk factors and prevention

The maternal and pregnancy characteristics associated with an increased risk of pre-eclampsia have been reported in many cohort studies and include a previous history of HDP, nulliparity, family history, obesity, pre-existing medical disease, primiparity, assisted reproduction and short duration of sperm exposure, and extremes of maternal age.[20] A meta-analysis including 25 356 688 women analysed 40 studies from Europe and 30 from North America.[21] Previous HDP, chronic hypertension, and antiphospholipid syndrome were associated with the highest absolute risk of pre-eclampsia. However, in terms of population attributable risk, obesity and nulliparity (11%) accounted for the largest population risk.[22] Similar data have also been collated from low income and middle income settings, with data from 276 388 mothers and their infants analysed by investigators at the World Health Organization.[23] The prevalence of pre-eclampsia/eclampsia in this study population was 4%, and the odds ratios for development of the condition associated with body mass index ≥35, nulliparity, and chronic hypertension were 3.90 (95% confidence interval 3.52 to 4.33), 2.04 (1.92 to 2.16), and 7.75 (6.77 to 8.87), respectively.

No treatment is available for pre-eclampsia or fetal growth restriction once they have developed.[24] To prevent maternal complications and fetal death, intensive surveillance and iatrogenic preterm birth are the mainstay of management.[2] For decades, aspirin has been considered an effective preventive treatment for pre-eclampsia.[25 26] A range of effective aspirin dosages (50 to 150 mg) for prevention of pre-eclampsia have been presented in meta-analyses.[27-29] The current guidelines from the National Institute for Health and Care Excellence (NICE) recommend aspirin for women with one high risk factor or two moderate risk factors for pre-eclampsia (box 2).[30]

The algorithm from the Fetal Medicine Foundation (FMF) (https://www.fetalmedicine.org/research/assess/preeclampsia/first-trimester) incorporates maternal risk factors, blood pressure, placental biomarkers (pregnancy associated plasma protein A (PAPP-A) and protein placental growth factor (PlGF)), and uterine artery Doppler. The FMF's algorithm has been developed over a series of observational studies.[31-33] In 2018 an independent prospective cohort study reported a doubling of the detection rate of preterm pre-eclampsia with the algorithm. At a fixed screen positive rate of 10.3%, rates of preterm pre-eclampsia were 3.4% in women screen positive using NICE criteria and 6.8% in women screen positive using the FMF's algorithm; the test doubled the detection rate for preterm pre-eclampsia compared with the NICE guidelines (41% to 82%).[33] Although several trials had already shown a reduction in preterm pre-eclampsia with aspirin,[25 26] the ASPRE trial confirmed a significant reduction in risk when aspirin was used in conjunction with the FMF's algorithm.[34] In this RCT, 11% of the population were screen positive, of whom 60% were randomised to aspirin 150 mg daily or placebo. Rates of preterm pre-eclampsia were 4.3% in the placebo group and 1.6% in the treatment group (odds ratio 0.38, 0.20 to 0.74). Moreover, the effectiveness of aspirin is greatest in preventing births at <32 weeks' gestation,[35] when the consequences of pre-eclampsia

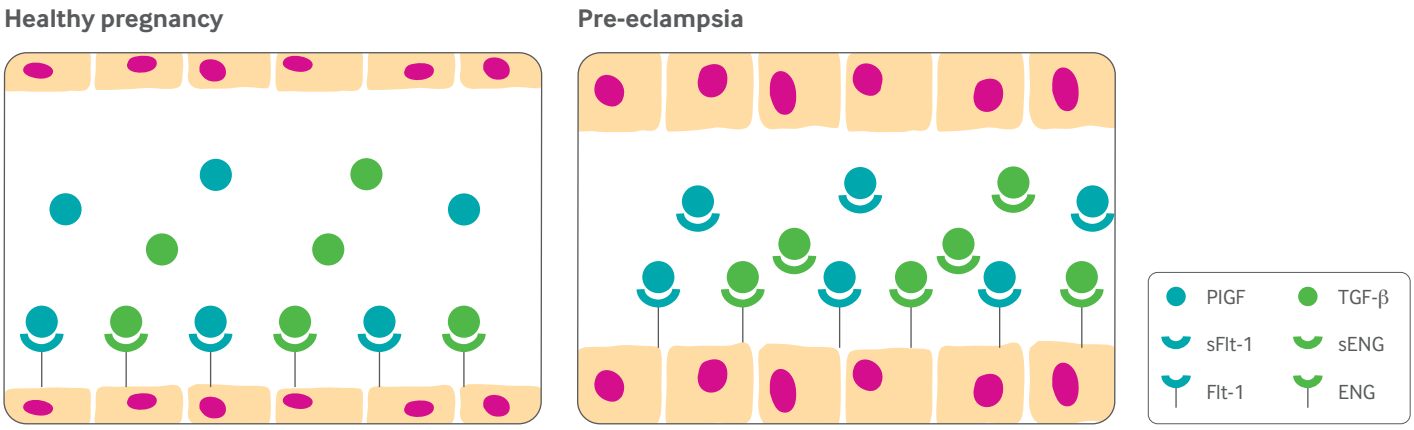

Fig 1 | In healthy pregnancy, soluble FMS-like tyrosine kinase 1(Flt-1) binds to placental growth factor (PlGF) and endoglin (ENG) binds to transforming growth factor β (TGF-β). In pre-eclampsia, soluble Flt-1 (sFlt-1) is cleaved off Flt-1 and competes with Flt-1 to bind to PlGF. Also soluble ENG (sENG) is cleaved off ENG and competes with ENG to bind to TGF-β

are most severe. First trimester screening using the FMF's algorithm combined with aspirin seems to outperform NICE screening, particularly in first time mothers and women from Black and minority ethnic backgrounds.[36 37]

Despite the ASPRE trial, the FMF's algorithm has not been widely adopted in the UK although ISSHP and the International Federation of Gynecology and Obstetrics now recommend combined screening with the FMF algorithm where possible.[2 38] Concerns about cost effectiveness and the logistics of implementation, given the low prevalence of the disease, are commonly cited as barriers among obstetricians. Only limited external validation of this screening test has been conducted.[39] However, in a single site study in London, its adoption led to a reduction in preterm pre-eclampsia by 80%.[36] To date, multimodal screening for pre-eclampsia using the FMF's algorithm has not been endorsed by the National Screening Committee; the updated statement concluded that evidence supports clinical effectiveness for early pregnancy screening combined with aspirin prophylaxis, but insufficient evidence "of harms and benefits of a screening programme in this population" is available.[40]

Implementation of the FMF's algorithm could achieve an absolute risk reduction in the rate of preterm pre-eclampsia of 0.4%,[33] which equates to around 17 cases per year of preterm pre-eclampsia avoided in an average maternity unit (4500 births per annum). Given the significant cost of implementation (approximately £170 000 ($210 000; €196 000) per year—£38 per pregnancy) and the logistical challenges of introducing the test, further evidence to evaluate cost effectiveness is likely to be needed before routine implementation can be recommended in the UK.

Calcium supplementation has also shown promise in Cochrane systematic reviews for the prevention of HDP, particularly in areas with low dietary calcium.[41 42] The ongoing CaPE RCT (ISRCTN12033893), expected to complete in 2025, is investigating the clinical effectiveness and cost effectiveness of calcium supplementation in preventing pre-eclampsia in the UK.

Recent advances in diagnosis

The clinical presentation is heterogeneous and frequently atypical, leading to ambiguity in the classification of HDP in both clinical practice and research studies. Unsurprisingly, a diagnosis based on highly variable clinical observations such as blood pressure and proteinuria, and which relies on parameters with poor diagnostic accuracy (eg, fetal ultrasonography and urine protein measurement),[43 44] is often inaccurate. Transient and sustained gestational hypertension is common in pregnancy, particularly towards term and intrapartum. The distinction between a transient excursion in blood pressure above 140/90 mm Hg and the diagnosis of a syndrome attributable to endothelial dysfunction therefore continues to pose a frequent diagnostic challenge. The diagnosis of pre-eclampsia is even more complicated in women who have chronic hypertension and/or other medical or obstetric disorders that are associated with the development of hypertension, proteinuria, compromised kidney function (eg, diabetes, chronic kidney disease), abnormal liver function (eg, obstetric cholestasis), or abnormal haematology (gestational thrombocytopenia). Although many studies have attempted to adjudicate the diagnosis of pre-eclampsia, the use of clinical definitions is limited and inevitably many pre-eclampsia research studies will have inaccuracies.

Progress towards a more accurate diagnostic test for pre-eclampsia was accelerated by the discovery of an abnormal angiogenic imbalance in pre-eclampsia. The initial study identified very high concentrations of the protein soluble FMS-like tyrosine kinase 1 (sFlt) in the placentas of women with pre-eclampsia.[45] This observation was followed by a second study that showed high concentrations of the antiangiogenic protein sFlt and low concentrations of the proangiogenic PlGF in the maternal circulation of women before clinical diagnosis of pre-eclampsia.[46]

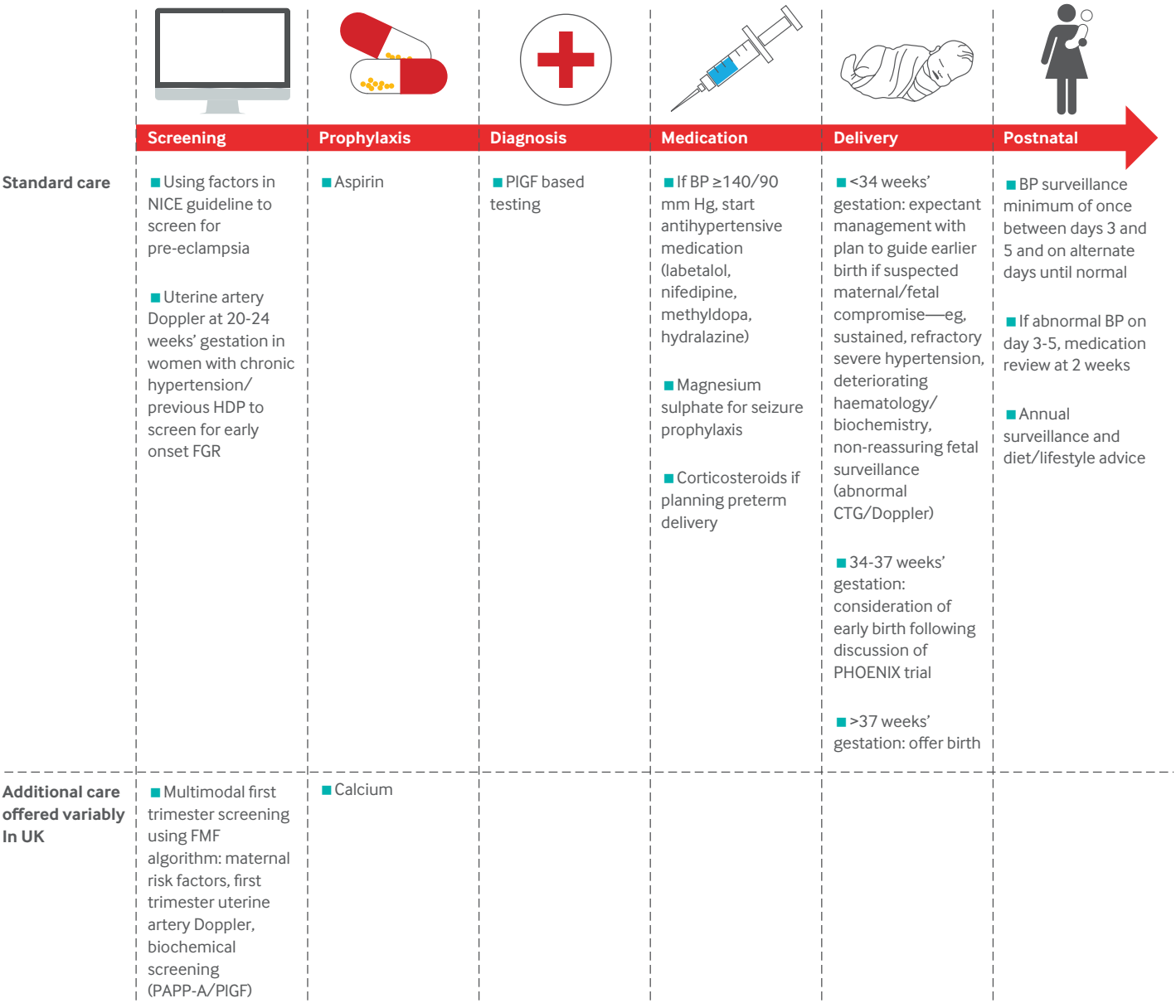

Fig 2 | Standard care according to National Institute for Health and Care Excellence guidance in the UK.[30 61 62] BP=blood pressure; CTG=cardiotocography; FGR=fetal growth restriction; FMF=Fetal Medicine Foundation; PAPP-A=pregnancy associated plasma protein A; PlGF=placental growth factor

The association between this angiogenic marker imbalance and a clinical diagnosis of pre-eclampsia has been consistently reproduced in many subsequent studies.[47 48] Furthermore, a relation between the severity of the clinical features of the disease and the scale of the angiogenic imbalance has also been observed.[49 50]Figure 1 illustrates the angiogenic markers in the pathophysiology of pre-eclampsia.[51]

Two large prospective observational studies have since confirmed the accuracy of a high sFlt to PlGF ratio or a low PlGF concentration as a diagnostic marker for pre-eclampsia presenting before 37 weeks' gestation.[52 53] On the basis of these two studies, the NICE Diagnostic Assessment Panel made a recommendation that PlGF based testing should be offered to women presenting with clinical signs suggestive of pre-eclampsia before 37 weeks' gestation. This recommendation was recently updated following a review of further evidence showing the clinical utility of PlGF based testing as an adjunct to the diagnosis of pre-eclampsia.[54] The PARROT trial, a multicentre cluster randomised step wedged study, showed that a clinical diagnosis was made more promptly (median 4 days to 2 days) when PlGF based testing (Quidel) was incorporated into the diagnosis and that severe, rare adverse

maternal outcomes were avoided.[55] An embedded cost utility study also confirmed that PlGF based testing was associated with cost savings associated with fewer outpatient attendances, reduced numbers of ultrasound scans, and reduced neonatal unit bed days in the intervention arm.[56] A single centre study also confirmed that inclusion of the sFlt to PlGF ratio test (Roche Diagnostics) was associated with improved diagnostic accuracy and improved triage of women at the highest risk to high surveillance pathways.[57]

Funding from NHS England following adoption of PlGF based testing by the NHS Accelerated Access Collaborative and Innovation Technology Payment programmes has resulted in widespread adoption of PlGF based testing in English maternity units; a sustained effort is needed to ensure that testing is available to women across the UK. The recent NICE guidance includes several alternatives for PlGF based testing, and to date comparison between the available assays has not suggested that any of the available tests have superior diagnostic accuracy.[58]

In clinical practice, PlGF based testing has most impact as part of the ongoing, holistic assessment of women in whom a confident clinical diagnosis is not possible. This includes women with borderline hypertension, but more importantly women with chronic hypertension and other chronic medical conditions for whom preterm birth is often offered and justified by a clinical suspicion of developing pre-eclampsia. A lack of consistency between the clinical diagnosis and the biochemical diagnosis has been reported,[59] and as experience of using PlGF based testing develops, the greatest clinical impact is likely to be in women with clinical features that confound the diagnosis.[60] For example, a cohort study (n=979) in a real world clinical setting showed that low PlGF concentrations are associated with increased rates of preterm birth within two weeks (standardised survival difference −0.43, 95% confidence interval −0.76 to −0.09) irrespective of the clinical diagnosis, as well as increased risk of early onset pre-eclampsia (odds ratio 58.2, 32.1 to 105.4) and stillbirth (15.9, 7.6 to 33.3).[60] In summary, PlGF based testing helps to inform the frequency and location of surveillance for women with HDP by adding confidence to the exclusion of disease and justifying close surveillance in those with an intermediate or positive test. The evidence supports the test as a short term (up to four weeks) diagnostic test; it should not be used to guide timing of birth following a diagnosis of pre-eclampsia.

Antepartum management

Chronic hypertension

Figure 2 shows a summary of standard care according to NICE guidance in the UK. In women with hypertension before 20 weeks, clinical judgment should determine whether investigations (eg, renal imaging, echocardiography, catecholamines) for secondary hypertension are justified; as a minimum, a detailed medical history, clinical cardiovascular examination, renal function tests, proteinuria assessment, and diabetes screen should be offered. Women with chronic hypertension are at risk of developing superimposed pre-eclampsia, and most guidelines recommend starting aspirin for prevention.[27 63 64] A recent meta-analysis concluded that low dose aspirin did not reduce the risk of superimposed pre-eclampsia in women with chronic hypertension. However, a significant reduction in all preterm birth was seen.[65] This may reflect inaccuracies in the diagnosis of preterm pre-eclampsia in women with chronic hypertension.

A Cochrane systematic review on antihypertensive treatments for women with mild to moderate hypertension during pregnancy (n=3485) was inconclusive on the treatment benefits for reducing adverse outcomes such as pre-eclampsia (risk ratio 0.92, 95% confidence interval 0.75 to 1.14; n=2851), small for gestational age infant (0.96, 0.78 to 1.18; n=2686), and preterm birth (0.96, 0.83 to 1.12; n=2141), except for the reduction in severe hypertension (0.49, 0.40 to 0.60; n=2558).[66] The mainstay of management in women with chronic hypertension includes maintenance of a safe blood pressure, surveillance of fetal growth, and early detection of pre-eclampsia, which affects up to 25% of women.[67] The threshold for instigation of antihypertensive treatment in chronic hypertension has long been debated; recent evidence has shown significant maternal benefits without additional concerns about fetal growth. The CHIPS RCT (n=987; 75% with chronic hypertension), showed no difference in severe composite maternal or neonatal outcomes (pregnancy loss/high level neonatal care: odds ratio 1.02, 0.77 to 1.35; serious maternal complications: 1.74, 0.79 to 3.84) between less tight control (target dBP<100 mm Hg) and tight control (target dBP<85 mm Hg), with the exception of an increased risk of severe hypertension (odds ratio 1.80, 1.34 to 2.38) in the less tight control group.[68] More recently, the CHAP RCT (n=2408 women with chronic hypertension) reported that a target blood pressure <140/90 mm Hg, compared with no medication unless blood pressure was ≥160/105 mm Hg, led to a reduction in adverse composite outcomes including pre-eclampsia with severe features, preterm birth, abruption, and fetal or neonatal death (risk ratio 0.82, 0.74 to 0.92), without harming fetal growth (birth weight <10th centile: 1.04, 0.82 to 1.31).[69] NICE guidance recommends treatment for all HDP if blood pressure exceeds 140/90 mmHg.[30]

Data on the timing of delivery for women with chronic hypertension that is well controlled are limited. Cohort studies suggest that delivery between 38 and 39+6 weeks' gestation is optimal for the fetus in women not taking antihypertensive drugs.[70 71] However, other studies have shown that delivery beyond 39 weeks is associated with increased risk of developing superimposed pre-eclampsia.[72 73] Therefore, most guidelines recommend delivery between 38 and 39 weeks' gestation,[2 74-78]

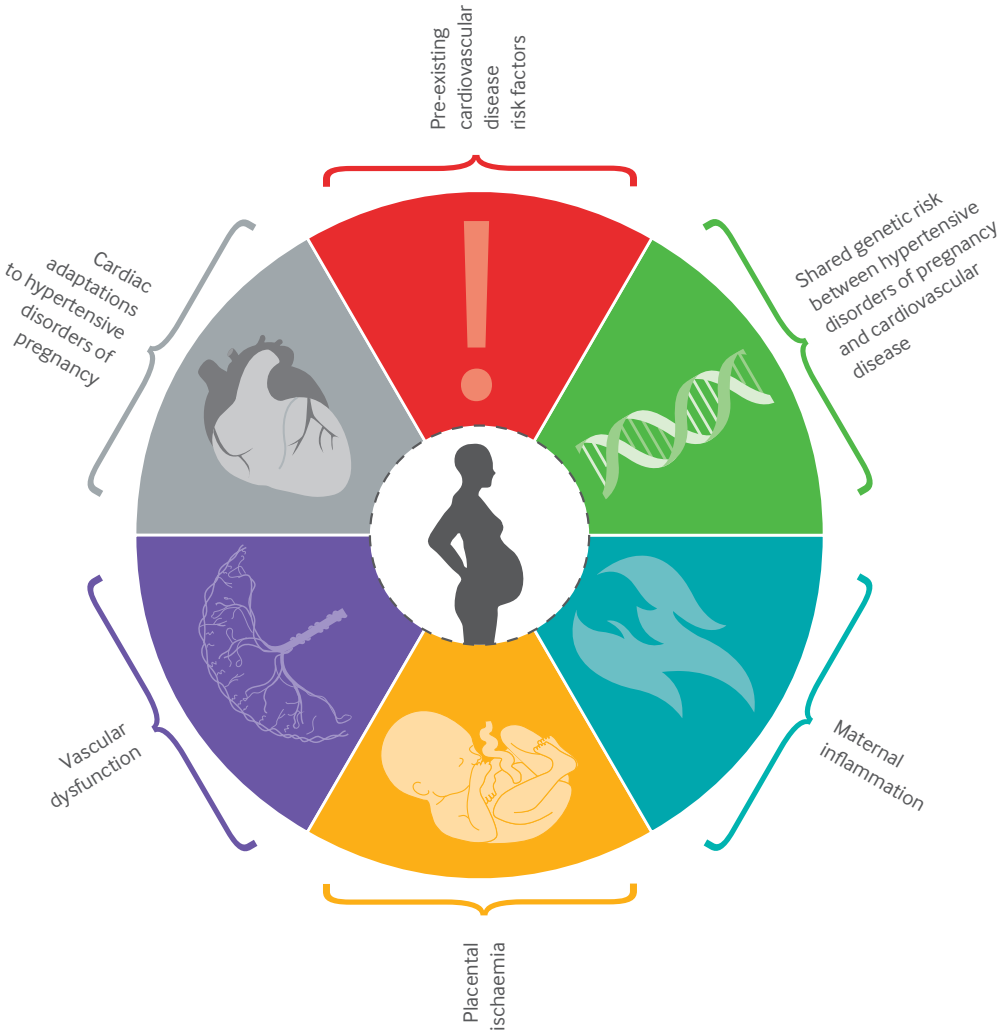

Fig 3 | Potential underlying mechanisms for association between hypertensive disorders of pregnancy (HDP) and future cardiovascular disease (CVD). Adapted with permission from Wu et al. *Eur Cardiol Rev* 2021 [118]

whereas others suggest offering delivery from 37 weeks' gestation,[79] particularly if maintenance antihypertensive treatment is used.[30 74] The WILL trial (ISRCTN77258279), completing in 2024, is attempting to close this gap in knowledge by comparing birth at 38+0 to 38+3 weeks' gestation with usual care, usually birth after 39 weeks' gestation, in women with chronic or gestational hypertension.[80]

Gestational hypertension

Approximately 10-25% of women with gestational hypertension will develop pre-eclampsia,[81] and the risk is highest in those who present at earlier gestations (<34 weeks).[82 83] Predicting which women will develop pre-eclampsia at the time of presentation on the basis of clinical features alone is not possible, but the addition of PlGF based testing allows surveillance to be targeted to those at highest risk of developing pre-eclampsia.[30 54] The threshold for antihypertensive treatment in the NICE guidelines is the same as that for chronic hypertension and pre-eclampsia (≥140/90 mm Hg).[30 63]

The optimal timing of delivery for women with gestational hypertension remains unclear, as no data from a large trial are available specifically for this group. The HYPITAT RCT randomised women with gestational hypertension (n=496) and pre-eclampsia with non-severe features (n=246) to induction of labour or expectant management.[84] Induction of labour at 37 weeks' gestation was associated with a reduction in composite adverse maternal outcomes including pre-eclampsia with severe features and eclampsia (risk ratio 0.71, 0.59 to 0.86), without differences in rates of caesarean delivery (0.75, 0.55 to 1.04) or neonatal complications (0.75, 0.45 to 1.26), compared with expectant management. However, the intervention group had worse neurodevelopment outcomes at age of 2 years (odds ratio 0.48, 0.24 to 0.96).[85] On the other hand, a large retrospective observational study of women with gestational hypertension (n=228 668) found that a later delivery gestation between 38 and 39 weeks' gestation balances the lowest maternal and fetal risk of morbidity and mortality.[86] The rate of maternal morbidity/mortality at 38 weeks was 89.9 (95%

Table 1 | Prevalence of recurrent hypertensive disorders of pregnancy

	Type of hypertension in affected pregnancy		
Prevalence in future pregnancy	Any hypertension	Pre-eclampsia	Gestational hypertension
Any hypertension	~21%	~20%	~22%
Pre-eclampsia	~14%	~16%; birthed 28-34 weeks' gestation ~33%; birthed 34-37 weeks' gestation 23%	~7%
Gestational hypertension	~9%	~6-12%	~11-15%
Chronic hypertension	NA	~2%	~3%

Adapted from National Institute for Health and Care Excellence guideline.[30]

confidence interval 68.1 to 111.8) per 1000 live births, whereas the rate of fetal morbidity/mortality at 38 weeks was 10.5 (2.8 to 18.2) per 1000 live births.

Pre-eclampsia

Pre-eclampsia with non-severe features can progress to pre-eclampsia with severe features within days. Therefore, many national guidelines recommend a minimum of twice weekly blood pressure monitoring and blood testing.[2 13 30 87] The externally validated fullPIERS or PREP prognostic models referred to in the NICE guidance may be used to identify women at risk of adverse maternal outcomes and help with making a decision on place of care and threshold for intervention.[30 88-90] Studies have shown that PlGF based testing can also predict adverse maternal outcomes.[55 57 91] Treatment of hypertension for women with pre-eclampsia with non-severe features at ≥140/90 mm Hg is recommended by most guidelines,[2 63 92 93] with the exception of the ACOG which advocates a treatment threshold of ≥160/110 mm Hg.[13]

For pre-eclampsia with severe features at a previable gestation, termination of pregnancy should be considered owing to the high risks of maternal complications. Between 24 and 34 weeks' gestation, a Cochrane systematic review (n=748) showed that expectant care until 34 weeks' gestation may be associated with less fetal morbidity if no maternal or fetal indication for immediate delivery is present.[94] Babies whose mothers were in the intervention group (delivery within 24-48 hours of presenting with pre-eclampsia with severe features) had more intraventricular haemorrhage (risk ratio 1.94, 1.15 to 3.29) and respiratory distress (2.30, 1.39 to 3.81) and needed more ventilation (1.50, 1.11 to 2.02). For pre-eclampsia with non-severe features between 34 and 37 weeks' gestation, the PHOENIX RCT (n=901) showed that induction of labour within 48 hours was associated with reduced adverse composite maternal morbidity (risk ratio 0.86, 0.79 to 0.94), increased likelihood of vaginal birth, and reduced magnesium sulfate administration but increased composite perinatal adverse outcome, primarily composed of increased neonatal unit admission (1.25, 1.05 to 1.48).[95] These findings are consistent with subsequent individual participant data meta-analyses.[96 97] Once at or beyond 37 weeks' gestation, delivery is recommended on the basis of the HYPITAT findings.[84]

Fetal monitoring

The suggested frequency of third trimester scans should be dictated by the clinical presentation and fetal wellbeing assessments. Most guidelines recommend a minimum of four weekly assessment in women with controlled chronic hypertension in the absence of concerns about fetal wellbeing.[2 13 30 74 87 98]

Intrapartum management

Control of blood pressure and prevention of seizures are central to peripartum management of HDP. Given the significant risk of cerebrovascular haemorrhage associated with untreated hypertension in pre-eclampsia,[99 100] guidelines recommend that women with severe hypertension (≥160/110 mm Hg) should be treated as inpatients, using intravenous labetalol, oral nifedipine, or intravenous hydralazine as necessary.[63] Women with sustained severe hypertension in the context of pre-eclampsia, or with symptoms consistent with end organ disease (headache, visual disturbance, epigastric pain, vomiting), should be treated with intravenous magnesium sulfate for seizure prophylaxis. Most national guidelines emphasise that decisions on mode of delivery should be dictated by usual obstetric considerations.[63]

Eclampsia

Without magnesium sulfate prophylaxis, the rate of seizures in women with pre-eclampsia with severe features is four times higher than in those with pre-eclampsia with non-severe features.[13] The Magpie RCT (n=10 141) showed a reduction in eclamptic seizures (58% (95% confidence interval 40% to 71%) reduction),[101] and a Cochrane systematic review (n=1396) showed a reduction in maternal death (risk ratio 0.59, 0.38 to 0.92) and recurrent eclamptic seizures (0.43, 0.33 to 0.55) with the use of intravenous magnesium sulfate.[102] Magnesium sulfate also has a role in fetal neuroprotection for preterm birth.[103 104]

Antihypertensive agents

Recommended antihypertensive agents for HDP include labetalol, modified release nifedipine (12 hourly), and methyldopa. For the treatment of mild to moderate hypertension, a Cochrane systematic review (n=2774) concluded that labetalol and nifedipine were preferable to methyldopa for the avoidance of severe hypertension (risk ratio 0.70, 0.56

to 0.88).[66] For pre-eclampsia with severe features, a network meta-analysis including 46 studies reported similar efficacy between intravenous labetalol, oral nifedipine, and intravenous hydralazine.[105] In a low resource setting, an RCT (n=2307) showed that oral nifedipine led to significantly better blood pressure control than oral methyldopa.[106] The Giant PANDA study (ISRCTN12792616), completing in 2024, is recruiting in the UK and will compare oral labetalol with oral nifedipine in women with HDP; a subgroup analysis to investigate the impact of self-reported ethnicity will be included.

Labetalol is a mixed α and β adrenoreceptor blocker. Current UK guidance advises neonatal surveillance for hypoglycaemia following exposure to labetalol,[107] although little definitive evidence is available to guide this practice. Nifedipine is a calcium channel antagonist and can cause maternal headache and tachycardia.[108] Nicardipine has also been evaluated in a retrospective case series (n=830).[109] It was shown to be effective in lowering sBP ≥160 mmHg and/or dBP ≥110 mmHg in 77% of study participants within two hours of treatment. Methyldopa acts by stimulating α2 receptors in the brainstem and decreasing the central sympathetic output. Although methyldopa has a good safety profile, studies have shown that it may be marginally less effective than labetalol or nifedipine and often causes side effects.[66 110-112] Hydralazine, an arterial vasodilator, is indicated only in severe hypertension. In a meta-analysis (n=893), hydralazine was more effective than labetalol in treating severe hypertension (risk ratio 0.29, 0.08 to 1.04) but was linked with more adverse maternal and perinatal outcomes (maternal hypotension: 3.29, 1.50 to 7.23; placental abruption: 4.17, 1.19 to 14.28; caesarean section: 1.30, 1.08 to 1.59; maternal oliguria: 4.00, 1.22 to 12.50; 1 minute Apgar score <7: 2.70, 1.27 to 5.88).[113]

Amlodipine, as an alternative calcium channel blocker and doxazosin/prazosin (α-adrenegic receptor blockers) are frequently used to treat HDP, although limited published evidence supports their use as first line options. Owing to teratogenicity, renin-angiotensin-aldosterone inhibitors are contraindicated during pregnancy[114]; some international guidelines also recommend against diuretics, atenolol, and thiazides during pregnancy.[63]

Postnatal antihypertensive treatment

All antihypertensive drugs are detectable at low concentrations in breast milk,[115] but they are considered safe to prescribe in the context of breast feeding.[30] Calcium channel blockers and angiotensin converting enzyme (ACE) inhibitors, such as captopril and enalapril, are all considered safe for breastfeeding women.[74] ACE inhibitors have the disadvantage of requiring dose titration and monitoring of renal function; adequate blood pressure treatment may require an additional agent until a satisfactory dose is reached. Adherence is also a consideration in the postnatal period, and longer acting, once daily drugs are also likely to be advantageous.[30] Diuretics may decrease milk production and therefore should be avoided.

Postnatal follow-up

Short term management

Postpartum blood pressure is often higher than blood pressure during pregnancy, and a sustained risk of cerebrovascular haemorrhage exists in the postpartum period.[100] Poorly controlled hypertension is a frequent cause of postnatal readmission, so proactive management is likely to be beneficial. Blood pressure is commonly highest three to five days after birth and should be measured at least once during this period. We consider it good practice to anticipate an increase in blood pressure if primary hospital discharge occurs before day 3-5 and to have a lower threshold for antihypertensive treatment during the first two weeks after birth. Normalisation of blood pressure in the early weeks after HDP is very important to avoid the rare occurrence of cerebrovascular accidents. It may also have significant benefits for future cardiovascular health by reducing the effects of hypertensive cardiac remodelling.[116 117]

Long term implications

Cardiovascular disease

Figure 3 illustrates the potential underlying mechanisms underpinning the association between HDP and future cardiovascular disease.[116] The association between HDP and increased long term risk of developing cardiovascular disease is now well established and discussed in several reviews of meta-analyses.[119 120] Pre-eclampsia is associated with a twofold increase in risk of coronary heart disease, stroke, and death from cardiovascular disease and a fourfold increase in risk of heart failure,[121 122] with recurrent pre-eclampsia having the highest risk.[123] Gestational hypertension is associated with a 1.8-fold increase in risk of coronary heart disease, heart failure, and composite cardiovascular disease and a 1.4-fold increase in risk for composite cardiovascular disease.[124 125] Although the relative risk is highest within the first year postpartum, the cardiovascular risks of women with HDP persist decades after the pregnancy, when the absolute risks are greater than those immediately postpartum.[121 126]

Pre-eclampsia is also associated with an up to 3.9-fold increase in risk of hypertension and a 1.3-fold increase in risk of dyslipidaemia.[122 127] The SNAP-HT pilot trial showed that self-management of blood pressure in the puerperium resulted in lower dBP at six months and 3.6 years,[116 128] even without antihypertensive treatment. As a follow-up study, the recently completed POP-HT trial is adequately powered to formally assess whether this self-management is associated with blood pressure reduction at six to nine months.[129] The BP-PRESELF trial included women who were 12 years after their index pregnancy with pre-eclampsia or haemolysis,

elevated liver enzymes, and low platelets (HELLP) syndrome.[130] It showed that home blood pressure monitoring reduces blood pressure at one year follow-up.

Women with a history of pre-eclampsia have higher left ventricular mass index and relative wall thickness, as well as mild diastolic dysfunction postnatally.[131 132] The PICK-UP feasibility trial showed that enalapril treatment following pregnancy affected by preterm pre-eclampsia may lead to improved cardiac remodelling and diastolic function at six months postpartum.[117]

Diabetes

HDP are associated with type 2 diabetes, even without coexisting gestational diabetes, with an up to 2.6-fold and 2.2-fold increase in risk of diabetes for pre-eclampsia and gestational hypertension, respectively, in meta-analyses.[133-135] Pre-eclampsia itself is associated with an up to 4.3-fold increase in risk of developing metabolic syndrome.[127 136 137]

Other conditions

Meta-analyses have shown the association between HDP and long term kidney disease. Pre-eclampsia is associated with up to 6.4-fold and 2.1-fold increase in risk of end stage kidney disease and chronic kidney disease, respectively.[138 139] By contrast, gestational hypertension is associated with a 3.6-fold increase in risk of end stage kidney disease and a 1.5-fold increase in risk of chronic kidney disease.[138] Overall, HDP are associated with a 1.4-fold increase in risk of dementia,[140] with pre-eclampsia being associated with a 2.6-fold increase in risk of vascular dementia.[141] Pre-eclampsia has been associated with a 1.5-fold and 1.8-fold increase in risk of venous thromboembolism and premature mortality, respectively.[122] HDP lead to lower scores for health related quality of life in the postpartum period compared with postpartum haemorrhage.[142 143] A meta-analysis (n=893), including studies conducted up to 40 years after the affected pregnancy, showed that pre-eclampsia is associated with development of more severe depression outside the perinatal period (standardised mean difference 0.18, 95% confidence interval 0.05 to 0.31; P=0.007).[144]

Lack of awareness about cardiovascular risk

Recent studies show that healthcare professionals are aware of the long term risks for cardiovascular disease after HDP, with most counselling women about their increased cardiovascular risks.[145 146] However, this rising awareness has not translated into knowledge among women, with fewer than half being aware of their risk and having received heart health advice.[147 148] Maternal HDP was suggested to be an opportunity for cardiovascular screening and early intervention 20 years ago,[149] but its potential has not been realised. More resources are urgently needed to improve adherence to postnatal guidelines and improve the long term cardiovascular health of this high risk population.[150]

Counselling for next pregnancy

Risk of recurrence

A meta-analysis of individual patient data reported a 20% recurrence rate of HDP.[151] The risk of recurrence increases with concomitant HELLP syndrome, preterm delivery, or small for gestational age infant. Women with previous pre-eclampsia are equally likely to develop either pre-eclampsia (14%) or gestational hypertension (14%), whereas women with previous gestational hypertension are more likely to develop gestational hypertension (26%) than pre-eclampsia.[152] Table 1 illustrates the likelihood of recurrence of HDP.[30]

Management for next pregnancy

If the hypertension has not resolved within three months postpartum, investigations for secondary hypertension should be considered. If women are taking ACE inhibitors or angiotensin II receptor blockers, a plan should be made to switch antihypertensive drugs before or as soon as pregnancy is diagnosed, as some studies have reported increased risk of congenital malformations with first trimester exposure, compared with both non-exposure and exposure to other antihypertensive drugs.[153 154] Low dose aspirin should be offered from 12 weeks' gestation to reduce the risk of recurrence of pre-eclampsia in these women at high risk.

Women with other risk factors that are modifiable, such as poor glycaemic control or obesity, should be encouraged to lose weight, eat healthily, and reduce salt and excessive caffeine intake. Although stopping smoking improves other pregnancy outcomes, it does not decrease the recurrence rate of HDP.[155 156] Women should also be counselled about the risk of developing recurrent HDP and what that means to their planned pregnancy care. A systematic review (n=77 561) showed a small increase in risk (odds ratio 1.10, 1.02 to 1.19) of recurrent pre-eclampsia with an inter-pregnancy interval of more than four years.[157]

Guidelines

Diagnosis and management

Five international guidelines are available (WHO's 2011 guideline,[158] the Society of Obstetric Medicine of Australia and New Zealand's 2014 guideline,[159] the European Society of Cardiology's 2018 guideline,[160] the International Federation of Gynecology and Obstetrics' 2021 guideline,[161] and the ISSHP's 2021 guideline[2]), with the ISSHP guideline having the shortest cycle for guideline update. These guidelines agreed on the definitions of HDP, prevention of pre-eclampsia with low dose aspirin, treatment of severe hypertension, use of magnesium sulfate for prevention of eclampsia, and delivery for pre-eclampsia by term. The areas of disagreement are the definition of "severe" pre-eclampsia; target blood pressure when hypertension is not severe; timing of delivery for women with chronic hypertension, gestational hypertension, or pre-term pre-eclampsia; and use of magnesium sulfate for fetal

neuroprotection when pre-eclampsia is not "severe." Similar findings were reported in a systematic review that identified 17 national and international clinical practice guidelines on hypertension in pregnancy.[63]

Postnatal screening for cardiovascular disease and diabetes

What to screen for

In a review of guidelines, eight of the 16 guidelines identified recommended follow-up beyond the immediate postpartum period,[162] but no consensus existed about who to monitor more closely, the duration and frequency of follow-up, and what parameters to screen for.[162] Guidelines from cardiology societies are more detailed than those from the obstetrics and gynaecology communities, with some recommending annual blood pressure monitoring and assessment of cardiovascular and metabolic risk factors including lipids, fasting blood glucose, and body mass index,[160 163] whereas others recommend periodic monitoring.[75 164 165] Of 13 US guidelines or society recommendation publications relevant to primary care based cardiovascular risk management in the year following pregnancy outcome, eight included recommendations specifically for HDP.[166] These include early postnatal follow-up in primary care or cardiology outpatient settings,[167] close monitoring to ensure that hypertension resolves within 12 weeks postpartum,[142] and, for women who had preterm pre-eclampsia, annual cardiovascular risk assessment.[163] A prediction model including demographic, clinical, and echocardiographic variables has been developed to identify women with HDP with persistent hypertension at three months postpartum.[143]

Advice on lifestyle modification

In a systematic review of national and international clinical practice guidelines for HDP, 11 of the 17 identified guidelines suggested lifestyle counselling for cardiovascular risk reduction.[63] These include guidelines from the ACOG, the American Heart Association, NICE, and the European Society of Cardiology.[30 160 165 167] Lifestyle modifications include exercise, healthy eating, maintaining healthy weight, and smoking cessation. A systematic review found only two intervention trials for cardiovascular risk reduction in women who had HDP.[144] The authors concluded that limited evidence suggested that lifestyle intervention may be effective. A recent trial suggests that web based interventions have high acceptability among women who had pre-eclampsia.[168]

Emerging treatments

The PI2 trial, involving 180 women with pre-eclampsia at <32 weeks' gestation in South Africa, randomised women to metformin or placebo and showed that metformin prolonged gestation by 7.6 days compared with placebo.[169] Although the difference was not statistically significant, no serious adverse events relating to the intervention were reported[169]; a larger trial is under way in South Africa. Phase 3 trials are ongoing for treatment of pre-eclampsia to evaluate beetroot juice (NCT05241327) and recombinant antithrombin γ (NCT04182373), which are due to complete in May and July 2023, respectively.[170 171] Another phase 3 trial (ACTRN12618000216213) to assess broccoli spout extract has been registered but not yet started.[172] Other therapeutic approaches have been studied, albeit in early phase clinical trials only. For example, increasing vasodilator nitric oxide concentrations through infusion of a nitric oxide donor (S-nitrosoglutathione) was shown to reduce the augmentation index, a measure of small blood vessel tone, by 6% at 30 µg/min in a phase 1 study including six women with pre-eclampsia at <32 weeks' gestation.[173] Melatonin was shown to extend the diagnosis-to-delivery interval by a mean of 6 (standard error 2.3) days and reduce the need for antihypertensive agents in a phase 1 study involving 68 women with pre-eclampsia at <37 weeks' gestation (20 treated; 48 control).[174] The results of a pharmacokinetics study of sulfasalazine (ACTRN12617000226303) are yet to be reported.[174 175] Another pilot study evaluated plasmapheresis to remove sFlt-1 in 11 women with pre-eclampsia at <32 weeks' gestation.[176] The pregnancies continued for eight to 15 days, compared with only three days in 22 women in the control group. Administration of recombinant PlGF siRNA to silence sFlt-1 or angiotensinogen genes has shown promise in pre-clinical studies.[177-180]

Conclusions

Globally, HDP are a major cause of maternal and fetal morbidity and mortality. The development of more accurate screening tools coupled with targeted aspirin prophylaxis could significantly reduce cases of preterm pre-eclampsia. Placental growth factor based testing has been shown to improve the accuracy of diagnosis of pre-eclampsia in women with HDP and identify those women at highest risk of complications. Future research may offer further

GLOSSARY OF ABBREVIATIONS

- ACE—angiotensin converting enzyme
- ACOG—American College of Obstetricians and Gynecologists
- dBP—diastolic blood pressure
- FMF—Fetal Medicine Foundation
- HDP—hypertensive disorders of pregnancy
- HELLP—haemolysis, elevated liver enzymes, and low platelets
- ISSHP—International Society for the Study of Hypertension in Pregnancy
- NICE—National Institute for Health and Care Excellence
- PAPP-A—pregnancy associated plasma protein A
- PlGF—placental growth factor
- RCT—randomised controlled trial
- sBP—systolic blood pressure
- sFlt—soluble FMS-like tyrosine kinase 1

QUESTIONS FOR FUTURE RESEARCH

- Is universal first trimester screening cost effective for the prevention of preterm pre-eclampsia?
- What are the therapeutic options for prevention and treatment of pre-eclampsia?
- Do different subtypes of pre-eclampsia exist that should be managed differently in clinical practice?
- What are the most effective screening strategy and intervention to reduce the risk of cardiovascular disease following hypertensive disorders of pregnancy?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

MG brings wide insight as a father whose child was born following an episode pre-eclampsia, As CEO of the Action on Pre-eclampsia (APEC) national charity, he has been involved in numerous academic and non-academic outputs related to hypertensive disorders of pregnancy. His insight contributed to the direction of the paper, making language accessible and ensuring that the other authors remained focused on outcomes for patients.

refinement of disease phenotypes and further progress the development of much needed treatments to ameliorate the disease process and prolong gestation in preterm pre-eclampsia. Although the link between HDP and cardiovascular disease is well established, the most effective screening strategy and the type of interventions that can help to reduce future risk of cardiovascular disease remain unproven and require further research if we are to improve the long term cardiovascular disease profile for the millions of women affected by HDP.

Contributors: All authors planned the overall content of the article and edited and critically revised the whole article for intellectual content. PW and JEM did the literature review and wrote the initial draft of the article. PW is the guarantor.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following interests: JEM has led research studies related to the implementation of angiogenic markers for the diagnosis of pre-eclampsia, received industry funding from Alere and Roche to fund biomarker research/implementation, and is a member of the NICE Diagnostic Assessment Panel; PW was a member of the NICE Guideline Committee for the hypertension in pregnancy guideline (2019 update).

Provenance and peer review: Commissioned; externally peer reviewed.

1 Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health* 2014;2:e323-33. doi:10.1016/S2214-109X(14)70227-X
2 Magee LA, Brown MA, Hall DR, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens* 2022;27:148-69. doi:10.1016/j.preghy.2021.09.008
3 Jiang L, Tang K, Magee LA, et al. A global view of hypertensive disorders and diabetes mellitus during pregnancy. *Nat Rev Endocrinol* 2022;18:760-75. doi:10.1038/s41574-022-00734-y
4 Vos T, Lim SS, Abbafati C, et al, GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;396:1204-22. doi:10.1016/S0140-6736(20)30925-9
5 Lawn JE, Blencowe H, Waiswa P, et al, Lancet Ending Preventable Stillbirths Series study group, Lancet Stillbirth Epidemiology investigator group. Stillbirths: rates, risk factors, and acceleration towards 2030. *Lancet* 2016;387:587-603. doi:10.1016/S0140-6736(15)00837-5
6 STRIDE BP. Validated blood pressure monitors. 2022. https://stridebp.org/bp-monitors.
7 Chappell LC, Tucker KL, Galal U, et al, BUMP 2 Investigators. Effect of Self-monitoring of Blood Pressure on Blood Pressure Control in Pregnant Individuals With Chronic or Gestational Hypertension: The BUMP 2 Randomized Clinical Trial. *JAMA* 2022;327:1666-78. doi:10.1001/jama.2022.4726
8 Tucker KL, Mort S, Yu L-M, et al, BUMP Investigators. Effect of Self-monitoring of Blood Pressure on Diagnosis of Hypertension During Higher-Risk Pregnancy: The BUMP 1 Randomized Clinical Trial. *JAMA* 2022;327:1656-65. doi:10.1001/jama.2022.4712
9 Rodrigues Â, Barata C, Marques I, Almeida MC. Diagnosis of White Coat Hypertension and pregnancy outcomes. *Pregnancy Hypertens* 2018;14:121-4. doi:10.1016/j.preghy.2018.08.452
10 Brown MA, Mangos G, Davis G, Homer C. The natural history of white coat hypertension during pregnancy. *BJOG* 2005;112:601-6. doi:10.1111/j.1471-0528.2004.00516.x
11 Brown MA, Magee LA, Kenny LC, et al, International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. *Hypertension* 2018;72:24-43. doi:10.1161/HYPERTENSIONAHA.117.10803
12 Redman CW, Staff AC. Preeclampsia, biomarkers, syncytiotrophoblast stress, and placental capacity. *Am J Obstet Gynecol* 2015;213(Suppl):9. doi:10.1016/j.ajog.2015.08.003
13 Gestational Hypertension and Preeclampsia. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. *Obstet Gynecol* 2020;135:e237-60. doi:10.1097/AOG.0000000000003891
14 McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. *Am Heart J* 2008;156:918-30. doi:10.1016/j.ahj.2008.06.042
15 Pittara T, Vyrides A, Lamnisos D, Giannakou K. Pre-eclampsia and long-term health outcomes for mother and infant: an umbrella review. *BJOG* 2021;128:1421-30. doi:10.1111/1471-0528.16683
16 Conti-Ramsden FI, Nathan HL, De Greeff A, et al. Pregnancy-Related Acute Kidney Injury in Preeclampsia: Risk Factors and Renal Outcomes. *Hypertension* 2019;74:1144-51. doi:10.1161/HYPERTENSIONAHA.119.13089
17 Ganzevoort W, Rep A, Bonsel GJ, et al, PETRA investigators. A randomised controlled trial comparing two temporising management strategies, one with and one without plasma volume expansion, for severe and early onset pre-eclampsia. *BJOG* 2005;112:1358-68. doi:10.1111/j.1471-0528.2005.00687.x
18 Augustin G, Hadzic M, Juras J, Oreskovic S. Hypertensive disorders in pregnancy complicated by liver rupture or hematoma: a systematic review of 391 reported cases. *World J Emerg Surg* 2022;17:40. doi:10.1186/s13017-022-00444-w
19 Ananth CV, Savitz DA, Williams MA. Placental abruption and its association with hypertension and prolonged rupture of membranes: a methodologic review and meta-analysis. *Obstet Gynecol* 1996;88:309-18. doi:10.1016/0029-7844(96)00088-9
20 Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2011;25:391-403. doi:10.1016/j.bpobgyn.2011.01.006
21 Bartsch E, Medcalf KE, Park AL, Ray JG, High Risk of Pre-eclampsia Identification Group. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. *BMJ* 2016;353:i1753. doi:10.1136/bmj.i1753
22 Catov JM, Ness RB, Kip KE, Olsen J. Risk of early or severe pre-eclampsia related to pre-existing conditions. *Int J Epidemiol* 2007;36:412-9. doi:10.1093/ije/dyl271
23 Bilano VL, Ota E, Ganchimeg T, Mori R, Souza JP. Risk factors of pre-eclampsia/eclampsia and its adverse outcomes in low- and middle-income countries: a WHO secondary analysis. *PLoS One* 2014;9:e91198. doi:10.1371/journal.pone.0091198
24 Sibley CP. Treating the dysfunctional placenta. *J Endocrinol* 2017;234:R81-97. doi:10.1530/JOE-17-0185
25 Askie LM, Duley L, Henderson-Smart DJ, Stewart LA, PARIS Collaborative Group. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. *Lancet* 2007;369:1791-8. doi:10.1016/S0140-6736(07)60712-0
26 Bujold E, Roberge S, Lacasse Y, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstet Gynecol* 2010;116:402-14. doi:10.1097/AOG.0b013e3181e9322a
27 Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications.

Cochrane Database Syst Rev 2019;2019:CD004659. doi:10.1002/14651858.CD004659.pub3
28 Henderson JT, Vesco KK, Senger CA, Thomas RG, Redmond N. Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA* 2021;326:1192-206. doi:10.1001/jama.2021.8551
29 Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. *Am J Obstet Gynecol* 2018;218:287-293.e1. doi:10.1016/j.ajog.2017.11.561
30 National Institute for Health and Care Excellence. Hypertension in pregnancy: diagnosis and management. 2019. www.nice.org.uk/guidance/ng133.
31 Akolekar R, Syngelaki A, Sarquis R, Zvanca M, Nicolaides KH. Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11-13 weeks. *Prenat Diagn* 2011;31:66-74. doi:10.1002/pd.2660
32 O'Gorman N, Wright D, Syngelaki A, et al. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks gestation. *Am J Obstet Gynecol* 2016;214:103. doi:10.1016/j.ajog.2015.08.034
33 Tan MY, Wright D, Syngelaki A, et al. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. *Ultrasound Obstet Gynecol* 2018;51:743-50. doi:10.1002/uog.19039
34 Rolnik DL, Wright D, Poon LC, et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. *N Engl J Med* 2017;377:613-22. doi:10.1056/NEJMoa1704559
35 Wright D, Rolnik DL, Syngelaki A, et al. Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin on length of stay in the neonatal intensive care unit. *Am J Obstet Gynecol* 2018;218:612-6. doi:10.1016/j.ajog.2018.02.014
36 Guy GP, Leslie K, Diaz Gomez D, et al. Implementation of routine first trimester combined screening for pre-eclampsia: a clinical effectiveness study. *BJOG* 2021;128:149-56. doi:10.1111/1471-0528.16361
37 Liu B, Nadeem U, Frick A, Alakaloko M, Bhide A, Thilaganathan B. Reducing health inequality in Black, Asian and other minority ethnic pregnant women: impact of first trimester combined screening for placental dysfunction on perinatal mortality. *BJOG* 2022;129:1750-6. doi:10.1111/1471-0528.17109
38 Poon LC, Shennan A, Hyett JA, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention. *Int J Gynaecol Obstet* 2019;145(Suppl 1):1-33. doi:10.1002/ijgo.12802
39 Chaemsaithong P, Sahota DS, Poon LC. First trimester preeclampsia screening and prediction. *Am J Obstet Gynecol* 2022;226(2S):S1071-97, 1097.e2. doi:10.1016/j.ajog.2020.07.020
40 National Screening Committee. Antenatal screening programme: Pre-eclampsia. 2023. https://view-health-screening-recommendations.service.gov.uk/pre-eclampsia/.
41 Hofmeyr GJ, Lawrie TA, Atallah ÁN, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database Syst Rev* 2018;10:CD001059. doi:10.1002/14651858.CD001059.pub5
42 Hofmeyr GJ, Manyame S, Medley N, Williams MJ. Calcium supplementation commencing before or early in pregnancy, for preventing hypertensive disorders of pregnancy. *Cochrane Database Syst Rev* 2019;9:CD011192. doi:10.1002/14651858.CD011192.pub3
43 Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. *Lancet* 2015;386:2089-97. doi:10.1016/S0140-6736(15)00131-2
44 Correa ME, Côté A-M, De Silva DA, et al. Visual or automated dipstick testing for proteinuria in pregnancy?*Pregnancy Hypertens* 2017;7:50-3. doi:10.1016/j.preghy.2017.01.005
45 Maynard SE, Min J-Y, Merchan J, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest* 2003;111:649-58. doi:10.1172/JCI17189
46 Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med* 2004;350:672-83. doi:10.1056/NEJMoa031884
47 Agrawal S, Shinar S, Cerdeira AS, Redman C, Vatish M. Predictive Performance of PlGF (Placental Growth Factor) for Screening Preeclampsia in Asymptomatic Women: A Systematic Review and Meta-Analysis. *Hypertension* 2019;74:1124-35. doi:10.1161/HYPERTENSIONAHA.119.13360
48 Agrawal S, Cerdeira AS, Redman C, Vatish M. 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;71:306-16. doi:10.1161/HYPERTENSIONAHA.117.10182
49 Rana S, Burke SD, Karumanchi SA. Imbalances in circulating angiogenic factors in the pathophysiology of preeclampsia and related disorders. *Am J Obstet Gynecol* 2022;226(2S):S1019-34. doi:10.1016/j.ajog.2020.10.022
50 Hastie R, Bergman L, Walker SP, et al. Associations Between Soluble fms-Like Tyrosine Kinase-1 and Placental Growth Factor and Disease Severity Among Women With Preterm Eclampsia and Preeclampsia. *J Am Heart Assoc* 2022;11:e024395. doi:10.1161/JAHA.121.024395
51 Armaly Z, Jadaon JE, Jabbour A, Abassi ZA. Preeclampsia: Novel Mechanisms and Potential Therapeutic Approaches. *Front Physiol* 2018;9:973. doi:10.3389/fphys.2018.00973
52 Chappell LC, Duckworth S, Seed PT, et al. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. *Circulation* 2013;128:2121-31. doi:10.1161/CIRCULATIONAHA.113.003215
53 Zeisler H, Llurba E, Chantraine F, et al. Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. *N Engl J Med* 2016;374:13-22. doi:10.1056/NEJMoa1414838
54 National Institute for Health and Care Excellence. PLGF-based testing to help diagnose suspected preterm pre-eclampsia: Diagnostics guidance. 2022. https://www.nice.org.uk/guidance/dg49.
55 Duhig KE, Myers J, Seed PT, et al, PARROT trial group. Placental growth factor testing to assess women with suspected pre-eclampsia: a multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial. *Lancet* 2019;393:1807-18. doi:10.1016/S0140-6736(18)33212-4
56 Duhig KE, Seed PT, Myers JE, et al. Placental growth factor testing for suspected pre-eclampsia: a cost-effectiveness analysis. *BJOG* 2019;126:1390-8. doi:10.1111/1471-0528.15855
57 Cerdeira AS, O'Sullivan J, Ohuma EO, et al. Randomized Interventional Study on Prediction of Preeclampsia/Eclampsia in Women With Suspected Preeclampsia: INSPIRE. *Hypertension* 2019;74:983-90. doi:10.1161/HYPERTENSIONAHA.119.12739
58 McCarthy FP, Gill C, Seed PT, Bramham K, Chappell LC, Shennan AH. Comparison of three commercially available placental growth factor-based tests in women with suspected preterm pre-eclampsia: the COMPARE study. *Ultrasound Obstet Gynecol* 2019;53:62-7. doi:10.1002/uog.19051
59 Leaños-Miranda A, Graciela Nolasco-Leaños A, Ismael Carrillo-Juárez R, et al. Usefulness of the sFlt-1/PlGF (Soluble fms-Like Tyrosine Kinase-1/Placental Growth Factor) Ratio in Diagnosis or Misdiagnosis in Women With Clinical Diagnosis of Preeclampsia. *Hypertension* 2020;76:892-900. doi:10.1161/HYPERTENSIONAHA.120.15552
60 McLaughlin K, Snelgrove JW, Audette MC, et al. PlGF (Placental Growth Factor) Testing in Clinical Practice: Evidence From a Canadian Tertiary Maternity Referral Center. *Hypertension* 2021;77:2057-65. doi:10.1161/HYPERTENSIONAHA.121.17047
61 National Institute for Health and Care Excellence. Antenatal care. 2021. https://www.nice.org.uk/guidance/ng201.
62 NHS England. Saving Babies' Lives Version Two: A care bundle for reducing perinatal mortality. 2019. https://www.england.nhs.uk/publication/saving-babies-lives-version-two-a-care-bundle-for-reducing-perinatal-mortality/.
63 Scott G, Gillon TE, Pels A, von Dadelszen P, Magee LA. Guidelines-similarities and dissimilarities: a systematic review of international clinical practice guidelines for pregnancy hypertension. *Am J Obstet Gynecol* 2022;226(Supplement):S1222-36. doi:10.1016/j.ajog.2020.08.018
64 Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E. The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. *Am J Obstet Gynecol* 2017;216:110-120.e6. doi:10.1016/j.ajog.2016.09.076
65 Richards EMF, Giorgione V, Stevens O, Thilaganathan B. Low-dose aspirin for the prevention of superimposed preeclampsia in women with chronic hypertension: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2023;228:395-408. doi:10.1016/j.ajog.2022.09.046
66 Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2018;10:CD002252. doi:10.1002/14651858.CD002252.pub4
67 Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. *BMJ* 2014;348:g2301. doi:10.1136/bmj.g2301
68 Magee LA, von Dadelszen P, Rey E, et al. Less-tight versus tight control of hypertension in pregnancy. *N Engl J Med* 2015;372:407-17. doi:10.1056/NEJMoa1404595
69 Tita AT, Szychowski JM, Boggess K, et al, Chronic Hypertension and Pregnancy (CHAP) Trial Consortium. Treatment for Mild Chronic

Hypertension during Pregnancy. *N Engl J Med* 2022;386:1781-92. doi:10.1056/NEJMoa2201295
70 Hutcheon JA, Lisonkova S, Magee LA, et al. Optimal timing of delivery in pregnancies with pre-existing hypertension. *BJOG* 2011;118:49-54. doi:10.1111/j.1471-0528.2010.02754.x
71 Ram M, Berger H, Geary M, et al, Diabetes, Obesity and Hypertension in Pregnancy Research Network (DOH-NET) and the Southern Ontario Obstetrical Network (SOON) Investigators. Timing of Delivery in Women With Chronic Hypertension. *Obstet Gynecol* 2018;132:669-77. doi:10.1097/AOG.0000000000002800
72 Harper LM, Biggio JR, Anderson S, Tita ATN. Gestational Age of Delivery in Pregnancies Complicated by Chronic Hypertension. *Obstet Gynecol* 2016;127:1101-9. doi:10.1097/AOG.0000000000001435
73 Grover S, Brandt JS, Reddy UM, Ananth CV. Chronic hypertension, perinatal mortality and the impact of preterm delivery: a population-based study. *BJOG* 2022;129:572-9. doi:10.1111/1471-0528.16932
74 American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 203: Chronic Hypertension in Pregnancy. *Obstet Gynecol* 2019;133:e26-50. doi:10.1097/AOG.0000000000003020
75 Magee LA, Smith GN, Bloch C, et al. Guideline No. 426: Hypertensive Disorders of Pregnancy: Diagnosis, Prediction, Prevention, and Management. *J Obstet Gynaecol Can* 2022;44:547-571.e1. doi:10.1016/j.jogc.2022.03.002
76 Prejbisz A, Dobrowolski P, Kosiński P, et al. Management of hypertension in pregnancy: prevention, diagnosis, treatment and longterm prognosis. *Kardiol Pol* 2019;77:757-806. doi:10.33963/KP.14904
77 Institute of Obstetricians and Gynaecologists; Royal College of Physicians of Ireland and the Clinical Strategy and Programmes Division. Health Service Executive. Clinical Practice Guideline. The Management of Hypertension in Pregnancy. 2019. https://rcpi-live-cdn.s3.amazonaws.com/wp-content/uploads/2021/12/HypertensionGuideline.pdf.
78 Mégevand N, Berkane N, Martinez De Tejada B, Pechère-Bertschi A. Troubles hypertensifs de la grossesse. *Rev Med Suisse* 2019;15:1603-6. doi:10.53738/REVMED.2019.15.662.1603
79 Te Whatu Ora - Health New Zealand. *Diagnosis and Treatment of Hypertension and Pre-eclampsia in Pregnancy in Aotearoa New Zealand: A clinical practice guideline.* Te Whatu Ora, 2022.
80 Magee LA, Tohill S, Kirkham K, et al, WILL Trial Study Group. WILL (When to Induce Labour to Limit risk in pregnancy hypertension): a multicentre randomised controlled trial - adaptations to deliver a timing-of-birth trial during the COVID-19 international pandemic. *Trials* 2022;23:884. doi:10.1186/s13063-022-06834-4
81 Saudan P, Brown MA, Buddle ML, Jones M. Does gestational hypertension become pre-eclampsia?*Br J Obstet Gynaecol* 1998;105:1177-84. doi:10.1111/j.1471-0528.1998.tb09971.x
82 Davis GK, Mackenzie C, Brown MA, et al. Predicting transformation from gestational hypertension to preeclampsia in clinical practice: a possible role for 24 hour ambulatory blood pressure monitoring. *Hypertens Pregnancy* 2007;26:77-87. doi:10.1080/10641950601147952
83 Barton JR, O'brien JM, Bergauer NK, Jacques DL, Sibai BM. Mild gestational hypertension remote from term: progression and outcome. *Am J Obstet Gynecol* 2001;184:979-83. doi:10.1067/mob.2001.112905
84 Koopmans CM, Bijlenga D, Groen H, et al, HYPITAT study group. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. *Lancet* 2009;374:979-88. doi:10.1016/S0140-6736(09)60736-4
85 Zwertbroek EF, Franssen MTM, Broekhuijsen K, et al, HYPITAT-II Study Group. Neonatal developmental and behavioral outcomes of immediate delivery versus expectant monitoring in mild hypertensive disorders of pregnancy: 2-year outcomes of the HYPITAT-II trial. *Am J Obstet Gynecol* 2019;221:154. doi:10.1016/j.ajog.2019.03.024
86 Cruz MO, Gao W, Hibbard JU. What is the optimal time for delivery in women with gestational hypertension?*Am J Obstet Gynecol* 2012;207:214. doi:10.1016/j.ajog.2012.06.009
87 Lowe SA, Bowyer L, Lust K, et al. SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014. *Aust N Z J Obstet Gynaecol* 2015;55:e1-29. doi:10.1111/ajo.12399
88 von Dadelszen P, Payne B, Li J, et al, PIERS Study Group. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. *Lancet* 2011;377:219-27. doi:10.1016/S0140-6736(10)61351-7
89 Thangaratinam S, Allotey J, Marlin N, et al. Development and validation of Prediction models for Risks of complications in Early-onset Pre-eclampsia (PREP): a prospective cohort study. *Health Technol Assess* 2017;21:1-100. doi:10.3310/hta21180
90 Duffy J, Cairns AE, Richards-Doran D, et al, International Collaboration to Harmonise Outcomes for Pre-eclampsia (iHOPE). A core outcome set for pre-eclampsia research: an international consensus development study. *BJOG* 2020;127:1516-26. doi:10.1111/1471-0528.16319
91 Dröge LA, Perschel FH, Stütz N, et al. Prediction of Preeclampsia-Related Adverse Outcomes With the sFlt-1 (Soluble fms-Like Tyrosine Kinase 1)/PlGF (Placental Growth Factor)-Ratio in the Clinical Routine: A Real-World Study. *Hypertension* 2021;77:461-71. doi:10.1161/HYPERTENSIONAHA.120.15146
92 World Health Organization. *WHO recommendations on drug treatment for non-severe hypertension in pregnancy.* WHO, 2020.
93 Poon LC, Magee LA, Verlohren S, et al. A literature review and best practice advice for second and third trimester risk stratification, monitoring, and management of pre-eclampsia: Compiled by the Pregnancy and Non-Communicable Diseases Committee of FIGO (the International Federation of Gynecology and Obstetrics). *Int J Gynaecol Obstet* 2021;154(Suppl 1):3-31. doi:10.1002/ijgo.13763
94 Churchill D, Duley L, Thornton JG, Moussa M, Ali HS, Walker KF. Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation. *Cochrane Database Syst Rev* 2018;10:CD003106. doi:10.1002/14651858.CD003106.pub3
95 Chappell LC, Brocklehurst P, Green ME, et al, PHOENIX Study Group. Planned early delivery or expectant management for late preterm pre-eclampsia (PHOENIX): a randomised controlled trial. *Lancet* 2019;394:1181-90. doi:10.1016/S0140-6736(19)31963-4
96 Beardmore-Gray A, Seed PT, Fleminger J, et al. Planned delivery or expectant management in preeclampsia: an individual participant data meta-analysis. *Am J Obstet Gynecol* 2022;227:218-230.e8. doi:10.1016/j.ajog.2022.04.034
97 Bernardes TP, Zwertbroek EF, Broekhuijsen K, et al. Delivery or expectant management for prevention of adverse maternal and neonatal outcomes in hypertensive disorders of pregnancy: an individual participant data meta-analysis. *Ultrasound Obstet Gynecol* 2019;53:443-53. doi:10.1002/uog.20224
98 Sotiriadis A, Hernandez-Andrade E, da Silva Costa F, et al, ISUOG CSC Pre-eclampsia Task Force. ISUOG Practice Guidelines: role of ultrasound in screening for and follow-up of pre-eclampsia. *Ultrasound Obstet Gynecol* 2019;53:7-22. doi:10.1002/uog.20105
99 Martin JNJr, Thigpen BD, Moore RC, Rose CH, Cushman J, May W. Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure. *Obstet Gynecol* 2005;105:246-54. doi:10.1097/01.AOG.0000151116.84113.56
100 Knight M, Nair M, Tuffnell D, et al. *Saving Lives, Improving Mothers' Care: Surveillance of maternal deaths in the UK 2012–14 and lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–14. National Perinatal Epidemiology Unit.* University of Oxford, 2016.
101 Altman D, Carroli G, Duley L, et al, Magpie Trial Collaboration Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet* 2002;359:1877-90. doi:10.1016/S0140-6736(02)08778-0
102 Duley L, Henderson-Smart DJ, Walker GJ, Chou D. Magnesium sulphate versus diazepam for eclampsia. *Cochrane Database Syst Rev* 2010;2010:CD000127.
103 Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. *Cochrane Database Syst Rev* 2009;(1):CD004661. doi:10.1002/14651858.CD004661.pub3
104 Crowther CA, Middleton PF, Voysey M, et al, AMICABLE Group. Assessing the neuroprotective benefits for babies of antenatal magnesium sulphate: An individual participant data meta-analysis. *PLoS Med* 2017;14:e1002398. doi:10.1371/journal.pmed.1002398
105 Sridharan K, Sequeira RP. Drugs for treating severe hypertension in pregnancy: a network meta-analysis and trial sequential analysis of randomized clinical trials. *Br J Clin Pharmacol* 2018;84:1906-16. doi:10.1111/bcp.13649
106 Easterling T, Mundle S, Bracken H, et al. Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial. *Lancet* 2019;394:1011-21. doi:10.1016/S0140-6736(19)31282-6
107 Levene I, Wilkinson D. Identification and management of neonatal hypoglycaemia in the full-term infant (British Association of Perinatal Medicine-Framework for Practice). *Arch Dis Child Educ Pract Ed* 2019;104:29-32. doi:10.1136/archdischild-2017-314050
108 Vermillion ST, Scardo JA, Newman RB, Chauhan SP. A randomized, double-blind trial of oral nifedipine and intravenous labetalol in hypertensive emergencies of pregnancy. *Am J Obstet Gynecol* 1999;181:858-61. doi:10.1016/S0002-9378(99)70314-5

109 Nij Bijvank SW, Hengst M, Cornette JC, et al. Nicardipine for treating severe antepartum hypertension during pregnancy: Nine years of experience in more than 800 women. *Acta Obstet Gynecol Scand* 2022;101:1017-25. doi:10.1111/aogs.14406
110 Mah GT, Tejani AM, Musini VM. Methyldopa for primary hypertension. *Cochrane Database Syst Rev* 2009;2009:CD003893.
111 Plouin PF, Breart G, Maillard F, Papiernik E, Relier JP. Comparison of antihypertensive efficacy and perinatal safety of labetalol and methyldopa in the treatment of hypertension in pregnancy: a randomized controlled trial. *Br J Obstet Gynaecol* 1988;95:868-76. doi:10.1111/j.1471-0528.1988.tb06571.x
112 Slim R, Ben Salem C, Hmouda H, Bouraoui K. Hepatotoxicity of alpha-methyldopa in pregnancy. *J Clin Pharm Ther* 2010;35:361-3. doi:10.1111/j.1365-2710.2009.01078.x
113 Magee LA, Cham C, Waterman EJ, Ohlsson A, von Dadelszen P. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. *BMJ* 2003;327:955-60. doi:10.1136/bmj.327.7421.955
114 Weber-Schoendorfer C, Kayser A, Tissen-Diabaté T, et al. Fetotoxic risk of AT1 blockers exceeds that of angiotensin-converting enzyme inhibitors: an observational study. *J Hypertens* 2020;38:133-41. doi:10.1097/HJH.0000000000002233
115 Beardmore KS, Morris JM, Gallery EDM. Excretion of antihypertensive medication into human breast milk: a systematic review. *Hypertens Pregnancy* 2002;21:85-95. doi:10.1081/PRG-120002912
116 Cairns AE, Tucker KL, Leeson P, et al, SNAP-HT Investigators. Self-Management of Postnatal Hypertension: The SNAP-HT Trial. *Hypertension* 2018;72:425-32. doi:10.1161/HYPERTENSIONAHA.118.10911
117 Ormesher L, Higson S, Luckie M, et al. Postnatal Enalapril to Improve Cardiovascular Function Following Preterm Preeclampsia (PICk-UP): A Randomized Double-Blind Placebo-Controlled Feasibility Trial. *Hypertension* 2020;76:1828-37. doi:10.1161/HYPERTENSIONAHA.120.15875
118 Wu P, Park K, Gulati M. The Fourth Trimester: Pregnancy as a Predictor of Cardiovascular Disease. *Eur Cardiol* 2021;16:e31. doi:10.15420/ecr.2021.18
119 Okoth K, Chandan JS, Marshall T, et al. Association between the reproductive health of young women and cardiovascular disease in later life: umbrella review. *BMJ* 2020;371:m3502. doi:10.1136/bmj.m3502
120 Pittara T, Vyrides A, Lamnisos D, Giannakou K. Pre-eclampsia and long-term health outcomes for mother and infant: an umbrella review. *BJOG* 2021;128:1421-30. doi:10.1111/1471-0528.16683
121 Wu P, Haththotuwa R, Kwok CS, et al. Preeclampsia and Future Cardiovascular Health: A Systematic Review and Meta-Analysis. *Circ Cardiovasc Qual Outcomes* 2017;10:e003497. doi:10.1161/CIRCOUTCOMES.116.003497
122 Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ* 2007;335:974. doi:10.1136/bmj.39335.385301.BE
123 Brouwers L, van der Meiden-van Roest AJ, Savelkoul C, et al. Recurrence of pre-eclampsia and the risk of future hypertension and cardiovascular disease: a systematic review and meta-analysis. *BJOG* 2018;125:1642-54. doi:10.1111/1471-0528.15394
124 Lo CCW, Lo ACQ, Leow SH, et al. Future Cardiovascular Disease Risk for Women With Gestational Hypertension: A Systematic Review and Meta-Analysis. *J Am Heart Assoc* 2020;9:e013991. doi:10.1161/JAHA.119.013991
125 Grandi SM, Filion KB, Yoon S, et al. Cardiovascular Disease-Related Morbidity and Mortality in Women With a History of Pregnancy Complications. *Circulation* 2019;139:1069-79. doi:10.1161/CIRCULATIONAHA.118.036748
126 Honigberg MC, Zekavat SM, Aragam K, et al. Long-Term Cardiovascular Risk in Women With Hypertension During Pregnancy. *J Am Coll Cardiol* 2019;74:2743-54. doi:10.1016/j.jacc.2019.09.052
127 Dall'Asta A, D'Antonio F, Saccone G, et al. Cardiovascular events following pregnancy complicated by pre-eclampsia with emphasis on comparison between early- and late-onset forms: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2021;57:698-709. doi:10.1002/uog.22107
128 Kitt JA, Fox RL, Cairns AE, et al. Short-Term Postpartum Blood Pressure Self-Management and Long-Term Blood Pressure Control: A Randomized Controlled Trial. *Hypertension* 2021;78:469-79. doi:10.1161/HYPERTENSIONAHA.120.17101
129 Kitt J, Frost A, Mollison J, et al. Postpartum blood pressure self-management following hypertensive pregnancy: protocol of the Physician Optimised Post-partum Hypertension Treatment (POP-HT) trial. *BMJ Open* 2022;12:e051180. doi:10.1136/bmjopen-2021-051180
130 Muijsers HEC, Wu P, van der Heijden OWH, et al. Home blood pressure monitoring detects unrevealed hypertension in women with a history of preeclampsia: Results of the BP-PRESELF study. *Am J Prev Cardiol* 2022;12:100429. doi:10.1016/j.ajpc.2022.100429
131 Reddy M, Wright L, Rolnik DL, et al. Evaluation of Cardiac Function in Women With a History of Preeclampsia: A Systematic Review and Meta-Analysis. *J Am Heart Assoc* 2019;8:e013545. doi:10.1161/JAHA.119.013545
132 Melchiorre K, Sutherland GR, Liberati M, Thilaganathan B. Preeclampsia is associated with persistent postpartum cardiovascular impairment. *Hypertension* 2011;58:709-15. doi:10.1161/HYPERTENSIONAHA.111.176537
133 Zhao G, Bhatia D, Jung F, Lipscombe L. Risk of type 2 diabetes mellitus in women with prior hypertensive disorders of pregnancy: a systematic review and meta-analysis. *Diabetologia* 2021;64:491-503. doi:10.1007/s00125-020-05343-w
134 Wang Z, Wang Z, Wang L, et al. Hypertensive disorders during pregnancy and risk of type 2 diabetes in later life: a systematic review and meta-analysis. *Endocrine* 2017;55:809-21. doi:10.1007/s12020-016-1075-6
135 Wu P, Kwok CS, Haththotuwa R, et al. Pre-eclampsia is associated with a twofold increase in diabetes: a systematic review and meta-analysis. *Diabetologia* 2016;59:2518-26. doi:10.1007/s00125-016-4098-x
136 Jenabi E, Afshari M, Khazaei S. The association between preeclampsia and the risk of metabolic syndrome after delivery: a meta-analysis. *J Matern Fetal Neonatal Med* 2021;34:3253-8. doi:10.1080/14767058.2019.1678138
137 Alonso-Ventura V, Li Y, Pasupuleti V, Roman YM, Hernandez AV, Pérez-López FR. Effects of preeclampsia and eclampsia on maternal metabolic and biochemical outcomes in later life: a systematic review and meta-analysis. *Metabolism* 2020;102:154012. doi:10.1016/j.metabol.2019.154012
138 Barrett PM, McCarthy FP, Kublickiene K, et al. Adverse Pregnancy Outcomes and Long-term Maternal Kidney Disease: A Systematic Review and Meta-analysis. *JAMA Netw Open* 2020;3:e1920964. doi:10.1001/jamanetworkopen.2019.20964
139 Covella B, Vinturache AE, Cabiddu G, et al. A systematic review and meta-analysis indicates long-term risk of chronic and end-stage kidney disease after preeclampsia. *Kidney Int* 2019;96:711-27. doi:10.1016/j.kint.2019.03.033
140 Schliep KC, Mclean H, Yan B, et al. Association Between Hypertensive Disorders of Pregnancy and Dementia: a Systematic Review and Meta-Analysis. *Hypertension* 2023;80:257-67. doi:10.1161/HYPERTENSIONAHA.122.19399
141 Samara AA, Liampas I, Dadouli K, et al. Preeclampsia, gestational hypertension and incident dementia: A systematic review and meta-analysis of published evidence. *Pregnancy Hypertens* 2022;30:192-7. doi:10.1016/j.preghy.2022.10.008
142 American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine. 8: Interpregnancy Care. *Obstet Gynecol* 2019;133:e51-72. doi:10.1097/AOG.0000000000003025
143 Giorgione V, Khalil A, O'Driscoll J, Thilaganathan B. Peripartum Screening for Postpartum Hypertension in Women With Hypertensive Disorders of Pregnancy. *J Am Coll Cardiol* 2022;80:1465-76. doi:10.1016/j.jacc.2022.07.028
144 Lui NA, Jeyaram G, Henry A. Postpartum Interventions to Reduce Long-Term Cardiovascular Disease Risk in Women After Hypertensive Disorders of Pregnancy: A Systematic Review. *Front Cardiovasc Med* 2019;6:160. doi:10.3389/fcvm.2019.00160
145 Palmrich P, Binder C, Zeisler H, Kroyer B, Pateisky P, Binder J. Awareness of obstetricians for long-term risks in women with a history of preeclampsia or HELLP syndrome. *Arch Gynecol Obstet* 2022;305:581-7. doi:10.1007/s00404-021-06181-w
146 Wu P, Mamas MA, Gulati M. Health Care Professional's Knowledge of Pregnancy Complications and Women's Cardiovascular Health: An International Study Utilizing Social Media. *J Womens Health (Larchmt)* 2022;31:1197-207. doi:10.1089/jwh.2021.0298
147 Sutherland L, Neale D, Henderson J, Clark J, Levine D, Bennett WL. Provider Counseling About and Risk Perception for Future Chronic Disease Among Women with Gestational Diabetes and Preeclampsia. *J Womens Health (Larchmt)* 2020;29:1168-75. doi:10.1089/jwh.2019.7767
148 Andraweera PH, Lassi ZS, Pathirana MM, et al. Pregnancy complications and cardiovascular disease risk perception: A qualitative study. *PLoS One* 2022;17:e0271722. doi:10.1371/journal.pone.0271722
149 Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening?*BMJ* 2002;325:157-60. doi:10.1136/bmj.325.7356.157
150 Bick D, Silverio SA, Bye A, Chang Y-S. Postnatal care following hypertensive disorders of pregnancy: a qualitative study of views and experiences of primary and secondary care clinicians. *BMJ Open* 2020;10:e034382. doi:10.1136/bmjopen-2019-034382
151 van Oostwaard MF, Langenveld J, Schuit E, et al. Recurrence of hypertensive disorders of pregnancy: an individual patient data metaanalysis. *Am J Obstet Gynecol* 2015;212:624. doi:10.1016/j.ajog.2015.01.009

152 Brown MA, Mackenzie C, Dunsmuir W, et al. Can we predict recurrence of pre-eclampsia or gestational hypertension?*BJOG* 2007;114:984-93. doi:10.1111/j.1471-0528.2007.01376.x
153 Buawangpong N, Teekachunhatean S, Koonrungsesomboon N. Adverse pregnancy outcomes associated with first-trimester exposure to angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers: A systematic review and meta-analysis. *Pharmacol Res Perspect* 2020;8:e00644. doi:10.1002/prp2.644
154 Fu J, Tomlinson G, Feig DS. Increased risk of major congenital malformations in early pregnancy use of angiotensin-converting-enzyme inhibitors and angiotensin-receptor-blockers: a meta-analysis. *Diabetes Metab Res Rev* 2021;37:e3453. doi:10.1002/dmrr.3453
155 Wei J, Liu CX, Gong TT, Wu QJ, Wu L. Cigarette smoking during pregnancy and preeclampsia risk: a systematic review and meta-analysis of prospective studies. *Oncotarget* 2015;6:43667-78. doi:10.18632/oncotarget.6190
156 Wang J, Yang W, Xiao W, Cao S. The association between smoking during pregnancy and hypertensive disorders of pregnancy: A systematic review and meta-analysis. *Int J Gynaecol Obstet* 2022;157:31-41. doi:10.1002/ijgo.13709
157 Cormick G, Betrán AP, Ciapponi A, Hall DR, Hofmeyr GJ, calcium and Pre-eclampsia Study Group. Inter-pregnancy interval and risk of recurrent pre-eclampsia: systematic review and meta-analysis. *Reprod Health* 2016;13:83. doi:10.1186/s12978-016-0197-x
158 World Health Organization. *WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia.* WHO, 2011.
159 Lowe SA, Bowyer L, Lust K, et al. SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014. *Aust N Z J Obstet Gynaecol* 2015;55:e1-29. doi:10.1111/ajo.12399
160 Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al, ESC Scientific Document Group. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J* 2018;39:3165-241. doi:10.1093/eurheartj/ehy340
161 Poon LC, Magee LA, Verlohren S, et al. A literature review and best practice advice for second and third trimester risk stratification, monitoring, and management of pre-eclampsia: Compiled by the Pregnancy and Non-Communicable Diseases Committee of FIGO (the International Federation of Gynecology and Obstetrics). *Int J Gynaecol Obstet* 2021;154(Suppl 1):3-31. doi:10.1002/ijgo.13763
162 Gamble DT, Brikinns B, Myint PK, Bhattacharya S. Hypertensive Disorders of Pregnancy and Subsequent Cardiovascular Disease: Current National and International Guidelines and the Need for Future Research. *Front Cardiovasc Med* 2019;6:55. doi:10.3389/fcvm.2019.00055
163 Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol* 2013;122:1122-31.
164 Bushnell C, McCullough LD, Awad IA, et al, American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council for High Blood Pressure Research. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;45:1545-88. doi:10.1161/01.str.0000442009.06663.48
165 Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the american heart association. *Circulation* 2011;123:1243-62. doi:10.1161/CIR.0b013e31820faaf8
166 Murray Horwitz ME, Fisher MA, Prifti CA, et al. Primary Care-Based Cardiovascular Disease Risk Management After Adverse Pregnancy Outcomes: a Narrative Review. *J Gen Intern Med* 2022;37:912-21. doi:10.1007/s11606-021-07149-x
167 American College of Obstetricians and Gynecologists' Presidential Task Force on Pregnancy and Heart Disease and Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 212: Pregnancy and Heart Disease. *Obstet Gynecol* 2019;133:e320-56. doi:10.1097/AOG.0000000000003243
168 Hutchesson MJ, Taylor R, Shrewsbury VA, et al. Be Healthe for Your Heart: A Pilot Randomized Controlled Trial Evaluating a Web-Based Behavioral Intervention to Improve the Cardiovascular Health of Women with a History of Preeclampsia. *Int J Environ Res Public Health* 2020;17:5779. doi:10.3390/ijerph17165779
169 Cluver CA, Hiscock R, Decloedt EH, et al. Use of metformin to prolong gestation in preterm pre-eclampsia: randomised, double blind, placebo controlled trial. *BMJ* 2021;374:n2103. doi:10.1136/bmj.n2103
170 Ormesher L, Myers JE, Chmiel C, et al. Effects of dietary nitrate supplementation, from beetroot juice, on blood pressure in hypertensive pregnant women: A randomised, double-blind, placebo-controlled feasibility trial. *Nitric Oxide* 2018;80:37-44. doi:10.1016/j.niox.2018.08.004
171 Saito S, Takagi K, Moriya J, et al. A randomized phase 3 trial evaluating antithrombin gamma treatment in Japanese patients with early-onset severe preeclampsia (KOUNO-TORI study): Study protocol. *Contemp Clin Trials* 2021;107:106490. doi:10.1016/j.cct.2021.106490
172 Langston-Cox AG, Marshall SA, Palmer KR, Wallace EM. Prolong: a double-blind randomised placebo-controlled trial of broccoli sprout extract in women with early onset preeclampsia. A clinical trial protocol. *BMJ Open* 2019;9:e027493. doi:10.1136/bmjopen-2018-027493
173 Everett TR, Wilkinson IB, Mahendru AA, et al. S-Nitrosoglutathione improves haemodynamics in early-onset pre-eclampsia. *Br J Clin Pharmacol* 2014;78:660-9. doi:10.1111/bcp.12379
174 Hobson SR, Gurusinghe S, Lim R, et al. Melatonin improves endothelial function in vitro and prolongs pregnancy in women with early-onset preeclampsia. *J Pineal Res* 2018;65:e12508. doi:10.1111/jpi.12508
175 Brownfoot FC, Hannan NJ, Cannon P, et al. Sulfasalazine reduces placental secretion of antiangiogenic factors, up-regulates the secretion of placental growth factor and rescues endothelial dysfunction. *EBioMedicine* 2019;41:636-48. doi:10.1016/j.ebiom.2019.02.013
176 Thadhani R, Hagmann H, Schaarschmidt W, et al. Removal of soluble fms-like tyrosine kinase-1 by dextran sulfate apheresis in preeclampsia. *J Am Soc Nephrol* 2016;27:903-13. doi:10.1681/ASN.2015020157
177 Makris A, Yeung KR, Lim SM, et al. Placental Growth Factor Reduces Blood Pressure in a Uteroplacental Ischemia Model of Preeclampsia in Nonhuman Primates. *Hypertension* 2016;67:1263-72. doi:10.1161/HYPERTENSIONAHA.116.07286
178 Turanov AA, Lo A, Hassler MR, et al. RNAi modulation of placental sFLT1 for the treatment of preeclampsia. *Nat Biotechnol* 2018;36:1164-73. doi:10.1038/nbt.4297
179 Haase N, Foster DJ, Cunningham MW, et al. RNA interference therapeutics targeting angiotensinogen ameliorate preeclamptic phenotype in rodent models. *J Clin Invest* 2020;130:2928-42. doi:10.1172/JCI99417
180 Tong S, Kaitu'u-Lino TJ, Hastie R, Brownfoot F, Cluver C, Hannan N. Pravastatin, proton-pump inhibitors, metformin, micronutrients, and biologics: new horizons for the prevention or treatment of preeclampsia. *Am J Obstet Gynecol* 2022;226(2S):S1157-70. doi:10.1016/j.ajog.2020.09.014