

Hypertensive disorders of pregnancy

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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 \geq 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 \geq 135/85 mm Hg outside clinic

 \geq 20 weeks' gestation

Gestational hypertension:

- Hypertension de novo \geq 20 weeks' gestation without proteinuria or other features suggestive of pre-eclampsia

Pre-eclampsia:

- Gestational hypertension with \geq 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/ μ L, disseminated intravascular coagulation, haemolysis)
 - Acute kidney injury (such as creatinine \geq 90 μ mol/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 \geq 160 mm Hg or diastolic BP \geq 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) \geq 90 mm Hg, with sBP \geq 160 mm Hg and/or a DBP \geq 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 guideline³⁰**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

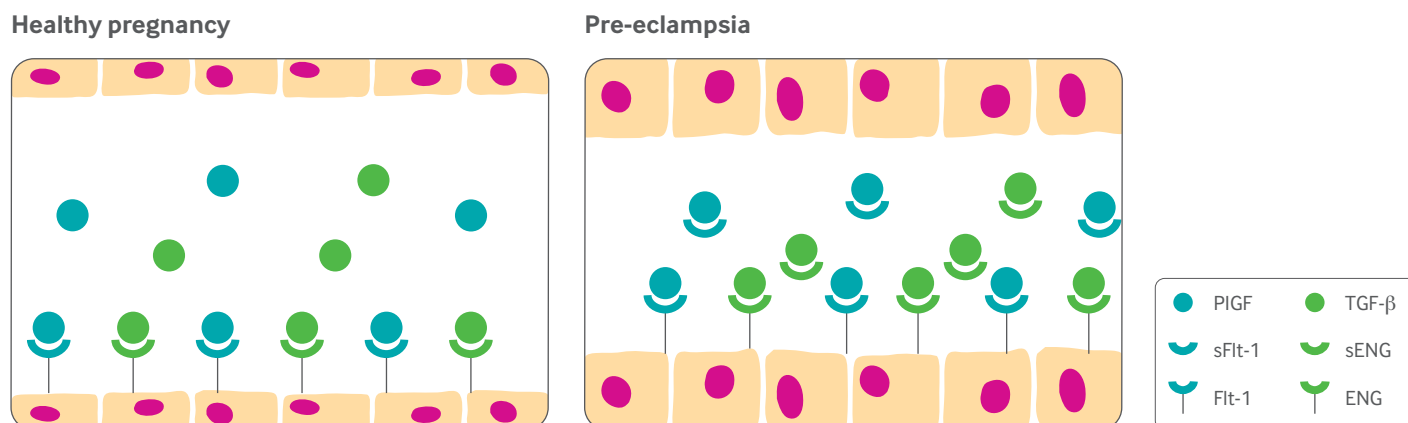


Fig 1 | In healthy pregnancy, soluble FMS-like tyrosine kinase 1 (Flt-1) binds to placental growth factor (PIGF) and endoglin (ENG) binds to transforming growth factor β (TGF- β). In pre-eclampsia, soluble Flt-1 (sFlt-1) is cleaved off Flt-1 and competes with Flt-1 to bind to PIGF. Also soluble ENG (sENG) 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 PIGF in the maternal circulation of women before clinical diagnosis of pre-eclampsia.⁴⁶







						
	Screening	Prophylaxis	Diagnosis	Medication	Delivery	Postnatal
Standard care	<ul style="list-style-type: none"> Using factors in NICE guideline to screen for pre-eclampsia Uterine artery Doppler at 20-24 weeks' gestation in women with chronic hypertension/previous HDP to screen for early onset FGR 	<ul style="list-style-type: none"> Aspirin 	<ul style="list-style-type: none"> PIGF based testing 	<ul style="list-style-type: none"> If BP $\geq 140/90$ mm Hg, start antihypertensive medication (labetalol, nifedipine, methyldopa, hydralazine) Magnesium sulphate for seizure prophylaxis Corticosteroids if planning preterm delivery 	<ul style="list-style-type: none"> <34 weeks' gestation: expectant management with plan to guide earlier birth if suspected maternal/fetal compromise—eg, sustained, refractory severe hypertension, deteriorating haematology/biochemistry, non-reassuring fetal surveillance (abnormal CTG/Doppler) 34-37 weeks' gestation: consideration of early birth following discussion of PHOENIX trial >37 weeks' gestation: offer birth 	<ul style="list-style-type: none"> BP surveillance minimum of once between days 3 and 5 and on alternate days until normal If abnormal BP on day 3-5, medication review at 2 weeks Annual surveillance and diet/lifestyle advice
Additional care offered variably in UK	<ul style="list-style-type: none"> Multimodal first trimester screening using FMF algorithm: maternal risk factors, first trimester uterine artery Doppler, biochemical screening (PAPP-A/PIGF) 	<ul style="list-style-type: none"> Calcium 				

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; PIGF=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 PIGF ratio or a low PIGF 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 PIGF 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 PIGF 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 PIGF 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 PIGF 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 PIGF 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 PIGF based testing by the NHS Accelerated Access Collaborative and Innovation Technology Payment programmes has resulted in widespread adoption of PIGF 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 PIGF 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, PIGF 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 PIGF 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 PIGF 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, PIGF 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}

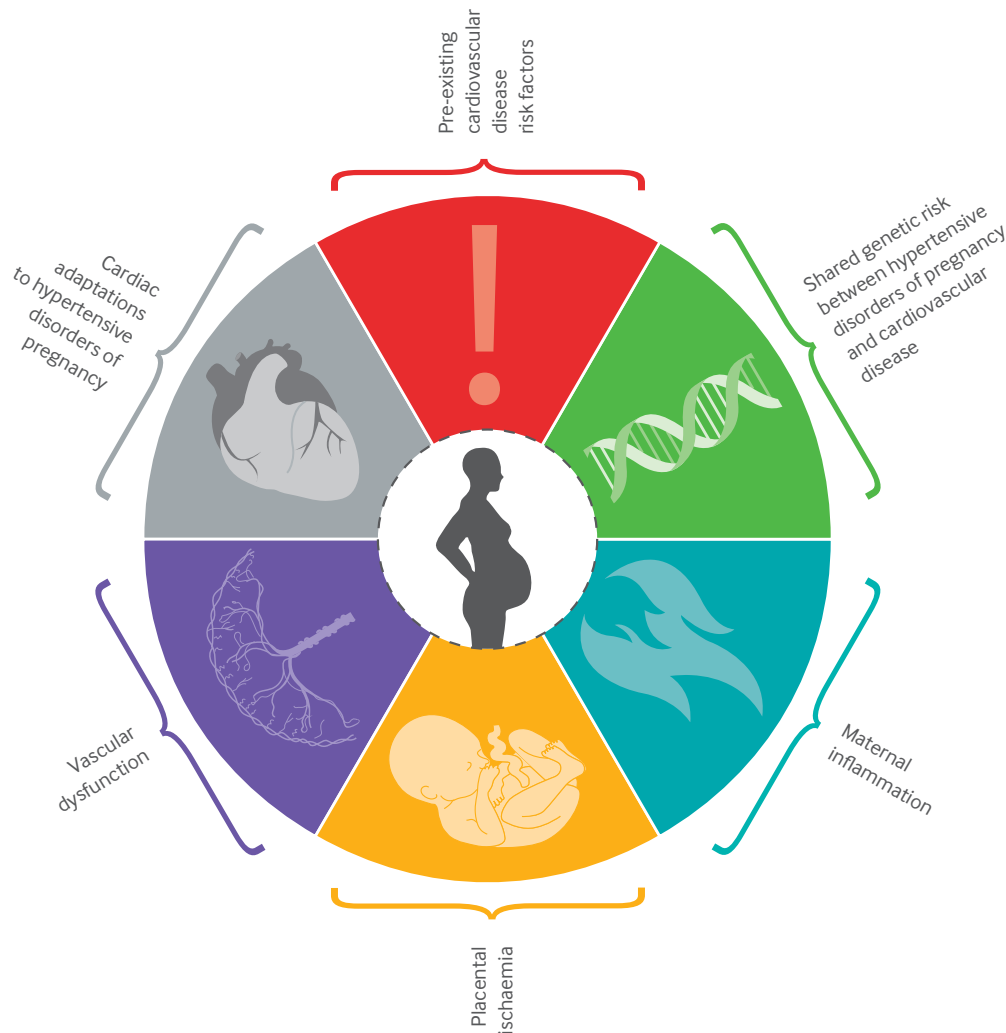


Fig 3 | Potential underlying mechanisms for association between hypertensive disorders of pregnancy (HDP) and future cardiovascular disease (CVD). Adapted with permission from Wu et al. *Eur Cardiol Rev* 2021¹¹⁸

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 ($\geq 140/90$ 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

Prevalence in future pregnancy	Type of hypertension in affected 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 $\geq 140/90$ mm Hg is recommended by most guidelines,^{2 63 92 93} with the exception of the ACOG which advocates a treatment threshold of $\geq 160/110$ 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 ($\geq 160/110$ 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=10141) 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 α_2 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 -adrenergic 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 pregnancy¹¹⁴; 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 guideline²), 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 reported¹⁶⁹; 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 μ g/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.

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