Review Article

Recent Advances In Management Of Pre-Eclampsia

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Pre-eclampsia is a multisystem disorder of pregnancy that forms an integral part of the spectrum known as hypertensive diseases of pregnancy. The National High Blood Pressure Education Program (NHBPEP) Working Group[1] classifies hypertensive diseases in pregnancy into 4 groups:

1) Gestational hypertension
   - New onset hypertension in pregnancy presenting after 20 weeks
   - No proteinuria
   - BP returns to normal less than 12 weeks postpartum
   - Final diagnosis made only postpartum
2) Chronic hypertension
   - BP >140/90 mm Hg before pregnancy or diagnosed before 20 weeks gestation not attributable to gestational trophoblastic disease
     or
   - Hypertension first diagnosed after 20 weeks gestation but persistent after 12 weeks postpartum.
3) Pre-eclampsia/eclampsia
   - BP > 140/90 mm Hg after 20 weeks gestation in a women with previously normal blood pressure
   - Proteinuria (>0.3 gm urine protein in 24 hr).
   - Eclampsia is defined as seizures that cannot be attributed to other causes in a woman with pre-eclampsia
4) Superimposed pre-eclampsia (on chronic hypertension)
   - New onset proteinuria (>300 mg/24 hr) in a woman with hypertension but no proteinuria before 20 weeks gestation
   - A sudden increase in proteinuria or blood pressure, or platelet count less than 100,000 in women with hypertension and proteinuria before 20 weeks gestation

Epidemiology

Pregnancy induced hypertension complicates about 10% of pregnancies, but there is a widespread geographic variation in its incidence. The incidence is higher in developing countries. The highest reported rate of pre-eclampsia is 7.1% (deliveries) from Zimbabwe[2], while the incidence is as low as 0.81% (deliveries) in Colombia[3]. In UK, the incidence of severe pre-eclampsia is 5/1000 maternities[4], while the incidence of eclampsia is 4.9/10,000 maternities[5]. The incidence of severe pre-eclampsia in European countries ranges from 2/1000 (deliveries) in Norway to 6.4/1000 (deliveries) in Belgium and Hungary[6].

The 8th Confidential Enquiry into maternal and child heath[7] revealed pre-eclampsia and eclampsia as the second leading cause of direct maternal death, thereby contributing to a maternal death rate of 0.83 / 100,000 maternities.

Worldwide studies show that mortality from pre-eclampsia can be as high as 0.4%, while that in eclampsia varies from 6.1% in developing countries to 1.8% in UK [5, 8-9].

Estimates of maternal mortality from the developing countries (in Asia, Africa, Latin America and the Caribbean) suggest that 10-15% of maternal deaths are associated with hypertension in pregnancy, while eclampsia is associated with 10% maternal mortality[10].

Severe pre-eclampsia is also associated with significant maternal morbidity, including eclamptic seizures, intracerebral haemorrhage, pulmonary oedema due to capillary leak or heart failure, acute renal failure, liver dysfunction, and coagulation abnormalities.

Fetal complications include abruptio placentae, intrauterine growth restriction, premature delivery, and intrauterine fetal death. The incidence of stillbirths and neonatal deaths in mothers who suffered eclampsia was 22.2/1000 and 34.1/1000, respectively, in the UK with a higher incidence in developing countries[5].

More than half a million women die each year from pregnancy related causes across the globe. The Millennium Development Goals have placed maternal health as a basic human right, one that is integral to the core of the fight against poverty and inequality. The high incidence of pre-eclampsia and its complications makes its prevention and effective management important. The following article attempts to outline the pathophysiology and management of pre-eclampsia.

Aetiology & Risk factors

Pre-eclampsia is commonly referred as the "disease of theories" making its prevention and management an ongoing challenge worldwide. Although the aetiology is still largely unknown, there are a few hypotheses regarding the pathophysiology and prediction of pre-eclampsia.

It has been postulated that pre-eclampsia may be autoimmune in nature. Seminal-vesicle-derived transforming growth factor 1 (TGF-1) initiates a post mating inflammatory reaction, which is a type 2 immune response towards paternal antigens resulting in maternal-fetal (paternal) immune maladaptation[11]. This idea originates from epidemiological studies demonstrating the protective effect of long-term sperm exposure and is supported by the fact that frequency of pre-eclampsia is higher in nulliparous women or multiparous women with a new partner, teenagers, women who conceive after donor insemination or oocyte donation, and women with autoimmune conditions.

Another potential mechanism responsible for pathogenesis of pre-eclampsia is placental hypoperfusion which in turn releases various factors that trigger endothelial activation / dysfunction. Nitric oxide, disordered endothelin metabolism, thromboxane/prostaglandin imbalance, cellular fibronectin, inflammatory cytokines (TNF-α, IL-6, IL-1α, and IL-1β) and otherfactors such as lipid peroxides and reactive oxygen intermediateshave all been implicated in mediating the endothelial cell injury[12]. This is well-supported by the fact that pre-eclampsia commonly occurs in pre-existing metabolic (diabetes, hypercholesterolemia), renal, vascular disorders (hypertension) and connective tissue disorders that result in poor placental circulation. In cases of multiple gestation or increased placental mass, it is not surprising for the placenta to become underperfused.

However, majority of the pre-eclamptic women do not suffer from any underlying medical conditions. In these women, lack of placental cytotrophoblastic invasion of uterine spiral arterioles and arrest of arteriolar remodelling results from failure of pseudo-vascularisation of the invasive cytotrophoblasts[13]. Deregulation of angiogenesis-related gene products such as vascular endothelial growth factor (VEGF), angiopoietin and ephrin family proteins, placental growth factor (PlGF) and their receptors have been implicated in this process[14].Shallow placentation leads to reduced placental perfusion and subsequent ischaemia.

Obese (BMI ≥30 Kg/m2) women are at higher risk for pre-eclampsia compared to lean women (odds ratio = 3.3). The exact mechanism is not completely understood but possible explanations are: increased stress due to the hyperdynamic circulation associated with obesity; dyslipidaemia or increased cytokine-mediated oxidative stress; and direct haemodynamic effects of hyperinsulinaemia[15] (increased sympathetic activity and increased tubular sodium resorption).

On the other hand, smoking actually decreases a woman's risk of pre-eclampsia. Inhibition of thromboxane A_2production by nicotine might explain the decreased risk. However, the adverse effects of smoking on pregnancy significantly outweigh any beneficial effects[16].

Epidemiological and clinical risk factors for pre-eclampsia are classified as maternal, paternal, and/or pregnancy-specific[2, 17] (Table 1, below).

Table 1: Pre-eclampsia Risk Factors

> *Maternal Considerations*
> Inherent
> - Age < 20 or 35–40 years
> - Nulliparity
> - Afro-Caribbean origin
> - Prior or family history of PE or cardiovascular disease
> - Woman born small for gestational age
>
> Medical conditions
> - Obesity
> - Chronic hypertension
> - Chronic renal disease
> - Diabetes mellitus (insulin resistance, type 1, and gestational)
> - Antiphospholipid antibody syndrome
> - Connective tissue diseases
> - Thrombophilia
> - Stress
>
> Pregnancy specific
> - Multiple gestation
> - Oocyte donation
> - New partner
> - Urinary tract infection
> - Congenital conditions affecting the fetus
> - Hydatidiform mole
> - Hydrops fetalis
> - Structural anomalies
>
> *Paternal Considerations*
> - Limited sperm exposure
> - Barrier contraception
> - First-time father
> - Donor insemination
> - Partner who fathered a pre-eclamptic pregnancy in another woman

What exactly happens in Pre-eclampsia?

The triad of physiological derangements in pre-eclampsia include

1. Vasospasm
2. Plasma volume contraction
3. Local or disseminated intravascular coagulation.

Although the cause of pre-eclampsia is unknown, we have already discussed that the placenta is largely implicated. The sequence of events starts with vasospasm caused by increased production or sensitivity to vasoconstrictors (angiotensin II, serotonin and endothelin) and/or decreased production or sensitivity to vasodilators (prostacyclin and nitric oxide). This is followed by plasma volume contraction, increased capillary permeability and, in severe cases, low plasma oncotic pressures. Redistribution of fluid occurs from the intravascular to interstitial fluid spaces causing peripheral tissue oedema. Along with this, intravascular coagulation may occur due to platelet activation, thrombocytopenia and, often, reduced production of anti-thrombin III.

The net effect is organ hypoperfusion. Commonly affected systems are kidney (manifested by reduced GFR, proteinuria, hyperuricaemia and occasionally oliguria), liver (manifested by elevated transaminases with or without epigastric and right upper quadrant pain), and the brain (manifested by headaches, transient visual disturbances due to occipital lobe ischaemia and rarely convulsions, i.e. eclampsia). This leads to increased maternal morbidity.

Placental insufficiency resulting from uterine hypoperfusion is characterised by intrauterine fetal growth retardation and less commonly placental abruption or fetal death. Preterm delivery, low birth weight, respiratory distress syndrome, and admission to the neonatal intensive care lead to increased perinatal morbidity.

In spite of major advances in understanding the pathophysiology of the disease in recent years, interventions to prevent hypertensive disorders in pregnancy have had disappointing results, hence early detection, continued surveillance and timely intervention still remains the key towards decreasing the inherent maternal and fetal morbidity and mortality associated with severe pre-eclampsia and eclampsia.

Prevention of pre-eclampsia

Till date there is no well-established measure for prevention of pre-eclampsia in the general population. Calcium is clearly of benefit amongst high risk women in communities where low dietary calcium intake is prevalent. A Cochrane systematic review in 2010 concludes that calcium supplementation approximately halves the risk of pre-eclampsia, reduces the risk of preterm birth and the rare occurrence of the composite outcome 'death or serious morbidity[18].

Low dose aspirin (antiplatelet agent) therapyefficiently reduces the development of pre-eclampsia in women with abnormal uterine artery Doppler studies. If started in early gestation (< 16 weeks), it also causes a significant reduction in the incidence of severe pre-eclampsia, gestational hypertension and IUGR[19].

Some studies have suggested that prophylactic use of antioxidants (vitamin C, E) may be beneficial as well but this is not routinely recommended[20] in practice.

Evidence is also lacking to support lifestyle preventative interventions for pre-eclampsia, such as rest, exercise and reduced dietary salt intake.

The pre-eclampsia community guideline (PRECOG)

This has been developed for screening and detection of onset of pre-eclampsia in the community[21]. It includes:

➢ Initial risk assessment at community booking using pre-determined criteria, to identify factors that predispose women to pre-eclampsia in a given pregnancy. Following this, women are offered referral before 20 weeks gestation for specialist input to their antenatal care plan if they have been identified as high risk: this may be for clarification of risk, necessary investigations, advice on early intervention or pharmacological treatment.

➢ Systematic community assessment for onset of pre-eclampsia from 20 weeks gestation. The frequency of assessment is determined by the likelihood of developing pre-eclampsia. Women with no risk factors for pre-eclampsia are offered assessments at weeks 16, 28, 34, 36, 38, 40, and 41 weeks.Women with one risk factor for developing pre-eclampsia (excluding previous pre-eclampsia, multiple pregnancy and underlying medical conditions like hypertension, renal disease, diabetes, antiphospholipid syndrome) are reviewed in the community at least once every three weeks before 32 weeks, and then at least once every two weeks, until delivery. At every visit, recommendation is to look for presence of any signs or symptoms like new hypertension, new proteinuria, headache/visual disturbance, or both, epigastric pain/vomiting, or both, reduced fetal movements, small for gestational age infant. In the presence of two such, they are referred for early specialist input, individual assessment, and discussion of obstetric risk.

➢ Recommendations have been made within the scope of this guideline for improving accuracy inblood pressure measurement, increasing reliability of proteinuria test with dipstick and community assessment of fetal growth and well being which provide the parameters for referral. Referral is made forstep-up assessment in hospital day unit within 24/48 hoursor admission in accordance with set criteria. All pregnant women are also made aware that pre-eclampsia may develop between antenatal assessments, and they could self-refer at any time.

➢ It is recognised that all women benefit from a continuity of care in the community and need midwifery or GP care as part of their individual antenatal care plan, whatever be their obstetric risk.

Management of Pre-eclampsia

Antenatal Care

These patients should be under consultant led care with multidisciplinary input from the anaesthetic and neonatal teams as necessary.

Women with risk factors for developing pre-eclampsia may be considered for uterine artery doppler velocimetry at 20-24 weeks to look for increased impedance to flow (resistance index >95th centile or early diastolic notch), which is predictive of developing pre-eclampsia or IUGR in late gestation, however the specificity and sensitivity varies widely between different studies[22-25].

At diagnosis of pre-eclampsia, the best practice is to offer initial hospital admission for assessment and formulation of follow-up care. Assessment of proteinuria should be done by automated reagent strip reading device. Visual assessment of the dipstick is not recommended nowadays because of high error rates[26-28]. If the automated reagent strip reading of urine yields a result of 1+ or more, this should be followed up with a spot urinary protein:creatinine ratio or a 24 hour urine collection to quantify the proteinuria. Significant proteinuria is diagnosed if the urinary protein:creatinine ratio is more than 30mg/mmol or the validated 24 hr urine sample has more than 300 mg of protein. Baseline blood investigations should include full blood count, liver function (bilirubin and transaminases), electrolytes and kidney function tests. Antihypertensive medications may need to be commenced with the aim of maintaining the systolic blood pressure below 150 mm Hg, and the diastolic pressure between 80 - 100 mm Hg. Labetalol is the first line treatment. However, in patients in whom labetalol cannot be used (e.g. in patients with bronchial asthma), alternatives include nifedipine (contraindicated before 20 weeks of gestation), methyldopa, atenolol and metoprolol. 4-6 hourly blood pressure, daily assessment of proteinuria, along with haematological and biochemical monitoring are also carried out. Inpatient management is required till the blood pressure stabilises.

Following discharge blood pressure can be checked in the community or in antenatal day assessment 2-3 times a week depending on clinical circumstances. Quantification of urinary protein is not necessary after the initial assessment, however, blood tests for full blood count, liver and kidney functions need to be repeated at least twice weekly (thrice weekly if the hypertension is moderate or severe). There is often a rise in serum uric acid level, which has been associated with poor maternal and fetal outcome[29, 30]. However, there is no evidence to use serum uric acid levels for clinical management.

Fetal monitoring:

Ultrasound assessment of fetal growth and amniotic fluid volume along with umbilical artery doppler velocimetry needs to be done at initial diagnosis of pre-eclampsia to exclude IUGR and then every 2 weeks if the pregnancy is managed conservatively and the results remain normal CTG monitoring is commonly done at diagnosis, along with the ultrasound assessment. If normal, further CTG should be performed weekly unless otherwise clinically indicated.

Delivery

In pre-eclampsia with mild or moderate hypertension, women may be delivered between 34 and 37 weeks of gestation, depending on maternal and fetal condition, presence of risk factors and availability of neonatal intensive care facilities. If severe pre-eclampsia develops, refractory to treatment or fetal wellbeing delivery may need to be done earlier.

Pre-eclampsia is considered to be severe in case of

1) Severe hypertension with proteinuria **or**
2) Mild / moderate hypertension and proteinuria with one or more of the following signs / symptoms:
   - Severe headache , not responding to medications
   - Visual disturbance (blurring or flashing of light)
   - Severe pain in upper abdomen or vomiting
   - Papillo-oedema
   - Signs of clonus (³ 3 beats)
   - Liver tenderness
   - HELLP syndrome
   - Decrease in platelet count to less than 100 x 109 per litre
   - Abnormal liver enzymes (ALT or AST rising to above 70 iu/litre).

HELLP syndrome

HELLP Syndrome (haemolysis, elevated liver enzyme, low platelets) is a form of severe pre-eclampsia that is associated with high maternal and perinatal morbidity and mortality and may be present without hypertension or, in some occasions, without proteinuria.

A diagnosis of HELLP syndrome is made after confirmation of haemolysis, either by blood film microscopy showing fragmented red cells or increased serum LDH level. An AST or ALT level of above 70 iu/l is significant while a level more than 150 iu/l is associated with increased morbidity to the mother, though neither of them are independent risk factors for increased maternal morbidity [31]. A low platelet count (less than 100 x 10 [6]/ml) supports the diagnosis.

There is some evidence to suggest that the severity of pre-eclampsia differs according to the time of onset. More severe form occurs with the onset of pre-eclampsia prior to 34 weeks of gestation. This form is associated with abnormal uterine artery blood flow, IUGR and adverse maternal and fetal outcomes[32-33].

There may be some difference in the pathophysiology of these two disease types. The early onset disease may be associated with placental abnormalities, while the late onset one is more linked to maternal constitutional factors such as increased BMI[34].

In severe pre-eclampsia, delivery is appropriate anytime beyond 34 weeks of gestation following corticosteroid administration to achieve fetal lung maturity. Delivery before 34 weeks is only indicated in maternal/fetal compromise or hypertension refractory to treatment[35-37]. Prolonging pregnancy at early gestation may improve the perinatal outcome but has to be carefully balanced against maternal wellbeing. If conservative management is planned, ultrasound assessment of fetal growth, amniotic fluid volume and umbilical artery doppler flow should be done at admission, and thereafter, every two weeks. In case of normal ultrasound findings, weekly CTG monitoring should suffice, unless clinically indicated otherwise (for e.g. reduced fetal movement, vaginal loss, abdominal pain or deterioration of maternal condition).

Eclampsia

Generalised tonic-clonic seizures, with or without raised blood pressure and proteinuria, occurring during or after pregnancy with no other identifiable cause is classified as eclampsia. The cause is usually multi-factorial including cerebral vasoconstriction, ischaemia, vasogenic oedema, or other pathology. Although it is more likely to occur in women with severe rather than mild pre-eclampsia, there is no convincing test for predicting the onset of eclampsia. Convulsions may occur antepartum (38-53%), intrapartum (18-36%), or postpartum (11-44%)[38]. Women with a history of previous eclampsia are at increased risk of eclampsia (1-2%) and pre-eclampsia (22-35%) in subsequent pregnancies[39].

Intrapartum Care

During labour, hourly blood pressure monitoring in women with mild or moderate hypertension, and continuously in severe hypertension is ideal. Antenatal hypertensive treatment should be continued, with the aim of maintaining the systolic blood pressure below 150 mm Hg, and the diastolic pressure between 80-100 mmHg. If oral medications fail to control the blood pressure, then intravenous anti-hypertensives are indicated to prevent the known risk of vascular damage due to uncontrolled hypertension.

Hydralazine, a peripheral arteriolar vasodilator, has been widely used as the first-line treatment for acute hypertension in pregnancy, in the past.It is administered as bolus doses (5-10 mg) intravenously, every 20 minutes to a maximum dose of 30 mg, with careful monitoring of blood pressure. The side effects include headache, nausea, and vomiting. Importantly, hydralazine may result in maternal hypotension, which may subsequently cause fetal distress. Preloading with 500 ml of crystalloid fluid before or with the first dose of intravenous hydralazine may avoid this[40]. Labetalol is another antihypertensive that can be given intravenously, either as bolus doses or as an infusion to manage severe hypertension. It is commonly used as the first line drug in many centers in UK. However, it is not suitable for patients with bronchial asthma. Nifedipine may also be used orally to control blood pressure (sublingual administration is not recommended).However, it can interact with magnesium sulphate to produce profound muscle weakness, maternal hypotension and fetal distress[41-43]. Recent evidence suggests labetalol and nifedipine as better alternatives than hydralazine[40]. In all cases, the blood pressure should be monitored closely, along with fetal monitoring, as sudden decrease in maternal blood pressure will reduce the utero-placental blood flow, resulting in fetal distress.

Magnesium sulphate isthe agent of choice for treatment of eclampsia. It is also used in women with severe pre-eclampsia for prophylaxis of eclampsia andis usually commenced once delivery decision is made or in immediate postpartum period. In women with less severe disease the decision will depend on individual case assessment. Evidence shows that magnesium sulphate more than halves the risk of eclamptic seizures[44].It has also been shown to reduce maternal morbidity related to pneumonia, mechanical ventilation and intensive care[45].However, there is little evidence to suggest that it decreases the risk of stillbirth or neonatal death.Magnesium sulphate is usually continued for 24 hours following delivery or 24 hours after the last seizure, whichever is the later, unless there is a clinical reason to do otherwise. This is based on the findings of the Collaborative Eclampsia Trial, 1995. However, recent evidence suggests that magnesium infusion may be stopped earlier (12 hours postpartum), especially when used in conjunction with other clinical parameters[46, 47]. Regular assessment of the urine output, deep tendon reflexes, respiratory rate, oxygen saturation and serum concentration is done as long as magnesium sulphate is continued to avoid toxicity. Features of magnesium toxicity include suppression/loss of patellar reflexes, drowsiness and respiratory depression. Intravenous calcium gluconate is used for reversal of magnesium toxicity.

Fluid restriction is the usual practice, unless there is associated maternal haemorrhage, to reduce the chance of fluid overload and pulmonary oedema. As per NICE guidelines, total fluids should be limited to 80 ml/hour in women with severe pre-eclampsia. Strict intake-output chart should be maintained. The regime of fluid restriction should continue until postpartum diuresis commences.

The mode of delivery should be individualised taking into account the gestation, presentation, cervical favourability for induction of labour and well-being of the fetus. Vaginal delivery is generally preferable but in case of extreme prematurity or fetal compromise, caesarean section is more likely.

Haematological and biochemical monitoring needs to be continued in labour and is dictated by the patient condition and need for analgesia/anaesthesia. For those on magnesium sulphate, bloods must be repeated every 6 hours.

Anaesthetic management

The anaesthetic management in pre-eclamptic patients is important, and should start with a detailed pre-anaesthetic assessment. Appropriate history and physical examination are important. Pre-eclamptic patients are at increased risk of oedema of the pharyngolarynx and assessment of airway is vital[48-49]. Clinical assessment of the cardiopulmonary and fluid status is required, along with laboratory investigations including renal biochemistry and coagulation status.An appropriate understanding of the obstetric interventions such as antihypertensive medications, and magnesium sulphate infusion is required.

Anaesthetic management should include appropriate monitoring, and should include NIBP, pulse oximetry and urine output. Invasive blood pressure monitoring (arterial line) is indicated in patients with poorly controlled blood pressure, or when NIBP is difficult to obtain (e.g. in the obese patients).

Pulmonary oedema is a rare but serious complication of severe pre-eclampsia, which can lead to increased maternal mortality (10%) and perinatal mortality as high as 50%[50]. Central venous pressure monitoring is indicated in patients with pulmonary oedema, poor urine output or when difficulty in fluid management is anticipated in the peripartum period. Pulmonary arterial catheters are rarely needed. Non-invasive monitoring of cardiac output may be required in patients with difficult fluid management or coexisting cardiac problems.

The safety of regional anaesthesia in pre-eclamptic patients is now well established[51]. Lumbar epidural may be used for labour analgesia in women with pre-eclampsia if the mothers opt for it. Early epidural should be considered as it helps to diminish the hypertensive responses to pain. Platelet count >75x10^9/L in the absence of other coagulation abnormalities is not associated with increased likelihood of regional anaesthetic complications in the setting of pre-eclampsia[52]. The presence of a functioning epidural catheter allows the epidural block to be titrated for LSCS if indicated. If central neuraxial block is contraindicated, then intravenous opioids may be used for labour analgesia[53-54]. Few studies have mentioned the successful use of remifentanil PCA in these patients[55].Regional blockade is currently the preferred mode of anaesthesia for caesarean section. It has long been argued that while titrated epidural blocks are safe, single shot spinal or CSE techniques may produce profound hypotension. However, multiple studies have demonstrated the safety of spinal and CSE in pre-eclamptic patients for LSCS with no adverse effects on mother or fetus[56-58]. In fact the incidence of hypotension in pre-eclamptic patients following regional anaesthesia is less than that in healthy patients, and is

successfully managed by intravenous boluses of ephedrine or phenylephrine[59-60].Doses of local anaesthetics in regional anaesthesia remain the same in pre-eclamptic patients as in normal healthy parturients.

Though regional anaesthesia is preferred for LSCS, a general anaesthesia may still be needed if regional anaesthesia is contraindicated (e.g. coagulopathy as in HELLP syndrome), and in emergency situations where the baby has to be delivered as early as possible. General anaesthesia increases the risk of hypertension during induction and emergence, loss of airway due to pharyngolaryngeal oedema, aspiration and transient neonatal depression. Extreme care is to be undertaken to obtund the hypertensive response during induction-intubation, as this has been a significant past cause of maternal mortality[61]. Several agents (alfentanil, fentanyl, remifentanil, magnesium sulphate, intravenous lignocaine and esmolol) have been suggested for induction, and clinicians should use familiar ones. All opioids rapidly cross the placenta and increase the risk of neonatal depression, and appropriate facilities for neonatal resuscitation must be available. Remifentanil has the advantage as it is rapidly metabolised by the neonate, and any respiratory depression is usually brief[62- 63].Maintenance of anaesthesia is done by inhalational anaesthetic agents. Isoflurane is considered to be a good choice, because of its vasodilating properties. Vigilance is also required during emergence from anaesthesia, to prevent hypertension, as well as aspiration.

Anaesthetists must also be aware of the potential drug interactions of agents commonly used in pre-eclampsia. Magnesium sulphate and calcium channel blockers may potentiate the action of muscle relaxants and appropriate monitoring is vital.

Post delivery analgesia

This is maintained by simple analgesics like paracetamol. Non-steroidal anti-inflammatory agents have been used; however, caution must be exercised due to their effect on cyclo-oxygenase pathway, especially those with renal insufficiency and coagulopathy. A few case reports of significant increase in blood pressure in postpartum women have been reported following their use[64]. Patient controlled analgesia with opioids has been used widely, and is considered to be a safe option.

Use of oxytocic agents

Syntocinon is the drug of choice. Ergometrine should be avoided because of its propensity to cause hypertension. Synthetic prostaglandins such as Carboprost (15 methyl PGF $_2$ alpha) may be given with caution after considering the risk-benefit ratio, especially because it can aggravate hypertension.

Use of thromboprophylaxis

This should be considered in all patients with pre-eclampsia.

Table 2: Management strategies for chronic hypertension and gestational hypertension

	Preconception	Antenatal	Delivery	Postpartum	Further follow-up
Chronic Hypertension	Optimise antihypertensives, change ACE inhibitors, diet and lifestyle modification	Continue treatment to maintain BP <150/100. Offer uterine artery dopplers to detect risk of developing pre-eclampsia/IUGR	At 37 weeks, if BP is controlled.	Aim to maintain BP <140/90 with antihypertensives	Medical review at 6-8 weeks
Gestational Hypertension	Assessment of risk factors	Hospital admission if severe hypertension. Antihypertensive if BP > 150/100. Test for proteinuria at each visit, blood tests as indicated	At 37 weeks, if BP <160/110, with/without antihypertensives	Titrate antihypertensives to keep BP <140/90	Medical review at 6-8 weeks, or earlier if need to continue antihypertensives
Pre-eclampsia	Assessment of risk factors.	Hospital admission at diagnosis. Antihypertensives to be started if BP>150/100. Regular blood investigations (2-3/week)	Delivery between 34-37 weeks, depending on maternal/ foetal condition	Initial monitoring as inpatient, to be discharged to the community when BP <149/99 with/without treatment and blood results are stable	Medical review at 2 weeks, if continuing antihypertensives. Otherwise at 6-8 weeks

Postpartum Care

increasing the blood pressure. This fluid shift also increases the risk of pulmonary oedema, cerebral oedema and eclampsia.

Most of the existing guidance focuses on management of blood pressure and its associated problems in the antenatal and intrapartum period but the postpartum phase can often be poorly looked after [65]. Regular blood pressure monitoring at an interval of 4-6 hours should be done as an inpatient initially and blood platelet count, transaminases and creatinine should be measured to note any changing trends. The aim is to maintain blood pressure <160/110mmHg, thereby preventing cerebral injury from occurring. In order to achieve this, beta-blockers, calcium-channel blockers and ACE inhibitors can be used in a stepwise manner. Use of methyldopa is usually avoided as it has the potential to cause depression and psychosis in postpartum period. Women are discharged to the community care if they are asymptomatic, blood pressure, with or without treatment, is 149/99 mmHg or lower and blood test results are stable or improving. Blood pressure isthen checked daily/alternate days in the community till 2 weeks postpartum. Antihypertensives should continue till blood pressure falls below 130/80 mm of Hg and the dose adjustments need to be made by the GP. If blood pressure becomes uncontrolled, then women would require urgent referral to the hospital.

In most cases, the hypertension and/or proteinuria resolve within six weeks postpartum. Any women whohad pre-eclampsia complicating their pregnancy, needs to have blood pressure and urine protein checked at 6-8 week postnatal visit at the GP surgery. If still requiring antihypertensive treatment at that stage or persistent proteinuria further assessment is warranted to find out cause for raised blood pressure if any and also identify and advise on risk factors for cardiovascular disease and lifestyle changes.

Following childbirth, mobilisation of the extravascular fluid occurs increasing the intravascular volume, and consequently

For all these women preconception counselling should be offered for subsequent pregnancies especially if risk factors are identified so that potentially preventative strategies can be initiated.

Table 2 outlines briefly the management strategies for mothers with chronic hypertension and gestational hypertension. However, a detailed discussion is outside the scope of this article.

Competing Interests
None Declared
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REFERENCES

1. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol. Jul 2000;183(1):S1-S22.

2. Crowther CA. Eclampsia at Harare Maternity Hospital. An epidemiological study. S Afr Med J. 1985;68:927-9

3. Conde-3. Agudelo A, Kafury-Goeta AC. Epidemiology of eclampsia in Colombia. Int J Gynaecol Obstet. 1998;61:1-8.

4. Tuffnell DJ, Jankowicz D, Lindow SW, Lyons G, Mason GC, Russell IF, Walker JJ. Outcomes of severe pre-eclampsia/eclampsia in Yorkshire 1999/2003.BJOG 2005;112:875–80.

5. Douglas KA, Redman CW. Eclampsia in the United Kingdom.BMJ 1994;309:1395–400.

6. Centre for Maternal and Child Enquiries (CMACE). Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer- 2006-2008. The Eighth Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG 2011; 118:1-203.

7. The Magpie Trial Collaborative Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet 2002; 359: 1877-1890.

8. Conde-Agudelo A, Kafury-Goeta AC. Epidemiology of eclampsia in Colombia. Int J Gynaecol Obstet. 1998 ;61:1-8.

9. Douglas KA, Redman CW. Eclampsia in the United Kingdom.BMJ 1994;309:1395–1400.

10. Duley L. Maternal mortality associated with hypertensive disorders of pregnancy in Africa, Asia, Latin America and the Caribbean. Br J Obstet Gynaecol. 1992; 99:547-53.

11. Robertson SA, Ingman WV, O'Leary S, Sharkey DJ, Tremellen KP. Transforming growth factor beta—a mediator of immune deviation in seminal plasma. J Reprod Immunol 2002; 57: 109–28.

12. Redman CW, Sargent IL. Latest advances in understanding pre-eclampsia. Science. Jun 10 2005;308:1592-4.

13. RobertsJM, Redman CW. Pre-eclampsia: more than pregnancy-induced hypertension. Lancet1993; 341: 1447–51

14. Zhou Y, McMaster M, Woo K, Janatpour M, Perry J, Karpanen T, Alitalo K, Damsky C, Fisher SJ: Vascular endothelial growth factor ligands and receptors that regulate human cytotrophoblast survival are dysregulated in severe preeclampsia and hemolysis, elevated liver enzymes, and low platelets syndrome. Am J Pathol 2002; 160: 1405–1423, 2002

15. Dekker GA, Sibai BM, Etiology and pathogenesis of pre-eclampsia: current concepts. Am J Obstet Gynecol 1998; 179: 1359–75.

16. Marcoux S, Brisson J, Fabia J. The effect of cigarette smoking on the risk of preeclampsia and gestational hypertension. Am J. Epidemiol.1989; 130 (5): 950-957.

17. Dekker G, Sibai B. Primary, secondary, and tertiary prevention of pre-eclampsia. Lancet 2001;357:209–15.

18. Hofmeyr GJ, Lawrie TA, Atallah AN, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev. 2010 Aug 4;(8):CD001059.

19. Bujold E, Morency AM, Roberge S, Lacasse Y, Forest JC, Giguère Y. Acetylsalicylic acid for the prevention of pre-eclampsia and intra-uterine growth restriction in women with abnormal uterine artery Doppler: a systematic review and meta-analysis. Obstet Gynaecol Can. 2009 ;31:818-26

20. Rumbold A, Duley L, Crowther CA, Haslam RR. Antioxidants for preventing pre-eclampsia. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD004227.

21. F. Milne, C. Redman, J Walker et al. The pre-eclampsia community guideline (PRECOG): how to screen for and detect onset of pre-eclampsia in the community. BMJ 2005; 330 : 576

22. Magee LA, Ornstein MP, von Dadelszen P. Management of hypertension in pregnancy. BMJ 1999; 318 : 1332.

23. Bower S, Schuchter K, Campbell S. Doppler ultrasound screening as part of routine antenatal scanning: prediction of pre-eclampsia and intrauterine growth retardation. Br J Obstet Gynaecol 1993;100:989–94

24. Harrington K, Cooper D, Lees C, Hecher K, Campbell S. Doppler ultrasound of the   uterine arteries: the importance of bilateral notching in the prediction of pre-eclampsia, placental abruption or delivery of a small-for-gestational-age baby. Ultrasound Obstet Gynecol 1996;7:182–8

25. Roncaglia N, Crippa I, Locatelli A, Cameroni I, Orsenigo F, Vergani P, Ghidini A. Prediction of superimposed pre-eclampsia using uterine artery Doppler velocimetry in women with chronic hypertension. Prenat Diagn. 2008 ;28:710-4

26. Waugh J, Bell SC,Kilby M,Seed P,Blackwell C,Shennan AH, et al. Optimal bedside urinalysis for the detection of proteinuria in hypertensive proteinuria: a study of diagnostic accuracy? BJOG 2005:112:412–17.

27. Waugh JJ, Clark TJ, Divakaran TG, Khan KS, Kilby MD. Accuracy of urinalysis dipstick techniques in predicting significant proteinuria in pregnancy. Obstet Gynecol 2004;103:769–77.

28. Phelan LK, Brown MA, Davis GK, Mangos G.A prospective study of the impact of automated dipstick urinalysis on the diagnosis of pre-eclampsia. Hypertens Pregnancy 2004;23: 135–42.

29. Martin JN Jr,May WL, Magann EF,Terrone DA, Rinehart BK, Blake PG. Early risk assessment of severe pre-eclampsia: admission battery of symptoms and laboratory tests to predict likelihood of subsequent significant maternal morbidity. Am J Obstet Gynecol 1999;180:1407–14.

30. Redman CW, Bonnar J. Plasma urate changes in preeclampsia.Br Med J 1978;i(6125):1484–5.

31. Martin JN Jr,May WL, Magann EF, Terrone DA, Rinehart BK, Blake PG. Early risk assessment of severe pre-eclampsia: admission battery of symptoms and laboratory tests to predict likelihood of subsequent significant maternal morbidity. Am J Obstet Gynecol 1999;180:1407–14.

32. Sibai BM, Caritis S, Hauth J. What we have learned about preeclampsia.Semin Perinatol. 2003; 27:239–246.

33. Lindheimer MD, Taler SJ, Cunningham FG. Hypertension in pregnancy. J Am Soc Hypertens.2008; 2:484–494.

34. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late pre-eclampsia: Two different maternal hemodynamic states in the latent phase of the disease. Hypertension. 2008;52:873–880.

35. Rath W, Fischer T. The diagnosis and treatment of hypertensive disorders of pregnancy: New findings for the antenatal and inpatient care. Dtsch Arztebl Int. 2009;106(45):733–738.

36. Sibai BM, Barton JR. Expectant management of severe pre-eclampsia remote from term: Patient selection, treatment, and delivery indications. Am J Obstet Gynecol. 2007;196(6):514.e1–e9.

37. Chammas MF, Nguyen TM, Li MA, et al. Expectant management of severe pre-eclampsia: Is intrauterine growth restriction an indication for immediate delivery? Am J Obstet Gynecol. 2000;183(4):853–858.

38. Turner JA. Diagnosis and management of pre-eclampsia: an update. Int J Womens Health. 2010 ;2:327-37.

39. Sibai BM. Diagnosis, prevention and management of eclampsia. Obstet Gynecol. 2005 105:402–410

40. Magee LA, Cham C, Waterman EJ, et al. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. BMJ. 2003; 327:955-60.

41. Waisman GD, Mayorga LM, Camera MI, Vignolo CA, Martinotti A. Magnesium plus nifedipine: Potentiation of hypotensive effect in pre-eclampsia. Am J Obstet Gynecol 1988; 159: 308-309

42. Ben-Ami M, Giladi Y, Shaley E. The combination of magnesium sulphate and nifedipine: a cause of neuromuscular blockade. Br J Obstet Gynaecol 1994; 101: 262-263

43. Scott W, Snyder MD, Cardwell MS. Neuromuscular blockade with magnesium sulfate and nifedipine. Am J Obstet Gynecol 1989; 161: 3

44. Duley L, Gülmezoglu AM, & Henderson-Smart DJ 2003a, 'Magnesium sulphate and other anticonvulsants for women with pre-eclampsia', Cochrane Database of Systematic Reviews, Issue 2. Art. No.: CD000025.

45. Duley L & Henderson-Smart D 2003c, 'Magnesium sulphate versus phenytoin for eclampsia', Cochrane Database of Systematic Reviews, Issue 4. Art. No.: CD000128. DOI: 10.1002/14651858.CD000128.

46. Ehrenberg HM & Mercer BM .Abbreviated postpartum magnesium sulfate therapy for women with mild pre-eclampsia: a randomized controlled trial. Obstet Gynecol 2006;108: 833-8.

47. Isler CM, Barrilleaux PS, Rinehart BK, Magann EF & Martin JN. Postpartum seizure prophylaxis: using maternal clinical parameters to guide therapy. Obstet Gynecol, 2003;101:66-9.

48. Heller PJ, Scheider EP, Marx GF. Pharyngolaryngeal edema as a presenting symptom in pre-eclampsia. Obstet Gynecol. 1983;62: 523–525.

49. Goldszmidt E. Principles and practices of obstetric airway management. Anesthesiol Clin. 2008;26:109–125.

50. Sibai BM, Mabie BC, Harvey CJ, Gonzalez AR. Pulmonary edema in severe pre-eclampsia-eclampsia: Analysis of thirty-seven consecutive cases. Am J Obstet Gynecol. 1987; 156: 1174 –1179.

51. Dyer RA, Piercy JL, Reed AR. The role of the anaesthetist in the management of the pre-eclamptic patient. Curr Opin Anaesthesiol. 2007;20:168-74.

52. Sharma SK, Philip J, Whitten CW, Padakandha UB & Landers DF 1999, 'Assessment of changes in coagulation in parturients with pre-eclampsia using thromboelastography', Anesthesiology; 90: 385-90.

53. Head BB, Owen J, Vincent RD, Shih G, Chestnut DH & Hauth JC .A randomized trial of intrapartum analgesia in women with severe pre-eclampsia, Obstet Gynecol. 2002; 99: 452-7.

54. Lucas MJ, Sharma SK, McIntire DD, 'Wiley J, Sidawi JE, Ramin SM, Leveno KJ & Cunningham FG 2001, 'A randomized trial of labor analgesia in women with pregnancy-induced hypertension', Am J Obstet Gynecol, 2001,vol. 185, pp. 970-5.

55. El-Kerdawy H, Farouk A. Labor analgesia in pre-eclampsia: remifentanil patient controlled intravenous analgesia versus epidural analgesia. Middle East J Anesthesiol. 2010; 20: 539 -45.

56. Dyer RA, Els I, Farbas J, Torr GJ, Schoeman LK & James MF 2003, 'Prospective, randomized trial comparing general with spinal anesthesia for cesarean delivery in preeclamptic patients with a non-reassuring fetal heart trace', Anesthesiology;99: 561-9.

57. Visalyaputra S, Rodanant O, Somboonviboon W, Tantivitayatan K, Thienthong S, Saengchote W. Spinal versus epidural anesthesia for cesarean delivery in severe pre-eclampsia: A prospective randomized, multicenter study. Anesth Analg. 2005;101:862–868.

58. Santos AC, Birnbach DJ. Spinal anesthesia for cesarean delivery in severely preeclamptic women: Don't throw out the baby with the bathwater! Anesth Analg. 2005;101:859–861.

59. Aya AG, Mangin R, Vialles N, et al. Patients with severe pre-eclampsia experience less hypotension during spinal anesthesia for elective caesarean delivery than healthy parturients: A prospective cohort comparison.Anesth Analg. 2003;97:867–872

60. Berends N, Teunkens A, Vandermeersch E, Van de Velde M. A randomized trial comparing low-dose combined spinal-epidural anesthesia and conventional epidural anesthesia for cesarean section in severe pre-eclampsia. Acta Anaesthesiol Belg 2005; 56: 155-62.

61. Lewis G (ed) 2007. The Confi dential Enquiry into Maternal and Child Health (CEMACH). Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer- 2003-2005. The Seventh Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. London: CEMACH.

62. Ngan Kee WD, Khaw KS, Ma KC, Wong AS, Lee BB, Ng FF. Maternal and neonatal effects of remifentanil at induction of general anesthesia for cesarean delivery. Anesthesiology. 2006;104:14–20.

63. Yoo KY, Jeong CW, Park BY, et al. Effects of remifentanil on cardiovascular and bispectral index responses to endotracheal intubation in severe pre-eclamptic patients undergoing Cesarean delivery under general anesthesia. Br J Anaesth. 2009;102:812–819.

64. Makris A, Thornton C, Hennessy A. Postpartum hypertension and nonsteroidal analgesia. American Journal of Obstetrics & Gynecology, 2004; 190: 577-578.

65. Chandiramani M, Shennan A H, Waugh J J S. Modern management of postpartum hypertension. Trends in Urology, Gynaecology & Sexual Health 2007; 12: 37–42