Review Article

Hypertensive disorders in pregnancy

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ABSTRACT

Hypertensive disorders of pregnancy (HDP) remain among the most significant and intriguing unsolved problems in obstetrics. In India, the prevalence of HDP was 7.8% with pre-eclampsia in 5.4% of the study population. The anaesthetic problems in HDP may be due to the effects on the cardiovascular, respiratory, neurologic, renal, haematologic, hepatic and uteroplacental systems. The basic management objectives should be facilitating the birth of an infant who subsequently thrives and completes restoration of health to the mother, or the termination of pregnancy with the least possible trauma to mother and foetus in severe pre-eclampsia. This comprises obstetric management, adequate foetal surveillance, antihypertensive management, anticonvulsant therapy, safe analgesia for labour and management of anaesthesia for delivery.

Key words: Hypertensive disorders of pregnancy, pre-eclampsia, eclampsia, HELLP syndrome, magnesium sulphate

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) remain among the most significant and intriguing unsolved problems in obstetrics. HDP are common and complicate obstetric practice in India. The incidence of pre-eclampsia in hospital practice in India varies from 5% to 15% and that of eclampsia about 1.5%.[1,2]

The most recent revised classification for hypertensive disorders in pregnancy is by the International Society for the Study of Hypertension in Pregnancy (ISSHP)[2] in 2014:

1. Chronic hypertension
2. Gestational hypertension
3. Pre-eclampsia – de novo or superimposed on chronic hypertension
4. White coat hypertension.

The American College of Obstetricians and Gynecologists task force continues to use the more practical classification proposed by it in 1972 and modified by the National High Blood Pressure Education Program and the American Society of Hypertension guidelines.[3] This also considers hypertension during pregnancy in four categories:

1. Pre-eclampsia–eclampsia
2. Chronic hypertension (of any cause)
3. Chronic hypertension with superimposed pre-eclampsia
4. Gestational hypertension.

1. **Pre-eclampsia:** The minimum criteria for diagnosis of pre-eclampsia are a blood pressure (BP) ≥140/90 mmHg after 20 weeks' gestation and proteinuria ≥300 mg/24 h or ≥1+ with dipstick. There is an increased certainty of pre-eclampsia if the following clinical and laboratory findings are reported: a BP ≥160/110 mmHg, proteinuria 2.0 g/24 h or ≥2+ dipstick, serum creatinine >1.2 mg/dL unless known to be previously elevated; platelets <100,000/mm^3; micro-angiopathic haemolysis (increased lactate dehydrogenase [LDH]); elevated

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Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST); persistent headache or other cerebral or visual disturbance and persistent epigastric pain

2. **Eclampsia:** Pre-eclampsia with the onset of convulsions is called eclampsia. In eclamptics, seizures cannot be attributed to other causes in a woman with pre-eclampsia, which are generalised, and may appear before, during or after labour
3. **Chronic hypertension:** These are gravidae with hypertension as defined by a BP ≥140/90 mmHg before pregnancy or diagnosed before 20 weeks' gestation (not attributable to gestational trophoblastic disease), or hypertension first diagnosed after 20 weeks' gestation and persistent after 12 weeks' postpartum. Chronic HT may lead to ventricular hypertrophy, cardiac decompensation, cerebrovascular accidents and renal damage. It may cause about 25% of superimposed pre-eclampsia
4. **Gestational hypertension** has the following features: a BP ≥140/90 mmHg for the first time during pregnancy, which returns to normal <12 weeks' postpartum and without proteinuria. The final diagnosis is made only postpartum (with the disappearance of signs and symptoms). Patients may have other signs or symptoms of pre-eclampsia, for example epigastric discomfort or thrombocytopaenia.

Literature search and selection

We performed an electronic search in Google Scholar, PubMed and Cochrane databases for original and review articles on HDP from 1998 to 2018. The search terms included 'hypertensive disorders of pregnancy', 'pre-eclampsia', 'eclampsia' and 'pregnancy-induced hypertension'. Only full text articles were reviewed. The current evidence and guidelines around HDPs are summarised.

INCIDENCE AND RISK FACTORS FOR HDP

Some of the risk factors increasing the likelihood of HDPs are: nulliparous women[4] (in about 7.6% of nulliparae, severe in 3.3%); wide variation between ethnic groups/populations (3 times × as common in Negroid as Caucasians), parity (incidence about 5% in singleton and 13% in twin gestations), chronic hypertension, multi-foetal gestation, high maternal age (>35 years) and obesity. Maternal weight and the risk of pre-eclampsia are progressive. The morbidity in percentage is about 4.3 with a body mass index (BMI) <19.8 and 13.3 with BMI >35 kg/m^2.[2] Smoking during pregnancy reduced risk of hypertension during pregnancy;[5] placenta previa also reduced the risk of hypertension.

Aetiopathogenesis

The basic concepts of the aetiology of HDPs could be that these women are exposed to chorionic villi for the first time (in primiparity), exposed to a superabundance of chorionic villi (as with twins or hydatidiform mole), have a pre-existing vascular disease and are genetically predisposed to hypertension developing during pregnancy. Sibai *et al.*[6] have listed the currently plausible potential causes as an abnormal trophoblastic invasion of uterine vessels, immunological intolerance between maternal and foeto-placental tissues, maternal maladaptation to cardiovascular or inflammatory changes of normal pregnancy, dietary deficiencies and genetic influences.

In normal implantation, endovascular trophoblasts invade the uterine spiral arteries. In pre-eclampsia, there is incomplete trophoblastic invasion; the magnitude of defective trophoblastic invasion of the spiral arteries correlated with the severity of the hypertensive disorder.[7]

The nitric oxide system is also affected in HDP. Pre-eclampsia is associated with decreased endothelial nitric oxide synthase expression, which increases cell permeability.[8]

There may be life-threatening thrombocytopaenia caused by platelet activation, aggregation and consumption. This may persist up to 5 days after delivery. There may also be neonatal thrombocytopaenia.[9]

Dietary deficiencies and excesses have been blamed as the cause of eclampsia. Supplementation with various elements such as zinc, calcium, and magnesium has been suggested to prevent pre-eclampsia. Obesity is a potent risk factor for pre-eclampsia.

Hereditary hypertension is linked to pre-eclampsia; preclampsia–eclampsia is highly heritable in sisters, daughters, granddaughters and daughters-in-law and is hence thought to have a congenital/familial component. There is also a 60% concordance in monozygotic female twin pairs, and HLA-DR4 has been thought to be linked to pre-eclampsia.

Indicators of severity in hypertensive disorders of pregnancy

HDP can be graded into mild or severe based on clinical abnormalities. Mild HDP shows diastolic BP <100 mmHg, trace to 1+ proteinuria and minimal (if any) hepatic enzyme elevation. Severe HDP exhibits diastolic BP ≥110 mmHg, persistent severe proteinuria, clinical symptoms of eclampsia including convulsions and pulmonary oedema, elevated serum creatinine and hepatic enzymes with thrombocytopaenia and foetal growth restriction.[10]

MANAGEMENT OF HDP

The basic management objectives should be facilitating the birth of an infant who subsequently thrives and complete restoration of health to the mother, or the termination of pregnancy with the least possible trauma to mother and foetus in severe pre-eclampsia. The most important information to salvage the foetus is the precise knowledge of the age of the foetus.

Early prenatal detection of HDP is usually by new onset rise in diastolic BP (≥81–89 mmHg) and a sudden abnormal weight gain (more than about 900–1000 g/week during the third trimester). Once a HDP is detected, outpatient surveillance is continued unless supervened by overt hypertension, proteinuria, visual disturbances or epigastric discomfort. Hospitalisation is considered if there is persistent or worsening hypertension or development of proteinuria.

In mild pre-eclampsia, reduced physical activity throughout much of the day is beneficial. Absolute bed rest is not necessary. Sedatives and tranquilisers are not prescribed. Ample, but not excessive, protein and calories should be included in the diet. Sodium and fluid intakes should not be limited or forced.

Delivery or termination of pregnancy is the cure for severe pre-eclampsia or eclampsia. The prime objectives in this situation are to forestall convulsion, prevent intracranial haemorrhage and serious damage to vital organs, ultimately to deliver a healthy infant if possible.

Antihypertensive drug therapy

Sibai *et al*. evaluated the effectiveness of labetalol, an α1 and non-selective β-blocker), in the treatment of severe HDP in 200 nulliparous patients at 26–35 weeks gestation. In the women given labetalol, there were significantly lower mean BPs, and no differences in mean pregnancy prolongation, gestational age at delivery and birth-weight from normal. The caesarean delivery rates and the number of infants admitted to special care nurseries were similar. The treatment regimen for labetalol is a 20-mg intravenous bolus dose followed by 40 mg if not effective within 20 min, followed by 80 mg every 20 min up to a maximum dose of 300 mg.[11]

Hydralazine is also used to control severe hypertension; it is remarkably effective in the prevention of cerebral haemorrhage. It is indicated if the systolic pressure >160 mmHg or the diastolic pressure >105 mmHg.[12] It is administered at 5–10 mg doses at 15–20-min intervals until a satisfactory response is achieved (decrease in diastolic BP to 90–100 mmHg, but no lower lest placental perfusion be compromised).

Nifedipine, 10 mg oral to be repeated in 30 min, has also been used. Compared with hydralazine, fewer doses were required to achieve BP control without increased adverse effects. It has potent and rapid antihypertensive effects, and some women develop worrisome hypotension.

The use of angiotensin-converting enzyme inhibitors during the second and third trimesters should be avoided, as they cause oligohydramnios, foetal growth restriction, bony malformation, persistent patent ductus arteriosus, pulmonary hypoplasia etc.

Sodium nitroprusside is not recommended unless there is no response to hydralazine, labetalol or nifedipine. A continuous infusion is begun with a dose of 0.25 μg/kg/min increased as necessary to 5 μg/kg/min. Foetal cyanide toxicity may occur after 4 h.

The persistence or refractoriness of hypertension with these drugs may be due to underlying chronic hypertension or mobilisation of oedema fluid with redistribution into the intravenous compartment. Effective treatment may require addition of diuretics.

Patients being treated with delayed delivery and expectant management are advised bed rest, magnesium sulphate for 48 h, bolus doses of antihypertensive medications to control BPs exceeding 160/110 mmHg, volume expansion and glucocorticoids like dexamethasone to promote foetal maturation. Glucocorticoids do not seem to worsen maternal hypertension but produce a decrease in the incidence

of neonatal respiratory distress, neonatal ventricular haemorrhage and improve foetal survival.

The indications for immediate delivery are uncontrollable BP, foetal distress, placental abruption, renal function deterioration, HELLP syndrome, persistent severe systemic symptoms or attainment of 34 weeks gestation.

Eclampsia

This is pre-eclampsia complicated by generalised tonic–clonic convulsions. They are most common in the last trimester, become increasingly more frequent as term approaches and may occur up to more than 48 h postpartum. High fever in eclampsia is a very grave sign, which may be the consequence of a central nervous system haemorrhage. Proteinuria is almost always present and frequently pronounced. Urine output may be diminished appreciably, occasionally to anuria. Haemoglobinuria is common. Oedema may be pronounced, at times massive.

The major complications are placental abruption (10%), neurological deficits (7%), aspiration pneumonia (7%), pulmonary oedema (5%), cardiopulmonary arrest (4%), acute renal failure (4%) and maternal death (1%).[13]

The treatment of eclampsia consists of the control of convulsions by intravenously/intramuscularly administered loading dose of magnesium sulphate, followed by a continuous infusion of magnesium sulphate; lowering the BP by intermittent intravenous or oral administration of antihypertensive medication whenever the diastolic pressure is considered dangerously high; fluid therapy, with avoidance of diuretics, limitation of intravenous fluid administration unless fluid loss is excessive, and expedited delivery.

Magnesium sulphate to control convulsions

Magnesium sulphate is an effective anticonvulsant agent in severe pre-eclampsia and eclampsia, without producing central nervous system depression in either the mother or the infant.[14] It is usually given during labour and for 24 h postpartum, as this period is the most likely time for convulsion to develop. It is not given to treat hypertension.

Magnesium is cleared by renal excretion. Magnesium intoxication is avoided by ensuring that the urine output is adequate, the patellar or biceps reflex is present and that there is no respiratory depression. Plasma magnesium levels must be checked periodically.

Eclamptic convulsions are prevented by plasma magnesium levels maintained at 4–7 mEq/L (4.8–8.4 mg/dL or 2.0–3.5 mmol/L). To establish a prompt therapeutic level, the initial intravenous infusion of 4–6 g is followed by continuous infusion at 2–3 g/h, and the initial intramuscular injection of 10 g is followed by 5 g every 4 h. Observe for toxic symptoms. As the plasma magnesium level reaches 10 mEq/L, patellar reflexes disappear – this sign serves to warn of impending magnesium toxicity. As the plasma levels rise above 10 mEq/L, respiratory depression develops. At plasma levels of 12 mEq/L or more, respiratory paralysis and arrest follow. For mild-to-moderate respiratory depression, treatment is with calcium gluconate, 1 g and withholding further magnesium sulphate. The effects of IV calcium may be short lived. Severe respiratory depression and arrest have to be treated with prompt tracheal intubation and mechanical ventilation.

Other effects: Magnesium ions at relatively high concentration depress myometrial contractility; the mechanisms by which Mg might inhibit uterine contractility are not established. Magnesium administered to the mother promptly crosses the placenta to achieve equilibrium in foetal serum and in amniotic fluid. Neonatal depression occurs only if there is severe hyper-magnesemia at delivery.

The clinical efficacy of magnesium sulphate therapy was studied by the multinational Eclampsia Trial Collaborative Group[15]: women allocated to Mg therapy were less likely to be artificially ventilated, to develop pneumonia, to be admitted to intensive care unit (ICU) and to die. Neonates of women given Mg therapy were less likely to require intubation at delivery and require to be admitted to the neonatal ICU.

Alternative magnesium doses: A Cochrane systematic review concluded that 'although strong evidence supports the use of magnesium sulphate for prevention and treatment of eclampsia, trials comparing alternative treatment regimens are too small for reliable conclusions'.[16] Begum *et al*. studied a low dose magnesium sulphate regime for eclampsia – the 'Dhaka regime'. Their loading dose of magnesium was 10 g, followed by 2.5 g given intramuscularly at 4 hourly intervals for 24 h after administration of the first dose. They concluded that half of the standard dose of magnesium sulphate appeared to be sufficient to control convulsions effectively and serum levels of magnesium remained lower than levels which produce toxicity.[17]

Fluid therapy

Routine administration should be with lactated ringer solution at the rate of 60 ≤-125 mL/h (1–2 mL/kg/h), unless unusual fluid loss from vomiting, diarrhoea, diaphoresis or excessive blood loss at delivery occur.[18] Haemo-concentration and reduced central venous and pulmonary capillary wedge pressures require attempts to expand the blood volume to relieve vasospasm and to reverse organ deterioration. Infusion of large fluid volumes enhances the maldistribution of extravascular fluid and increase the risk of pulmonary and cerebral oedema. Invasive haemodynamic monitoring is required to prevent the serious complication of fluid overload, pulmonary oedema.

Low-dose aspirin

Low-dose aspirin therapy has been tried for the prevention of morbidity and mortality from pre-eclampsia. A group of investigators from the Agency for Healthcare Quality and Research (United States) conducted a systematic review of the efficacy of aspirin therapy in pre-eclamspia.[19] The daily dosage administered in these trials was 60–150 mg. Based on pooled results, they found that low-dose aspirin administered after the first trimester of pregnancy to women at elevated risk of pre-eclampsia reduced the risk of pre-eclampsia by at least 10%, intrauterine growth restriction (IUGR) by 20% and preterm birth by about 14%. Consistent with findings of lower rates of preterm birth and IUGR, birth weight averaged 130 g more in infants whose mothers took low-dose aspirin. They did not find evidence of serious harms from aspirin use (i.e., no effect on perinatal mortality).

A tested aspirin as a treatment for primary prevention of pre-eclampsia in patients considered to be at high risk following screening in the first-trimester.[20] The ASPRE (Aspirin for Evidence-Based PREeclampsia Prevention) trial, a multi-centre, double-blind, randomised, placebo-controlled trial evaluated the effect of prophylactic low-dose aspirin administered in the first trimester of pregnancy on the incidence of delivery with pre-eclampsia before 37 weeks of gestation in patients at high risk. The study clarified that low doses of aspirin are effective in secondary prevention of pre-eclampsia in high-risk patients, mainly those with a history of pre-eclampsia. Aspirin inhibits thromboxane A2 production by platelets, increases the prostacyclin/TXA2 ratio and reduces platelet aggregation. It also decreases production of the tissue factor thrombin.

Different doses of aspirin have been shown to be safe in patients given neuraxial anaesthesia or analgesia. Aspirin and other non-steroidal anti-inflammatory drugs do not increase the risk of spinal haemorrhagic complications and do not represent a contra-indication to neuraxial blocks or catheter procedures. There is the important proviso that this needs to be studied in the context of parturients with HDP, in whom coagulopathy may increase the risk of a spinal haematoma with neuraxial techniques. However, aspirin crosses the placental barrier and inhibits foetal platelet aggregation.[21]

Recovery after delivery

An increase in urinary output is an early sign of improvement. Proteinuria and oedema ordinarily disappear with a week. The BP returns to normal within a few days to 2 weeks. The longer the persistence of hypertension post-partum, the more is the consequence of chronic vascular disease.

ANAESTHETIC IMPLICATIONS

Anaesthetic problems in HDP may be due to the effects on the cardiovascular, respiratory, neurologic, renal, hematologic, hepatic and uteroplacental systems[22] Obstetric management consists of expectant management (<34 weeks) – with bed rest and sedation, antihypertensive therapy, monitoring of weight, urine output and magnesium sulphate ($MgSO_4$) for seizure prophylaxis with monitoring of deep tendon reflexes (DTRs). Aggressive management in severe HDP consists of induction of labour/delivery within 48–72 h. Delivery is the only curative treatment. If possible, time is allowed for 2 doses of steroids to the parturient to promote foetal lung maturity, especially if the gestation is < 34 weeks. The indications for immediate delivery are an uncontrolled hypertension (HTN) >160/110, oliguria/renal dysfunction, hepatic dysfunction, imminent eclampsia, pulmonary oedema or foetal compromise

Foetal surveillance should be continuous, and should consist of serial foetal ultrasound and continuous electronic foetal monitoring. Monitor for loss of beat-to-beat variability of the foetal heart rate (FHR) and periodic late decelerations.

Antihypertensive management should be aggressive, the goal being to control hypertension and maintain uteroplacental perfusion

Anticonvulsant therapy is with $MgSO_4$ as first-line agent. Other anticonvulsants used with less efficacy are phenytoin and diazepam

Careful pre-anaesthetic assessment is required for airway oedema and compromise, aspiration prophylaxis, auscultation of lungs for pulmonary oedema, fluid balance with correction of haemo-concentration, haemodynamic status, left uterine displacement causing uterine vascular hypotension, renal function and coagulation status.

Analgesia for labour should be provided with the placement of a continuous lumbar epidural catheter. The advantages of labour analgesia are the decreased circulating catecholamines, less uterine vascular resistance with improved uteroplacental blood flow. It may also avoid the risk of general anaesthesia.

Anaesthesia for delivery

Accelerated delivery of the baby after investigation and optimisation is the goal in the management of severe HDP.

The options for a non-emergent caesarean section would be as follows:

1. *Epidural anaesthesia*: thought to allow for incremental dosing, potentially avoiding precipitous hypotension or
2. *Spinal anaesthesia*: a retrospective survey of practice by Hood and Curry[23] in 1999 found no difference in haemodynamic changes after spinal or epidural anaesthesia; the conclusion was that a spinal anaesthetic is a safe alternative to an epidural, with an added advantage of quicker onset and better quality of sensory blockade especially in urgent situations.

Anaesthesia for delivery or an emergent caesarean section can be with an epidural – if previously placed and well-functioning; a spinal – if no epidural placed and if FHR stable; and general anaesthesia if there is coagulopathy, patient refusal of regional techniques and foetal bradycardia which prohibits placement of a block in time.

Anaesthetic management of eclampsia is by immediately instituting aspiration precautions, careful airway assessment and selection of technique. The guidelines for use of regional versus general anaesthesia are similar to patients with severe pre-eclampsia. The present consensus on use of regional anaesthesia in HDP[24] seems to be that if the platelet counts are >80–100,000, it is usually safe for the patient to receive regionals. The 'ABCDs of seizure control' should be remembered as airway, breathing, circulation and the control of BP with drugs.

There does not seem to be a 'blood pressure cut off' to consider while deciding on the type of anaesthetic. Neuraxial anaesthetic techniques are preferable to GA for elective caesarean delivery in the absence of HELLP syndrome. The administration of neuraxial anaesthesia for labour or caesarean delivery reduces serum catecholamine levels and improves uteroplacental blood flow. The sympathetic blockade that results from neuraxial anaesthetic techniques has shown to improve intervillous blood flow in pre-eclamptic parturients by decreasing uteroplacental resistance.[25] Neuraxial techniques have been associated with better Apgar at 1 min and 5 min compared to systemic opioids.[26] In the absence of contraindications (HELLP syndrome or caogulopathy on thromboelastography), lumbar neuraxial analgesia is appropriate for women with pre-eclampsia during labour and neuraxial anaesthesia is the preferred method for anaesthesia for caesarean birth in women with pre-eclampsia.[22]The pressor response to laryngoscopy with GA can lead to a dangerously high surge in BP that may cause intracranial haemorrhage in these parturients.

HELLP SYNDROME

This is severe pre-eclampsia complicated by haemolysis elevated liver enzymes and low platelets. It was first reported by Weinstein[27] in his landmark paper in 1982 and occurs in about 12% of pregnancies complicated by pre-eclampsia or eclampsia. The clinical presentation (which is extremely variable) may consist of right upper quadrant or epigastric pain, nausea/vomiting, malaise, headache, visual disturbances and weight gain/oedema.

The laboratory findings in HELLP consist of haemolysis, an abnormal peripheral smear, total bilirubin >1.2 mg/dL, LDH >600 IU/L, raised liver enzymes like AST (SGOT) >70 IU/L and a platelet count <100,000.

Management of HELLP syndrome is to stabilise the mother – to control BP, prevent seizures; evaluate foetus for well-being; determine optimal timing and route for delivery, as early as possible after optimisation and provide continued monitoring and management

during the postpartum period and all the parturients should receive $MgSO_4$.

The new alternative therapies being considered for HELLP[28] are dexamethasone 10 mg IV q12h when platelets <100,000, platelets for active bleeding, or if <20,000 and plasmapheresis which has had only limited success and is not routinely recommended.

SUMMARY

HDP are common in India; various risk factors increase the occurrence. The basic management objectives should be facilitating the birth of an infant who subsequently thrives and complete restoration of health to the mother. This comprises obstetric management, adequate foetal surveillance, antihypertensive management, anticonvulsant therapy, the anaesthetic management of labour and safe analgesia for labour and anaesthesia for delivery. Antihypertensive drugs and magnesium therapy are used to control hypertension and prevent seizures. Invasive haemodynamic monitoring is required to prevent the serious complication of fluid overload, pulmonary oedema. Anaesthetic problems in HDP may be due to the systemic effects. Careful pre-anaesthetic assessment, optimising physiology and expedited delivery is the goal. Risks and benefits of techniques should be weighed – there is no conclusive evidence towards the advantage of regional or general anaesthesia.

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Conflicts of interest
There are no conflicts of interest.

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