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Hypertensive Disorders of Pregnancy – A Review

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

High blood pressure is a common medical problem faced during pregnancy. Hypertensive diseases in pregnancy are one of the major causes of maternal morbidity and mortality worldwide. The compendious update of the various literature related to hypertension in pregnancy is presented in this review. The classification of hypertensive disorders of pregnancy, their definitions, the current treatment guidelines, objectives of treatment and the potential risks of various hypertensive diseases of pregnancy has been reviewed. The recent advance in this field has been summarized. There are some changes in the diagnostic criteria and measurement of the severity of preeclampsia which has also been summarized. The short and long-term consequences of preeclampsia have been highlighted. We hope that this comprehensive discussion will stimulate the flourishing research in the field and facilitate clinicians to identify women at risk and thereby undertake more effective treatment of those affected individuals.

Keywords: Hypertension in pregnancy; preeclampsia; eclampsia.

1. INTRODUCTION

Hypertension during pregnancy is a common medical problem, seen in up to 10% cases [1]. Hypertensive diseases of pregnancy are a major cause of maternal and perinatal mortality and morbidity worldwide. A survey report has revealed that these disorders account for 24% of

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maternal death in Bangladesh [2]. It has been assumed that this situation will worsen more due to rising prevalence of obesity and metabolic syndrome among women of childbearing age. The "National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy" has classified hypertensive disorders during pregnancy into 4 categories [3]. "These are (a) chronic hypertension, (b) gestational hypertension, (c) preeclampsia-eclampsia, and (d) preeclampsia superimposed on chronic hypertension. It appears that these terminologies are more precise and better than the older ones including pregnancy-induced hypertension (PIH). These terminologies reflect mainly the relation of pregnancy with either the onset or first detection of high blood pressure (BP) as well as the question of causation and pathogenesis. This classification considers HELLP syndrome as a type of preeclampsia rather than a different 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].

Till now a lot of research is going on in relation to diagnosis, evaluation and treatment of hypertensive disorders of pregnancy. The aim of the review paper is to evaluate the recent recommendations of various international guidelines regarding the diagnosis and management of this clinical condition.

2. METHODOLOGY

PubMed and relevant online guidelines were searched manually to identify articles that included the keyword 'hypertensive disorders of pregnancy', 'pregnancy with chronic hypertension' and 'preeclampsia-eclampsia'.

2.1 Diagnosis of Hypertension and Proteinuria

The definition of hypertension is well established meaning a systolic BP ≥ 140 and a diastolic BP ≥90 mmHg recorded two times at least 4 hours apart. However, if systolic BP is ≥ 160 and diastolic BP ≥110 mmHg, the high BP should be confirmed within 15 minutes.

Proteinuria should be assessed initially by automated dipstick urine analysis; if unavailable, visual dipstick analysis can be done. If the dipstick test for protein is positive (≥1 plus), 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 ACR ≥8 mg/mmol is abnormal. If the dipstick test is negative for protein, no further PCR or ACR testing is required. Early morning urine sample is not used to quantify proteinuria in pregnant women [6]. Proteinuria is considered not essential for the diagnosis of preeclampsia. Twenty- four- hour urine collection is needed for diagnosis of massive proteinuria [6]. Massive proteinuria (>5 g/24 h) has been found to be associated with more severe adverse neonatal outcomes as well as needing thromboprophylaxis.

2.2 Chronic Hypertension

The term chronic hypertension is applied to hypertension that has been present prior to the pregnancy or detected before 20 weeks of gestation. The majority of cases of chronic hypertension belong to essential hypertension; secondary causes are uncommon. The International Society for the Study of Hypertension in Pregnancy (ISSHP) recommends that all women with pregnancy having such type of hypertension should do some investigations at first prenatal visit. This will provide a baseline reference if suspicion of superimposed preeclampsia arises [7]. The useful investigations are (a) full blood counts, (b) liver function tests (aspartate aminotransferase, alanine aminotransferase, serum bilirubin, serum albumin, international normalized ratio) and lactate dehydrogenase, (c) serum creatinine and electrolytes (d) serum uric acid (elevated gestation-corrected serum uric acid levels are associated with worse maternal and fetal outcome and should prompt a detailed assessment of fetal growth) [8], (e) urine analysis as well as PCR or ACR if proteinuria is present on dipstick testing, and (f) renal ultrasound if serum creatinine is raised or any abnormality of the urine testing is detected.

In pregnancy with chronic hypertension, medications should be reviewed when first diagnosed. Acceptable first line antihypertensive drugs are labetalol, oxyprenolol, nifedipine, and methyldopa. Prazosin and hydralazine are considered as second line agents. Atenolol and other beta-blockers should be avoided as they might cause fetal growth restriction. Angiotensin-converting enzyme (ACE) inhibitors are contraindicated in the second and third trimester because they might cause congenital anomalies, oligohydramnios, reduced ossification, renal

dysgenesis, pulmonary hypoplasia, and fetal and neonatal death. Patients on an ACE inhibitor who presents during the first trimester, should change ACE inhibitor to another appropriate agent. Exposure to ACE inhibitors during this time is not an indication for pregnancy termination. Due to similarity with ACE inhibitors, angiotensin II receptor antagonists are also contraindicated during pregnancy. Patients should also be advised about weight management, exercise, healthy eating habits with dietary salt restriction.

The key risks of chronic hypertension in pregnancy are superimposed preeclampsia, fetal growth restriction, intrauterine death, placental abruption and prematurity. Complications are related with severity and duration of hypertension. If the patient has severe hypertension in the first trimester, then they are at >50% risk of developing superimposed preeclampsia [9]. Throughout pregnancy, all hypertensive patients need increased surveillance, serial laboratory tests and serial ultrasound scans to follow fetal growth. They should be monitored for developing preeclampsia by urine analysis at each visit along with clinical assessment and blood tests (haemoglobin, platelet count, liver enzymes, uric acid and creatinine) at-least at 28 and 34 weeks of gestation [7]. Fetal well-being should be assessed with ultrasound from 26 weeks of gestation and onwards at 2-4 week intervals if fetal biometry is normal and more frequently in the presence of suspected fetal growth restriction. Indications for delivery are similar to those for preeclampsia; if no such indication arises, delivery at 39 weeks seems reasonable [10].

2.3 Gestational Hypertension

Gestational hypertension, previously termed PIH, is the origin of hypertension after 20 weeks of gestation. It is usually diagnosed retrospectively when the patient does not develop preeclampsia and if BP returns to normal by the 12-week after delivery. It is not a benign condition, as preeclampsia may develop in 25% cases and the rate is higher the earlier the presentation [11]. Gestational hypertension like preeclampsia might be associated with cardiovascular risk in the long run [12]. Gestational hypertension may become apparent as chronic hypertension in later life. Females with gestational hypertension, delivery can be delayed until 39^{+6} weeks provided BP is well controlled, fetal monitoring is satisfactory, and preeclampsia has not developed.

2.4 Preeclampsia

Preeclampsia is hypertension that is accompanied by a new appearance of significant proteinuria or other maternal organ dysfunction that occurs at or after 20 weeks of gestation. The examples of maternal organ dysfunctions are (a) acute kidney injury (AKI); creatinine ≥90μmol/L (1 mg/dl) (b) liver dysfunction (elevated alanine aminotransferase or aspartate aminotransferase >40 IU/L) with or without right upper quadrant or epigastric abdominal pain, (c) neurological complications (e.g., altered mental status, severe headaches, blindness, stroke, clonus, and persistent visual scotomata), (d) hematological complications (thrombocytopenia (platelet count <150 000/μL), disseminated intravascular coagulation, hemolysis), and (e) uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery (UA) Doppler waveform analysis or stillbirth).

ISSHP does not classify preeclampsia as mild or severe, as preeclampsia can deteriorate rapidly even without warning. American College of Obstetrician & Gynecologist (ACOG) recommends recognizing it as preeclampsia with or without severe features [13].

2.5 Risk Factors for Preeclampsia

The risk factors for preeclampsia can be categorized as major and minor risk factors and they are as follows [14]. Major risk factors include (a) prior preeclampsia, (b) chronic hypertension, (c) chronic kidney disease, (d) antiphospholipid syndrome, (e) pre-gestational diabetes mellitus and (f) maternal body mass index >30 kg/m^2. Minor risk factors include (a) primiparity, (b) pregnancy interval of more than 10 years, (c) advanced maternal age (d) connective tissue disorders and (e) family history of preeclampsia.

2.6 Prediction and Prevention of Preeclampsia

In a pregnant woman, it is often difficult to predict properly who will develop preeclampsia. However, presence of risk factors (e.g., hypertension), and uterine artery Doppler can select women who may benefit from prophylactic doses 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 [7]. Pregnant women should be advised to exercise at least 3 days per week for an average 50 minutes using a combination of aerobic, muscle

strengthening, and flexibility exercise; this might benefit by reduced incidence of hypertensive disorders in pregnancy [15]. 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 over low-dose aspirin even in women at high risk for preeclampsia [16].

3. MANAGEMENT OF PREECLAMPSIA

3.1 Antenatal

It is recommended that if BP is found consistently at or >140/90 mmHg then it needs to be treated aiming for a target BP of 110-140/85 mmHg [7]. Antihypertensive drugs should be reduced or stopped if diastolic BP falls <80 mm Hg. Antihypertensive drugs are the same as those used for chronic hypertension in pregnancy. However, $MgSO_4$ for convulsion prophylaxis should be used in women with preeclampsia, who have proteinuria with severe hypertension, or hypertension with neurological signs or symptoms.

Monitoring in preeclampsia should include BP checking, repeated urine testing for proteinuria if not present, clinical assessment (including clonus), and blood tests for Hb, platelet count, liver transaminases, creatinine and uric acid. Blood tests should be done at least twice weekly (and again when required e.g., in response to a change in clinical status) in most women with preeclampsia [7]. Fetal monitoring should include assessment of fetal biometry along with amniotic fluid volume and UA Doppler waveform analysis. These should be performed at first diagnosis and thereafter at 2 weekly intervals if the initial assessment is normal but more frequently in the presence of fetal growth restriction. The ACOG and Royal College of Obstetricians and Gynecologists (RCOG) recognize that the risk of perinatal morbidity and mortality increases once the estimated fetal weight or the abdominal circumference $<10^{th}$ centile [13,17]. There is a controversy among various guidelines in recognizing the use of amniotic fluid as a diagnostic tool in fetuses with intrauterine growth restriction. As for example, ACOG considers amniotic fluid an important diagnostic and prognostic parameter in fetuses with intrauterine growth restriction, whereas RCOG considers that amniotic fluid assessment has minimal role in diagnosing intrauterine growth restriction [13,17]. Both the guidelines recognize that UA Doppler is not a reliable screening method for fetal growth restriction but is a useful assessment tool once fetal growth restriction is diagnosed.

For fetal lung maturation corticosteroids should be given between 24^{+0} and 34^{+0} weeks of gestation which can be extended until 38^{+0} weeks in cases of elective delivery by caesarean section; however, multiple steroid courses are not recommended. For fetal neuroprotection $MgSO_4$ should be administered before 32 weeks of gestation [18].

It has been well recognized that an estimated fetal weight <third centile and UA Doppler abnormality significantly increase the risk of adverse perinatal outcome. If the UA Doppler shows increased resistance (pulsatility index >95th centile) the sonographic monitoring should be increased to weekly intervals or more frequently. Guidelines recommend that if there is absent end-diastolic flow in the UA before 34 weeks of gestation, daily cardiotocograph (CTG) monitoring, twice weekly UA Doppler, and amniotic fluid volume monitoring should be done [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 is recommended. Earlier delivery may be indicated by a deterioration of sonographic variables. In cases of absent end-diastolic flow, delivery should be considered by 34-weeks of 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. Mode of delivery should be on an individual basis; however, caesarean section is likely when there is absent or reversed end-diastolic flow or in cases of very preterm gestation.

Women with preeclampsia should be delivered if they have reached 37 weeks of gestation or they develop any of the following: (a) repeated episodes of severe hypertension despite treatment with 3 classes of antihypertensive agents, (b) progressive thrombocytopenia, (c) progressively abnormal renal or liver enzyme tests, (d) pulmonary edema, (e) abnormal neurological features, such as severe intractable headache, repeated visual scotomata or convulsions, and (f) placental abruption or non-reassuring fetal status. Neither the serum uric acid level nor the degree of proteinuria should be used as an indication for delivery [7].

3.2 Intrapartum

Patients with preeclampsia should receive antihypertensives to treat hypertension at the start of labor. If BP rises ≥160/110 mmHg, it should be treated urgently with oral nifedipine or either intravenous labetalol or hydralazine. Total fluid intake should be restricted to 60 to 80 mL/h to avoid risks of pulmonary edema. It should be noted that, there is no justification to "run dry" a preeclamptic woman as they are already at risk of AKI.

3.3 Postpartum

BP should be monitored 4 to 6 hourly for at least 3 days postpartum. If there is any laboratory test abnormality before delivery, those tests (e.g., Hb, platelets, creatinine, liver enzymes) should be done the day after delivery and then every alternate day until stable. Antihypertensive drugs should be restarted after delivery and dose adjusted slowly downwards only after 3 to 6 days postpartum unless BP becomes low (<110/70 mmHg). A considerable number of women can be discharged by day 5 postpartum, if they are able to monitor their BP at home. Nephrotoxic drugs like NSAIDs should be avoided in women with preeclampsia, especially in the setting of AKI and other alternative drugs should be used.

3.4 HELLP Syndrome

This is an important and significant complication of preeclampsia occurring in 25% cases. The abbreviation HELLP syndrome comprises "H" for haemolysis, "EL" for elevated liver enzymes and "LP" for low platelet. This syndrome is a distinct form of severe preeclampsia where hypertension is less marked, but liver and coagulation systems are involved, and it may progress to liver failure and severe hemorrhage. If HELLP syndrome is suspected, some investigations need to be done e.g., a full blood count (specially to see the platelet levels), liver enzymes, serum creatinine, electrolytes and coagulation profiles. Often fibrin degradation products (FDP) and D-dimers are raised. D-dimer is a more sensitive indicator of sub-clinical coagulopathy because it can be positive before other coagulation profiles are abnormal. A positive D-dimer test in preeclampsia has been reported by a researcher to be a predictor of HELLP syndrome [19]. However, another study showed that accuracy of this test to predict development of HELLP syndrome or severe preeclampsia was too low to recommend its use routinely [20]. A patient with HELLP syndrome may develop DIC with severe bleeding manifestations.

HELLP syndrome needs urgent treatment and the most effective one is prompt delivery. The DIC is treated with fresh frozen plasma if there is a bleeding manifestation to replace the coagulation factors; the anemia may require red cell transfusion. In mild cases of HELLP syndrome corticosteroids and antihypertensives may be sufficient.

3.5 Eclampsia

The term eclampsia is used when a patient with preexisting preeclampsia develops convulsions; however, it may appear unanticipated and abruptly in a patient with minimally elevated BP and without proteinuria. The exact etiology is unknown but cerebral ischaemia and oedema has been suggested in the pathogenesis of eclampsia. The timing of an eclamptic convulsion can be antepartum (53%), intrapartum (19%), or postpartum (28%) [21].

Eclampsia is an obstetrical emergency. Convulsion should be treated immediately. Cochrane review showed that in women with eclampsia, magnesium sulphate had better results than traditionally used drugs like diazepam, phenytoin and lytic cocktail in preventing recurrence of convulsion and maternal death [22-24]. Severe hypertension must be controlled after treating convulsion. The objective is to maintain systolic BP 140-160 mmHg and diastolic BP 90-100 mmHg [7]. Labetalol or hydralazine can be administered intravenously. Labetalol can be given bolus or infusion form. Labetalol should be avoided in women with asthma, or congestive cardiac failure. Diuretics are used if there is pulmonary edema. Accordingly, patient's neurological status including signs of raised intracranial pressure (eg., fundoscopic examination) should be monitored regularly. The patient with eclampsia also needs continuous monitoring for fluid intake and urine output, respiratory rate, oxygenation and fetal wellbeing. Prompt delivery is the treatment for eclampsia which is to be undertaken once the patient is stabilized.

4. PREECLAMPSIA SUPERIMPOSED ON CHRONIC HYPERTENSION

Preeclampsia superimposed on chronic hypertension is characterized by new-onset

proteinuria or a sudden increase in the protein level if proteinuria is already present, a sudden increase in the level of BP, or development of the HELLP syndrome [25]. Fetal growth restriction is sometimes associated with chronic hypertension, but this is not a diagnostic criterion for preeclampsia. About 25% of women with chronic hypertension develop superimposed preeclampsia. This rate might be higher in women with kidney disease. However, the incidence of development of preeclampsia in hypertension can be reduced by using prophylactic low dose aspirin. Cochrane review revealed that the use of low dose aspirin is associated with a considerable (17%) reduction in developing preeclampsia [26].

Once the diagnosis of superimposed preeclampsia on chronic hypertension is made, the treatment is like that of preeclampsia as discussed previously. Magnesium sulphate is used in patients with severe features to prevent seizure. Delivery is 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 on chronic hypertension should be counseled about future pregnancies because of the chances of recurrence. In nulliparous women with preeclampsia before 30 weeks of gestation, the recurrence rate for the disorder is as high as 40% and for multiparous women even more in future pregnancies [3].

5. CONCLUSION

High BP and the related disorder in pregnancy remains a threat for women and their fetus. To reduce the maternal-fetal morbidity and mortality, optimum management includes adequate prenatal care, identification of the serious features and treating promptly as well as close monitoring and follow-up. In women with hypertensive disorders of pregnancy, lifestyle modifications may reduce their risk for cardiovascular disease. Ongoing researches in these fields are promising and further advancements will hopefully provide more clarity to prediction, prevention and management of hypertensive disorders of pregnancy and its deleterious effects.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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