Mini-Review

Hypertension in Pregnancy

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Abstract

Hypertension is commonly encountered in the course of pregnancy. It can predate or manifest during pregnancy. It requires prompt recognition and treatment. If left untreated, hypertension in pregnancy will lead to significant maternal and fetal morbidity and mortality. This mini-review will discuss the classification of hypertension in pregnancy, identify treatment goals, discuss preeclampsia in some detail and discuss management of these disorders based on recent guidelines. This review is intended as a quick summary and a practical guide. Extensive reviews of the subject are widely available.

Keywords: Hypertension; Pregnancy; Preeclampsia

1. Classification

Hypertension in pregnancy is divided into three categories [1]:

1. Chronic hypertension is diagnosed prior to pregnancy or before 20 weeks of gestation.
2. Gestational hypertension arises after 20 weeks of gestation.
3. Preeclampsia is diagnosed after 20 weeks of gestation and can be superimposed on chronic hypertension. About 25% of women with chronic hypertension develop preeclampsia.

2. Definition

Hypertension in pregnancy is defined as systolic BP ≥ 140 and/or diastolic BP ≥ 90. It affects 10%-15% of pregnancies [2]. Blood pressure is preferably measured using automated devices. If Aneroid devices are used, they should be regularly calibrated. Abnormal readings should be confirmed by repeat measurements. These issues are detailed in American College of Cardiology/American Heart Association hypertension

guidelines [3]. Ideally hypertension is confirmed with 24 h ambulatory blood pressure monitoring or home monitoring. The vast majority of pregnant women have essential hypertension. Clinicians should always be vigilant to the presence of secondary hypertension because failure to recognize secondary forms of hypertension may lead to serious complications [2].

3. Treatment Goals

The International Society for the Study of Hypertension in Pregnancy (ISSHP) guidelines [1] state that antihypertensives are indicated in all of the above-mentioned three categories to maintain BP in the range of 110-140/80-85.Treatment is initiated for BP ≥ 140/90 while urgent treatment and hospitalization are indicated for BP ≥ 160/110. In contrast, The American College of Obstetrician and Gynecologists Practice Bulletin [4] recommends initiating treatment for BP ≥160/110 in the absence of evidence of end organ damage.

4. Preeclampsia

Preeclampsia affects 2%-8% of pregnancies globally and is the cause of 10% to 15% of maternal death [4]. It is also associated with increased maternal morbidity. Preeclampsia may result in perinatal morbidity and mortality due to intrauterine growth restriction (IUGR), preterm birth and oligohydramnios. Preeclampsia is due to abnormal placental implantation with subsequent increase in anti-angiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1) and decrease in angiogenic factors such as placental growth factor (PIGF) [5, 6]. Risk factors for preeclampsia include [7]: nulliparity, history of chronic kidney disease, hypertension, previous episodes of preeclampsia, obesity, gestational diabetes and multiple gestation pregnancy. Preeclampsia is diagnosed after 20 weeks of gestation. Onset can be intrapartum and postpartum as well. The diagnosis is established when hypertension (defined as systolic BP ≥ 140 and/or diastolic BP ≥ 90 on two occasions at least 4 hours apart) is associated with proteinuria (≥ 300 mg/24 h or random urine protein/creatinine ratio ≥ 0.3) [1]. In order to establish a timely diagnosis, BP measurement and urine dipstick for protein are recommended at each prenatal visit.

If the patient does not have proteinuria, a new onset of one of the following severe features is needed [1, 4]:

1. Acute kidney injury (creatinine > 1.1 mg/dl or doubling of serum creatinine)
2. Elevated liver enzymes to two times the upper limit of normal
3. Epigastric or right upper quadrant pain
4. Thrombocytopenia (platelet count < 100,000 x 10^9/L)
5. Neurological complications including visual disturbances and severe headache
6. Pulmonary edema

Severe preeclampsia is defined as systolic BP ≥ 160 and/or diastolic BP ≥ 110 (severe BP elevation) in addition to one of the aforementioned six manifestations. In severe preeclampsia BP elevation should be confirmed within minutes (rather than 4 hours) for prompt initiation of antihypertensive therapy [1]. A 24 h urine collection for creatinine clearance is required to evaluate kidney function in pregnancy. Equations for estimation of glomerular filtration rate (eGFR) such as MDRD and CKD-EPI formulae cannot be utilized as they underestimate GFR in pregnant women [8].

4.1 Eclampsia

Eclampsia (preeclampsia + seizures) is a severe complication of preeclampsia. The patient develops a new-onset tonic-clonic, multifocal or focal seizures. It

carries significant morbidity and mortality. It complicates about 0.1% of all pregnancies [9].

4.2 Differential diagnosis of preeclampsia

A diagnostic renal biopsy is not recommended to establish

1. HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets) is a severe form of preeclampsia characterized by right upper quadrant abdominal pain and elevated lactate dehydrogenase (LDH) > 600 IU/L. It is associated with significant morbidity and mortality [10]. Prompt delivery is indicated.
2. Acute fatty liver of pregnancy (AFLP) is a rare condition. It presents with vomiting, hypoglycemia, lactic acidosis, increased INR and elevated liver enzymes [11]. It can progress to acute kidney injury and disseminated intravascular coagulation (DIC). As in HELLP syndrome prompt delivery is indicated. AFLP is attributed to abnormal fatty acids beta-oxidation in fetal mitochondria.
3. Thrombotic Microangiopathies (TTP/HUS) are associated with high morbidity and mortality. Acute kidney injury, hemolysis and thrombocytopenia are prominent [12]. Pregnancy can trigger TTP in a patient with ADAMTS-13 deficiency and can also be a trigger for acquired HUS by activating the alternative complement pathway [13, 14]. A diagnostic renal biopsy is not recommended to establish the diagnosis of preeclampsia, HELLP syndrome, AFLP or TTP/HUS during pregnancy. Measurement of sFlt-1 and PIGF in urine or plasma may help in differentiating preeclampsia from other disorders with hypertension and proteinuria. This testing is not available commercially in the USA. PROGNOSIS study showed that a low sFlt1/PIGF ratio (≤ 38) in women with preeclampsia features was highly sensitive in ruling out the diagnosis [15].

4.3 Prevention of preeclampsia

A randomized controlled trial in women with singleton pregnancies and high risk for preeclampsia showed that aspirin had resulted in a lower incidence of preterm preeclampsia compared to placebo. Aspirin dose was 150 mg daily starting at week 11-14 of gestation until week 36 [16]. Calcium carbonate is unlikely to have a role in prevention of preeclampsia especially in women with adequate calcium intake [17].

4.4 Management of preeclampsia

BP should be controlled (see below). Bedrest is recommended. Delivery if feasible is the definitive management. Women with gestational age of 37 weeks or greater should be delivered. Initial evaluation should include a complete blood count, serum creatinine, LDH, AST, ALT, uric acid, and urinary testing for proteinuria (preferably a 24 h urine collection). A detailed fetal and maternal evaluation is paramount [1, 4]. Observation may be appropriate for women with preterm fetuses without the severe features mentioned above. In case of observation (expectant management), evaluation of fetal growth with serial ultrasounds is indicated. Laboratory testing is done at least weekly along with close BP monitoring. Abnormal fetal testing and persistently uncontrolled severe hypertension defined as systolic BP ≥ 160 and/or diastolic BP ≥ 110 are contraindications to expectant management [1, 4]. Magnesium sulfate is the drug of choice for seizure prevention and is more effective than phenytoin or diazepam. It reduces the incidence of seizures by over 50% [18, 19]. There are multiple regimens. One such regimen includes a loading dose of 6 g IV over 15-20 minutes followed by a continuous infusion at 2 g per hour. The therapeutic

range is not well defined; however, a range of 4.8-8.4 mg/dl is reasonable [20]. Magnesium sulfate is contraindicated in patients with myasthenia gravis. Magnesium toxicity is rare except in women with chronic kidney disease or acute kidney injury. Management includes IV calcium, discontinuation of magnesium sulfate and intravenous normal saline to facilitate magnesium excretion. Loop diuretics may be utilized as well. Hemodialysis is indicated in severe cases [19].

4.5 Outcome of preeclampsia

Proteinuria and hypertension improve after delivery in 80% of women and resolve completely after 12 weeks. In 20% of women hypertension persists. In mild preeclampsia the risk of chronic hypertension increases by more than threefold, while it increases by more than sixfold in severe preeclampsia [21, 22].

5. Drug Management of Hypertension in Pregnancy

Aggressive BP lowering in not indicated in pregnancy as it impairs fetal growth and result in placental ischemia [4]. In patients with preeclampsia BP should be monitored every 4-6 hours for the first 3 days postpartum. Oral agents (Table 1) should be started first. If adequate control is not achieved, the patient should be hospitalized for administration of intravenous agents (Table 2). Labetalol and extended-release nifedipine are first line agents as they are safe and effective [1, 4, 23]. Methyldopa and hydralazine may be utilized, but are associated with more frequent adverse reactions. Atenolol should be avoided because a study in 33 pregnant women showed that atenolol was associated with IUGR [24]. Beta-Blockers other than labetalol are less well investigated. If labetalol cannot be used metoprolol, propranolol, pindolol and acebutolol may be considered. Extended-release nifedipine is the most widely used calcium channel blocker. Amlodipine has been used, but the data are limited [25]. If an intravenous agent is required labetalol and nicardipine are good choices. Hydralazine is less desirable because of increased risk of maternal hypotension and maternal oliguria. Nitroprusside should be avoided due to the risk of fetal cyanide toxicity if used for more than 4 hours [26]. Diuretics should not be used in preeclampsia because extracellular volume contraction is undesirable. They may be continued in gestational hypertension if the patient had been taking them prior to pregnancy [27]. Inhibitors of the renin-angiotensin-aldosterone system (RAAS) are absolutely contraindicated. This includes angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and direct renin inhibitors. The package insert of these agents comes with a black box warning [28] stating that usage during the second and third trimesters can cause injury and death to the developing fetus; therefore, discontinuation is indicated as soon as pregnancy is detected. RAAS inhibitors use in the second and third trimesters is associated with renal agenesis, pulmonary hypoplasia and IUGR. The evidence of fetal injury during first trimester exposure is unclear. Post-delivery lactating mothers may use enalapril, captopril or quinapril because they have low concentration in breast milk. Labetalol may be continued in lactating mothers. Diuretics may decrease milk production [29]. Spironolactone use in pregnancy is not recommended. It is a category C medication (animal reproductive studies have shown fetal adverse effects with inadequate human studies). Spironolactone carries a possible risk of feminization of male fetuses [30]. The Control of Hypertension in Pregnancy Study (CHIPS) [31] examined the effect of tight versus less-tight BP control on pregnancy complications. It enrolled approximately

1000 pregnant women with office diastolic BP of 90-105 mmHg. Less-tight control target was 100 mmHg while the control target was 85 mmHg. The study concluded that there was no difference between the two targets with regard to pregnancy complications including maternal complication, preeclampsia, loss of pregnancy or high-level neonatal care. Severe maternal hypertension (≥ 160/110) was more frequent in the less-tight control group. Tight control was not associated with major fetal or neonatal risks.

Antihypertensive	Dosage	Potential Adverse Reactions
Methyldopa	250-750 mg twice a day	Sedation, headache, hepatic impairment, hemolytic anemia
Labetalol	200-600 mg twice a day	Fatigue, bradycardia, do not use in patients with asthma
Extended-release nifedipine	30-90 mg once daily	Peripheral edema, headache, dizziness, flushing
Hydralazine	10-100 mg two to three times daily	Palpitations, tachycardia, diarrhea, headache

Table 1: Oral Antihypertensives in Pregnancy.

Antihypertensive	Dosage	Potential Adverse reactions	Onset of action
Labetalol	10-20 mg IV bolus followed by infusion at 1-2 mg/min	Avoid in patients with asthma or acute congestive heart failure	1-2 minutes
Nicardipine	Infuse at 2.5-5 mg/h, maximum dose: 15 mg/h	Edema, tachycardia, headache	1-2 minutes
Hydralazine	5-10 mg every 2-4 h, switch to PO ASAP	Headache, tachycardia, hypotension	10-20 minutes

Table 2: Intravenous Antihypertensives in Pregnancy.

6. Secondary Causes of Hypertension in Pregnancy

Secondary hypertension should be diagnosed and treated prior to pregnancy. Clues to a secondary cause of hypertension include absence of family history of hypertension, hypokalemia, chest pain, pallor, palpitations, early onset of hypertension (< 30 years), resistant and severe hypertension [2].

6.1 Pheochromocytoma

Pheochromocytoma is a very rare cause of hypertension during pregnancy and is associated with high morbidity and mortality [32, 33]. The diagnosis is usually made during the second and third trimesters. Labor should be avoided by performing a Cesarean section. If left undiagnosed labor and spinal anesthesia can precipitate a severe hypertensive crisis.

6.2 Primary hyperaldosteronism

The diagnosis is suspected when hypokalemia complicates hypertension in pregnancy [33]. Most women have adrenal adenomas. Hypokalemia is not expected in pregnancy in absence of hyperemesis. Potassium should be supplemented. Hypertension is treated with one of the above-mentioned agents. As stated, spironolactone is not recommended in pregnancy. Definitive surgical management is done post-delivery.

6.3 Renovascular hypertension

Fibromuscular dysplasia is the most common form of renal artery stenosis in pregnancy [34, 35]. The diagnosis is made with renal arterial doppler ultrasound. Endovascular management is usually delayed until delivery.

7. Conclusion

- Hypertension in pregnancy may lead to significant maternal and fetal morbidity and mortality.
- It is critical to recognize hypertension early and to initiate treatment in a timely manner.
- Many excellent guidelines exist and are helpful in navigating multiple clinical scenarios.
- Several safe antihypertensive medications exist.
- Understanding of the pathophysiology of preeclampsia has greatly improved over the past decade and may lead to more specific diagnostic testing and treatment.
- Aspirin is useful in women with high risk for preeclampsia.
- Delivery is the treatment of choice for preeclampsia.
- Magnesium sulfate is the preferred agent for seizure prevention in preeclampsia.
- Secondary hypertension should be considered in the appropriate clinical setting.

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