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HYPERTENSIVE DISORDERS OF PREGNANCY

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This term, used in the *Reports on Confidential Enquiries into Maternal Deaths in the United Kingdom*,[1] covers the spectrum of disorders encompassing pre-eclampsia, eclampsia, and the syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP). Acute fatty liver of pregnancy and other microangiopathies of pregnancy are related disorders that can arise simultaneously.[2]

Pre-eclampsia is a multisystem disorder of generalised vasospasm. It is thought that placental ischaemia might cause trophoblastic fragmentation. Widespread platelet aggregation on these fragments could release *serotonin*. This mediator would account for the widespread vasopasm and consequent endothelial cell dysfunction. Cardiovascular, central nervous, renal, respiratory, hepatic and coagulation systems are affected to variable extents.[3]

The circulating volume is expanded relative to the non-pregnant state, but less so than in normal pregnancy. The demonstration from pulmonary artery (PA) catheter data of flow-dependent oxygen consumption indicates that severe pre-eclampsia is associated with an oxygen extraction defect at the tissue level, similar to that found in critically ill patients with multi-organ failure.[4]

Pre-eclampsia is characterised by the variability of its presentation and rate of progression. The only definitive treatment is delivery of the fetoplacental unit. However, in the 24 hours following delivery, clinical and laboratory indices of the disease often continue to deteriorate before recovery begins.

Cardiovascular

Before delivery, the aim is to prevent intracerebral haemorrhage secondary to uncontrolled hypertension, whilst preserving uteroplacental blood flow and maternal renal perfusion. A systemic arterial pressure (BP) of >170/110mmHg is an indication for urgent treatment - although BP should not be reduced acutely to below 130/90mmHg.[5] For acute therapy, the following are suitable:

- A vasodilator such as **hydralazine** is effective given initially as 2.5 - 5mg boluses every 20 mins, thereafter by continuous infusion. Side effects of headache, tremor and vomiting can mimic impending eclampsia. Prior administration of a colloid bolus of no more than 500ml has been advocated to prevent acute fetal compromise secondary to vasodilatation.

- **Labetalol** has both vasodilating (αadrenergic blocking activity and (βblockade which mitigates tachycardia. 10 - 20mg increments (up to 100mg) at 5-10min intervals are usually effective.

- The calcium channel antagonist **nifedipine** has been used as an antihypertensive agent in pre-eclampsia, although there is a possibility of myocardial depression and excessive hypotension if it is given in conjuction with magnesium sulphate ($MgSO_4$), also a calcium antagonist.

- **Ketanserin**, a serotonin-2 receptor antagonist, has been shown to have an antihypertensive effect comparable to that of hydralazine, but with a lower incidence of headache, visual complaints, and nausea/vomiting. Notably, HELLP, oliguria, pulmonary oedema and placental abruption developed less frequently in women treated with ketanserin. This selective serotonin-2 blocker, currently unlicensed in the UK, appears to work at the level of the disturbed platelet-endothelial cell interaction (rather than acting merely as a vasodilator).[6]

Pre-eclampsia alone rarely causes cardiac failure in young, otherwise healthy women. Only a minority of pre-eclamptic women who develop pulmonary oedema have reduced systolic function and a dilated left ventricle.[7] Peripartum cardiomyopathy is unexplained heart failure associated with pregnancy in previously healthy women without detectable organic heart disease. The nature of its relationship with pre-eclampsia is unclear.8 Women with pre-eclampsia and pulmonary oedema should have echocardiography to establish whether there is evidence of cardiomyopathy, which might benefit from early treatment with ACE inhibition. Iatrogenic fluid administration, steroids given to promote fetal lung maturation, and (2 agonists (e.g. ritodrine) given for tocolysis, can all contribute to the development of pulmonary oedema.

Renal

Glomerular involvement causes proteinuria. The appearance of ≥300 mg protein over 24 hours was a traditional diagnostic feature of pre-eclampsia. However, proteinuria is no longer considered an *inevitable* feature of the disease.[9] Its degree and rate of increase are not - unlike serum uric acid concentrations - important predictors of maternal or perinatal outcome. Hyperuricaemia precedes significant proteinuria in pre-eclampsia and is thought to result from either enhanced tubular reabsorption of uric acid, or breakdown of nuclear (and therefore purine) rich syncytiotrophoblast.

Up to 6 hours of oliguria (urine output <30 ml/hr) after delivery is extremely common, and does not necessarily imply volume depletion. Acute tubular necrosis is exceptionally rare in the absence of a compounding factor such as major haemorrhage, or injudicious administration of a non-steroidal anti-inflammatory drug.

- There is little evidence upon which to base management of fluid balance in pre-eclampsia - no large prospective outcome studies have been performed.[10] No study has shown that crystalloid or colloid is superior. The use of crystalloid may reduce plasma colloid oncotic pressure, but the longer half-life of colloid may contribute to circulatory overload during the period of postpartum mobilisation of the increased extracellular fluid volume of pregnancy. Fluid input and output must be charted meticulously. If Syntocinon® is to be continued post-delivery, it should be administered in small diluent volumes by syringe pump (e.g. 40 units in 40ml Normal saline at 10ml/hr).

- Unless delivery has been complicated - for example by haemorrhage (e.g. abruption) or sepsis (e.g. chorioamnionitis), invasive monitoring is indicated only rarely. Measurement of CVP will help substantiate a diagnosis of *hypovolaemia*, and assist its correction. A brachial 'long' line is vastly safer than other approaches, particularly in the presence of coagulopathy. Airway obstruction secondary to inadvertent carotid puncture in the course of attempted jugular venous cannulation has been responsible for maternal mortality, and a number of near misses.

- Volume expansion can reasonably be undertaken if CVP (5mmHg. However, the circulating volume should be considered as *full* if CVP is >5mmHg. Minimal i.v. fluids (e.g. Normal saline or Hartmann's at 20ml/hr) will suffice.

- Dopamine 1-5μg/kg/min has been shown to increase urine output in oliguric postpartum pre-eclamptic patients who have not responded to a 300ml crystalloid challenge, although the benefit is questionable.

- There is a disparity between CVP and pulmonary artery wedge pressure (PAWP) at CVP measurements of greater than 6 mmHg, when PAWP may be *considerably higher*, as a result of left ventricular dysfunction.

Pulmonary artery (PA) catheterisation is warranted for situations where the benefits of knowing PAWP, cardiac output, and systemic vascular resistance (SVR) are judged to outweigh the risks. Potential indications are pulmonary oedema unresponsive to diuretic therapy, persistent severe oliguria, and hypertension refractory to standard therapy. Although oesophageal Doppler appears to underestimate cardiac output measured by PA catheter, the direction and magnitude of sequential changes are accurately reflected.[11]

CNS

Fits occurring in late pregnancy and labour should be regarded as eclamptic unless proven otherwise. Alternative diagnoses include epilepsy, intracerebral pathology (tumours, vascular malformations, haemorrhage), water intoxication, local anaesthetic toxicity, and amniotic fluid embolism (anaphylactoid syndrome of pregnancy).

Eclampsia complicates about 1:2000 maternities in Europe and developed countries. In 32 (60%) of 53 cases of eclampsia in two American centres over 10 years, seizures were the first manifestation of a hypertensive disorder of pregnancy.[12] When asked subsequently about prodromal symptoms, severe headache was noted by two thirds, and visual symptoms in one third. Only 7 women had a diagnosis of severe pre-eclampsia. This study suggests that eclampsia is not necessarily preceded by mild pre-eclampsia which has progressed to severe pre-eclampsia.

In the event of eclampsia

- Maintain airway patency and give 100% oxygen. Avoid aortocaval compression, and attempt to prevent trauma to the mother and fetus.

- Most initial fits will be self-limiting. If not, administer without delay a loading dose of 5g (10ml of 50%) **Magnesium sulphate** ($MgSO_4$) over at least 5 minutes. If i.v. Mg has already been started, treat with a further 2g bolus, unless a recent serum concentration was at the high end of the therapeutic range (see below).

- If $MgSO_4$ is not readily available, **diazepam** 10mg i.v. over 2 min is an appropriate alternative anticonvulsant. Phenytoin has been rendered obsolete in pre-eclampsia/eclampsia.

- After the convulsion has terminated, examine the mother for signs of pulmonary aspiration (tachypnoea, crackles/wheeze), and institue SpO_2 monitoring. Ensure that an obstetrician or midwife determines the fetal heart rate without delay. Fetal compromise secondary to maternal hypoxaemia or placental abruption will signal the need for emergency Caesarean section under general anaesthesia.

- In the rare event of a continuing seizure or difficulty maintaining maternal oxygenation, summon skilled anaesthetic assistance and transfer swiftly to theatre. Induce general anaesthesia with thiopental or propofol, ensure cricoid pressure is applied, and intubate the trachea following neuromuscular blockade with succinylcholine.

- Eclamptic patients who have an emergency GA Caesarean section should be transferred to ICU for a period of sedation and ventilation. Ideally, brain imaging should be performed *en route* in order to exclude intracranial haemorrhage and ascertain whether there is evidence of cerebral ischaemia.

- Treat as for a non-pregnant patient with cerebral ischaemia secondary to traumatic brain injury. If neuromuscular blockade is used, neurophysiological monitoring (e.g. cerebral function analysing monitor) will allow identification of further seizure activity.

- In the presence of therapeutic serum Mg concentrations, doses of non-depolarising neuromuscular blockers must be reduced, and the degree of block monitored with a peripheral nerve stimulator.

Magnesium sulphate

$MgSO_4$ has been shown to reduce the incidence both of eclampsia complicating severe pre-eclampsia, and further fits in eclamptic patients. In the Magpie study[13] over 10 000 women with hypertension and proteinuria were randomised to magnesium sulphate or placebo. Women allocated Mg had the incidence of eclampsia halved compared to those who had placebo. However, the number needed to treat was 91 (for each patient who had a seizure prevented, 91 patients received Mg).[14]

Mg reduces both systemic and cerebral vasospasm by antagonism of calcium. Increased oxygen delivery and consumption accompany systemic vasodilatation.[4] The anticonvulsant action of Mg is consistent with the theory that eclamptic seizures are caused by cerebral vasospasm. Nimodipine, a calcium channel antagonist (used extensively in neurosurgical practice to reduce cerebral ischaemia after subarachnoid haemorrhage) has also been used successfully to treat eclampsia. Resolution of cerebral ischaemia has been imaged by magnetic resonance. Nimodipine 1 mg/hr by i.v. infusion (increasing to 2mg/hr after 20 minutes) reduced SVR and BP in a small series of eclamptic women. Nimodipine 30mg 4-hrly, orally, has been shown to control BP effectively in pre-eclampsia.

The following is a suggested dose regimen for $MgSO_4$ used with laboratory support for estimations of serum magnesium concentrations.

1. Initial loading dose - **5g $MgSO_4$** (10 ml of 50% solution) either by i.v. bolus over (5 minutes or by adding to 40ml Normal Saline (total volume 50ml) and infusing over 20 minutes (150ml/hr).

2. Maintenance dose - infuse $MgSO_4$ at **2g/hr** e.g. add 20ml of 50% solution to 30 ml Normal Saline (total volume 50ml) and infuse at 10ml/hr. For women <50 kg, infuse at **1g/hr** (5ml/hr)

3. Check serum Mg concentration 60min after loading dose, then every 6hr. Adjust to maintain serum concentration in the therapeutic range **2 to 3.5mmol/l.**

4. If concentration is <2mmol/l, give an extra 2 g (increase rate to 40ml/hr *for 15 minutes only*).

5. If serum concentration is 3.5 - 4mmol/l, decrease rate to 5 ml/hr; if >4mmol/l, stop infusion until serum concentration has decreased.

6. Continue for 24hr, or as long as woman is symptomatic or has labile BP.

- ECG changes (widened QRS) may occur within therapeutic range. Renal impairment will reduce Mg clearance; nausea, vomiting and flushing are early signs of toxicity. Loss of deep tendon reflexes and respiratory muscle weakness occur at 5 - 7.5mmol/l, cardiac arrest at around 12.5mmol/l.

- In the event of toxicity, stop the $MgSO_4$ infusion and administer ventilatory and circulatory support as required. Calcium chloride or gluconate (10 - 20ml of 10% solution) will oppose the effects of magnesium on neural transmission.

Hepatic

Patients with the HELLP syndrome usually present pre-delivery, with malaise, nausea and vomiting, and epigastric or right upper quadrant pain and tenderness. Hypertension and proteinuria may be minimal or absent. As with eclampsia, presentation in the postpartum period is not uncommon.

- Haemolysis (seen on blood film) and a platelet count falling to <100 (10-9/l may be associated with DIC.

- Elevated bilirubin, alanine transaminase and lactate dehydrogenase concentrations are indicative of hepatocellular injury.

- Other associated maternal morbidities include placental abruption, subcapsular liver haematoma, acute renal failure, and pulmonary oedema.

Differential diagnoses include the related microangiopathies: thrombotic thrombocytopaenic purpura, haemolytic uraemic syndrome, and acute fatty liver of pregnancy. The treatment is delivery, with specific organ system support as necessary. There is evidence that postpartum i.v. administration of dexamethasone (10 mg 12-hrly) hastens recovery and reduces disease severity.

Whereas liver enzyme abnormalities are usually more pronounced in HELLP, acute fatty liver of pregnancy is more likely to result in marked hypoglycaemia, hyperammonaemia, and coagulopathy. In addition to coagulopathy, raised intracranial pressure (suggested by somnolence) dictates GA rather than a regional block for Caesarean section. In a recent case report, a serum Mg concentration at the upper limit of the therapeutic range was associated with respiratory depression necessitating mechanical ventilation. It was postulated that combined hepatic and renal dysfunction rendered the patient more susceptible to Mg toxicity.[2]

Analgesia and Anaesthesia

The risk of fetal compromise and placental abruption in labour is increased in pre-eclamptic women, therefore early establishment of good regional analgesia is recommended. BP should be controlled (e.g. with hydralazine) before the procedure is undertaken. The subsequent sympathetic blockade and relief of pain will prevent hypertensive surges during contractions. Early communication amongst midwives, obstetricians and anaesthetists should allow time for conversion to surgical anaesthesia if Caesarean section becomes necessary. The catheter will enable provision of optimal postoperative analgesia by continuous or patient-controlled infusion of a fentanyl/bupivacaine mixture in a high-dependency environment.

Concerns about regional anaesthesia for Caesarean section in pre-eclampsia include

- The risk of vertebral canal haematoma (VCH). Thromboelastography has shown that pre-eclamptic women with platelets >100 (10^{-9}/l are *hypercoagulable*. At platelet counts below 100 (10^{-9}/l there is a risk of *hypocoagulability*, and measurement of coagulation times (APTT/TCT) is indicated.[15] Thromboelastographic indices of coagulation in pre-eclampsia are not significantly altered by attainment of therapeutic serum magnesium concentrations. Logically, the risk of VCH should be less following single passage of a 26g pencil-point spinal needle as opposed to identification of the epidural space with a 16g Tuohy needle and insertion of a catheter.

- Haemodynamic instability. Prior vasodilatation by effective antihypertensive treatment (e.g. oral methyldopa or i.v. hydralazine) seems to prevent problematic hypotension following epidural or spinal anaesthesia. Judicious increments of ephedrine or phenylephrine do not cause arterial pressure overshoot.

A recent study demonstrated that women who have had an eclamptic seizure but were fully conscious and co-operative, treated with magnesium, and with platelet count >100 (10^{-9}/l could safely undergo regional anaesthesia.[16]

Concerns about general anaesthesia include

- The pressor response to laryngoscopy and intubation/extubation. The cerebral circulation must be protected from hypertensive surges at intubation and extubation - as in a neuroanaesthetic for cerebral aneurysm clipping. Despite pretreatment with Mg and labetalol, BP and middle cerebral artery velocity (measured by transcranial Doppler, and assumed to be indicative of cerebral blood flow) increased significantly after tracheal intubation in a series of pre-eclamptic women.[17]

- Laryngeal oedema. A real risk - particularly for the patient whose larynx was noted to be swollen at laryngoscopy, or in whom intubation was traumatic. Those undertaking postoperative care must be alert to the ominous significance of stridor.

- Interaction of Mg with neuromuscular blockers. Although the onset and duration of suxamethonium is unaffected by therapeutic Mg concentrations in pre-eclampsia, Mg affects the actions of all *non-depolarising* drugs. The onset time of vecuronium 0.1mg/kg is halved by prior bolus of Mg. Significant *recurarisation* has been demonstrated following administration of a bolus of Mg after recovery from vecuronium block to a train-of-four ratio of 0.7. The onset time of rocuronium 0.6mg kg^{-1} is not shortened by prior administration of magnesium, but the mean time to recovery of T1 to 25% during isoflurane anaesthesia is increased by 50%. In pre-eclamptic women treated with magnesium, mivacurium 0.15mg/kg given after recovery from suxamethonium has a mean duration of 35 min.

General anaesthesia is indicated if there is uncorrected coagulopathy or symptoms/signs consistent with impending eclampsia. Prior communication with a neonatal paediatrician is essential in order that preparation can be made for antagonism of opioid/provision of ventilatory support.

- Have a low threshold for direct arterial pressure monitoring.

- Attenuate the pressor response to intubation with alfentanil 10μg/kg or remifentanil 2μg/kg before rapid sequence induction with a generous dose of thiopental.

- Do *not* limit the end-tidal inhalational agent concentration on account of (spurious) concerns about neonatal depression.

- Before extubation, consider antihypertensive therapy (e.g. labetalol in 10-20mg increments) to avert a dangerous pressor response.

- A peripheral nerve stimulator is essential to indicate the degree of neuromuscular block.

Non-steroidal anti-inflammatory drugs (NSAID) are absolutely contra-indicated if pre-eclampsia has been complicated by haemorrhage, or there is concern about adequacy of haemostasis (e.g. uterine atony). In women with mild renal disease (good urine output and no serum indices of renal failure), there seems little reason to deny women the benefit of the morphine-sparing effect of NSAID. However, successive doses should not be given without repeated confirmation of sustained satisfactory urine output.

Maternal mortality

The need for clear delivery suite protocols and early consultant input, particularly to co-ordinate fluid balance, have been recurring themes in the Reports. In the '94-'96 triennium[1], 20 direct deaths were attributed to hypertensive disorders of pregnancy - the same number as over the previous 3 years. This is a mortality rate of 1 in 100 000 maternities. Pulmonary complications (e.g. ARDS) outnumbered intracranial haemorrhage as a cause of death.

The '97-'99 Report[18] saw fewer deaths[16], with the majority[7] swinging back to intracerebral haemorrhage. Only one death was attributed to ARDS.

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