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Primer

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Pre-eclampsia

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Abstract

Pre-eclampsia is a life-threatening disease of pregnancy unique to humans and a leading cause of maternal and neonatal morbidity and mortality. Women who survive pre-eclampsia have reduced life expectancy, with increased risks of stroke, cardiovascular disease and diabetes, while babies from a pre-eclamptic pregnancy have increased risks of preterm birth, perinatal death and neurodevelopmental disability and cardiovascular and metabolic disease later in life. Pre-eclampsia is a complex multisystem disease, diagnosed by sudden-onset hypertension (>20 weeks of gestation) and at least one other associated complication, including proteinuria, maternal organ dysfunction or uteroplacental dysfunction. Pre-eclampsia is found only when a placenta is or was recently present and is classified as preterm (delivery <37 weeks of gestation), term (delivery ≥37 weeks of gestation) and postpartum pre-eclampsia. The maternal syndrome of pre-eclampsia is driven by a dysfunctional placenta, which releases factors into maternal blood causing systemic inflammation and widespread maternal endothelial dysfunction. Available treatments target maternal hypertension and seizures, but the only 'cure' for pre-eclampsia is delivery of the dysfunctional placenta and baby, often prematurely. Despite decades of research, the aetiology of pre-eclampsia, particularly of term and postpartum pre-eclampsia, remains poorly defined. Significant advances have been made in the prediction and prevention of preterm pre-eclampsia, which is predicted in early pregnancy through combined screening and is prevented with daily low-dose aspirin, starting before 16 weeks of gestation. By contrast, the prediction of term and postpartum pre-eclampsia is limited and there are no preventive treatments. Future research must investigate the pathogenesis of pre-eclampsia, in particular of term and postpartum pre-eclampsia, and evaluate new prognostic tests and treatments in adequately powered clinical trials.

Sections

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Introduction

Pre-eclampsia is a complex multisystem disease, diagnosed by sudden-onset hypertension (>20 weeks of gestation) and at least one other associated complication, including proteinuria, maternal organ dysfunction or uteroplacental dysfunction (for example, fetal growth restriction (FGR) or angiogenic imbalance). Pre-eclampsia is one of the most severe complications of pregnancy and a leading cause of maternal and perinatal morbidity and mortality[1]. Worldwide, an estimated 4 million women are diagnosed with pre-eclampsia (previously called toxaemia) each year, causing the deaths of >70,000 women and 500,000 babies[1,2]. Women who survive pre-eclampsia have reduced life expectancy, with increased risks of stroke, cardiovascular disease and diabetes[1,3,4], while babies from a pre-eclamptic pregnancy have increased risks of preterm birth, perinatal death, neurodevelopmental delay, and cardiovascular and metabolic disease later in life[1,3]. Worldwide, >300 million women and children are estimated to be at increased risk of chronic health problems due to previous exposure to pre-eclampsia[5].

Pre-eclampsia is classified based on the gestational age at clinical presentation (Box 1). The International Society for the Study of Hypertension in Pregnancy (ISSHP) classifies pre-eclampsia into preterm (delivery <37 weeks of gestation), term (delivery ≥37 weeks of gestation) and postpartum pre-eclampsia[2]. Classifications of early-onset (delivery at <34 weeks of gestation) pre-eclampsia and late-onset (delivery at ≥34 weeks of gestation) pre-eclampsia are also used, particularly for mechanistic studies, although these are not favoured clinically as they do not adequately reflect the maternal and fetal prognosis. The terms preterm, term, early-onset and late-onset are used throughout this Primer to precisely reflect the study populations from which the data was obtained. The time of pre-eclampsia onset is thought to reflect an underlying difference in the aetiology. This is supported by differences in the efficacy of early pregnancy pre-eclampsia prediction tests[6] and preventive aspirin prophylaxis, which show utility for preterm but not term pre-eclampsia[7]. However, it is also clear that basing classification on the time of diagnosis carries inherent imprecision[8], particularly associated with the variation in disease progression and the timing of presentation to hospital for diagnosis. A recent retrospective population-based study determined that classifying pre-eclampsia on delivery timing alone may underestimate early-onset pre-eclampsia incidence by up to 20%[9]. While the clinical impact of this underestimation may be negligible, correct classification based on time of onset in research studies may improve the development of new predictive tests and preventive treatments.

Whether pre-eclampsia can be classified based on symptoms is unresolved. Pre-eclampsia is associated with complications such as eclampsia (seizures), haemorrhagic stroke, haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome, placental abruption, renal failure, and pulmonary oedema[10,11] (Fig. 1). All women with pre-eclampsia are at risk of rapid deterioration and severe disease regardless of the timing of onset[2,8,12]; thus, ISSHP guidelines[2,13] no longer support the classification of 'severe' or 'mild' pre-eclampsia in ongoing pregnancies. HELLP syndrome (Box 1) or eclampsia may be severe subtypes of pre-eclampsia with principally hepatic or neurological involvement, respectively[8].

In this Primer, we summarize current knowledge of the epidemiology, risk factors, pathophysiology, clinical presentation, diagnosis, prediction, management and outcomes of pre-eclampsia. We also discuss patient quality of life and the outstanding research questions aimed at improving clinical practice and understanding the aetiology of pre-eclampsia.

Epidemiology

Incidence and mortality

The global prevalence of all pre-eclampsia in the years 2002–2010 was estimated at 4.6% of deliveries but reported regional rates varied between 1% and 5.6%[14]. Where reported, the prevalence of preterm pre-eclampsia is <1%[15–18]. The prevalence of pre-eclampsia is generally reported as lower in low-income and middle-income countries (LMICs) (except sub-Saharan Africa) than in high-income countries (HICs)[19,20]; however, it is likely that differences in classification, access to prenatal care and under-reporting in LMICs affect prevalence data[20,21]. Furthermore, most pre-eclampsia research is performed in HICs, potentially leading to bias and generalizability concerns in the populations sampled and the research questions asked.

Hypertensive disorders of pregnancy (including pre-eclampsia) are the second most common cause (behind haemorrhage) of maternal

Box 1

Classification of pre-eclampsia

Based on gestational age at clinical presentation

International Society for the Study of Hypertension in Pregnancy definition

- Preterm (<37 weeks of gestation)
- Term (≥37 weeks of gestation)
- Postpartum (diagnosed after delivery)

Based on symptoms

Symptom severity[a]

- Severe: blood pressure >160/110 mmHg and at least one other condition, including haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome or fetal growth restriction <tenth percentile
- Mild: blood pressure >140/90 mmHg, and at least one other condition, including proteinuria (urine protein to creatinine ratio ≥30 mg/mmol, albumin to creatinine ratio ≥8 mg/mmol) or 24-h urine collection ≥0.3 g/day

Eclampsia

- Severe complication of pre-eclampsia characterized by new onset multifocal, focal or tonic–clonic seizure activity or unexplained coma during pregnancy or postpartum

HELLP syndrome

- Severe complication of pre-eclampsia characterized by haemolysis, elevated liver enzymes and low platelet count (lactate dehydrogenase ≥600 IU/l; aspartate aminotransferase >70 IU/l; platelet count <150,000 cells/μl)[350]

Also commonly used

Early onset (<34 weeks of gestation) and late onset (≥34 weeks of gestation)

[a]Classifying by severity of symptoms in this way is not recommended for use in ongoing pregnancies but may be used in research.

deaths worldwide (14% of deaths, 95% CI 11.4–17.4), causing an estimated 62,000–77,000 deaths per year[22,23]. Maternal mortality is higher in a pre-eclamptic pregnancy than in a non-pre-eclamptic pregnancy (adjusted odds ratio (aOR) 3.73, 95% CI 2.15–6.47)[20]. The risk of fetal death in pre-eclamptic pregnancies is higher than that in non-pre-eclamptic pregnancies (aOR 3.12, 95% CI 2.77–3.51)[20] as a result of FGR and placental abruption. High rates of medically indicated preterm birth also result in an increase in neonatal deaths, which are 2.7 times higher (aOR 2.7, 95% CI 2.28–3.21) than in pregnancies resulting in a term birth[20].

Risk factors

There are many risk factors identified as associated with pre-eclampsia (Table 1); however, individually, none of these has strong power to predict pre-eclampsia risk and, even in combination, their predictive power is weak[24]. Recognized high-risk factors are broadly similar among ISSHP[2], American College of Obstetricians and Gynecologists (ACOG)[25] and National Institute for Health and Care Excellence (NICE)[26] guidelines and include obstetric history (for example, previous pre-eclampsia, multiple pregnancy (ACOG only)) and maternal factors (for example, chronic renal disease, chronic hypertension, diabetes mellitus, systemic lupus erythematosus (SLE), antiphospholipid syndrome). Only ISSHP classifies BMI >30 kg/m^2 and assisted reproductive technologies as high-risk factors. A recent comparison of clinical practice guidelines and evidence supporting these risk factors found that many guidelines had a lack of close alignment between the risk factors and the evidence supporting them[24]. Furthermore, these guidelines are mostly produced in HICs; thus, they do not include factors important to LMICs such as access to health-care providers/clinical instrumentation to perform tests and risk-factors particular to LMICs including adolescence, malaria or anaemia[24,27]. Moreover, few models are validated in low-resource settings[24,27].

Genetic risk factors. Recognition that eclampsia was commonly reported in mothers, sisters and daughters suggests genetic involvment[28]; yet, to date, no single high-risk gene has been identified. Population-wide and large cohort studies confirm that maternal family history of pre-eclampsia increases pre-eclampsia risk by threefold to fourfold[29–33]. This association is stronger for preterm pre-eclampsia (risk ratio (RR) 2.15, 95% CI 1.69–2.73) than for term pre-eclampsia (RR 1.49, 95% CI 1.4–1.58)[32]. There are multiple maternal and fetal gene alleles and mutations associated with pre-eclampsia[33–39], possibly reflecting the syndromic nature of this disease. Many of these identified genes are associated with thrombophilic factors[34–37], angiogenic factors[33,40] or immune responses[38,39]. Fetal trisomy 13 is also associated with increased risk of pre-eclampsia likely due to the extra copy of *FLT1* (encoding Fms-related receptor tyrosine kinase 1; FLT1), which is located on chromosome 13 (ref. [41]).

Women lacking the activating *KIR* (killer-cell immunoglobulin-like receptor; AA genotype) have a much greater risk of pre-eclampsia when the fetus expresses the HLA-C2 genotype, a major histocompatibility complex (MHC) class I factor expressed on the cell surface that has a dimorphism at position 80 (ref. [39]). The KIR family are expressed on natural killer (NK) cells and interact with paternal HLA-C expressed on the trophoblast cell surface to control invasion and fetal vascular supply. Individuals with an AA genotype do not express activating receptors and may, therefore, have poor trophoblast invasion of the maternal uterine arteries and placental development.

A genome-wide association meta-analysis of European and Central Asian mothers and offspring[33] identified three sequence variants associated with pre-eclampsia: one in the *FLT1* gene of individuals born of pre-eclamptic pregnancies and two in the *FTO* (encoding α-ketoglutarate-dependent dioxygenase) and *ZNF831* (encoding zinc finger protein 831) genes in women with pre-eclamptic pregnancies[33]. The soluble form of FLT1 (sFLT1) is a placental-released anti-angiogenic factor used in diagnostic tests for pre-eclampsia[42]. Variants in *FTO* and *ZNF831* have previously been associated with blood pressure[43,44], obesity, BMI and type 2 diabetes[45]. However, the causality of these associations and the clinical utility of identifying such changes are yet to be examined in larger studies.

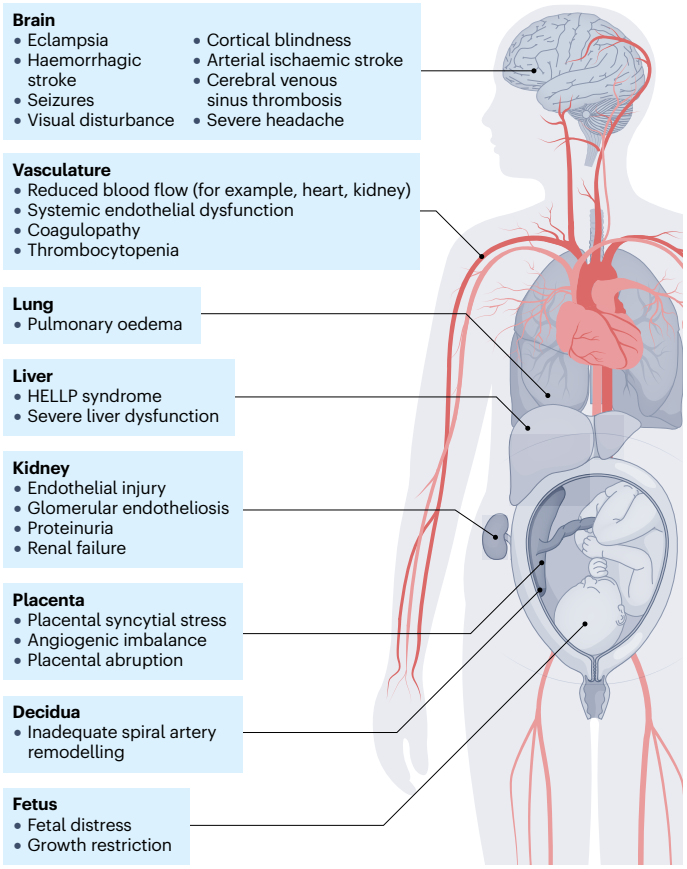

Fig. 1 | Organs affected by pre-eclampsia. Pre-eclampsia affects the fetus and multiple maternal tissues. Pre-eclampsia is defined as new-onset hypertension after 20 weeks of gestation in a patient with previous normotension plus one other symptom of maternal organ dysfunction, which can include kidney, lung, brain, liver or placental dysfunction. Pre-eclampsia is associated with complications such as eclampsia, haemorrhagic stroke, haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome, placental abruption, renal failure and pulmonary oedema.

Racial disparities. Caution is required when interpreting studies that investigate pre-eclampsia risk associated with racial background as many do not correctly account for possible mediators and confounding factors, including health-care disparities and differing cardiovascular profiles. In epidemiological studies, Black women and women of South Asian origin have a higher risk of developing pre-eclampsia than white women, even when accounting for social deprivation[17,46–48] and

Table 1 | Risk assessment checklists from ISSHP[2], ACOG[25] and NICE[26]

Risk factor level	ISSHP	ACOG	NICE
High-risk factors	Previous pre-eclampsia	Previous pre-eclampsia	Previous pre-eclampsia
	Chronic renal disease	Chronic renal disease	Chronic renal disease
	Chronic hypertension	Chronic hypertension	Chronic hypertension
	Diabetes mellitus	Diabetes mellitus	Diabetes mellitus
	SLE or APS	SLE or APS	SLE or APS
	Body mass index ≥30 kg/m^2	–	–
	Assisted reproductive therapy	–	–
	–	Multiple pregnancy	–
Moderate-risk factors	First pregnancy	First pregnancy	First pregnancy
	Age ≥40 years	Age ≥40 years	Age ≥35 years
	Multifetal pregnancy	–	–
	Prior placental abruption	–	–
	Prior stillbirth	–	–
	Prior fetal growth restriction	–	–
	–	Body mass index ≥35 kg/m^2	Body mass index ≥30 kg/m^2
	–	Inter-pregnancy interval >10 years	Inter-pregnancy interval >10 years
	–	Family history of pre-eclampsia	Family history of pre-eclampsia
	–	–	Black ethnicity
	–	–	Low socioeconomic status

ACOG, American College of Obstetricians and Gynecologists; APS, antiphospholipid syndrome; ISSHP, International Society for the Study of Hypertension in Pregnancy; NICE, National Institute for Health and Care Excellence; SLE, systemic lupus erythematosus.

increased risk of chronic hypertension and cardiovascular disease[49–51]. In a large cohort study involving >168,000 women with singleton pregnancies in the UK, Black women had twice the risk of developing pre-eclampsia at any stage of gestation than white women[52]. This association was strongest for early-onset (3.5-fold) and preterm (2.5-fold) pre-eclampsia[52]. Women of South Asian origin had a 1.5-fold higher risk of preterm pre-eclampsia than white women, but there was no association when all pre-eclampsia was measured[52]. In women of East Asian origin, there was no significant difference in risk of pre-eclampsia or hypertensive disorders[52]. This study adjusted for mediators and confounding factors in maternal characteristics and medical history. First-trimester screening following the Fetal Medicine Foundation algorithm improves perinatal outcomes in the non-white population by 60%[53], suggesting that health disparity is avoidable with personalized risk assessment and correct care pathway allocation.

Maternal age. The relationship between pre-eclampsia risk and maternal age follows a J-shaped curve, with increased risk in adolescents and in women older than 35 years of age[54–56]. Advanced maternal age (≥35 years) is associated with an increased risk of pre-existing cardiometabolic dysfunction and medical disorders, multiple pregnancies, and use of artificial reproductive technologies, all of which increase the risk of pre-eclampsia. It has been reported that the risk of pre-eclampsia increases for every additional year after the age of 32 years[56], even after adjustment for mediators, confounders and interactions[55]. Mothers <20 years old may be at increased risk due to a combination of obstetric, immunological and socioeconomic factors, including primiparity and access to prenatal care. Maternal age younger than 20 years is mainly associated with late-onset pre-eclampsia (≥34 weeks of gestation)[57].

Pre-existing maternal medical conditions. Pre-existing medical conditions may increase the risk of developing hypertensive disease in pregnancy, including pre-eclampsia. Many of these risk factors can be identified before or during early pregnancy, enabling interventions to modify the risk of later developing pre-eclampsia.

Chronic hypertension (or hypertension diagnosed <20 weeks of gestation) is associated with a fivefold increase in the risk of pre-eclampsia compared with normotension[58]. Treatment of even mild chronic hypertension with antihypertensive medication from before or in early pregnancy reduces the risk of developing pre-eclampsia by 18% (adjusted RR 0.82, 95% CI 0.74–0.92)[59].

Pre-pregnancy BMI >30 kg/m^2 confers a twofold to fourfold increase in the risk of pre-eclampsia[30,56,60] and there is a higher prevalence of late-onset pre-eclampsia among women with overweight and obesity[61–63]. This is likely, in part, due to the association of pre-eclampsia with obesity and cardiometabolic dysfunction[64]. While weight loss during pregnancy is not recommended, antenatal lifestyle modifications are important to minimize weight gain and reduce the risk of pre-eclampsia. A meta-analysis demonstrated that exercise-only interventions during pregnancy significantly reduced the odds of developing pre-eclampsia (OR 0.59, 95% CI 0.37–0.90)[65].

The risk of developing pre-eclampsia in women with pre-gestational diabetes mellitus is more than three times higher than in women without diabetes mellitus[30,66]. These women might have existing microvascular and macrovascular complications of diabetes, including renal

disease, which contributes to this risk. Diabetes can also increase oxidative stress, inflammation and endothelial dysfunction, a shared pathway with the development of pre-eclampsia[67].

Women with pre-eclampsia are three times more likely to have chronic kidney disease than the general population[68], with some evidence that women with chronic kidney disease are more likely to develop late-onset than early-onset pre-eclampsia[57]. Glomerulonephritis, diabetic kidney disease and polycystic kidney disease are commonly associated with an increased risk[68]. The severity of kidney disease and degree of proteinuria are important predictors of the risk of developing pre-eclampsia, even in the absence of associated pathologies, including chronic hypertension.

Thyroid dysfunction before and during pregnancy is associated with an increased risk of pre-eclampsia[69]. Untreated overt hypothyroidism and hyperthyroidism have a high risk of pre-eclampsia[70], which may be reduced by treatment with thyroxine replacement[71] or antithyroid drugs, respectively[72]. Treating subclinical hypothyroidism is controversial and not associated with a reduction in pre-eclampsia[73] and subclinical hyperthyroidism is not associated with pre-eclampsia[69].

Pre-eclampsia risk is increased in SLE and antiphospholipid syndrome, particularly in the active disease state, indicated by the presence of lupus nephritis in SLE (OR 2.84, 95% CI 1.87–4.30) or of lupus anticoagulant (OR 2.45, 95% CI 1.18–4.64) or anticardiolipin antibodies (OR 1.52, 95% CI 1.05–2.20) in antiphospholipid syndrome[2,74–82]. Adequate treatment and conception in the absence of active disease are associated with a reduction in the risk of pre-eclampsia.

Disrupted gut microbiota profiles have been identified in women with pre-eclampsia, with changes persisting up to 6 weeks postpartum[83,84]. A disrupted gut microbiota has also been linked to other diseases that are risk factors for pre-eclampsia, including obesity and metabolic disorders[84].

Obstetric history. Primiparity is associated with a threefold increase in the likelihood of developing pre-eclampsia[30]. It is proposed that one mechanism by which pre-eclampsia arises is due to immune maladaptation and a maternal alloimmune reaction triggered by rejection of paternal antigens on the fetal allograft[85]. This response is greatest in the first pregnancy; hence, primiparous mothers are more likely to develop pre-eclampsia[57], whereas multiparity is protective and reduces the risk of pre-eclampsia[86]. This protective effect is lost when a subsequent pregnancy involves exposure to new paternally inherited antigens[87]. Epidemiological studies have shown an increase in the risk of pre-eclampsia with increasing inter-pregnancy interval, equivalent to that of primiparity, when the interval is >10 years[58,88]. This hypothesis is also consistent with the finding that women who conceived by in vitro fertilization (IVF) or intrauterine insemination using donor gametes are at significantly higher risk than those who undergo IVF with autologous egg or partner sperm[89,90].

Multiple fetal pregnancies are associated with a significantly higher rate of pre-eclampsia (OR 2.93, 95% CI 2.04–4.21) than singleton pregnancies, with the rate increasing with the number of fetuses present[30]. Neither chorionicity nor zygosity alters the risk, although the rate may be underestimated in monochorionic pregnancies, which are likely to be electively delivered preterm for fetal indications, unlike dichorionic pregnancies, which are mostly delivered at term[91].

A previous pre-eclamptic pregnancy increases the risk of recurrence in subsequent pregnancies by sevenfold to tenfold[92–95]. Recurrence risk is more strongly associated with a previous pregnancy complicated by early-onset pre-eclampsia rather than with previous pregnancy complicated by late-onset pre-eclampsia, with gestation time at recurrence often being weeks later in subsequent pregnancies[57,62]. A meta-analysis including data from 94 studies reported a risk of recurrence of 13.8%, inversely related to gestational age at delivery in the previous pregnancy affected by pre-eclampsia[96,97].

Previous pregnancies complicated by FGR, placental abruption and stillbirth increase the risk of pre-eclampsia, especially when previously associated with early-onset pre-eclampsia or evidence of placental malperfusion[57]. There is limited evidence linking pre-eclampsia to previous ectopic pregnancy; however, one national cohort study in Scotland (1981–2000) identified a higher risk of developing pre-eclampsia in women who had an ectopic first pregnancy than in women who had a live birth[98]. There is no evidence suggesting that a previous history of early pregnancy loss or termination is associated with pre-eclampsia[57,60,99,100].

Conception by IVF, intracytoplasmic sperm injection or egg donation increases the risk of pre-eclampsia compared with pregnancies conceived naturally or via intrauterine insemination; the risk is even higher with frozen-thawed embryo transfer cycles than with fresh cycles[101]. This may be because of impaired vascular health and maternal adaptation to pregnancy in women who lack a corpus luteum at conception[102–104]. Hormonal treatments are often given to women undergoing frozen-thawed embryo transfer, which suppress the pituitary–ovarian axis, resulting in the absence of corpora lutea[102,103]. Additionally, differences in the hormonal preparation of the endometrium before a frozen-thawed cycle may have a detrimental effect on maternal adaptation to pregnancy[104], including abnormal decidualization (formation of the decidua)[105]. Single embryo transfer also reduces the risk of a multiple pregnancy, thus reducing the risk of pre-eclampsia.

Since the COVID-19 pandemic, there has been data to suggest a link between SARS-CoV-2 infection in pregnancy and an increased risk of developing pre-eclampsia. Some systematic reviews found an increase in risk when collating data from different cohorts[106,107]; however, other studies have reported that COVID-19 infection during pregnancy does not increase the risk of pre-eclampsia[108–110]. Pre-eclampsia is more likely to be associated with severe COVID-19, although whether one is causal of the other has not been definitively proven[107,111]. Both pre-eclampsia and COVID-19 are characterized by increased circulating pro-inflammatory cytokines and endothelial dysfunction, suggesting common mechanisms[111]. Given that there seems to be a dose–response relationship and similarity in the activation of many of the same molecular pathways such as angiogenesis and endothelial dysfunction, this finding warrants further investigation.

Environmental factors. Residence at high altitudes (>2,700 m) is associated with increased risk of pre-eclampsia (for example, Colorado, USA, 33% of pregnancies; Peru, 22% of pregnancies; Bolivia, 20% of pregnancies; worldwide prevalence, 4.6% of pregnancies)[14,112–114]. Maternal hypoxia affecting multiple physiological systems, including placenta/decidual vasculature, is thought to drive this increased rate of pre-eclampsia[112], and it has been reported that multigenerational residents at high altitudes may be protected against pre-eclampsia compared with immigrants[113].

Air quality and exposure to ambient pollutants are also risk factors for pre-eclampsia. Associations between exposure to ambient particulate matter with diameter <2.5 μm ($PM_{2.5}$)[115–117] and nitrogen dioxide[116] during pregnancy and increased pre-eclampsia have been reported; for $PM_{2.5}$ exposure, this association may be more pronounced in pre-eclampsia with FGR[115].

Mechanisms/pathophysiology

Establishment of a healthy pregnancy

Placentation. The placenta is central to pre-eclampsia: pre-eclampsia is found only when a placenta is or was recently present. Healthy placental function depends on extensive placental villus branching and vascularization during early pregnancy, with the mature placenta largely formed by the end of the first trimester[118].

Pregnancy is initiated following implantation of a competent blastocyst into a receptive endometrium[119]. The endometrium is transiently receptive to blastocyst implantation during the mid-luteal phase of the menstrual cycle[119]. Following implantation, the placenta is formed from extra-embryonic lineages in the blastocyst: trophectoderm cells differentiate into villus progenitor cytotrophoblasts, which fuse to form the syncytiotrophoblast or differentiate into invasive extravillous trophoblasts[120], and extra-embryonic mesoderm differentiates into villus core stromal tissue and blood vessels[120]. The placental villus is lined by two layers of trophoblast: the multinucleated syncytiotrophoblast, which covers the entire placenta and is in direct contact with maternal blood, and the cytotrophoblast, which formed the extravillous trophoblast and anchors the placental villus to the maternal decidua via cell columns[120] (Fig. 2a). Extravillous trophoblasts invade from cell columns into the upper third of the myometrium from as early as 14 days after implantation[120] until 18 weeks of gestation, when placentation is largely completed[121]. Factors released by the extravillous trophoblasts (including progesterone) enhance decidualization[122,123], creating the semi-permanent decidual tissue maintained throughout pregnancy.

Placental villi bathed in maternal blood facilitate all nutrient and gas exchange required to support the fetus during pregnancy. Blood vessels within the villus core transport nutrients and gases to and from the fetus via the umbilical blood vessels. During the first trimester, uterine spiral arteries are remodelled to create wide-bore, high-flow, low-resistance vessels[124] capable of accommodating increased placental perfusion requirements in the later stages of pregnancy. Remodelling is initiated by uterine-resident innate immune cells, including uterine NK cells and T regulatory (T_{reg}) cells, which cause the loss of vascular smooth muscle cells surrounding the spiral arteries and regulate extravillous trophoblast invasion through the decidua via the secretion of angiogenic growth factors and cytokines[125]. Endovascular extravillous trophoblasts invade the arteries, replacing vascular endothelial cells and temporarily plugging the maternal arteries, blocking blood flow to the developing placenta, and leading to embryo development under low oxygen conditions. At around 10–12 weeks of gestation, the trophoblast endovascular plugs dislodge[126,127], enabling increasing volumes of maternal blood to perfuse the intervillous space and thus increasing fetoplacental oxygenation.

Vascular adaptations during pregnancy. In a healthy pregnancy, the maternal cardiovascular system undergoes significant expansion, including increased plasma volume and increased cardiac output from as early as 3–4 weeks of gestation, primarily driven by placental-released factors[128]. Resultant increases in blood pressure are prevented by concomitant decreases in systemic vascular (peripheral) resistance, increased arterial compliance, increased peripheral vasodilation, blunted contractility, enhanced endothelial release of vasodilatory factors and activation of the renal renin–angiotensin–aldosterone system[129–132]. There is little evidence for autonomic regulation driving changes in the cardiovascular system during pregnancy: the primary adaptations are endothelial and myogenic[128]. The endothelium is the interface between blood and vascular smooth muscle and is highly responsive to humoral factors and physical forces[128].

Pathophysiology of pre-eclampsia

The underlying aetiology of pre-eclampsia, both preterm and term, remains uncertain. It is likely that maternal and placental factors are involved and that there is overlap in the pathogenesis of preterm and term pre-eclampsia[133], but there is a remarkable gap in research to determine the pathogenesis of term pre-eclampsia, which is more common and often associated with maternal complications[134].

The two-stage model of pre-eclampsia proposes that pre-eclampsia results from placental dysfunction causing syncytiotrophoblast stress (stage 1), which leads to the maternal clinical manifestation of pre-eclampsia (stage 2)[135,136]. The cause and timing of the placental insult are proposed to differ between preterm and term disease[136]. Syncytiotrophoblast stress (stage 1) manifests as oxidative stress, endoplasmic reticulum stress, mitochondrial damage, dysregulated metabolism and apoptosis[137,138]. The stressed syncytiotrophoblast abnormally releases pro-inflammatory cytokines, reactive oxygen species, extracellular vesicles, anti-angiogenic agents (for example, soluble FLT1 (sFLT1) and cell-free fetal DNA) into the maternal circulation[135,139–141]. These factors promote maternal endothelial dysfunction and systemic multiorgan disorder that involves reduced vasodilation, systemic inflammation and thrombosis[142–144] (stage 2). The effects include hypertension, liver and renal impairment, thrombocytopenia, and coagulopathy.

Placental dysfunction in preterm pre-eclampsia. Syncytiotrophoblast stress in preterm pre-eclampsia is thought to arise from abnormal placentation during early pregnancy, characterized by inadequate extravillous trophoblast invasion and spiral artery remodelling[145,146] (Fig. 2b). This reduces blood flow to the placenta, resulting in placental hypoxia and placental ischaemia and reperfusion injury, causing syncytiotrophoblast stress. Inadequate trophoblast invasion of the spiral arteries and associated placental hypoperfusion also directly contribute to the FGR that often accompanies preterm pre-eclampsia.

Placental dysfunction in term pre-eclampsia. The abnormal placental histopathological findings common in preterm pre-eclampsia are relatively uncommon in term disease[147,148]. It is hypothesized that placental development is normal in term pre-eclampsia and that syncytiotrophoblast stress is initiated later in gestation. It is proposed that there are two mechanisms by which syncytiotrophoblast stress arises in term pre-eclampsia: compression of chronic villus when there is insufficient space for the larger placenta in late pregnancy and syncytiotrophoblast senescence associated with premature placental ageing[135,149] (Fig. 2b). Syncytiotrophoblast stress increases as gestation proceeds, even during an uncomplicated pregnancy, driven by the increasing mismatch between normal maternal perfusion and the metabolic demands of the placenta and fetus[135], leading to the hypothesis that pre-eclampsia is inevitable if gestation continues beyond the capacity of the placenta[125].

It is hypothesized that syncytiotrophoblast stress is not present early in gestation of a pregnancy that is later complicated by term pre-eclampsia[149], explaining why early pregnancy predictive models for pre-eclampsia, which often include risk factors and biomarkers of abnormal placentation, demonstrate high accuracy in the prediction of preterm pre-eclampsia (detection rates of 75–90%) but underperform in the prediction of term pre-eclampsia (detection rate below 50%)[150]. However, these hypotheses have been difficult to test experimentally due to the inherent problem of obtaining early pregnancy placenta from ongoing pregnancies.

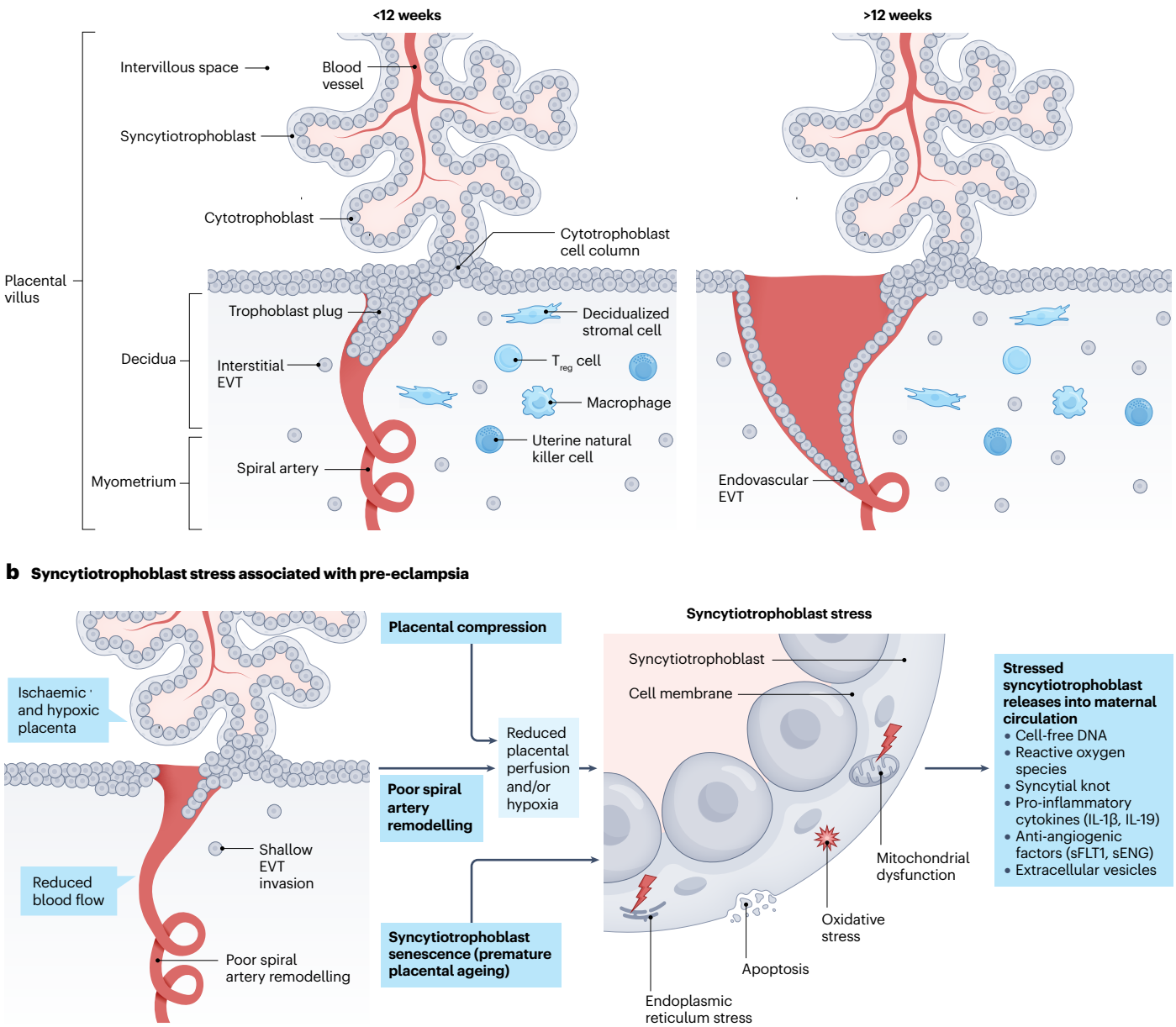

Fig. 2 | Syncytiotrophoblast stress is driven by dysfunctional placental perfusion. a, Each placental villus has a mesodermal core surrounded by an inner layer of progenitor cytotrophoblasts and an outer syncytiotrophoblast layer. Cytotrophoblasts at the villous tip interrupt the syncytiotrophoblast to form a columnar structure, which anchors the placenta to the decidua. Extravillous trophoblasts (EVTs) differentiate from the columnar cytotrophoblasts and migrate into the decidua into the upper myometrium (interstitial EVTs) or plug maternal spiral arteries (endovascular EVTs), preventing maternal blood flow into the intervillous space until ~12 weeks of gestation, when the trophoblast plugs are lost. EVTs and uterine-resident immune cells, including uterine natural killer cells and regulatory T (T_{reg}) cells, actively remodel the maternal spiral arteries into wide-bore, low-flow uterine arteries by removing vascular smooth muscle cells that surround the artery. **b**, There are multiple proposed drivers of syncytiotrophoblast stress associated with pre-eclampsia. Poor spiral artery remodelling, which is associated with shallow EVT invasion, is proposed to drive syncytiotrophoblast stress by causing an ischaemic blood supply to the placenta. Overcrowding and compression of the placental villus are proposed to cause reduced placental perfusion and a hypoxic placenta, driving syncytiotrophoblast stress. Syncytiotrophoblast senescence from premature placental ageing may also lead to syncytiotrophoblast stress. Syncytiotrophoblast stress manifests as endoplasmic reticulum stress, mitochondrial dysfunction, oxidative stress, and apoptosis and leads to abnormal syncytiotrophoblast release of factors, including cell-free DNA, reactive oxygen species, syncytial knots, exosomes/microvesicles, pro-inflammatory cytokines and anti-angiogenic factors, into the maternal circulation. sEng, soluble endoglin; sFLT1, soluble Fms-related receptor tyrosine kinase 1. Adapted from ref. [349], Springer Nature Limited.

Immune system dysfunction. Maternal immunological problems are associated with abnormalities at the fetal–maternal interface. Immunological tolerance to the fetus and placenta, whose genes are half-paternal, is facilitated, in part, by reduced placental expression of MHC and the human leukocyte antigen (HLA) system; this mechanism endeavours to avoid innate rejection of semi-allogeneic fetal cells[151]. Uterine NK cells and T lymphocytes are located in the decidua and have a critical role in promoting maternal immune tolerance to the fetus. In particular, T_{reg} cells exert immune tolerance functions by mechanisms including antigen presentation, secretion of inhibitory cytokines and cytolysis of target cells[152,153]. Abnormal release of T_{reg} cell factors, including cytokines and microRNA, is found in pre-eclampsia[154]. Epidemiological studies support experimental data reporting that the maternal immune response to paternally derived antigens on the trophoblast[155] is decreased by previous exposure to seminal fluid[156]: a higher incidence of pre-eclampsia is found in primiparity, pregnancies in which the paternity has changed, pregnancies after a prolonged inter-pregnancy interval (>10 years), pregnancies conceived soon after first coitus, and pregnancies conceived with the use of donor egg[157] and sperm[90]. Angiotensin II receptor type 1 auto-antibodies (AT1-AAs) are elevated in the serum of women with pre-eclampsia[158]. AT1-AAs have a sustained effect on vasoconstriction and can cause endothelial cell damage[158].

Maternal metabolic and cardiovascular health. Accumulating evidence suggests that pre-eclampsia is associated with impaired maternal metabolic and cardiovascular function, leading to inadequate adaptation to the demands of pregnancy[159–163]. Altered metabolic and cardiovascular function is proposed to contribute to pre-eclampsia by causing reduced spiral artery remodelling in preterm pre-eclampsia and altered placental metabolic function in both preterm and term pre-eclampsia[163]. Metabolomic studies undertaken in serum of women at 11–13 weeks of gestation who later developed late-onset pre-eclampsia identified that insulin resistance and metabolic syndrome, mitochondrial dysfunction, disturbance of energy metabolism, oxidative stress, and lipid dysfunction are present in late-onset pre-eclampsia[164], suggesting that disturbances can be identified early in the disease process.

Dysregulated placental gene expression. Two small studies using chorionic villus samples (CVS) collected from pregnancies that subsequently developed early-onset (<34 weeks of gestation) pre-eclampsia identified dysregulated placental and decidual gene expression at the end of the first trimester[165–167]. The placental tissue exhibited dysregulated expression of genes associated with angiogenesis and oxidative stress[165] and, in decidual tissue, genes associated with inflammation/immunoregulation, cell motility, decidualization and NK cell function were altered[166,167]. Many of these factors have since been validated in preterm pre-eclampsia, including complement factor H and prothrombin[35–37,168]. No study to date has examined the gene expression of CVS collected from pregnancies that subsequently develop late preterm (35–36 weeks of gestation) or term pre-eclampsia (≥37 weeks of gestation).

Meta-analysis on placenta samples collected at delivery has identified dysregulated genes involved in carbohydrate and energy utilization, immune response, and developmental/pregnancy processes in all forms of pre-eclampsia[169]. Smaller studies that distinguished between early-onset and late-onset pre-eclampsia identified that early-onset placenta samples had increased gene expression for genes involved in metabolic processes, and late-onset placenta samples had increased expression of genes involved in immune processes[170,171]. These findings further suggest that the mechanisms involved in the three forms of pre-eclampsia are different.

Dysregulated placental release of factors. Alterations in placental secreted factors, including angiogenic proteins, pro-inflammatory cytokines and small extracellular vesicles, before the development of pre-eclampsia have been demonstrated in maternal blood[139,172–176].

Placental-released angiogenic factors, including sFLT1 and placental growth factor (PGF), have been implicated in the development of pre-eclampsia[177–179]. There is a steep increase of serum sFLT1 levels and decreased PGF from approximately 5 weeks before the onset of pre-eclampsia[178]. The ratio of sFLT1 to PGF is therefore used as a helpful tool when diagnosing placental dysfunction in pre-eclampsia, with higher sensitivity and specificity being achieved for early-onset pre-eclampsia[177,178]. Soluble endoglin is another notable anti-angiogenic factor released by the pre-eclamptic placenta with a similar pattern in serum as sFLT1 (refs. [177,180]). It is thought that elevated maternal serum levels of the cleaved soluble form of endoglin lead to disturbed angiogenesis and vasoconstriction, causing pre-eclampsia symptoms[180]. A recent meta-analysis suggests that maternal serum soluble endoglin may be useful as a predictive biomarker of pre-eclampsia but may not distinguish between early-onset and late-onset disease[181].

Inflammasome activation and its associated pro-inflammatory cascade are elevated in pre-eclampsia[182,183]. Inflammasomes are innate immune system receptors and sensors comprised of multimeric proteins that regulate the activation of caspase 1 and induce inflammation in response to infectious microbes and molecules derived from host proteins (called sterile inflammation)[184]. The NACHT, LRR and PYD domains-containing protein 3 (NLRP3) and NLRP7 and their associated adaptor protein PYCARD are elevated in placenta and blood of women with pre-eclampsia[182,183]. There are several strategies being developed to inhibit inflammasome activation[185] that may be useful to treat inflammation-related pathways in pre-eclampsia.

Circulating IL-11 is increased in early pregnancy of women who subsequently develop pre-eclampsia[186]. However, it is important to determine whether IL-11 levels in the placenta are dysregulated during placental development in humans, which may be critical in driving the pathogenesis of pre-eclampsia.

Galectins are a family of β-galactoside-binding lectins with important roles in the development of pre-eclampsia[187]. Galectins 1, 2, 3, 7, 9, 13 and 14 have all been implicated in the pathogenesis of pre-eclampsia[187], likely due to their functions in promoting maternal fetal tolerance[169,187] or causing alterations to the renin–angiotensin–aldosterone system and oxidative stress[188,189]. A correlation between maternal serum levels and CVS expression of galectin 7 has been found in preterm pre-eclampsia[188,190].

Increased syncytiotrophoblast release of extracellular vesicles (Fig. 2b) into the maternal circulation is found in pre-eclampsia[191–193]. These extracellular vesicles are enriched in anti-angiogenic factors, apoptosis-inducing ligands and active caspase 3, especially in early-onset pre-eclampsia[192,193]. Emerging evidence suggests that syncytiotrophoblast-released extracellular vesicles are internalized by endothelial cells, into which they release these factors and drive the maternal endothelial dysfunction and inflammation observed in pre-eclampsia[176,194–196].

Systemic consequences of pre-eclampsia onset

Vascular involvement. The maternal endothelium is thought to be an important target of the placental-released factors hypothesized to drive pre-eclampsia[197]. Widespread endothelial dysfunction can

also explain systemic organ damage in women with pre-eclampsia[198]. The endothelium controls smooth muscle tone and the production and release of vasoconstrictor and vasodilatory factors (including nitric oxide) as well as regulating anti-coagulation, anti-platelet and fibrinolysis functions[197]. Endothelial dysfunction can lead to reduced blood flow to organs such as the heart and kidney[133] and reduced venous blood drainage and associated venous congestion. This contributes to organ dysfunction and can induce reflex constriction of arteries[199]. Altogether, it is hypothesized that the endothelial dysfunction driven by placental-released factors initiates and drives hypertension in pre-eclampsia.

Abnormal uterine artery Doppler findings (vessel blood flow) are more common in early-onset than in late-onset pre-eclampsia[62], confirming the high impedance to blood flow associated with the failure of physiological remodelling of spiral arteries and the consequent poor placental perfusion, hypoxia and reperfusion injuries in early-onset pre-eclampsia[133,134]. By contrast, late-onset pre-eclampsia is often related to maternal endothelial cell dysfunction[200] and is thought to be influenced by pre-existing maternal conditions that could affect endothelial integrity[131]. However, machine learning approaches using biochemical data retrieved from electronic medical records (for example, systolic blood pressure, serum blood urea nitrogen, potassium, calcium, and creatinine, platelet and white blood cell counts, and urinary protein) from 11,006 women at 14–17 to 34 weeks of gestation have been documented to predict late-onset pre-eclampsia early in the second trimester[92], suggesting that early pregnancy placental vascular impairment also occurs in late-onset pre-eclampsia.

Pulmonary oedema. Characterized by excessive fluid accumulation in the lungs, pulmonary oedema is a rare (in 0.6–5% of women with pre-eclampsia), acute, life-threatening condition, primarily associated with severe pre-eclampsia[201,202]. Pulmonary oedema is the second most common cause of death in pregnancies complicated by hypertension[203]. There are multiple causes of pulmonary oedema, including decreased oncotic pressure, increased capillary permeability, increased hydrostatic pressure and diastolic dysfunction. Antihypertensive medications and excessive fluid administration are risk factors for pulmonary oedema[204]. Pulmonary oedema is most common (39%) postpartum[204], when fluid sequestered in the extravascular space is mobilized into the vascular space, increasing central venous and pulmonary capillary wedge pressure.

Renal involvement. The kidney is the organ most likely to be affected by endothelial injury in pre-eclampsia[198]. Renal biopsies of women with pre-eclampsia show glomerular endotheliosis (swelling of endothelial cells, obliteration of fenestrations and invasion of the capillary space) that seems to be responsible for the decreased glomerular filtration rate noted in pre-eclampsia[205]. The characteristic proteinuria in pre-eclampsia is caused by high concentrations of sFLT1 inhibiting the expression of proteins of the podocyte slit diaphragm, such as synaptopodin and nephrin[206], which increases inter-podocyte separation. In turn, the lack of vascular endothelial growth factor (VEGF) and PGF availability in the glomerular endothelium stimulates endothelin 1 expression that promotes podocyte detachment[207].

Liver involvement. Liver damage in pre-eclampsia is characterized by periportal inflammation and hepatocellular damage (manifested as right-upper quadrant or epigastric pain and elevated transaminases), subcapsular haematoma and, in rare cases, hepatic failure or rupture[208]. Widespread microangiopathy causes vasospasm of hepatic sinusoids and promotes fibrin deposition in the microcirculation[209], leading to ischaemia. Hepatic endothelial cells are highly dependent on VEGF, and its antagonism with sFLT1 significantly alters their function given the decreased availability of nitric oxide[210]. The resulting ischaemia causes oxidative stress and inflammation that affect hepatic acini, elevating the concentration of liver enzymes in blood and contributing to the onset of HELLP syndrome.

HELLP syndrome encompasses microangiopathic haemolysis, elevation of liver enzymes and thrombocytopenia. The most common symptoms in affected patients are right-upper quadrant pain, epigastralgia, nausea and vomiting, headache and visual changes. In hyperbilirubinaemia, indirect bilirubin predominates; thus, only in advanced cases can the patient present clinical jaundice[211]. Changes in the coagulation system may occur. The cause of thrombocytopenia is believed to be consumption due to exaggerated platelet activation caused by diffuse endothelial injury. Evolution, in severe cases, to disseminated intravascular coagulation corroborates the worsening of the case and is diagnosed by decreased levels of fibrinogen, antithrombin, and increased prothrombin time and fibrin[212].

Neurological involvement. Neurological symptoms have been recognized as high-risk features of eclampsia for thousands of years[213]. Neurological complications are the direct cause of many maternal deaths due to pre-eclampsia, particularly in LMICs, and include eclampsia (seizures), visual scotomata, cortical blindness, arterial ischaemic stroke, cerebral venous sinus thrombosis, subarachnoid and intracerebral haemorrhage, reversible cerebral vasoconstriction syndrome, and posterior reversible encephalopathy syndrome[213,214]. Cerebral venous sinus thrombosis, reversible cerebral vasoconstriction syndrome and posterior reversible encephalopathy syndrome occur most commonly in the postpartum period and often with little warning[215]. The mechanisms leading to neurological complications are being uncovered; the maternal cerebral vasculature is highly sensitive to pre-eclampsia[215]. Neurovascular dysfunction is clear in pre-eclampsia, with studies showing increased sympathetic activity of the autonomic nervous system[213,216] (arterial stiffness and endothelial dysfunction are, in part, under sympathetic control[216]), impaired cerebral autoregulation (which prevents hyperperfusion injury to the brain[213,217]), increased blood–brain barrier permeability[132], and vasogenic oedema, with cerebral markers, including neurofilament light chain, being dysregulated in pre-eclamptic cerebrospinal fluid, serum and plasma[218].

Fetal growth restriction. FGR occurs mainly due to placental dysfunction and is therefore highly associated with preterm pre-eclampsia[219–222]. Abnormalities in trophoblast invasion during early pregnancy lead to inadequate uterine spiral artery remodelling and can lead to hypoxia and nutritional deficiency, eventually causing FGR[220]. Late-onset pre-eclampsia complicated by FGR is generally accompanied by lower placental weight and more vascular and villous abnormalities than late-onset pre-eclampsia alone[223]. In any pregnancies with suspected FGR, ISSHP recommends fetal growth velocity, amniotic fluid volume and umbilical artery Doppler be assessed by ultrasonography every 2 weeks, although the utility of umbilical artery Doppler close to term may be limited[2]. In low-resource settings, ISSHP recommends that monitoring fetal heart rate, cardiotocography performed 6-hourly and maternal characteristics plus proteinuria can be used to estimate perinatal risk at ≥32 weeks of gestation as, before this, low gestational age drives most risk[2].

Diagnosis, screening and prevention

Diagnosis

The ISSHP guidelines[2,13] specify that pre-eclampsia can be diagnosed after 20 weeks of gestation by new-onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg; average of two measurements) in a patient previously with normotension plus one other pre-eclampsia-related symptom or sign. These can include proteinuria (protein/creatinine ≥30 mg/mmol in a spot urine sample or ≥300 mg/mmol in >0.3 g/day), acute kidney injury (creatinine ≥90 µmol/l), liver involvement (elevated transaminases, for example, ALT or AST >40 IU/l), neurological symptoms (eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, persistent visual scotomata), haematological abnormalities (thrombocytopenia (platelet count below 150,000/µl), disseminated intravascular coagulation, haemolysis), cardiorespiratory complications (pulmonary oedema, myocardial ischaemia or infarction, oxygen saturation <90%, ≥50% inspired oxygen for more than 1 h, intubation other than for caesarean) or uteroplacental dysfunction (FGR, angiogenic imbalance, placental abruption). This new set of diagnostic criteria published in 2014 and revised in 2018 and 2021, represents a significant change compared with the previous recommendations published in 2001 (ref. [224]), which required the presence of proteinuria and new-onset hypertension in a patient with previous normotension. Use of the ISSHP guidelines increases pre-eclampsia diagnoses when compared with guidelines published before 2014, improving the identification of women and neonates at risk of adverse outcomes[225], although most women newly identified have only mild disease and low risk of adverse outcomes[226]. ACOG[25] and NICE[26] both updated their guidelines for the diagnosis of pre-eclampsia in 2019 to be broadly similar to the ISSHP guidelines[227].

For suspected pre-eclampsia, ISSHP recommends evaluation of angiogenic imbalance as a marker of uteroplacental dysfunction, whereas normal angiogenic balance would strengthen a diagnosis of gestational hypertension[2]. NICE guidelines and meta-analyses support the measurement of PGF alone or in combination with sFLT1 to rule out suspected pre-eclampsia within the 14 days following measurement[26,42,228–234]. A stepped-wedge cluster trial demonstrated that measurement of PGF in women with suspected pre-eclampsia reduces the time to clinical confirmation and may reduce the incidence of adverse maternal outcomes[235]. Similarly, a ratio of sFLT1 to PGF below a certain cut-off (commonly <38) can reliably rule out pre-eclampsia among women with suspected disease[42].

Small, retrospective trials have identified total thiols as increased in late-onset pre-eclampsia[236], and serum ADT-ProteoStat protein aggregates[237] and podocalyxin[238] as elevated in both early-onset and late-onset pre-eclampsia. These small studies require validation in larger cohorts.

Disease progression

All women with pre-eclampsia are at risk of rapid progression and severe disease regardless of the timing of onset[8,12], with up to 18% of HELLP syndrome and 55% of eclampsia occuring in term (≥37 weeks of gestation) pre-eclampsia[239,240]. A history of chronic hypertension and elevated systolic blood pressure or serum creatinine on admission can be associated with increased risk of progressing to severe disease in late preterm (34–36 (+6 days) weeks of gestation)[241] or term[12] pre-eclampsia. However, the best-performing model to predict risk of severe outcomes in early-onset pre-eclampsia (gestational age, chest pain or dyspnoea, oxygen saturation, platelet count, and creatinine and aspartate transaminase concentrations) does not include chronic hypertension or blood pressure at admission[242], possibly reflecting differences in the underlying aetiology of disease. Larger, multicentre studies are required to confirm this[243,244].

The ratio of sFLT1 to PGF has been investigated in the prediction of adverse pregnancy outcomes. In a study in Asia, an sFLT1 to PGF ratio of ≤38 had a negative predictive value of 98.9% (95% CI 97.6–99.6%) and a ratio of >38 had a positive predictive value of 53.5% (95% CI 45.0–61.8%) for a composite of adverse maternal outcomes (including death, pulmonary oedema, acute renal failure, cerebral haemorrhage, cerebral thrombosis and disseminated intravascular coagulation)[245]. A recent study demonstrated that the ratio of sFLT1 to PGF performs better in the prediction of adverse perinatal outcomes (area under the receiver-operating characteristics curve (AUROC) 0.87, 95% CI 0.81–0.93) than in the prediction of adverse maternal outcomes (AUROC 0.69, 95% CI 0.59–0.78)[246]. Conversely, multivariable predictive models, such as the fullPIERS model, seem to predict adverse maternal outcomes reasonably well (AUROC 0.88, 95% CI 0.84–0.92) in both early-onset and late-onset pre-eclampsia[242,247].

Screening

NICE and ACOG have published guidelines for risk assessment based on elements from maternal characteristics and medical history such as a history of chronic hypertension (Table 1). The Fetal Medicine Foundation (FMF) competing-risks model[248,249] incorporates maternal age, ethnic background, weight and height, medical and obstetric history, mean arterial blood pressure, uterine artery pulsatility index on ultrasonography, and maternal circulating PGF levels at 11–13 weeks of gestation to estimate the individual risk of developing pre-eclampsia. These two approaches to screening were assessed in the UK NHS Screening Programme for Pre-eclampsia (SPREE) study involving 16,747 participants[14]. At a screen-positive rate of 10% (where 10% of the study population was considered to be at high risk using the NICE criteria), the detection rate of preterm pre-eclampsia was 41% with the risk scoring system recommended by NICE compared to 82% when screening was based on the FMF competing-risks model[15]. FMF screening is particularly effective for preterm pre-eclampsia, identifying ~90% of women who will develop pre-eclampsia at <34 weeks of gestation and ~80% of women who will develop pre-eclampsia at <37 weeks of gestation[250] but only 44% of women who will develop pre-eclampsia at ≥37 weeks of gestation[15]. ISSHP and the International Federation of Gynecology and Obstetrics (FIGO) now recommend combined screening with the FMF algorithm where possible[2,251]; however, uterine artery ultrasonography and PGF assays are not routinely performed worldwide. It has been found that a step-wise screening protocol with an initial screen of maternal risk factors (maternal characteristics, medical history and blood pressure) followed by either uterine artery ultrasonography or PGF assays only on women with positive risk has a similar detection rate[250] (Table 2).

The FMF first-trimester screening tool for preterm pre-eclampsia has been extensively validated in several different communities across the world. Implementation studies showed significant reductions in the rates of preterm pre-eclampsia and improvement in maternal and perinatal outcomes in the UK[15] and Australia[252], and the screen-and-treat approach based on the FMF algorithm seems highly cost-effective[253], now being the recommended approach by various institutions[13,251,254].

Screening tests under development. Using a similar prediction tool published by the FMF, screening at 19–24 weeks of gestation of women identified as being at low risk in the first trimester or who missed screening in the first trimester enables the identification of almost all women

who will develop pre-eclampsia by 32 weeks and of up to 90% of women who will develop pre-eclampsia between 32 and 35 (+6 days) weeks of gestation[255,256]. This can be used to stratify women needing intensive monitoring at 24–31 (+6 days) weeks of gestation and women that require reassessment at 35–37 weeks of gestation[255] (Fig. 3).

Prediction of term pre-eclampsia at 35–37 weeks of gestation (Fig. 3) can identify up to 85% of all women who will develop pre-eclampsia at >36 weeks of gestation[250,257]. When ethnicity is included in the predictive algorithm, this screening was found to have stronger predictive power for Afro-Caribbean women (88%) than for white women (66%) in London[258]. The screening at 35–37 weeks of gestation includes maternal circulating sFLT1 but not the uterine artery pulsatility index as it is not useful for identifying women at high risk of developing pre-eclampsia at >36 weeks of gestation[258].

As the prediction of preterm pre-eclampsia is so effective, new methods to predict risk of term pre-eclampsia are now urgently required. A small study using machine learning to aggregate maternal characteristics and laboratory parameters from the second and third trimesters identified 77.1% of late-onset pre-eclampsia (false-positive rate 0.9%)[92]. The most influential variables were systolic blood pressure, serum urea, nitrogen, potassium, calcium, and creatinine, platelet and white blood cell counts and urinary protein[92]. However, this study has not been validated in other cohorts. Other potential factors that may improve the prediction of late-onset pre-eclampsia but which require validation in large cohorts or meta-analyses include second-trimester circulating HtrA3 (ref. [259]), cell-free RNA[260,261], and third-trimester circulating ELABELA[262] and progranulin[263].

Prevention

The severe short-term and lifelong health risks of being exposed to a pre-eclamptic pregnancy for both the mother and child emphasize the need for new treatments to prevent pre-eclampsia. Adequately powered, multi-centre studies are required to identify patient populations who may benefit from the different preventive treatments under development.

Preventive treatments with good evidence. The use of aspirin to prevent pre-eclampsia has long been proposed. Despite a randomized trial published in 1985 showing that prophylactic aspirin leads to a large reduction in pre-eclampsia, FGR and stillbirth in women at high risk[264], further trials were highly heterogeneous regarding aspirin dose, time of initiation and, importantly, the method used to select women at increased risk[265–267]. An individual-participant data meta-analysis concluded that aspirin provides a statistically significant but clinically modest 10% reduction in pre-eclampsia risk[268]. Further meta-analysis suggested that aspirin is highly effective in preventing preterm pre-eclampsia when given to women at high risk from before 16 weeks of gestation[268] (Fig. 3). The Aspirin for Evidence-Based PREeclampsia (ASPRE) prevention trial, a multicentre, randomized, double-blind placebo-controlled trial of 1,776 women at high risk identified by means of combined screening with the FMF algorithm, provided further convincing evidence that daily aspirin from the first trimester reduces the risk of preterm pre-eclampsia by 62% (95% CI 20–80%), with no significant effect on the rate of term disease[7].

A meta-analysis of 30 trials identified that low-dose calcium supplementation halves the risk of pre-eclampsia (both for early and late onset) in women at high risk of developing pre-eclampsia and with low dietary calcium intake[269], and is therefore recommended by ISSHP guidelines.

Table 2 | Comparison of the detection rates of first-trimester screening for pre-eclampsia at a fixed 10% false-positive rate[15]

Method of screening	Detection rate		
	<34 weeks of gestation	<37 weeks of gestation	≥37 weeks of gestation
Maternal factors	48.3%	41.5%	30.2%
MF+MAP	65.0%	49.3%	38.7%
MF+MAP+UtA-PI	88.3%	73.9%	43.5%
MF+MAP+PGF	73.3%	68.3%	39.6%
MF+MAP+UtA-PI+PGF	90.0%	81.7%	42.6%

MAP, mean arterial pressure; MF, maternal factors; PGF, placental growth factor; UtA-PI, uterine artery pulsatility index.

Furthermore, the ISSHP guidelines recommend exercise to reduce the likelihood of gestational hypertension and pre-eclampsia[2]. A meta-analysis of 27 trials found that exercise of at least 260 metabolic equivalents of task minutes/week reduced the odds of developing pre-eclampsia by 25%[65].

Preventive treatments under development. A multicentre trial of 6,000 nulliparous women at low risk randomly assigned to induction at 39 weeks of gestation or expectant monitoring showed labour induction reduced risks of adverse outcomes, including hypertensive disorders of pregnancy[270]. Further studies are required to determine whether the incidence of pre-eclampsia itself and the long-term, poor outcomes for mother and baby are improved by routine induction.

Pravastatin is an oral statin used to lower LDL cholesterol and triglycerides, which also has anti-inflammatory actions. A trial in 173 women at high risk of developing pre-eclampsia reported that daily pravastatin from the second trimester (14–20 weeks of gestation) until delivery significantly reduced the rate of preterm pre-eclampsia (13.8% versus 26.7% in the control group) and preterm birth[271]. Pravastatin may not be effective at preventing term pre-eclampsia: there was no reduction in the incidence of term pre-eclampsia in this[271] or another trial of 1,120 women at high risk of developing term pre-eclampsia given daily pravastatin from 35–37 weeks of gestation to delivery[272].

Metformin is an oral, insulin-sensitizing and glucose-lowering drug widely prescribed during pregnancy for gestational diabetes mellitus. A meta-analysis taking advantage of trials in which metformin was prescribed for other conditions and where participants fell pregnant identified a reduction in the likelihood of pre-eclampsia[273]. In a randomized control trial of singleton pregnancies in which women with a BMI >35 kg/m^2 were given metformin daily from 12–18 weeks until delivery, a significant reduction in pre-eclampsia (OR 0.25, 95% CI 0.1–0.61) and a significant reduction in gestational weight gain were reported[274].

A meta-analysis including 313 women from three randomized controlled trials found that daily vitamin D supplementation significantly reduced pre-eclampsia risk (RR 0.29, 95% CI 0.09–0.95)[275]. Another meta-analysis including 2,464 women from 13 studies found a significantly reduced incidence of pre-eclampsia with prophylactic, low-molecular-weight heparin started before 16 weeks of gestation[276]; however, the ISSHP guidelines currently do not recommend heparin treatment[2].

Management

In a pre-eclamptic pregnancy, the mother and fetus have competing interests. For the mother, delivery of the placenta will alleviate symptoms (Box 2); however, this may cause preterm birth and the resulting

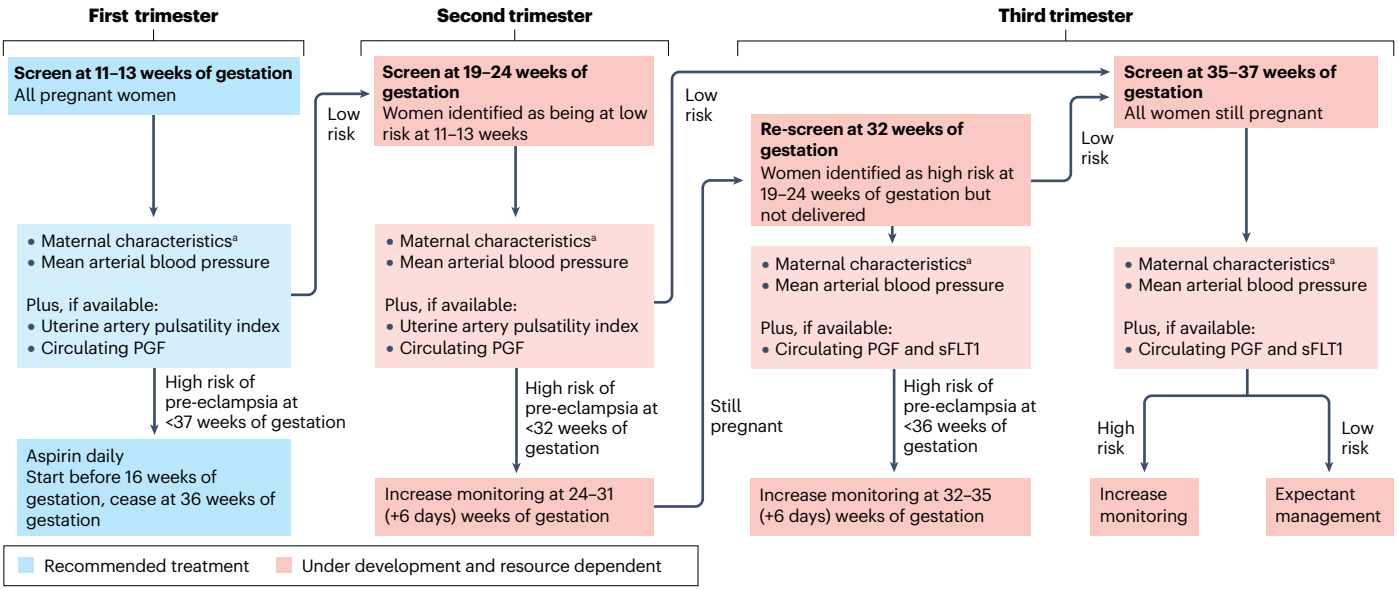

Fig. 3 | Algorithms to screen for pre-eclampsia in first, second and third trimesters. All pregnant women should be screened at 11–13 weeks of gestation with the Fetal Medicine Foundation competing-risks model[248,249] to determine their risk of pre-eclampsia at <37 weeks of gestation. Women identified as being at high risk of pre-eclampsia at <37 weeks of gestation should be prescribed aspirin from before 16 weeks of gestation and cease taking aspirin at 36 weeks of gestation. Screening in the second and third trimesters is showing promise as a tool to identify risk of all pre-eclampsia but should be considered in the context of resource availability. Any woman identified as being at low risk in the screen at 11–13 weeks of gestation should be re-screened at 19–24 weeks of gestation to determine risk of pre-eclampsia at <32 weeks of gestation. Women identified as being at high risk should have increased monitoring from 24–31 (+6 days) weeks of gestation and, if they are still pregnant at 32 weeks of gestation, they should be screened again then to determine their risk of pre-eclampsia at <36 weeks of gestation. Women at high risk of pre-eclampsia at <36 weeks of gestation should continue to have increased monitoring from 32–35 (+6 days) weeks of gestation and induction of labour should be considered at 37/38 weeks of gestation. All women still pregnant at 35–37 weeks of gestation should be re-screened to assess their risk of pre-eclampsia >37 weeks of gestation. Women at high risk of pre-eclampsia at >37 weeks of gestation should have increased monitoring and induction of labour should be considered at >37 weeks of gestation. [a]Maternal characteristics: age, BMI, smoking, mother of pregnant woman had pre-eclampsia, conception method, comorbidities (for example, chronic hypertension, diabetes types 1 or 2, systemic lupus erythematosus, antiphospholipid syndrome) and obstetric history. PGF, placental growth factor; sFLT1, soluble Fms-related receptor tyrosine kinase 1.

complications of prematurity for the neonate. Preterm management of pre-eclampsia (Fig. 4) requires treatment of maternal high blood pressure with the goal of preventing severe maternal outcomes and prolonging pregnancy with surveillance of fetal health and timing of delivery to provide the best outcome for both mother and neonate.

Treatment common to all disease subtypes

Hypertension is the predominant diagnostic feature of pre-eclampsia and typically becomes progressively worse with advancing gestation. Severe hypertension (≥160/110 mmHg) may lead to intracerebral haemorrhage, eclampsia and placental abruption and should be treated in all circumstances[277]. The aim of treatment is to reduce blood pressure to a target range of 140–155/90–105 mmHg (ref. [277]).

Oral antihypertensive medications. Although intravenous antihypertensive agents may be indicated in an acute situation, oral medications that are commonly used to manage hypertension in pregnancy include methyldopa, labetalol and nifedipine. These agents are typically available even in low-resource settings. A recent multicentre, parallel-group, open-label, randomized controlled trial compared these three agents (hourly doses of either nifedipine or labetalol or a daily dose of methyldopa) and reported that, although as a single drug, nifedipine resulted in a greater frequency of blood pressure control (120–150 mmHg systolic and 70–100 mmHg diastolic blood pressure) within 6 h, all three agents are potentially viable initial options for the treatment of severe hypertension in pregnancy[278].

Nifedipine is a calcium channel antagonist and causes peripheral vasodilatation. It has a rapid onset of action[279] and women may complain of severe headaches (particularly in the first 24 h), dizziness, flushing, palpitations and increasing ankle oedema. Initially, sublingual dosing was supported for rapid correction of severe hypertension in pregnancy but there have been significant adverse outcomes in non-pregnant adults, and this can also cause acute fetal distress due to reduced placental perfusion pressure[280].

Labetalol blocks β1, β2 and α1 adrenergic receptors and reduces peripheral vascular resistance[281]. It is a negative inotrope and may promote pulmonary oedema and cardiac failure. It may cause bronchospasm and should be avoided in women with a history of asthma. Women may report headaches and nausea, particularly within the first 24 h of use. Peak plasma doses are reached within 2 h of oral dosing and the peak effect is reached within 48 h of treatment.

Methyldopa is a centrally acting sympathomimetic acting as an α2 adrenergic receptor agonist. Women commonly report feeling lethargic and drowsy, particularly within the first 72 h of use, and methyldopa may worsen depression[282]. Peak plasma doses are reached 6 h after oral dosing with the peak effect reached following 72 h of treatment,

potentially making other treatment strategies more useful at acute presentation. Abrupt cessation (following long-term use) may cause rebound hypertension.

Interventions to manage mild hypertension. Previously, there has been concern that aggressive treatment of mild hypertension in pregnancy (defined in most jurisdictions as blood pressure ≥140/90 mmHg) may affect placental perfusion, leading to an increased prevalence of adverse perinatal outcomes. Two randomized controlled trials that addressed these concerns have demonstrated that this is not the case, and that maintaining blood pressure <140/90 mmHg improves maternal and potentially perinatal outcomes[59,283] (Table 3). The Control of Hypertension In Pregnancy Study (CHIPS; including women with chronic hypertension and gestational hypertension) and Control of Hypertension And Pregnancy (CHAP; including women with chronic hypertension) trials have some differences but both reached similar conclusions. CHIPS predominantly recruited women with hypertension >140/90 mmHg at 14–33 weeks of gestation (75% with chronic hypertension; 25% with gestational hypertension)[283]. The intervention involved assigning women to two different diastolic blood pressure target groups (<85 mmHg versus <100 mmHg) to determine the effect of acceptance of higher diastolic blood pressure on pregnancy outcomes. The primary outcome measure was a composite of perinatal death and significant neonatal admission, with no significant differences between groups. The main finding was a reduction in severe hypertension in the <85 mmHg group, supporting the conclusion that there was no apparent benefit to more relaxed control given the known association between severe hypertension and severe maternal morbidity and mortality.

By contrast, the CHAP trial was restricted to women with chronic hypertension presenting at <23 weeks of gestation[59]. The intervention involved treatment of hypertension >140/90 mmHg compared with the control group, who only received antihypertensive medication if their blood pressure was ≥160/105 mmHg. The incidence of a primary outcome event (small-for-gestational-age birthweight, serious maternal complications, severe neonatal complications, pre-eclampsia and preterm birth) was significantly lower in the active-treatment group than in the control group.

The findings of these two trials are complementary and suggest that an aggressive approach to managing mild hypertension in pregnancy results in a reduction in maternal morbidity without affecting fetal safety. The potential reduction in preterm delivery may in fact be beneficial from a fetal perspective. These trials support a meta-analysis that reviewed the use of antihypertensive medications in pregnancy[284]. This meta-analysis also concluded that labetalol or nifedipine may be preferred when compared with methyldopa in women with mild to moderate hypertension during pregnancy[284].

Planned delivery. The Hypertension and Preeclampsia Intervention Trial At Near Term-I (HYPITAT-I) trial showed a significant decrease in adverse maternal outcomes with active management (induction of labour) than expectant monitoring of women with gestational hypertension or mild pre-eclampsia at >36 weeks of gestation, and concluded that induction of labour should be advised for these women[243]. However, the HYPITAT-II trial showed a significant increase in the risk of neonatal respiratory distress syndrome with immediate delivery (induction of labour or caesarean section within 24 h of randomization into trial groups) than with expectant monitoring (prolonging pregnancy until 37 weeks of gestation) in women with non-severe pre-eclampsia at 34–37 weeks of gestation, and concluded that it is generally safe and beneficial to prolong pregnancy until 37 weeks of gestation[244]. By contrast, the Planned early delivery or expectant monitoring for late preterm pre-eclampsia (PHOENIX)[285] study showed a significantly lower incidence of the co-primary maternal outcome, a composite of maternal morbidity or recorded systolic blood pressure of >160 mmHg, and a significantly higher incidence of the co-primary perinatal outcome (composite of perinatal deaths or neonatal unit admission) in the planned delivery group than in the expectant monitoring group in women with late preterm pre-eclampsia at 34–37 weeks of gestation. The authors recommended that this trade-off between the maternal and neonatal prognosis should be discussed with patients to enable shared decision-making on the timing of delivery[285,286].

Treatments for specific patient populations

Some signs and symptoms in pre-eclampsia deserve special attention, including several continuous or recurrent headaches, visual scotomas (blind spots), nausea/vomiting, epigastric pain and severe hypertension as well as changes in laboratory tests, such as increased creatinine or liver transaminases, thrombocytopenia, and altered fetal growth

Box 2

Management of planned delivery in pre-eclamptic pregnancies

Triggers for delivery

- Haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome or significant biochemical derangements
- Eclampsia
- Inability to control blood pressure despite maximum dose of antihypertensive medication
- Abnormal fetal wellbeing parameters and/or fetal distress

Managing delivery

- Induction of labour or caesarean delivery
- Avoiding maternal morbidity
- Avoiding fetal morbidity

Postpartum management and follow-up

- Acute management of hypertension

Short-term follow-up: continued regular monitoring of blood pressure postpartum and treatment with antihypertensive medications to prevent postpartum eclamptic fit. Management of any other acute sequelae of pre-eclampsia such as the development of pulmonary oedema or deranged renal/hepatic function

Long-term follow-up and inter-pregnancy advice: ensure blood pressure returns to normal pre-pregnancy levels by ~6 weeks postpartum. Prescribe appropriate antihypertensive medications if there is residual chronic hypertension. Identify other risk factors for maternal cardiovascular disease and encourage risk mitigation

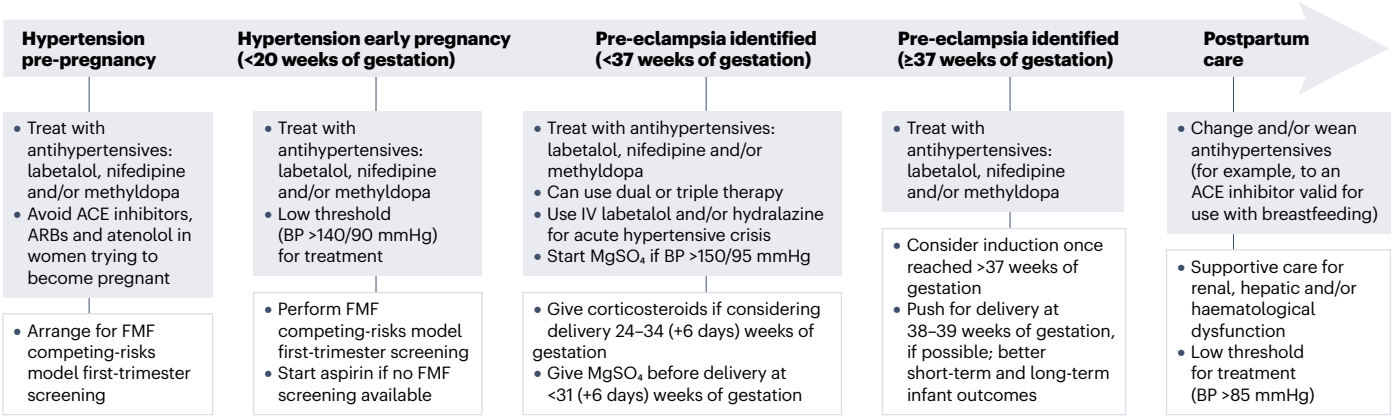

Fig. 4 | Treatment algorithm for pregnancies presenting with hypertension. Antihypertensive medications should be given to all women with hypertension (blood pressure (BP) >140/90 mmHg) trying to become pregnant or who are pregnant. Labetalol, nifedipine and methyldopa are recommended. Women who have hypertension before pregnancy or during early pregnancy should be screened using the Fetal Medicine Foundation (FMF) competing-risks model[248,249] in the first trimester. If this screening is unavailable, women with hypertension in early pregnancy should be started on aspirin. When pre-eclampsia is diagnosed preterm, corticosteroids and $MgSO_4$ should be given to mature fetal lungs and for fetal neuroprotection, respectively. When pre-eclampsia is diagnosed at ≥37 weeks of gestation, induction should be considered. Women should be weaned from antihypertensive medications at postpartum or they should be changed to antihypertensive medications valid for use while breastfeeding. Support for renal/hepatic/haematological dysfunction should be given. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; IV, intravenous.

and fetal wellbeing tests. All of these are signs and symptoms that manifest when special conditions, such as eclampsia and HELLP syndrome, occur in pre-eclampsia. If a woman has had a chronic disease before pregnancy, especially hypertension, problems often occur during pregnancy, requiring close blood pressure control, including drug switching, from early pregnancy.

Chronic hypertension. Factors such as increasing maternal age and obesity are associated with chronic hypertension, which affects ~2% of pregnant women[59]. Aspirin prophylaxis against pre-eclampsia may be less effective in these women, who have a significant risk of a range of adverse maternal and perinatal outcomes, including a higher prevalence of 'superimposed' pre-eclampsia (pre-eclampsia complicating hypertension of another cause), FGR and placental abruption[287].

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are commonly used to manage hypertension in a non-pregnant population but have been associated with adverse outcomes, including FGR, oligohydramnios, fetal renal failure and stillbirth[288]. Angiotensin-converting enzyme inhibitors may also be teratogenic, with increased rates of cardiac anomalies, although it is not clear whether this is independent of other risk factors (such as diabetes). Ideally, women taking these medications should be transferred to oral antihypertensive medications that have a recognized safety profile, such as methyldopa, labetalol and nifedipine, before pregnancy or by 12 weeks of gestation[2].

Eclampsia. The initial management in patients with eclampsia should be the use of measures for clinical stabilization of critically ill patients (fasting, oxygenation, tongue protection with Guedel cannula, venous access, bed with raised guardrails and in a semi-sitting position). The patient should preferably be kept in a calm environment but under intense monitoring. $MgSO_4$ is used worldwide as an anticonvulsant to stop and prevent seizures[289]; however, due to its increased risk of caesarean delivery and maternal adverse effects, intense clinical monitoring is required. It is reasonable therefore to restrict the use of $MgSO_4$ to patients who have presented with eclampsia or 'severe' pre-eclampsia as defined by the Magpie trial (160/110 mmHg, 3 + proteinuria) or a slightly lower threshold (150/100 mmHg, 2 + proteinuria) if accompanied by two or more signs of imminent eclampsia (headache, visual symptoms, clonus)[2,290]. Medication administration schedules and clinical signs of magnesium intoxication should be monitored. Delivery is generally indicated when eclampsia is present, especially if the gestational age is above viability in the given clinical care setting[291]. If gestational viability is not yet reached, expectant monitoring can be used in cases close to viability, provided there is rigorous monitoring[291].

HELLP syndrome. HELLP syndrome cases are very serious and delivery is usually indicated. In patients with uncontrolled blood pressure and without prior treatment, treatment optimization can be attempted; early reassessment of laboratory tests (within a maximum of 6 h after admission) and if there is laboratory and clinical improvement, expectant monitoring is possible[291].

Postpartum management

The American Heart Association (AHA)[292] considers pre-eclampsia as a significant risk factor for future cardiovascular disease. The Health after Preeclampsia Patient and Provider Engagement Network (HAPPEN) makes recommendations for awareness campaigns (for patients and primary care physicians) and yearly physical exams and laboratory evaluations for all women with prior pre-eclampsia[293], including blood pressure monitoring, BMI calculation, and fasting glucose or haemoglobin A1C to assess the risk of glucose intolerance/diabetes. These recommendations are broadly in line with the AHA and ACOG recommendations[25,292]. A randomized control trial of women with gestational hypertension or pre-eclampsia showed that self-measurement of blood pressure for 6 months postpartum significantly reduced 24-h diastolic blood pressure at 6 months (−4.5 mmHg, 95% CI −8.1 to −0.8)[294] and 3.6 years postpartum (−7.4 mmHg, 95% CI −10.7 to −4.2)[295].

Quality of life

Long-term health outcomes

Effect on women with a pre-eclamptic pregnancy. It is well established that pre-eclampsia is a risk factor for long-term adverse cardiovascular, renal and cerebrovascular events. Consequently, women with a history of early-onset and late-onset pre-eclampsia have a 5-fold and 1.65-fold increased risk from cardiovascular disease-related death, respectively, compared with women without a previous history of pre-eclampsia[296]. Compared with women who had late-onset pre-eclampsia, women who have had early-onset pre-eclampsia are at increased risk of cardiovascular and cerebrovascular disease[133,297]. To improve this, a clinical programme, Heart Health 4 Moms from Brigham and Women's Hospital (Boston, MA, USA), has recently been developed in an effort to increase awareness of preventing future cardiovascular disease[293,298]. Observational studies have also recorded a 5–12-fold increased risk of having end-stage renal disease for women with a previous history of pre-eclampsia[299,300]. Within pre-eclampsia groups, women who have had early-onset pre-eclampsia have a higher burden of kidney disease than women with late-onset pre-eclampsia[297]. Pre-eclampsia also leads to long-term cognitive dysfunction[301,302] and neurological complications, including stroke[303], cerebral white matter lesions[304,305] and posterior reversible encephalopathy syndrome[306]. Compared with late-onset pre-eclampsia, some of the neurological symptoms are more common in early-onset pre-eclampsia[304]. For cognitive outcomes, it remains uncertain if there is a difference between early-onset and late-onset pre-eclampsia[302]. An effect of pre-eclampsia on malignancies has recently been identified[307]. In a meta-analysis of >5 million women, a history of pre-eclampsia was associated with a lower risk of breast cancer (RR 0.88, 95% CI 0.83–0.93) and increased risk of ovarian cancer (RR 1.82, 95% CI 1.16–2.85)[307].

Effect on the child of a pre-eclamptic pregnancy. The long-term effect of pre-eclampsia on the child's health is mainly caused by FGR and medically indicated preterm birth[308]; therefore, these effects are most often associated with preterm pre-eclampsia[309]. It has been shown that children with fetal exposure to early-onset pre-eclampsia are more susceptible to cardiovascular dysfunction[310] and hypertension[311]. In addition, children born from severe early-onset pre-eclamptic pregnancies are at higher risk of impaired cognitive ability and neurodevelopmental outcomes[312].

Psychosocial effects

Pre-eclampsia has severe negative effects on the psychosocial profile of women. Such effects are associated with the severity of pre-eclampsia, timing of diagnosis and pregnancy outcomes. Independent observational studies report that a diagnosis of severe pre-eclampsia has a worse impact on mental health and quality of life than a diagnosis of mild pre-eclampsia[313–317]. In this case, within the preterm group, diagnosis of severe pre-eclampsia before 30 weeks has worse psychosocial consequences than diagnosis at 30–34 weeks of gestation[315]. Three independent time-course studies have investigated psychological effects, including depression and post-traumatic stress disorder, between 6 and 12 weeks postpartum, and recorded an overall decline of effect over time[316–318]; however, the psychosocial impact of pre-eclampsia can be long lasting. For women with early-onset pre-eclampsia with preterm birth, post-traumatic stress symptoms have been recorded 7 years post pregnancy[319]. The psychosocial impact of pre-eclampsia is also highly associated with pregnancy outcomes. Adverse outcomes, such as perinatal death and admission to the neonatal intensive care unit, have a significant impact on the psychological wellbeing of mothers[315,316].

Outlook

There are still many outstanding questions and opportunities to improve the prevention and treatment of pre-eclampsia, particularly term pre-eclampsia. A major obstacle in the field is how to detect placental dysfunction well before diagnosis so that preventive strategies to reverse placental dysfunction can be developed. Predictive biomarkers and causative pathways caused by abnormal placental development/function likely precede diagnosis and, to date, have been difficult to define even though some inroads have been made to predict and prevent preterm pre-eclampsia. One major consideration is that subtypes of pre-eclampsia, particularly preterm versus term pre-eclampsia, most likely have a different pathophysiology, yet much research does not distinguish between the two subtypes. Indeed, whether abnormal placental development and function drive term pre-eclampsia is yet to be experimentally proven. Examining placental-specific products directly through CVS or indirectly via liquid biopsies, such as microparticles, extracellular non-coding RNA and cell-free DNA, in maternal blood can provide a clue of the placental dysfunction that may occur in term pre-eclampsia.

The development of new in vitro and in vivo systems to model pre-eclampsia is required to substantially progress knowledge on pathogenesis.

Animal models

There is no ideal animal in vivo model that can completely cover all pathophysiological changes recorded in pre-eclampsia[320,321] although models that mimic preterm versus term pre-eclampsia subtypes are available[321]. These models serve as useful strategies to identify the mechanistic basis of pre-eclampsia subtypes and test novel therapies. Existing models include spontaneous genetic models (for example, BPH/5 mice[322]), transgenic animals, including placental-specific transgenic rodents (for example, sFLT1 (ref. [323])), human renin/angiotensin[324,325], human STOX1 (ref. [326]), *C1q*$^{-/-}$ (ref. [327])), surgically induced animal models (for example, rodent reduced uterine perfusion pressure[328] and uterine artery ligation in baboon[329]), pharmacologically

Table 3 | Comparison of reported outcomes from the CHIPS[283] and CHAP[59] trials

Outcome measure	CHIPS	CHAP
	Adjusted risk ratio (95% CI)	
Development of severe hypertension	0.56 (0.42–0.74)[a]	0.82 (0.74–0.90)[a]
Development of severe pre-eclampsia	NA	0.80 (0.70–0.92)[b]
Development of pre-eclampsia	0.88 (0.68–1.13)	0.79 (0.69–0.89)[a]
Maternal platelet <100×10^9/l	0.38 (0.17–0.87)[a]	NA
Elevated transaminases	0.43 (0.19–0.95)[a]	NA
Placental abruption	1.01 (0.43–2.35)	0.88 (0.49–1.59)[b]
Serious maternal complications	0.57 (0.26–1.27)	0.77 (0.45–1.30)
Perinatal death/NICU admission >48 h	0.98 (0.74–1.30)[c]	NA
Perinatal death	0.78 (0.35–1.76)	0.81 (0.54–1.22)[b]
Birthweight <tenth centile	1.28 (0.93–1.79)	1.04 (0.82–1.31)
Preterm birth	0.85 (0.64–1.11)	0.87 (0.77–0.99)[a]
Preterm birth <35 weeks of gestation	NA	0.73 (0.60–0.89)[b]

CHAP, Control of Hypertension And Pregnancy; CHIPS, Control of Hypertension In Pregnancy Study; NA, not available; NICU, neonatal intensive care unit. [a]Significant differences. [b]Components of primary outcome measure in the CHAP study. [c]Primary outcome measure in the CHIPS study.

Glossary

Anticardiolipin antibodies
Auto-antibodies found in antiphospholipid syndrome.

Antiphospholipid syndrome
Autoimmune disease characterized by recurring thromboses, recurrent pregnancy loss and thrombocytopenia.

Chorionicity
The number of placentas in a pregnancy.

Cytotrophoblasts
Trophoblast progenitor stem cells located interior to the syncytiotrophoblast in placental villus and in cell columns that anchor placental villus to the decidua.

Decidua
The modified endometrial layer during pregnancy into which the placenta is anchored.

Extravillous trophoblasts
Differentiated cytotrophoblasts that invade from cell columns into the decidua and engraft maternal spiral arteries.

Lupus anticoagulant
Immunoglobulin that binds to phospholipids and increases the risk of developing thromboses.

Placental malperfusion
Reduced maternal blood flow to the intervillous space of the placenta.

Primiparity
Term used to describe a first pregnancy and/or to have given birth only once.

Syncytiotrophoblast
Multinucleated, continuous trophoblast that covers the entire surface of the placental villus and is in direct contact with maternal blood.

Trophoblast
Non-embryonic fetal cells derived from the trophectoderm of the blastocyst.

Uterine spiral arteries
Small arteries that supply blood to the endometrium of the uterus during the menstrual cycle and the intervillus space of the placenta during pregnancy.

Zygosity
Genetic similarity of fetuses in multifetal pregnancies.

induced animal models (for example, N^{ω}-nitro-L-arginine methyl ester (L-NAME)[330], lipopolysaccharide[331]), human pre-eclamptic serum/extracellular vesicle-induced animal models[332,333], or animal models induced by exogenous administration of placental-released factors (for example, sFLT1 (ref. [179])). Notably, a time frame modification of treatment enables the pharmacologically induced L-NAME model of pre-eclampsia to mimic both preterm (treatment from gestational day 4–8) and term (treatment from gestational day 8–14) pre-eclampsia[334]. This model has been used to determine the effects of sildenafil citrate[335,336], sodium hydrosulfide[337], L-arginine[338], omega 3 fatty acids and vitamin E[339].

Ex vivo human models

Despite substantial progress in establishing new technologies, challenges in identifying suitable therapeutic treatments remain. Maternal hypertension and proteinuria observed in pre-eclampsia are caused by increased vascular tone and resistance[340]. Wire myography on arteries collected from patients both with or without pre-eclampsia is used as an ex vivo approach to investigate vascular reactivity and test potential therapeutic options[341], including sulforaphane[342]. Dual placental perfusion is another ex vivo approach commonly used to investigate pre-eclampsia within placental tissue[343]. Generally, term placentas are collected and fetal and maternal circulations are re-established via cannulae, with oxygen levels controlled via connection with gas exchange devices[344,345]. Modification of oxygen levels enables the investigation of pre-eclampsia under both normoxia and hypoxic conditions. Perfusion medium can also be modified, for instance, with the addition of haemoglobin to introduce pre-eclampsia-like injuries and supplementing with potential reagents to test therapeutic potentials[345]. In addition, dual placental perfusion also enables the collection of maternal perfusates, which can be used to determine released factors and their implications in pre-eclampsia[346,347]. Such technologies will enable insight into vascular damage that leads to pre-eclampsia.

Future directions

Single-cell sequencing is an exciting opportunity to understand the heterogeneity of cell responses during placental development. However, presently, it is difficult to determine how placental single-cell RNA sequencing data can be interpreted with respect to the syncytium as it is a multinucleated single cell that covers the whole of the placenta. Combining single-cell sequencing with spatial transcriptomics and/or proteomics may better define the molecular interactions during placental development. Multiomic analyses are also now possible with the development of new bioinformatic approaches to identify the molecular pathways and cellular interactions that are critical for both placental and pre-eclampsia development. However, what is lacking is the ability to spatially map the placental dysfunction that contributes to disease development. One way to circumvent this is to use placental organoids that have recently been developed[348]. Organoids can enable the modelling of disease states and may be useful in testing responses of potential therapeutics targeting the placenta. This can be further expanded in developing organoid models that incorporate immune cells, vascular cells and immune cells that are already being developed in other pathologies such as cancer.

While strides have been made in understanding the aetiology and pathogenesis of pre-eclampsia, there are still many gaps in knowledge that require collaborative efforts worldwide to make inroads. Prevention must form part of the approach to combat pre-eclampsia and its significant lifelong effects for both mother and baby. In particular, the sharing of well-characterized clinical samples and undertaking robust and large multicentre clinical trials examining potential therapeutics are required to make a significant impact in the prevention and treatment of pre-eclampsia.

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