

Pre-eclampsia: prevention, diagnosis and management

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Summary

Pre-eclampsia causes significant morbidity and mortality to both mother and foetus worldwide, the major causes being delayed diagnosis and poor management. Identifying the parturient at risk of developing pre-eclampsia is paramount and optimising this patient cohort is key. Early management of pre-eclampsia favours a better outcome with magnesium sulphate and anti-hypertensive medications being the mainstay of treatment. A multi-disciplinary approach involving Anaesthesia is most likely to confer more favourable outcomes to both mother and foetus. This review article will describe the diagnosis, pathogenesis, prevention and management of pre-eclampsia; in particular its treatment options with reference to anaesthetic practice.

DEFINITION AND DIAGNOSIS

Pre-eclampsia or pre-eclamptic toxemia (PET) is defined as a hypertensive syndrome that occurs in pregnant women after 20 weeks' gestation, consisting of new-onset, persistent hypertension (defined as a BP ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic, based on at least 2 measurements taken at least 4 hours apart) with one or more of the following:

- 1) proteinuria (defined as urinary excretion of ≥ 0.3 g/24 hours of protein, or $\geq 1+$ (on 2 random urine samples, collected at least 4 hours apart))
- 2) evidence of systemic involvement, such as renal insufficiency (elevated creatinine - >1.1 mg/dL or >97.2 μ mol/L), liver involvement (elevated transaminases and/or right upper quadrant pain), neurological complications, haematological complications
- 3) foetal growth restriction.

Pre-eclampsia usually resolves within 48 hours of the post-partum period, however it can be diagnosed up to six weeks post-partum without any signs during the pregnancy.

AETIOLOGY AND RISK FACTORS

PET is associated with hyper-placentation disorders such as diabetes, hydatidiform mole, and multiple pregnancy. There are numerous risk factors that increase the probability and severity of pre-eclampsia, including primiparity, previous maternal history or family history, BMI >30 , maternal age >35 years, multiple pregnancy, pre-gestational

diabetes, autoimmune disease, renal disease, chronic hypertension, hypertension at booking, and an interval of 10 years or more since a previous pregnancy. However, these risk factors do not account for all cases and complications such as eclampsia, HELLP syndrome (a subtype of severe pre-eclampsia characterised by haemolysis [H], elevated liver enzymes [EL], and low platelets [LP]), and foetal growth restriction are not present in all patients.

PATHOGENESIS

There is much, on-going, research regarding the pathophysiology of PET, currently thought to be multifactorial in origin with genetics, immunology, and endothelial dysfunction each playing a role. However, it is generally accepted that there is an association with a failure of the normal invasion of trophoblast cells leading to maladaptation of maternal spiral arterioles. The maladaptation of these vessels can interfere with normal villous development; leading to placental insufficiency and subsequently hypoxia leading to foetal growth restriction, and the release of both vasoconstrictors and vasodilators leading to increased perfusion of vascular beds with endothelial damage and hypertension.

The cardiac pathophysiology subsequently manifests in other organ dysfunctions, such as:

- cerebral vascular dysregulation leading to cerebral oedema
- liver vascular dysregulation and associated oedema
- pulmonary oedema.

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SEVERITY OF PRE-ECLAMPSIA

The National Institute for Health and Care Excellence (UK), (NICE) have classified the severity of pre-eclampsia based on blood pressure measurement:

- Mild – Systolic BP 140-149mmHg and/or diastolic BP 90-99mmHg
- Moderate - Systolic BP 150-159mmHg and/or diastolic BP 100-109mmHg
- Severe – Systolic BP \geq 160mmHg and/or diastolic BP \geq 110mmHg

In addition, severe pre-eclampsia can be associated with the following features:

- severe headache
- visual disturbance eg. flashing lights or blurred vision
- vomiting
- papilloedema
- clonus (\geq 3 beats)
- liver tenderness and subcostal pain
- thrombocytopaenia ($<$ 100x10⁹ litre⁻¹)
- abnormal liver enzymes (AST or ALT $>$ 70iu litre⁻¹)
- HELLP syndrome (haemolysis, elevated liver enzymes and low platelets)

PREVENTION

The significant morbidity associated with pre-eclampsia has led to considerable interest in preventative measures. Although it is difficult to assess what measures will show a positive outcome due to an incomplete understanding of the pathogenesis, a number of preventative measures are currently recommended.

Aspirin

NICE have recommended a daily dose of 75mg aspirin from 12 weeks until 36-37 weeks' gestation for any woman with on high, or two or more moderate risk factors² (Table 1). This was based on a sub-group comparison of a large Cochrane meta-analysis demonstrating a 50% relative risk reduction for the development of PET. The mechanism of action is thought to be as a result of reduced platelet production of thromboxane relative to prostacyclin and hence reduced vasoconstriction.

Calcium

A Cochrane review found evidence from 13 studies that calcium supplementation in high doses (\geq 1 gram daily) during pregnancy may be a safe way of reducing the risk of pre-eclampsia, especially

in women from communities with low dietary calcium and those at increased risk of pre-eclampsia.

One drawback of routine calcium supplementation is the development of HELLP syndrome, found by a Cochrane review. The absolute numbers were very small (high-quality evidence) and further research is needed into the ideal dosage of supplementation.

Folic acid

There was thought to be a clear dose-response relationship between increasing folic acid supplementation and decreasing risk of pre-eclampsia in women with additional identified risk factors. However, the recently published Folic Acid Clinical Trial (FACT) suggests that high dose folic acid supplementation in later pregnancy has no benefit for preventing pre-eclampsia. Folic acid supplementation remains indicated in pre-conception and early pregnancy but there is a need to define when to discontinue supplementation as current clinical practice guidelines do not provide clear guidance beyond the first trimester.

Other preventative management

Women with the diagnoses of hypertension and renal disease prior to pregnancy should be optimised prior to conception. Women with hypertension, including those with an isolated elevated diastolic blood pressure at booking, should be followed up in an increased-frequency surveillance programme.

A controlled weight loss program reduces the incidence of pre-eclampsia and as such, evidence suggests that exercise in pregnancy should be encouraged, albeit in the absence of complications, such as risk factors for bleeding, premature delivery, and maternal comorbidities.

MANAGEMENT

Blood Pressure

The main aim of blood pressure management in pre-eclampsia is to prevent intra-cerebral haemorrhage. It is recommended to aim for systolic and diastolic blood pressures of $<$ 150 and 80–100mmHg, respectively, although rapid reductions in blood pressure may result in complications to both mother and foetus. Oral labetalol is often first choice, but alternatives include nifedipine and methyldopa.

Caution must be taken when administering calcium channel blockers with magnesium as they may precipitate profound hypotension. If the blood pressure remains elevated, intravenous agents may be required to lower the blood pressure – hydralazine or labetalol can be titrated to effect and will more reliably reduce blood pressure as they did not rely on absorption from the gastrointestinal tract.

Table 1: Risk factors for PET

High risk factors	Moderate risk factors
Hypertensive disease in previous pregnancy	First pregnancy
Chronic kidney disease	Age \geq 40 years
Autoimmune disease (eg. antiphospholipid syndrome)	Pregnancy interval \geq 10years
Type 1 or 2 diabetes mellitus	Family history of PET
Chronic hypertension	Multiple pregnancy

Table 2: Pharmacological agents to reduce blood pressure³

	Medication	Dosing regime	Cautions
Oral	Labetolol	100mg bds, increasing in 100mg increments to a maximum of 2.4g daily; >800mg daily qds regime	Diabetes (may mask signs of hypoglycaemia); first-degree AV block; history of obstructive airways disease (introduce cautiously) and asthma; symptoms of thyrotoxicosis may be masked
	Methyldopa	250mg bds/tds, increasing every 3 days to a maximum of 3g/day	Acute porphyria, depression, phaeochromocytoma
	Nifedipine MR	10mg bds increasing to a maximum of 40mg bds	Poor cardiac reserve, significantly impaired left ventricular function, *modified release must be used as large blood pressure variations occur with short-acting preparations
Intravenous	Labetolol	50mg over 1 minute for rapid control, then 20mg/hour increased by 20mg/hour every 30 minutes to a maximum of 160mg/hour	Same as oral labetolol
	Hydralazine	5-10mg by slow IV injection for rapid control, or; 200-300mcg/min for rapid control then 50-150mcg/min for maintenance control	Acute porphyria, cor pulmonale, idiopathic systemic lupus erythematosus; severe tachycardia, *patient may require fluid bolus 250-500ml prior to administration

Annotation: bds (latin: bis die sumendum) twice daily; tds (latin: ter die sumendum) three time daily; qds (latin: quarter die sumendum) four times daily

Table 3: Magnesium toxicity

Magnesium concentration (mmol/L)	Effects
0.8-1.0	Normal plasma levels
1.7-3.5	Suggested therapeutic range
2.5-5.0	ECG changes, increased PR interval, widened QRS
4.0-5.0	Reduced deep tendon reflexes, sedation, slurred speech, nausea, diplopia
>5.0	Loss of deep tendon reflexes
>7.5	Respiratory paralysis, CNS depression, SA and AV node blockade
>12	Complete heart block, cardiac arrest

If intravenous agents are required to reduce the blood pressure, fluid restriction, hourly urine output monitoring and six-hourly blood tests to monitor platelet count, renal and liver function must be carried out as well as continuous monitoring of the foetus using CTG or foetal scalp electrode (FSE).

Seizures

Eclamptic seizures may develop as a consequence of not recognising or inappropriate management of PET. This can lead to significant morbidity and mortality due to intracerebral haemorrhage and cardiac arrest. First-line therapy for eclampsia and its prevention is with magnesium sulphate. The Collaborative Eclampsia Trial recommended a loading dose of 4–5g over 5 min followed by an infusion of 1g.h⁻¹ for 24 hours through an infusion device. Any further seizures are treated with a further 2g bolus of magnesium whilst observing the patient for signs of magnesium toxicity (see Table 3).

Where infusion devices are not widely available, similar plasma concentrations can be achieved by a slow manual push of 4g, administered over 20 minutes, followed by deep intramuscular (IM) loading of 10g (10ml in each buttock) followed by one 5g deep IM injection every 4 hours .

Whilst magnesium alone is not recommended as the sole antihypertensive agent in PET, repeated boluses may cause cardiovascular instability and invasive blood pressure monitoring is advised, especially if the urine output is diminished and magnesium clearance is reduced.

Magnesium also has the added benefit of neuroprotection for the foetus if preterm delivery is anticipated; reducing the risk of cerebral palsy.

The treatment for magnesium toxicity is calcium gluconate (10ml of 10% solution over 10min).

PULMONARY OEDEMA

Approximately 3% of pre-eclamptic patients will develop acute-onset pulmonary oedema following delivery due to excess fluid administration in the antenatal period. Fluid restriction to 80ml.hour⁻¹ is recommended including intravenous fluids, medications and oral intake, provided there are no on-going fluid losses. Clinical examination, chest x-ray and echocardiogram can all be useful to assess left ventricular dysfunction.

Treatment includes sitting the patient upright, supplementary oxygen, fluid restriction and intravenous furosemide boluses (20-

Table 4: HELLP syndrome diagnosis

Blood test	Result
Haemolysis	LDH >600iu litre ⁻¹ , total bilirubin >20mmol litre ⁻¹ , blood film
Elevated liver enzymes	AST, ALT or GGT >70iu litre ⁻¹
Low platelets	<100x10 ⁹ litre ⁻¹

60mg) titrated to effect. Oxygen can be delivered in a number of different ways, however non-invasive ventilation may be required to achieve oxygen saturations >95%. Opioid analgesics are not routinely used; although they dilate the pulmonary vasculature, they have the negative effect of sedation and reducing ventilatory drive.

HAEMOLYSIS, ELEVATED LIVER ENZYMES AND LOW PLATELETS (HELLP) SYNDROME

HELLP and ELLP (without the presence of haemolysis) syndrome are very serious manifestations of pre-eclampsia.

Both syndromes are associated with a high maternal and foetal morbidity. The commonest complaint is due to engorgement of the liver leading to right upper-quadrant abdominal pain however patients can often present with disseminated intravascular coagulation (DIC), placental abruption or hepatic rupture or infarction. The severity of the maternal disease state or in the presence of a non-reassuring CTG, urgent delivery of the foetus (and placenta) is indicated.

Consideration must be given to the timing of such deliveries, for example if the administration of corticosteroids may benefit foetal lung maturation in the preterm foetus (<37 weeks gestation). The World Health Organisation (WHO) recommend four doses of intramuscular (IM) dexamethasone 6mg twelve hours apart or two doses of IM betamethasone 12mg twenty-four hours apart. It is important to consider dosing frequency and timing of preterm birth to ensure the woman receives preferably the total dose, or at least a substantial amount, prior to delivery .

HELLP syndrome can progress very rapidly, however, and a full blood count within the preceding 2 hours of performing central neuraxial blockade is vital as platelet count can fall extremely quickly. In the presence of thrombocytopenia or a rapidly falling platelet count the use of regional techniques are precluded and the use of general anaesthesia is required for operative delivery. In these circumstances, eclamptic seizures are common, so magnesium sulphate should be strongly considered.

ANALGESIA

Neuraxial analgesia can be used to obtund the hypertensive response to pain and block the sympathetically-mediated hypertension that women with PET encounter. Care must be taken to ensure it is safe to perform such blocks; a platelet count >75-100x10⁹ litre⁻¹ is required within 6 hours of such techniques but shorter if there is suspicion of a rapidly decreasing platelet count. Careful titration of low concentration epidural mixtures does not normally require administration of intravenous fluid boluses nor vasopressors; but care must be taken not to induce hypotension as this is poorly tolerated by the foetus; there is no utero-placental autoregulation.

Postpartum analgesia can be provided by paracetamol, in combination with intrathecal, epidural or intravenous opioids, abdominal wall nerve blocks or local infiltration depending on the mode of delivery.

Non-steroidal anti-inflammatory drugs (NSAIDs) must be avoided in PET as they can precipitate renal and platelet dysfunction.

ANAESTHESIA

Regional techniques are the anaesthetic of choice when performing a caesarean section. They provide a profound depth of block and obtund the surgical stress response during both the intra-operative and the immediate post-operative period. They also serve to manage blood pressure control, however caution must be given to inducing maternal hypotension leading to poor utero-placental perfusion. A phenylephrine infusion can be used to antagonise the peripheral vasodilatory actions of the central neuraxial techniques by using its actions as an alpha-agonist. Due consideration must be given to the highly responsive nature of the maternal vasculature system, therefore lower infusion rates must be used compared to normal. Invasive blood pressure monitoring can be invaluable to titrate the blood pressure carefully, avoiding periods of profound hypo- and hypertension but also large variations between both.

Caution must be used when administering uterotonic agents; syntocinon causes profound hypotension and must be administered slowly, ergometrine may cause hypertension and myocardial infarction and must therefore be avoided in PET.

Where the use of regional anaesthetic techniques are precluded, general anaesthetic technique must be adapted.

Pre-eclamptic patients are prone to desaturation; standard pre-oxygenation may still lead to profound hypoxaemia during induction of anaesthesia. The use of the Head Elevating Laryngoscopy Position (HELP) pillow and Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) can aid in reducing the rate at which the parturient desaturates. In the absence of this equipment, using the ramped position (inducing anaesthesia in the semi-recumbent position) and the use of high-flow oxygen through standard nasal cannulae may be advantageous .

When performing intubation, the airway may be oedematous requiring a smaller endotracheal tube than usual and the frequency of difficult intubations are increased. This should be anticipated and the Obstetric Anaesthetists Association (OAA) and Difficult Airway Society (DAS) guidelines should be followed. Use of video laryngoscopes can aid intubation and are more commonly being used as the first line equipment in Obstetric Anaesthesia.

Blood pressure control must be carefully titrated, with the expectation of hypertension commonly associated with laryngoscopy, surgical stimulation and emergence. Where the blood pressure is not adequately controlled, significant morbidity and mortality can occur from intra-cerebral haemorrhage and is demonstrated in the EMBRACE reports. Appropriate medications can include opioid analgesics (alfentanil, remifentanil), beta-blockers (labetolol, esmolol), local anaesthetic agents (intravenous lidocaine) and magnesium sulphate or a combination of the aforementioned. These medications are not without their side effects however; maternal

Table 5: Contraindications to neuraxial techniques

Absolute contraindication	Relative contraindication
Patient refusal	Platelet count (<100 epidural, <70 spinal) (x10 ⁹ /L)
Local anaesthetic allergy	INR and APTTr ≥ 1.5
Active infection at site of insertion	Continuing anticoagulation
Previous lumbar back surgery - epidural	Severe stenotic cardiac valve lesions
	Thrombophilia
	Raised intra-cranial pressure
	Previous lumbar back surgery - spinal

Table 6: Pharmacologic uterotonic agents

Medication		Contraindications and Side Effects
Syntocinon - bolus - infusion	5 units, repeated once iv/im 10 units.hour ⁻¹ iv	Tachycardia, hypotension, nausea and vomiting
Ergometrine	500mcg im	Hypertension, contra-indicated in PET
Carboprost	250mcg im every 15 minutes up to 8 doses	Reactive airways disease, bronchospasm
Misoprostol	800mcg rectally or sublingually	Ischaemic heart disease, arrhythmia

beta-blockade may induce foetal bradycardia or hypoglycaemia, opioids can precipitate respiratory depression in the neonate and magnesium inhibits platelet aggregation and can prolong blockade with non-depolarising neuromuscular blockers.

Care must be taken during emergence from anaesthesia; to ensure adequate respiratory effort, ensure that airway oedema will not obstruct spontaneous ventilation and that blood pressure is controlled. Frequently, patients are being nursed in a high dependency environment with invasive blood pressure and central venous pressure monitoring to ensure their care standard is optimised.

POST-PARTUM HAEMORRHAGE

Pre-eclampsia is a recognized risk factor for postpartum haemorrhage (PPH) possibly due to the associated disease characteristics mentioned previously along with the limited use of uterotonic agents. As such, a second large-bore peripheral intravenous cannula should be considered and good communication with the haematology laboratory ensuring group specific blood cross-matched, where available. Tranexamic acid can be used as an antifibrinolytic agent to help reduce blood loss.

Table 6 shows the pharmacological uterotonic agents that can normally be used to enhance uterine tone. Ergometrine is not recommended in PET as it precipitates hypertension.

Alternatively, surgical techniques such as the Bakri balloon or B-Lynch suture (if intra-operative) can be used to optimise uterine tone. In the case of a significant PPH associated with large fluid shifts, a central venous cannula may be useful in determining right heart filling pressures and the patient managed accordingly.

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