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The Management of Hypertension in Pregnancy

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Abstract

Hypertensive pregnancy disorders complicate 6–8% of pregnancies and cause significant maternal and fetal morbidity and mortality. The goal of treatment is to prevent significant cerebrovascular and cardiovascular events in the mother, without compromising fetal well-being. Current guidelines differentiate between the treatment of women with acute hypertensive syndromes of pregnancy and women with preexisting chronic hypertension in pregnancy. This review will address the management of hypertension in pregnancy, review the various pharmacologic therapies, and discuss the future directions in this field.

Keywords

hypertension; anti-hypertensive agents; preeclampsia; pregnancy; gestational hypertension

Introduction

Hypertensive pregnancy disorders cover a spectrum of conditions, including preeclampsia/eclampsia, gestational hypertension, chronic hypertension, and preeclampsia superimposed on chronic hypertension (Table 1). According to the National High Blood Pressure Education Program (NHBPEP) Working Group Report on High Blood Pressure (BP) in Pregnancy, hypertension occurs in 6–8% of pregnancies in the United States. [1] Hypertensive pregnancy disorders represent the most significant complications of pregnancy and contribute significantly to maternal and perinatal morbidity and mortality. [2] Most of the current recommendations for the treatment of these disorders are based on expert opinion and observational studies, with a lack of evidence from randomized controlled trials. The overall strategy in the treatment of hypertension in pregnancy is to prevent maternal cerebrovascular and cardiac complications, while preserving the uteroplacental and fetal circulation and limiting medication toxicity to the fetus.

Treatment strategies fall into two general categories – the management of acute hypertensive syndromes of pregnancy, such as preeclampsia/eclampsia, and the management of chronic hypertension. While the definitive treatment for acute hypertensive syndromes of pregnancy is delivery, expectant management with close observation may be appropriate in carefully selected patients, especially before 32 weeks gestation. Women with chronic hypertension should ideally be evaluated prior to pregnancy, with a focus on the presence of end-organ damage, evidence of secondary causes of hypertension (such as renal artery stenosis due to fibromuscular dysplasia, primary hyperaldosteronism and pheochromocytoma), medication adjustments, and counseling regarding the risks of preeclampsia and adverse fetal events.

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Women with hypertensive pregnancy disorders should have a comprehensive plan of care, which includes prenatal counseling, frequent visits during pregnancy, timely delivery, appropriate intrapartum monitoring and care, and postpartum follow up. Care of these patients involves counseling at every step of the pregnancy to ensure that the woman is aware of the risks to her and her fetus such that she can make informed decisions.

Blood Pressure Measurement

Hypertension in pregnancy is defined as a systolic BP ≥ 140 mm Hg and a diastolic BP ≥ 90 mm Hg on two separate measurements at least 4–6 hours apart. However, the diagnosis of hypertension, in pregnancy or otherwise, requires first and foremost an accurate measurement of BP. Many automated BP cuffs have not been tested during pregnancy, and therefore obtaining a manual BP is the preferred technique. The 2000 NHBPEP Working Group Report on High BP in Pregnancy recommends that the Korotkoff phase V (disappearance) sound be used to determine the diastolic BP.[1] In the outpatient setting, proper BP technique is essential and includes the subject being in a seated position, legs uncrossed, back supported, and no tobacco or caffeine for 30 minutes prior. In recumbent, hospitalized patients, the provider should measure the BP in the left lateral decubitus position to minimize the BP change caused by the compression of the inferior vena cava by the gravid uterus.

Blood pressure measurements should be interpreted in the context of the stage of pregnancy and the expected changes in blood pressure for each trimester. BP drops during the first and second trimesters, nadirs at around 20 weeks of gestation, and returns to preconception levels by the third trimester. Women who have not had regular medical care prior to pregnancy may be labeled as 'gestational hypertension' based on elevated BPs in the third trimester, when in reality, they were hypertensive prior to pregnancy, which was masked by the physiologic changes during mid-pregnancy. If a woman has gestational hypertension that does not resolve after delivery, she will subsequently be diagnosed as having chronic hypertension.

Ambulatory blood pressure monitoring (ABPM) and the hyperbaric index (HBI) have been suggested as alternative methods for diagnosing elevated blood pressure in pregnancy.[3] The HBI is defined as the amount of BP excess during a given time period above a 90% tolerance limit, with units of mm Hg X hours. One promising study suggested that HBI calculated from a 48-hour ABPM performed in the first trimester had a 93% sensitivity and 100% specificity for predicting preeclampsia,[4] although other researchers have not been able to replicate this high degree of accuracy and reliability. [5,6] There is currently no official role of ABPM in the diagnosis of hypertensive pregnancy disorders. [7] Home monitoring of blood pressure by automated cuffs in pregnancy has not been validated and some monitors have been shown to inaccurate in pregnancy and, therefore, in-office, manual BPs remain the gold-standard for the diagnosis and monitoring of hypertension in pregnancy. [8,9] This may involve frequent outpatient visits, especially in those with severe hypertension.

Blood Pressure Management in Pregnancy

Hypertension in Preeclamptic Patients

The NHBPEP Working Group Report on High BP in Pregnancy and the American College of Obstetrics and Gynecology (ACOG) guidelines recommend treatment in preeclampsia when the diastolic BP (DBP) is persistently above 105–110 mm Hg, [1] but there is no official recommendation regarding a systolic BP threshold for treatment. Most experts agree that pharmacologic therapy should be initiated when the BP approaches 150/100 mm Hg, [10] with the goal of preventing cerebral and cardiovascular events in the mother. If a woman has mild

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preeclampsia (DBP<100 mm Hg) with normal laboratory tests, other than low-level proteinuria, management as an outpatient can be appropriate, provided that there are frequent outpatient visits and that fetal nonstress testing (NST) is favorable. The frequency of formal ultrasound testing depends on the clinical condition and is at the discretion of an obstetrician. In the setting of severe preeclampsia that is being managed expectantly in the hospital, daily ultrasounds for fetal well-being may be indicated.

While treatment of hypertension may improve the risk profile of the mother, and therefore delay delivery, it does not cure preeclampsia, nor does it delay the progression to preeclampsia. [11] The diagnosis of severe preeclampsia includes greater than 1 of the following criteria – severe hypertension (defined as DBP>100 mm Hg), proteinuria > 5 g/24 hours or > 3+ on 2 random urine samples 4 hours apart, oliguria, cerebral or visual disturbances, pulmonary edema, epigastric or right upper quadrant pain, impaired liver function, thrombocytopenia or fetal growth restriction. The only definitive therapy for preeclampsia is delivery. When urgent control of BP is necessary, or when delivery is expected within the next 48 hours, intravenous agents, such as labetalol or hydralazine, are the drugs of choice. Oral agents may be considered if delivery is not imminent, and the choices of medications will be discussed further below.

Eclampsia may occur in the absence of gestational hypertension or preeclampsia in up to 20% of cases.[12] Magnesium sulfate has been shown to decrease the risk of eclampsia and maternal death without evidence of significant harm to the mother or baby.[13] Therefore, intravenous magnesium sulfate should be administered for seizure prophylaxis both during delivery and for 24 hours after delivery. The rate of continuous infusion, but not the loading dose, should be decreased for women with renal failure (as magnesium is renally excreted), and serum magnesium should be checked every 1–2 hours, as compared to women with normal renal function, for whom the level can be checked every 4–6 hours.

Timing of Delivery

The decision regarding the timing of delivery should be made after a careful assessment of the risks to the fetus and the mother. In appropriately selected patients, especially those before 32 weeks gestation, delivery can be postponed to allow for fetal maturation, particularly of the respiratory system. Women with mild preeclampsia, i. e., those with a diastolic BP < 100 mm Hg, without evidence of cerebral involvement, hemolysis with elevated liver enzymes and low platelets (HELLP) syndrome, or significant proteinuria (> 1 g/24 hours), may be candidates for this approach.

In women with severe preeclampsia before 34 weeks gestation, the timing of delivery is more complicated. In an interventional trial of 38 women with severe preeclampsia between 28–34 weeks gestation who were randomized to either aggressive therapy (betamethasone and delivery 48 hours later) or expectant management (betamethasone, and delivery only for prespecified indications, including low urine output, thrombocytopenia, abnormal liver function tests, imminent eclampsia, pulmonary edema or severe hypertension despite therapy), there was no difference in the maternal complications between the two groups. There was advanced gestational age at delivery (an addition of 7.1 vs. 1.3 days, $p<0.05$), with fewer neonatal complications in the expectant management group (33% vs. 75%, $p<0.05$).[14]. Another larger trial of 95 women with severe preeclampsia between 28–32 weeks gestation, randomized to aggressive versus expectant management, also showed advanced gestational age at delivery in the expectant group, with fewer visits to the neonatal intensive care unit and fewer episodes of respiratory distress in the infants.[15] However, this study excluded women with underlying medical disease or obstetrical complications. A meta-analysis published in 2002 evaluating expectant versus interventional strategies in the management of women with early onset severe preeclampsia found insufficient evidence to

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recommend one approach over the other. [16] One approach that has been suggested by the Society for Maternal-Fetal Medicine is to admit women with early (< 34 weeks gestation), severe preeclampsia for observation and corticosteroid administration if delivery is not imminent, followed by daily laboratory tests, including liver and renal function tests, daily fetal assessments by ultrasound, and delivery at 34 weeks or earlier if any of the following develop – severe hypertension despite therapy, HELLP syndrome, pulmonary edema, eclampsia, severe renal dysfunction, disseminated intravascular coagulation, placental abruption, fetal growth restriction, oligohydramnios or abnormal fetal stress testing.[17] In cases of severe hypertension (BP > 160/110 mm Hg), a trial of anti-hypertensive therapy may be undertaken, but if the BP is not reduced within 24–48 hours, delivery should be strongly considered. Given the complexity of such cases, including the risks to both mother and fetus, the decision must be made on an individual basis after thoughtful discussion with the mother. A nephrology consultation should be considered, especially in the management of severe preeclampsia, hypertension, and medication choices. In addition, a nephrologist can follow proteinuria levels and help risk-stratify patients into those who need closer follow-up for monitoring of renal disease in the post-partum setting.

If a woman is at greater than 34 weeks gestation and develops severe preeclampsia, delivery is still the treatment of choice, while expectant management may be reasonable in those with mild preeclampsia. At greater than 36–37 weeks gestation, induction of labor should pursued. Recent evidence for this approach comes from the Hypertension and Preeclampsia Intervention Trial at Term (HYPITAT) trial published in 2009 that compared the induction of labor versus expectant monitoring for gestational hypertension or mild preeclampsia after 36 weeks gestation. The HYPITAT trial was a multicenter randomized-controlled trial that included 756 women with a singleton pregnancy at 36–41 weeks, with mild gestational hypertension or mild preeclampsia. [18] The subjects were randomized to either expectant monitoring or induction of labor, with the primary outcomes being progression to severe disease, HELLP syndrome, eclampsia, pulmonary edema, placental abruption, postpartum hemorrhage, thromboembolic disease or death. There were no maternal or neonatal deaths and no cases of eclampsia or placental abruption in either group. The women randomized to the induction group had a relative risk reduction of 0.71 (95% CI 0.59–0.86) for the primary outcome, mainly due to a difference in the rate of progression to severe disease. The study was not powered to compare differences in primary outcomes between those with preeclampsia versus gestational hypertension. However, it does support the induction of labor in preeclamptic pregnancies beyond 36 weeks gestation.

Chronic Hypertension in Pregnancy

Data from the National Health and Nutrition Examination Survey (1999–2008), indicates that the prevalence of hypertension in women aged 20–44 years is 7.7%, and an estimated 4.9% of women use anti-hypertensive pharmacologic therapy, [19] with the two most common categories of medications being diuretics (47.9%) and angiotension-converting enzyme (ACE) inhibitors (44.0%). Prenatal counseling in women with chronic hypertension is an important component of their care. The goals of the visit should be to evaluate for end-organ damage, to adjust medications as necessary, to discuss appropriate lifestyle modifications, and to consider secondary causes of hypertension. Given the teratogenic potential of ACE inhibitors (see below), women should be counseled on the importance of birth control while on ACE inhibitors, and this class of medication should be changed prior to attempting to conceive.

There is continued controversy over whether women with mild-moderate chronic hypertension on anti-hypertensive therapy prior to pregnancy should stop these medications, be kept under close observation, and only reinstitute therapy for blood pressure elevations of