Review Article

Hypertensive Disorders of Pregnancy – An Update

Abstract

Hypertension is the most common medical disorder encountered during pregnancy. Hypertensive disorders are one of the major causes of pregnancy related maternal deaths in Bangladesh. In this review, we will present a comprehensive update of the literature related to hypertension in pregnancy. It begins by definition and classification of hypertensive disorders in pregnancy. We will summarize on the recent advances in this field. We review the current management guidelines, goals of treatment and the potential risks of various hypertensive disorders of pregnancy. There is a change in the diagnostic criteria and measurement of the severity of preeclampsia which is described here. We also highlight the short and long term implications of preeclampsia. We are hopeful that this in depth discussion will stimulate the blossoming research in the field and assist practitioners to identify women at risk and thereby more effectively treat the affected individuals.

Key word: Hypertension in pregnancy, Preeclampsia, Eclampsia.

Introduction

Hypertension is the most common medical problem encountered during pregnancy, complicating up to 10% cases [1].Hypertensive disorders of pregnancy are a leading cause of maternal and perinatal mortality and morbidity worldwide. In Bangladesh it accounts for 24% of maternal death [2].It is anticipated that this situation will worsen more due to rising prevalence of obesity and metabolic syndrome among women of childbearing age.Hypertensive disorders during pregnancy are classified into 4 categories as recommended by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy [3]. These are: chronic hypertension, gestational hypertension, preeclampsia-eclampsia, preeclampsia superimposed on chronic hypertension.This terminology is preferred over the older but widely used term pregnancy-induced hypertension (PIH) because it is more precise. The newer terminology reflects simply relation of pregnancy with either the onset or first detection of hypertension and that the question of causation, while pathogenically interesting is not the important point for most health care purposes. This classification treats HELLP syndrome as a type of preeclampsia rather than a parallel entity [4]. Population-based data shows that approximately 1% of pregnancies are complicated by chronic hypertension, 5-6% by gestational hypertension, and 3-6% by preeclampsia [5].

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Till now lot of researches is going on in relation to diagnosis, evaluation and treatment of hypertensive disorder of pregnancy. Guidelines and recommendations for management of hypertension in pregnancy are been updated. The aim of this review is to evaluate various international guidelines regarding the diagnosis and management of this clinical condition.

Methodology

Pub Med, other electronic databases and relevant guidelines were searched to identify articles that included the keyword 'hypertensive disorder of pregnancy', 'pregnancy with chronic hypertension' and 'preeclampsia-eclampsia'. The relevant papers were searched manually for further information.

Diagnosis of Hypertension and Proteinuria

Hypertension is defined as systolic BP ≥ 140 and diastolic BP ≥90 mm Hg recorded two times at least 4 hours apart. However, if systolic BP is ≥ 160 and diastolic BP ≥110 mm Hg then the BP should be confirmed within 15 minutes.

Proteinuria should be assessed initially by automated dipstick urine analysis when possible; if not available, careful visual dipstick analysis can be done. If positive (≥1+, 30 mg/dL), then spot urine protein/creatinine (PCR) ratio or albumin: creatinine ratio (ACR)should be done. A PCR ratio ≥30 mg/mmol (0.3 mg/mg) or albumin:creatinine ≥8 mg/mmol is abnormal. A negative dipstick test can usually be accepted, and further PCR testing is not required at that time. First morning urine void is not used to quantify proteinuria in pregnant women [6].Proteinuria is not required for diagnosis of preeclampsia. Twenty- four- hour urine collection is needed for diagnosis of massive proteinuria [6].Massive proteinuria (>5 g/24 h) is associated with more severe neonatal outcomes as well as need thromboprophylaxis.

Chronic Hypertension

Chronic hypertension refers to hypertension predating the pregnancy or detected before 20 weeks of gestation. The majority of cases are because of essential hypertension. Secondary causes are uncommon. International Society for the Study of Hypertension in Pregnancy (ISSHP) recommends that all women with chronic hypertension in pregnancy should do some investigations at first prenatal visit. This will provide a baseline references if suspicion of superimposed preeclampsia arises [7]. These are as follows:

- A full blood count (including haemoglobin and platelet count).
- Liver enzymes (aspartate aminotransferase, alanine aminotransferase and lactate dehydrogenase) and functions tests(international normalized ratio, serum bilirubin, and serum albumin).
- Serum creatinine, electrolytes and uric acid. Serum uric acid is not a diagnostic criterion for preeclampsia, but elevated gestation-corrected serum uric acid levels are associated with worse maternal and fetal outcomeand should prompt a detailed assessment of fetal growth even in women with gestational hypertension [8].However uric acids should not be used to determine the timing of delivery.
- Urine analysis and microscopy as well as PCR or ACR if proteinuria present.
- Renal ultrasound if serum creatinine or any of the urine testing is abnormal.

In pregnancy with chronic hypertension, medications should be reviewed when first diagnosed. Acceptable initial antihypertensive are labetalol, oxyprenolol, methyldopa, and nifedipine. Prazosin and hydralazine are considered as second and third line agents.Atenolol and other pure beta-blockers should be avoided as they are associated with fetal growth restriction. Angiotensin-converting enzyme (ACE) inhibitors are contraindicated in the second and third trimester because they are associated with congenital anomalies, oligohydramnios, renal dysgenesis, reduced ossification, pulmonary hypoplasia, and fetal and neonatal death. Patients presenting in the first trimester on an ACE inhibitor should be switchedover to another agent. Exposure during this time is not an indication for pregnancy termination. Due to similarity to ACE inhibitor, Angiotensin II receptor antagonists are also contraindicated during pregnancy.Patients shouldalso be advised about weight management, exercise, healthy eating habit withdietary salt restriction.

The key risks are superimposed preeclampsia, fetal growth restriction, intrauterine death, placental abruptionand prematurity. Complications are related with severity and duration of elevated blood pressures.Patients with severe hypertension in the first trimester have a greater than 50% risk of developing superimposed preeclampsia. All hypertensive patients should undergo increased surveillance, serial laboratory tests throughout pregnancyand serial ultrasound scans to follow fetal growth. Patient should be monitored for developing preeclampsia by urine analysis at each visit along with clinical assessment and blood tests (Haemoglobin, platelet count, liver transaminases, uric acid and creatinine) at 28 and 34 weeks as a minimum [7].Fetal well-being should be assessed with ultrasound from 26 weeks' gestation and thereafter at 2 to 4 weekly intervals if fetal biometry is normal and more frequently in the presence of suspected fetal growth restriction. Indications for delivery are similar to those of preeclampsia; if no such indication arises, delivery at 39 weeks seems optimum [9].

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Gestational hypertension

Gestational hypertension previously known as PIH is the new onset of hypertension after 20 weeks of gestation. It is actually diagnosed retrospectively when the patient does not develop preeclampsia and if blood pressure returns to normal by the 12-week postpartum visit. It is not a benign condition. Preeclampsia may develop in 25% cases and the rate is higher the earlier the presentation [10]. Gestational hypertension like preeclampsia is also associated with cardiovascular risk in the long run [11].Delivery can be delayed until 39+6 weeks provided BP can be controlled, fetal monitoring is reassuring and preeclampsia has not developed. Gestational hypertension may be a forerunner of chronic hypertension in later life.

Preeclampsia

Preeclampsia is hypertension accompanied by one or more new onset conditions like significant proteinuria or evidence of other maternal organ dysfunction occurring at or after 20 weeks of gestation. The maternal organ dysfunctions are as follows:

- Acute kidney injury (creatinine≥90µmol/L; 1 mg/dl)
- Liver involvement (elevated transaminases, eg. alanine aminotransferase or aspartate aminotransferase >40 IU/L) with or without right upper quadrant or epigastric abdominal pain
- Neurologicalcomplications (examples include eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomata)
- Hematologicalcomplications (thrombocytopenia–platelet count <150 000/µL, disseminated intravascular coagulation, hemolysis)
- Uteroplacentaldysfunction (such as fetal growth restriction, abnormal umbilical artery (UA)Doppler waveform analysis or stillbirth)

ISSHP do not classify it as mild or severe as it can deteriorate rapidly and without warning. The American College of Obstetrician & Gynecologist (ACOG) recommend to recognize it as preeclampsia with or without severe features [12].

Risk factors for Preeclampsia

The risk factors for preeclampsia can be categorized as major and minor risk factors and they are as follows [13].

Major risk factors

- Prior preeclampsia

- Chronic hypertension
- Pre-gestational diabetes mellitus
- Maternal body mass index >30 kg/m^2
- Chronic kidney disease
- Antiphospholipid syndrome

Minor risk factors

- Advanced maternal age
- Family history of preeclampsia
- Primiparity
- Pregnancy interval of more than 10 years
- Connective tissue disorders

Prediction & Prevention of Preeclampsia

Development of preeclampsia cannot be predicted properly. However, a combination of risk factors, BP, placental growth factorand uterine artery Doppler can select women who may benefit from prophylactic dose of aspirin (75- 150 mg/d) starting before 16 weeks. Women can also take supplemental calcium (1.2- 2.5 gm/d) if their intake is low (<600 mg/d) [7].Pregnant women should exercise at least 3 days per week for an average 50 minutes using a combination of aerobic exercise, strength, and flexibility training; this has been associated with less weight gain and reduced incidence of hypertensive disorders in pregnancy [14].There are no significant adverse effects of exercise in pregnancy. Dietary salt restriction is not advocated for prevention of preeclampsia [6].Low molecular weight heparin does not offer any preventative advantage above low-dose aspirin even in women at high risk for preeclampsia [15].

Management of Preeclampsia

a. Antenatal

It is recommended that BP consistently at or >140/90 mm Hg will be treated aiming for a target BP of 110-140/85 mmHg [7]. Antihypertensive drugs should be reduced or ceased if diastolic BP falls <80 mm Hg. Acceptable agents are same like those used in chronic hypertension. Women with preeclampsia who have proteinuria and severe hypertension, or hypertension with neurological signs or symptoms, should receive $MgSO_4$ for convulsion prophylaxis.

Maternal monitoring in preeclampsia should include BP monitoring, repeated assessments for proteinuria if not already present, clinical assessment including clonus, and twice weekly blood tests for Hb, platelet count, liver transaminases, creatinine and uric acid. Blood test evaluation should be performed at least twice weekly (and again in response to a change in clinical status) in most women with preeclampsia [7].

Fetal monitoring in preeclampsia should include assessment of fetal biometry, amniotic fluid volume and UADoppler waveform analysis at first diagnosis and thereafter at 2 weekly intervals if the initial assessment is normal and more frequent in the presence of fetal growth restriction.The ACOG and Royal College of Obstetricians and Gynecologists (RCOG) agree that the risk of perinatal morbidity and mortality increases once the estimated fetal weight or the abdominal circumference $<10^{th}$centile [12,16].

ACOG considers amniotic fluid an important diagnostic and prognostic parameter in fetuses with intrauterine growth restriction, whereas RCOG notes that amniotic fluid assessment has minimal value in diagnosing growth restriction [12,16]. Both guidelines agree that UA

Doppler is not a reliable screening technique for fetal growth restriction but is a useful assessment tool once fetal growth restriction is diagnosed.
Prenatal corticosteroids for fetal lung maturation should be given between 24^{+0} and 34^{+0} weeks gestation but may be given until 38+0 weeks in cases of elective delivery by caesarean section; multiple steroid courses are not recommended. $MgSO_4$ for fetal neuroprotection should be administered in gestations before 32 weeks [7].
In particular, an estimated fetal weight <third centile and abnormal UA Doppler significantly increase the risk of adverse perinatal outcome. If the UA Doppler shows increased resistance (pulsatility index >95th centile) the sonographic surveillance should be increased to weekly intervals or more frequently. If there is absent end-diastolic flow in the UA before 34 weeks' gestation, daily cardiotocograph (CTG) monitoring, twice weekly UA Doppler, and amniotic fluid volume assessment are recommended [7]. If there is reversed end-diastolic flow in the UA before 30-week gestation, admission to hospital with daily CTG monitoring, thrice weekly UA Doppler and amniotic fluid volume assessment are recommended. In cases of absent end-diastolic flow, delivery should be considered no later than 34-week gestation. Earlier delivery may be indicated in cases of poor interval growth or a deterioration of sonographic variables (Doppler, amniotic fluid). In cases of reversed end-diastolic flow, delivery should be considered no later than 30-week gestation. Earlier delivery may be indicated by a deterioration of sonographic variables [7]. Mode of delivery should be on individual basis but caesarean section is likely when there is absent or reversed end-diastolic flow or in cases of very preterm gestation.
Womenwith preeclampsia should be delivered if they have reached 37 weeks' gestation or they develop any of the following: repeated episodes of severe hypertension despite maintenance treatment with 3 classes of antihypertensive agents; progressive thrombocytopenia; progressively abnormal renal or liver enzyme tests; pulmonary edema; abnormal neurological features, such as severe intractable headache, repeated visual scotomata or convulsions,placental abruptionor non-reassuring fetal status. Neither the serum uric acid nor the level of proteinuria should be used as an indication for delivery [7].

b. Intrapartum
Oral antihypertensives should be given at the start of labor. Hypertension should be treated urgently with oral nifedipine or either intravenous labetalol or hydralazine if BP rises ≥160/110 mm Hg. Total fluid intake should be limited to 60 to 80 mL/h to avoid risks of pulmonary edema. Also there is no rationale to "run dry" a preeclamptic woman as she is already at risk of acute kidney injury(AKI).

c. Postpartum
BP should be monitored 4 to 6 hourly for at least 3 days postpartum. Blood tests ((Hb, platelets, creatinine, liver transaminases) should be done the day after delivery and then every alternate day until stable, if any of these were abnormal before delivery. Antihypertensives should be restarted after delivery and tapered slowly only after days 3 to 6 postpartum unless BP becomes low (<110/70 mm Hg). Most women can be discharged by day 5 postpartum, especially when they are able to monitor their BP at home. NSAIDs should be avoided in women with preeclampsia if possible, especially in the setting of AKI and other alternative analgesic should be used.

HELLP Syndrome
It is a recognized complication of preeclampsia occurring in 25% cases. It is a syndrome having a combination of "H" for haemolysis, "EL" for elevated liver enzymes and "LP" for low platelet. It is a variant of severe preeclampsia where hypertension is less marked but

there is severe involvement of liver and coagulation system and may lead to liver failure and severe bleeding. In a patient with possible HELLP syndrome some specific blood tests are performed e.g. a full blood count, liver enzymes, renal function, electrolyte and coagulation studies. Often fibrin degradation product (FDP) is determined which can be elevated. D-dimer is a more sensitive indicator of sub-clinical coagulopathy and may be positive before coagulation studies are abnormal. A positive D-dimer test in the presence of preeclampsia has been reported to be predictive of patients who will develop HELLP syndrome [17]. The only effective treatment is prompt delivery. The DIC is treated with fresh frozen plasma to replenish the coagulation proteins and the anaemia may require blood transfusion. In mild cases corticosteroids and antihypertensives may be sufficient. Hepatic haemorrhage can be treated with embolization if there is life threatening bleeding.

Eclampsia

Eclampsia is the development of convulsions in a preexisting pre-eclampsia or it may appear unexpectedly in a patient with minimally elevated blood pressure and no proteinuria. The exact cause is unknown but cerebral ischaemia and oedema was suggested. The timing of an eclamptic seizure can be antepartum (53 percent), intrapartum (19 percent), or postpartum (28 percent) [18].

The first step in the management of eclampsia is treatment of convulsion. Cochrane review showed that in women with eclampsia magnesium sulphate had statistically better results than previously used drugs like diazepam, phenytoin and lytic cocktail in preventing maternal death and recurrence of convulsion [19-21]. Severe hypertension must be controlled after controlling convulsion. The goal is to maintain SBP 140-160 mm Hg and DBP 90-100 mm Hg [7]. Labetalol or hydralazine can be administered intravenously. Parenteral labetalol should be avoided in women with asthma, heart disease, or congestive heart failure. Labetalol can be given bolus or infusion form. Diuretics are used only in cases of pulmonary edema. Depending on the clinical course, patient's neurological status for signs of increased intracranial pressure or bleeding (eg. fundoscopic examination, cranial nerves) should be checked regularly. Maternal fluid intake and urine output, respiratory rate, oxygenation and continuous fetal monitoring are required. Delivery is the treatment for eclampsia after the patient has been stabilized.

Preeclampsia superimposed on chronic hypertension

Preeclampsia superimposed on chronic hypertension is characterized by new-onset proteinuria (or by a sudden increase in the protein level if proteinuria is already present), an acute increase in the level of hypertension (assuming proteinuria already exists), or development of the HELLP syndrome [22]. Fetal growth restriction may be associated with chronic hypertension but is not a diagnostic criterion for superimposed preeclampsia. About 25% women with chronic hypertensionwill develop superimposed preeclampsia. This rate may be higher in women with kidney disease.Systematic reviews demonstrate that the use of low dose aspirin is associated with a significant (17%) reduction in developing preeclampsia [23].Once the diagnosis of superimposed preeclampsia is made it will be managed accordingly. Magnesium sulphate will be used in patients with severe features to prevent seizure. Delivery should be considered in patients with severe features at or beyond 34 weeks and without severe features at or beyond 37 weeks of gestation. Women with superimposed preeclampsia should be counseled about future pregnancy. In nulliparous women with preeclampsia before 30 weeks of gestation, the recurrence rate for the disorder may be as high as 40% in future pregnancies and for multiparous women even higher rate [3].

Conclusion

Hypertensive disorders in pregnancy remain a major health concern for women and their infants. Optimizing management including prenatal care, identification of the severe features and treating appropriately as well as close postpartum follow-up are key to reduce maternal-fetal morbidity and mortality.Lifestyle modifications in women affected by hypertensive disorders in pregnancy might reduce their risk for cardiovascular disease at a later point in their lives. Research in this field is promising and advancements both on the basic science as well as clinical fronts will hopefully provide further clarity to prediction, prevention and management of hypertensive disorders in pregnancy.

References

1. The Task Force on Hypertension in Pregnancy. *Hypertension in Pregnancy*. ACOG; 2013.

2. Bangladesh Maternal Mortality and Health Care Survey 2016.

3. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol*. 2000; 183(1):S1-22.

4. Mammaro A, Carrara S, Cavaliere A, Ermito S, Dinatale A, Pappalardo EM et al.Hypertensive disorders in pregnancy. J Perinat Med. 2009, Jan; 3(1):1-5.

5. Baldisseri MR. Hypertensive Disorders in Pregnancy. Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP. *Textbook of Critical Care*. 7th Edition. Philadelphia, PA: Elsevier; 2016.

6.Hypertension in pregnancy: Diagnosis and management. NICE guideline. Published date: 25 June 2019.

7.Mark AB, Laura AM, Louise C, Karumanchi SA, Fergus PM, Saito S et al. Hypertensive disorders of pregnancy- ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. Hypertension. 2018;72:24-43.

8.Livingston JR, Payne B, Brown MA, Roberts JM, Côté AM, Magee LA, et al. PIERS Study Group. Uric acid as a predictor of adverse maternal and perinatal outcomes in women hospitalized with preeclampsia.J Obstet Gynaecol, 2014;*36*:870–877.

9.Harper LM, Biggio JR, Anderson S, Tita AT. Gestational age of delivery in pregnancies complicated by chronic hypertension. Obstet Gynecol. 2016;*127*:1101–1109.

10.Saudan P, Brown MA, Buddle ML, Jones M. Does gestational hypertension become pre-eclampsia?Br J Obstet Gynaecol. 1998;*105*:1177–1184.

11.Davis GK, Mackenzie C, Brown MA, Homer CS, Holt J, McHugh L et al. Predicting transformation from gestational hypertension to preeclampsia in clinical practice: a possible role for 24 hour ambulatory blood pressure monitoring.Hypertens Pregnancy. 2007;*26*:77–87.

12.ACOG. Hypertension in pregnancy: executive summary. Obstet Gynecol. 2013; 122:1122-1131. doi: 10.1097/01.AOG. 000047382.03963.88.

13.Bartsch E, Medcalf KE, Park AL, Ray JG; High Risk of Pre-eclampsia Identification Group. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ. 2016;*353*:i1753.

14.Berghella V, Saccone G. Exercise in pregnancy. Am J Obstet Gynecol. 2017;*216*:335–337.

15. Groom K, McCowan L, MacKay L, Said J, Kane S, Walker S et al. Enoxaparin for the prevention of preeclampsia and intrauterine growth restriction in women with a prior history (the eppi trial): an open-label international multicentre randomized controlled trial. Am J Obstet Gynecol. 2017;*216*(suppl 1):S4.

16. https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg31

17. Padden MO "HELLP syndrome: recognition and perinatal management". American Family Physician. 1999;60(3): 829-36.

18.Mattar F, Sibai BM. Eclampsia. VIII. Risk factors for maternal morbidity. Am J Obstet Gynecol. 2000;182(2):307–312.

19.Duley L and Handerson-Smart D. Magnesium sulphate versus diazepam for eclampsia. Cochrane Database of Systematic Reviews 2008:3.

20.Duley L and Handerson-Smart D. Magnesium sulphate versus phenytoin for eclampsia. Cochrane Database of Systematic Reviews 2008:3.

21.Duley L and Handerson-Smart D. Magnesium sulphate versus lytic cocktail for eclampsia. Cochrane Database of Systematic Reviews 2008:3.

22. ACOG Committee on Obstetric Practice. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. No. 33, January 2002. American College of Obstetrician and Gynaecologist. Obstet Gynecol. 2002; 99: 159-67.

23.Askie LM, Duley L, Henderson-Smart DJ, Stewart LA, Group PC. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. *Lancet*.2007;369(9575):1791–1798.