SPECIAL ARTICLE

Hypertensive disorders in pregnancy

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ABSTRACT

Hypertensive disorders in pregnancy (HDP) affect 10% of pregnant patients and are the second most common cause of maternal mortality and adverse fetal outcomes in developed countries. HDP is a group of diseases that includes preeclampsia, eclampsia, pregnancy induced hypertension and HELLP syndrome.

Inadequate placentation, immune intolerance and genetics are accounted as possible etiological factors. Clinically, HDP manifests as hypertension, multi-organ dysfunction and placental insufficiency due to vasoconstriction, endothelial dysfunction and micro-thrombosis. Moderate to severe disease requires inpatient management with antihypertensive drugs, magnesium and early delivery. Early epidural analgesia is beneficial in reducing blood pressure and providing effective block for obstetric interventions.

Early diagnosis, adequate blood pressure control, seizure prophylaxis and identification of the most suitable time for delivery improve feto-maternal outcomes.

Key words: Pregnancy; Hypertension; Blood pressure; Proteinuria; Magnesium; HELLP; Preeclampsia; Eclampsia

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Abbreviations used:

PIH	Pregnancy induced hypertension	ECG	Electrocardiogram
HDP	Hypertensive disorders of pregnancy	VEGF	Vascular endothelial growth factor
SDB	Systolic blood pressure	PIGF	Placental growth factor
DBP	Diastolic blood pressure	sFlt-1	Placental soluble fms-like tyrosine kinase 1
CVP	Central venous pressure	ACE	Angiotensin converting enzyme
CTG	Cardiotocograph	ARBs	Angiotensin receptor blockers

INTRODUCTION

Hypertensive disorders in pregnancy (HDP) are the second direct leading cause of maternal mortality in developed countries whereas it accounts for 9% of total maternal deaths in Africa and Asia.[1,2] In general, 10% of pregnancies are complicated by HDP. However, there is slight geographical variation in the distribution of HDP. For instance, incidence of gestational-hypertension and pre-eclampsia is 5-6% in UK whereas it is 2 to 12% in US.[1,2] Nulliparous women experience higher rates of gestational hypertension (6 to 17%) compared to multiparous women (2 to 4%).[3,4]

HDP is not only a major contributor of maternal deaths, it is also responsible for significant immediate and long-term morbidity of affected parturients. It is found that lifetime cardiovascular risks are increased in women who develop HDP.[5]

Neonatal outcomes are also adversely affected by HDP. It is estimated that 5% of stillbirths and 0.4% of preterm births are due to HDP. In addition, 25% of preterm and 19% of term infants born to preeclamptic mothers are small for gestational age[1].

CLASSIFICATION

According to 'National Education Program Working Group on High Blood Pressure in Pregnancy', HDP is classified in to following four categories:[6]

1. Chronic hypertension of any cause
2. Preeclampsia–eclampsia
3. Preeclampsia superimposed on chronic

hypertension and
4. Gestational hypertension

In addition, there are two other conditions, which are not included in this classification but are closely related to HDP. These are;
1. HELLP syndrome
2. Acute fatty liver of pregnancy

1. Chronic hypertension continued in pregnancy

Hypertension diagnosed before 20 weeks is classified as chronic hypertension. Similarly, any hypertension diagnosed for the first time after 20 weeks that persists after 12 weeks postpartum, also falls in this category. About 25.8% of women aged 20-44 years in USA have chronic hypertension.[7] Neonatal mortality and morbidity is four times higher and serious maternal complications are nine times higher among hypertensive patients compared to normotensive counterparts. These patients also carry 25% risk of developing superimposed preeclampsia.[8]

2. Preeclampsia – Eclampsia

Preeclampsia: There is a recent change in the diagnostic criteria of preeclampsia by 'American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy'. Preeclampsia diagnosis does not depend on the presence of proteinuria any more. New diagnostic criteria are as follows:[9]

A. Hypertension after 20 weeks of gestation (≥140/90 mmHg on two occasions 4 hr apart or a single reading of ≥160/110 mmHg).
AND
B. Proteinuria of ≥300 mg /day
OR
C. Any of following if proteinuria is not present;
   a. Platelets count of <100,000
   b. Creatinine of >1.1 mg/dl or doubling of creatinine
   c. Doubling of AST or ALT

Terms of *mild* and *severe* preeclampsia are also abolished and replaced with preeclampsia with or without severe features. Preeclampsia with severe features is diagnosed if one of the following is present:

a. Systolic blood pressure of ≥160 mmHg or diastolic blood pressure of ≥110 mmHg on 2 occasions taken 4 hours apart
b. Headaches, visual symptoms or other neurological symptoms
c. Pulmonary edema
d. Platelet count <100,000 /μL
e. Right upper quadrant pain not explained by other pathology or doubling of AST or ALT
f. Creatinine of >1.1 mg/dl or doubling of creatinine

The other two criteria, *proteinuria >5g/day* and *intrauterine growth retardation* are also excluded from the new definition of preeclampsia with severe features.

Eclampsia: Eclampsia is defined as generalized tonic clonic seizure, which is in context with preeclampsia. It is estimated that 0.4% of preeclamptic patients develop eclampsia if magnesium prophylaxis is not given.[10,11] Although incidence of eclampsia has decreased due to better management of preeclampsia, the risks of serious complications remain high among women who develop seizures. There is up to 8% perinatal fetal loss in pregnancies that are complicated by eclampsia.[8]

3. Preeclampsia superimposed on chronic hypertension

These patients have chronic hypertension that is diagnosed before pregnancy but also develop features of preeclampsia after 20 weeks of gestation[6].

4. Gestational hypertension

Patients who develop hypertension after 20 weeks of gestation without other features of preeclampsia and become normotensive within 12 weeks of delivery falls into this group.[6]

RISK FACTORS[8]

Risk factors for developing preeclampsia are given in Table 1.

ETIOLOGY

Preeclampsia develops only if trophoblastic tissue is present in the body.[12,13] Though not entirely clear, factors like abnormal development of placenta, remodeling of spiral arteries and defective trophoblastic differentiation with subsequent placental ischemia are key factors in preeclampsia development. Abnormal immune response to developing fetus, genetics and abnormal calcium homeostasis are also suggested as possible

Table 1: Risk Factors for developing preeclampsia

• Nulliparity
• Preeclampsia in prior pregnancy (7-15% chance of recurrence)
• Age > 40 years
• Black race
• BMI ≥30
• Family history of preeclampsia
• Chronic renal disease
• Chronic hypertension (25% chance of developing preeclampsia)
• Diabetes mellitus
• Anti phospholipid syndrome
• Angiotensinogen gene T235
• Multiple gestations
v Trophoblastic tumors

etiological factors.[14]

PATHOPHYSIOLOGY

Endothelial dysfunction plays a key role in the development of hypertension, proteinuria and other complications of preeclampsia.[15] Normal placental development requires a fine balance of pro-angiogenic (VEGF, PIGF) and anti-angiogenic factors (sFlt-1).[16] Increased production of anti-angiogenic factors in preeclampsia lead to placental ischemia and generalized endothelial dysfunction. In fact, markers of endothelial dysfunction (e.g. endothelin, plasminogen, PIF-1, fibronectin and alerted prostacyclin:thromboxane) are present well before clinical manifestation of preeclampsia. In addition, increased hypersensitivity of arterioles to angiotensin is described in preeclamptic patients.[17] Generalized vasoconstriction and widespread micro-thrombosis result in hypertension, microvascular ischemia and multiorgan dysfunction.

Respiratory & cardiovascular function

Patients with preeclampsia manifest features of intravascular volume depletion due to vasoconstriction and high vascular permeability.[18] Paradoxically, cardiac output is abnormally high during early pregnancy in patients who develop preeclampsia later; however, cardiac output is gradually reduced with disease progression.[19] These patients are also prone to develop pulmonary edema due to low oncotic pressure, myocardial depression and increased vascular permeability.[20] In addition, extracellular fluid accumulation leads to generalize as well as upper airway edema[21]. For these reasons, fluid administration in preeclamptic patients should be restricted and given in a controlled manner.

Hematological function

Preeclampsia is started as a state of hypercoagulability. However, later in course, platelets and coagulation factors are consumed in microcirculation resulting in thrombocytopenia (platelets counts <100,000/μL) and coagulopathy.[22] Liver dysfunction also contributes to these defects.[23] Because of rapid platelet turnover, frequent measurements of platelet counts are recommended especially before performing any invasive procedures.

Hepatic function

Liver enzymes are frequently elevated in mild preeclampsia;[23] however, gross hepatic dysfunction is uncommon and signifies severe preeclampsia or HELLP syndrome.[24]

Sub-capsular hematoma should be considered in patients experiencing right upper quadrant pain. If not managed urgently, it can lead to rupture with devastating outcome.

Renal function

Renal function deteriorates early and progresses with increasing disease severity. Both glomerular and tubular functions are affected to varying degrees.[25] While proteinuria is common in mild disease, oliguria implies severe preeclampsia.[26]

Neurological function

Neurological changes in preeclampsia are attributed to cerebral vasoconstriction and edema.[27] Any moderate to severe headache, visual disturbances or hyper-reflexia signify severe disease and needs urgent attention to prevent eclamptic seizures. About 1 in 250 patients with severe preeclampsia develop eclamptic seizures in the absence of prophylactic magnesium therapy.[10,11]

Uterine function

Placenta is the major source of vasoconstrictor and thrombogenic factors in preeclampsia.[28] There is varying degree of placental insufficiency that can cause fetal growth impairment and oligohydramnios.[6] In addition, serve hypertension is a major risk factor for placental abruption and any sudden onset of severe uterine pain suggests placental separation.[6]

PREDICTION OF PREECLAMPSIA

Preeclampsia can be predicted during early pregnancy by identification of certain biological

markers[29] or doppler calculation of uterine artery velocities.[30]

However, routine use of these diagnostic tests is not recommended at present, because there is no clear evidence of improved outcomes with early preeclampsia prediction.[31]

DIAGNOSIS OF PREECLAMPSIA

Blood pressure

Two BP readings of ≥140/90 mmHg taken at least 4 hours apart or a single reading of ≥160/110 mmHg after 20 weeks of gestation confirms the diagnosis of hypertension in pregnancy.[9] In patients with chronic hypertension, an increase in SBP of ≥30 mmHg or DBP of ≥15 mmHg from baseline implies pregnancy induced hypertension superimposed on chronic hypertension.[32]

Proteinuria

Presence of proteinuria is not considered necessary for the diagnosis of preeclampsia any more, if other manifestations of organ dysfunction are present.

Significant proteinuria is confirmed if >300 mg/day of protein is present in urine.[31] This can be diagnosed by one of following ways;

1. Determination in 24 hours collected urine sample.
2. Spot urine dipstick test repeated 4-6 hours apart showing ≥1+ proteinuria.
3. Determination of protein to creatinine ratio (PCR) in a sample of urine repeated 4-6 hours apart. Ratio of 30 mg/mmol corresponds to >300 mg/day of proteinuria.

Spot urine dipstick is a good screening tool, whereas 24-hour urine protein is most accurate in diagnosing proteinuria. PCR is practical, accurate and corresponds well with 24 hour urine protein.[33]

Some patients may present with atypical preeclampsia, which is characterized by presence of clinical and laboratory abnormalities without hypertension, or presence of hypertension and clinical symptoms without significant proteinuria.[2]

Other tests

After confirming hypertension and proteinuria, further tests are warranted to diagnose any complications. Full blood count, liver function tests, serum electrolytes, urea, creatinine and urate are required as initial tests. It is important to repeat these tests at regular intervals (frequency of which depends upon disease severity) because of dynamic nature of disease. Fetal monitoring is also recommended to establish and monitor fetal distress.

PROPHYLAXIS AGAINST PREECLAMPSIA

Patients identified as high risk on the basis of history should be offered low dose prophylactic aspirin (75 mg/day), starting early in the pregnancy and continued throughout. It has been shown that low dose aspirin reduces the risk of severe preeclampsia by 12% and risk of premature delivery by 14 percent.[34]

Calcium 1 g/day is also recommended in patients whose dietary calcium intake is less than 600 mg/day.

MANAGEMENT OF HDP

Diet and life style changes

There is no strong evidence that favors salt restriction; however, salt excess should be avoided. There is no evidence to suggest limiting exercise or doing bed rest in preeclampsia[9].

Treatment of chronic hypertension in pregnancy

For patients with chronic hypertension without end organ damage, BP should be kept bellow 150/110 mmHg[31]. In general, BP drops during pregnancy so it is possible to manage chronic hypertension without regular antihypertensive medications. Patients on ACE inhibitors or ARBs should be switched to medications with safe pregnancy profile.

Treatment of pregnancy induced hypertension

While the only curative treatment of preeclampsia is delivery of placenta, delaying delivery as late as safe for both baby and mother should be aimed by carefully evaluating the risks and benefits of early delivery with complications of PIH.

Mild PIH is usually managed with frequent outpatient followups[9]. Severe PIH requires inpatient management[1]. Blood pressure should be treated if ≥160/110 mmHg (or ≥ 140/90 with end organ damage) and reduced to 130-159/80-105 mmHg range[31] with the help of oral nifedipine, parenteral hydralazine or intravenous labetalol. Refractory hypertension requires intravenous nitroglycerine or sodium nitroprusside.

Corticosteroids should also be administered simultaneously to all patients with preeclampsia

who are <34 weeks to accelerate fetal lung maturity[35].

Prevention and treatment of neural hyper-excitability

Magnesium is the drug of choice for prevention and treatment of eclamptic seizure[10,11]. It should be started in all patients with severe preeclampsia or eclampsia. It is given as 4g bolus over 10-15 minutes followed by 1g/hr infusion keeping plasma levels between 2-4 mmol/L. Although frequent serum magnesium level monitoring is not mandatory, toxicity should be observed clinically by frequent monitoring of deep tendon reflexes[1].

Magnesium causes muscle weakness at plasma levels of 4-5 mmol/L, loss of deep tendon reflexes >5 mmol/L, respiratory paralysis >8 mmol/L and cardiac arrest above 10mmol/L. Toxicity should be treated by stopping Magnesium and giving intravenous calcium chloride.

Timing of delivery

All patients with severe preeclampsia should be delivered urgently (vaginal or caesarean) irrespective of their gestational age[31]. Similarly, patients with mild preeclampsia with ≥37 weeks should be considered for labour induction[9]. For patients who are 24-34 weeks of gestation with non-severe preeclampsia, expectant management is considered with delivery is recommended if disease worsens.

Between 34-37 weeks, evidence of expectant management over induction is less clear therefore management should be individualized.

Mode of delivery

Vaginal delivery is recommended whenever possible; indications of caeserain section in preeclampsia are same as of non-preeclamptic patients[36].

Fluid management

Preeclamptic patients are sensitive to rapid fluid administration because of increased capillary permeability and low oncotic pressures. Fluid intake therefore should be restricted to avoid pulmonary complications. Oliguria should not be treated by giving repeated fluid boluses or by diuretics as it almost always improves after delivery.

Monitoring

In moderate to severe disease, patient should be monitored in high dependency area. Minimal monitoring is: ECG, non-invasive blood pressure, oxygen saturation, urine output, deep tendon reflexes and CTG. An arterial line may be used to monitor BP and to obtain frequent blood samples. CVP or pulmonary artery catheter are not routinely recommended but should be considered in patients with pre-existing cardiac disease.

Platelet counts should be repeated frequently and especially before performing invasive procedures. Trend in platelet count is more important than a single count at any one point in time.

ANESTHETIC CONSIDERATIONS

Early epidural analgesia is beneficial as it reduces sympathetic tone and improves blood pressure. It can also provide effective and rapid anesthesia if instrumental or caesarean delivery is needed. It is acceptable to perform neuraxial block if platelet count is above 80,000 /μL immediately before the procedure and if coagulation profile is normal.[1] However, regional anesthesia may be difficult to perform due to soft tissue edema that makes anatomical landmarks difficult to identify. Spinal anesthesia can be used for caesarean section if epidural is not already in place though sudden drop in blood pressure with subarachnoid block may be a problem. Volume preloading before neuraxial anesthesia is not recommended and hypotension should be treated with small doses of vasoconstrictors.[37]

General anesthesia is also acceptable if adequate precautions are taken. However, incidence of difficult intubation is high as a result of upper airway edema. In addition, exaggerated presser response during intubation can lead to intracranial haemorrhage.[8] It is therefore recommended to choose half a size smaller endotracheal tube and suppress intubation response by giving opioids, labetalol, nitroglycerine or lignocaine. Pediatrician should be altered for potential neonatal respiratory depression if opioids are given before delivery. Neuromuscular function should be monitored when muscle relaxants are used because of potentiation of motor block with magnesium. Oxytocin is preferable for achieving uterine contraction and ergometrine is contraindicated due to its presser effects.

It is also important to keep patient under observation for some time after delivery because preeclampsia can deteriorates in immediate postpartum period before improving subsequently. Likewise, preeclampsia can present for the first time after delivery so high degree of suspicion is required in a patient whose blood pressure increases

unexpectedly in postnatal period.[38] In most cases, however, PIH improves dramatically after delivery and treatment is usually not required beyond 48-72 hours of postnatal period.

CONCLUSION

HDP is a group of disorders of uncertain etiology that affects pregnant patients with multi organ involvement. Routine screening of pregnant patients with blood pressure measurements and urine protein analysis is recommended after 20 weeks of gestation.

Meticulous management by frequent fetal and maternal monitoring, control of blood pressure and identification of best time for delivery by individualized approach is aimed to improve maternal and fetal outcome.

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