**Hypertensive Disorders of Pregnancy**

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**Abstract**

Hypertensive disorders of pregnancy (HDP) are one of the most commonly occurring pregnancy complications, and include chronic hypertension, gestational hypertension, and pre-eclampsia. New developments in early pregnancy screening to identify high-risk women 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 confer improvements in identifying those pregnancies at highest risk of severe complications. Evidence from trials have refined the target blood pressure and timing for delivery to manage chronic hypertension and pre-eclampsia with non-severe features, respectively. Importantly, there is now a wealth of epidemiological data linking HDP to future cardiovascular disease and diabetes decades after an affected pregnancy. In this review, we discuss the current guidelines and research data on prevention, diagnosis, management, and postnatal follow-up of HDP. We also discuss the gap in knowledge regarding the long-term risks for cardiovascular disease following HDP and illustrate the importance of improving adherence with postnatal guidelines to monitor hypertension and the need for more research focused on primary prevention of future cardiovascular disease in women identified as 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 prevention, diagnosis, management, postnatal sequelae and follow-up of HDP. We highlight contemporary evidence on screening and diagnosis of pre-eclampsia and 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 priority of the studies to be included based on quality (systematic reviews and meta-analyses, randomised controlled trials, 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 there was a strong case for their inclusion due to its relevance.

**EPIDEMIOLOGY**

The prevalence of HDP varies according to region with the global prevalence being 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, while the Western Pacific region had the lowest prevalence of HDP (16 per 100,000 women of childbearing age) (3). Worldwide, 18.1 million incident HDP cases were estimated for 2019, with HDP thought 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 HDPs**

Hypertension in pregnancy is defined by ISSHP as a blood pressure (BP) of sBP ≥140 mmHg and/or a dBP ≥90 mmHg, with sBP ≥160 mmHg and/or a dBP ≥110 mmHg 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/days. Ideally, the diagnosis would be confirmed by ambulatory monitoring, which is gold standard outside of pregnancy, but for logistical reasons the diagnosis in pregnancy is usually confirmed by repeated hospital of clinic-based measurements. Self-monitoring of blood pressure is now increasingly common in the management of HDP. The BUMP trials confirmed this practice was acceptable to women and not associated with increased risk of adverse outcomes (7, 8).

The classification of HDP has been refined over the years by ISSHP (Table 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). In masked hypertension, as the blood pressure appears to be normal in clinic, the diagnosis is usually only sought when there are unexplained features of organ damage from hypertension. 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 multi-system disease characterised by widespread endothelial dysfunction, and requires at least two features of the syndrome to be present (see Table 1). In addition to hypertension (de novo or chronic), proteinuria is the most frequent additional sign of endothelial dysfunction and therefore most used to make the diagnosis. The clinical diagnosis is based on the presence of signs/symptoms including vasoconstriction (hypertension), increased capillary permeability (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 (Table 1). The combination of placental dysfunction and hypertension is therefore considered by most 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 HDPs continues to be 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, 15, 16, 17, 18, 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 HDPs therefore include missed diagnoses and avoidable adverse outcomes, but also inappropriate iatrogenic preterm births which lead 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 prior 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). The available cohort studies were synthesised by Bartsch et al. in a meta-analysis (21). 25,356,688 women were included from 40 studies in Europe and 30 studies in North America. Previous HDP, chronic hypertension and antiphospholipid syndrome were demonstrated to be 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- and middle-income settings with data from 276,388 mothers and their infants analysed by investigators at the World Health Organisation (23). The prevalence of pre-eclampsia/eclampsia in this study population was 4% and the odds ratio for development of the condition associated with BMI ≥35, nulliparity and chronic hypertension were 3.90 [3.52–4.33], 2.04 [1.92–2.16] and 7.75 [6.77–8.87], respectively.

There is no treatment 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 preventative 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, 28, 29). The current NICE guidelines recommend aspirin for women with one high risk factor or two moderate risk factors (Table 2) (30).

The Fetal Medicine Foundation (FMF) algorithm (<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 algorithm has been developed over a series of observational studies (31, 32, 33). In 2018, an independent prospective cohort study reported a doubling of the detection rate of preterm pre-eclampsia with the FMF algorithm. At a fixed screen positive rate of 10.3%, rates of preterm pre-eclampsia were 3.4% in women screen positive using NICE and 6.8% in women screen positive using the FMF algorithm; the test doubled the detection rate for preterm pre-eclampsia compared to the NICE guidelines (41% to 82%) (33). Whilst several trials had already demonstrated a reduction in preterm pre-eclampsia with aspirin (25, 26), the ASPRE trial confirmed a significant risk reduction when aspirin was used in conjunction with the FMF algorithm (34). In this randomised controlled trial, 11% of the population were screen positive, of whom 60% were randomised to aspirin 150mg daily or placebo. Rates of preterm pre-eclampsia were 4.3% in the placebo group and 1.6% in the treatment group. Moreover, the effectiveness of aspirin is greatest in preventing births at <32 weeks’ gestation (35), when the consequences of PE are most severe. First trimester screening using the FMF algorithm combined with aspirin appears 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 algorithm has not been widely adopted in the United Kingdom (UK). Concerns regarding cost effectiveness and the logistics of implementation, given the low prevalence of the disease, are commonly cited as barriers amongst obstetricians. Only limited external validation of this screening test has been conducted (38). However, in a single site study in London, adoption led to a reduction in preterm pre-eclampsia by 80% (36). To date, multimodal screening for pre-eclampsia using the FMF algorithm has not been endorsed by the National Screening Committee (NSC); the updated statement concluded that there is evidence to support clinical effectiveness for early pregnancy screening combined with aspirin prophylaxis, but insufficient evidence “of harms and benefits of a screening programme in this population” (39).

Implementation of the FMF 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 (4,500 births per annum). Given the significant cost of implementation (approx. £170,000 per year, £38 per pregnancy) and the logistical challenges of introducing the test, further evidence to evaluate cost effectiveness evaluation is likely to be required 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 (40, 41). The ongoing CaPE RCT (ISRCTN12033893), expected to complete in 2025, is investigating the clinical and cost effectiveness of calcium supplementation in preventing pre-eclampsia in the UK.

**Recent advances in diagnosis**

The clinical presentation is heterogenous and frequently atypical, leading to ambiguity in the classification of HDPs in both clinical practice and research studies. It is not surprising that a diagnosis based on highly variable clinical observations such as blood pressure and proteinuria, and which relies on parameters with poor diagnostic accuracy (e.g. fetal ultrasound (42) and urine protein measurement (43)), 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 mmHg 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 which are associated with the development of hypertension, proteinuria, compromised kidney function (e.g. diabetes, chronic kidney disease), abnormal liver function (e.g. 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 suffered from inaccuracies.

Progress towards a more accurate diagnostic test for pre-eclampsia was accelerated by the discovery of abnormal angiogenic imbalance in pre-eclampsia. The initial study identified very high levels of the protein soluble FMS like Tyrosine kinase 1 (sFlt) in the placentas of women with pre-eclampsia (44). This observation was followed by a study by Levine et al. which demonstrated high levels of the antiangiogenic protein sFlt and low levels of the proangiogenic PlGF in the maternal circulation of women prior to their clinical diagnosis of pre-eclampsia (45). The association between this angiogenic marker imbalance and a clinical diagnosis of pre-eclampsia has been consistently reproduced in many subsequent studies (46, 47). Furthermore, a relationship between the severity of the clinical features of the disease and the scale of the angiogenic imbalance has also been observed (48, 49). Figure 1 illustrates the angiogenic markers in the pathophysiology of pre-eclampsia (50).

Two large prospective observational studies have since confirmed the accuracy of a high sflt:PlGF ratio or a low PlGF as diagnostic markers for pre-eclampsia presenting before 37 weeks’ gestation (51, 52). Based on these two studies, the National Institute for Health and Care Excellence (NICE) Diagnostic Assessment Panel, made a recommendation that PlGF-based testing should be offered to women presenting with clinical signs suggestive of pre-eclampsia prior to 37 weeks’ gestation. This recommendation was recently updated following a review of further evidence which has demonstrated the clinical utility of PlGF-based testing as an adjunct to the diagnosis of pre-eclampsia (53). The PARROT trial, a multicentre cluster randomised step wedged study, demonstrated 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 (54). 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 (55). A single centre study also confirmed that inclusion of the sFlt:PlGF ratio test (Roche Diagnostics) was associated with improved diagnostic accuracy and improved triage of the highest risk women to high surveillance pathways (56).

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 required to ensure testing is available to women across the UK. The recent NICE Guidance includes a number of 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 (57).

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 in women with chronic hypertension and other chronic medical conditions where preterm birth is often offered and justified by a clinical suspicion of developing pre-eclampsia. The lack of consistency between the clinical diagnosis and the biochemical diagnosis has been reported (58) and as experience of using PlGF-based testing develops, it is likely that there will be most clinical impact in women with clinical features which confound the diagnosis (59). For example, A cohort study (n=979) in a real-world clinical setting showed that low PlGF levels are associated with increased rates of preterm birth within 2 weeks (standardized survival difference −0.43, 95% CI, −0.76 to −0.09) irrespective of the clinical diagnosis, as well as increased risk of early-onset pre-eclampsia (OR 58.2, 95% CI 32.1-105.4) and stillbirth (OR 15.9, 95% CI 7.6-33.3) (59). 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 4 weeks) diagnostic test; it should not be used to guide timing of birth following a diagnosis of pre-eclampsia.

**Antepartum management**

**Chronic hypertension**

A summary of standard care according to NICE guidance in the UK is shown in Figure 2. In women with hypertension before 20 weeks, clinical judgement should determine whether investigations (e.g. renal imaging, echocardiogram, catecholamines) for secondary hypertension are justified; as a minimum a detailed medical history, clinical cardiovascular examination, renal function, proteinuria assessment and diabetes screen should be offered. Women with chronic hypertension are at risk of developing superimposed pre-eclampsia and most guidelines recommend commencing aspirin for prevention (27, 60, 61). A recent meta-analysis concluded that low dose aspirin did not reduce the risk of superimposed pre-eclampsia in women with chronic hypertension. There was however a significant reduction in all preterm birth (62). 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=3,485) was inconclusive on the treatment benefits on reducing adverse outcomes such as pre-eclampsia (RR 0.92, 95% CI 0.75-1.14, n=2,851), small-for-gestational-age babies (RR 0.96, 95% CI 0.78-1.18, n=2,686), and preterm birth (RR 0.96, 95% CI 0.83-1.12, n=2,141), except for the reduction in severe hypertension (RR 0.49, 95% CI 0.40-0.60, n=2,558) (63). 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 (64). The threshold for instigation of antihypertensive medication in chronic hypertension has long been debated; recent evidence has demonstrated significant maternal benefits without additional concerns regarding fetal growth. The CHIPS RCT (n=987, 75% with chronic hypertension), demonstrated no difference in severe composite maternal or neonatal outcomes (pregnancy loss/high-level neonatal care OR 1.02, 95% CI 0.77-1.35; serious maternal complications OR 1.74, 95% CI 0.79-3.84) between less tight control (target blood pressure below 100 mmHg) and tight control (target diastolic blood pressure below 85 mmHg) , with the exception of an increased risk of severe hypertension (OR 1.80, 95% CI 1.34-2.38) in the less tight group (65). More recently, the CHAP RCT (n=2,408 women with chronic hypertension) reported that a target blood pressure <140/90 mmHg, compared with no medication unless blood pressure ≥160/105 mmHg, led to a reduction in adverse composite outcomes which including pre-eclampsia with severe features, preterm birth, abruption and fetal or neonatal death (RR 0.82, 95% CI 0.74-0.92), without harming fetal growth (birth weight <10th centile RR 1.04, 95% CI 0.82-1.31) (66). NICE guidance recommends treatment for all HDP if exceeds 140/90 mmHg (30).

There is limited data on the timing of delivery for women with chronic hypertension which is well controlled. Cohort studies suggest that delivery between 38 to 39+6 weeks’ gestation is optimal for fetus in women not on antihypertensive treatment (67, 68). However, other studies have shown delivery beyond 39 weeks is associated with increased risk of developing superimposed pre-eclampsia (69, 70). Therefore, most guidelines recommend delivery between 38 and 39 weeks’ gestation (2, 71, 72, 73, 74, 75), while others suggest offering delivery from 37 weeks’ gestation (76), particularly if maintenance antihypertensive treatment is used (30, 71). The WILL trial (ISRCTN77258279), completing in 2024, is addressing 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 (77).

**Gestational hypertension**

Approximately 10-25% of women with gestational hypertension will develop pre-eclampsia (78), the risk is highest in those who present at earlier gestations (<34 weeks) (79, 80). It is not possible to predict which women will develop pre-eclampsia at the time of presentation based on clinical features alone, but the addition of PlGF-based testing allows surveillance to be targeted to those at highest risk of developing pre-eclampsia (30, 53). The threshold for antihypertensive treatment in the NICE guidelines is the same as that for chronic hypertension and pre-eclampsia (≥140/90mmHg) (30, 60).

The optimal timing of delivery for women with gestational hypertension remains unclear as there is no large trial data 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 (81). 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 (RR 0.71, 95% CI 0.59-0.86), without differences in rates of Caesarean delivery (RR 0.75, 95% CI 0.55-1.04) or neonatal complications (RR 0.75, 95% CI 0.45-1.26), compared to expectant management. However, the intervention group had worse neurodevelopment outcomes at age of 2 years (OR 0.48, 95% CI 0.24-0.96) (82). On the other hand, a large retrospective observational study of women with gestational hypertension (n=228,668) found a later delivery gestation between 38 and 39 weeks’ gestation balances the lowest maternal and fetal risk of morbidity and mortality (83). The rate of maternal morbidity/mortality at 38 weeks was 89.9 (95% CI 68.1-111.8) per 1,000 live births, while the rate of fetal morbidity/mortality at 39 weeks was 10.5 (95% CI 2.8-18.2) per 1,000 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, 84). The externally validated fullPIERS (85) or PREP (86) prognostic models referred to in the NICE guidelines (30) may be used to identify women at risk of adverse maternal outcomes (87) and help with decision on place of care and threshold for intervention . Studies have shown PlGF-based testing can also predict adverse maternal outcomes (54, 56, 88). Treatment of hypertension for women with pre-eclampsia with non-severe features at ≥140/90 mmHg is recommended by most guidelines (2, 60, 89, 90) , with the exception of ACOG which advocates a treatment threshold of ≥160/110 mmHg (13).

For pre-eclampsia with severe features at a previable gestation, termination of pregnancy needs to be considered due to the high risks of maternal complications. Between 24 to 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 there is no maternal or fetal indication for immediate delivery (91). 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 (RR 1.94, 95% CI 1.15-3.29), more respiratory distress (RR 2.30, 95% CI 1.39-3.81), and required more ventilation (RR 1.50, 95% CI 1.11-2.02). For pre-eclampsia with non-severe features between 34 to 37 weeks’ gestation, the PHOENIX RCT (n=901) showed induction of labour within 48 hours was associated with reduced adverse composite maternal morbidity (RR 0.86, 95% CI 0.79-0.94), increased likelihood of vaginal birth and reduced magnesium sulfate administration, but increased composite perinatal adverse outcome, primarily composed of increased neonatal unit admission (RR 1.25, 95% CI 1.05-1.48) (92). These findings are consistent with subsequent individual participant data meta-analyses (93, 94). Once ≥37 weeks’ gestation, delivery is recommended based on the HYPITAT findings (81).

**Fetal monitoring**

The suggested third trimester scan frequency should be dictated by the clinical presentation and fetal wellbeing assessments; most guidelines recommend a minimum of 4-weekly assessment in women with controlled chronic hypertension in the absence of fetal wellbeing concerns (2, 13, 30, 71, 84, 95).

**Intrapartum management**

Blood pressure control and seizure prevention are central to peripartum management of HDP. Given the significant risk of cerebrovascular haemorrhage associated with untreated hypertension in pre-eclampsia (96, 97), guidelines recommend that severe hypertension ((≥ 160/110 mmHg) should be treated as an inpatient, using intravenous labetalol, oral nifedipine or intravenous hydralazine as necessary (60). 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 the mode of delivery decisions should be dictated by usual obstetric considerations (60).

**Eclampsia**

Without magnesium sulfate prophylaxis, the rate of seizures in pre-eclampsia with severe features is four times more common than pre-eclampsia with non-severe features (13). The Magpie RCT (n=10,141) showed a reduction in eclamptic seizures (58% reduction, 95% CI 40-71%) (98), while a Cochrane systematic review (n=1,396) showed a reduction in maternal death (RR 0.59, 95% CI 0.38-0.92) and recurrent eclamptic seizures (RR 0.43, 95% CI 0.33-0.55) (99) with the use of intravenous magnesium sulfate. Magnesium sulfate also has a role in fetal neuroprotection for preterm birth (100, 101).

**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=2,774) concluded that labetalol and nifedipine were preferable to methyldopa for the avoidance of severe hypertension (RR 0.70, 95% CI 0.56-0.88) (63). For pre-eclampsia with severe features, a network meta-analysis including 46 studies, reported similar efficacy between intravenous labetalol, oral nifedipine, and intravenous hydralazine (102). In a low-resource setting, an RCT (n=2,307) showed oral nifedipine had better blood pressure control than oral labetalol and oral methyldopa (103). The Giant PANDA study ([ISRCTN12792616](https://www.bmj.com/external-ref?link_type=ISRCTN&access_num=ISRCTN12792616)), completing in 2024, is currently 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 alpha- and beta-adrenoreceptor block. Current UK guidance advises neonatal surveillance for hypoglycaemia following labetalol exposure (104) although there is little definitive evidence to guide this practice. Nifedipine is a calcium channel antagonist and can cause maternal headache and tachycardia (105). Nicardipine, has also been evaluated in a retrospective case series (n=830) (106). It was shown to be effective in lowering sBP ≥160mmHg and/or dBP ≥110mmHg in 77% of study participants within 2 hours of treatment. Methyldopa acts by stimulating alpha 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 (63, 107, 108, 109). Hydralazine, an arterial vasodilator, is indicated only in severe hypertension. In a meta-analysis (n=893), hydralazine was more effective in treating severe hypertension than labetalol (RR 0.29, 95% CI 0.08-1.04), but was linked with more adverse maternal and perinatal outcomes (maternal hypotension: RR 3.29 (95% CI 1.50-7.23), placental abruption: RR 4.17 (95% CI 1.19-14.28), Caesarean section: RR 1.30 (95% CI 1.08-1.59), maternal oliguria: RR 4.00 (95% CI 1.22-12.50), 1 minute Apgar score <7: RR 2.70 (95% CI 1.27-5.88)) (110).

Amlodipine, as an alternative calcium channel blocker and doxazosin/prazosin (α‐adrenegic receptor blockers) are frequently used to treat HDP, although there is limited published evidence to support their use as first line options. Due to teratogenicity, renin–angiotensin–aldosterone inhibitors are contraindicated during pregnancy (111), some international guidelines also recommend against diuretics, atenolol, and thiazides during pregnancy (60).

**Postnatal antihypertensive treatment**

All antihypertensive medications are detectable at low levels in breast milk (112) but are considered safe to prescribe in the context of breastfeeding (30). Calcium channel blockers and angiotensin-converting enzyme inhibitors, such as captopril and enalapril, are all considered safe for breastfeeding women (71). ACE inhibitors have the disadvantage of requiring dose titration and renal function monitoring; adequate blood pressure treatment may require an additional agent until a satisfactory dose is reached. Compliance is also a consideration in the postnatal period and longer acting, once daily medications 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 during pregnancy and there is a sustained risk of cerebrovascular haemorrhage in the postpartum period (97). Poorly controlled hypertension is a frequent cause of postnatal readmission and therefore proactive management is likely to be beneficial. Blood pressure is commonly highest 3-5 days after birth and blood pressure should be measured at least once during this period. It is considered good practice (by these authors) to anticipate an increase in BP if primary hospital discharge occurs before day 3-5 and to have a lower threshold for antihypertensive medication during the first two weeks after birth. Normalisation of blood pressure in the early weeks after a 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 remodeling (113, 114).

**Long-term implications**

* Cardiovascular disease

Figure 3 illustrates the potential underlying mechanisms underpinning the association between HDP and future CVD (115).The association between HDP and increased long-term risk of developing CVD is now well established and discussed in several reviews of meta-analyses (116, 117). Pre-eclampsia is associated with a 2-fold increased risk of coronary heart disease, stroke and CVD death, and a 4-fold increase in risk for heart failure (118, 119), with recurrent pre-eclampsia having the highest risk (120). Gestational hypertension is associated with a 1.8-fold increased risk of coronary heart disease, heart failure and composite CVD and a 1.4-fold increase in risk for composite CVD (121, 122). 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 (118, 123).

Pre-eclampsia is also associated with an up to 3.9-fold increased risk of hypertension (119, 124) and a 1.3-fold increase in dyslipidemia (124). The SNAP-HT pilot trial showed self-management of blood pressure in the puerperium resulted in lower diastolic blood pressure at 6 months (113) and 3.6 years (125), 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 6-9 months (126). 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 (127). It demonstrated that home blood pressure monitoring reduces blood pressure at 1 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 (128, 129). The PICK-UP feasibility trial showed enalapril treatment following pregnancy affected by preterm pre-eclampsia may lead to improved cardiac remodelling and diastolic function at 6 months postpartum (114).

* Diabetes

HDP are associated with type 2 diabetes, even without co-exiting gestational diabetes, with an up to 2.6-fold and 2.2-fold increase in diabetes risk for pre-eclampsia (130, 131, 132), and gestational hypertension (130, 131), respectively in meta-analyses. Pre-eclampsia itself is associated with an up to 4.3-fold risk of developing metabolic syndrome (124, 133, 134).

* Other conditions

Meta-analyses have demonstrated the association between HDP and long-term kidney disease. Pre-eclampsia is associated with up to 6.4- and 2.1-fold increased risk of end-stage kidney disease and chronic kidney disease, respectively (135, 136). In contrast, gestational hypertension is associated with a 3.6-fold increased risk of end-stage kidney disease, and 1.5-fold increased risk of chronic kidney disease (135). Overall HDP are associated with 1.4-fold risk of dementia (137), with pre-eclampsia being associated with a 2.6-fold risk of vascular dementia (138), Pre-eclampsia has been associated with a 1.5-fold and 1.8-fold increase in risk of venous thromboembolism and premature mortality, respectively (119). HDP lead to lower scores of health-related quality of life in the postpartum period compared to postpartum haemorrhage (162, 163). A meta-analysis (n=893), including studies conducted up to 40 years after the affected pregnancy, showed pre-eclampsia is associated with developing more severe depression outside the perinatal period (standard mean difference 0.18, 95% CI 0.05-0.31, p=0.007) (164).

**Lack of awareness in healthcare professionals and women**

Recent studies show that healthcare professionals are aware of the long-term risks for CVD after HDP and with the majority counselling women regarding their increased cardiovascular risks (139, 140). However, this rising awareness has not translated into knowledge amongst women, with fewer than half being aware of their risk and having received heart health advice (141, 142). Maternal HDP, as an opportunity for cardiovascular screening and early intervention, was suggested 20 years ago (143), 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 (144).

**Counselling for next pregnancy**

**Risk of recurrence**

An individual patient data meta-analysis reported a 20% recurrence rate of HDP (145). The risk of recurrence increases with concomitant HELLP syndrome, preterm delivery, or small-for-gestational infant. Women with previous pre-eclampsia are equally likely to develop either pre-eclampsia (14%) or gestational hypertension (14%), while women with previous gestational hypertension are more likely to develop gestational hypertension (26%) than pre-eclampsia (146). Table 3 illustrates the likelihood of HDP recurrence (30).

**Management for next pregnancy**

If the hypertension has not resolved within 3 months postpartum, then investigations for secondary hypertension should be considered. If women are on angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, a plan should be made to switch antihypertensive medication 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 anti-hypertensive medications (147, 148). Low dose aspirin should be offered from 12 weeks‘ gestation to reduce the risk of pre-eclampsia recurrence in these high-risk women.

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 (149, 150). Women should also be counselled about risks of developing recurrent HDP and what that means to her planned pregnancy care should be discussed. A systematic review (n=77,561) showed a small increase in risk (OR 1.10, 95% CI 1.02-1.19) of recurrent pre-eclampsia with an inter-pregnancy interval of over 4 years (151).

**Guidelines**

**Diagnosis and management**

There are 5 international guidelines (the World Health Organization 2011 guideline (152), the Society of Obstetric Medicine of Australia and New Zealand 2014 guideline (153), the European Society of Cardiology 2018 guideline (154), the International Federation of Gynecology and Obstetrics 2021 guideline (155) and the ISSHP 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 area of disagreement are: 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 which identified 17 national and international clinical practice guidelines on pregnancy hypertension (60).

**Postnatal screening for cardiovascular disease and diabetes**

* What to screen for

In a review of guidelines, 8 out of the 16 guidelines identified recommended follow-up beyond the immediate post-partum period (156), but there was no consensus regarding who to monitor more closely, the duration and frequency of follow-up, and what parameters to screen for (156). Guidelines from cardiological 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 (154, 157), while others recommend periodic monitoring (72, 158, 159). Out of 13 US guidelines or society recommendation publications relevant to primary care-based CVD risk management in the year following pregnancy outcome, 8 included recommendations specifically for HDP (160). These include early postnatal follow-up in primary care or cardiology outpatient settings (161), close monitoring to ensure hypertension resolves within 12 weeks postpartum (162), or for women who had preterm pre-eclampsia, annual CVD risk assessment (157). A prediction model including demographic, clinical and echocardiographic variables has been developed to identify women with HDP with persistent hypertension at 3 months postpartum (163).

* Advice on lifestyle modification

In a systematic review of national and international clinical practice guidelines for HDP, 11 out of the 17 identified guidelines suggested lifestyle counselling for cardiovascular risk reduction (60). These include guidelines from the ACOG, AHA, NICE and the European Society of Cardiology (30, 154, 159, 161). Lifestyle modifications include exercise, healthy eating, maintaining healthy weight and smoking cessation. A systematic review found only 2 intervention trials for CVD risk reduction in women who had HDP (164). The authors concluded there was limited evidence to suggest lifestyle intervention may be effective. A recent trial suggest web-based interventions have high acceptability amongst women who had pre-eclampsia (165).

**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 metformin prolonged gestation by 7.6 days compared to placebo (166). Although the difference was not statistically significant, there were no serious adverse events relating to the intervention (166); a larger trial is currently underway in South Africa. There are ongoing phase 3 trials for treatment of pre-eclampsia to evaluate beetroot juice (NCT05241327) following mixed results from a small study in HDP (167), and recombinant antithrombin gamma (NCT04182373), which are estimated to complete in May and July 2023 (168), respectively. Another phase 3 trial (ACTRN12618000216213) to assess broccoli spout extract has been registered but not yet started (169). Other therapeutic approaches have been studied albeit in early phase clinical trials only. For example, increasing vasodilator nitric oxide levels 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 mcg/min in a phase 1 study including 6 women with pre-eclampsia at <32 weeks’ gestation (170). Melantonin was shown to extend the diagnosis-to-delivery interval by 6±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) (171). The results of a pharmacokinetics study of sulfasalazine (ACTRN12617000226303) remain to be reported (171, 172). Another pilot study evaluated plasmapheresis to remove sFlt-1 in 11 women with pre-eclampsia at <32 weeks’ gestation (173). The pregnancies continued for 8-15 days, compared to only 3 days in 22 women of the control group. The results of a pharmacokinetics study of sulfasalazine (ACTRN12617000226303) remain to be reported. Administering recombinant PlGF (174), siRNA to silence sFlt-1 or angiotensinogen genes (175, 176), (177) have shown promise in pre-clinical studies.

**Future research**

Globally HDP is 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 pre-eclampsia diagnosis amongst women with HDP and identify those women at highest risk of complications. Future research may offer further 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 CVD is well established, the most effective screening strategy, and the type of interventions that can help to reduce future CVD risk remain unproven and require further research if we are to improve the long-term CVD profile for the millions of women affected by HDP.

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| **Research Questions** |
| * 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? * Are there different sub-types of pre-eclampsia which should be managed differently in clinical practice? * What is the most effective screening strategy and intervention to reduce the risk of cardiovascular disease following hypertensive disorders of pregnancy? |

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| **How patients were involved in the creation of this article** |
| MG brings wide insight as a father whose child was born following a pre-eclampsia episode, As CEO of the Action on Pre-eclampsia (APEC) national charity, he has been involved in numerous academic and non-academic outputs related to HDP. His insight contributed to the direction of the paper, making language accessible and ensuring the other authors remained focused on outcomes for patients. It is intended that when published, this article will be promoted through APEC. |

**CONTRIBUTORS**

All authors planned the overall content of the article, edited and critically revised the whole article for intellectual content. PW and JEM conducted 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).

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**Figure Legends**

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

Figure 2. Standard care according to NICE guidance in the UK (30, 178, 179). BP, blood pressure. CTG, cardiotocography. FGR, fetal growth restriction. FMF, fetal medicine foundation. NICE, National Institute for Health and Care Excellence. PAPP-A, pregnancy associated plasma protein-A. PlGF, placental growth factor.

Figure 3. Potential underlying mechanisms for association between hypertensive disorders of pregnancy and future cardiovascular disease. Adapted from “The Fourth Trimester: Pregnancy as a Predictor of Cardiovascular Disease”, by P Wu et al., European Cardiology Review, 2021 (115). Adapted with permission.

Table 1. ISSHP classification of hypertensive disorders of pregnancy. Adapted from ISSHP 2021 guideline.

|  |  |
| --- | --- |
| Type of HDP | Definition |
| Pre-pregnancy or <20 weeks’ gestation | |
| Chronic hypertension | Hypertension pre-pregnancy or <20 weeks’ gestation |
| White-coat hypertension | BP ≥140/90 mmHg in clinic, but BP <135/85 mmHg with home or ambulatory BP monitoring |
| Masked hypertension | BP <140/90 mmHg in clinic, but BP ≥135/85 mmHg outside clinic |
| ≥20 weeks’ gestation | |
| Gestational hypertension | Hypertension de novo ≥20 weeks’ gestation without proteinuria or other features suggestive of pre-eclampsia |
| Pre-eclampsia   * with severe features (according to ACOG) | Gestational hypertension with ≥1 new-onset conditions of organ or uteroplacental dysfunction:   * Proteinuria * Other maternal end-organ dysfunction, including: * Neurological complications (e.g., eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, or persistent visual scotomata) * Pulmonary oedema * Haematological complications (e.g., platelet count <150,000/μL, disseminated intravascular coagulation, haemolysis) * AKI (such as creatinine ≥90 μmol/L or 1 mg/dL) * Liver involvement (e.g., elevated transaminases such as ALT or AST >40 IU/L) with or without right upper quadrant or epigastric abdominal pain) * Uteroplacental dysfunction (e.g., placental abruption, angiogenic imbalance, fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or intrauterine fetal death) * sBP ≥160 mmHg or a dBP ≥110 mmHg on 2 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 shown above. |

ACOG, American College of Obstetrics and Gynecology. AKI, acute kidney injury. BP, blood pressure. ISSHP, International Society for the Study of Hypertension in Pregnancy.

Table 2. Major and moderate risk factors for pre-eclampsia in the NICE guideline.

|  |  |
| --- | --- |
| Major | Moderate |
| HDP during previous pregnancy | Nulliparity |
| Chronic kidney disease | Age ≥40 years |
| Autoimmune disease e.g., SLE or APS | Pregnancy interval >10 years |
| Diabetes – type 1 | BMI ≥35 kg/m2 at first clinic visit |
| – type 2 | Family history of pre-eclampsia |
| Chronic hypertension | Multi-fetal pregnancy |

APS, antiphospholipid syndrome. BMI, body mass index. HDP, hypertensive disorders of pregnancy. NICE, National Institute for Health and Care Excellence. SLE, systemic lupus erythematosus.

Table 3. Prevalence of recurrent hypertensive disorders of pregnancy. Adapted from NICE guideline.

|  |  |  |  |
| --- | --- | --- | --- |
|  | 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% |