The diagnosis and management of pre-eclampsia

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Key points

Pre-eclampsia is a multi-system disorder.

Close monitoring is essential.

Mean arterial pressure should be kept between 100–140 mmHg.

Regional analgesia is beneficial in labour.

30% of cases manifest post-partum.

Clear, written, management protocols should be available.

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Pre-eclampsia causes increased mortality and morbidity in both mother and fetus. Worldwide, the incidence of maternal death directly related to pregnancy varies widely (6–686 per 100,000 live births) but the consistent feature is that pre-eclampsia is the first or second commonest cause of such death in most countries, and responsible for up to 50% of deaths directly due to pregnancy and its complications.

Definition

Pre-eclampsia is a multisystem disorder occurring after the 20th week of pregnancy, with variable features, severity and rate of progress. The main features are hypertension and proteinuria. Pre-eclampsia occurs in 2–3% of all pregnancies and is more common in primigravida or the first pregnancy with a particular partner. Other risk factors include a positive family history, pre-existing hypertensive disease, diabetes mellitus, multiple pregnancy, increasing maternal age and obesity. It is associated with an increase in morbidity and mortality for both mother and child. Pre-eclampsia may be further classified into mild, moderate and severe. Severe pre-eclampsia is defined as any one of the following occurring after the 20th week of pregnancy: (i) severe hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 110 mmHg); (ii) proteinuria > 5 g per 24 h; (iii) oliguria < 400 ml per 24 h; (iv) cerebral irritability; (v) epigastric or right upper quadrant pain (liver capsule distension); or (vi) pulmonary oedema.

Eclampsia is the occurrence of convulsions in a woman with pre-eclampsia. This only occurs in about 1 in 2000 deliveries in the industrialised world but the incidence is much higher in non-industrialised countries. In a significant percentage of cases, both pre-eclampsia and eclampsia may only manifest post-partum, usually within 48 h of delivery.

Pregnancy-induced hypertension is defined as a rise in blood pressure during the second half of pregnancy, without proteinuria. It occurs in about 10% of all pregnancies and is not associated with any increased risk to the mother or fetus. Some women may develop pre-eclampsia.

Pre-existing hypertension is defined as known hypertension prior to pregnancy or raised blood pressure prior to 20 weeks of gestation. It is usually due to essential hypertension but may be secondary to underlying disease. Perinatal mortality is increased in women with severe essential hypertension.

Diagnosis

Hypertension

Hypertension during pregnancy is defined as diastolic BP ≥ 110 mmHg on any one occasion or diastolic BP ≥ 90 mmHg on 2 or more consecutive occasions ≥ 4 h apart, not measured during labour.

Blood pressure should be regularly monitored as part of routine antenatal care but just how it should be measured in pregnancy is controversial. Mean arterial pressure usually falls in the first half of pregnancy as a result of vascular smooth muscle relaxation caused by progesterone. Conventional measurement using a mercury sphygmomanometer is still the gold standard. However, observer and device error, and natural variability of the blood pressure can affect readings. It should be measured with the woman seated, with her feet supported or on the ground, and the arm at the level of the heart. Use of an appropriate

sized cuff is important and readings should be recorded to the nearest 2 mmHg. It has previously been argued that diastolic blood pressure should be taken at Korotkoff sound IV (muffling) in pregnant women. However, the current consensus view is that Korotkoff sound V is most accurate. Several ambulatory blood pressure devices have been specifically validated for use in pregnancy and provide accurate data and objective, repeatable measurements, even in a non-clinical environment. However, they have not been validated for use in hypertensive or pre-eclamptic pregnant women. Indeed, in these situations, such devices tend to under-read blood pressure.

Proteinuria

Proteinuria is defined as one 24-hour collection with total protein excretion ≥ 300 mg per 24 h or 2 specimens of urine collected ≥ 4 h apart with ≥ 2+ on the protein reagent strip. Routine dipstick testing of urine for protein may reveal a progressive problem requiring quantitative measurement.

Plasma uric acid concentrations are elevated in women with pre-eclampsia and may be used as a marker of the disease. Measurement of uric acid may aid the diagnosis, particularly in those with pre-existing hypertension. Concentrations > 360 μmol litre^{-1} (6.0 mg dl^{-1}) are associated with pre-eclampsia and there is often a further rise in those who develop eclampsia.

Aetiology

The precise aetiology of pre-eclampsia is unknown. A genetic predisposition is likely and an autoimmune reaction against the placenta may be involved. Deficient placental implantation and platelet aggregation within the placental bed result in placental ischaemia. Vasoactive substances released by the ischaemic placenta lead to widespread endothelial damage and profound vasospasm which have multisystem effects. Platelet adherence occurs at sites of endothelial damage. Prostaglandin metabolism is also disordered with an increase in thromboxane and a decrease in prostacyclin concentrations leading to platelet dysfunction and further vasoconstriction. It would, therefore, seem logical that aspirin may reduce the incidence and severity of pre-eclampsia. However, a large multicentre study investigating the effect of a daily low dose aspirin did not confirm this.

Pre-eclampsia affects all organs of the body. As with any disease, there is a spectrum of severity. Endothelial damage and arteriolar vasospasm lead to a wide variety of end-organ effects, affecting maternal and fetal well-being. These are summarised in Table 1.

Table 1 Effects of pre-eclampsia

		Effects
Maternal		
	CVS	Widespread vasoconstriction
		Normal or increased systemic vascular resistance
		Left ventricular failure
		Increased vascular permeability and oedema
		Decreased circulating blood volume
	CNS	Headaches
		Visual disturbances
		Hyper-reflexia
		Cerebral haemorrhage
		Convulsions
	Renal	Reduced glomerular filtration rate
		Reduced urea clearance and increased uric acid concentrations
		Proteinuria and hypoproteinaemia
		Oliguria
		Acute renal failure
	Respiratory	Pulmonary oedema
		Facial and laryngeal oedema
		Adult respiratory distress syndrome
	Liver	Abnormal liver function tests
		Subcapsular haemorrhage and epigastric pain
		Liver rupture
	Coagulation	Increased turnover of fibrinogen, fibrin and platelets
		Thrombocytopaenia
		Impaired platelet function
		Disseminated intravascular coagulation
		HELLP syndrome (haemolysis, elevated liver enzymes, low platelets)
Fetal		Decreased placental perfusion
		Placental ischaemia and infarction
		Intra-uterine growth retardation
		Placental abruption
		Preterm labour

HELLP syndrome

The haemolysis, elevated liver enzymes and low platelet (HELLP) syndrome describes the combination of micro-angiopathic haemolytic anaemia, thrombocytopaenia and hepatic ischaemia with periportal haemorrhage and necrosis which can occur with severe pre-eclampsia. Some studies suggest that HELLP occurs in up to 50% of such cases. Partial HELLP may be diagnosed if only 1 or 2 of the criteria are present. Occasionally, it may occur when hypertension or proteinuria is absent or minimal; 20% of cases present post-partum. It may present with epigastric/right hypochondrial pain, malaise, nausea and vomiting. It may be asymptomatic and revealed by detecting hypertension on routine checking. Differential diagnosis includes acute fatty liver of pregnancy, cholestasis, viral hepatitis and thrombocytopaenia from other causes. Early haemolysis can be detected by measuring serum haptoglobin concentrations.

Table 2 Drugs used to control the blood pressure in pregnancy

Drug	Dose	Mechanism of action	Comments
Hydralazine	5 mg increments IV every 20 min IV infusion 5–20 mg h^{-1}	Directly acting vasodilator, mainly arterioles	Widely used Side-effects (headache, tremor, vomiting) may mimic impending eclampsia
Labetalol	50 mg increments IV every 20 min 100 mg increments PO every 30 min IV infusion 20–160 mg h^{-1}	α- and β-blocker	Few maternal side-effects Contraindicated in asthma May impair capacity of fetus to cope with stress Safety of long-term use not known
Methyldopa	1–3 g PO per day in 3–4 divided doses	Centrally acting, reduces sympathetic outflow	Side-effects include drowsiness, depression, postural hypotension Safe for long-term use
Nifedipine	20 mg, slow release preparation, PO	Calcium channel blocker	Short acting Can get profound hypotension in combination with magnesium Safety of long-term use not known
Sodium nitroprusside	IV infusion starting at 0.25 μg kg^{-1} min^{-1}	Directly acting vasodilator, mainly arterial	Rapid onset and offset Good for hypertensive emergencies May cause excessive hypotension Risk of cyanide toxicity to fetus
Glyceryl trinitrate	IV infusion starting at 10 μg min^{-1}	Directly acting vasodilator, mainly venous	May cause excessive hypotension Risk of methaemoglobinaemia

HELLP syndrome is associated with an increased risk of developing other serious complications of pre-eclampsia (*e.g.* seizures) and both maternal and fetal mortality is increased. After onset, the syndrome worsens rapidly for 24–48 h but usually resolves within 6 days.

Management of pre-eclampsia

Early diagnosis, control of blood pressure, prevention of convulsions and timely delivery are the goals of management. A heightened awareness of pre-eclampsia as a possible diagnosis is necessary because of its variable presentation. Close monitoring is essential in severe or unstable pre-eclampsia. Good intravenous access is essential in all cases because of the risk of complications, particularly haemorrhage and convulsions. The level of monitoring should be tailored to each individual patient. Blood pressure should be frequently measured and invasive monitoring may be necessary in unstable patients. Fluid balance should be meticulously recorded and central venous pressure (CVP) monitoring may be required if there is any uncertainty regarding volume status. Peripherally inserted central catheters are safer in patients with existing or potential coagulation abnormalities. Studies have shown a poor correlation between CVP and left atrial pressure in severe pre-eclampsia, particularly at pressures > 6 mmHg. Therefore, pulmonary artery catheters may be needed in some cases, although these in themselves are associated with maternal morbidity and mortality and careful consideration should be given to their use. Full blood count, urea, electrolytes and creatinine, and liver function tests should be regularly checked. If the platelet count is < 100,000 x 10^9 litre^{-1}, further clotting studies are needed.

Management of HELLP

This is the same as for pre-eclampsia. Meticulous and frequent monitoring of the cardiovascular system, haematological status and renal and hepatic function is required with supportive therapy as indicated by the measured parameters. Changes in haematological state may occur rapidly and require aggressive treatment (in discussion with a haematologist).

Control of blood pressure

The aim should be to maintain mean arterial pressure between 100–140 mmHg (130/90–170/110 mmHg). A sudden drop in blood pressure, or reductions below these mean pressures, should be avoided as this will further compromise placental perfusion. Careful volume expansion should be achieved prior to the use of vasodilators or epidural analgesia to maintain perfusion. Anti-hypertensive therapy may need reducing or stopping post-partum. Drugs that may be used for hypertension are shown in Table 2.

Fluid therapy

Intravenous fluid therapy is often necessary as there is usually intravenous volume depletion. However, there is also a propensity to develop pulmonary oedema. There is an inverse relationship between intravascular volume and severity of hypertension, with

plasma volume 30–40% below normal in severe pre-eclampsia. A significant decrease in plasma volume may precede the clinical appearance of the disease. The risk to the fetus correlates with the degree of maternal plasma and protein depletion. Volume expansion alone has been shown to reduce systemic vascular resistance and systolic blood pressure.

Optimum fluid therapy is difficult to achieve since the combination of low colloid oncotic pressure and left ventricular dysfunction in severe pre-eclampsia makes pulmonary oedema a great risk. Crystalloid alone causes a further decrease in colloid oncotic pressure, whereas colloid will increase the CVP and thus the risk of pulmonary oedema. Usual regimens involve crystalloid at 1–2 ml kg^{-1} h^{-1} with colloid used if the CVP and serum albumin are low. Blood and blood products should be given as necessary. Oliguria should be treated with a fluid challenge of 250 ml of crystalloid. If there is no response, CVP monitoring should be instituted before any further fluid is given. The aim is to keep the CVP between 3–5 mmHg and maintain a urine output of > 0.5 ml kg^{-1} h^{-1}. However, a urine output as low as 0.25 ml kg^{-1} h^{-1} for several hours is rarely associated with acute renal failure, unless there is another event such as haemorrhage, hypotension or DIC. It is important to minimise the risk of pulmonary oedema.

Delivery

The timing and management of delivery require close collaboration between obstetric, paediatric and anaesthetic teams. Prior to 32 weeks' gestation, attempts should be made to prolong the pregnancy, at least until corticosteroids have been given to aid fetal lung maturity. Women should be optimised as far as possible prior to delivery, with attention to blood pressure control and adequate fluid resuscitation. As with all women in late pregnancy, supine hypotension should be avoided at all times by the use of left uterine displacement.

Local analgesia and anaesthesia

Epidural analgesia is the preferred choice for labour. It is beneficial both in controlling the blood pressure and improving placental perfusion due to vasodilatation. It also reduces the stress response and release of catecholamines which occurs with pain. A platelet count $< 50,000$ x 10^9 litre^{-1} is considered an absolute contra-indication to regional techniques. Platelet counts of 50–100,000 x 10^9 litre^{-1} may be considered acceptable, provided that a coagulation screen is otherwise normal. Bleeding time gives a better indication of platelet function but there is significant operator variability. Thrombo-elastography may be used where available. Fluid pre-loading may precipitate pulmonary oedema and should be under-

taken with extreme caution. The use of low doses of local anaesthetic reduces fluctuations in blood pressure and low dose epidural infusions are preferred in some institutions.

Regional anaesthesia is again the preferred choice for Caesarean section because of the potential problems associated with general anaesthesia. It is also reduces the stress response to surgery. Epidurals have traditionally been used to avoid the risks of a sudden and precipitous drop in blood pressure associated with spinal anaesthesia. The main dose should be given in increments rather than as a single bolus to gradually increase the height of the block to the desired level. The use of epinephrine in epidural mixtures should be avoided and fentanyl is added to improve the sensory component of the block. The pharmacokinetics of lidocaine are altered in pre-eclampsia (*e.g.* reduced drug clearance) and so bupivacaine or ropivacaine are the best options.

Recent studies have shown that the severity of hypotension after spinal or epidural anaesthesia is similar. When spinals do cause hypotension, uteroplacental perfusion has not been shown to be reduced – it may even increase. Therefore, spinals or combined spinal and epidural (CSE) techniques are now increasingly used. They are thought to be a safe alternative if undertaken with caution, particularly in those patients who are already on vasodilator therapy. Hypotension should be treated with a combination of crystalloid, colloid and ephedrine, bearing in mind the potential risk of pulmonary oedema. Sensitivity to vasopressors is increased in pre-eclampsia and so ephedrine should be administered cautiously and in low doses. Phenylephrine may be used as an alternative to ephedrine.

General anaesthesia

Problems associated with general anaesthesia in pre-eclampsia include an increased risk of difficult intubation (oedema of the upper airway) and cardiovascular instability, in addition to the usual risks associated with pregnancy. Convulsions may occur during operative delivery and some would argue that these are easier to manage under general anaesthesia. General anaesthesia will be required for emergency Caesarean sections, in the case of failed regional techniques or if the latter are contra-indicated.

The airway should be fully assessed prior to induction with regards to the airway. Signs of upper body oedema, especially facial, are particularly worrying. Awake intubation may be considered to be the safest approach, although nasal intubation can precipitate significant bleeding (venous engorgement, disordered coagulation). Bleeding may also occur with oral intubation. Drugs used to obtund the hypertensive response to laryngoscopy

and intubation include magnesium sulphate 40 mg kg^{-1}, short-acting opioids (*e.g.* alfentanil 10 μg kg^{-1}), β-blockers (*e.g.* esmolol 0.5 mg kg^{-1} or labetalol 10–20 mg) and lidocaine (1.5 mg kg^{-1} given 5 min prior to intubation). Extubation may also cause an exaggerated cardiovascular response which should be attenuated. Esmolol or lidocaine are logical choices. It is important to remember that magnesium will prolong the effects of depolarising and non-depolarising neuromuscular junction blockers and reduce the fasciculations when succinylcholine is given. Nerve stimulators should be used in all cases. Laryngeal oedema may worsen during the operation and, prior to extubation, the endotracheal tube cuff should be deflated to ensure that there is still air leaking around the tube.

Post-delivery

Although delivery of the fetus is the only long-term cure for the condition, pre-eclampsia often worsens after delivery and up to 30% of cases are only diagnosed post-partum. Most maternal deaths from pre-eclampsia occur following delivery. Thus, all the preceding advice regarding control of blood pressure and meticulous fluid balance applies equally after delivery, using invasive monitoring if necessary. Fluid overload must be avoided. Transient rises in plasma urea and creatinine concentrations are acceptable in the short-term as a spontaneous diuresis is usual within 1–2 days of delivery. Improvement may take several days, during which time close observations should be continued, at least in a high dependency unit and in an intensive care unit, if necessary. Anti-hypertensive treatment should be continued as long as is necessary. Good analgesia is also important after operative delivery to reduce the stress response caused by uncontrolled pain. Epidural or CSE techniques offer the advantage of providing a route for effective post-operative analgesia.

Eclampsia

Eclampsia may occur ante-partum (40%), intra-partum (20%) or post-partum (40%). The severity of hypertension does not correlate well with the incidence of convulsions. Signs and symptoms of impending eclampsia include headache, visual disturbances (including cortical blindness), hyper-reflexia and abdominal pain (liver capsule distension). Seizures are generalised and often self limiting. Magnesium sulphate is now the treatment of choice for the treatment of convulsions and for the prevention of recurrent fits. Its exact mechanism of action is not known. However, it is thought to reduce the intense cerebral vasospasm which may be the cause of convulsions. A loading dose of 4 g is given over 5–10 min, followed by an infusion of 1 g h^{-1}. Debate exists as to whether

monitoring of serum concentration (2–4 mmol litre^{-1}) is essential. Close monitoring of oxygen saturation and patellar tendon reflexes (hourly) is necessary. Magnesium crosses the placenta and may lead to neonatal hypotonia and respiratory depression. Phenytoin and diazepam have been widely used in the past but have now been replaced by magnesium. Any further treatment of seizures is supportive (*e.g.* intubation and ventilation).

New developments

Women with pre-eclampsia have been found to have increased concentrations of plasma and placental serotonin (5-hydroxytryptamine). Serotonin acts at serotonin-1-receptors on endothelial cells causing release of prostacyclin and nitric oxide producing vasodilation. Serotonin-2-receptors are found on smooth muscle cells and platelets, and stimulation results in vasoconstriction and platelet aggregation. If the endothelial cells are damaged, such as in pre-eclampsia, serotonin then acts only at serotonin-2-receptors producing unopposed vasoconstriction.

Ketanserin is a selective serotonin-2-receptor antagonist; it also has some antagonistic effect at α_1-adrenoreceptors at high doses. It has been shown to reduce the systolic and diastolic blood pressure in non-pregnant patients with acute and chronic hypertension. In severe pre-eclampsia, intravenous ketanserin is at least as effective as hydralazine at reducing blood pressure and it is associated with fewer side-effects. It may also be useful orally for chronic hypertension in pregnancy. Used in combination with aspirin in patients with mild hypertension, ketanserin has been shown to reduce the risk of developing pre-eclampsia. It has a low incidence of side-effects, which include somnolence, dizziness and dry mouth.

Studies are still on-going to evaluate the role of ketanserin in hypertension in pregnancy; it is not used routinely in the UK at present. However, it may provide an effective and well-tolerated treatment for the control of blood pressure in pregnancy.

Key references

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See multiple choice questions 25–28.