Pre-eclampsia

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Pre-eclampsia affects 3–5% of pregnancies and is traditionally diagnosed by the combined presentation of high blood pressure and proteinuria. New definitions also include maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological or haematological complications, uteroplacental dysfunction, or fetal growth restriction. When left untreated, pre-eclampsia can be lethal, and in low-resource settings, this disorder is one of the main causes of maternal and child mortality. In the absence of curative treatment, the management of pre-eclampsia involves stabilisation of the mother and fetus, followed by delivery at an optimal time. Although algorithms to predict pre-eclampsia are promising, they have yet to become validated. Simple preventive measures, such as low-dose aspirin, calcium, and diet and lifestyle interventions, show potential but small benefit. Because pre-eclampsia predisposes mothers to cardiovascular disease later in life, pregnancy is also a window for future health. A collaborative approach to discovery and assessment of the available treatments will hasten our understanding of pre-eclampsia and is an effort much needed by the women and babies affected by its complications.

Introduction

Pre-eclampsia is a pregnancy-specific syndrome that affects 3–5% of pregnancies and is traditionally diagnosed when a pregnant woman presents with increased blood pressure and proteinuria.[1] Pre-eclampsia is one of the main causes of maternal, fetal, and neonatal mortality, especially in low-income and middle-income countries.[2] In this Seminar, we describe the current management of pre-eclampsia in terms of prediction, prevention, diagnosis, treatment, and long-term consequences. Our aim is to provide a guide for the optimal management of pre-eclampsia, both in low-resource and high-resource settings.

The acute clinical importance of pre-eclampsia lies in its relation to maternal and neonatal mortality and morbidity. When left untreated, pregnant women with pre-eclampsia have severe complications such as eclampsia, liver rupture, stroke, pulmonary oedema, or kidney failure, which can all be lethal.[3] Pre-eclampsia is also related to fetal growth restriction and preterm birth, either spontaneous or through iatrogenic delivery. Children born to mothers with pre-eclampsia have an increased risk of bronchopulmonary dysplasia and cerebral palsy, caused by preterm birth and being small for gestational age.[4,5] Pre-eclampsia decreases health-related quality of life and increases the risk of post-partum depression.[6,7]

The cause of pre-eclampsia is unclear. Some women are genetically predisposed to developing the disease which may run in families.[8] Robust associations have been identified between pre-eclampsia and gene variants involved in thrombophilia, inflammation, oxidative stress and the renin angiotensin system.[9,10] In a meta-analysis of studies to identify gene variants associated with pre-eclampsia, 22 variants were reproducible across studies with 7 remaining significant upon meta-analysis. However, thrombophillic gene variants in F2 and F5 have been consistently associated with the disease.[11–13] Interactions between maternal gene variants and genes encoding fetal HLA-C have been shown to predispose pregnancies to pre-eclampsia in white people, sub-Saharan Africans, and the Chinese Han population, suggesting a role of an impaired immune tolerance in the pathogenesis of pre-eclampsia.[14–16] In women with pre-eclampsia, placental antiangiogenic factors are upregulated and disrupt the maternal endothelium, leading to an antiangiogenic state that can result in clinical signs of pre-eclampsia.[17]

Definition of pre-eclampsia

The diagnostic criteria for pre-eclampsia were changed by the International Society for the Study of Hypertension in Pregnancy (ISSHP) in 2014.[18] ISSHP defines pre-eclampsia as de-novo hypertension present after 20 weeks of gestation combined with proteinuria (>300 mg/day), other maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological or haematological complications, uteroplacental dysfunction, or fetal growth restriction. As proteinuria is no longer required in the new definition, proteinuric and non-proteinuric pre-eclampsia are now two separate categories.

Hypertension is defined as systolic blood pressure higher than 140 mm Hg or diastolic blood pressure higher than 90 mm Hg on two occasions that are 4–6 h apart.[19–21] Blood pressure should be measured in a seated and upright position or in a left lateral recumbent

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Search strategy and selection criteria

We searched PubMed and the Cochrane Library with the terms "pre-eclampsia" and "hypertension and pregnancy", and cross-referenced them with the following terms: "epidemiology", "definition", "prediction", "prevention", "management", "clinical trials", "preconception care", and "thrombophilia". We restricted the search to studies done in humans and published in English. We limited our search to publications between January, 2010, and January, 2015, with a focus on publications after 2012. We also referred to older key publications. We then specifically looked at the themes of the review—ie, diagnostic studies, prognostic studies, intervention studies, and studies on long-term maternal risk.

position, using an appropriate size cuff and either manual or semi-automatic oscillometric devices that are validated for use in pre-eclampsia (Omron T9P or Omron MIT Elite devices).[22,23] Superimposed pre-eclampsia is diagnosed when women with underlying idiopathic hypertension present with one or more of the above features.

Women with proteinuria have high antenatal blood pressure, deliver at early stage of gestation, and often need operative delivery. Proteinuria is not an indicator of maternal morbidity or perinatal mortality, which could suggest a treatment paradox—ie, more aggressive treatment of women with severe pre-eclampsia might prevent complications. Optimum management (for example, of women with non-proteinuric pre-eclampsia or positive biomarkers) will be difficult to define without intervention studies that define the clinical effect of a diagnosis.[24,25]

Prediction of pre-eclampsia

Although perfect prediction of pre-eclampsia has been a noble but hitherto elusive goal, distinction between women who are at low risk and high risk is possible. Strong risk factors are previous pre-eclampsia or hypertension in pregnancy, chronic kidney disease, hypertension, diabetes (type 1 or type 2), and autoimmune disorders, including systemic lupus erythematosus or antiphospholipid syndrome.[20,26] Moderate risk factors are first pregnancy, age 40 years or more, a pregnancy interval greater than 10 years, body-mass index of 35 kg/m² or more, polycystic ovarian syndrome, family history of pre-eclampsia, and multiple pregnancy.[20,27] Furthermore, women who have donated a kidney were twice as likely to have pre-eclampsia than matched women who had not donated a kidney.[28] However, in clinical practice, these factors predict just 30% of women who develop pre-eclampsia.[29]

Additional clinical and lifestyle factors that predict pre-eclampsia in early pregnancy include mean arterial pressure at 15 weeks of gestation, maternal birthweight, family history of coronary heart disease or pre-eclampsia, and vaginal bleeding for more than 5 days in the current pregnancy.[30] A previous single miscarriage with the same partner, time to conception of at least 12 months, and high fruit consumption were associated with a reduced risk of pre-eclampsia, but the combination of these factors resulted in only modest risk prediction (area under the receiver-operating characteristic curve [AUC] 0·71).[30]

Biomarkers in maternal blood have modest predictive potential in early pregnancy or have not been replicated across populations. Serum concentrations of maternal placental growth factor (proangiogenic) decreased in the blood 5 weeks before diagnosis of pre-eclampsia whereas those of soluble fms-like tyrosine kinase 1 (antiangiogenic) increased. However, the clinical value of these biomarkers has not been assessed in appropriately designed intervention studies.[31–33]

The combination of late first-trimester uterine artery Doppler ultrasound examination, placental growth factor, and pregnancy-associated plasma protein-A in maternal blood predict early-onset pre-eclampsia (sensitivity 93% [95% CI 76–98%]; specificity 95% [94–96%]), but this model still needs validation.[34,35] Results of a meta-analysis confirmed the accuracy of first-trimester uterine artery Doppler ultrasound for the prediction of early-onset pre-eclampsia (sensitivity 48%; specificity 92%).[36] The concentrations of circulating placental growth factor, vascular endothelial growth factor soluble fms-like tyrosine kinase 1, and soluble endoglin differ significantly before 30 weeks of gestation in women who developed pre-eclampsia, but the test accuracy of these markers is too poor to allow their use in clinical practice.[37]

In a large multicentre US study,[38] clinical risk factors combined with a change in maternal blood concentrations of angiogenic factors between first and early second trimester predicted early-onset pre-eclampsia (sensitivity 88%; specificity 80%). Results of another study showed that a combination of 11 biomarkers, clinical risk factors, and uterine artery Doppler ultrasound at 20 weeks of gestation had very good accuracy for prediction of pre-eclampsia (AUC 0·90 [95% CI 0·79–1·0]),[39] whereas investigators who took a metabolomics approach[40] found 14 metabolites at 15 weeks of gestation were predictive of pre-eclampsia (sensitivity 70%; specificity 95%). All these models need validation before they can be used in clinical practice.

Prevention of pre-eclampsia

With reliable risk prediction for pre-eclampsia on the horizon, interventions to prevent pre-eclampsia become more important (table 1). Aspirin is the drug of choice for the prevention of pre-eclampsia, based on the findings of an individual patient data (IPD) meta-analysis that showed moderate benefit of aspirin (RR 0·90, 95% CI 0·84–0·97).[41] Other pharmacological drugs, such as heparin and dalteparin, show promising effects in women who are at increased risk for pre-eclampsia, but unlike trials of aspirin, the studies were too small to draw definite conclusions.[42,51,52]

Low dietary calcium and low serum calcium concentrations are associated with pre-eclampsia.[53] In women with low dietary calcium intake, high-dose calcium supplementation reduces pre-eclampsia (RR 0·36, 95% CI 0·20–0·65).[43] Although calcium supplementation is not recommended in women with normal dietary calcium intake, WHO recommends calcium supplementation (1·5–2 g daily) in the second half of pregnancy for women with low dietary calcium intake.[54] This recommendation applies to most settings in which the main dietary source of calcium is grains, such as wheat or maize, and is based on the systematic review of high-dose calcium supplementation during pregnancy.[55] The hypothesis that dietary calcium supplementation in early pregnancy might effectively

	Population	Relative risk (95% CI)
Pharmacological interventions		
Aspirin	Women at risk of pre-eclampsia, gestational hypertension, or fetal growth restriction	0·90 (0·84–0·97)[41]
Low molecular weight heparin	Women at risk of placental dysfunction (eg, past history of pre-eclampsia, renal disease, placental abruption, fetal death, or fetal growth restriction)	0·47 (0·22–1·03)[42]
Non-pharmacological interventions		
Calcium	Women with low dietary calcium intake	0·36 (0·20–0·65)[43]
Vitamin C and E	Women at low, moderate, or high risk of pre-eclampsia	1·00 (0·92–1·09)[44]
Magnesium	Women at normal or high risk of pre-eclampsia	0·87 (0·58–1·3)[45]
L-arginine with antioxidants	Women at risk of pre-eclampsia	0·34 (0·21–0·55)[46]
Vitamin D and calcium	Women at any risk of pre-eclampsia	0·67 (0·33–1·4)[47]
Diet and lifestyle	Women at any risk of pre-eclampsia;* women who are overweight or obese; women who eat vegetables, fruits, and vegetable oils	0·74 (0·60–0·92);[48] 1·03 (0·71–1·5);[49] 0·72 (0·62–0·85)[50]

*Includes women with mild gestational diabetes on insulin.

Table 1: Interventions for prevention of pre-eclampsia

prevent pre-eclampsia is being tested in a randomised trial in women with previous pre-eclampsia.[56]

Dietary supplementation with vitamin C and vitamin E (RR 1·00, 95% CI 0·92–1·09) or magnesium (0·87, 0·58–1·32) does not reduce the risk of pre-eclampsia.[44,45] Nutritional supplementation with marine oil or other long-chain polyunsaturated fatty acids is not effective in the prevention of pre-eclampsia either.[57] Vitamin D insufficiency is associated with an increased risk of gestational diabetes, pre-eclampsia, and small size for gestational age, but prophylactic vitamin D supplementation has only been assessed in one randomised controlled trial (0·67, 0·33–1·35).[47,58]

In a large randomised controlled trial of women at high risk of pre-eclampsia, the nitric oxide precursor L-arginine, reduced the risk of pre-eclampsia when given in combination with antioxidants (RR 0·17, 95% CI 0·12–0·21),[46] a finding that was later confirmed in a meta-analysis (0·34, CI 0·21–0·55).[59] Further studies of women at low risk are needed before supplementation of L-arginine in pregnancy can be routinely recommended.[60]

In response to the threat of the global obesity epidemic, the focus on healthy lifestyles to prevent pre-eclampsia is increasing. In a large cohort of nulliparous women, a diet rich in vegetables, fruits, and vegetable oils was associated with a reduced risk of pre-eclampsia (RR 0·72, 95% CI 0·62–0·85).[50] Systematic reviews[48,61] have shown that diet and lifestyle interventions can reduce the risk of pre-eclampsia in pregnant women, including women with gestational diabetes although this effect was not confirmed in a more recent randomised controlled trial[49] of diet and lifestyle interventions in pregnant women who are overweight or obese. In summary, treatment with aspirin is the only intervention to prevent pre-eclampsia for which robust evidence exists, but its effect is not large. Except for calcium supplementation in women with low dietary calcium intake, all other preventive interventions need

further assessment and should not be prescribed outside the context of clinical trials.

Clinical presentation of pre-eclampsia

The clinical presentation of pre-eclampsia is varied.[1] Women are mostly asymptomatic, and the disease is often diagnosed during routine antenatal care. Maternal adverse outcomes are recorded in 10% of women with pre-eclampsia, whereas this risk increases to 15% in women with early-onset disease.[62]

The clinical presentation and findings could be indicative of the underlying multisystem morbidity. Women with severe pre-eclampsia might present with symptoms such as headache, visual disturbances (including blindness), epigastric pain, or nausea and vomiting. Neurological complications include eclamptic seizures, stroke, or reversible ischaemic neurological deficit, cortical blindness, retinal detachment, and posterior reversible encephalopathy. Hepatic involvement manifests as liver dysfunction, haematoma, or rupture, and renal involvement includes acute renal insufficiency requiring dialysis. Cardiorespiratory complications include myocardial ischaemia or infarction and pulmonary oedema. Women might also present with disseminated intravascular coagulation or placenta-related complications, such as abruption.

Severe pre-eclampsia could also be manifest as HELLP syndrome, characterised by microangiopathic haemolytic anaemia, hepatic dysfunction, and thrombocytopenia, with or without proteinuria or severe hypertension. HELLP syndrome often has an acute onset, with rapid deterioration of the maternal condition, and a third of cases present before 28 weeks of gestation.[63] Fetal complications include growth restriction, stillbirth, neonatal death, and prematurity-associated complications from early delivery.

Because of the heterogeneous clinical presentation of severe pre-eclampsia, many other disorders should be considered before definitive diagnosis (table 2).

	Presentation	Differential diagnosis
Central nervous system	Seizures, headache	Epilepsy, subarachnoid haemorrhage, hypoglycaemia, thrombotic thrombocytopenic purpura, hypertensive encephalopathy, central venous sinus thrombosis, local anaesthetic toxicity (epidural), amniotic fluid embolism, cerebral systemic lupus erythematosus, idiopathic intracranial hypertension
Renal	Proteinuria, hypertension, abnormal renal function tests, oliguria	Pyelonephritis, nephrotic syndrome, acute and chronic glomerulonephritis, lupus nephritis, haemolytic uraemic syndrome, interstitial nephritis
Vascular	Severe hypertension	Thyrotoxicosis, phaeochromocytoma, Cushing's syndrome, white coat hypertension, hyperaldosteronism
Cardiorespiratory	Chest pain, dyspnoea, low oxygen saturation	Pulmonary oedema, pulmonary embolism, pneumonia, myocardial infarction or ischaemia, peripartum cardiomyopathy
Hepatic	Abnormal liver function tests, epigastric pain, nausea, vomiting	Acute fatty liver of pregnancy, viral hepatitis, drug-induced hepatotoxicity, acute pancreatitis, obstetric cholestasis, gastritis, hyperemesis gravidarum
Ophthalmological	Visual disturbances	Retinal detachment due to injury or eye diseases, retinal arterial or venous thrombosis due to vasculitis, trauma and other causes, retinal ischaemia, central serous retinopathy
Haematological	Bleeding, coagulation abnormality, disseminated intravascular coagulation, shock	Idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, placental abruption, septic shock, acute fatty liver of pregnancy

Table 2: Differential diagnosis of medical conditions with presentation similar to severe pre-eclampsia, by organ system involvement

Signs and symptoms

Clinicians routinely obtain information on the presence of symptoms associated with progression to severe disease. However, individual symptoms of pre-eclampsia such as headache (AUC 0·58, 95% CI 0·24–0·86), epigastric pain (0·70, 0·30–0·93), and visual disturbances (0·74, 0·33–0·94) do not adequately predict adverse maternal outcomes.[64] Chest pain and dyspnoea also have limited predictive value (0·64, 0·54–0·74) for composite adverse maternal outcomes.[62] Authors of a systematic review reported that mean arterial pressure of 140 mm Hg or higher or a blood pressure of 170/110 mm Hg or higher had limited accuracy for the prediction of eclampsia, placental abruption, and renal, neurological, and liver impairment (AUC for any adverse maternal outcome 0·68 [95% CI 0·29–0·92]).[65] Once pre-eclampsia has been diagnosed, blood pressure should be measured regularly in a day-assessment or inpatient setting, depending on the severity of the disorder.[20,66] Overall, history and physical examination to assess the severity of pre-eclampsia or predict complications have limited accuracy and should not be used alone to make management decisions such as delivery (table 3).

Laboratory tests

The maternal spot urine estimate of the protein:creatinine ratio is promising for the detection of proteinuria in women with suspected pre-eclampsia. There is insufficient knowledge of how the protein:creatinine ratio should be used in clinical practice because test accuracy and prevalence across studies are heterogeneous.[71] The degree of proteinuria is not predictive for placental abruption or HELLP syndrome, whereas data on the capacity of proteinuria to predict eclampsia are conflicting.[67,72] Oxygen saturation predicts adverse maternal outcomes in the first 48 h after presentation fairly well (AUC 0·71, 95% CI 0·65–0·77).[62]

The monitoring of women with pre-eclampsia includes the assessment of haematological parameters (haemoglobin, platelets) and biochemical tests (hepatic and renal function) to track progression to severe disease and to diagnose deterioration of the disease. Individual tests, such as the detection of liver transaminases (AUC 0·79, 95% CI 0·51–0·93) perform fairly well, whereas others, such as the detection of a platelet count of less than 100×10⁹ per L (0·69, 0·63–0·75), serum creatinine (0·63, 0·57–0·69), and serum albumin (0·62, 0·56–0·68), have limited value in the prediction of complications.[62,68] Serum uric acid is a poor predictor of adverse outcomes and should not be measured.[69]

Routine assessment of the clotting profile is not necessary if the platelet count is more than 100×10⁹ platelets per L. Platelet count is not a sensitive indicator of coagulopathy. Outside pregnancy, neuraxial haematomas have not been reported with platelet counts of more than 75×10⁹ per L without platelet dysfunction or coagulopathy. Platelet transfusion (with or without other blood components) is indicated on the basis of platelet count, mode of delivery, presence of active bleeding, and coagulopathy.[73]

Prediction models

Because all the above-mentioned tests have limited accuracy individually to predict complications, attempts have been made to integrate these tests into multivariable models. The full pre-eclampsia integrated estimate of risk (PIERS) multivariable model predicts composite adverse maternal outcome within 48 h in women admitted to hospital for pre-eclampsia (AUC ROC 0·88, 95% CI 0·84–0·92). In PIERS, the predictive factors are gestational age, platelet count, chest pain or dyspnoea, oxygen saturation, serum creatinine concentration, and aspartate transaminase concentration.[62] Surprisingly, blood pressure was not identified as a predictor of

	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)
Symptoms					
Headache					
Adverse maternal outcome*	0·58 (0·24–0·86)[64]	0·54 (0·27–0·79)[64]	0·59 (0·38–0·76)[64]	..	..
Epigastric pain					
Adverse maternal outcome*	0·70 (0·30–0·93)[64]	0·34 (0·22–0·50)[65]	0·83 (0·76–0·89)[64]	..	..
Visual disturbances					
Adverse maternal outcome*	0·74 (0·33–0·94)[64]	0·27 (0·07–0·65)[65]	0·81 (0·71–0·88)[64]	..	..
Nausea and vomiting					
Adverse maternal outcome*	0·54 (0·48–0·60)[62]	0·24 (0·21–0·27)[60]	0·87 (0·85–0·89)[60]	..	..
Chest pain or dyspnoea					
Adverse maternal outcome*	0·64 (0·54–0·74)[62]	..	..	..	..
Examination					
Blood pressure					
Adverse maternal outcome*	0·68 (0·29–0·92)[64,65]	..	..	..	..
Systolic blood pressure					
Adverse maternal outcome†	0·65 (0·59–0·70)[62]	..	..	..	..
Diastolic blood pressure					
Adverse maternal outcome*	0·63 (0·57–0·68)[62]	..	..	..	..
Mean arterial pressure					
Adverse maternal outcome*	0·65 (0·60–0·71)[62]	..	..	..	..
Oxygen saturation					
Adverse maternal outcome*	0·72 (0·67–0·78)[62]	..	..	..	..
Investigation					
24 h urine proteinuria increased by 2 g/24 h					
Eclampsia	..	..	..	0·41 (0·04–4·5)[67]	2·0 (0·83–4·6)[67]
Abruption	..	..	..	1·1 (0·75–1·6)[67]	0·88 (0·42–1·9)[67]
HELLP syndrome	..	..	..	1·1 (0·74–1·6)[67]	0·86 (0·38–2·0)[67]
Dipstick proteinuria					
Adverse maternal outcome†	0·65 (0·59–0·71)[62]	..	..	..	..
Liver transaminases					
Adverse maternal outcome*	0·79 (0·51–0·93)[68]	..	..	..	..
Serum creatinine					
Adverse maternal outcome†	0·63 (0·57–0·69)[62]	..	..	..	..
Platelet count					
Adverse maternal outcome*	0·69 (0·63–0·75)[62]	..	..	..	..
Uric acid					
Eclampsia	..	..	..	2·1 (1·4–3·5)[69]	0·38 (0·18–0·81)[69]
Severe hypertension	..	..	..	1·7 (1·3–2·2)[69]	0·49 (0·38–0·64)[69]
Adverse maternal outcome†	0·59 (0·53–0·65)[62]	..	..	..	..
Prediction models					
Full PIERS model‡					
Adverse maternal outcome†	0·88 (0·84–0·92)[62]	..	..	..	..
Mini PIERS model§					
Adverse maternal outcome*	0·77 (0·74–0·80)[70]	..	..	..	..

AUC=area under the curve. LR+=likelihood ratio of positive test. LR–=likelihood ratio of negative test. HELLP=haemolysis, elevated liver enzymes, low platelet count. *Maternal adverse outcome to be present if any of the following occurs: maternal death, eclampsia, pulmonary oedema, abruption, disseminated intravascular coagulation, renal failure, intracerebral haemorrhage, adult respiratory distress syndrome, and retinal detachment. †Maternal adverse outcome to be present if any of the following occurs: maternal mortality or one or more serious adverse events (central nervous system, cardiorespiratory, hepatic, renal, or haematological morbidity). ‡Based on gestational age, platelet count, symptoms such as chest pain or dyspnoea, oxygen saturation, and serum creatinine and aspartate transaminase concentrations. §Based on gestational age, headache or visual disturbances, chest pain or dyspnoea, vaginal bleeding with abdominal pain, systolic blood pressure, and dipstick proteinuria.

Table 3: Accuracy of individual clinical tests and models in the prediction and diagnosis of maternal complications in women with pre-eclampsia

maternal complications, defined as the composite adverse maternal outcome in the model. The model findings might be affected by treatment paradox, where antihypertensive treatment or delivery might reduce high blood pressure-related events such as stroke, eclampsia, and transient ischaemic attack. Furthermore, the model might be affected by the low number of blood pressure-related components in the composite outcome. External validation of the PIERS model in an independent dataset showed high discrimination but poor calibration, perhaps because the external dataset was limited to women with severe pre-eclampsia.[70]

Clinical management of women diagnosed with pre-eclampsia

Novel therapies for pre-eclampsia target various aspects of pre-eclampsia pathogenesis and are in development, yet the only cure for pre-eclampsia is delivery of the placenta (panel 1).[86] On the basis of consensus, severe hypertension or end-organ complications should be managed in an inpatient setting. Subspecialty consultation is advised to address underappreciation of the risks of pre-eclampsia. An early epidural catheter will attenuate pain-induced hypertension and enable neuraxial anaesthesia for emergency caesarean delivery, thereby avoiding difficult intubation or a hypertensive response to the intubation.[74] Bed rest does not prevent pre-eclampsia and is known to cause harm in general obstetrics.[87] To avoid potentially lethal pulmonary oedema, clinical practice has seen a trend towards fluid restriction, including the restrained use of fluids for oliguria, which has not been associated with an increase in renal failure. Avoidance of fluid preloading before neuraxial analgesia or anaesthesia is also recommended.[88]

International guidelines strongly recommend antihypertensive drugs for severe hypertension during pregnancy.[20–22,74] Repeated doses of nifedipine, intravenous hydralazine, or labetalol every 15–30 min all achieve blood pressure control in at least 80% of women.[75–78] Sufficiently powered randomised controlled trials are needed to compare regimens to achieve blood pressure control without overshoot. Because most severe pregnancy-related hypertension is not associated with end-organ dysfunction, lowering of blood pressure during a period of several hours is reasonable.[79] Contemporaneous use of nifedipine and magnesium sulphate is safe.[89]

Results of the recent CHIPS trial[90] showed that women with hypertension in pregnancy, be it chronic or pregnancy-induced, whose blood pressure was tightly controlled (target diastolic blood pressure 85 mm Hg) achieved a lower blood pressure (by 5 mm Hg) than women whose blood pressure was less tightly controlled (target diastolic blood pressure 100 mm Hg), resulting in similar rates of adverse perinatal outcome (adjusted odds ratio 0·98, 95% CI 0·74–1·3), a birthweight less than the tenth percentile (1·3, 0·93–1·8), and fewer women with severe maternal hypertension (0·56,

0·42–0·75) or serious maternal complications (2·0% vs 3·7%; 0·57, 0·26–1·27). Treatment of maternal hypertension benefits the mother, and although treatment might affect fetal growth, it does not increase illness or death of the infant.

Guidance for choice of the antihypertensive drug, including effects on fetal heart rate or neurodevelopment, is sparse.[80,83] Oral labetalol is not widely available in low-income and middle-income countries,[81] angiotensin converting enzyme inhibitors and receptor blockers are fetotoxic, prazosin can cause stillbirth, and atenolol might reduce fetal growth, the latter being controversial.[74] Individual variation in pre-eclampsia haemodynamics, assessed by cardiac output or peripheral vascular resistance, might interact with effects of antihypertensive drugs, but whether individualised therapy improves outcomes is unknown.

Intravenous magnesium sulphate is effective for treatment and prevention of eclampsia.[84] The high number of women with non-severe pre-eclampsia that need to be treated to prevent one seizure is an issue, especially in view of the cost of magnesium sulphate and its side-effects. Restricted use of magnesium sulphate or reduced magnesium sulphate dose or treatment duration, or both, have been suggested. The aim to give magnesium sulphate to women with severe (rather than any) pre-eclampsia might be associated with higher adverse outcome rates (ie, eclampsia, general anaesthesia, and neonatal morbidity).[91] Interest in magnesium sulphate dose reduction has been fuelled by fear of serious side-effects, which are not actually increased by magnesium sulphate (143 reports, 23916 women) and are infrequent (median <2%) in low-income and middle-income countries (24 studies, 9556 women).[92,93] In six randomised controlled trials (625 women), a reduction of magnesium sulphate dose or treatment duration, or both, resulted in outcomes similar to standard therapy, but sample sizes were too small for reliable conclusions.[94] Treatment of eclampsia with magnesium sulphate at the community level reduced recurrence (1 trial, 265 women),[95] and use of magnesium sulphate for pre-eclampsia is being tested in a cluster-randomised controlled trial (NCT01911494). Corticosteroids for HELLP help to improve laboratory parameters (11 trials, 550 women),[85] and the COHELLP trial (NCT00711841) will assess whether post-partum dexamethasone decreases maternal morbidity.[96]

All complications of pre-eclampsia can also occur post partum, particularly in the first 48 h. Intravenous labetalol and hydralazine are first-line drugs for the management of acute-onset, severe hypertension in the post-partum period, but oral nifedipine might also be considered as a first-line treatment post partum.[97]

When to deliver the woman with pre-eclampsia

Because delivery of the placenta is the only cure for pre-eclampsia, optimal timing of delivery is crucial. The decision to deliver is based on the balance between the

Panel 1: Management of women diagnosed with pre-eclampsia

Ante partum (irrespective of gestational age) and post partum (unless otherwise specified)

Place of care[74]
- Inpatient care of patients with severe hypertension or maternal symptoms, signs, or abnormal laboratory tests
- Outpatient care can be considered, recognising that many women are not eligible and hospital readmission rates are high after home care

Subspecialty consultation[74]
- Obstetrics to ensure that pre-eclampsia risk is recognised and appropriate maternal and fetal surveillance is implemented
- Obstetric medicine (where available) to aid in management of hypertension and end-organ complications
- Anaesthesia to advise on monitoring of the woman and plan neuraxial analgesia or anaesthesia in labour to assist with blood pressure control and facilitate delivery by caesarean section (should it be necessary)

Fluid management[74]
- Restrict to a maximum of 80 mL/h when an intravenous drip is inserted

Antihypertensive therapy[75–83]
- For severe hypertension (≥160/110 mm Hg), consider oral or parenteral agents that can be repeated in 30 min if blood pressure remains at ≥160 mm Hg systolic or ≥110 mm Hg diastolic: nifedipine capsule (10 mg orally without biting to a maximum of 30 mg); nifedipine tablet (10 mg orally to a maximum of 30 mg); hydralazine (5 mg intravenous bolus then 5–10 mg intravenous to a maximum of 45 mg if needed); labetalol (20 mg intravenous then, if needed, 40 mg then 80 mg to a maximum of 300 mg). Alternative oral drugs that can be repeated in 1 h (supported by less evidence in pregnancy): labetalol (200 mg orally); clonidine (0·1–0·2 mg orally);*† captopril (only post partum 6·25–12·5 mg orally)*

- For non-severe hypertension: methyldopa (500–2000 mg/dose in three or four divided doses); labetalol (300–2400 mg/dose in three or four divided doses; nifedipine (20–120 mg/dose once daily)

Magnesium sulphate (MgSO₄)[74,84]
- Eclampsia treatment: 4 g intravenous (over 5 min), then 1 g/h intravenous; if patient is already receiving MgSO₄, give additional 2–4 g intravenous (over 5 min) and increase infusion to 2 g/h intravenous
- Eclampsia prevention in women with pre-eclampsia: 4 g intravenous (over 5 min), then 1 g/h intravenous
- Fetal neuroprotection: 4 g intravenous (with or without 1 g/h until delivery or 24 h maximum) for women with imminent delivery at less than 34 weeks 0 days who do not otherwise qualify for eclampsia prevention or treatment

Corticosteroids[85]
- Antenatally only, to promote fetal pulmonary maturity when delivery is anticipated within the next 7 days and at less than 34 weeks 0 days
- HELLP syndrome (10 mg dexamethasone intravenous every 12 h for 48 h) if improvement in laboratory parameters alone will change management, such as eligibility for neuraxial anaesthesia or analgesia or platelet transfusion

Platelet transfusion for HELLP syndrome[74]
- Recommended for platelet counts <20 × 10⁹ per L, 20 × 10⁹–49 × 10⁹ per L before caesarean, or ≥50 × 10⁹ per L (with or without packed erythrocytes) if patient is showing excessive active bleeding, platelet dysfunction, a rapidly diminishing platelet count, or coagulopathy

HELLP=haemolysis, elevated liver enzyme, low platelet. *Captopril (25 mg) and clonidine (0·1 mg) are being compared in a post-partum randomised controlled trial (ClinicalTrials. gov, number NCT01761916) based on the effectiveness of these drugs in severe hyperten-sion treatment outside pregnancy. †Clonidine therapy is not recommended during breast-feeding (http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm).

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maternal and fetal risks of continuing the pregnancy and the neonatal risks of ending the pregnancy. In pre-eclampsia, the main driver is an assessment of the risk to the mother, but sometimes a growth-restricted child can become compromised and necessitate induction.

In a study that compared induction of labour and expectant management in women with pregnancy-induced hypertension or mild pre-eclampsia at term, induction of labour reduced the number of women with severe maternal hypertension, thus reducing the risk of severe maternal outcomes without affecting neonatal outcome; induction of labour also decreased the risk of caesarean section.[98] Women with an unripe cervix at term will, without induction, have a longer pregnancy and so will benefit most from an induction.[99] Oral misoprostol and mechanical induction with a transcervical balloon are safer than vaginal prostaglandins.[100,101]

For women with non-severe hypertensive disorders between 34 weeks and 37 weeks of gestation, immediate delivery, either through induction, or, if indicated, elective caesarean section, might reduce the already small risk of adverse maternal outcomes compared with expectant monitoring. However, immediate delivery increases the risk of neonatal respiratory distress syndrome. Therefore, routine immediate delivery does not seem justified, and a strategy of expectant monitoring until the clinical situation deteriorates can be considered until 37 weeks of gestation.[102] This strategy is only recommended if there are sufficient resources for safe monitoring while continuing the pregnancy.

Randomised studies that address risks at a gestational age of 34 weeks are scarce. In a South American multicentre trial,[103] women with early severe pre-eclampsia had an 8 day delay in birth after expectant management

compared with immediate delivery. Although neonatal outcome was comparable between the groups, expectant management was associated with an increase in placental abruption (RR 5·1, 95% CI 1·1–23). Timing of delivery in women with severe pre-eclampsia before 34 weeks remains a subject of research, but expectant management seems reasonable in well resourced settings. In women who present before 34 weeks of gestation with suspected pre-eclampsia, the ratio of circulating soluble fms-like tyrosine kinase 1 to placental growth factor predicts adverse outcomes occurring within 2 weeks.[104] The introduction of these biomarkers in clinical practice should be preceded by intervention studies.

In case of delivery before 34 weeks of gestation, infants benefit from a single course of antenatal corticosteroids to accelerate fetal lung maturation.[105] Exposure to antenatal corticosteroids after 34 weeks of gestation does not affect respiratory outcomes in infants with a subsequent late-preterm birth and is being assessed in the Antenatal Late Preterm Steroids (ALPS) trial (NCT01222247).[106] Babies born before 30 weeks of gestation are likely to benefit from the neuroprotective effect of antenatal treatment with magnesium sulphate (RR for cerebral palsy 0·68, 95% CI 0·54–0·87), although most women included in the underlying studies had premature rupture of membranes preceding spontaneous preterm birth.[107]

Cardiovascular risk after pre-eclampsia

In 1964, Epstein showed that women with pre-eclampsia were at increased risk of developing cardiovascular disease later in life.[108] Until recently, women who have had a pregnancy complicated by hypertensive disorders, including pre-eclampsia, were not offered preventive measures. Evidence now overwhelmingly suggests that women who had pregnancy-related complications such as hypertensive disorders, gestational diabetes, intrauterine growth restriction, or preterm delivery have increased risk of cardiovascular disease later in life.[107–112] Pregnancy can therefore be considered as a window for future health.

Women with hypertension during pregnancy often have an unfavourable cardiovascular risk factor profile shortly after pregnancy. At 2 years after delivery, 30% of the women who had pre-eclampsia at term had hypertension and 25% had metabolic syndrome.[113,114] Pregnancy could possibly elicit metabolic syndrome, which then predisposes to vascular endothelial dysfunction.[115] The occurrence of gestational hypertension or gestational diabetes can re-emerge later in life as hypertension or type 2 diabetes.[116] Alternatively, pregnancy temporarily unmasks subclinical disease to return later in life. Women with a history of pre-eclampsia have an increased risk of microalbuminuria, with a prevalence similar to patients with type 1 diabetes.[117] Consequently, women who develop hypertension in pregnancy might qualify for a preventive strategy. This group of women tend to also be motivated for lifestyle adjustment through smoking cessation and weight loss.[118] Several studies of post-partum caregivers revealed that there is limited knowledge of the association between hypertensive disorders in pregnancy and risk of cardiovascular disease, and only few health-care providers offer post-partum counselling for cardiovascular risk.[119–121] Although there is an association between pre-eclampsia and cardiovascular disease in later life, it is unclear whether early screening and subsequent treatment reduce this increased cardiovascular risk. Enhancing awareness of cardiovascular risk has suggested to be effective by personal education postpartum.[122] Awareness is crucial but not sufficient for a healthy lifestyle post partum.[123] Recently, Berks and colleagues[124] reported that after pre-eclampsia, lifestyle interventions including exercise, dietary habits, and smoking cessation decreased cardiovascular risk by 4–13%. However, a history of gestational diabetes did not interact with the effect of a lifestyle intervention because rates of type 2 diabetes after 1 year were similar in women with and without gestational diabetes.[125] Before prevention measures for cardiovascular disease after pregnancy-related hypertension can be implemented, this knowledge gap must be filled.

In its 2011 guidelines for the prevention of cardiovascular disease in women, the American Heart Association[126] deemed a previous history of pre-eclampsia or gestational diabetes to be a major risk factor as part of its risk assessment system. The American Heart Association advises a yearly follow-up of blood pressure, lipid profile, and blood glucose concentration for women who had hypertension in pregnancy. However, intervention studies must be undertaken before such policies are implemented in clinical practice.

Management of pre-eclampsia in low-resource settings

Pre-eclampsia and its serious consequences, including death, are many times more common in low-resource settings than in well resourced settings.[20,127] This epidemiological finding provides a model for seeking clues to the cause of pre-eclampsia and an obligation to direct global efforts to reduce mortality and morbidity from pre-eclampsia towards low-resource settings. Demographic risk factors for pre-eclampsia include young or advanced maternal age, family or personal history of hypertensive disorders, and poverty. Specifically in low-resource settings, an important strategy to reduce pre-eclampsia is the prevention of unintended pregnancy, particularly at the extremes of the reproductive age range, with high-quality, accessible family planning services.

Substantial progress is being made with smartphone-based systems to allow sophisticated prediction of pre-eclampsia risk in low-resource settings, using algorithms based on simple clinical data with or without

smartphone-based pulse oximetry.[128] In women who are admitted to hospital with pre-eclampsia, deterioration can now be predicted with the miniPIERS model, an adaption of the PIERS model developed to predict the risk of adverse composite outcome in low-income and middle-income settings. The model integrates gestational age at the time of admission, headache or visual disturbances, chest pain or dyspnoea, vaginal bleeding with abdominal pain, systolic blood pressure, and dipstick proteinuria.[74]

Early detection and delivery before dangerous or irreversible complications arise is the mainstay of management of pre-eclampsia and is particularly difficult to implement in low-resource settings. Early pre-eclampsia is largely devoid of symptoms that would alert women to the need to seek medical care. Neither are there sufficiently sensitive predictors to allow identification of all women at risk. Regular routine antenatal assessments, including tests of blood pressure and proteinuria, are necessary for all pregnant women. Yet women with limited resources to invest in antenatal care are difficult to persuade to attend antenatal assessments when they feel well. Moreover, the principle of increased visit frequency in the last trimester when pre-eclampsia is most common has been abandoned in many low-resource settings in line with WHO's so-called basic antenatal care schedule of four antenatal visits for women at low risk of pre-eclampsia.[129] In view of evidence, including that from the original WHO Antenatal Care Trial,[130] that fewer visits are associated with increased perinatal mortality, we recommend that health services reassess the cost-effectiveness of more frequent antenatal visits in the third trimester (referred to as basic antenatal care plus).[131]

Dietary calcium intake is generally poor in low-resource settings.[132] The finding that pre-eclampsia was less common than expected in Mayan Indians living in Guatemala, who had relatively higher dietary calcium in their diets, led to the hypothesis that the links between poverty and pre-eclampsia might include dietary calcium deficiency.[133] Subsequent meta-analysis showed that calcium supplementation in the second half of pregnancy reduced pre-eclampsia in populations with low dietary calcium intake.[46]

The cost of 1·5–2 g calcium daily, as recommended by WHO, might be a limiting factor in low-resource settings.[47] A review of randomised trials assessing low-dose calcium supplementation (usually 500 mg daily) showed a consistent reduction in pre-eclampsia with calcium supplementation compared with placebo.[134] Pending review of the guidelines by WHO, 500 mg daily might be a reasonable alternative for women living in settings where diets are generally low in calcium if the recommended 1·5 g dosage is unachievable. The use of low-dose aspirin for women at high risk of pre-eclampsia is probably just as valid for women in low-resource settings as in well resourced settings.

Panel 2: Pre-eclampsia management strategies in low-resource settings

- Effective family planning services
- Algorithms for prediction of pre-eclampsia
- Calcium supplementation (1·5–2 g daily) for women with low dietary calcium intake
- Consider treatment with low-dose calcium (500 mg daily) if a high dose is unachievable
- Aspirin (75 mg daily) for women at high risk
- Frequent routine screening in the third trimester (basic antenatal care plus)
- Appropriate for prediction of disease progression
- Use of low-cost antihypertensive drugs, such as α-methyldopa
- Availability of magnesium sulphate for treatment of eclampsia
- Consideration of the cost *vs* benefit ratio of routine prophylaxis with magnesium sulphate in settings with limited resources for maternal monitoring
- Consider delivery in case of proteinuria and severe hypertension
- Use of a transcervical balloon with traction for labour induction to minimise uterine hyperstimulation,[98] with low-cost titrated oral misoprostol solution as second-line treatment[99]
- Conservative use of caesarean section
- Investment in health services

Once pre-eclampsia is diagnosed, the mainstay of treatment is to control blood pressure and deliver the placenta when the benefits of delivery outweigh the risks of conservative management. A substantial reduction in pre-eclampsia-related mortality could be achieved in low-income countries by widespread screening for hypertension and proteinuria and early delivery of women with severe disease.[135] Magnesium sulphate might reduce mortality but should not be the cornerstone of maternal mortality reduction programmes. Results of a cluster-randomised controlled trial[136] to assess increased use of antenatal corticosteroids in a low-resource setting showed that neonatal mortality did not decrease in infants with low birthweight, although neonatal mortality increased in the population overall.

Modelling of 2012 data has estimated that in sub-Saharan Africa, effective diagnosis, transfer, labour induction, and caesarean section would reduce annual maternal deaths from pre-eclampsia from 17 520 deaths with standard care at present to 4060 deaths, whereas further reduction with use of magnesium sulphate was limited from 4060 deaths to 3750 deaths.[137] Some modifications to reduce costs are possible, but there is no magic bullet. Reduction of maternal and perinatal mortality from pre-eclampsia in low-resource settings requires substantial investment in health systems, transport, health facilities, and skills training. Pragmatic

approaches specific to low-resource settings are shown in panel 2.

Future research

Despite the scientific efforts (>17 000 PubMed citations on pre-eclampsia since 2010) to increase knowledge of the aetiological and clinical aspects of pre-eclampsia, the incidence of the disease is not decreasing[138] and is still the main cause of maternal mortality, with significant adverse effects mainly in low-income and middle-income countries. Standardisation and collaboration in research will probably improve the use of resources. The Core Outcome Measures in Effectiveness Trials (COMET)[139] is developing a standardised outcome set for studies of hypertensive disorders in pregnancy. Such standardisation of study design in basic pre-eclampsia research has already been developed by the Global Pregnancy Collaboration (CoLab).[140] CoLab has also defined a pathway to optimise sample collection for placental research.[141] In another initiative, the Global Obstetric network (GONet) aims to coordinate and standardise the conduct of perinatal clinical trials[142] and the development of prediction models for pre-eclampsia through the global International Prediction of Pre-eclampsia IPD Collaborative Network, funded by the National Institute for Health Research. Adherence to standardised research protocols in a collaborative effort will result in larger datasets with standardised variables and will hasten the development of an understanding of the causes and prediction of pre-eclampsia and its complications. Development and assessment of targeted treatment strategies is an effort very much needed by the women and babies affected by pre-eclampsia.

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