**Hypertensive Disorders of Pregnancy**

Pensée Wu1,2,3, Marcus Green4 and Jenny E. Myers5

1School of Medicine, Keele University, Keele, Staffordshire, UK

2Academic Department of Obstetrics and Gynaecology, University Hospital of North Midlands, Stoke-on-Trent, UK

3Department of Obstetrics and Gynecology, College of Medicine, National Cheng Kung University, Tainan, Taiwan

4Action on Pre-eclampsia, Evesham, Worcestershire, UK

5Maternal and Fetal Health Research Centre, University of Manchester, Manchester, UK

Correspondence to:

Pensée Wu

School of Medicine, Keele University, Keele, Staffordshire, UK

p.wu@keele.ac.uk

Word count: 6,397 (excluding abstract), 195 (abstract)

**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.

|  |
| --- |
| **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?
 |

|  |
| --- |
| **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).

**Licence for publication**

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the author licence), an exclusive licence on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd (“BMJ”) its licensees.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge (“APC”) for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which licence will apply to this Work are set out in our licence referred to above.

**References**

1. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323-33.

2. Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Karumanchi SA, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. Pregnancy Hypertension. 2022;27:148-69.

3. Jiang L, Tang K, Magee LA, von Dadelszen P, Ekeroma A, Li X, et al. A global view of hypertensive disorders and diabetes mellitus during pregnancy. Nature Reviews Endocrinology. 2022;18(12):760-75.

4. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet. 2020;396(10258):1204-22.

5. Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. Lancet. 2016;387(10018):587-603.

6. Stride BP. Validated blood pressure monitors 2022 [Available from: <https://stridebp.org/bp-monitors>].

7. Chappell LC, Tucker KL, Galal U, Yu LM, Campbell H, Rivero-Arias O, et al. Effect of Self-monitoring of Blood Pressure on Blood Pressure Control in Pregnant Individuals With Chronic or Gestational Hypertension: The BUMP 2 Randomized Clinical Trial. Jama. 2022;327(17):1666-78.

8. Tucker KL, Mort S, Yu L-M, Campbell H, Rivero-Arias O, Wilson HM, et al. Effect of Self-monitoring of Blood Pressure on Diagnosis of Hypertension During Higher-Risk Pregnancy: The BUMP 1 Randomized Clinical Trial. JAMA. 2022;327(17):1656-65.

9. Rodrigues Â, Barata C, Marques I, Almeida MC. Diagnosis of White Coat Hypertension and pregnancy outcomes. Pregnancy Hypertension. 2018;14:121-4.

10. Brown MA, Mangos G, Davis G, Homer C. The natural history of white coat hypertension during pregnancy. Bjog. 2005;112(5):601-6.

11. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. Hypertension. 2018;72(1):24-43.

12. Redman CW, Staff AC. Preeclampsia, biomarkers, syncytiotrophoblast stress, and placental capacity. Am J Obstet Gynecol. 2015;213(4 Suppl):S9.e1, S9-11.

13. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gynecol. 2020;135(6):e237-e60.

14. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: A systematic review and meta-analyses. American Heart Journal. 2008;156(5):918-30.

15. Pittara T, Vyrides A, Lamnisos D, Giannakou K. Pre-eclampsia and long-term health outcomes for mother and infant: an umbrella review. Bjog. 2021;128(9):1421-30.

16. Conti-Ramsden FI, Nathan HL, greeff AD, Hall DR, Seed PT, Chappell LC, et al. Pregnancy-Related Acute Kidney Injury in Preeclampsia. Hypertension. 2019;74(5):1144-51.

17. Ganzevoort W, Rep A, Bonsel GJ, Fetter WP, van Sonderen L, De Vries JI, et al. A randomised controlled trial comparing two temporising management strategies, one with and one without plasma volume expansion, for severe and early onset pre‐eclampsia. BJOG: An International Journal of Obstetrics & Gynaecology. 2005;112(10):1358-68.

18. Augustin G, Hadzic M, Juras J, Oreskovic S. Hypertensive disorders in pregnancy complicated by liver rupture or hematoma: a systematic review of 391 reported cases. World Journal of Emergency Surgery. 2022;17(1):40.

19. Ananth CV, Savitz DA, Williams MA. PLACENTAL ABRUPTION AND ITS ASSOCIATION WITH HYPERTENSION AND PROLONGED RUPTURE OF MEMBRANES: A METHODOLOGIC REVIEW AND META-ANALYSIS. Obstetrics & Gynecology. 1996;88(2):309-18.

20. Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol. 2011;25(4):391-403.

21. Bartsch E, Medcalf KE, Park AL, Ray JG. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. Bmj. 2016;353:i1753.

22. Catov JM, Ness RB, Kip KE, Olsen J. Risk of early or severe preeclampsia related to pre-existing conditions. International Journal of Epidemiology. 2007;36(2):412-9.

23. Bilano VL, Ota E, Ganchimeg T, Mori R, Souza JP. Risk factors of pre-eclampsia/eclampsia and its adverse outcomes in low- and middle-income countries: a WHO secondary analysis. PLoS One. 2014;9(3):e91198.

24. Sibley CP. Treating the dysfunctional placenta. J Endocrinol. 2017;234(2):R81-R97.

25. Askie LM, Duley L, Henderson-Smart DJ, Stewart LA, Group PC. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. Lancet. 2007;369(9575):1791-8.

26. Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. Obstet Gynecol. 2010;116(2 Pt 1):402-14.

27. Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre‐eclampsia and its complications. Cochrane Database of Systematic Reviews. 2019(10).

28. Henderson JT, Vesco KK, Senger CA, Thomas RG, Redmond N. Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. Jama. 2021;326(12):1192-206.

29. Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. Am J Obstet Gynecol. 2018;218(3):287-93.e1.

30. National Institute for Health and Care Excellence. Hypertension in pregnancy: diagnosis and management London Department of Health; 2019 [Available from: <www.nice.org.uk/guidance/ng133>].

31. Akolekar R, Syngelaki A, Sarquis R, Zvanca M, Nicolaides KH. Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11-13 weeks. Prenat Diagn. 2011;31(1):66-74.

32. O'Gorman N, Wright D, Syngelaki A, Akolekar R, Wright A, Poon LC, et al. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks gestation. Am J Obstet Gynecol. 2016;214(1):103 e1- e12.

33. Tan MY, Wright D, Syngelaki A, Akolekar R, Cicero S, Janga D, et al. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. Ultrasound Obstet Gynecol. 2018;51(6):743-50.

34. Tan MY, Syngelaki A, Poon LC, Rolnik DL, O'Gorman N, Delgado JL, et al. Screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. Ultrasound Obstet Gynecol. 2018;52(2):186-95.

35. Wright D, Rolnik DL, Syngelaki A, de Paco Matallana C, Machuca M, de Alvarado M, et al. Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin on length of stay in the neonatal intensive care unit. Am J Obstet Gynecol. 2018;218(6):612 e1- e6.

36. Guy GP, Leslie K, Diaz Gomez D, Forenc K, Buck E, Khalil A, et al. Implementation of routine first trimester combined screening for pre-eclampsia: a clinical effectiveness study. BJOG. 2021;128(2):149-56.

37. Liu B, Nadeem U, Frick A, Alakaloko M, Bhide A, Thilaganathan B. Reducing health inequality in Black, Asian and other minority ethnic pregnant women: impact of first trimester combined screening for placental dysfunction on perinatal mortality. BJOG. 2022.

38. Chaemsaithong P, Sahota DS, Poon LC. First trimester preeclampsia screening and prediction. Am J Obstet Gynecol. 2022;226(2S):S1071-S97 e2.

39. NSC. Antenatal screening programme: Pre-eclampsia 2023 [Available from: <https://view-health-screening-recommendations.service.gov.uk/pre-eclampsia/>].

40. Hofmeyr GJ, Lawrie TA, Atallah Á N, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev. 2018;10(10):Cd001059.

41. Hofmeyr GJ, Manyame S, Medley N, Williams MJ. Calcium supplementation commencing before or early in pregnancy, for preventing hypertensive disorders of pregnancy. Cochrane Database of Systematic Reviews. 2019(9).

42. Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. Lancet. 2015;386(10008):2089-97.

43. Correa ME, Côté A-M, De Silva DA, Wang L, Packianathan P, von Dadelszen P, et al. Visual or automated dipstick testing for proteinuria in pregnancy? Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health. 2017;7:50-3.

44. Maynard SE, Min J-Y, Merchan J, Lim K-H, Li J, Mondal S, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. The Journal of Clinical Investigation. 2003;111(5):649-58.

45. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med. 2004;350(7):672-83.

46. Agrawal S, Shinar S, Cerdeira AS, Redman C, Vatish M. Predictive Performance of PlGF (Placental Growth Factor) for Screening Preeclampsia in Asymptomatic Women. Hypertension. 2019;74(5):1124-35.

47. Agrawal S, Cerdeira AS, Redman C, Vatish M. Meta-Analysis and Systematic Review to Assess the Role of Soluble FMS-Like Tyrosine Kinase-1 and Placenta Growth Factor Ratio in Prediction of Preeclampsia. Hypertension. 2018;71(2):306-16.

48. Rana S, Burke SD, Karumanchi SA. Imbalances in circulating angiogenic factors in the pathophysiology of preeclampsia and related disorders. Am J Obstet Gynecol. 2022;226(2s):S1019-s34.

49. Hastie R, Bergman L, Walker SP, Kaitu'u-Lino T, Hannan NJ, Brownfoot F, et al. Associations Between Soluble fms-Like Tyrosine Kinase-1 and Placental Growth Factor and Disease Severity Among Women With Preterm Eclampsia and Preeclampsia. J Am Heart Assoc. 2022;11(16):e024395.

50. Armaly Z, Jadaon JE, Jabbour A, Abassi ZA. Preeclampsia: Novel Mechanisms and Potential Therapeutic Approaches. Frontiers in Physiology. 2018;9.

51. Chappell LC, Duckworth S, Seed PT, Griffin M, Myers J, Mackillop L, et al. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. Circulation. 2013;128(19):2121-31.

52. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, et al. Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. New England Journal of Medicine. 2016;374(1):13-22.

53. National Institute for Health and Care Excellence. PLGF-based testing to help diagnose suspected preterm pre-eclampsia: Diagnostics guidance. 2022.

54. Duhig KE, Myers J, Seed PT, Sparkes J, Lowe J, Hunter RM, et al. Placental growth factor testing to assess women with suspected pre-eclampsia: a multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial. Lancet. 2019;393(10183):1807-18.

55. Duhig K, Seed P, Myers J, Bahl R, Bambridge G, Barnfield S, et al. Placental growth factor testing for suspected pre-eclampsia: a cost-effectiveness analysis. BJOG: An International Journal of Obstetrics & Gynaecology. 2019;126(11):1390-8.

56. Cerdeira AS, O'Sullivan J, Ohuma EO, Harrington D, Szafranski P, Black R, et al. Randomized Interventional Study on Prediction of Preeclampsia/Eclampsia in Women With Suspected Preeclampsia: INSPIRE. Hypertension. 2019;74(4):983-90.

57. McCarthy FP, Gill C, Seed PT, Bramham K, Chappell LC, Shennan AH. Comparison of three commercially available placental growth factor-based tests in women with suspected preterm pre-eclampsia: the COMPARE study. Ultrasound in Obstetrics & Gynecology. 2019;53(1):62-7.

58. Leaños-Miranda A, Nolasco-Leaños AG, Carrillo-Juárez RI, Molina-Pérez CJ, Sillas-Pardo LJ, Jiménez-Trejo LM, et al. Usefulness of the sFlt-1/PlGF (Soluble fms-Like Tyrosine Kinase-1/Placental Growth Factor) Ratio in Diagnosis or Misdiagnosis in Women With Clinical Diagnosis of Preeclampsia. Hypertension. 2020;76(3):892-900.

59. McLaughlin K, Snelgrove JW, Audette MC, Syed A, Hobson SR, Windrim RC, et al. PlGF (Placental Growth Factor) Testing in Clinical Practice: Evidence From a Canadian Tertiary Maternity Referral Center. Hypertension. 2021;77(6):2057-65.

60. Scott G, Gillon TE, Pels A, von Dadelszen P, Magee LA. Guidelines—similarities and dissimilarities: a systematic review of international clinical practice guidelines for pregnancy hypertension. American Journal of Obstetrics and Gynecology. 2022;226(2, Supplement):S1222-S36.

61. Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E. The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. American Journal of Obstetrics and Gynecology. 2017;216(2):110-20.e6.

62. Richards EMF, Giorgione V, Stevens O, Thilaganathan B. Low-dose aspirin for the prevention of superimposed preeclampsia in women with chronic hypertension: a systematic review and meta-analysis. Am J Obstet Gynecol. 2022.

63. Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev. 2018;10(10):Cd002252.

64. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. BMJ. 2014;348:g2301.

65. Magee LA, von Dadelszen P, Rey E, Ross S, Asztalos E, Murphy KE, et al. Less-Tight versus Tight Control of Hypertension in Pregnancy. New England Journal of Medicine. 2015;372(5):407-17.

66. Tita AT, Szychowski JM, Boggess K, Dugoff L, Sibai B, Lawrence K, et al. Treatment for Mild Chronic Hypertension during Pregnancy. N Engl J Med. 2022;386(19):1781-92.

67. Hutcheon JA, Lisonkova S, Magee LA, Von Dadelszen P, Woo HL, Liu S, et al. Optimal timing of delivery in pregnancies with pre-existing hypertension. Bjog. 2011;118(1):49-54.

68. Ram M, Berger H, Geary M, McDonald SD, Murray-Davis B, Riddell C, et al. Timing of Delivery in Women With Chronic Hypertension. Obstet Gynecol. 2018;132(3):669-77.

69. Harper LM, Biggio JR, Anderson S, Tita ATN. Gestational Age of Delivery in Pregnancies Complicated by Chronic Hypertension. Obstet Gynecol. 2016;127(6):1101-9.

70. Grover S, Brandt JS, Reddy UM, Ananth CV. Chronic hypertension, perinatal mortality and the impact of preterm delivery: a population-based study. Bjog. 2022;129(4):572-9.

71. ACOG Practice Bulletin No. 203: Chronic Hypertension in Pregnancy. Obstet Gynecol. 2019;133(1):e26-e50.

72. Magee LA, Smith GN, Bloch C, Côté A-M, Jain V, Nerenberg K, et al. Guideline No. 426: Hypertensive Disorders of Pregnancy: Diagnosis, Prediction, Prevention, and Management. Journal of Obstetrics and Gynaecology Canada. 2022;44(5):547-71.e1.

73. Prejbisz A, Dobrowolski P, Kosiński P, Bomba-Opoń D, Adamczak M, Bekiesińska-Figatowska M, et al. Management of hypertension in pregnancy: prevention, diagnosis, treatment and long‑term prognosis. Kardiologia Polska (Polish Heart Journal). 2019;77(7-8):757-806.

74. Institute of Obstetricians and Gynaecologists; Royal College of Physicians of Ireland and the Clinical Strategy and Programmes Division; Health Service Executive. Clinical Practice Guideline. The Management of Hypertension in Pregnancy; 2019. [Available from: https://rcpi-live-cdn.s3.amazonaws.com/wp-content/uploads/2021/12/HypertensionGuideline. pdf].

75. Megevand N, Berkane N, De Tajada BM, Pechere-Bertschi A. Troubles hypertensifs de la grossesse. Rev Med Suisse. 2019;15:1603-6.

76. Zealand TWOHN. Diagnosis and Treatment of Hypertension and Pre-eclampsia in Pregnancy in Aotearoa New Zealand: A clinical practice guideline. Wellington, New Zealand: Te Whatu Ora; 2022.

77. Magee LA, Tohill S, Kirkham K, Evans R, Gkini E, Moakes CA, et al. WILL (When to Induce Labour to Limit risk in pregnancy hypertension): a multicentre randomised controlled trial - adaptations to deliver a timing-of-birth trial during the COVID-19 international pandemic. Trials. 2022;23(1):884.

78. Saudan P, Brown MA, Buddle ML, Jones M. Does gestational hypertension become pre-eclampsia? Br J Obstet Gynaecol. 1998;105(11):1177-84.

79. Davis GK, Mackenzie C, Brown MA, Homer CS, Holt J, McHugh L, et al. Predicting transformation from gestational hypertension to preeclampsia in clinical practice: a possible role for 24 hour ambulatory blood pressure monitoring. Hypertens Pregnancy. 2007;26(1):77-87.

80. Barton JR, O'Brien J M, Bergauer NK, Jacques DL, Sibai BM. Mild gestational hypertension remote from term: progression and outcome. Am J Obstet Gynecol. 2001;184(5):979-83.

81. Koopmans CM, Bijlenga D, Groen H, Vijgen SMC, Aarnoudse JG, Bekedam DJ, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. The Lancet. 2009;374(9694):979-88.

82. Zwertbroek EF, Franssen MTM, Broekhuijsen K, Langenveld J, Bremer H, Ganzevoort W, et al. Neonatal developmental and behavioral outcomes of immediate delivery versus expectant monitoring in mild hypertensive disorders of pregnancy: 2-year outcomes of the HYPITAT-II trial. American Journal of Obstetrics and Gynecology. 2019;221(2):154.e1-.e11.

83. Cruz MO, Gao W, Hibbard JU. What is the optimal time for delivery in women with gestational hypertension? Am J Obstet Gynecol. 2012;207(3):214.e1-6.

84. Lowe SA, Bowyer L, Lust K, McMahon LP, Morton M, North RA, et al. SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014. Aust N Z J Obstet Gynaecol. 2015;55(5):e1-29.

85. von Dadelszen P, Payne B, Li J, Ansermino JM, Broughton Pipkin F, Côté AM, et al. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. Lancet. 2011;377(9761):219-27.

86. Thangaratinam S, Allotey J, Marlin N, Mol BW, Von Dadelszen P, Ganzevoort W, et al. Development and validation of Prediction models for Risks of complications in Early-onset Pre-eclampsia (PREP): a prospective cohort study. Health Technol Assess. 2017;21(18):1-100.

87. Duffy J, Cairns AE, Richards-Doran D, van 't Hooft J, Gale C, Brown M, et al. A core outcome set for pre-eclampsia research: an international consensus development study. Bjog. 2020;127(12):1516-26.

88. Dröge LA, Perschel FH, Stütz N, Gafron A, Frank L, Busjahn A, et al. Prediction of Preeclampsia-Related Adverse Outcomes With the sFlt-1 (Soluble fms-Like Tyrosine Kinase 1)/PlGF (Placental Growth Factor)-Ratio in the Clinical Routine. Hypertension. 2021;77(2):461-71.

89. WHO Guidelines Approved by the Guidelines Review Committee. WHO recommendations on drug treatment for non-severe hypertension in pregnancy. Geneva: World Health Organization; 2020.

90. Poon LC, Magee LA, Verlohren S, Shennan A, von Dadelszen P, Sheiner E, et al. A literature review and best practice advice for second and third trimester risk stratification, monitoring, and management of pre-eclampsia: Compiled by the Pregnancy and Non-Communicable Diseases Committee of FIGO (the International Federation of Gynecology and Obstetrics). Int J Gynaecol Obstet. 2021;154 Suppl 1(Suppl 1):3-31.

91. Churchill D, Duley L, Thornton JG, Moussa M, Ali HS, Walker KF. Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation. Cochrane Database Syst Rev. 2018;10(10):Cd003106.

92. Chappell LC, Brocklehurst P, Green ME, Hunter R, Hardy P, Juszczak E, et al. Planned early delivery or expectant management for late preterm pre-eclampsia (PHOENIX): a randomised controlled trial. Lancet. 2019;394(10204):1181-90.

93. Beardmore-Gray A, Seed PT, Fleminger J, Zwertbroek E, Bernardes T, Mol BW, et al. Planned delivery or expectant management in preeclampsia: an individual participant data meta-analysis. Am J Obstet Gynecol. 2022;227(2):218-30.e8.

94. Bernardes TP, Zwertbroek EF, Broekhuijsen K, Koopmans C, Boers K, Owens M, et al. Delivery or expectant management for prevention of adverse maternal and neonatal outcomes in hypertensive disorders of pregnancy: an individual participant data meta-analysis. Ultrasound in Obstetrics & Gynecology. 2019;53(4):443-53.

95. Sotiriadis A, Hernandez-Andrade E, da Silva Costa F, Ghi T, Glanc P, Khalil A, et al. ISUOG Practice Guidelines: role of ultrasound in screening for and follow-up of pre-eclampsia. Ultrasound Obstet Gynecol. 2019;53(1):7-22.

96. Martin JN, Jr., Thigpen BD, Moore RC, Rose CH, Cushman J, May W. Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure. Obstet Gynecol. 2005;105(2):246-54.

97. Knight M, Nair M, Tuffnell D, Kenyon S, Shakespeare J, Brocklehurst P, et al. Saving Lives, Improving Mothers’ Care: Surveillance of maternal deaths in the UK 2012–14 and lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–14. Oxford: National Perinatal Epidemiology Unit, University of Oxford 2016.

98. Altman D, Carroli G, Duley L, Farrell B, Moodley J, Neilson J, et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet. 2002;359(9321):1877-90.

99. Duley L, Henderson-Smart DJ, Walker GJ, Chou D. Magnesium sulphate versus diazepam for eclampsia. Cochrane database systematic reviews (Online). 2010;12:CD000127.

100. Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. Cochrane Database Syst Rev. 2009(1):Cd004661.

101. Crowther CA, Middleton PF, Voysey M, Askie L, Duley L, Pryde PG, et al. Assessing the neuroprotective benefits for babies of antenatal magnesium sulphate: An individual participant data meta-analysis. PLoS Med. 2017;14(10):e1002398.

102. Sridharan K, Sequeira RP. Drugs for treating severe hypertension in pregnancy: a network meta-analysis and trial sequential analysis of randomized clinical trials. Br J Clin Pharmacol. 2018;84(9):1906-16.

103. Easterling T, Mundle S, Bracken H, Parvekar S, Mool S, Magee LA, et al. Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial. The Lancet. 2019;394(10203):1011-21.

104. Levene I, Wilkinson D. Identification and management of neonatal hypoglycaemia in the full-term infant (British Association of Perinatal Medicine-Framework for Practice). Arch Dis Child Educ Pract Ed. 2019;104(1):29-32.

105. Vermillion ST, Scardo JA, Newman RB, Chauhan SP. A randomized, double-blind trial of oral nifedipine and intravenous labetalol in hypertensive emergencies of pregnancy. Am J Obstet Gynecol. 1999;181(4):858-61.

106. Nij Bijvank SW, Hengst M, Cornette JC, Huigen S, Winkelen AV, Edens MA, et al. Nicardipine for treating severe antepartum hypertension during pregnancy: Nine years of experience in more than 800 women. Acta Obstet Gynecol Scand. 2022;101(9):1017-25.

107. Mah GT, Tejani AM, Musini VM. Methyldopa for primary hypertension. Cochrane Database Syst Rev. 2009;2009(4):Cd003893.

108. Plouin PF, Breart G, Maillard F, Papiernik E, Relier JP. Comparison of antihypertensive efficacy and perinatal safety of labetalol and methyldopa in the treatment of hypertension in pregnancy: a randomized controlled trial. Br J Obstet Gynaecol. 1988;95(9):868-76.

109. Slim R, Ben Salem C, Hmouda H, Bouraoui K. Hepatotoxicity of alpha-methyldopa in pregnancy. J Clin Pharm Ther. 2010;35(3):361-3.

110. Magee LA, Cham C, Waterman EJ, Ohlsson A, von Dadelszen P. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. Bmj. 2003;327(7421):955-60.

111. Weber-Schoendorfer C, Kayser A, Tissen-Diabaté T, Winterfeld U, Eleftheriou G, Te Winkel B, et al. Fetotoxic risk of AT1 blockers exceeds that of angiotensin-converting enzyme inhibitors: an observational study. J Hypertens. 2020;38(1):133-41.

112. Beardmore KS, Morris JM, Gallery EDM. EXCRETION OF ANTIHYPERTENSIVE MEDICATION INTO HUMAN BREAST MILK: A SYSTEMATIC REVIEW. Hypertension in Pregnancy. 2002;21(1):85-95.

113. Cairns AE, Tucker KL, Leeson P, Mackillop LH, Santos M, Velardo C, et al. Self-Management of Postnatal Hypertension: The SNAP-HT Trial. Hypertension. 2018;72(2):425-32.

114. Ormesher L, Higson S, Luckie M, Roberts SA, Glossop H, Trafford A, et al. Postnatal Enalapril to Improve Cardiovascular Function Following Preterm Preeclampsia (PICk-UP). Hypertension. 2020;76(6):1828-37.

115. Wu P, Park K, Gulati M. The Fourth Trimester: Pregnancy as a Predictor of Cardiovascular Disease. European Cardiology Review 2021;16:e31. 2021.

116. Okoth K, Chandan JS, Marshall T, Thangaratinam S, Thomas GN, Nirantharakumar K, et al. Association between the reproductive health of young women and cardiovascular disease in later life: umbrella review. BMJ. 2020;371:m3502.

117. Pittara T, Vyrides A, Lamnisos D, Giannakou K. Pre-eclampsia and long-term health outcomes for mother and infant: an umbrella review. BJOG: An International Journal of Obstetrics & Gynaecology. 2021;128(9):1421-30.

118. Wu P, Haththotuwa R, Kwok CS, Babu A, Kotronias RA, Rushton C, et al. Preeclampsia and Future Cardiovascular Health. Circulation: Cardiovascular Quality and Outcomes. 2017;10(2):e003497.

119. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. Bmj. 2007;335(7627):974.

120. Brouwers L, van der Meiden-van Roest AJ, Savelkoul C, Vogelvang TE, Lely AT, Franx A, et al. Recurrence of pre-eclampsia and the risk of future hypertension and cardiovascular disease: a systematic review and meta-analysis. Bjog. 2018;125(13):1642-54.

121. Lo CCW, Lo ACQ, Leow SH, Fisher G, Corker B, Batho O, et al. Future Cardiovascular Disease Risk for Women With Gestational Hypertension: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2020;9(13):e013991.

122. Grandi SM, Filion KB, Yoon S, Ayele HT, Doyle CM, Hutcheon JA, et al. Cardiovascular Disease-Related Morbidity and Mortality in Women With a History of Pregnancy Complications. Circulation. 2019;139(8):1069-79.

123. Honigberg MC, Zekavat SM, Aragam K, Klarin D, Bhatt DL, Scott NS, et al. Long-Term Cardiovascular Risk in Women With Hypertension During Pregnancy. Journal of the American College of Cardiology. 2019;74(22):2743-54.

124. Dall'Asta A, D'Antonio F, Saccone G, Buca D, Mastantuoni E, Liberati M, et al. Cardiovascular events following pregnancy complicated by pre-eclampsia with emphasis on comparison between early- and late-onset forms: systematic review and meta-analysis. Ultrasound in Obstetrics & Gynecology. 2021;57(5):698-709.

125. Kitt JA, Fox RL, Cairns AE, Mollison J, Burchert HH, Kenworthy Y, et al. Short-Term Postpartum Blood Pressure Self-Management and Long-Term Blood Pressure Control: A Randomized Controlled Trial. Hypertension. 2021;78(2):469-79.

126. Kitt J, Frost A, Mollison J, Tucker KL, Suriano K, Kenworthy Y, et al. Postpartum blood pressure self-management following hypertensive pregnancy: protocol of the Physician Optimised Post-partum Hypertension Treatment (POP-HT) trial. BMJ Open. 2022;12(2):e051180.

127. Muijsers HEC, Wu P, van der Heijden OWH, Wijnberger LDE, van Bijsterveldt C, Buijs C, et al. Home blood pressure monitoring detects unrevealed hypertension in women with a history of preeclampsia: Results of the BP-PRESELF study. Am J Prev Cardiol. 2022;12:100429.

128. Reddy M, Wright L, Rolnik DL, Li W, Mol BW, Gerche AL, et al. Evaluation of Cardiac Function in Women With a History of Preeclampsia: A Systematic Review and Meta‐Analysis. Journal of the American Heart Association. 2019;8(22):e013545.

129. Melchiorre K, Sutherland GR, Liberati M, Thilaganathan B. Preeclampsia Is Associated With Persistent Postpartum Cardiovascular Impairment. Hypertension. 2011;58(4):709-15.

130. Zhao G, Bhatia D, Jung F, Lipscombe L. Risk of type 2 diabetes mellitus in women with prior hypertensive disorders of pregnancy: a systematic review and meta-analysis. Diabetologia. 2021;64(3):491-503.

131. Wang Z, Wang Z, Wang L, Qiu M, Wang Y, Hou X, et al. Hypertensive disorders during pregnancy and risk of type 2 diabetes in later life: a systematic review and meta-analysis. Endocrine. 2017;55(3):809-21.

132. Wu P, Kwok CS, Haththotuwa R, Kotronias RA, Babu A, Fryer AA, et al. Pre-eclampsia is associated with a twofold increase in diabetes: a systematic review and meta-analysis. Diabetologia. 2016;59(12):2518-26.

133. Jenabi E, Afshari M, Khazaei S. The association between preeclampsia and the risk of metabolic syndrome after delivery: a meta-analysis. J Matern Fetal Neonatal Med. 2021;34(19):3253-8.

134. Alonso-Ventura V, Li Y, Pasupuleti V, Roman YM, Hernandez AV, Pérez-López FR. Effects of preeclampsia and eclampsia on maternal metabolic and biochemical outcomes in later life: a systematic review and meta-analysis. Metabolism. 2020;102:154012.

135. Barrett PM, McCarthy FP, Kublickiene K, Cormican S, Judge C, Evans M, et al. Adverse Pregnancy Outcomes and Long-term Maternal Kidney Disease: A Systematic Review and Meta-analysis. JAMA Network Open. 2020;3(2):e1920964-e.

136. Covella B, Vinturache AE, Cabiddu G, Attini R, Gesualdo L, Versino E, et al. A systematic review and meta-analysis indicates long-term risk of chronic and end-stage kidney disease after preeclampsia. Kidney Int. 2019;96(3):711-27.

137. Schliep KC, Mclean H, Yan B, Qeadan F, Theilen LH, Havenon ADE, et al. Association Between Hypertensive Disorders of Pregnancy and Dementia: a Systematic Review and Meta-Analysis. Hypertension.0(0).

138. Samara AA, Liampas I, Dadouli K, Siokas V, Zintzaras E, Stefanidis I, et al. Preeclampsia, gestational hypertension and incident dementia: A systematic review and meta-analysis of published evidence. Pregnancy Hypertens. 2022;30:192-7.

139. Palmrich P, Binder C, Zeisler H, Kroyer B, Pateisky P, Binder J. Awareness of obstetricians for long-term risks in women with a history of preeclampsia or HELLP syndrome. Arch Gynecol Obstet. 2022;305(3):581-7.

140. Health Care Professional's Knowledge of Pregnancy Complications and Women's Cardiovascular Health: An International Study Utilizing Social Media. Journal of Women's Health. 2022;31(8):1197-207.

141. Sutherland L, Neale D, Henderson J, Clark J, Levine D, Bennett WL. Provider Counseling About and Risk Perception for Future Chronic Disease Among Women with Gestational Diabetes and Preeclampsia. J Womens Health (Larchmt). 2020;29(9):1168-75.

142. Andraweera PH, Lassi ZS, Pathirana MM, Plummer MD, Dekker GA, Roberts CT, et al. Pregnancy complications and cardiovascular disease risk perception: A qualitative study. PLoS One. 2022;17(7):e0271722.

143. Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? Bmj. 2002;325(7356):157-60.

144. Bick D, Silverio SA, Bye A, Chang Y-S. Postnatal care following hypertensive disorders of pregnancy: a qualitative study of views and experiences of primary and secondary care clinicians. BMJ Open. 2020;10(1):e034382.

145. van Oostwaard MF, Langenveld J, Schuit E, Papatsonis DN, Brown MA, Byaruhanga RN, et al. Recurrence of hypertensive disorders of pregnancy: an individual patient data metaanalysis. Am J Obstet Gynecol. 2015;212(5):624.e1-17.

146. Brown M, Mackenzie C, Dunsmuir W, Roberts L, Ikin K, Matthews J, et al. Can we predict recurrence of pre-eclampsia or gestational hypertension? BJOG: An International Journal of Obstetrics & Gynaecology. 2007;114(8):984-93.

147. Buawangpong N, Teekachunhatean S, Koonrungsesomboon N. Adverse pregnancy outcomes associated with first-trimester exposure to angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers: A systematic review and meta-analysis. Pharmacology Research & Perspectives. 2020;8(5):e00644.

148. Fu J, Tomlinson G, Feig DS. Increased risk of major congenital malformations in early pregnancy use of angiotensin-converting-enzyme inhibitors and angiotensin-receptor-blockers: a meta-analysis. Diabetes Metab Res Rev. 2021;37(8):e3453.

149. Wei J, Liu CX, Gong TT, Wu QJ, Wu L. Cigarette smoking during pregnancy and preeclampsia risk: a systematic review and meta-analysis of prospective studies. Oncotarget. 2015;6(41):43667-78.

150. Wang J, Yang W, Xiao W, Cao S. The association between smoking during pregnancy and hypertensive disorders of pregnancy: A systematic review and meta-analysis. Int J Gynaecol Obstet. 2022;157(1):31-41.

151. Cormick G, Betrán AP, Ciapponi A, Hall DR, Hofmeyr GJ, on behalf of the c, et al. Inter-pregnancy interval and risk of recurrent pre-eclampsia: systematic review and meta-analysis. Reproductive Health. 2016;13(1):83.

152. WHO. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. WHO Library Cataloguing-in-Publication Data; 2011.

153. Lowe SA, Bowyer L, Lust K, McMahon LP, Morton M, North RA, et al. SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2015;55(5):e1-e29.

154. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomström-Lundqvist C, Cifkova R, De Bonis M, et al. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy: the task force for the management of cardiovascular diseases during pregnancy of the European Society of Cardiology (ESC). European heart journal. 2018;39(34):3165-241.

155. Poon LC, Magee LA, Verlohren S, Shennan A, von Dadelszen P, Sheiner E, et al. A literature review and best practice advice for second and third trimester risk stratification, monitoring, and management of pre-eclampsia. International Journal of Gynecology & Obstetrics. 2021;154(S1):3-31.

156. Gamble DT, Brikinns B, Myint PK, Bhattacharya S. Hypertensive Disorders of Pregnancy and Subsequent Cardiovascular Disease: Current National and International Guidelines and the Need for Future Research. Front Cardiovasc Med. 2019;6:55.

157. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists’ Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122(5):1122-31.

158. Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(5):1545-88.

159. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the american heart association. Circulation. 2011;123(11):1243-62.

160. Murray Horwitz ME, Fisher MA, Prifti CA, Rich-Edwards JW, Yarrington CD, White KO, et al. Primary Care-Based Cardiovascular Disease Risk Management After Adverse Pregnancy Outcomes: a Narrative Review. J Gen Intern Med. 2022;37(4):912-21.

161. ACOG Practice Bulletin No. 212: Pregnancy and Heart Disease. Obstetrics & Gynecology. 2019;133(5):e320-e56.

162. Obstetric Care Consensus No. 8: Interpregnancy Care. Obstetrics & Gynecology. 2019;133(1):e51-e72.

163. Giorgione V, Khalil A, O’Driscoll J, Thilaganathan B. Peripartum Screening for Postpartum Hypertension in Women With Hypertensive Disorders of Pregnancy. Journal of the American College of Cardiology. 2022;80(15):1465-76.

164. Lui NA, Jeyaram G, Henry A. Postpartum Interventions to Reduce Long-Term Cardiovascular Disease Risk in Women After Hypertensive Disorders of Pregnancy: A Systematic Review. Front Cardiovasc Med. 2019;6:160.

165. Hutchesson MJ, Taylor R, Shrewsbury VA, Vincze L, Campbell LE, Callister R, et al. Be Healthe for Your Heart: A Pilot Randomized Controlled Trial Evaluating a Web-Based Behavioral Intervention to Improve the Cardiovascular Health of Women with a History of Preeclampsia. International Journal of Environmental Research and Public Health. 2020;17(16):5779.

166. Cluver CA, Hiscock R, Decloedt EH, Hall DR, Schell S, Mol BW, et al. Use of metformin to prolong gestation in preterm pre-eclampsia: randomised, double blind, placebo controlled trial. Bmj. 2021;374:n2103.

167. Ormesher L, Myers JE, Chmiel C, Wareing M, Greenwood SL, Tropea T, et al. Effects of dietary nitrate supplementation, from beetroot juice, on blood pressure in hypertensive pregnant women: A randomised, double-blind, placebo-controlled feasibility trial. Nitric Oxide. 2018;80:37-44.

168. Saito S, Takagi K, Moriya J, Kobayashi T, Kanayama N, Sameshima H, et al. A randomized phase 3 trial evaluating antithrombin gamma treatment in Japanese patients with early-onset severe preeclampsia (KOUNO-TORI study): Study protocol. Contemp Clin Trials. 2021;107:106490.

169. Langston-Cox AG, Marshall SA, Palmer KR, Wallace EM. Prolong: a double-blind randomised placebo-controlled trial of broccoli sprout extract in women with early onset preeclampsia. A clinical trial protocol. BMJ Open. 2019;9(10):e027493.

170. Everett TR, Wilkinson IB, Mahendru AA, McEniery CM, Garner SF, Goodall AH, et al. S-Nitrosoglutathione improves haemodynamics in early-onset pre-eclampsia. Br J Clin Pharmacol. 2014;78(3):660-9.

171. Hobson S, Gurusinghe S, Lim R, Alers N, Miller S, Kingdom J, et al. Melatonin improves endothelial function in vitro and prolongs pregnancy in women with early-onset preeclampsia. Journal of Pineal Research. 2018;65:e12508.

172. Brownfoot FC, Hannan NJ, Cannon P, Nguyen V, Hastie R, Parry LJ, et al. Sulfasalazine reduces placental secretion of antiangiogenic factors, up-regulates the secretion of placental growth factor and rescues endothelial dysfunction. EBioMedicine. 2019;41:636-48.

173. Thadhani R, Hagmann H, Schaarschmidt W, Roth B, Cingoez T, Karumanchi SA, et al. Removal of soluble fms-like tyrosine kinase-1 by dextran sulfate apheresis in preeclampsia. Journal of the American Society of Nephrology. 2016;27(3):903-13.

174. Makris A, Yeung KR, Lim SM, Sunderland N, Heffernan S, Thompson JF, et al. Placental Growth Factor Reduces Blood Pressure in a Uteroplacental Ischemia Model of Preeclampsia in Nonhuman Primates. Hypertension. 2016;67(6):1263-72.

175. Turanov AA, Lo A, Hassler MR, Makris A, Ashar-Patel A, Alterman JF, et al. RNAi modulation of placental sFLT1 for the treatment of preeclampsia. Nature Biotechnology. 2018;36(12):1164-73.

176. Haase N, Foster DJ, Cunningham MW, Bercher J, Nguyen T, Shulga-Morskaya S, et al. RNA interference therapeutics targeting angiotensinogen ameliorate preeclamptic phenotype in rodent models. The Journal of Clinical Investigation. 2020;130(6):2928-42.

177. Tong S, Kaitu'u-Lino TJ, Hastie R, Brownfoot F, Cluver C, Hannan N. Pravastatin, proton-pump inhibitors, metformin, micronutrients, and biologics: new horizons for the prevention or treatment of preeclampsia. Am J Obstet Gynecol. 2022;226(2s):S1157-s70.

178. National Institute for Health and Care Excellence. Antenatal care: NICE guideline [NG201]. 2021. [Available from: https://www.nice.org.uk/guidance/ng201].

179. NHS England. Saving Babies’ Lives Version Two: A care bundle for reducing perinatal mortality. 2019.

**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% |