Pre-eclampsia

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Pre-eclampsia is a multisystem pregnancy disorder characterised by variable degrees of placental malperfusion, with release of soluble factors into the circulation. These factors cause maternal vascular endothelial injury, which leads to hypertension and multi-organ injury. The placental disease can cause fetal growth restriction and stillbirth. Pre-eclampsia is a major cause of maternal and perinatal mortality and morbidity, especially in low-income and middle-income countries. Prophylactic low-dose aspirin can reduce the risk of preterm pre-eclampsia, but once pre-eclampsia has been diagnosed there are no curative treatments except for delivery, and no drugs have been shown to influence disease progression. Timing of delivery is planned to optimise fetal and maternal outcomes. Clinical trials have reported diagnostic and prognostic strategies that could improve fetal and maternal outcomes and have evaluated the optimal timing of birth in women with late preterm pre-eclampsia. Ongoing studies are evaluating the efficacy, dose, and timing of aspirin and calcium to prevent pre-eclampsia and are evaluating other drugs to control hypertension or ameliorate disease progression.

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See Online for appendix

Introduction

Pre-eclampsia complicates about 3–5% of all pregnancies and is estimated to cause at least 42 000 maternal deaths annually.[1–3] For every loss related to pre-eclampsia, at least 50–100 women have substantial morbidity.[2,4,5] Low-income and middle-income countries (LMIC) have the highest burden of major complications because of scarce resources and poorer access to adequate obstetric care and family planning services than high-income countries.[6,7]

Pre-eclampsia can present in many ways; it can be diagnosed after a woman presents with a seizure, breathlessness, severe epigastric pain, and massive placental abruption, or diagnosed at a routine antenatal consultation if a woman is asymptomatic but hypertensive.

Although keenly sought, no treatment has been found that affects disease progression. Current approaches to improving clinical outcomes in pre-eclampsia centre on prevention, prompt diagnosis, and stratification of care. If a woman diagnosed with pre-eclampsia is at an early gestation, the mainstay is expectant management with timing of birth planned to optimise maternal and fetal outcomes.

New trials and cohort studies have given insights into the prevention of pre-eclampsia, diagnostic and prognostic tools, and the optimal gestation to plan birth. This Seminar provides an update on the clinical management of pre-eclampsia. It focuses on evidence generated in the past 5 years and puts current findings into context as to how they could be used to improve clinical care and pregnancy outcomes.

Diagnosis and clinical definition

Pre-eclampsia is a progressive disease of pregnancy involving multiple organ systems. The clinical definition has evolved over time, from simply hypertension and proteinuria, to a broader classification that recognises the complex multi-organ system involvement caused by the disease. International guidelines agree that pre-eclampsia can be defined as new onset hypertension (systolic blood pressure sustained at ≥140 mm Hg or diastolic blood pressure sustained at ≥90 mm Hg, or both) with proteinuria, or end organ dysfunction after 20 weeks' gestation (panel), or both; appendix p 1 summarises how major international guidelines define pre-eclampsia.[8–12] Organs affected by pre-eclampsia include the brain, causing severe headache, visual disturbances, or eclamptic seizures; the liver, causing epigastric pain or abnormal liver function tests; the kidneys, causing abnormal renal function tests or proteinuria; the haematological system, causing haemolysis, thrombocytopaenia, or coagulopathy; the lungs, causing low oxygen saturation or pulmonary oedema; and the placenta, causing fetal growth restriction.[8–13]

When a pregnancy is complicated by underlying hypertension, superimposed pre-eclampsia is diagnosed when either new onset proteinuria or maternal end organ dysfunction develops. Challenges arise in diagnosis when women are diagnosed late in the disease pathway with no medical history (often the case in LMICs) or when women have pre-existing hypertension and kidney disease at the start of pregnancy.

Blood pressure should ideally be measured in a seated position with the correctly sized cuff on the upper arm at the level of the heart.[14] Although auscultatory devices are widely used and reliable, a validated automated device calibrated for pregnancy and pre-eclampsia can be used.[15,16]

Search strategy and selection criteria

We searched PubMed and Cochrane Library from Jan 1, 2000, to April 30, 2020, with the search terms "pre-eclampsia" and "hypertensive disorders in pregnancy". We cross-referenced these terms with: "pathophysiology", "definition", "guidelines", "prediction", "prevention", "management", "clinical trials", "aspirin", and "calcium". We also searched for guidelines from international societies and clinical specialty colleges and limited our search to publications in English. We focused on publications between 2015 and 2020 but also referenced important older publications.

Panel: Clinical diagnosis of pre-eclampsia*

Gestational hypertension (defined as systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg, or both) together with one or more of the following new-onset conditions at or after 20 weeks' gestation:

- Proteinuria (eg, protein to creatinine ratio of ≥30 mg/mmol [0·3 mg/mg])
- Other maternal organ dysfunction, including:
  - acute kidney injury (creatinine ≥90 μmol/L [1 mg/dL])
  - liver involvement (elevated alanine aminotransferase or aspartate aminotransferase >40 IU/L) with or without right upper quadrant or epigastric abdominal pain
- Neurological complications (eg, eclampsia, altered mental state, blindness, stroke, clonus, severe headaches, or persistent visual scotomata)
- Haematological complications (eg, platelet count <150 000 platelets per μL, disseminated intravascular coagulation, or haemolysis)
- Uteroplacental dysfunction (eg, fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, or stillbirth)

ISSHP=International Society for the Study of Hypertension in Pregnancy. *Based on ISSHP definition of pre-eclampsia;[10] full definitions given in appendix p 1.

	Pooled unadjusted relative risk (95% CI)[21]	Unadjusted relative risk (95% CI)[22]
Prior pre-eclampsia	8·4 (7·1–9·9)	7·19 (5·85–8·83)
Chronic hypertension	5·1 (4·0–6·5)	..
Pregestational diabetes	3·7 (3·1–4·3)	3·56 (2·54–4·99)
Maternal age <17 years	..	2·98 (0·39–22·76)
Multifetal pregnancy	2·9 (2·6–3·1)	2·93 (2·04–4·21) if twin, 2·83 (1·25–6·40) if triplet
Family history of pre-eclampsia	..	2·90 (1·70–4·93)
Antiphospholipid syndrome	2·8 (1·8–4·3)	9·72 (4·34–21·75)
Pre-pregnancy body-mass index >30 kg/m²	2·8 (2·6–3·1)	..
Systemic lupus erythematosus	2·5 (1·0–6·3)	..
Previous stillbirth	2·4 (1·7–3·4)	..
Nulliparity	2·1 (11·9–2·4)	2·91 (1·28–6·61)
Previous placental abruption	2·0 (1·4–2·7)	..
Assisted reproductive technologies	1·8 (1·6–2·1)	..
Chronic kidney disease	1·8 (1·5–2·1)	..
Maternal age >40 years	1·5 (1·2–2·0)	1·68 (1·23–2·29) if primiparous, 1·96 (1·34–2·87) if multiparous
Fetal growth restriction	1·4 (0·6–3·0)	..
Maternal age >35 years	1·2 (1·1–1·3)	..

Table 1: **Risk factors for pre-eclampsia with unadjusted relative risks from two systematic reviews (listed in descending order of risk)**

Proteinuria is detectable in most women with pre-eclampsia. Although a 24-h urine collection has been the gold standard to detect proteinuria, it is cumbersome to collect and inaccurate if done incorrectly. A spot protein to creatinine ratio of 30 mg/mol or more or an albumin to creatinine ratio of greater than 8 mg/mol are quick and reliable alternatives to diagnose clinically significant proteinuria and are now incorporated into many guideline definitions.[9,17–19] A 24-h urine collection is now only considered necessary to diagnose nephrotic-range proteinuria that might merit post-partum renal investigations. In settings where laboratory estimation is not available, a urinary dipstick showing a 2+ reading or higher is strongly suggestive of clinically significant proteinuria.[20]

Most international guidelines recognise that severe features of pre-eclampsia can be identified, and recommend that the appearance of particular symptoms and signs should either trigger delivery or necessitate admission to hospital for safety and intensive surveillance (appendix p 2).

Risk factors

Clinical risk factors for pre-eclampsia are summarised in table 1,[21,22] with the highest risk factors being history of pre-eclampsia (an 8-times increase in risk, although the risk might be lower for those with pre-eclampsia in a first pregnancy but not in subsequent pregnancy) and chronic hypertension (a 5-times increase in risk). A history of preterm pre-eclampsia carries the greatest risk of developing pre-eclampsia with around 25–30% of women experiencing recurrent disease.[23–27] Obstetric complications in a previous pregnancy, such as fetal growth restriction, stillbirth, and abruption, also incur an increased risk of pre-eclampsia, reflecting the potentially shared pathophysiology of clinical phenotypes linked to placental dysfunction.

Some risk factors for developing pre-eclampsia might be more amendable to pre-pregnancy modification than others; interventions including weight reduction, avoiding multifetal pregnancies from assisted reproduction technologies, increasing societal awareness of the adverse pregnancy outcomes associated with maternal age, and optimally treating chronic medical conditions (eg, systemic lupus erythematosus and chronic hypertension) might all be beneficial in reducing pre-eclampsia risk.

Pathogenesis of pre-eclampsia

In normal early pregnancy, the placenta remodels local uterine vasculature, setting up optimal conditions for nutrient and oxygen exchange throughout pregnancy. Extravillous placental trophoblast cells migrate through the inner third of the myometrium of the uterus and remove the smooth muscle from the maternal spiral arterioles,[28] rendering the ends of the vessels unable to constrict. Consequently, the terminal part of the spiral arterioles remains wide open and the net result is a high capacitance, low resistance system at the maternal–fetal interface. The maternal–fetal interface promotes plentiful blood flow to the implantation site allowing for efficient maternal-to-fetal nutrient exchange.

Impaired spiral arteriole remodelling is seen in some women who develop pre-eclampsia,[29] and is often present when the disease results in preterm delivery with fetal growth restriction.[13] The consequent underperfusion, high velocity, and turbulent blood flow (emanating from the poorly remodelled spiral arterioles) causes placental ischaemia[30] and oxidative stress,[31,32] damages the placental villi, and leads to abnormal angiogenic protein levels in the maternal blood.[33] This pathology of the maternal blood supply has been re-termed maternal vascular malperfusion,[28,34] and is histologically characterised by reduced placental size, infarction, abnormal development of the placental villi, and a scarcity of transformation of the maternal decidual spiral arterioles.[28] The histological severity of maternal vascular malperfusion disease correlates with the clinical severity of maternal-fetal manifestations of pre-eclampsia, and inversely correlated with gestational age at delivery.[35–38]

Although the sentinel upstream event triggering the cascade that leads to poor placental implantation and subsequent maternal vascular malperfusion disease has not been completely elucidated, a potentially major contributor is immunological mismatching between maternal and paternal antigens.[31] The immune system has an active role in normal and pathological interactions between the extravillous trophoblast cells and the host decidua, and abnormal cellular interactions occurring in the early first trimester might increase the risk of developing pre-eclampsia.[39]

As pregnancy continues into the second trimester, the diseased placenta progressively secretes elevated amounts of anti-angiogenic factors that cause vascular inflammation, endothelial dysfunction, and maternal vascular injury.[31] The net result of this altered angiogenic profile is the clinical manifestation of hypertension and injury to multiple maternal organs (figure 1). First proposed in 1993,[40] this two-stage paradigm of poor early placental development followed by systemic endothelial dysfunction and severe maternal organ injury is an effective model to frame the pathogenesis of pre-eclampsia (figure 1).

There are many candidate factors secreted in excess by the pre-eclamptic placenta that could contribute to endothelial dysfunction: proinflammatory cytokines, exosomes,[41] and extracellular vesicles;[42] and anti-angiogenic molecules such as soluble fms-like tyrosine kinase-1 (sFlt1)[43,44] and soluble endoglin.[45] These placenta-derived factors can act on the maternal vascular endothelium to incite local endothelial release of other factors that worsen the dysfunction, such as thromboxane, proinflammatory cytokines, and possibly sFlt-1 itself.[46] This event is combined with suppression of the release of pro-angiogenic placental growth factor (PlGF).

sFlt-1 is an anti-angiogenic protein that binds to the functional receptor binding domain of vascular endothelial growth factor (VEGF), neutralising the ability of VEGF to signal to endothelial cells lining arteriolar blood vessels to maintain vasorelaxation. Although the binding of sFlt-1 to VEGF is not the primary pathogenic event triggering pre-eclampsia, sFlt-1 has many features implicating it as a major disease driver. For example, elevated concentrations of sFlt-1 are seen weeks before the clinical onset of pre-eclampsia[44] and during pre-eclampsia;[44,47] given that sFlt-1 is anti-angiogenic, a pathogenic role is biologically plausible;[31] and administrating sFlt-1 into animals can phenocopy aspects of clinical disease.[43] A genome-wide association study found that the only gene variant across the entire fetal genome that was significantly associated with pre-eclampsia was a locus near the *FLT1* gene (codes sFlt-1) on chromosome 13[48] (concurring with an increased pre-eclampsia risk in pregnancies complicated by trisomy 13[49]).

The two-stage paradigm accounts for many risk factors for pre-eclampsia. Poor placental implantation explains why fetal growth restriction often coexists with pre-eclampsia. Immunological involvement is the postulated reason for why nulliparity is a risk factor.[21,22] Increased placental mass could explain why twins and gestational trophoblastic disease are risk factors for pre-eclampsia. Women who are older than 40 years, are obese, have diabetes, or have chronic hypertension are likely to have pre-existing endothelial dysfunction, making them more susceptible to developing pre-eclampsia.

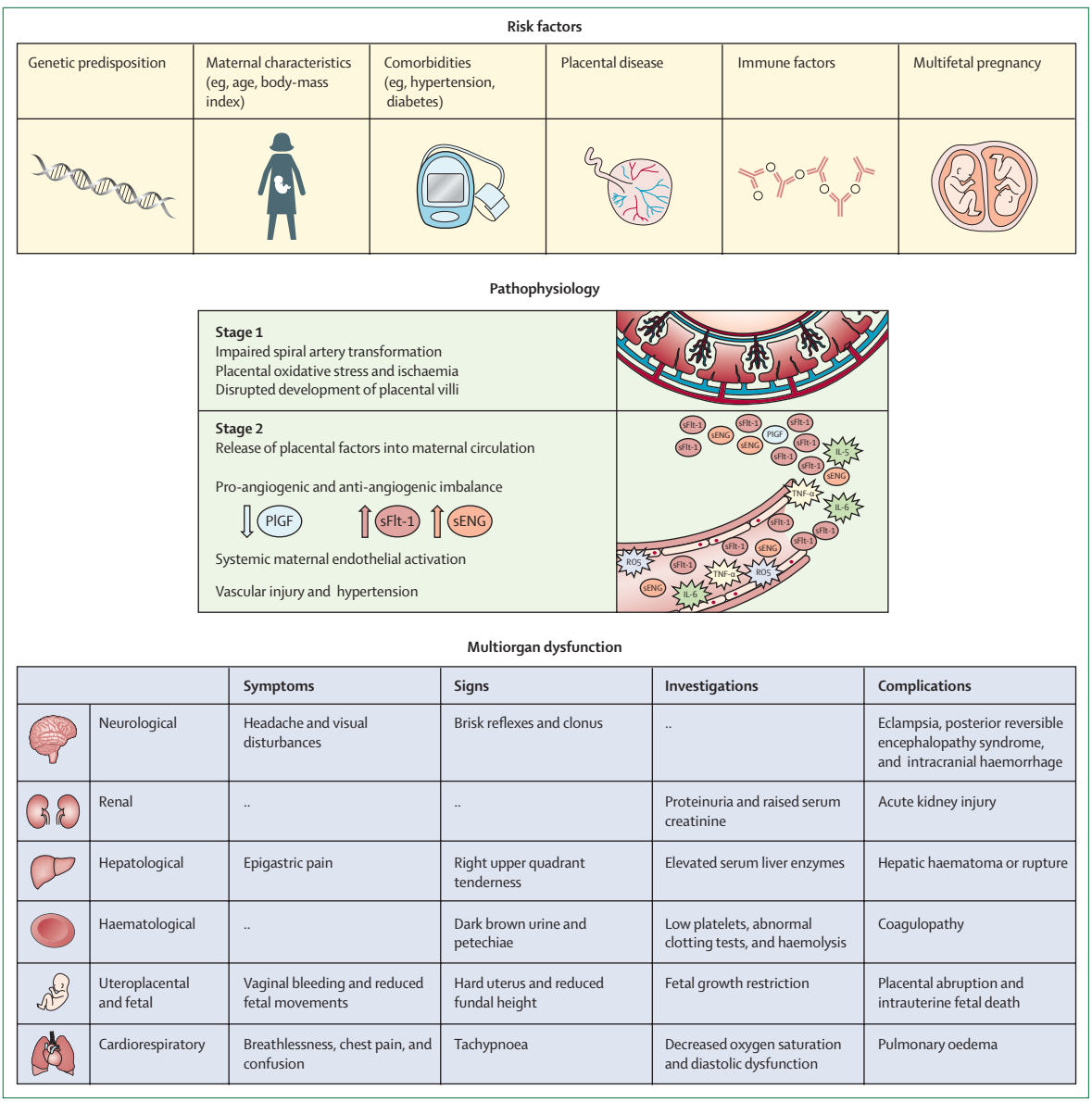
Predictive and diagnostic tools for pre-eclampsia

The two active strategies being pursued to decrease short-term and long-term adverse outcomes caused by pre-eclampsia are predicting who is at high risk of developing the disease (screening for pre-eclampsia), and using tests as diagnostic adjuncts to exclude the likelihood that a woman has pre-eclampsia.

Screening in early pregnancy

Current screening strategies are based on the combined use of clinical risk factors, maternal plasma or serum biomarkers, and imaging modalities such as uterine artery Doppler flow velocity waveform analysis. These methods are variably integrated into predictive algorithms used to stratify antenatal care surveillance and identify women most suitable for prophylactic treatment with aspirin. Many predictors have been reported in primary research studies, with a 2019 umbrella review identifying 90 predictors and 52 prediction models. However, independent and external validation of prediction models is rare.[50]

Because the predictive performance of using either clinical risk factors[51] or serum biomarkers alone[52] is modest, researchers have attempted to improve predictive ability by combining variables, such as maternal demographic, comorbidity-related, and pregnancy-related variables, circulating levels of biomarkers (typically PlGF and pregnancy-associated plasma protein A), and uterine



		Symptoms	Signs	Investigations	Complications
	Neurological	Headache and visual disturbances	Brisk reflexes and clonus	..	Eclampsia, posterior reversible encephalopathy syndrome, and intracranial haemorrhage
	Renal	..	..	Proteinuria and raised serum creatinine	Acute kidney injury
	Hepatological	Epigastric pain	Right upper quadrant tenderness	Elevated serum liver enzymes	Hepatic haematoma or rupture
	Haematological	..	Dark brown urine and petechiae	Low platelets, abnormal clotting tests, and haemolysis	Coagulopathy
	Uteroplacental and fetal	Vaginal bleeding and reduced fetal movements	Hard uterus and reduced fundal height	Fetal growth restriction	Placental abruption and intrauterine fetal death
	Cardiorespiratory	Breathlessness, chest pain, and confusion	Tachypnoea	Decreased oxygen saturation and diastolic dysfunction	Pulmonary oedema

Figure 1: **Pathophysiology of pre-eclampsia**

artery Doppler flow velocity waveforms (measured at around 13 weeks' gestation), into an algorithm. One such algorithm has been reported to have a higher detection rate for subsequent pre-eclampsia (42·5% detection rate; 95% CI 38·0–46·9) than using clinical risk factors alone (30·4%; 95% CI 26·3–34·6).[51] Two screening algorithms have had external validation (comprehensively presented in the US Preventive Services Task Force preeclampsia screening evidence report and systematic review[53]), but the limitations of both the primary research and validation studies include small numbers of cases, incomplete reporting (especially calibration statistics), and, considering the high false-positive rates, the absence of information on potential harms of risk prediction. These multivariable prediction algorithms have a higher test performance for pre-eclampsia that requires early delivery (typically before 34 weeks' gestation) than for late-onset pre-eclampsia or all pre-eclampsia; however, as the prevalence of early onset disease is less than 1% of pregnancies, positive predictive values are low (typically around 10%[54]), although these could be deemed high enough to initiate prophylactic treatment. The clinical implications and cost of implementing such a screening strategy need further consideration.[53] Although this first trimester screen and treat approach is already endorsed in some international guidelines,[10,55] whether it is cost-effective compared with screening approaches based on clinical risk factors is unclear. An integrated algorithm

requiring additional ultrasound scanning (for Doppler waveforms) and biochemical analysis of blood might be feasible in private health-care systems, but not affordable in nationalised health systems or resource-limited settings.

Diagnostic adjuncts

Research has also focused on use of biomarkers as diagnostic adjuncts in women with suspected pre-eclampsia; these tests can help to clarify the likelihood of pre-eclampsia when the clinical picture is uncertain.

Numerous potential biomarkers for pre-eclampsia have been reported,[56] but few have survived prospective evaluation in cohort studies or have been assessed in randomised controlled trials. In healthy pregnancies, the concentration of PlGF (a pro-angiogenic protein secreted by the placenta) in circulation increases as gestation advances before decreasing towards term and is decreased in women with pre-eclampsia.[44,57] By contrast, circulating sFlt-1 concentrations, which increase towards term in healthy pregnancies, are elevated in the circulation of women with pre-eclampsia. The finding that low PlGF and high sFlt-1 concentrations predate the clinical diagnosis of pre-eclampsia by some weeks[44] enables their potential use as diagnostic adjuncts.

Prospective multicentre cohort studies have evaluated the sFlt-1 to PlGF ratio[58] and PlGF alone[59] in women with suspected pre-eclampsia, principally to predict adverse pregnancy outcomes[58] or pre-eclampsia requiring delivery within 2 weeks.[59] These angiogenic factor-based tests have high-performance characteristics, particularly to support the possibility that a woman with suspected pre-eclampsia and a normal test result is unlikely to need imminent delivery for pre-eclampsia. For example, testing for circulating PlGF at a threshold of 100 pg/mL has a sensitivity of 96% (95% CI 89–99) and negative predictive value of 98% (95% CI 93·0–99·5) for a diagnosis of pre-eclampsia within 14 days, outperforming clinical variables such as blood pressure measurement and blood markers (eg, uric acid and alanine aminotransferases).[59] Similarly, testing for a sFlt-1 to PlGF ratio of 38 or lower had 80·0% (95% CI 51·9–95·7) sensitivity and a negative predictive value of 99·3% (95% CI 97·9–99·9) for detecting pre-eclampsia in the subsequent 7 days.[47] Head-to-head comparison of these angiogenic factor-based tests suggests that they perform similarly in predicting the need for a women with suspected pre-eclampsia to deliver within 14 days of the test,[60] but the commercial assays measure different isoforms of the angiogenic factors, which means that numerical test thresholds are not interchangeable across platforms.

A single-centre trial found that sFlt-1 to PlGF ratio testing improved the clinical identification of women who developed pre-eclampsia within 7 days (100% in revealed testing group *vs* 83% in non-revealed testing group; p=0·038), without changing the overall maternal admission rate (primary outcome) or altering gestational age at birth, birthweight, or neonatal unit admission rate.[61] In a multicentre randomised controlled trial, the use of revealed PlGF testing halved the time it took for clinicians to diagnose pre-eclampsia compared with concealed testing, from 4·1 to 1·9 days (time ratio 0·36; 95% CI 0·15–0·87) and significantly reduced a composite of severe maternal adverse outcomes (adjusted odds ratio [aOR] 0·32; 95% CI 0·11–0·96), again with no significant differences in preterm birth incidence, birthweight centiles, or neonatal unit admission rate.[62] A linked cost-effectiveness analysis reported that clinical care incorporating PlGF testing costs less than the current standard practice (cost-saving UK£149 per patient tested) after accounting for the cost of the test in the UK.[63] With this evidence, UK guidelines now recommend that PlGF-based testing is used for women who have suspected pre-eclampsia before 35 weeks' gestation,[9] and recommend it to be integrated into the overall clinical assessment of the woman and to direct surveillance strategies for future management (eg, using the management algorithm provided in supplementary material from the trial).[62]

Prevention of pre-eclampsia

Aspirin

Aspirin is the only preventive drug treatment for pre-eclampsia that is supported by strong evidence. A 2019 Cochrane review concluded there is high-quality evidence that low-dose aspirin taken daily from the end of the first trimester until 36 weeks' gestation reduces the risk of developing pre-eclampsia by around 18% (relative risk 0·82; 95% CI 0·77–0·82).[64] The risk reduction for preterm pre-eclampsia is likely to be greater than for pre-eclampsia in general.[65,66]

How aspirin prevents pre-eclampsia is unclear. Theories include: that aspirin enhances placental implantation, which would necessitate aspirin intake early in the pregnancy; and that aspirin protects the maternal vasculature by decreasing platelet reactivity, decreasing thromboxane concentrations, and increasing prostacyclin production,[67] which would entail continuing aspirin treatment throughout pregnancy.

Screening approaches to select who is offered aspirin prophylaxis commonly involve the use of clinical risk factors (table 2), such as treating those with two moderate-risk factors or one high-risk factor for pre-eclampsia.[8–10]

The ASPRE trial recruited 1776 participants identified at high risk of developing pre-eclampsia based on first trimester risk screening test algorithm that combines maternal biomarker information, biophysical (ultrasonographic uterine artery Doppler waveform analysis) information, and maternal history.[51] The trial found that administering 150 mg of aspirin at night to those who screened as high risk reduced their risk of preterm pre-eclampsia before 37 weeks' gestation by 62% (relative risk [RR] 0·38; 95% CI 0·20–0·74).[65] However, if false negatives are taken into account,[68]

this approach could prevent just less than half of all cases of preterm pre-eclampsia. The trial showed that frequency of term pre-eclampsia, the most prevalent subtype, did not decrease, but the trial was probably underpowered for this outcome.[65] This trial used night-time dosing,[65] which is endorsed by International Federation of Gynecology and Obstetrics guidance on pre-eclampsia prophylaxis.[55] However, the evidence for night-time dosing is weak because it is based on a small trial[69] that contains methodological limitations (eg, unregistered, power calculation not based on the primary outcome) and whether aspirin prophylaxis is more effective if taken at night than during the day is unclear.

There is no consensus on the dose of aspirin to prevent pre-eclampsia, with no randomised trials comparing different aspirin doses. Most guidelines recommend 75–100 mg aspirin daily,[8–10] (table 2) and this might be appropriate given the majority of trials in the 2019 Cochrane meta-analysis used doses within this range.[64,70] Although 150 mg of aspirin might be a suitable dose if the first trimester screening algorithm is used,[65] there is not enough evidence to support the use of this dose widely. A large trial for women who were nulliparous (ASPIRIN

	ACOG[8]	NICE[9]	ISSHP[10]	FIGO[55]*
Clinical risk factors				
Chronic hypertension	High	High	High	Included
Type 1 or type 2 diabetes	High	High	High	Included
Renal disease	High	High	High	Included
Autoimmune disease (SLE, APLS)	High	High	High	Included
History of pre-eclampsia	High	High	High	Included
Multifetal gestation	High	Moderate	High	Included
History of other pregnancy hypertensive disorder	Moderate	High	Not included	Included
Use of ART	Not included	Not included	High	Included
High BMI (BMI threshold)	Moderate (>30 kg/m^2)	Moderate (≥35 kg/m^2)	High (>30 kg/m^2)	Included
Nulliparity	Moderate	Moderate	Not included	Included
Family history of pre-eclampsia (mother or sister)	Moderate	Moderate	Not included	Included
More than 10-year pregnancy interval	Moderate	Moderate	Not included	Included
Maternal age (age)	Moderate (>35 years)	Moderate (≥40 years)	Not included	Included
Maternal height	Not included	Not included	Not included	Included
Obstetric history (LBW, SGA, or previous adverse pregnancy outcome)	Moderate	Moderate	Not included	Included
Sociodemographic characteristics (Black and low socioeconomic status)	Moderate	Not included	Not included	Included
Recommendations for aspirin prophylaxis				
When to offer aspirin	Presence of any high-risk factor or presence of any two moderate-risk factors	Presence of any high-risk factor or presence of any two moderate-risk factors	Presence of any high-risk factor; no recommendation to take aspirin in the presence of the moderate-risk factors	High-risk on the Fetal Medicine Foundation first trimester combined test
Universal first trimester screening	Does not recommend universal first trimester screening	Does not recommend universal first trimester screening	Supports its use when integrated into the local health system but does not specifically recommend it	Supports universal first trimester screening
Recommended daily dose of aspirin	81 mg† initiated between 12 and 28 weeks' gestation, ideally before 16 weeks	75–150 mg from 12 weeks	75–162 mg, ideally before 16 weeks' gestation but definitely before 20 weeks' gestation	150 mg at night initiated between 11 and 14 weeks' (+6 days) gestation
When to cease aspirin	Continue until delivery	Continue until delivery	No recommendation	Continue until 36 weeks' gestation, delivery, or when pre-eclampsia is diagnosed

ACOG=American College of Obstetricians and Gynecologists. NICE=National Institute for Health and Care Excellence. ISSHP=International Society for the Study of Hypertension in Pregnancy. FIGO=The International Federation of Gynecology and Obstetrics. SLE=systemic lupus erythematosus. APLS=antiphospholipid syndrome. ART=assisted reproduction techniques. BMI=body-mass index. LBW=low birthweight. SGA=small for gestational age. *FIGO recommends the Fetal Medicine Foundation multivariate regression algorithm and does not list factors as high or moderate risk. †The ACOG guideline acknowledges that other doses have been studied in systematic reviews but recommends 81 mg as it is the only dose available in the USA.

Table 2: **Clinical risk factors to identify women at risk of pre-eclampsia recommendations for aspirin prophylaxis from four international guidelines**

trial, 11 976 randomised women) in LMICs showed that 81 mg of aspirin daily started during the first trimester was associated with a risk reduction in the primary outcome of preterm birth (RR 0·89; 95% CI 0·81–0·98), and a secondary outcome (specified after the trial had concluded) of hypertensive disorders and preterm pre-eclampsia requiring delivery before 34 weeks' gestation (RR 0·38; 95% CI 0·17–0·85), with reduced perinatal mortality.[66] This finding suggests that universal treatment for particular groups of women, especially nulliparous women in LMICs, could be an alternative approach (given the higher incidence of pre-eclampsia in LMICs than in high-income countries) and that low doses (75–100 mg) might be as effective as high doses (150 mg). However, the lack of an overall reduction in hypertensive disorders in the ASPIRIN trial (RR 1·08; 95% CI 0·94–1·25) suggests that aspirin does not always prevent pre-eclampsia but might delay clinical onset to an advanced gestation.[66]

National guidelines recommend commencing aspirin before 16 weeks' gestation and this recommendation is supported by a meta-analysis[71] and the ASPRE trial.[65] However, an individual participant meta-analysis found aspirin decreased rates of pre-eclampsia even if commenced after 16 weeks' gestation.[72] A sensible approach might be to start aspirin before 16 weeks' gestation but still offer it to women who are up to 22 weeks' gestation.[73]

In addition, meta-analyses have suggested that aspirin is associated with a small post-partum bleeding risk[64,70] supported by a large 2020 registry study from Sweden (where 75 mg aspirin daily with cessation at 36 weeks' gestation is recommended), reporting an increased risk of intra-partum (aOR 1·63; 95% CI 1·30–2·05) and post-partum (aOR 1·23; 95% CI 1·08–1·39) haemorrhage.[74] Such risks should be weighed against potential net benefit.

Calcium

Oral calcium might prevent pre-eclampsia, especially when dietary calcium intake is low. A meta-analysis concluded that 1 g of calcium daily reduced rates of pre-eclampsia (RR 0·45; 95% CI 0·31–0·65).[75] Calcium supplementation could be more effective in reducing the risk of pre-eclampsia among women with a low dietary calcium intake (RR 0·36; 95% CI 0·2–0·65) than in those with adequate intake (RR 0·62; 95% CI 0·32–1·2).[75] Calcium supplementation might reduce the risk of the composite outcome of maternal death or serious morbidity (RR 0·80; 95% CI 0·66–0·98) and preterm birth (RR 0·76; 95% CI 0·60–0·92), but the authors of this meta-analysis cautioned that the treatment effects of calcium in all these analyses might be overestimated because of small-study effects or publication bias. We suggest offering calcium in areas of low intake but are awaiting more trials in settings where most women are calcium replete.

Other preventive treatments

An individual participant meta-analysis reported that administering low-molecular-weight heparins trended towards a reduced risk of pre-eclampsia (9% *vs* 15%, absolute difference –6·2% [–13·1 to 0·6]; p=0·08; n=877).[76] However, the authors noted that risk reductions were observed only in single-centre trials and not multicentre trials. A subsequent multicentre trial of enoxaparin did not find a trend towards a reduced risk of pre-eclampsia.[77] Unless new trials elucidate whether they reduce the risk of pre-eclampsia, low-molecular-weight heparins should not be used to prevent pre-eclampsia.[76]

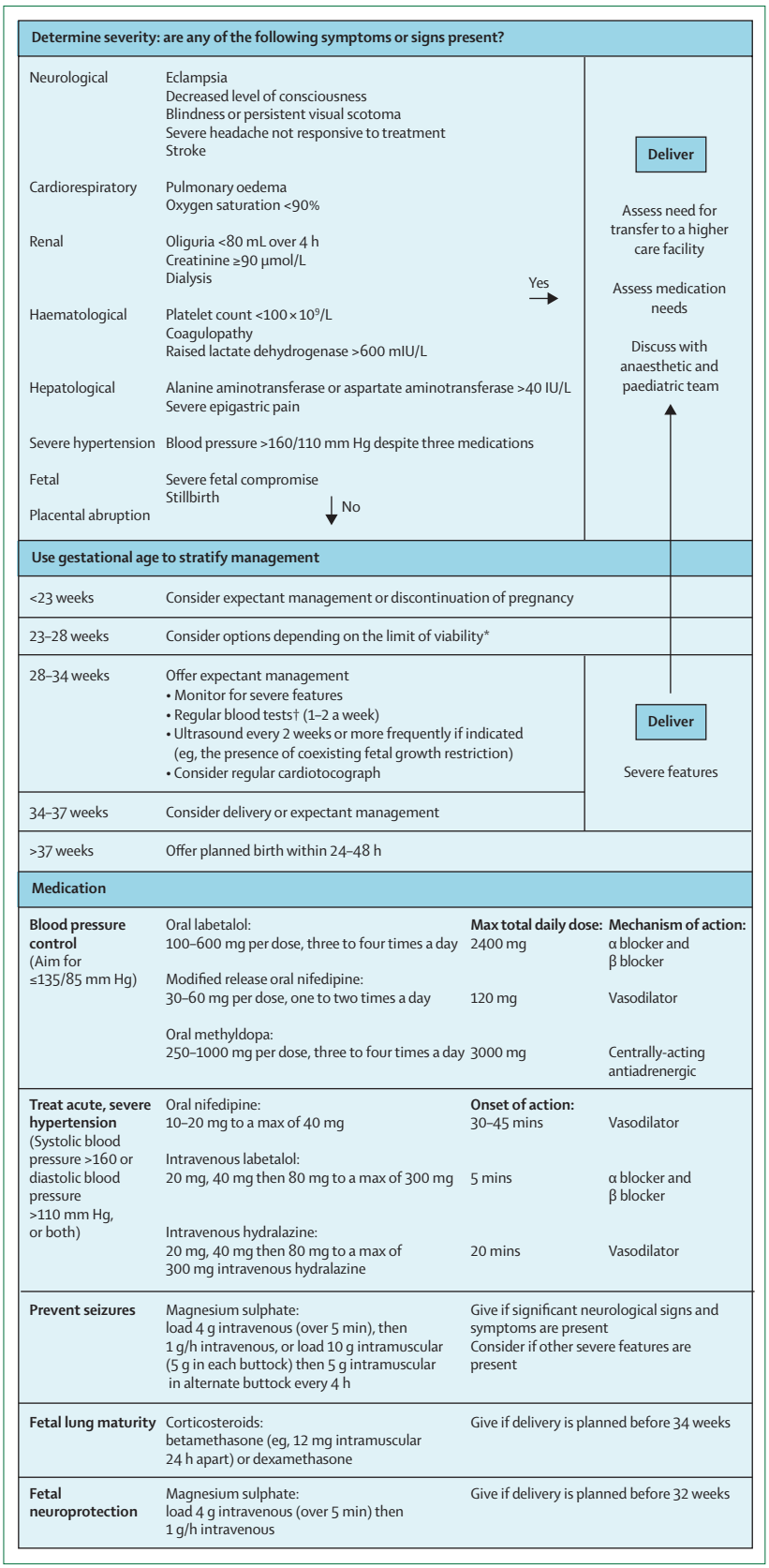
There are other agents that could prevent pre-eclampsia, but still require further evaluation. Metformin has biological actions that means it could reduce the risk of pre-eclampsia,[78] but meta-analyses[79] and trial outcomes[80,81] have yielded conflicting results. None of the trials of metformin in pregnant populations have studied pre-eclampsia as the primary outcome. Arginine decreased pre-eclampsia occurrence in two trials;[82–84] pravastatin has shown some promise in small trials[84,85] and there are large randomised trials ongoing (EudraCT 2016–005206–19; NCT01717586) or planned (NCT03944512). Vitamin C and vitamin E supplementation does not prevent pre-eclampsia.[86] Although some cohort studies had reported an association between low maternal serum vitamin D levels and increased risk of pre-eclampsia,[87] a systematic review of clinical trials has not supported the benefit of vitamin D supplementation in preventing pre-eclampsia.[88]

Management of women with pre-eclampsia

Once diagnosed, pre-eclampsia is often a progressive condition and maternal organ function deteriorates with time. No drug has been discovered that clearly slows disease progression and the only option to stop the disease is to deliver the fetus and placenta. Therefore, the overall approach to management is to deliver the baby and placenta at term gestation, or, if preterm pre-eclampsia is diagnosed, to try expectant management of the pregnancy until a more advanced gestation is reached (figure 2). If the decision is made to continue the pregnancy, the woman and baby need to be closely monitored, and the baby needs to be delivered if there is evidence that either are clinically compromised.

Timing of birth

For pre-eclampsia at 37 weeks' gestation or beyond, initiating birth is warranted because expectant management will increase the likelihood of adverse maternal outcomes with little or no fetal gain.[89] At preterm gestations before 34 weeks, a Cochrane review of four trials concluded that expectant management might be associated with decreased morbidity for the baby.[90] Therefore, a common management strategy is to continue the pregnancy so that the fetus reaches a more advanced gestation. Pre-eclampsia is closely monitored, and delivery is expedited if there is evidence of clinically



important maternal organ dysfunction or fetal compromise (appendix p 2).

For pre-eclampsia diagnosed between 34 and 37 weeks' gestation, a 2019 meta-analysis examining the timing of birth concluded that women with a higher risk of progression to complications of pre-eclampsia, such as those women who are nulliparous, could benefit from earlier delivery;[91] by 36 weeks' gestation, neonatal risks (eg, respiratory distress syndrome) reduce such that the threshold for initiating planned delivery becomes lower than before 36 weeks' gestation. Since this meta-analysis, an additional trial has been published that compared planned early delivery with expectant management until 37 weeks' gestation; findings showed that immediate delivery decreased the risk of a composite of adverse maternal outcomes (RR 0·86; 95% CI 0·79–0·94) but increased admission to the neonatal unit (RR 1·26; 95% CI 1·08–1·47), although the proportions of infants with neonatal morbidity were very similar between the two groups.[92] Between 34 and 37 weeks' gestation, timing birth is a trade-off between maternal and fetal risk, and the decision should be shared with the woman.

Monitoring the woman and fetus during expectant management

With expectant management, birth should be expedited irrespective of the gestation if there is evidence of severe maternal end organ dysfunction, such as an eclamptic seizure, pulmonary oedema, or a placental abruption (table 2, appendix p 2).[9] Delivery should also be considered if biochemical testing (generally done twice a week) reveals thrombocytopenia, haemolysis, coagulopathy, or worsening renal or liver dysfunction.[9] The degree of proteinuria itself is a poor predictor of maternal or fetal complications and should not trigger birth.[93] Antenatal steroids should be administered if birth is expedited before 34 weeks' gestation.[94] As a guide to duration of pregnancy, women with late preterm pre-eclampsia (34–37 weeks' gestation) managed expectantly in the PHOENIX trial delivered a median of 6 days after diagnosis; in 55% of women, their delivery plans needed to be expedited before 37 weeks' gestation due to maternal or fetal clinical concerns.[92]

Researchers have aimed to develop prognostic tools to stratify a woman's risk of subsequent adverse pregnancy outcome, so that surveillance can be tailored to women at highest risk (eg, women who are inpatients, or are transferred for a high level of maternal or neonatal care), and birth can be optimally timed. Two prognostic tools

Figure 2: **Overview for managing pre-eclampsia adapted from international guidelines**

*Viability is dependent on the resources available. Either consider offering discontinuation of the pregnancy or expectant management. †Haemoglobin, platelet count, urea, creatinine, aspartate aminotransferase, or alanine aminotransferase where the purpose is to monitor for the development of severe features.

that have undergone external validation incorporate a varied combination of maternal clinical variables, symptoms, signs, and bedside and laboratory investigations.[95,96] The UK National Institute for Health and Care Excellence guidelines recommend that decisions on place of care and timing of delivery are best made by considering the full clinical picture, not only the results from prognostic models;[9] trials of implementation of the prognostic tools in high-income countries are awaited.

Most women with pre-eclampsia will require antihypertensive treatment with the aim of reducing the risk of severe hypertension, and other maternal complications. If a women is given antihypertensive treatment, their target blood pressure should be 135/85 mm Hg or less, because less tight control (eg, a diastolic blood pressure of 100 mm Hg) incurs an increased risk of severe hypertensive episodes.[97] Antihypertensive agents that are commonly used to control blood pressure include labetalol, nifedipine, and methyldopa.[9] They all have favourable safety profiles and can be combined to achieve better blood pressure control if needed. There are no large-scale trials indicating which agent is the most effective, but the current Cochrane meta-analysis concluded that β blockers (typically labetalol) and calcium-channel blockers (usually nifedipine) are more effective than other alternatives for preventing severe hypertension.[98] The authors of this systematic review commented that high-quality randomised trials that are adequately powered are needed to delineate the benefits and adverse effects of these agents for the woman and the fetus. Some have proposed that choice of antihypertensive treatment might be guided by maternal haemodynamic assessment; this proposal is based on observations that early-onset pre-eclampsia can be characterised by vasoconstriction and thus women might respond preferentially to a calcium-channel blocker (because it reduces systemic vascular resistance), whereas a β blocker might be suitable for women with late-onset disease who have normal to high cardiac output.[99] However, this approach needs evaluation before it is recommended for clinical practice. Angiotensin converting enzyme inhibitors and diuretics should not be used in pregnancy because of potential safety concerns.

For the treatment of sustained severe hypertension (a systolic blood pressure of ≥160 mm Hg or a diastolic blood pressure of ≥110 mm Hg), a network meta-analysis reported similar efficacy between nifedipine, hydralazine, and labetalol, although differences are apparent in their side-effect profile with hydralazine less preferred.[100] Intravenous agents (eg, labetalol or hydralazine) can be used to control severe hypertension, but fetal heart-rate monitoring should be done because fetal bradycardia arising from acute maternal hypotension and reduced placental perfusion is a risk of treatment with these intravenous agents. Oral agents might also be used and can be more accessible in LMIC than intravenous agents; a 2019 trial in India found a single dose of oral nifedipine (10 mg) or labetalol (100 mg) were effective around 80% of the time in controlling severe hypertension, with lower efficacy for methyldopa.[101] Persistent severe hypertension refractory to treatment might be a trigger for delivery.

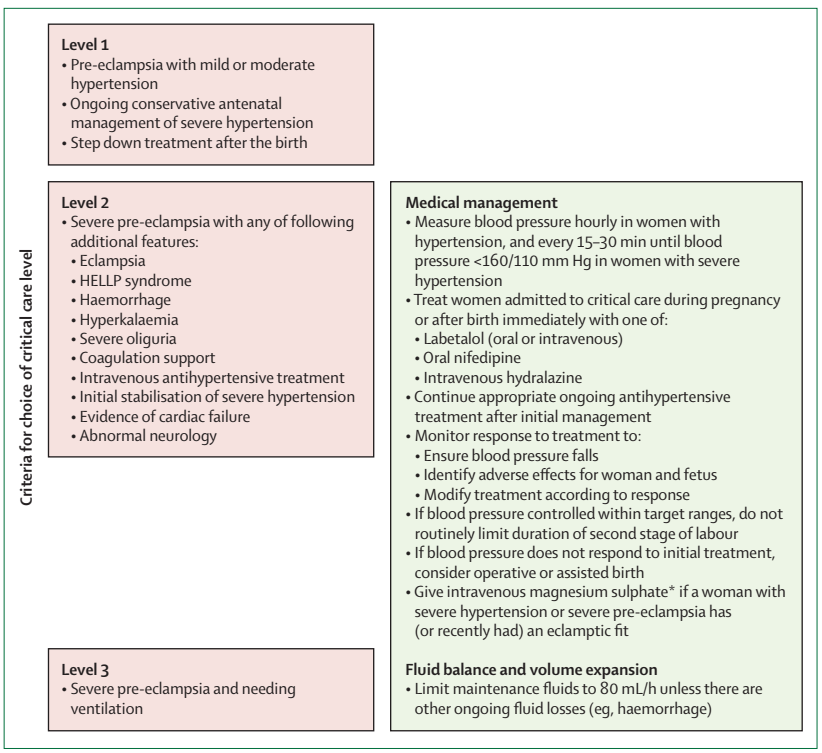


Figure 3: **Features of severe pre-eclampsia and management in critical care**
*Intravenous magnesium sulphate doses are shown in figure 2.

In women with pre-eclampsia, magnesium sulphate reduces the risk of an eclamptic seizure by 58%.[102] Neurological symptoms such as severe, intractable headache or repeated visual scotoma might suggest a high risk of an eclamptic seizure[9] and warrant starting magnesium sulphate. Symptoms modestly predict eclampsia but no better tools exist.[103] Magnesium sulphate is preferably administered intravenously rather than intramuscularly (figure 2) as intramuscular administration can cause bruises or abscesses, but intramuscular magnesium sulphate could be useful in settings where intravenous administration is not available. In LMICs, eclampsia is much more prevalent in pregnant women than in high-income settings,[104] but the main barrier for prevention of eclampsia is timely access to effective antenatal care and magnesium sulphate. Optimising the place of care and tailored management will depend on the health-care setting and severity of disease (figure 3).

There is a strong association between pre-eclampsia and coexisting fetal growth restriction, particularly in women with preterm disease. Therefore, the diagnosis of pre-eclampsia should prompt an assessment of fetal size and umbilical artery Doppler with ultrasound; if growth

is restricted, the fetus should be monitored with serial tests of wellbeing.[9] Delivery for preterm pre-eclampsia can be prompted for fetal indications (eg, abnormal fetal Doppler waveforms or fetal heart rate monitoring) rather than maternal concerns.[105]

Long-term complications of pre-eclampsia

Large cohort studies and meta-analyses have established that pre-eclampsia confers an increased risk of major chronic diseases in later life including many cardiovascular complications.[106–110] A 2017 systematic review including more than 6·4 million women showed that those with a history of pre-eclampsia have a 4-times greater risk of heart failure, a 2·5-times greater risk of coronary heart disease, a 1·8-times greater risk of stroke, and an overall 2·2-times greater risk of death from cardiovascular disease than do women with no history of pre-eclampsia.[108] There is also a 2-times greater risk of developing cardiomyopathy[111] and a 4·5-times greater risk of chronic hypertension.[9] The risk of hypertension is apparent within 10 years of the index pregnancy, even for those who had their pregnancy at age 20–30 years.[112]

Diabetes is also more common in women with a history of pre-eclampsia even if they did not develop gestational diabetes.[113,114] Women with a history of pre-eclampsia are more likely to develop chronic renal conditions, particularly chronic kidney disease and hypertensive kidney disease, and have a 5-times greater risk of end-stage kidney disease than do women without a history of pre-eclampsia (9-times for those who had preterm pre-eclampsia).[115–117] There is also an increased risk of developing neurological conditions, such as a 3-times greater risk for vascular dementia[118] and, potentially, an increased probability of developing deficits in perception, memory, and motor function.[118,119] The risks of developing many of these long-term complications rise more sharply if birth was preterm, if there was coexistent fetal growth restriction, if severe complications occurred, or if pre-eclampsia occurred in more than one pregnancy.[107,120,121]

It is unclear whether the increased risk of these major chronic conditions is merely an association (ie, some women might have adverse vascular risk profiles that make them prone to both pre-eclampsia and the development of long-term health complications[122,123]) or if pre-eclampsia itself is part of the causal pathway. It is plausible that the maternal vascular and organ injury caused by pre-eclampsia induces permanent physiological and metabolic rewiring that increases their predisposition to these chronic diseases.

The American Heart Association has now listed pre-eclampsia as a major risk factor for the development of cardiovascular disease.[124] For women who have had pre-eclampsia, healthy lifestyle interventions, frequent blood pressure checks, and possibly diabetes screening should be instituted lifelong and commenced soon after the affected pregnancy;[112] high-quality evidence of effective interventions to reduce subsequent cardiovascular disease in these women is still needed.

Conclusion and future directions

The 2019 Maternal Mortality update from the WHO report[125] illuminated the major contribution of pre-eclampsia and eclampsia to worldwide maternal deaths. There is much to be done to decrease the morbidity and mortality caused by this disease.

Most of the maternal deaths arising from pre-eclampsia occur in LMICs. There needs to be implementation research to determine how best to allocate scarce resources to save the greatest number of lives. Options might include improving access to antenatal care, with an adequate number of visits to identify and manage the disease before it becomes perilously advanced;[126,127] better access to medications to treat hypertension[101] and to magnesium sulphate to prevent eclampsia;[102] and provision of obstetric services that can facilitate timely delivery. Furthermore, improving dietary calcium, through nutritional advice (in areas with regular antenatal care), making calcium supplements widely available, or possibly food fortification, alongside provision of aspirin for those at risk of pre-eclampsia could also be worthwhile in LMICs to reduce the prevalence of disease.[75]

During the past two decades there have been major advances in the development of screening tests.[47,59,95,128] Large trials that implemented specific interventions to those who screen positive have proven an important concept—that screening tests can improve clinical outcomes for pre-eclampsia.[62,68] More research is needed to refine, validate, and implement tests that have been developed[47,59,95,128] and to discover other high-performing biomarkers. In particular, term pre-eclampsia is challenging to predict at a gestation when prevention can be implemented.

There is now high-level evidence to show aspirin is effective at preventing pre-eclampsia, although modestly so.[64–66,68] However, the most cost-effective approach to identify those who should be offered aspirin is unresolved; the optimal dose is unclear and clinical trials that compare doses of aspirin are needed. Drugs such as pravastatin[85] and arginine[82] also merit adequately powered trials to determine whether they could be added to the armamentarium, with further scope to discover new ones. A drug treatment that slows disease progression does not currently exist. The discovery of an effective and inexpensive treatment for pre-eclampsia could be transformative, especially in LMICs. Possible drug targets might be the pre-eclamptic placenta, the maternal vessels, or both; creative options are being explored, such as apheresis,[129] repurposing drugs,[130] infusions of nitrous oxide donors,[131] siRNA technology,[132,133] and other novel treatments.[134]

A diagnosis of pre-eclampsia is a major risk factor for subsequent diseases of the vascular system, such as hypertension, cardiovascular disease, stroke, and renal disease. It might be time for major trials or cohort studies to examine whether these risks can be reduced by using similar strategies to those used to decrease cardiovascular

risk, including regular visits to a primary care physician for metabolic and blood pressure screening, lifestyle modifications, and administering preventive agents (eg, statins and aspirin).

Contributors

All authors reviewed the literature and contributed subsections of the text. LC and ST then combined these sections to unify the draft. All authors then reworked the subsequent drafts and reviewed the final manuscript.

Declaration of interests

JK declares that he was paid for his time and travel for two lectures on PlGF in pre-eclampsia for Roche, Canada in 2018–19. LCC, CAC, and ST declare no competing interests.

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