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Severe pre-eclampsia and hypertensive crises

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Hypertensive disorders of pregnancy are one of the leading causes of peripartum morbidity and mortality globally. Hypertensive disease in pregnancy is associated with a spectrum of severity, ranging from mild pregnancy-induced hypertension to eclampsia. Although most cases of pre-eclampsia may be managed successfully, severe pre-eclampsia is a life-threatening multisystem disease associated with eclampsia, HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome, acute kidney injury, pulmonary oedema, placental abruption and intrauterine foetal death. Management of severe pre-eclampsia includes identification of high-risk patients, optimisation of antenatal care, early intervention and the identification and early management of complications. In the first instance, oral anti-hypertensive agents, including labetalol, nifedipine and methyldopa, should be tried. If oral anti-hypertensive agents have failed to adequately control blood pressure, intravenous anti-hypertensives should be considered. Commonly used intravenous anti-hypertensives include labetalol, hydralazine and glyceryl trinitrate. In addition to anti-hypertensive agents, close attention should be given to regular clinical examination, assessment of fluid balance, neurologic status and monitoring of other vital signs. Magnesium sulphate should be considered early to prevent seizures. Delivery of the baby is the definitive management of severe pre-eclampsia.

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Introduction

Hypertensive disorders of pregnancy, along with peripartum haemorrhage, account for the majority of peripartum morbidity and mortality globally. Hypertensive disease in pregnancy ranges from mild pregnancy-induced hypertension to eclampsia. The majority of hypertensive disorders in pregnancy are successfully managed on the maternity ward or in the community. However, severe pre-eclampsia is a potentially life-threatening multisystem disease that requires urgent management, in a high-dependency setting.

Epidemiology and risk factors

Up to 10% of women have elevated blood pressure during pregnancy [1]. Three percent to 8% of women in developed countries develop pre-eclampsia [2,3] and 0.56 per 1000 births are complicated by eclampsia [4]. However, eclampsia affects almost 10–30 times as many women in low-income countries [1]. The incidence of pre-eclampsia is rising in the United States and may be attributable to the rising prevalence of risk factors including advanced maternal age, obesity, diabetes and pre-existing hypertension [5].

Risk factors for the development of pre-eclampsia include nulliparity, previous pre-eclampsia, family history of pre-eclampsia and advancing maternal age. Pre-existing medical disorders that increase the maternal risk of pre-eclampsia include hypertension, diabetes, renal disease and anti-phospholipid syndrome [6]. The risk of maternal mortality is significantly elevated with pre-eclampsia developing before 32 weeks gestation (compared to pre-eclampsia at term), with a 20-fold relative risk of mortality [7].

The underlying mechanism of pre-eclampsia is multifactorial. Pathological placental blood flow, endothelial activation, oxidative stress and generalised inflammation are strongly associated with this systemic disease. [8,9].

Clinical presentation

Hypertension in pregnancy is diagnosed on systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg occurring before 20 weeks gestation. Pregnancy-induced hypertension occurs after this period. Pre-eclampsia is defined as having a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg after 20 weeks gestation in a previously normotensive woman and the presence of ≥300 mg proteinuria in a 24-h urine collection [2]. Rarely, pre-eclampsia may occur in the immediate post-partum period, and the condition must resolve within 6 weeks of the post-partum period.

Severe pre-eclampsia is associated with at least one of the following: systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg, proteinuria of ≥1 g in a 24-h urine collection and evidence of target organ damage (Table 1). In addition to new-onset hypertension and proteinuria, pre-eclampsia may present with a myriad of nonspecific clinical features. These include headaches, visual disturbance, vomiting and epigastric pain. The majority of patients presenting with eclamptic fits have one or more of these features in the weeks leading up to the event [10].

Other less common causes of severe hypertension, including thyrotoxicosis, phaeochromocytoma and recreational drug use, should be considered in the differential diagnosis. Severe pre-eclampsia is a medical emergency and patients should be managed on a critical care unit to facilitate close monitoring of vital signs, titration of treatment and early recognition and management of associated complications.

The maternal and neonatal morbidity and mortality associated with hypertensive crises are significant. All cases of severe pre-eclampsia should be referred to the intensive care team early. Up to 70% of mothers with severe pre-eclampsia admitted to the intensive care unit develop multi-organ dysfunction [11]. Maternal complications associated with severe pre-eclampsia include eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes and low platelets, 10–25%), acute kidney injury (AKI) (1–5%), pulmonary oedema (2–5%) and placental abruption (1–4%) [12–14]. Eclampsia is the occurrence of generalised tonic clonic seizures in the absence of other neurologic disorders. The foetus

Table 1
Definitions of preeclampsia and severe preeclampsia.

Preeclampsia	Severe preeclampsia
1. Systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg after 20 weeks gestation in a previously normotensive woman	1. Systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg on 2 separate occasions at least 6 hours apart
AND	
2. Proteinuria ≥ 300 mg in a 24 hour urine collection	OR
	2. Proteinuria of ≥ 1 g in a 24 hour urine collection in association with preeclampsia
	OR
	3. End-organ involvement in association with preeclampsia:
	a. Oliguria (<400 ml/day)
	b. Thrombocytopenia
	c. Impaired liver function tests
	d. Epigastric/right upper quadrant pain (liver capsule distension)
	e. Cerebral or visual disturbances
	f. Pulmonary oedema

may be small for gestational age with reduced foetal movements [15]. Severe pre-eclampsia is a significant risk factor for intrauterine foetal death, with an estimated stillbirth rate of 21 per 1000 [16].

Management

General measures

In addition to anti-hypertensive therapy, the management of severe pre-eclampsia should include the following:

1. monitoring and management of blood pressure (detailed below),
2. monitoring of other vital signs including heart rate, urine output, oxygen saturation, respiratory rate, deep tendon reflexes and Glasgow Coma Scale,
3. twenty-four-hour urine collection for protein estimation,
4. TED stockings,
5. ultrasound assessment of the foetus to assess foetal size, umbilical artery Doppler and liquor volume,
6. infusion of magnesium sulphate,
7. continuous foetal monitoring,
8. consideration for steroids in the case of <34 weeks gestation and
9. prevention and management of complications.

Blood pressure management

The mother with pre-eclampsia should be stabilised prior to delivery. Accurate blood pressure measurement is vital. Automated blood pressure monitors should be avoided as they lack accuracy in women with pre-eclampsia [17], and manual aneroid sphygmomanometers are preferable. Invasive blood pressure measurements provide continuous blood pressure readings and should be considered when rapidly acting intravenous infusions of anti-hypertensive agents are used.

Targeting a systolic blood pressure <140–150 mmHg and diastolic blood pressure <80–90 mmHg minimises the risk of haemorrhagic stroke, as cerebral autoregulation is impaired when the mean arterial pressure exceeds 145 mmHg [18]. Rapid reduction in systolic blood pressure may result in acute hypoperfusion and ischaemia of vital organs. There is no evidence to support the choice of any one

anti-hypertensive agent over another for management of severe pre-eclampsia and should be based on the clinician's experience [19].

In the first instance, oral agents should be tried. Commonly used oral agents include labetalol, nifedipine and methyldopa. Labetalol is an α- and β-adrenoceptor blocker, with greater selectivity for β receptors. It reduces blood pressure almost immediately primarily by vasodilation and by reduction of heart rate at higher doses. Oral labetalol is commonly used and, unlike vasodilators, is not associated with maternal tachycardia. Oral labetalol may be started at 100 mg twice daily and may be increased to 2.4 g daily in three to four divided doses. Nifedipine is a commonly used second-line oral anti-hypertensive agent and is a calcium channel blocker that results in vascular smooth muscle relaxation and vasodilation. Only the slow release preparation should be used: in particular, sublingual nifedipine may cause a precipitous fall in maternal blood pressure and should be avoided. Slow-release nifedipine is administered orally starting at 5 mg followed by 10 mg bd and may be increased to 40 mg bd. Blood pressure falls within 30 min of oral administration. Although there is less experience and evidence behind the use of nifedipine compared to methyldopa, there is no evidence to suggest long-term foetal harm. Methyldopa is a centrally acting oral anti-hypertensive. Due to its good safety record, it is often used as a first-line anti-hypertensive agent [20]. Occasionally, methyldopa is associated with maternal transaminitis or a positive Coomb's test.

If oral anti-hypertensive agents have failed to adequately control blood pressure, intravenous anti-hypertensives should be considered. Commonly used intravenous anti-hypertensives include labetalol, hydralazine and glyceryl trinitrate. The potential benefits and risks of anti-hypertensive agents in pregnancy do not seem to be associated with any particular drug or drug class [21].

Labetalol

Labetalol may be given intravenously as an initial bolus dose of 20 mg, followed by 20–80 mg every 30 min, up to a maximum cumulative dose of 220 mg. Alternatively, labetalol may be administered as a continuous infusion started at 1–2 mg min^{-1}, followed by 5–10 mg h^{-1} up to 300 mg. Compared to hydralazine, labetalol is as good as or more effective in reducing blood pressure [22] and does not affect uterine function [23]. Labetalol is an ideal anti-hypertensive agent when hypertension is associated with tachycardia or myocardial ischaemia.

Hydralazine

Intravenous hydralazine acts directly on vascular smooth muscle to cause vasodilation. It is often used in hypertensive crises and can be administered as a bolus (5 mg) repeated after 20 min up to a total cumulative dose of 20 mg or as a continuous infusion (0.5–10.0 mg h^{-1}). The onset of action is rapid (within 20 min) and lasts for 2–6 h. Repeated boluses of hydralazine may be required to maintain the target blood pressure [24]. Hydralazine may cause reflex tachycardia and should therefore be avoided if the maternal heart rate exceeds 100 bpm. Coadministration of methyldopa may prevent this (1 mg orally).

Nitrates

Sodium nitroprusside has a very short half-life, facilitating rapid titration. Accumulation of cyanide or thiocyanate may occur, usually with >24 h of sodium nitroprusside infusion and in patients with renal insufficiency [25]. Sodium nitroprusside is therefore rarely used in pre-eclampsia and should be reserved for scenarios where other anti-hypertensive agents have failed to control blood pressure. Intravenous glyceryl trinitrate is a particularly useful intravenous anti-hypertensive agent in the context of acute pulmonary oedema. An infusion of 1–10 mg h^{-1} is often effective, though prolonged use may result in tachyphylaxis.

Assessment and management of fluid balance

Acute respiratory failure may complicate severe pre-eclampsia and is a frequent reason for critical care unit admission (discussed below). Accurate assessment of fluid balance is therefore important to avoid iatrogenic pulmonary oedema.

The renal response to intense vasoconstriction is increased salt and water elimination ('pressure natriuresis'), with a reduction in circulating volume. Therefore, patients with severe hypertension may

be intravascular volume deplete. The theoretical benefit of 'preloading' patients with up to 500 ml of intravenous crystalloids to prevent precipitous fall in blood pressure following administration of a vasodilator is not backed by clinical evidence [26].

Central venous pressure (CVP) has traditionally been used as a surrogate of intravascular volume. However, absolute CVP readings and changes in CVP in response to a fluid challenge are unreliable in predicting fluid responsiveness among critically ill patients [27] and there is little correlation between the CVP and left-atrial pressure (measured by the pulmonary artery catheter) among critically ill pregnant patients [28]. Although the use of the pulmonary artery catheter has the benefit of being able to measure right-heart pressures, the use of the pulmonary artery catheter has significantly declined due to concerns that the invasive procedure does not reduce mortality [29]. No specific cardiac output monitor has been shown to improve clinical outcome in critically ill pregnant patients.

Complications of severe pre-eclampsia requiring intensive care admission

Eclampsia

Eclampsia is the occurrence of tonic clonic seizures associated with pre-eclampsia in the absence of other neurologic disorders. Magnesium sulphate is superior to phenytoin, diazepam and lytic cocktails in preventing initial and recurrent seizures in severe pre-eclampsia [30–32]. The use of magnesium sulphate may halve the rate of eclampsia even in cases of less severe pre-eclampsia [33]. Four grams should be administered intravenously over 15 min in severe pre-eclampsia (or 5 min if actively seizing) followed by an infusion of 1 g h^{-1} for 24 h. This should be maintained for 24 h following delivery of the baby or from the last seizure. Between 5% and 20% of eclamptic seizures recur, for which a further 2 g should be given. Intravenous diazepam (10 mg) or thiopentone (50 mg) should be administered if seizures persist despite this. Serum magnesium levels should be maintained between 2 and 4 mmol l^{-1} [34]. If the patient has renal dysfunction, the loading dose of magnesium sulphate may be administered but clinical signs of magnesium toxicity and serum levels of magnesium should be monitored closely. A dose reduction in the continuous infusion of magnesium sulphate may be required.

Following a seizure, a patient with reduced level of consciousness may need to be intubated. A profound hypertensive response to laryngoscopy has been reported to result in intracranial haemorrhage [18]. Pre-intubation blood pressure should always be adequately controlled.

Acute respiratory failure

Patients with severe pre-eclampsia are at risk of acute respiratory distress syndrome (ARDS) [35,36]. The associated maternal and perinatal mortality and morbidity remain high [18,35]. The incidence of ARDS associated with pre-eclampsia is unclear, due in part to the varying definitions of ARDS in pregnancy [37]. The definition of ARDS has recently been updated and acknowledges that cardiogenic and 'non-cardiogenic' pulmonary oedema co-exist [38]. Equilibrium between forces that drive fluid into the alveolar spaces and the mechanisms responsible for its clearance (Starling's forces) maintain pulmonary fluid homeostasis. Alterations in Starling's forces may result in acute pulmonary oedema. Factors predisposing to acute pulmonary oedema in pre-eclampsia include increased pulmonary capillary hydrostatic pressure, reduced plasma oncotic pressure, endothelial dysfunction and iatrogenic fluid overload.

Severe hypertension may result in left-ventricular failure due to an increased afterload. This increases the hydrostatic pressure within the capillaries, with a net flux of water into the interstitial space (pulmonary oedema). Reduction in blood pressure will improve cardiac performance and aid resolution of pulmonary oedema. Glyceryl trinitrate is a particularly useful therapeutic agent under such circumstances. Plasma oncotic pressure is reduced in pregnancy due to reductions in plasma protein concentration. This results in net flux of water into the extravascular space contributing to pulmonary oedema. Endothelial dysfunction and inflammation associated with pre-eclampsia [39] may result in increased fluid shift from the intravascular space to the pulmonary interstitium, exacerbating pulmonary oedema.

Pulmonary oedema is a significant cause of maternal morbidity in pre-eclampsia. The volume and rate of fluid administration need to be closely monitored to avoid iatrogenic pulmonary

oedema. Management of fluid balance in hypertensive crises deserves close attention, as described earlier.

Acute kidney injury

AKI may occur in the context of severe pre-eclampsia (1–5%) and is more common in women with HELLP syndrome. Characteristic histological abnormalities observed on renal biopsy are localised to the endothelium and glomeruli [40]. Any sustained fall in urine output (<0.5 ml kg^{-1} h^{-1}) or a rising serum creatinine should alert the clinician to the likelihood of AKI. The management of AKI is largely supportive and includes optimising intravascular volume status (though erring on the side of under-hydration to avoid pulmonary oedema), avoiding nephrotoxic drugs and treating the underlying cause.

The use of frusemide or dopamine to increase urine output in the absence of fluid overload does not improve renal function or outcome [41–43]. Magnesium levels should be monitored closely, as toxicity, though uncommon, tends to occur in patients with renal impairment. The indications for renal replacement therapy (haemodialysis, or more commonly, continuous veno-veno haemofiltration) are similar to those for other critical illness:

1. hyperkalaemia resistant to medical therapy,
2. metabolic acidosis resistant to medical therapy,
3. uraemic pericarditis,
4. uraemic encephalopathy and
5. fluid overload resistant to medical therapy.

HELLP syndrome

The combination of haemolysis, elevated liver enzymes and low platelets is known as the HELLP syndrome. HELLP complicates up to 20% of patients with severe pre-eclampsia and occurs in the post-partum period in approximately 30% of cases. The maternal mortality associated with severe pre-eclampsia is significantly raised when associated with HELLP [11].

Criteria for the diagnosis of HELLP

HELLP is complicated by AKI in 15% of cases [11]. The main differential diagnoses of HELLP include thrombotic microangiopathies (thrombotic thromocytopaenic purpura (TTP) and haemolytic uraemic syndrome (HUS)) and acute fatty liver of pregnancy. Compared to acute fatty liver of pregnancy, HELLP tends to be more severe and its features are hepatic infarctions and subcapsular haematomas. Hepatic haemorrhage, parenchymal necrosis and subcapsular haematoma leading to hepatic rupture may complicate HELLP.

Platelet transfusion should be considered if the platelet count falls below 20,000 mm^{-3} or 50,000 mm^{-3} if an interventional procedure is required. The risk of bleeding into the epidural space is significantly reduced with a platelet count of $>75,000$ mm^{-3} [44]. HELLP may deteriorate in the 48 h following delivery. The maternal mortality associated with HELLP is approximately 1%, whereas perinatal mortality rates vary from 7% to 60%.

Delivery of the foetus

Delivery of the foetus is the definitive treatment of pre-eclampsia. When pre-eclampsia occurs in the pre-term period (<34 weeks gestation), expectant management (compared to interventional management) confers benefit to the foetus with minimal additional maternal risk [45]. When pre-eclampsia is severe, however, the benefits of continuing pregnancy to the foetus are limited in view of deteriorating maternal health. Under such circumstances, induction of labour and delivery should be considered. When pre-eclampsia occurs before 24 weeks gestation, expectant management is unlikely to offer any benefit to the foetus, whilst maternal risks accumulate [45]. Antenatal corticosteroids should be given to aid foetal lung maturation when gestation is <34 weeks [46].

Summary

Severe pre-eclampsia accounts for a significant proportion of maternal morbidity and mortality globally. It is a systemic disease that can lead to the development of multiple organ dysfunction. As such, a multidisciplinary approach to the management of the woman with severe pre-eclamptic tox-aemia (PET) is important, ideally in a critical care setting. There is no 'standard' guideline for the management of pre-eclampsia, as variations in practice depend on the experience of the clinician. The decision to induce labour will depend on the gestational age and maternal stability. Guidelines on the management of pre-eclampsia may vary between countries, depending on resource availability. However, identification of high-risk patients, optimisation of antenatal care and early intervention form the cornerstone of management of severe pre-eclampsia.

Practice points

1. Targeting a systolic blood pressure <140–150 mmHg and diastolic blood pressure <80–90 mmHg minimises the risk of haemorrhagic stroke.
2. In the first instance, oral anti-hypertensive agents should be tried. If oral anti-hypertensive agents have failed to adequately control blood pressure, intravenous anti-hypertensives should be considered. Commonly used intravenous anti-hypertensives include labetalol, hydralazine and glyceryl trinitrate.
3. Regular monitoring of other vital signs including heart rate, urine output, oxygen saturation, respiratory rate, deep tendon reflexes and Glasgow Coma Scale is crucial.
4. Magnesium sulphate should be considered early to prevent seizures.
5. Delivery of the foetus is the definitive management of severe pre-eclampsia.

Research agenda

1. A greater understanding of the underlying aetiology of pre-eclampsia and development of biomarkers to predict those at risk of developing severe pre-eclampsia is required.
2. The most appropriate blood pressure threshold and goal of anti-hypertensive treatment need to be determined.
3. Evidence relating to the ideal anti-hypertensive agent(s) and blood pressure targets needs to be determined by large randomised clinical trials.
4. The timing of delivery needs to be understood.

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