

Mini Review

Approach to Hypertensive Disorders in Pregnancy

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Submitted: 20 October 2016

Accepted: 28 October 2016

Published: 05 November 2016

ISSN: 2373-9258

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OPEN ACCESS**Keywords**

- Hypertensive Disorders
- Proteinuria
- Maternal age

Abstract

Hypertensive disorders of pregnancy, including preeclampsia, complicate up to 10% of pregnancies worldwide, constituting one of the greatest causes of maternal and perinatal morbidity and mortality worldwide. Preeclampsia is a leading cause of maternal and perinatal morbidity mortality, with an estimated 50,000-60,000 Preeclampsia – related deaths per year worldwide. Hypertensive disorders of pregnancy are major contributors to prematurity. Preeclampsia is a risk factor for future cardiovascular disease and metabolic disease in women. Within the past 10 years substantial advances in the understanding of preeclampsia pathophysiology as well as increased efforts of obtain evidence to guide therapy have emerged. However, this information has not translated into improved clinical practice. New best practice recommendations are greatly needed to guide clinicians in the care of women with all forms of preeclampsia and hypertension that occur during pregnancy, particularly women with severe hypertension and superimposed preeclampsia. Also needed is a system for continually updating these guidelines integrating them into daily obstetric practice.

INTRODUCTION

Hypertension occurs in approximately 10% of first pregnancies and 8% of all pregnancies. Preeclampsia (PE), defined as new onset of hypertension with proteinuria after 20 weeks' gestation, is a leading cause of maternal and neonatal mortality worldwide [1]. Though maternal mortality from Preeclampsia has fallen in developed countries, it remains a common cause of preterm delivery of low birth weight babies from intrauterine growth retardation [2]. Moreover, the rate of preeclampsia is increasing, likely from increasing maternal age and more multiple births [3]. Special attention will be directed at maternal obesity, which increases the risk for hypertension during pregnancy with resultant increases in large babies and caesarean delivery [4]. At present, 0.2–4% of all pregnancies are complicated by cardiovascular diseases (CVD), [5] and the number of the patients who develop cardiac problems during pregnancy is increasing. However, knowledge of the risks associated with CVD during pregnancy and their management are of pivotal importance for advising patients before pregnancy. Therefore, guidelines on disease management in pregnancy are of great relevance. Such guidelines have to give special consideration to the fact that all measures concern not only the mother, but the fetus as well. Therefore, the optimum treatment of both must be targeted. A therapy favourable for the mother can be associated with an impairment of the child, and in extreme cases treatment measures which protect the survival of the mother can cause the death of the fetus. Counselling and management

of women of childbearing age with suspected cardiac disease should start before pregnancy occurs; they should be managed by interdisciplinary teams; high risk patients should be treated in specialized centres; and diagnostic procedures and interventions should be performed by specialists with great expertise in the individual techniques and experience in treating pregnant patients. Registries and prospective studies are urgently needed to improve the state of knowledge. Hypertension is the most common medical problem encountered in pregnancy and is a leading cause of perinatal and maternal morbidity and mortality [6]. A rise in blood pressure (BP) during the peripartum period requires evaluation and review [7].

CLASSIFICATION [8,9]**Gestational Hypertension**

Gestational hypertension, formerly known as pregnancy-induced hypertension or PIH, is the new onset of hypertension after 20 weeks of gestation. Also known as transient hypertension. The diagnosis requires that the patient have:

Elevated blood pressure (systolic \geq 140 or diastolic \geq 90 mm Hg, the latter measured using the fifth Korotkoff sound), Previously normal blood pressures, No protein in the urine, No manifestations of preeclampsia, increased incidence of up to 30% in multiple gestation, 15-25% of women initially diagnosed with gestation HTN develop preeclampsia and earlier onset of gestation HTN are more likely to progress to preeclampsia [10].

Chronic Hypertension in pregnancy

Chronic hypertension is high blood pressure that either precedes pregnancy, is diagnosed within the first 20 weeks of pregnancy, or does not resolve by the 12-week postpartum check up. Two categories of severity are recognized: mild (up to 179 mm Hg systolic and 109 mm Hg) and severe (≥ 180 systolic or 110 diastolic). Chronic hypertension complicates about 5% of all pregnancies, and prevalence rates are increasing due to delayed childbearing. Medications should be reviewed when pregnancy is first diagnosed. Chronic hypertension accounts for a disproportionate amount of maternal and perinatal morbidity and mortality, mostly because of an increased risk of superimposed preeclampsia. There is an increased risk of prematurity, birth of infants who are small for their gestational age, intrauterine death, placental abruption, and caesarean delivery.

Complication rates are directly related to the 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. About 20-25% of women with chronic hypertension develop preeclampsia during pregnancy. All hypertensive patients should undergo increased surveillance, serial laboratory tests throughout pregnancy, serial ultrasound scans to follow growth, and antenatal testing. The baby should be delivered vaginally if possible.

When a patient's blood pressure is persistently greater than 150 to 180/100 to 110 mm Hg, pharmacologic treatment is needed to prevent maternal end-organ damage. Methyldopa, labetalol, and nifedipine are oral agents commonly used to treat chronic hypertension in pregnancy. Angiotensin-converting enzyme inhibitors and angiotensin-II receptor antagonists are not used because of teratogenicity, intrauterine growth restriction (IUGR), and neonatal renal failure [11].

Preeclampsia

Preeclampsia is a multiorgan disease process of unknown etiology characterized by the development of hypertension and proteinuria after 20 weeks of gestation. There are various theories of pathogenesis of preeclampsia. The most popular theory is immunologic. During a normal pregnancy, fetal syncytial trophoblasts penetrate and remodel maternal spiral arteries, causing them to dilate into large, flaccid vessels. This remodeling accommodates the vast, increased maternal circulation needed for adequate placental perfusion. This remodeling is somehow prevented in preeclamptic pregnancies: the placenta is unable to properly burrow into the maternal blood vessels, leading to intrauterine growth restriction and other fetal manifestations of the disorder. Investigators speculate that this incomplete placentation is due to maternal immunologic intolerance of foreign fetal genes. Evidence in support of this theory is that the risk of preeclampsia is highest in a first pregnancy and decreases with the length of time a woman has lived with the father before becoming pregnant. Other theories of pathogenesis of preeclampsia are angiogenic factors (increased sFlt-1, decreased placental growth factor levels) cardiovascular maladaptation and vasoconstriction, genetic predisposition (maternal, paternal, thrombophilias) immunologic intolerance between fetoplacental and maternal tissue, platelet activation, vascular endothelial

damage or dysfunction. Development of HTN proteinuria induced by pregnancy generally in the second half of gestation. More frequent at the extremes of reproductive years. Preeclampsia may present in two forms [12].

Mild: BP- Systolic greater than 140mmHg and/or diastolic greater than 90 mmHg. Proteinuria-Greater than 300 mg on 24 hours collection of +1 on single sample.

Severe: BP-Systolic greater than 160-180 mmHg and/or diastolic greater than 110 mmHg. Proteinuria- Greater than 5g on 24 hours collection or +2 on single sample, multi system alteration.

EPIDEMIOLOGY

The etiology of preeclampsia must explain the following features, as delineated by Chesley (1985): It occurs almost exclusively during the first pregnancy; nulliparas are six to eight times more susceptible than are multiparas. Older primigravidas are more susceptible than are younger. Cardiovascular risk factors associated with increased probability of preeclampsia, as are maternal age older than 40 years, diabetes, obesity and pre-existing hypertension. The increased prevalence of chronic hypertension and other comorbid medical illnesses in women older than 35 years may explain the increased frequency of preeclampsia among older women [13]. It occurs more frequently in those with multiple fetuses, hydatidiform mole, or diabetes. The incidence increases as term approaches; it is unusual before the end of the second trimester. The features of the syndrome are hypertension, edema, proteinuria, and, when advanced, convulsions and coma. There is characteristic hepatic and renal pathology. The syndrome has a hereditary tendency; in the families of women who had preeclampsia, the syndrome developed in 25% of their daughters and granddaughters but in only 6% of their daughters-in law. It rapidly disappears when the pregnancy is terminated [14].

PATHOPHYSIOLOGY

The pathogenesis of preeclampsia is thought to be triggered by excessive maternal immune response to the developing trophoblast leading to placental oxidative stress, hypoperfusion, and hypoxia, and the subsequent release of placental factors causing widespread endothelial dysfunction in the maternal circulation. In turn, the resulting placental hypoperfusion is probably further aggravated by reduced activity of growth factors, including vascular endothelial growth factor (VEGF), placental growth factor, and transforming growth factor β 1. Antiangiogenic factors, such as soluble fms-like tyrosine kinase-1 a soluble form of the VEGF-1 receptor, and soluble endoglin, a part of the transforming growth factor β receptor, are released from apoptotic trophoblast cells and interact with and reduce the systemic and local levels of VEGF, placental growth factor, and transforming growth factor β 1 [15].

Uterine vascular changes

Trophoblastic-mediated vascular changes- decreased musculature in spiral arterioles- development of low resistance. Low pressure, high-flow system, Inadequate maternal vascular response, Endothelial damage is also noted within the vessels.

Hemostatic changes

Increased platelet (PLT) activation with increased endothelial fibronectin and decreased ant thrombin III and α -2-antiplasmin further endothelial damage is thought to promote further vasospasm.

Changes in prostanoids

During pregnancy, both prostaglandin (PGI 2) (vasodilatation and decreased PLT aggregation) and thromboxane A2 (TXA 2) (vasoconstriction and PLT aggregation) are increased with balance favored to PGI 2, In preeclampsia TXA 2 is favored

Changes in endothelium-derived factors

Decreased in nitric oxide promoting vasoconstriction [16].

DIAGNOSIS

Hypertension developing after the 20th week of gestation with proteinuria in a young nullipara is preeclampsia, particularly if she has a positive family history for the syndrome. Because patients usually have no symptoms, prenatal care is crucial to detect the signs early and thereby prevent the dangerous sequelae of the fully developed syndrome. In keeping with the list of known risk factors, women with the following features should be more closely evaluated and monitored [17].

- First pregnancy
- Previous preeclampsia
- ≥ 10 years since last baby
- Body mass index ≥ 35
- Family history of preeclampsia (mother or sister)
- Patient had low birth weight
- Diastolic BP ≥ 80 mm Hg
- Proteinuria ($\geq +$ on more than one occasion and ≥ 300 mg per 24 hours)

- Multiple pregnancy
- Underlying medical causes
- Preexisting hypertension
- Preexisting renal disease
- Preexisting diabetes
- Presence of antihypertensive phospholipid antibodies

TREATMENT

Nonpharmacologic Management

Smoking Cessation: Through 2007, 26% of mothers smoked during pregnancy and their children had more hypertension, but this was mainly ascribed to their obesity [18].

Bed Rest: In women who were hospitalized for various preterm indications, strict bed rest was said to reduce the incidence of preeclampsia and IUGR [19].

Exercise: Most studies find a protection against preeclampsia by moderate exercise [20].

Sodium: Maintenance of usual sodium intake has been recommended to avoid further reducing placental perfusion [21].

Calcium Supplements: Although once claimed to be effective for prevention of preeclampsia in high-risk populations, they are not useful for therapy. However, in an in vitro study, calcium protected endothelial activation by trophoblastic debris [22].

Pharmacologic Therapy

The indications for drug therapy for hypertension during pregnancy remain uncertain since there is no evidence that such therapy improves neonatal outcomes. As stated by the 2013 ESH/ESC guidelines (Table 2)

Risks to Mother and Fetus

Women with chronic hypertension have a 30% increased risk

Table 1: Definition and Hypertension Disorders during Pregnancy	
Elevation of blood pressure (BP) is ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic and on two occasions at least 6 hours apart.	
Types	Description
Pregnancy-induced HTN(PIH)	<p>Gestational HTN: -Mild-to-moderate HTN after 20 weeks of pregnancy sustained systolic BP at or above 140 mmHg, or a diastolic BP 90 mmHg or greater.</p> <p>Preeclampsia: Development of HTN proteinuria induced by pregnancy generally in the second half of gestation.</p> <p>Mild: BP- Systolic greater than 140mmHg and/or diastolic greater than 90 mmHg. Proteinuria-Greater than 300 mg on 24 hours collection of +1 on single sample.</p> <p>Severe: BP-Systolic greater than 160-180 mmHg and/or diastolic greater than 110 mmHg. Proteinuria- Greater than 5g on 24 hours collection or +2 on single sample, multi system alteration.</p> <p>Eclampsia: Addition of convulsions in a woman with preeclampsia.</p>
Chronic HTN preceding pregnancy	Systolic pressure is greater than or equal to 140 mmHg, diastolic pressure greater than 90 mmHg or both present before 20 th week of pregnancy or persist longer than 12- week postpartum.
Chronic HTN with superimposed PIH	<ul style="list-style-type: none"> • Superimposed preeclampsia • Superimposed eclampsia
Eclampsia	Preeclampsia with seizures that cannot be attributed to other causes. Seizures may appear 2 or more days after delivery.

for superimposed preeclampsia and placental abruption, and at least their male babies have a threefold greater risk for perinatal mortality. Hormonal changes occur during pregnancy which leads to histological changes in the aorta, increasing the susceptibility to dissection. Dissection occurs most often in the last trimester of pregnancy (50%) or the early postpartum period (33%). In all women with known aortic disease and/or an enlarged aortic root diameter, the risks of pregnancy should be discussed before conception [25]. Even without superimposed preeclampsia, women with chronic hypertension have more complicated pregnancies with more intrauterine growth retardation and perinatal mortality. For those with serum creatinine exceeding 2.0 mg/dL, a one in three chance of entering end-stage renal failure after pregnancy has been reported, so that these women should be strongly advised against pregnancy. Nonetheless, successful pregnancies have been reported in most women who conceive during chronic dialysis [26].

CONCLUSION

Hypertensive disorders of pregnancy are one of the most serious complications in pregnancy because they cause serious maternal and perinatal morbidity and mortality. Although numerous hypertensive patients have relatively good outcome, difficulty in differentiating among various hypertensive conditions, inability to predict which patients are at highest risk,

and variability in the progression of preeclampsia make these disorders the greatest challenge of clinical medicine in obstetrics

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Table 2: Oral Drugs for Treatment Of Chronic Hypertension in Pregnancy [23].

Agent	Comments
Methyldopa	Preferred on the basis of long-term follow-up studies supporting safety
B-Blockers	Reports on intrauterine growth retardation(atenlol)
Labetalol	Increasing preferred to methyldopa because of reduces side effects.
Calcium antagonists (nifedipine)	Limited data No increase in major teratogenicity with exposure
Diuretics	Not first-line agents Probably safe to reduce fluid retention other agents
ACEIs, A-II receptor blockers, direct rennin inhibitors	Contraindicated: Reported fetal toxicity and death

Table 3: Treatment of Acute Severe Hypertension in Preeclampsia [24].

Drug	Comments
Hydralazine	5mg IV bolus, then 10 mg every 20-30 minutes to a maximum of 25 mg, repeat in several hours as necessary
Labetalol	20 mg IV bolus, then 40 mg 10 minutes later, 80 mg every 10 minutes for two additional doses to a maximum of 220 mg
Nifedipine	10 mg PO, repeat every 20 minutes to a maximum of 30 mg. Caution when using nifedipine with magnesium sulphate, can see precipitous BP drop.
Sodium nitroprusside (rarely when others fail)	0.25 µg/kg/min to a maximum of 5 µg/kg/min. Fetal cyanide poisoning may occur if used for > 4 h

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Cite this article

Natraj Setty HS, Vijay Kumar, Srinivas BC, Reddy ND, Manjunath CN (2016) Approach to Hypertensive Disorders in Pregnancy. *Ann Clin Exp Hypertension* 4(2): 1039.