Continuing Medical Education Article

Anaesthesia and pre-eclampsia

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Pre-eclampsia continues to be one of the major causes of maternal mortality.¹ Anaesthetic considerations in pre-eclampsia are important and may contribute to the overall management.²

Pre-eclampsia is characterized by the triad of (1) hypertension, (2) proteinuria and (3) oedema.³ Hypertension in pregnancy is usually associated with pre-eclampsia but can also be due to other hypertensive disorders. Hypertension occurs in 5–10 per cent of all pregnancies and is usually seen in primigravidae after the 20th week of pregnancy. Third trimester hypertension is defined as a diastolic blood pressure of more than 85 mmHg or a mean pressure exceeding 95 mmHg.³ Pre-eclampsia becomes eclampsia if convulsions occur. Convulsions can occur with only minimal blood pressure elevations and thus it can be misleading to categorize pre-eclampsia as mild or severe solely on the basis of the degree of blood pressure elevation. Severe pre-eclampsia is diagnosed when one or more of the following are present: (1) blood pressure of at least 160 mmHg systolic or 110 mmHg diastolic on two readings six hours apart, (2) proteinuria $\geq 5 \text{ g} \cdot 24 \text{ hr}^{-1}$, (3) oliguria/ $<400 \text{ ml} \cdot 24 \text{ hr}^{-1}$, (4) cerebral or visual disturbances, and (5) pulmonary oedema or cyanosis. The HELLP Syndrome, a particularly severe type of pre-eclampsia, is diagnosed in the presence of haemolysis, elevated liver function tests and low platelet counts.⁴ Eclampsia, though, is usually preceded by warning signs such as headache, hyperreflexia and epigastric pain.

Pathophysiology

The exact aetiology of pre-eclampsia remains unknown. The two main theories are (1) that it is the result of uteroplacental ischaemia, and (2) that it is a primary immunologic disorder.^{5–7} Vascular changes in the placenta in the first trimester may be the cause of pre-eclampsia. Placental vasculitis is activated by an antigen-antibody reaction between maternal and fetal tissue. As well, there

is an imbalance in the production of two placental prostaglandins – prostacyclin and thromboxane.⁸ Recently a model of pre-eclampsia has been developed in the pregnant primate and this may facilitate future research into the pathogenesis of pre-eclampsia.⁹ Hypertension is the major sign and is characteristically labile reflecting the sensitivity of the vasculature to endogenous pressor peptides and catecholamines. This sensitivity may be in part due to the decreased production of prostaglandins of the E and I series.¹⁰ There is an associated decrease in plasma volume but whether this is a primary event or secondary to vasoconstriction is controversial. However, recent data suggests the decrease in volume may be primary and precede the occurrence of hypertension.¹¹ The changes that occur in pre-eclampsia affect the cardio-vascular, renal, haematological, nervous and gastrointestinal systems. The Figure shows a proposed scheme of pathophysiologic changes in pre-eclampsia.

With the advent of more invasive cardiovascular monitoring techniques there is increasing information about the changes in the cardiovascular system in pre-eclampsia. Studies using pulmonary artery catheters have shown that in pre-eclamptic patients, right and left ventricular filling pressures are lower than normal and there is hyperdynamic left ventricular function and elevated systemic vascular resistance.^{12,13} Pulmonary arteriolar resistance has been found to be normal or slightly lower than normal, suggesting that the vasospasm associated with pre-eclampsia does not involve the pulmonary vasculature.¹⁴ Right atrial pressures (from a central venous pressure line), may not predict left atrial pressures (as determined by pulmonary capillary wedge pressures) in severely pre-eclamptic patients, including those with pulmonary oedema.^{15–17} In some patients, pulmonary capillary wedge pressures may be found to be high while right atrial pressures are normal.^{18,19} Colloid osmotic pressure has been found to be lower than in normal pregnant patients.

The glomerular filtration rate decreases in pre-eclampsia, partly because of a swelling of intracapillary glomerular cells (glomerular endotheliosis).¹¹ Plasma volume deter-

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FIGURE Proposed scheme of pathophysiologic changes in toxemia of pregnancy. (Reproduced by permission. From Speroff L: Toxemia of pregnancy: mechanism and therapeutic management. *Am J Cardiol* 1973; 32: 582-91.)

minations show that plasma volume is decreased in pre-eclamptic patients compared to normals and that this decrease precedes the development of pre-eclampsia.^{11,20} Uric acid levels have been noted to rise in patients with pre-eclampsia²¹ and may be helpful in the differential diagnosis between pre-eclampsia and other hypertensive disorders.

Coagulation disorders are common in pre-eclampsia. Thrombocytopenia is common and tends to worsen with the severity of the pre-eclampsia.²¹⁻²³ One-third of pre-eclamptic patients have thrombocytopenia and 50 per cent of these have an increased bleeding time.²⁴ In addition, thromboxane B₂ synthesis may be impaired and also be associated with increased bleeding times.²⁴ These defects return to normal within five days of delivery.

The most dramatic complication of pre-eclampsia is convulsions, which signifies progression to eclampsia.²⁵ The aetiology of convulsions is speculative; however, cerebral blood flow is decreased in pre-eclampsia and convulsions may be associated with disseminated intravascular coagulation causing platelet-fibrin clots obstructing the cerebral micro-circulation. The neurological changes in pre-eclampsia/eclampsia appear to be transient and, while the electroencephalogram may be abnormal, cerebral arteriograms and computerized axial tomographic scans are normal.²⁶ Hyperreflexia is common and is associated with generalized central nervous system irritability.

Hepatic involvement is usually mild, but occasionally there can be severe liver dysfunction, including periportal haemorrhages and ischaemic lesions associated with marked coagulation changes, as described in the HELLP Syndrome.^{4,27} This syndrome is associated with a poor maternal and neonatal outcome if therapy is not initiated early.⁴ Laryngeal oedema may occur along with the generalized oedema.²⁸ It has also been found that there is a shift to the left of the oxyhaemoglobin dissociation curve (reduced P₅₀) in pre-eclamptic patients, when compared to normal pregnant patients which will decrease availability of oxygen to the fetus.²⁹ Uteroplacental perfusion decreases in pre-eclampsia and this is a major reason for the high incidence of fetal loss, intrauterine growth retardation and small-for-date infants.²⁵

In summary, the major features of the pathophysiology of pre-eclampsia include extreme vasoconstriction, enhanced vascular reactivity to pressor peptides and amines, and decreased intravascular volume.

Management

Management of pre-eclampsia, for the most part, is symptomatic and designed to reduce maternal and fetal complications. As yet pre-eclampsia cannot be predicted though one report suggests that early vasospasm (at 9 to 12 weeks of gestation) occurs in women who develop pre-eclampsia.³⁰ Antiplatelet therapy (300 mg dipyridamole and 150 mg aspirin daily) from three months gestation onwards may prevent the development of pre-eclampsia.³¹ Once pre-eclampsia is diagnosed the only definitive treatment is delivery of the fetus and placenta.²

Pre-eclamptic patients should be hospitalized to decrease the frequency of convulsions and improve fetal outcome.³ Antihypertensive therapy is usually required and hydralazine is often the first drug of choice, because of its arteriolar vasodilator properties.² In refractory cases other agents such as diazoxide or methyl dopa are used.³² A maximum diastolic pressure of 90-105 mmHg is considered desirable. Controversy exists as to how much blood pressure should be reduced because of the possibility of decreasing utero-placental perfusion. Other types of hypotensive agents are usually avoided, i.e., beta-blockers can cause fetal bradycardia and hypoglycaemia, and captopril is associated with fetal death in some species.³³ Newer agents, such as nifedipine (a calcium channel blocker) have been investigated but their use is not yet routine.³⁴

Magnesium sulfate is used routinely in North America in order to prevent convulsions (eclampsia); however, in Europe it has never been popular. Its mode of action is not well understood. As well as preventing convulsions magnesium sulfate may cause hypotension, particularly

with the initial bolus dose.^{35,36} Magnesium therapy must be carefully controlled, because of the potential serious side effects. Magnesium therapy has particular significance because of its potentiation of neuromuscular blockers when general anaesthesia is needed. Therapeutic blood levels are 6–8 mEq·L⁻¹ and increasing blood levels can lead to respiratory paralysis (12–15 mEq·L⁻¹) and cardiac asystole (>24 mEq·L⁻¹).³⁷ Magnesium sulfate potentiates the action of both depolarizing and non-depolarizing relaxants. This is the result of a decrease in both the amount and action of acetylcholine liberated from motor nerve terminals.³⁸ In addition magnesium has a tocolytic action and may be used to control preterm labour. However, it has been shown that when used in therapeutic doses in mild pre-eclampsia it does not affect uterine activity or fetal heart rate variability.³⁹ Its anticonvulsant action is thought to be due to a specific action on the cerebral cortex and occurs at serum levels below those that produce paralysis.⁴⁰

Alternate modes of therapy, such as plasma volume expansion have been tried in preeclampsia;^{41,42} however, the mainstay of therapy remains bed rest, control of hypertension, prevention of seizures and early delivery of a viable fetus. Despite advances in management, pre-eclampsia remains a leading cause of maternal mortality but most of such deaths are considered preventable.^{1,43} The major cause of death is cerebral haemorrhage but other causes include pulmonary oedema, renal failure and hepatic coma.

Anaesthetic management

Anaesthetists can and should take an active role in the monitoring and management of pre-eclamptic patients in addition to providing analgesia for labour and anaesthesia for operative delivery.

Usually the anaesthetist becomes involved with a pre-eclamptic patient when asked to initiate epidural analgesia for control of labour pain. The use of epidurals in pre-eclampsia has been considered controversial. While some authors have felt that epidurals should be avoided, because of the potential for severe hypotension,³ most now consider that epidurals are the technique of choice for analgesia in pre-eclampsia.⁴⁴ The haemodynamic changes during epidural analgesia in pre-eclampsia have been well studied. There is usually a small fall (about 20 per cent) in blood pressure.^{45–47} One recent study found that in severe pre-eclamptics lumbar epidural anaesthetic reduced mean arterial pressure from 121.4 mmHg to 97.7 mmHg without altering cardiac index, pulmonary vascular resistance, central venous pressure or pulmonary capillary wedge pressure.⁴⁸ These measurements were made using a pulmonary artery catheter and as previously noted there may be a poor correlation between

central venous pressure and pulmonary capillary wedge pressure. The drop in blood pressure caused by epidural analgesia has been advocated as part of the hypotensive therapy in pre-eclamptic patients.⁴⁵ However, the fetal and maternal risk from hypertension is closely linked to the maximum levels of the blood pressure and epidural analgesia may not change the maximum recorded levels of blood pressure⁴⁹ and thus may not protect the pre-eclamptic from the dangers of hypertension.

Another important consideration in epidural analgesia is its effect on uterine blood flow, particularly if hypotension occurs. This has been well studied in both normal and hypertensive pregnant patients using a radioactive xenon method to measure intervillous blood flow.⁵⁰ In normal labour intervillous blood flow has been found to increase when 0.25 per cent bupivacaine or two per cent 2-chloroprocaine were used in an epidural block.⁵¹ Similarly, in pre-eclamptic patients it was found that intervillous blood flow increased when either 0.5 or 0.25 per cent bupivacaine were used.^{52,53} In all these studies the epidural block was performed after an appropriate intravenous "preload" (500 ml lactated Ringer's solution) and with the patient in a lateral tilt position to minimize hypotension. The choice of local anaesthetic does not seem critical, as bupivacaine (0.25 and 0.5 per cent), 2-chloroprocaine (two per cent) and lidocaine (two per cent) have all been used without adverse effects.^{52–55} The pharmacokinetics of lidocaine in pre-eclampsia are different from normotensive patients in that the total maternal body clearance is prolonged which could result in higher blood levels.⁵⁵ However, the effects on the newborn were no different in pre-eclamptic or normotensive patients.⁵⁵ Pre-eclamptic patients have higher levels of catecholamines than normal patients, which may be secondary to the toxæmic process, but these levels are reduced after epidural analgesia is initiated.⁵⁶ Because of the higher catecholamine levels it has been recommended that epinephrine should not be used with local anaesthetics.²

Epinephrine, however, has not been found to change intervillous blood flow in normal patients receiving epidural analgesia⁵⁶ and in four pre-eclamptic patients the use of epinephrine 1:200,000 to 1:400,000 was not associated with an increase in blood pressure.⁵⁷ Epinephrine is probably not required for epidural maintenance, particularly with the use of longer-acting local anaesthetics, such as bupivacaine.

Before institution of epidural analgesia it is important to check the coagulation status of the pre-eclamptic patient. The prothrombin time and partial thromboplastin time should be within normal limits and the platelet count >100,000. A bleeding time is indicated if the platelet count is between 100,000 and 150,000, particularly if the platelet count has been falling. The volume status of the

patient has to be assessed carefully and an appropriate intravenous "preload" infused. This should be assessed against central venous pressure measurements or pulmonary artery pressures, if indicated.⁴⁴ If the diastolic pressure is <100 mmHg then 1–2 L of a balanced salt solution are sufficient to raise central venous pressure to 4–6 cm H₂O. With diastolic pressures >100 mmHg, colloid (e.g., albumin) may be required to raise the central venous pressure to this level.⁵⁸

Anaesthesia for operative delivery raises further considerations. The choice in this situation lies between regional anaesthesia (i.e., epidural or spinal) and general anaesthesia. Caesarean section is often required because of the worsening fetal status and delivery of the infant is the only way to end pre-eclampsia. If time permits and there are no contra-indications (i.e., coagulopathy or non-acceptance by the patient) then epidural anaesthesia is the best choice for Caesarean section. Epidural anaesthesia has been found to be preferable to general anaesthesia, if hypotension is avoided by use of intravenous fluid loading and vasopressors, if necessary.^{59,61} If a vasopressor is needed to maintain blood pressure then ephedrine is the drug of choice as uterine perfusion and intervillous blood flow are not affected significantly.^{61,62} Ephedrine should be used cautiously in pre-eclampsia as there may be dramatic increases in blood pressure. Spinal anaesthesia may be used but is more likely to be associated with hypotension.⁴⁴ In an emergency situation or where epidural anaesthesia is contraindicated, then general anaesthesia is the only practical choice.

Apart from the normal concerns of general anaesthesia for Caesarean section such as aspiration, there are several specific concerns in a patient with pre-eclampsia. Tracheal intubation may be more difficult, because of laryngeal oedema.²⁸ Muscle relaxants have to be used cautiously, because of possible interaction with magnesium sulfate. If magnesium sulfate has been used, pre-curarization is not necessary as fasciculations with succinylcholine will not occur.⁶³ Doses of muscle relaxants should be titrated and monitored using a nerve stimulator. The major hazard with general anaesthesia is hypertension occurring at the time of intubation, as well as with surgical stimulation and emergence.⁵⁹ Such increases in blood pressure can be disastrous, with the occurrence of pulmonary oedema and cerebral haemorrhage which may be due to a ruptured cerebral aneurysm.⁶⁴ In order to avoid such pressor responses, particularly at the time of intubation, a number of approaches have been advocated. Because of the risk of aspiration a rapid-sequence induction must be performed and this does not readily allow for a method where a deep level of anaesthesia is achieved before intubation. Fentanyl can be used prior to intubation in a dose of 8 µg·kg⁻¹ to blunt the hypertensive responses to intuba-

tion.⁶⁵ However, in a Caesarean section fentanyl cannot be generally recommended, because of the possibility of fetal depression though its use has been reported in one pre-eclamptic patient with a cardiac anomaly without causing apparent problems for the newborn.⁶⁶ If fentanyl, or another narcotic, is used prior to delivery, then respiratory depression in the newborn may occur and require treatment. Various antihypertensive agents have been used to prevent the acute increase in blood pressure at induction but none is definitely superior to another. Hydralazine is used routinely for control of blood pressure in pre-eclampsia but it has a slow onset of action and thus it is difficult to titrate its action against the hypertensive response.⁶⁷ Nitroglycerine has a rapid onset of action and is an effective agent for prevention of the hypertensive response but it does cross the placenta and may increase maternal intracranial pressure.^{68,69}

Sodium nitroprusside also has a rapid onset of action but it has the potential for both fetal and maternal toxicity, because of its toxic metabolites (including cyanide).^{70–72} It also carries the potential for increased maternal intracranial pressure. Trimethaphan is also rapidly acting but may cause histamine release and prolonged paralysis after succinylcholine, but does not cause increased maternal intracranial pressure and because of its large molecular weight (597) has little, if any, placental transfer.^{73,74} Newer agents, such as calcium blockers (e.g., verapamil) may have a place in such therapy but as they may cause decreased uterine blood flow further study is needed.⁷⁵

Recommendations for anaesthetic management

Labour and vaginal delivery

Lumbar epidural anaesthesia is the method of choice, provided:

- 1 Coagulation status is normal (PT, PTT normal and platelet count >100,000).
- 2 Blood volume status is acceptable, i.e., central venous pressure 4–6 cm H₂O after fluid "pre-load" with 0.9 per cent saline or lactated Ringer's solution. "Pre-loading" with a colloid solution (e.g., albumin) may be needed in more severe cases.
- 3 Other contra-indications are not present.
- 4 Appropriate monitoring is in place, i.e., central venous pressure or pulmonary artery pressure if cardiac compromise is suspected.

Caesarean section

In non-urgent cases, as above, lumbar epidural anaesthesia is the method of choice, but as a higher level is required (T_{4–7}) the volume status should be monitored very closely. Bupivacaine 0.5 per cent or lidocaine two per cent are appropriate choices and should be given in

divided doses, to minimize the risk of hypotension. Spinal anaesthesia is an alternative and might be useful in some urgent situations⁷⁷ but the risk of hypotension is higher, because of the rapidity of onset of the block.

General anaesthesia is the usual choice in urgent situations or where contra-indications preclude the use of a regional technique. With the use of general anaesthesia the following considerations should be taken into account.

- 1 Usual precautions against aspiration should be taken – including preoperative antacid and rapid-sequence intubation.
- 2 Intubation may be difficult because of laryngeal oedema.
- 3 Maintenance of uterine blood flow (lateral tilt).
- 4 Administration of at least 50 per cent O₂.
- 5 Muscle relaxants should be used with caution and their effects monitored using a nerve stimulator. Pancuronium may not be a good choice because of the potential for increases in blood pressure and pulse rate.
- 6 Central venous pressure, pulmonary arterial pressure and intra-arterial pressure monitoring should be considered.
- 7 Precautions should be taken against dangerous increases in maternal blood pressure, i.e.
 - (a) use of hydralazine 5–10 mg IV at least ten minutes before induction or
 - (b) be ready to give a rapidly acting hypotensive agent if necessary, such as nitroglycerine.
- 8 Ketamine should be avoided for induction because of its hypertensive properties.⁴⁴

Postpartum the patient is still at risk from pre-eclampsia and eclampsia and so will need careful monitoring for at least 24 hours, with possible use of antihypertensive and anticonvulsant drugs, and monitoring of volume status.⁴⁴

Conclusions

Pre-eclampsia remains a major cause of maternal and fetal mortality but many complications can be prevented by appropriate intervention. The anaesthetist should play a role in the overall as well as anaesthetic management of these patients. Epidural analgesia remains the method of choice for pain relief in pre-eclamptic patients during labour. Epidural anaesthesia may also be safely used for operative delivery in pre-eclampsia, as can general anaesthesia if precautions against precipitate hypertension are taken.

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