Cardiovascular Disease and Pregnancy 2

Hypertensive disorders of pregnancy: risk stratification and management

Ana Sofia Cerdeira, Amy Sarma*, Jane Hirst, Amanda Henry, Edison Munoz Ortiz, Antonio Saad, Nandita S Scott, on behalf of the Cardiovascular Disease in Pregnancy Writing Group†*

Lancet Obstet Gynaecol Womens Health 2026; 2: e822–37

Published Online August 30, 2026 https://doi.org/10.1016/S3050-5038(26)00190-1

This is the second in a **Series** of three papers about cardiovascular disease and pregnancy (papers 1 and 3 appear in *The Lancet*). All papers in the Series are available at www.thelancet.com/series-do/cardiovascular-disease-and-pregnancy

*Contributed equally

†Members of the Cardiovascular Disease in Pregnancy Writing Group are listed at the end of the paper

Nuffield Department of Women's & Reproductive Health, University of Oxford, Oxford, UK (A S Cerdeira MD); **Royal London Hospital, Barts Health NHS trust, London, UK** (A S Cerdeira); **MGH Heart and Vascular Institute, Massachusetts General Hospital, Boston, MA, USA** (A Sarma MD, N S Scott MD); **George Institute for Global Health, Imperial College London, London, UK** (J Hirst PhD); **George Institute for Global Health, UNSW Medicine and Health, University of New South Wales, Sydney, NSW, Australia** (A Henry PhD); **Discipline of Women's Health, School of Clinical Medicine, UNSW Medicine and Health, University of New South Wales, Sydney, NSW, Australia** (A Henry); **St George Hospital, Kogarah, NSW, Australia** (A Henry); **Cardiovascular and Pulmonary Service, Hospital Universitario San Vicente Fundación, Medellín, Colombia** (E Munoz Ortiz MD); **Cardiology Section, Department of Internal Medicine, Universidad de Antioquia, Medellín, Colombia** (E Munoz Ortiz); **Department of Maternal–Fetal**

Hypertensive disorders of pregnancy (HDP) affect 5–10% of pregnancies globally and are a leading cause of maternal and fetal morbidity and mortality. HDP encompasses the diagnoses of gestational hypertension, pre-eclampsia and its severe forms (eg, eclampsia and HELLP [Haemolysis, Elevated Liver enzymes, and Low Platelets] syndrome), and postpartum hypertension. Despite heterogeneous pathophysiological processes, these conditions typically present after 20 weeks of gestation with new-onset of hypertension, with or without proteinuria, maternal end-organ perfusion, or uteroplacental dysfunction. In the second paper of a three-part Series on cardiovascular disease in pregnancy, we explore the global heterogeneity of HDP—the most common cardiovascular complication of pregnancy—focusing on epidemiology, definitions, screening recommendations, and management. This will lay the framework for understanding the long-term cardiovascular consequences of HDP, which is discussed in the third paper of the Series.

Introduction

Hypertensive disorders of pregnancy (HDP) are a leading cause of maternal morbidity and mortality, disproportionately affecting Black, Indigenous, and marginalised populations.[1–3] Severe maternal morbidity risk is elevated across HDP phenotypes, with the highest burden in chronic hypertension with superimposed pre-eclampsia, HELLP (Haemolysis, Elevated Liver enzymes, and Low Platelets) syndrome, and early-onset disease.[4,5] Perinatal outcomes are similarly affected, as HDP are an important cause of preterm birth, fetal growth restriction, neonatal low birthweight, neonatal intensive care unit admission, respiratory morbidity, and stillbirth.[6–8] In low-resource settings, untreated severe hypertension and eclampsia continue to cause preventable maternal and perinatal deaths.[9]

There are important variations in global disease trends. It is postulated that the primary mechanisms contributing to observed ethnic and regional disparities include social and environmental determinants of health, traditional cardiovascular risk factors, systemic racial inequities, and health-care system factors. Global burden of diseases data from 2023 on age-standardised mortality from HDP show substantial geographical variation: from approximately 0·006 deaths per 100 000 population in several European nations to nearly 15 deaths per 100 000 population in the Central African Republic and Haiti (appendix p 1).[10] This more than 2500-fold gap between national rates far exceeds what would be expected from differences in underlying fertility rates alone, highlighting the preventable nature of maternal deaths as well as global health inequities. Importantly, although age-standardised mortality from HDP has declined substantially in all sociodemographic index regions (figure 1), mortality reductions have been proportionally faster in high-sociodemographic index settings. As a result, relative inequalities (measured by the mortality rate ratio between low and high sociodemographic index regions) have widened over time, probably reflecting persistent inequities in access to high-quality antenatal and postpartum care.

Key messages

- Hypertensive disorders of pregnancy, particularly pre-eclampsia, are a major global health issue with profound inequities and effects on maternal and fetal morbidity and mortality. Interplay between placental dysfunction, maternal cardiovascular–kidney–metabolic disease, and genetic predisposition probably contributes to the heterogeneity of pre-eclampsia, leading to diverse manifestations and outcomes.
- Pre-eclampsia is a complex placental and cardiovascular disease. Advancements in early detection and management require a precision medicine approach to care. Emerging approaches aim to move beyond reactive, symptomatic treatment towards therapies that can directly target disease mechanisms.
- Hypertensive disorders of pregnancy offer a window of opportunity into future cardiovascular health, for which optimising care in the immediate postpartum period appears to be crucial and merits innovation in care strategies.

Heterogeneity in HDP definitions and international guidelines

There is wide agreement that the onset of hypertension (defined by a systolic blood pressure ≥140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg) at or beyond 20 weeks of gestation is a hallmark of HDP. There

is, however, no global consensus for HDP subtype classifications. Elevated blood pressure thresholds during pregnancy and chronic hypertension are generally defined in comparable terms. However, practical differences exist in confirmatory procedures, including timing of repeat blood pressure readings, use of home or ambulatory monitoring, and management of transient early elevations and postpartum disease. In the past decade, diagnostic criteria, particularly for pre-eclampsia, have evolved and differ between professional societies (appendix pp 2–3). These variations stem from a combination of factors: differing regional interpretations of the same clinical evidence, reliance on historical customs or expert consensus in areas without robust data, and necessary adaptations to local health-system capacities. Acknowledging whether these discrepancies are evidence-based or custom-driven is crucial to inform future research priorities and determine where international harmonisation is warranted.[11]

Mechanisms and pathophysiology of pre-eclampsia

Although classified as a single entity, pre-eclampsia is a heterogeneous disorder with incompletely understood pathophysiology. The placenta is central to its pathogenesis, with maternal susceptibility also playing a role. The interplay between placental dysfunction, maternal cardiovascular–kidney–metabolic disease, and genetic predisposition probably contributes to heterogeneity of disease and clinical presentation.[12] Evolving understanding of pathophysiology, particularly with respect to the maternal vascular system, has reframed pre-eclampsia not only as a pregnancy-specific disorder, but also as one with implications for long-term cardiovascular health, as will be discussed by Pabon and colleagues.[13]

Pre-eclampsia that arises from early abnormal placentation—characterised by the failure of extravillous trophoblasts to adequately invade the decidua and remodel maternal uterine spiral arteries, resulting in retained vascular smooth muscle, persistent vasoconstriction, and reduced uteroplacental perfusion[14–16]—is typically associated with earlier-onset disease, greater risk of maternal end-organ involvement, and fetal growth restriction.[17] Impaired placentation results in maternal vascular malperfusion (eg, infarcts and acute atherosis)[16] and syncytiotrophoblast stress with the subsequent release of toxic factors (extracellular vesicles, angiogenic factors, cytokines, reactive oxygen species, etc).[18] The ensuing maternal endothelial dysfunction manifests as reduced vasodilatation, systemic inflammation, and thrombogenesis. Clinical features reflect injury to organs with specialised or fenestrated endothelium, particularly the kidney (proteinuria), liver (hepatic dysfunction and HELLP syndrome), and brain (eclampsia).

Pre-eclampsia can also occur in the context of later-onset placental dysfunction, with typical or near-typical early placentation (figure 2).[12,18] This pathophysiology is less well understood but mechanisms of increased fetal placental demands, placental ageing, specific placental pathologies, and the maternal environment might converge on a similar downstream pathway.[18]

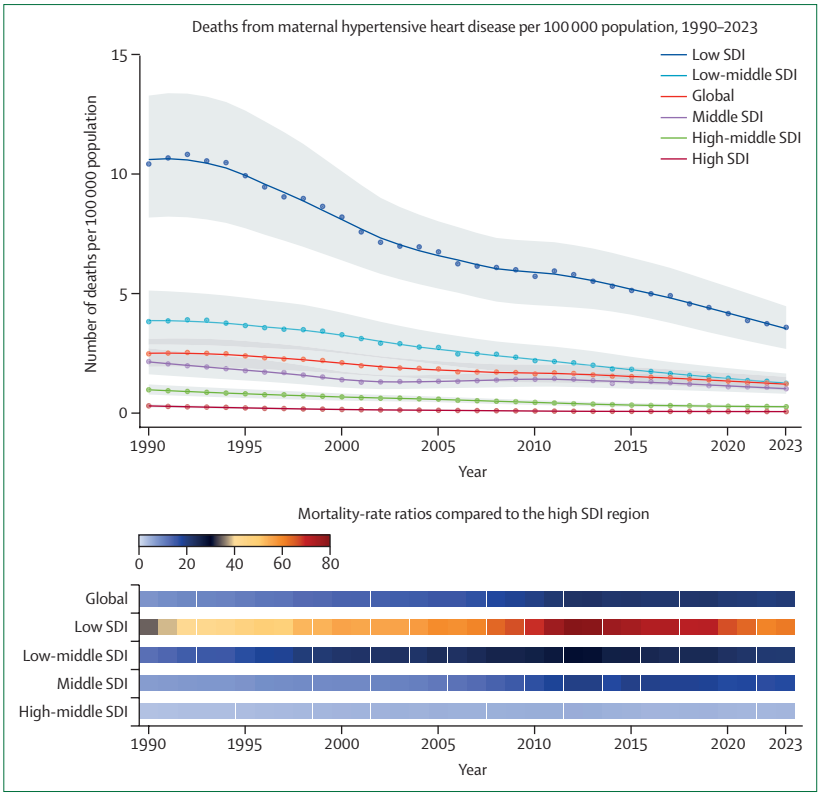

Figure 1: **Global trends in maternal hypertensive heart disease mortality by SDI, 1990–2023**
(A) Age-standardised mortality rate (deaths per 100 000 population) attributable to maternal hypertensive heart disease from 1990 to 2023, stratified by SDI group. Grey-shaded areas represent 95% uncertainty intervals. Time trends are smoothed using locally estimated scatterplot smoothing. (B) Mortality rate ratios comparing each SDI group with the high-middle SDI reference group for each year. Source: Institute for Health Metrics and Evaluation Global Burden of Disease data.[10] SDI=sociodemographic index.

In contrast to pre-eclampsia, gestational hypertension appears to be a pathophysiologically distinct entity. It is characterised predominantly by a state of volume overload and high cardiac output, but placental malperfusion and angiogenic imbalance, which are hallmarks of pre-eclampsia, are absent. Recent studies using placental RNA sequencing confirm distinct molecular signatures between the two conditions, indicating that gestational hypertension does not merely represent an early stage of pre-eclampsia.[19,20] Nevertheless, up to half of women with gestational hypertension progress to pre-eclampsia, particularly when diagnosed before 32 weeks of gestation. Therefore, both conditions require close clinical surveillance and similar management strategies when severe blood pressure elevations occur.[21]

Among the placental factors implicated in disease pathogenesis, soluble fms-like tyrosine kinase 1 (sFlt-1) is regarded as a key pathogenic mediator.[22,23] The placenta expresses approximately 40–50-fold more Flt-1 transcripts[24] than any other tissues, and sFlt-1 blood levels are elevated

Medicine, INOVA Health System, Falls Church, VA, USA
(A Saad MD)

Correspondence to:
Nandita S Scott, MGH Heart and Vascular Institute, Massachusetts General Hospital, Boston, MA 02114, USA
nsscott@mgh.harvard.edu

See **Online** for appendix

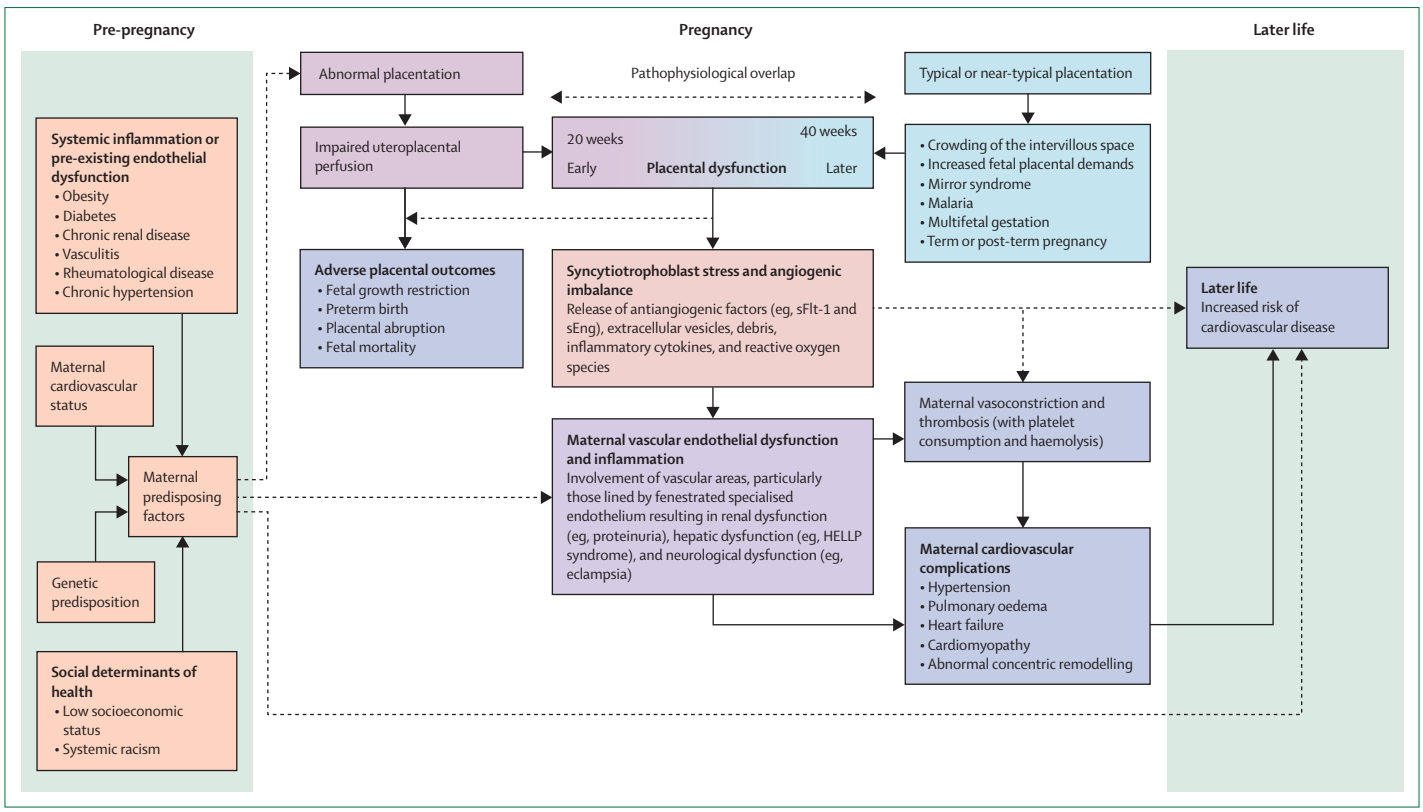

***Figure 2*: From pathogenesis to clinical manifestations: pre-eclampsia results from an interplay of dysfunction of the placenta and maternal vascular systems**
HELLP=Haemolysis, Elevated Liver enzymes, and Low Platelets. sEng=soluble endoglin. sFlt-1=soluble fms-like tyrosine kinase-1.

in pre-eclampsia and fall rapidly after delivery (>80% within hours).[25] Circulating sFlt-1 binds and reduces free vascular endothelial growth factor (VEGF) and placental growth factor (PlGF)—trophic factors essential for endothelial integrity—producing angiogenic imbalance and endothelial dysfunction.[22] Elevated sFlt-1:PlGF ratios correlate strongly with adverse maternal and fetal outcomes, reflecting underlying placental dysfunction.[26–29] Interestingly, VEGF-inhibiting cancer therapies—functionally analogous to sFlt-1—can induce a pre-eclampsia-like syndrome, sharing key clinical hallmarks such as hypertension, proteinuria, and renal thrombotic microangiopathy, all driven by reduced VEGF signalling at the vascular endothelium.[30–32] Given that this imbalance precedes clinical onset, correlates with disease severity, and is implicated in the pathophysiology, angiogenic (eg, PlGF) and anti-angiogenic (eg, sFlt-1) factors have emerged as biomarkers for diagnosis, risk stratification, and potential therapeutic targeting.

Risk factors

Several risk factors for HDPs, particularly pre-eclampsia, have been identified. Large systematic reviews and meta-analyses of cohort and controlled studies, encompassing broad, unselected obstetric populations and frequently adjusting for key demographic confounders, have quantified their individual contributions.[33,34] Based on these data, previous pre-eclampsia (pooled relative risk [RR] 8·4, 95% CI 7·1–9·9), chronic hypertension (5·1, 4·0–6·5), and anti-phospholipid syndrome (pooled rate 17·3%, 8·8–31·4) confer the greater risk[33,34] with the probability of disease increasing exponentially with the number of coexisting risk factors.[35] Categorisation of these risk factors into high risk and low risk forms the basis of current screening approaches outlined later in this paper.

Global variations in obesity prevalence across countries[36]—coupled with structural racial disparities that disproportionately increase pre-eclampsia risk in Black women[37]—create diverse demographic risk profiles. Because these factors interact non-additively,[38] and preventive interventions show differential efficacy across populations,[39] international guidelines appropriately diverge (eg, American College of Obstetricians and Gynecologists [ACOG] *vs* National Institute for Health and Care Excellence [NICE]).[40] Tailoring predictive models and management strategies to specific regional contexts is therefore essential to ensure that interventions are universally beneficial.

Prediction models and screening

Prediction and screening for HDP focus primarily on pre-eclampsia due to its large clinical impact and opportunities for intervention. Early identification of individuals at risk allows initiation of low-dose aspirin

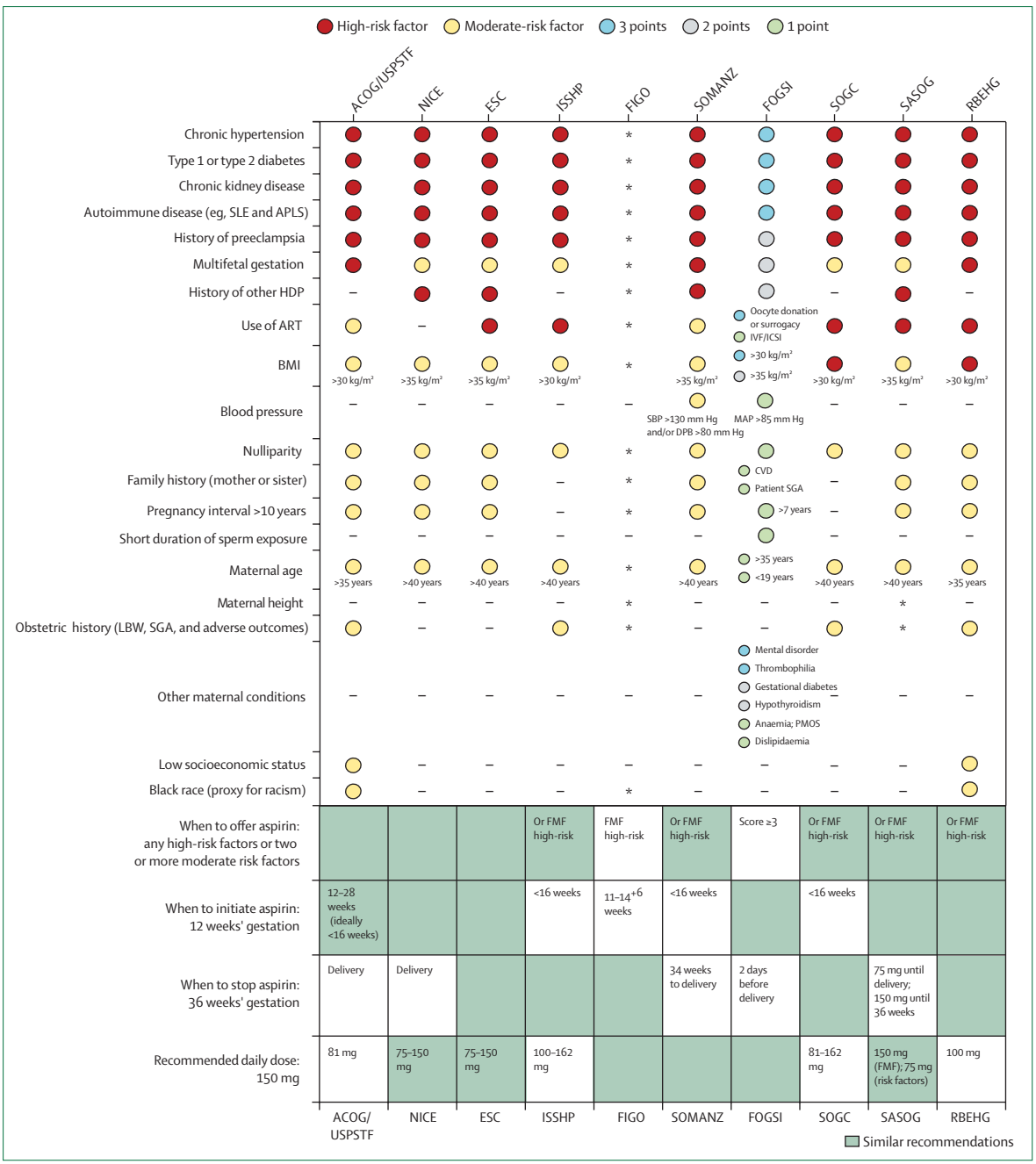

***Figure 3*: Risk factors for pre-eclampsia outlined by guidelines as intended to guide low-dose aspirin prophylaxis**

Asterisks (*) denote factors included in risk stratification but not further graded. Dashes (–) denote factors not included in the guideline. Green boxes show guidelines that share the specification (or a similar specification) to that noted on the left of the diagram. References are listed in the appendix (pp 4–6). ACOG=American College of Obstetricians and Gynecologists. APLS=antiphospholipid syndrome. ART=assisted reproductive technologies. CVD=cardiovascular disease. DBP=diastolic blood pressure. ESC=European Society of Cardiology. FIGO=International Federation of Gynecology and Obstetrics. FMF=Fetal Medicine Foundation. FOGSI=Federation of Obstetric and Gynaecological Societies of India. FMF=Fetal Medicine Foundation. HTN=hypertension, HDP=hypertensive disorders of pregnancy. ICSI=intracytoplasmic sperm injection. ISSHP=International Society for the Study of Hypertension in Pregnancy. IVF=in-vitro fertilisation. LBW=low birthweight. MAP=mean arterial pressure. NICE=National Institute for Health and Care Excellence. PMOS=polyendocrine metabolic ovarian syndrome. RBEHG=Rede Brasileira de Estudos sobre Hipertensao ne Gestecao (Brazilian Network for Studies on Hypertension in Pregnancy). SASOG=South African Society of Obstetricians and Gynaecologists. SBP=systolic blood pressure. SGA=small for gestational age. SLE=systemic lupus erythematosus. SOGC=Society of Obstetricians and Gynaecologists of Canada. SOMANZ=Society of Obstetric Medicine of Australia and New Zealand. USPSTF=US Preventive Services Task Force.

prophylaxis. Later in pregnancy, risk assessment can help to inform intensity of maternal–fetal surveillance and delivery timing.[41]

First-trimester screening

The two main approaches for identifying women at increased risk are traditional clinical risk factor assessment and multivariate models (figure 3). The traditional approach relies on maternal demographics and medical history, categorised into high and moderate risk groups. This two-tiered framework, endorsed by several international societies, identifies candidates for low-dose aspirin without complex investigations, although with limited sensitivity.[42,43] A recent systematic review showed substantial heterogeneity on recommended risk factors across existing guidelines.[44] This might reflect differences in evidence thresholds, population characteristics, and health-system capacity. Although global harmonisation remains a priority, such variation might also represent appropriate adaptation to local epidemiology and population-specific risk profiles.[45] Further research is required to establish more consistent, evidence-based criteria.

Multivariate models combine maternal demographics and medical history with biophysical and biochemical markers. The competing risks Fetal Medicine Foundation (FMF) algorithm (also known as the triple test) is an evidence-based tool that combines maternal factors (age, weight, height, ethnicity, obstetric history, medical history, and family history), mean arterial pressure, uterine artery doppler pulsatility index, and PlGF. This algorithm has reported detection rates of up to 90% for early pre-eclampsia (<34 weeks), 82% for preterm pre-eclampsia (<37 weeks), and 42% for term pre-eclampsia (>37 weeks) at a screen-positive rate of 10%.[46] By comparison, the NICE algorithm—which relies solely on maternal characteristics and medical history—achieves only 42% detection for preterm pre-eclampsia at a similar screen-positive rate.[46] Importantly, validation studies of the FMF algorithm were conducted in high-income tertiary settings and subsequent validation studies suggested slightly lower detection rates in diverse, global populations.[42,47–52] There is also recognition that variation in cardiometabolic profiles and risk factors might differ across populations as well,[53,54] further contributing to variation in model performance.

The FMF algorithm also permits tiered implementation, allowing adjustments for available clinical resources and biomarker access, and therefore can be applied in low-resource environments. The performance of a partial FMF (ie, omitting one or more components) is still superior to that of clinic risk-scoring systems alone.[43] Several innovative and scalable technologies—eg, point-of-care ultrasound for accurate gestational age estimation,[55] the CRADLE-VSA device[56] for blood pressure monitoring, and the expanding availability of point-of-care biomarker testing[57–62]—combined with community education, engagement, and clinical decision-support tools hold promise to help address unique barriers in low-income and low-resourced areas.[57,63] Ongoing studies in low-income and middle-income countries[64] aim to validate and optimise current existing models.

The clinical choice between these screening approaches often depends on regional health system infrastructure and resource availability. Traditional risk-factor-based screening (eg, ACOG and NICE) is straightforward to implement and requires no specialised equipment, making it highly accessible in primary care settings; however, its primary weakness is a lower sensitivity and higher false-positive rate compared with multivariate tools. Conversely, the FMF algorithm offers superior detection rates and is widely used in several European and Asian countries where first-trimester biochemistry and uterine artery doppler are integrated into routine antenatal care. Its implementation has shifted clinical practice towards more targeted prophylaxis, although barriers such as the cost of biomarkers and the need for standardised ultrasound training remain substantial challenges in many low-resource settings.

Second-trimester screening

For patients who present late to antenatal care or are initially classified as low risk, screening at the routine anatomy ultrasound (19–24 weeks of gestation) provides an opportunity for risk reassessment. A competing-risks model using maternal factors, uterine artery pulsatility index, mean arterial pressure, sFlt-1, and PlGF predicts early pre-eclampsia reasonably well.[65]

Third-trimester screening

Screening of asymptomatic individuals at 35–37 weeks of gestation using the FMF algorithm can identify up to 85% of all women who will develop pre-eclampsia beyond 36 weeks.[66] The PREVENT-PE multicenter randomised trial[41] showed that universal third-trimester screening, followed by risk-stratified scheduled birth at 37–39 weeks for those at high risk (≥1:50), resulted in a 30% reduction in pre-eclampsia incidence (3·9% *vs* 5·6%; adjusted RR 0·70, 95% CI 0·58–0·86).[41] Notably, this strategy—which uses the FMF algorithm—achieved this reduction without increasing rates of emergency caesarean section or neonatal intensive care unit admission.[41] Although previous trials such as HYPITAT focused on labour induction for patients already diagnosed with mild hypertensive disease,[67] PREVENT-PE is the first to show that a personalised, biomarker-based approach in the general obstetric population can prevent the clinical manifestation of term pre-eclampsia. However, the requirement for angiogenic biomarker access remains a substantial barrier for widespread implementation in low-resource settings.[41]

Short-term prediction in symptomatic patients (ie, sFlt and PlGF)

Among patients who present with suspected pre-eclampsia up to 37 weeks of gestation, angiogenic biomarkers (eg, sFlt-1 and PlGF, or PlGF alone) can aid in ruling out or confirming the presence of disease, as well as predicting its development over the subsequent 7–14 days. In particular, an sFlt:PlGF ratio of ≤38 or less or a PlGF value of more than 100 pg/mL have a negative predictive value more than 98% and have been validated across various health-care settings.[26,59,68–70] Compared with standard clinical practice, utilisation of this biomarker approach improves clinical precision,[71] reduces the time to diagnosis (from 4·1 days to 1·9 days; time ratio 0·36, 95% CI 0·15–0·87), and reduces a composite of severe maternal adverse effects (secondary outcome adjusted odds ratio [OR] 0·32, 95% CI 0·11–0·96).[72] In the PARROT-1 trial,[72] these severe maternal adverse outcomes included eclampsia, stroke, liver haemorrhage, and other major complications. The clinical benefit might be mediated by the adoption of targeted, enhanced surveillance directed by the PlGF results. Furthermore, cost-effectiveness analyses in the UK have shown that PlGF testing is cost-saving, reducing expenses by approximately £149 per patient tested.[15] Despite these strengths, including high negative predictive value to avoid unnecessary hospitalisations, implementation faces barriers such as high costs in other settings, lack of standardised global thresholds across platforms,[73,74] and the need for robust laboratory infrastructure in low-income and middle-income countries.

Given the broader cardiovascular implications of HDP, there is growing interest in the use of established cardiac biomarkers, such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin I (hs-cTnI), for disease prediction and risk stratification. Recent evidence suggests that hs-cThI levels independently correlate with development of pre-eclampsia and might afford complementary predictive value when combined with angiogenic markers and maternal factors.[75] In the first trimester, lower NTproBNP levels have been correlated with greater risk of future pre-eclampsia[76] compared with normotensive pregnancies. In the early third trimester, however, higher NTproBNP levels correlate with an increased risk of pre-eclampsia within 4 weeks (although reduced risk beyond 4 years) and did not enhance the prediction of either short-term or long-term pre-eclampsia risk as compared with sFlt-1 or PlGF.[77] Similarly, elevated high-sensitivity troponin reflects subclinical myocardial stress and serves as an independent predictors of pre-eclampsia and peripartum maternal–fetal complications. However, it is crucial to emphasise that the predictive utility of these cardiovascular and angiogenic biomarkers is currently validated specifically for pre-eclampsia rather than the broader spectrum of HDP, reflecting the distinct pathophysiological profile of placental dysfunction and maternal vascular malperfusion that is unique to pre-eclampsia.[19]

Emerging strategies include ophthalmic artery doppler measurement, point-of-care ultrasound and biomarker testing, polygenic risk scores,[78,79] haemodynamics,[80,81] cell-free RNA or DNA,[82–84] high-dimensional omics data (ie, proteomics, metabolomics, and transcriptomics), and machine-learning models.[85]

Prevention

Given the potential morbidity and mortality of HDP, prevention is a central goal, particularly for individuals at higher risk. For example, a strategy of screening for pre-eclampsia at 36 weeks of gestation followed by risk-stratified, planned, early-term delivery has reduced pre-eclampsia rates.[41]

Primary prevention focuses on modifying antenatal risk factors as discussed later in this section.

Obesity is a potentially modifiable preconception determinant of risk.[86] However, a distinction must be made regarding the method of weight loss; while randomised controlled trials of behavioural preconception interventions have not yet shown a significant reduction in pre-eclampsia risk,[87] robust evidence from matched cohort studies and meta-analyses indicates that bariatric surgery before pregnancy reduces the risk of pre-eclampsia by approximately 50–80%.[88–90] Clinicians should be aware of the associated trade-offs, as bariatric surgery is also linked to a nearly two-fold increase in the risk of small-for-gestational-age (SGA) infants.[88,90] Structural determinants, such as systemic racism and socioeconomic disadvantage, are increasingly recognised as potentially modifiable contributors to risk.

Low-dose aspirin

Although the mechanism of aspirin action is not fully understood, it is thought to improve spiral artery remodelling and confer maternal endothelial protection. Aspirin is not associated with change in mean arterial pressure[91] nor serum biomarkers,[92] but has been shown to increase placental blood flow as shown by a reduction of uterine artery resistance (measured by pulsatility index).[91] Meta-analyses and large randomised controlled trials consistently show that low-dose aspirin, initiated at or before 16–20 weeks of gestation, significantly reduces the risk of preterm pre-eclampsia and related fetal growth restriction, preterm birth, and perinatal morbidity and mortality.[93–97] This strategy is more effective when applied to a population at high risk rather than universal administration with adherence being important to achieving maximal risk reduction.[98] Although many studies have not shown a significant increase in haemorrhagic complications,[96,97,99] some report a modest increased risk and clinicians should remain aware of this possibility.[100–103]

In the ASPRE (Aspirin for Evidence-Based Preeclampsia Prevention) trial, individuals with increased risk (>1:100)

using the FMF algorithm were randomly assigned to aspirin 150 mg per day or placebo from the first trimester scan to 36 weeks of gestation. Aspirin reduced preterm pre-eclampsia by 62% and very early pre-eclampsia (<32 weeks) by 89%.[96] These effects were even more pronounced among women at high risk with good adherence (>90%) for which aspirin prevented nearly all pre-eclampsia up to 37 weeks of gestation in those with a FMF risk less than 1:20 and up to 35 weeks of gestation when the initial risk was more than 1:20.[104] However, there was no effect on term pre-eclampsia (>37 weeks).[96] Although ASPRE was conducted in a high-income setting, a multicentre study conducted in low-income settings found that 81 mg aspirin reduced preterm birth, early pre-eclampsia, and perinatal mortality.[97] Ongoing trials aim to determine the efficacy of different aspirin doses in the prevention of pre-eclampsia and gestational hypertension and their complications (NCT06468202).[105]

Despite the established efficacy of low-dose aspirin in populations at high risk, its specific benefit for preventing superimposed pre-eclampsia in women with pre-existing chronic hypertension remains uncertain. Although major international guidelines uniformly recommend aspirin prophylaxis for this demographic, the chronic hypertension subgroup in the landmark ASPRE trial did not show a reduction in the rate of pre-eclampsia, but rather aspirin extended gestation (with later onset of pre-eclampsia) by several weeks.[106] Furthermore, a recent meta-analysis confirmed that while low-dose aspirin does not significantly reduce the incidence of superimposed pre-eclampsia in this cohort, it does reduce preterm birth, providing a rationale for its continued use.[107] To definitively address this evidence gap, the ongoing CHASAP trial (NCT04356326) is evaluating the efficacy of 150 mg daily aspirin specifically in this growing population.[108]

Calcium

Previous meta-analyses have suggested that calcium supplementation during pregnancy might reduce the risk of pre-eclampsia among individuals with low baseline intake.[109] However, a recent Cochrane analysis now suggests a lack of benefit even in cases of low baseline intake.[110]

Exercise

A meta-analysis of 17 clinical trials showed that 30–60 mins of aerobic exercise, two to seven times per week reduced the incidence of HDP by 30% (RR 0·70, 95% CI 0·53–0·83).[111] A subsequent dose–response meta-analysis reported that approximately 140 mins per week of moderate-intensity exercise was associated with reduced odds of pre-eclampsia (OR 0·59, 95% CI 0·37–0·90) and gestational hypertension (0·61, 0·43–0·85).[112] Supervised multimodal interventions further improved outcomes, reducing HDPs by 46% (0·54, 0·40–0·72), with combined aerobic resistance and yoga outperforming aerobic-only exercise.[113] Low-to-moderate-intensity exercise initiated in the first trimester appears to confer the most consistent benefit.[114] Additional meta-analysis reinforces a protective role of strength-base modalities.[115] Proposed mechanisms for the benefit of exercise include improved endothelial function, microvascular vasodilatory capacity, reduced oxidative stress, and modulation of angiogenic factors.

Antenatal management

Antenatal management is guided by gestational age, HDP type, and associated maternal–fetal complications. General principles include: (1) control of maternal blood pressure; (2) monitoring for complications; (3) monitoring for evolution to pre-eclampsia among patients with chronic or gestational hypertension; (4) timing of birth that maximises fetal development while minimising adverse outcomes from severe maternal hypertension; and (5) preventing severe morbidity and mortality (both maternal and fetal). Despite these shared principles, there is global heterogeneity in blood pressure treatment threshold (ranging from 140/90 mm Hg to 160/110 mm Hg), goal blood pressure target (ranging from 135/85 mm Hg to 160/110 mm Hg), as well as variation in recommendations for monitoring frequency. Definitive treatment of pre-eclampsia is placental delivery however decisions regarding delivery timing also vary across guidelines.[11]

Management of hypertension

Recent data has shown the benefit on maternal and fetal outcomes with tighter maternal blood pressure goals. In the CHAP trial, patients with mild chronic hypertension and singleton gestations (<23 weeks) were randomly assigned to tight blood pressure treatment (<140/90 mm Hg) versus initiation of therapy at a systolic blood pressure of ≥160 mm Hg or greater and/or a diastolic blood pressure of 105 mm Hg or greater.[116] Those in the tighter control group had a significantly lower incidence of the primary outcome (composite of pre-eclampsia with severe features, medically indicated birth at <35 weeks' gestation, placental abruption, or fetal or neonatal death; 30·2% *vs* 37·0%, p<0·001). This was largely driven by a reduction in pre-eclampsia with severe features (adjusted RR 0·80, 95% CI 0·70–0·92).[116] Beyond the antenatal period, a secondary analysis of CHAP (n=1684), a greater percentage of patients randomly assigned to the active treatment group achieved blood pressure control (defined as <140/90 mm Hg) in the postpartum period (56·7%) as compared to those randomly assigned to the control group (51·5%; adjusted OR 1·22, 95% CI 1·0–1·48), suggesting that tighter control during pregnancy might affect postpartum blood pressure trajectories as well.[117]

Antihypertensive selection in pregnancy is limited by relatively sparse evidence for many medications as pregnant patients are frequently excluded from clinical trials.[118] Recent network meta-analysis suggests labetalol

for HDP might have slight superiority over nifedipine with respect to risk of pre-eclampsia development and preterm birth.[119] However, given that these differences are modest, the emphasis should remain on use of medications with secure availability.[119] Severe hypertension should be treated more urgently with either available oral or intravenous options with no clear evidence of superiority of a particular agent.[120]

Recent data support tighter maternal blood pressure goals, although historical concerns exist regarding fetal growth. The CHIPS trial previously noted an increase in SGA infants with tight control, particularly in the chronic hypertension subgroup.[121] The CHAP trial showed that treating mild chronic hypertension to a target of less than 140/90 mm Hg significantly reduces severe adverse outcomes without increasing SGA risk.[116] Recent secondary analyses further confirm that even low third-trimester blood pressures (<110/70 mm Hg) do not impair fetal growth.[122] Although the strongest evidence for these tight targets applies to pre-existing chronic hypertension, modern guidelines increasingly extrapolate them to de-novo gestational hypertension and pre-eclampsia to maximise maternal safety. In cases of acute severe hypertension (≥160/110 mm Hg), rapid intervention with intravenous labetalol, hydralazine, or oral nifedipine, alongside intravenous magnesium sulphate for seizure prophylaxis, remains the standard of care.

Delivery considerations

In the absence of complications or other indications for earlier delivery, birth at 39 weeks of gestation in chronic or gestational hypertension is recommended from a fetal perspective to minimise the neurodevelopmental issues associated with early-term birth (37–39 weeks).[123] Existing studies (eg, the WILL randomised controlled trial) are currently inclusive regarding benefits versus risks of routine early-term birth for all with chronic or gestational hypertension,[124] although the PREVENT-PE study supports planned early-term birth if individual women screen as high risk for pre-eclampsia development at 36-week multimodal screening.[41]

For pre-eclampsia, it is important to acknowledge the disease's progressive nature, with no proven therapies that halt its trajectory once established, and that birth regardless of gestation (including previable or extreme prematurity) might be required. However, optimising fetal outcomes must be counterbalanced against reducing the risk of adverse maternal outcomes from hypertensive complications. The HYPITAT study supports delivery beyond 36 weeks of gestation over expectant monitoring.[67] There is currently a lack of international consensus regarding recommendations for late preterm birth (34 weeks to >36 weeks) in pre-eclampsia. An individual participant data meta-analysis of six trials (n=1790) of planned delivery versus expectant management from 34 weeks onwards suggests superior maternal outcomes (maternal morbidity 2·6% *vs* 4·4%; adjusted RR 0·59, 95% CI 0·36–0·98) and mixed neonatal outcomes, with increased neonatal adverse composite outcome (20·9% *vs* 17·1%; 1·22, 1·01–1·47) driven by respiratory morbidity, but lower SGA rates (7·8% *vs* 10·6%; 0·74, 0·55–0·99).[125]

To better understand which factors might confer greatest maternal risk, the fullPIERS model was used in 2023 patients in a prospective, international, multicentre study.[126] Predictors of adverse maternal outcome included gestational age, symptoms of chest pain or dyspnoea, oxygen saturation, platelet count, creatinine, and aspartate transaminase concentrations. The model predicted adverse maternal outcomes within 48 h of study eligibility and performed well up to 7 days after eligibility, showing potential to better understand which patients (1) are at lowest risk of adverse outcomes and can therefore be more confidently offered expectant management; and (2) are at higher risk, requiring more urgent delivery consideration or triage to a higher level of care. The miniPIERS model (including factors readily applicable to low-resource settings of parity, gestational age, headache or visual disturbances, chest pain or dyspnea, vaginal bleeding with abdominal pain, systolic blood pressure, and dipstick proteinuria) was subsequently investigated in 2081 patients from low-income and middle-income countries.[127] In a relatively small sample size, the tool performed modestly in identifying women at increased risk of adverse maternal outcomes, which could ultimately be used to identify those who could benefit from further interventions (eg, magnesium or antihypertensive therapy) or a higher level of care.

Postnatal management

Women remain at elevated risk of cardiovascular and cerebrovascular events in the year after HDP, with a two-fold to four-fold increase in risk.[6,128,129] Current guidelines largely focus on antepartum and intrapartum care, and there is an absence of standardised recommendations for postpartum hypertension, resulting in wide variation in management.[11]

Postpartum blood pressure trajectories

As a result of the standard postpartum blood pressure trajectory, blood pressure at the time of standard hospital discharge often reflects a physiological nadir. In recognition of this pattern, ACOG recommends blood pressure assessment within 7–10 days postpartum and within 72 h for those with severe hypertension. Most values stabilise 2–4 weeks postpartum, but some develop persistent hypertension beyond 12 weeks (then reclassified as having chronic hypertension). Even when early postpartum blood pressure normalises, long-term risk of chronic hypertension remains, warranting at least annual monitoring.[130]

Globally, postpartum blood pressure thresholds and targets are poorly defined. Definitions differ between pregnant and non-pregnant populations, and most

guidelines do not specify postpartum targets, raising concern for undertreatment. Some experts recommend a goal of less than 130/80 mm Hg after 6 weeks, and NICE aligns postpartum thresholds with non-pregnant adults. Differences between ACOG and the American Heart Association/American College of Cardiology persist. In secondary analysis of CHAP, treatment of mild chronic hypertension postpartum reduced emergency department and triage visits, although overall unplanned care remained high.

As a result of the standard postpartum blood pressure trajectory, blood pressure at the time of standard hospital discharge often reflects a physiological nadir during the immediate postpartum phase. For context, in normotensive women without HDP, blood pressure typically peaks between day 3 and day 6 postpartum before gradually returning to pre-pregnancy baseline values. In recognition of this dynamic pattern, ACOG recommends blood pressure assessment within 7–10 days postpartum, and within 72 h for those with severe hypertension. Most values stabilise by 2–4 weeks postpartum, but individuals who develop persistent hypertension beyond 12 weeks receive a new diagnosis of chronic hypertension (if their HDP was de novo) or confirmation of their pre-existing condition.

A crucial component of this period is the transition of care. Currently, there is a large unmet need for risk stratification before discharge to effectively identify which women require closer follow-up, earlier specialist review, or an earlier transition back to primary care to mitigate long-term cardiovascular risk.

Panel: Emerging therapeutic approaches in pre-eclampsia

Therapeutic apheresis
Selective removal of circulating soluble fms-like tyrosine kinase-1 (sFlt-1) can reduce anti-angiogenic burden and appears to be safe. Early human studies suggest the potential for pregnancy prolongation in severe preterm pre-eclampsia.

RNA-based therapies
Small interfering RNA-mediated suppression of placental sFlt-1 has shown efficacy in preclinical models. First-in-human clinical trials are underway. Placenta-targeted vascular endothelial growth factor mRNA delivery represents an additional investigational approach.

Repurposed therapies
Metformin, statins, proton-pump inhibitors, and monoclonal antibodies are under investigation. Pravastatin has shown biological promise, although clinical evidence remains inconclusive.

Future directions
Recombinant-tissue kallikrein-1 and other novel biological therapies are entering clinical evaluation. Disease-modifying therapies could transform management by prolonging gestation and improving maternal and fetal outcomes.

References for this panel are listed in the appendix (pp 4–6).

Beyond hypertension: risk for postpartum heart failure

HDP, especially pre-eclampsia, is linked to peripartum cardiomyopathy and increasingly to heart failure with preserved ejection fractions, probably through shared mechanisms such as angiogenic imbalance. Although healthy pregnancy leads to eccentric hypertrophy, pre-eclampsia causes abnormal concentric remodelling due to increased vascular resistance, resulting in diastolic dysfunction, acute postpartum heart failure risk, and possibly higher lifetime heart failure risk.[14,131,132]

Many antihypertensives are safe during lactation (with appropriate contraceptive counselling when needed). Additionally, short courses of furosemide accelerate the return to normotension and reduce hypertension at 7 days postpartum,[133] although recent meta-analyses confirm this does not significantly reduce hospital readmissions or severe maternal morbidity.[134] Consequently, postpartum diuretics are currently viewed as an adjunct to antihypertensive therapy rather than standalone treatment, which is particularly useful in women with substantial fluid overload.[135]

In the POP-HT trial, an intervention consisting of physician-optimised self-management—which combined Bluetooth-enabled home blood pressure monitoring with an app-based algorithm for active medication titration and remote physician oversight—improved blood pressure at 9 months and was associated with favourable cardiac remodelling (lower left-ventricular mass, reduced wall thickness, smaller left-atrial volume, and improved systolic function), independent of medication duration.[136,137] In the PICk-UP trial, 6 months of enalapril after preterm pre-eclampsia improved diastolic function and left-ventricular remodelling compared with placebo.[138] Further studies are needed to clarify which therapies best prevent adverse remodelling and long-term cardiovascular disease.[136–139]

Counselling on subsequent pregnancy and preconception evaluation

Overall recurrence risk of HDP is 20% (range 15–55 by subtype).[140,141] After pre-eclampsia, recurrences can be either gestational hypertension or pre-eclampsia; after gestational hypertension, recurrence is usually gestational hypertension. Early-onset pre-eclampsia (<28 weeks) carries recurrence rates up to 55%. Recurrent disease is often milder, with later onset and fewer severe features. Although not inevitable or necessarily severe, subsequent pregnancies remain high risk and require close monitoring.[141]

Subsequent pregnancy planning

Care after HDP should extend to women planning another pregnancy, even though high-level evidence is limited. At 3–6 months postpartum, a full assessment is

	Description	Status	Registration number	Country
Prevention				
ASPIRIN	RCT comparing 81 mg *vs* 162 mg aspirin daily in pregnant women at high risk aged 14–35 years to prevent hypertensive disorders (eg, pre-eclampsia) with secondary biomarker discovery	Recruiting	NCT06468202	USA
CaPE	Triple-blind, placebo-controlled randomised trial of calcium supplementation initiated between 12 weeks and 22 weeks of gestation in women at high risk, evaluating whether calcium reduces the incidence of pre-eclampsia	Recruiting	ISRCTN12033893	UK
AVERT[105]	Multicentre double-blind RCT of three treatment groups: (1) 75 mg aspirin daily; (2) 150 mg aspirin daily; and (3) 75 mg aspirin with 1·5 g metformin daily from the first trimester to compare the incidence of preterm pre-eclampsia with delivery at <37 weeks of gestation between the treatment group	Recruiting	NCT05580523	China
PEARLS[63]	Large pre-eclampsia prevention trial; validates an FMF-based risk-screening algorithm adapted for African populations; randomly assigned women at high risk to 75 mg *vs* 150 mg aspirin daily from <16 weeks to 36 weeks of gestation; integrates artificial intelligence-powered point-of-care ultrasound for gestational age; validation cohort >12 000 women enrolled across 51 facilities; includes several substudies and establishment of biorepository	Recruiting	PACTR202403785563823	Ghana, Kenya, and South Africa
PREMET	Open-label RCT comparing metformin plus low-dose aspirin *vs* aspirin and standard of care in pregnant women at high risk, using sFLT-1:PlGF ratio as a prognostic biomarker alongside clinical outcomes	Completed	NCT04855513	Qatar
Metformin for pre-eclampsia prevention in pregnant women with type 1 diabetes	RCT evaluating whether metformin started before 20 weeks of gestation reduces hypertensive disorders of pregnancy in women with type 1 diabetes	Active; not recruiting	NCT03570632	USA
PE37	Multicentre RCT randomly assigned women 1:1 to revealed *vs* concealed sFlt-1:PlGF ratio at 35–37 weeks of gestation; those with ratio >90th percentile are offered planned delivery from 37 weeks of gestation to prevent term pre-eclampsia	Recruiting	NCT04766866	Spain, Belgium, Colombia, Czechia, Ecuador, India, Mexico, Panama, and Poland
STARshiP	A large, stepped-wedge, cluster-randomised trial evaluating whether transitioning hospitals from a traditional checklist screening strategy (eg, NICE) to an advanced, multimarker biological algorithm (eg, FMF; integrating maternal history, uterine artery doppler ultrasound, and PlGF blood tests) in the first trimester more effectively reduces preterm births caused by pre-eclampsia	Recruiting	ISRCTN71774663	UK
Treatment and management				
PI4	Phase 3 RCT testing extended-release metformin *vs* placebo in women with preterm pre-eclampsia to prolong pregnancy and reduce gestational age-related neonatal morbidity	Recruiting	NCT06033131	Finland, Norway, and Sweden
PI3	Phase 3 RCT testing whether sustained-release metformin *vs* placebo can prolong pregnancy and improve neonatal outcomes in women with preterm pre-eclampsia diagnosed between 26 + 0 weeks and 31 + 6 weeks of gestation	Recruiting	PACTR202104532026017	South Africa
STATIN-PRE	Phase 2/3 RCT of 40 mg pravastatin daily in women with pre-eclampsia, fetal growth restriction at 24–29·6 weeks, or both, aiming to reduce sFlt-1, prolong pregnancy, and improve perinatal outcomes	Recruiting	NCT07098975	Spain
Giant PANDA	Pragmatic, open-label, multicentre randomised controlled trial in ~2300 women across ~50 UK maternity units comparing a nifedipine-first versus labetalol-first antihypertensive treatment strategy in pregnancy hypertension; co-primary outcomes assess maternal blood pressure control (superiority) and fetal or neonatal safety (non-inferiority)	Completed	ISRCTN12792616	United Kingdom
Open-label, dose finding study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of single ascending subcutaneous doses of CBP-4888 in hospitalised participants with preterm preeclampsia receiving standard of care, expectant management	First dose-escalation study in pregnant patients of CBP-4888 (a subcutaneously delivered small interfering RNA therapeutic targeting two sFLT-1 mRNA isoforms in the placenta) for sFlt-1-mediated preterm pre-eclampsia; evaluates safety, pharmacokinetics, pharmacodynamics, and maternal–fetal outcomes	Recruiting	NCT07282171	Australia
Safety and potential efficacy of DM199 (a tissue kallikrein-1 analogue) for treating pre-eclampsia and fetal growth restriction	Phase Ib/IIa clinical study of DM199 (a recombinant human tissue kallikrein-1 analogue) in pre-eclampsia and fetal growth restriction; aims to improve endothelial function and uteroplacental perfusion via increased nitric oxide and prostacyclin signalling	Not yet recruiting	PACTR202404895013782	South Africa

(Table continues on next page)

	Description	Status	Registration number	Country
(Continued from previous page)				
PAPAGAIO	Multicentre RCT testing whether routine PlGF-based testing in women with suspected preterm pre-eclampsia reduces preterm birth and adverse maternal–neonatal outcomes through improved clinical decision making	Recruiting	ISRCTN70040289	Zambia, Sierra Leone, India, and Brazil
APHERESE2	Preparatory and biomarker study characterising angiogenic and anti-angiogenic profiles (especially sFlt-1) in women with pre-eclampsia to support development and optimisation of extracorporeal sFlt-1-removal strategies	Recruiting	NCT06464159	France
Postpartum				
ASAPP	Phase 2 RCT testing whether 81 mg aspirin given postpartum to women with severe pre-eclampsia accelerates recovery	Recruiting	NCT05924971	USA
PPPOCUS	Pilot prospective cohort using point-of-care ultrasound (inferior vena cava assessment) to guide diuretic therapy (furosemide) in postpartum pre-eclampsia, targeting fluid overload and expediting blood pressure normalisation	Not yet recruiting	NCT07167862	USA
PREDiCT-NPL	Pilot RCT using the sFlt-1:PlGF ratio measured before delivery to identify women at high risk of postpartum pre-eclampsia and guide early postpartum monitoring and antihypertensive management	Not yet recruiting	NCT07185204	USA and Nepal
Antenatal				
iPregnostic	Large-scale external validation study using circulating cell-free RNA profiles from a single first-trimester or second-trimester blood sample to predict early-onset and late-onset pre-eclampsia	Recruiting	NCT06716242	Spain
Non-invasive pre-eclampsia screening and biobank	Biobank study recruiting women at 11–14 weeks of gestation to validate the Labcorp Pre-eclampsia Screen (first-trimester blood-based test) for predicting early-onset, preterm, and term pre-eclampsia; samples stored for future biomarker discovery	Recruiting	NCT06643741	USA
HIPPA	Pilot study evaluating hyperspectral imaging as a non-invasive, point-of-care optical screening tool for pre-eclampsia, analysing spectral signatures of maternal vasculature without requiring blood sampling	Recruiting	NCT07106294	Germany
Pre-eclampsia registry	Longitudinal registry and biobank collecting clinical data, biological samples, and outcomes from women with pre-eclampsia, their relatives, and normotensive controls to identify genetic, biomarker, and environmental risk factors	Recruiting	NCT06377878	USA
GRAZ-PE	Recruiting observational cohort collecting detailed clinical data and biological samples from women with pre-eclampsia to better characterise disease subtypes, mechanisms, and short-term and long-term maternal–neonatal outcomes	Recruiting	NCT07513558	Austria
Postpartum				
MOM-Health	Observational cohort of 1100 women following pre-eclampsia or eclampsia to develop multiomic signatures predicting long-term cardiovascular risk after hypertensive pregnancy	Recruiting	NCT06340152	USA
Prediction of chronic kidney disease following preeclampsia: diagnosis and early care	Interventional study following women post-pre-eclampsia to identify early chronic kidney disease using renal biomarkers, aiming to establish surveillance protocols and reduce long-term maternal morbidity	Recruiting	NCT05056701	France

FMF=Fetal Medicine Foundation. NICE=National Institute for Health and Care Excellence. PlGF=placental growth factor. RCT=randomised controlled trial. sFlt-1=soluble fms-like tyrosine kinase-1.

Table: **Non-exhaustive list of ongoing registered clinical trials and observational studies for the prevention, management, treatment, and prediction of pre-eclampsia**

recommended, including blood pressure (24-h monitoring if needed to detect chronic or masked hypertension), urine protein, and liver and kidney function. Women should be advised to see their primary care provider early for pregnancy confirmation, followed by a first-trimester antenatal assessment and an individualised care plan. Low-dose aspirin and at least 150 mins per week of moderate aerobic exercise are recommended.[141]

Innovative care pathways

Once an individual has been identified to be at increased risk of pre-eclampsia, care should focus on ongoing monitoring of blood pressure and other clinical indicators to enable timely intervention. Globally, the approach varies and includes self-monitoring of blood pressure (SMBP) as well as the inclusion of health workers in community settings. Although monitoring is crucial, improvements in clinical outcomes are dependent on the timeliness and quality of the actions triggered, which in turn reflect the overall state of health-care delivery.

Outside of pregnancy, including the postpartum period, SMBP has been shown to aid blood pressure management, especially when combined with support from clinicians.[142] The evidence for SMBP in pregnancy is more controversial. The BUMP 1 randomised trial was conducted in the UK and recruited 2400 women at risk of pre-eclampsia from 20 weeks of gestation,[143] comparing SMBP to usual care alone. Conducted in parallel, the BUMP 2 trial recruited 850 women with either gestational hypertension or chronic hypertension in pregnancy and compared SMBP to usual care alone.[144] Neither study showed statistically or clinically significant improvements in clinic-based blood pressure control with the addition of SMBP. However, WHO has produced a digital adaptation toolkit for SMBP in pregnancy as a care adjunct in women who face barriers to regular clinical care, highlighting a continued role for SBMP.[145]

Other innovative approaches to improving detection and management of pre-eclampsia have used automated vital-sign monitoring. The CRADLE device is a low-cost, handheld, semi-automated tool that measures blood pressure and calculates the risk of impending shock. It is user friendly, requires minimal training, and displays data via a simple visual traffic-light system. This device was developed and validated for pregnancy and has been extensively tested across several low-income and middle-income settings. The CRADLE 3 trial, conducted across ten clusters in Africa, India, and Haiti, showed a significant reduction in the primary composite outcome of eclampsia, emergency hysterectomy, or maternal death (OR 0·60, 95% CI 0·50–0·72). However, effectiveness varied across sites, reflecting heterogeneity in implementation and uptake.[146] A subsequent study in Sierra Leone did not show a difference in the primary outcome of maternal death, eclampsia, stillbirth, and emergency hysterectomy. Nonetheless, the CRADLE device was shown to be feasible for large-scale implementation and to improve vital-sign monitoring in these contexts.[147]

Emerging therapies

Current interventions are limited to blood pressure control and seizure prophylaxis, with placental delivery remaining the only definitive treatment, often requiring iatrogenic preterm birth. Improved understanding of disease biology and expanding biomarker availability are driving the development of disease-modifying therapies (panel).

Future directions

The substantial heterogeneity across guidelines calls for harmonisation efforts acknowledging resource and population differences. A tiered equity-based framework could establish universal minimum standards while allowing structured escalation based on available resources—from basic clinical assessment to comprehensive biomarker-based and ultrasound-based protocols. This requires sustained international collaboration and must accommodate divergence in drug availability, neonatal intensive care capacity, screening infrastructure, and predictive models validated in the population of interest. Importantly, there must be a focus on using implementation science-based frameworks to ensure an effective and long-lasting change when introducing new care pathways.[148] Finally, this global harmonisation would also facilitate and improve pre-eclampsia research by standardising definitions.

There remain many unknowns with respect to the pathophysiology, optimal methods of prediction, and treatment of HDP. As HDP continues to contribute to both maternal morbidity and mortality, as well as affect future cardiovascular risk as discussed in this *Lancet* Series, novel therapeutics and a move towards precision-based medicine holds the promise to substantially improve the cardiovascular and peripartum care of women, particularly as current treatment methods (including delivery and antihypertensive management) represent relatively blunt tools for treatment. Potential future management directions are outlined in the table. The field of hypertensive disorders of pregnancy stands at an inflection point, with converging scientific and clinical advances poised to transform care and improve equity in the coming decade.

Cardiovascular Disease in Pregnancy Writing Group
Garima Sharma, Tiffany L Brazile, Nathalie Conrad, Lina Bergman, Karen Sliwa, Laxmi Mehta, Candice Silversides, Justin Paul Gnanaraj, Ana Sofia Cerdeira, Amy Sarma, Jane Hirst, Amanda Henry, Edison Munoz Ortiz, Antonio Saad, Nandita S Scott, Maria A Pabon, Graeme Smith, Janet Catov, Adam J Lewandowski, Adam Sumaiya, Michael C Honigberg.

Contributors
ASC, ASar, and NSS conceived and developed the manuscript structure. All authors conducted literature searches and drafted sections within their areas of expertise. ASC, ASar, and NSS coordinated revisions in order to prepare the final manuscript. All authors contributed to interpretation of the literature, critically revised the manuscript, and

approved the final version. The Cardiovascular Disease in Pregnancy Writing Group critically appraised the manuscript.

Declaration of interests

ASC is a consultant for Avilar Therapeutics. ASar is a consultant for Pfizer; a peer reviewer for UpToDate; and declares grants (not related to this manuscript) from the US National Institutes of Health (NIH; 5R01HL155301-04, 1R01HL166836-01A1, and 1R01HL181150-01) and American Heart Association (25SFRNPCKMS1463898). NSS is a consultant for Mediflix and declares grants (not related to this manuscript) from NIH (1R01HL166836-01A1). AH has received a NSW Health Early–Mid-Career Cardiovascular Fellowship (paid to their institution); and is Board Director of the Royal Australian and New Zealand College of Obstetricians and Gynecologists (unpaid governance role). JH declares a UK Research and Innovation Future Leaders Fellowship (MR/Y033833/1). All other authors declare no competing interests.

References

1 Petersen EE, Davis NL, Goodman D, et al. Vital signs: pregnancy-related deaths, United States, 2011-2015, and strategies for prevention, 13 states, 2013-2017. *MMWR Morb Mortal Wkly Rep* 2019; **68:** 423–29.

2 Howell EA. Reducing disparities in severe maternal morbidity and mortality. *Clin Obstet Gynecol* 2018; **61:** 387–99.

3 Kuklina EV, Ayala C, Callaghan WM. Hypertensive disorders and severe obstetric morbidity in the United States. *Obstet Gynecol* 2009; **113:** 1299–306.

4 Bucher V, Mitchell AR, Gudmundsson P, et al. Prediction of adverse maternal and perinatal outcomes associated with pre-eclampsia and hypertensive disorders of pregnancy: a systematic review and meta-analysis. *EClinicalMedicine* 2024; **76:** 102861.

5 Bateman BT. What's new in obstetric anesthesia: a focus on maternal morbidity and mortality. *Int J Obstet Anesth* 2019; **37:** 68–72.

6 Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol* 2009; **33:** 130–37.

7 Vogel JP, Souza JP, Mori R, et al. Maternal complications and perinatal mortality: findings of the World Health Organization Multicountry Survey on Maternal and Newborn Health. *BJOG* 2014; **121** (suppl 1): 76–88.

8 Villar J, Giuliani F, Bhutta ZA, et al. Postnatal growth standards for preterm infants: the preterm postnatal follow-up study of the INTERGROWTH-21(st) project. *Lancet Glob Health* 2015; **3:** e681–91.

9 Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health* 2014; **2:** e323–33.

10 Institute for Health Metrics and Evaluation. Global burden of diseases data. Institute for Health Metrics and Evaluation. https://vizhub.healthdata.org/gbd-compare (accessed May 3, 2026).

11 Scott G, Gillon TE, Pels A, von Dadelszen P, Magee LA. Guidelines-similarities and dissimilarities: a systematic review of international clinical practice guidelines for pregnancy hypertension. *Am J Obstet Gynecol* 2022; **226:** S1222–36.

12 Roberts JM, Rich-Edwards JW, McElrath TF, Garmire L, Myatt L, Global Pregnancy Collaboration. Subtypes of preeclampsia: recognition and determining clinical usefulness. *Hypertension* 2021; **77:** 1430–41.

13 Pabon MA, Smith G, Sharma G, et al. Adverse pregnancy outcomes and long-term cardiovascular disease risk. *Lancet* 2026; published online Sept 30. https://doi.org/10.1016/S0140-6736(26)01235-3.

14 Ives CW, Sinkey R, Rajapreyar I, Tita ATN, Oparil S. Preeclampsia—pathophysiology and clinical presentations: JACC state-of-the-art review. *J Am Coll Cardiol* 2020; **76:** 1690–702.

15 Chappell LC, Cluver CA, Kingdom J, Tong S. Pre-eclampsia. *Lancet* 2021; **398:** 341–54.

16 Staff AC, Fjeldstad HE, Fosheim IK, et al. Failure of physiological transformation and spiral artery atherosis: their roles in preeclampsia. *Am J Obstet Gynecol* 2022; **226:** S895–906.

17 Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. *Am J Obstet Gynecol* 2013; **209:** 544.e1–12.

18 Redman CW, Staff AC. Preeclampsia, biomarkers, syncytiotrophoblast stress, and placental capacity. *Am J Obstet Gynecol* 2015; **213** (suppl): S9.e1–4.

19 Horii M, Morey R, Chousal JN, et al. Clinical and molecular differences of hypertensive disorders during pregnancy. *Arterioscler Thromb Vasc Biol* 2026; **46:** e323457.

20 Gyselaers W. Hemodynamic pathways of gestational hypertension and preeclampsia. *Am J Obstet Gynecol* 2022; **226:** S988–1005.

21 American College of Obstetricians and Gynecologists. Gestational hypertension and preeclampsia: ACOG practice bulletin, number 222. *Obstet Gynecol* 2020; **135:** e237–60.

22 Maynard SE, Min JY, Merchan J, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest* 2003; **111:** 649–58.

23 Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med* 2004; **350:** 672–83.

24 Ashar-Patel A, Kaymaz Y, Rajakumar A, Bailey JA, Karumanchi SA, Moore MJ. FLT1 and transcriptome-wide polyadenylation site (PAS) analysis in preeclampsia. *Sci Rep* 2017; **7:** 12139.

25 Cerdeira AS, Kandzija N, Pargmae P, et al. Circulating soluble fms-like tyrosine kinase-1 is placentally derived in normal pregnancy: first in vivo evidence. *Pregnancy Hypertens* 2019; **16:** 145–47.

26 Zeisler H, Llurba E, Chantraine F, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. *N Engl J Med* 2016; **374:** 13–22.

27 Rana S, Salahuddin S, Mueller A, Berg AH, Thadhani RI, Karumanchi SA. Angiogenic biomarkers in triage and risk for preeclampsia with severe features. *Pregnancy Hypertens* 2018; **13:** 100–06.

28 Dröge LA, Perschel FH, Stütz N, et al. Prediction of preeclampsia-related adverse outcomes with the sFlt-1 (soluble fms-like tyrosine kinase 1)/PlGF (placental growth factor)-ratio in the clinical routine: a real-world study. *Hypertension* 2021; **77:** 461–71.

29 Hastie R, Bergman L, Walker SP, et al. Associations between soluble fms-like tyrosine kinase-1 and placental growth factor and disease severity among women with preterm eclampsia and preeclampsia. *J Am Heart Assoc* 2022; **11:** e024395.

30 Moslehi JJ. Cardiovascular toxic effects of targeted cancer therapies. *N Engl J Med* 2016; **375:** 1457–67.

31 Cohen JB, Brown NJ, Brown SA, et al. Cancer therapy-related hypertension: a scientific statement from the American Heart Association. *Hypertension* 2023; **80:** e46–57.

32 Eremina V, Jefferson JA, Kowalewska J, et al. VEGF inhibition and renal thrombotic microangiopathy. *N Engl J Med* 2008; **358:** 1129–36.

33 Bartsch E, Medcalf KE, Park AL, Ray JG, High Risk of Pre-eclampsia Identification Group. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. *BMJ* 2016; **353:** i1753.

34 Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ* 2005; **330:** 565.

35 Villa PM, Marttinen P, Gillberg J, et al. Cluster analysis to estimate the risk of preeclampsia in the high-risk Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (PREDO) study. *PLoS One* 2017; **12:** e0174399.

36 Geberu DM, Abera KM, Tsega Y, et al. Pooled prevalence and factors of overweight/obesity among women of reproductive age in low and middle-income countries with high maternal mortality: a multi-level analysis of recent demographic and health surveys. *PLoS One* 2025; **20:** e0316962.

37 Arechvo A, Voicu D, Gil MM, Syngelaki A, Akolekar R, Nicolaides KH. Maternal race and pre-eclampsia: cohort study and systematic review with meta-analysis. *BJOG* 2022; **129:** 2082–93.

38 Snowden JM, Mission JF, Marshall NE, et al. The impact of maternal obesity and race/ethnicity on perinatal outcomes: independent and joint effects. *Obesity* 2016; **24:** 1590–98.

39 Johnson JD, Louis JM. Does race or ethnicity play a role in the origin, pathophysiology, and outcomes of preeclampsia? An expert review of the literature. *Am J Obstet Gynecol* 2022; **226:** S876–85.

40 Febles M, Scott G, Gillon T, et al. Hypertensive disorders of pregnancy: a systematic review of international clinical practice guidelines. *Am J Obstet Gynecol* 2026; published online March 3. https://doi.org/10.1016/j.ajog.2026.02.042.

41 Goadsby J, Syngelaki A, Magee LA, et al. Scheduled birth at term for the prevention of pre-eclampsia (PREVENT-PE): an open-label randomised controlled trial. *Lancet* 2026; **407:** 67–77.

42 Chaemsaithong P, Pooh RK, Zheng M, et al. Prospective evaluation of screening performance of first-trimester prediction models for preterm preeclampsia in an Asian population. *Am J Obstet Gynecol* 2019; **221:** 650.e1–16.

43 Poon LC, Rolnik DL, Tan MY, et al. ASPRE trial: incidence of preterm pre-eclampsia in patients fulfilling ACOG and NICE criteria according to risk by FMF algorithm. *Ultrasound Obstet Gynecol* 2018; **51:** 738–42.

44 Diao S, Feng Y, Yang N, et al. Inconsistencies in recommendations for the preventive management of pre-eclampsia and quality assessment of international guidelines: a systematic review. *BMC Pregnancy Childbirth* 2026; **26:** 238.

45 Yang Y, Le Ray I, Zhu J, Zhang J, Hua J, Reilly M. Preeclampsia prevalence, risk factors, and pregnancy outcomes in Sweden and China. *JAMA Netw Open* 2021; **4:** e218401.

46 Tan MY, Wright D, Syngelaki A, et al. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. *Ultrasound Obstet Gynecol* 2018; **51:** 743–50.

47 Riishede I, Rode L, Sperling L, et al. Pre-eclampsia screening in Denmark (PRESIDE): national validation study. *Ultrasound Obstet Gynecol* 2023; **61:** 682–90.

48 Guerby P, Audibert F, Johnson JA, et al. Prospective validation of first-trimester screening for preterm preeclampsia in nulliparous women (PREDICTION Study). *Hypertension* 2024; **81:** 1574–82.

49 Cuenca-Gómez D, de Paco Matallana C, Rolle V, et al. Performance of first-trimester combined screening for preterm pre-eclampsia: findings from cohort of 10 110 pregnancies in Spain. *Ultrasound Obstet Gynecol* 2023; **62:** 522–30.

50 Tiruneh SA, Rolnik DL, Selvaratnam R, et al. External validation of the Fetal Medicine Foundation model for preterm pre-eclampsia prediction at 11–14 weeks in an Australian population. *Acta Obstet Gynecol Scand* 2025; **104:** 1774–82.

51 Martins JG, Miller E, Aboukhater D, Bittner M, Rolnik DL, Kawakita T. Performance of a first-trimester combined screening for preterm preeclampsia in the United States population using the fetal medicine foundation competing risks model. *Am J Obstet Gynecol MFM* 2025; **7:** 101803.

52 Tiruneh SA, Vu TTT, Moran LJ, et al. Externally validated prediction models for pre-eclampsia: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2024; **63:** 592–604.

53 Santorelli G, Lawlor DA, West J, Tuffnell D, Farrar D. Population reference and healthy standard blood pressure range charts in pregnancy: findings from the Born in Bradford cohort study. *Sci Rep* 2019; **9:** 18847.

54 Waage CW, Mdala I, Jenum AK, Michelsen TM, Birkeland KI, Sletner L. Ethnic differences in blood pressure from early pregnancy to postpartum: a Norwegian cohort study. *J Hypertens* 2016; **34:** 1151–59.

55 Pokaprakarn T, Prieto JC, Price JT, et al. AI estimation of gestational age from blind ultrasound sweeps in low-resource settings. *NEJM Evid* 2022; published online March 28. https://doi.org/10.1056/EVIDoa2100058.

56 Nathan HL, Boene H, Munguambe K, et al. The CRADLE vital signs alert: qualitative evaluation of a novel device designed for use in pregnancy by healthcare workers in low-resource settings. *Reprod Health* 2018; **15:** 5.

57 Kuhrt K, Mabula-Bwalya C, Boulding H, et al. A novel approach to expedite evidence to impact in pre-eclampsia: co-developed policy labs in Zambia and Sierra Leone. *BMC Glob Public Health* 2025; **3:** 3.

58 Elbarbary N, Pritsini F, Kazi A, Wang C, Thilaganathan B, Bhide A. Point-of-care tests for preeclampsia: systematic review and meta-analysis of diagnostic test accuracy studies. *BJOG* 2025; **132:** 414–25.

59 Kuhrt K, Cole R, M'Bayoh M, et al. Point-of-care placental growth factor for predicting adverse outcomes in Sierra Leone. *Hypertension* 2025; **82:** 1719–28.

60 Di Renzo GC, Arduini M, Bartha JL, et al. Clinical utility of a glycosylated fibronectin test (Lumella) for assessment of impending preeclampsia. *J Matern Fetal Neonatal Med* 2025; **38:** 2474674.

61 Kesireddy S, Reddy P, Gayathri V, Reddy P, Reddy B. Glycosylated fibronectin point-of-care test for triage and surveillance of hypertension in pregnancy cases: a retrospective observational case control study. *J Obstet Gynecol India* 2022; **72** (suppl 1)**:** 121–25.

62 Chen Z, Li W, Li C, et al. Smartphone dual-channel biosensor for simultaneous PLGF/sFlt-1 detection and signaling pathway analysis. *Small* 2025; **21:** e03452.

63 Minckas N, Swarray-Deen A, Fawcus S, et al. Formative research to optimize pre-eclampsia risk-screening and prevention (PEARLS): study protocol. *Reprod Health* 2025; **22:** 44.

64 McDougall ARA, Fawcus S, Tamatey AA, et al. Protocol for a prospective cohort study on pre-eclampsia risk prediction in Ghana, Kenya and South Africa. *Reprod Health* 2025; **22:** 209.

65 Litwinska M, Litwinska E, Astudillo A, Syngelaki A, Wright A, Nicolaides KH. Stratification of pregnancy care based on risk of pre-eclampsia derived from biophysical and biochemical markers at 19–24 weeks' gestation. *Ultrasound Obstet Gynecol* 2021; **58:** 360–68.

66 Panaitescu A, Ciobanu A, Syngelaki A, Wright A, Wright D, Nicolaides KH. Screening for pre-eclampsia at 35–37 weeks' gestation. *Ultrasound Obstet Gynecol* 2018; **52:** 501–06.

67 Koopmans CM, Bijlenga D, Groen H, 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. *Lancet* 2009; **374:** 979–88.

68 Nabweyambo S, Sande OJ, McGovern N, et al. Circulating levels of angiogenic factors and their association with preeclampsia among pregnant women at Mulago National Referral Hospital in Uganda. *PLoS One* 2021; **16:** e0251227.

69 March MI, Geahchan C, Wenger J, et al. Circulating angiogenic factors and the risk of adverse outcomes among Haitian women with preeclampsia. *PLoS One* 2015; **10:** e0126815.

70 Chappell LC, Duckworth S, Seed PT, et al. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. *Circulation* 2013; **128:** 2121–31.

71 Cerdeira AS, O'Sullivan J, Ohuma EO, et al. Randomized interventional study on prediction of preeclampsia/eclampsia in women with suspected preeclampsia: INSPIRE. *Hypertension* 2019; **74:** 983–90.

72 Duhig KE, Myers J, Seed PT, 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:** 1807–18.

73 Carlsson Y, Sandström A, Bergman L, et al. Comparing the results from a Swedish pregnancy cohort using data from three automated placental growth factor immunoassay platforms intended for first-trimester preeclampsia prediction. *Acta Obstet Gynecol Scand* 2023; **102:** 1084–91.

74 McCarthy FP, Gill C, Seed PT, Bramham K, Chappell LC, Shennan AH. Comparison of three commercially available placental growth factor-based tests in women with suspected preterm pre-eclampsia: the COMPARE study. *Ultrasound Obstet Gynecol* 2019; **53:** 62–67.

75 Bacmeister L, Goßling A, Buellesbach A, et al. High-sensitivity cardiac troponin I enhances preeclampsia prediction beyond maternal factors and the sFlt-1/PlGF ratio. *Circulation* 2024; **149:** 95–106.

76 Hauspurg A, Marsh DJ, McNeil RB, et al. Association of N-terminal pro-brain natriuretic peptide concentration in early pregnancy with development of hypertensive disorders of pregnancy and future hypertension. *JAMA Cardiol* 2022; **7:** 268–76.

77 Bacmeister L, Buellesbach A, Glintborg D, et al. Third-trimester NT-proBNP for pre-eclampsia risk prediction: a comparison with sFlt-1/PlGF in a population-based cohort. *JACC Adv* 2025; **4:** 101671.

78 Honigberg MC, Truong B, Khan RR, et al. Polygenic prediction of preeclampsia and gestational hypertension. *Nat Med* 2023; **29:** 1540–49.

79 Ardissino M, Nicolaides K, Conti-Ramsden F, et al. Polygenic risk scores for preeclampsia prediction beyond gold-standard clinical models in multiethnic populations. *J Am Heart Assoc* 2025; **14:** e046211.

80 Foo FL, Mahendru AA, Masini G, et al. Association between prepregnancy cardiovascular function and subsequent preeclampsia or fetal growth restriction. *Hypertension* 2018; **72:** 442–50.

81 Wang X, Sahota DS, Wong L, et al. Prediction of pre-eclampsia using maternal hemodynamic parameters at 12 + 0 to 15 + 6 weeks. *Ultrasound Obstet Gynecol* 2025; **65:** 173–82.

82 Moufarrej MN, Vorperian SK, Wong RJ, et al. Early prediction of preeclampsia in pregnancy with cell-free RNA. *Nature* 2022; **602:** 689–94.

83 Adil M, Kolarova TR, Doebley AL, et al. Preeclampsia risk prediction from prenatal cell-free DNA screening. *Nat Med* 2025; **31:** 1312–18.

84 Stanley KE, Thienpont B, Vermeesch JR. Expanding the scope of non-invasive prenatal screening. *Nat Genet* 2025; **57:** 2644–54.

85 Nguyen-Hoang L, Sahota DS, Pooh RK, et al. Validation of the first-trimester machine learning model for predicting pre-eclampsia in an Asian population. *Int J Gynaecol Obstet* 2024; **167:** 350–59.

86 Carr H, Johansson K, Snowden JM, et al. Maternal and interpregnancy factors and risks of first-time preeclampsia in second pregnancy: a Swedish national cohort study. *BJOG* 2026; **133:** 154–64.

87 Doumouras AG, Muraca GM, Darling EK, et al. Maternal, fetal, and infant outcomes associated with bariatric surgery: a matched cohort study. *Ann Surg* 2026; **283:** 634–41.

88 Stephenson J, Heslehurst N, Hall J, et al. Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health. *Lancet* 2018; **391:** 1830–41.

89 Johansson K, Wikström AK, Söderling J, et al. Risk of pre-eclampsia after gastric bypass: a matched cohort study. *BJOG* 2022; **129:** 461–71.

90 Getahun D, Fassett MJ, Jacobsen SJ, et al. Perinatal outcomes after bariatric surgery. *Am J Obstet Gynecol* 2022; **226:** 121.e1–16.

91 Rolnik DL, Syngelaki A, O'Gorman N, Wright D, Poon LC, Nicolaides KH. ASPRE trial: effects of aspirin on mean arterial blood pressure and uterine artery pulsatility index trajectories in pregnancy. *Ultrasound Obstet Gynecol* 2023; **61:** 691–97.

92 Rolnik DL, Syngelaki A, O'Gorman N, Wright D, Nicolaides KH, Poon LC. Aspirin for evidence-based preeclampsia prevention trial: effects of aspirin on maternal serum pregnancy-associated plasma protein A and placental growth factor trajectories in pregnancy. *Am J Obstet Gynecol* 2024; **231:** 342.e1–9.

93 Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev* 2019; **2019:** CD004659.

94 Henderson JT, Vesco KK, Senger CA, Thomas RG, Redmond N. Aspirin use to prevent preeclampsia and related morbidity and mortality: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 2021; **326:** 1192–206.

95 Turner JM, Robertson NT, Hartel G, Kumar S. Impact of low-dose aspirin on adverse perinatal outcome: meta-analysis and meta-regression. *Ultrasound Obstet Gynecol* 2020; **55:** 157–69.

96 Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med* 2017; **377:** 613–22.

97 Hoffman MK, Goudar SS, Kodkany BS, et al. Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a randomised, double-blind, placebo-controlled trial. *Lancet* 2020; **395:** 285–93.

98 Rolnik DL, Tan MY, Syngelaki A, et al. Combined impact of first-trimester risk and aspirin adherence on preterm preeclampsia prevention. *Am J Obstet Gynecol* 2026; **234:** 1759–67.

99 Nguyen-Hoang L, Dinh LT, Tai AST, et al. Implementation of first-trimester screening and prevention of preeclampsia: a stepped wedge cluster-randomized trial in Asia. *Circulation* 2024; **150:** 1223–35.

100 Hastie R, Tong S, Wikström AK, Sandström A, Hesselman S, Bergman L. Aspirin use during pregnancy and the risk of bleeding complications: a Swedish population-based cohort study. *Am J Obstet Gynecol* 2021; **224:** 95.e1–12.

101 Mone F, Mulcahy C, McParland P, et al. Trial of feasibility and acceptability of routine low-dose aspirin versus early screening test indicated aspirin for pre-eclampsia prevention (TEST study): a multicentre randomised controlled trial. *BMJ Open* 2018; **8:** e022056.

102 Souter V, Painter I, Sitcov K, Khalil A. Propensity score analysis of low-dose aspirin and bleeding complications in pregnancy. *Ultrasound Obstet Gynecol* 2024; **63:** 81–87.

103 Jiang Y, Chen Z, Chen Y, et al. Low-dose aspirin use during pregnancy may be a potential risk for postpartum hemorrhage and increased blood loss: a systematic review and meta-analysis. *Am J Obstet Gynecol MFM* 2023; **5:** 100878.

104 Bujold E, Rolnik DL, Poon L, Syngelaki A, Wright D, Nicolaides KH. The effect of aspirin on the risk of preeclampsia based on the Fetal Medicine Foundation first trimester risk. *Am J Obstet Gynecol* 2025.

105 Liu J, Shen L, Nguyen-Hoang L, et al. Aspirin versus metformin in pregnancies at high risk of preterm pre-eclampsia in China (AVERT): protocol for a multicentre, double-blind, 3-arm randomised controlled trial. *BMJ Open* 2024; **14:** e074493.

106 Bujold E, Rolnik DL, Poon L, Syngelaki A, Wright D, Nicolaides KH. Aspirin delays preeclampsia in women with chronic hypertension. *Am J Obstet Gynecol* 2025; **233:** e91–93.

107 Richards EMF, Giorgione V, Stevens O, Thilaganathan B. Low-dose aspirin for the prevention of superimposed preeclampsia in women with chronic hypertension: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2023; **228:** 395–408.

108 Lecarpentier E, Haddad B. Aspirin for the prevention of placenta-mediated complications in pregnant women with chronic hypertension. *J Gynecol Obstet Hum Reprod* 2020; **49:** 101845.

109 Woo Kinshella ML, Sarr C, Sandhu A, et al. Calcium for pre-eclampsia prevention: a systematic review and network meta-analysis to guide personalised antenatal care. *BJOG* 2022; **129:** 1833–43.

110 Cluver CA, Rohwer C, Rohwer AC. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database Syst Rev* 2025; **12:** CD001059.

111 Magro-Malosso ER, Saccone G, Di Tommaso M, Roman A, Berghella V. Exercise during pregnancy and risk of gestational hypertensive disorders: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand* 2017; **96:** 921–31.

112 Davenport MH, Ruchat SM, Poitras VJ, et al. Prenatal exercise for the prevention of gestational diabetes mellitus and hypertensive disorders of pregnancy: a systematic review and meta-analysis. *Br J Sports Med* 2018; **52:** 1367–75.

113 Danielli M, Gillies C, Thomas RC, et al. Effects of supervised exercise on the development of hypertensive disorders of pregnancy: a systematic review and meta-analysis. *J Clin Med* 2022; **11:** 793.

114 Martínez-Vizcaíno V, Sanabria-Martínez G, Fernández-Rodríguez R, et al. Exercise during pregnancy for preventing gestational diabetes mellitus and hypertensive disorders: an umbrella review of randomised controlled trials and an updated meta-analysis. *BJOG* 2023; **130:** 264–75.

115 Prevett C, Gingerich J, Sivak A, Davenport MH. Resistance training in pregnancy: systematic review and meta-analysis of pregnancy, delivery, fetal and pelvic floor outcomes and call to action. *Br J Sports Med* 2025; **59:** 1173–82.

116 Tita AT, Szychowski JM, Boggess K, et al. Treatment for mild chronic hypertension during pregnancy. *N Engl J Med* 2022; **386:** 1781–92.

117 Martin SL, Kuo HC, Boggess K, et al. Effects of antihypertensive therapy during pregnancy on postpartum blood pressure control. *Obstet Gynecol* 2024; **144:** 536–42.

118 Kane SC, Shanmugalingam R, Henry A. Pharmaceuticals in pregnancy: a multifaceted challenge in Australia. *Med J Aust* 2024; **221:** 357–59.

119 Hup RJ, Damen JAA, Terstappen J, et al. Oral antihypertensive treatment during pregnancy: a systematic review and network meta-analysis. *Am J Obstet Gynecol* 2025; **233:** 250–62.

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

121 Pels A, Mol BWJ, Singer J, et al. Influence of gestational age at initiation of antihypertensive therapy: secondary analysis of CHIPS trial data (Control of Hypertension in Pregnancy Study). *Hypertension* 2018; **71:** 1170–77.

122 Boggess K, Leach J, Dugoff L, et al. Relationship between third-trimester low maternal blood pressure and small-for-gestational-age birth weight in pregnant individuals with mild chronic hypertension. *Obstet Gynecol* 2025; **146:** 405–12.

123 Bentley JP, Roberts CL, Bowen JR, Martin AJ, Morris JM, Nassar N. Planned birth before 39 weeks and child development: a population-based study. *Pediatrics* 2016; **138:** e20162002.

124 Kirkham K, Gkini E, Moakes C, et al. Timing of birth to improve outcomes in chronic or gestational hypertension: the WILL RCT. *Health Technol Assess* 2026; **30:** 1–28.

125 Beardmore-Gray A, Seed PT, Fleminger J, et al. Planned delivery or expectant management in preeclampsia: an individual participant data meta-analysis. *Am J Obstet Gynecol* 2022; **227:** 218–230.e8.

126 von Dadelszen P, Payne B, Li J, et al. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. *Lancet* 2011; **377:** 219–27.

127 Payne BA, Hutcheon JA, Ansermino JM, et al. A risk prediction model for the assessment and triage of women with hypertensive disorders of pregnancy in low-resourced settings: the miniPIERS (Pre-eclampsia Integrated Estimate of Risk) multi-country prospective cohort study. *PLoS Med* 2014; **11:** e1001589.

128 Wu MY, Hu PJ, Wong CS, et al. Long-term clinical outcome of major adverse vascular events after hypertensive disorders of pregnancy. *Obstet Gynecol* 2021; **137:** 285–93.

129 Haas DM, Parker CB, Marsh DJ, et al. Association of adverse pregnancy outcomes with hypertension 2 to 7 years postpartum. *J Am Heart Assoc* 2019; **8:** e013092.

130 Countouris M, Mahmoud Z, Cohen JB, et al. Hypertension in pregnancy and postpartum: current standards and opportunities to improve care. *Circulation* 2025; **151:** 490–507.

131 Patten IS, Rana S, Shahul S, et al. Cardiac angiogenic imbalance leads to peripartum cardiomyopathy. *Nature* 2012; **485:** 333–38.

132 Vaught AJ, Kovell LC, Szymanski LM, et al. Acute cardiac effects of severe pre-eclampsia. *J Am Coll Cardiol* 2018; **72:** 1–11.

133 Lopes Perdigao J, Lewey J, Hirshberg A, et al. Furosemide for accelerated recovery of blood pressure postpartum in women with a hypertensive disorder of pregnancy: a randomized controlled trial. *Hypertension* 2021; **77:** 1517–24.

134 Trawick Roberts E, Quist-Nelson J, Brotkin EJ, et al. Postpartum diuretics for hypertensive disorders of pregnancy: a systematic review and meta-analysis. *Obstet Gynecol* 2025; **146:** 500–14.

135 Tol ID, Khalil A, Cairns AE, et al. Postpartum management of the hypertensive disorders of pregnancy: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2025; **234:** 1593–603.

136 Kitt J, Fox R, Frost A, et al. Long-term blood pressure control after hypertensive pregnancy following physician-optimized self-management: the POP-HT randomized clinical trial. *JAMA* 2023; **330:** 1991–99.

137 Kitt J, Krasner S, Barr L, et al. Cardiac remodeling after hypertensive pregnancy following physician-optimized blood pressure self-management: the POP-HT randomized clinical trial imaging substudy. *Circulation* 2024; **149:** 529–41.

138 Ormesher L, Higson S, Luckie M, et al. Postnatal Enalapril to Improve Cardiovascular Function Following Preterm Preeclampsia (PICk-UP): a randomized double-blind placebo-controlled feasibility trial. *Hypertension* 2020; **76:** 1828–37.

139 Kitt JA, Fox RL, Cairns AE, et al. Short-term postpartum blood pressure self-management and long-term blood pressure control: a randomized controlled trial. *Hypertension* 2021; **78:** 469–79.

140 van Oostwaard MF, Langenveld J, Schuit E, et al. Recurrence of hypertensive disorders of pregnancy: an individual patient data metaanalysis. *Am J Obstet Gynecol* 2015; **212:** 624.e1–17.

141 Shanmugalingam R, Barrett HL, Beech A, et al. A summary of the 2023 Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) hypertension in pregnancy guideline. *Med J Aust* 2024; **220:** 582–91.

142 Satoh M, Tatsumi Y, Nakayama S, et al. Self-measurement of blood pressure at home using a cuff device for change in blood pressure levels: systematic review and meta-analysis. *Hypertens Res* 2025; **48:** 574–91.

143 Tucker KL, Mort S, Yu LM, 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:** 1656–65.

144 Chappell LC, Tucker KL, Galal U, 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:** 1666–78.

145 WHO. Digital adaptation kit for self-monitoring of blood pressure during pregnancy: operational requirements for implementing WHO recommendations in digital systems. World Health Organization, 2025.

146 Vousden N, Lawley E, Nathan HL, et al. Effect of a novel vital sign device on maternal mortality and morbidity in low-resource settings: a pragmatic, stepped-wedge, cluster-randomised controlled trial. *Lancet Glob Health* 2019; **7:** e347–56.

147 Ridout AE, Moses FL, Herm-Singh S, et al. Evaluating the real-world scale-up of the CRADLE Vital Signs Alert intervention into routine maternity care in Sierra Leone (CRADLE-5): a stepped-wedge, type 2 hybrid implementation–effectiveness, cluster-randomised controlled trial. *Lancet Obstet Gynaecol Womens Health* 2025; **1:** e270–80.

148 Mahmoud Z, Crook L, Onyia C, et al. Aspirin prophylaxis for preeclampsia prevention in Nigeria: an explanatory sequential mixed methods study. *J Am Coll Cardiol* 2025; **86:** 2248–59.