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Pregnancy Hypertension and Impact on the Mother and Fetus

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Abstract

Pregnancy hypertension has a negative impact on the mother and fetus, therefore, early detection and treatment are essential to avoid complications. This is a systematic review of hypertension during pregnancy that aims to estimate its impact on the mother and fetus.

Nowadays, with the increase in gestational age, the number of women and babies suffering the consequences of hypertension constantly tends to increase. Pregnancy hypertension is considered an important risk factor for adverse cardiovascular events in a woman's life. Morbidity and mortality from cardiovascular causes in women are higher in those whose pregnancies are complicated by gestational hypertension. The threshold for starting antihypertensive drugs varies for gestational hypertension and pre-existing gestational hypertension, being lower for gestational hypertension. Pre-eclampsia/ eclampsia syndrome is a severe type of gestational hypertension that is only curable by delivering the fetus. Managing hypertension during pregnancy requires collaboration between obstetricians and cardiologists.

Careful assessment and diagnosis, accurate detection of the causes of hypertension during pregnancy, and successful management to have as few consequences for the mother and fetus as possible remain challenges today.

Keywords: Pregnancy hypertension, preeclampsia, complications during pregnancy

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INTRODUCTION

Clinical presentation and prevalence of hypertension in pregnancy

Hypertension is a worldwide healthcare problem that affects approximaly 25-40% of individuals. It is an important risk factor for cardiovascular complications (i.e. stroke, cardiac insufficiency). The prevalence is higher in Africa accounting around 46% of individuals including males and females (1).

Hypertension can affect someone at any age but women of reproductive age are affected at a rate of 22%. The prevalence of hypertension depends on age, race, and BMI (2). Gestational hypertension is a complication of 5-10% of pregnant women which makes it a major cause of morbidity and mortality for the mother and fetus (3,4). Approximately 5% of pregnant women suffer from the consequences of chronic hypertension, and this number is increasing as pregnant women get older (2). Within pregnant women with chronic hypertension around 95-98% have essential hypertension and only 2% of them have secondary hypertension as the result of renal disease, vascular disease, Cushing syndrome, hyperaldosteronism, connective tissue pathologies, or pheochromocytoma. Around 20-25% of women with chronic hypertension and approximately 1/3 of patients with gestational hypertension can be complicated with preeclampsia risking simultaneously the mother and fetus. Management and treatment of hypertensive disorders of pregnancy have not changed significantly in the last 50 years. Prevention of preeclampsia or eclampsia has been unsuccessful and the risk for this condition to repeat is high. The first publishing paper submitted in 1909 for emergency treatment with Cesarean Sectio on preeclampsia is still not definitive because of postpartum eclampsia which can occur afterward. More than a century later, researchers in obstetrics and gynecology, as well as other specialties, are still very interested in hypertension disorder during pregnancy. According to various clinical studies, hypertension during pregnancy is a short and long-term risk factor for cardiovascular complications during pregnancy. Since 1927 there has been a clear relationship between toxicity from hypertensive pregnancy diseases and chronic cardiovascular diseases (5,6). Cardiovascular morbidity is higher in pregnant women who had hypertensive pregnancy diseases during their course. The manner in which the situation intricately complicates cardiovascular diseases in subsequent years is complex. Hypertension disorders during pregnancy are seen affecting the patient even 40 years after delivery and are accompanied by damage to vascular function and metabolic function, despite adequate treatment of values of blood pressure. Despite the negative effects of hypertensive pregnancy diseases on mother and fetus health, the prediction of this group of diseases has been unsuccessful. Women who have a complicated pregnancy with preeclampsia are 4 times more at risk for having hypertension afterward and 2 times more at risk for ischemic diseases of the

heart, thromoboembolia and cerebral insults in later years (7,8,9).

Physiology and definition of hypertension in pregnancy

During the normal course of pregnancy, there are important physiological changes in arterial blood pressure which lowers during pregnancy. The rise of cardiac output is simultaneously accompanied by lower peripheral vascular resistance. Systolic and diastolic blood pressure begins as early as 7 weeks of pregnancy and reaches nadir between weeks 16 and 24 (10 mmHg lower), especially at the end of the second trimester of pregnancy. After the 28th week of pregnancy, there is a gradual growth of blood pressure on the way to the state before pregnancy on an upper limit of 140/90 mmHg at the end of pregnancy. In normal pregnancies, the incidence of blood pressure more or equal to 140/90 mmHg is less than 2% on the first visit and this incidence reaches 12 – 15% on term. Blood pressure falls immediately after delivery and rises again in a continuous way after 3-6 days (10). Diagnosis of hypertension during pregnancy is based on standardized blood pressure measurements. Blood pressure should be measured on both arms and as reference is used the higher value. Sphygmomanometers with mercury are still considered the best for measuring blood pressure in a state of high output, such as pregnancy. It is not recommended to use automated machines to measure blood pressure because they tend to under-evaluate blood pressure and are not very reliable during pregnancy. Even though ambulatory monitoring of blood pressure is more accurate in diagnosing hypertension and predicting the results (11), it cannot be used routinely because of limited time. It is also recommended to measure blood pressure at home, especially for pregnant patients. The median value of all measurements at home (6-7 measurements are preferred to be done daily) is the value to be considered. Before every clinic visit, the patient should take their measurements at home. They should do this in the morning and evening, in a quiet room, after five minutes of rest, while the patient is seated with their arm and spine supported in the sitting position. There should be two measurements 1-2 minutes apart from each other. In pregnancy, hypertension is defined as blood pressure values of 140/90 mmHg or higher with a 15-minute interval between measurements. Hypertensive disorders of pregnancy are classified as mild hypertension when systolic blood pressure is 140-159 mmHg and/or diastolic blood pressure is 90-109 mmHg and severe hypertension when BP ≥ 160/110 mmHg (12). There have been some efforts over time to create a more specific classification to clarify the development of this disease during pregnancy in order to understand the causes, which are still unknown. The hypertensive disorders during pregnancy are classified as below: (12)

1. Preexisting hypertension of pregnancy: Blood pressure ≥ 140/90 mm Hg before the 20th week of pregnancy that persists up to 42 days postpartum and can be accompanied by proteinuria. The term “chronic

hypertension" is less used nowadays and "pre-existing hypertension of pregnancy" is more accurate.

2. Pregnancy hypertension (PH): Blood pressure ≥ 140/90 mm after the 20th week of pregnancy without proteinuria. Transitory pregnancy hypertension can be diagnosed in the second half of pregnancy and should be treated within 42 days postpartum. The term "PH" (pregnancy hypertension) is preferred more than the old one "Pregnancy Induced Hypertension" which is still widely used.

3. Preeclampsia: It is defined as PH with positive proteinuria, blood pressure ≥ 140/90 mmHg after the 20th week of pregnancy, and proteinuria > 300 mcg in 24 hours.

4. Pregnancy hypertension with proteinuria superimposed over preexisting hypertension of pregnancy.

5. Antenatal not classified hypertension: Blood pressure ≥ 140/90 mmHg after 20th week of pregnancy re-evaluated 42 days postpartum. This term is used when hypertension is diagnosed for the first time after the 20th week of pregnancy but remains unclear if it has existed before. Re-evaluation six weeks after delivery will help to distinguish chronic hypertension from that of pregnancy.

COMPLICATIONS DURING PREGNANCY

Maternal risks include placental abruption and disseminated intravascular coagulation (DIC), in addition to the well-known risks of hypertension. Maternal mortality in the world from pregnancy hypertension is estimated to be 12%; meanwhile in the USA it is 9%. This is the reason why the preventive task force in the USA recommended the measurement of blood pressure in every prenatal visit (13,14). Intrauterine growth restriction (25% of preeclampsia cases), prematurity (27% of preeclampsia cases), and intrauterine death (4% of preeclampsia cases) are all risks for the fetus (12). Long-term risks of pregnancy hypertension and preeclampsia include: a four times higher risk for chronic hypertension and two times higher risk for stroke and heart ischemic diseases (15). Women who develop severe hypertension are at higher risk for developing maternal unfavourable events like preeclampsia, HELLP syndrome (hemolysis, high liver enzymes, low number of palates), and hospitalization time ≥ 10 days. Additionally, they have an increased risk of developing adverse fetal events such as: perinatal deaths, neonatal intensive care for more than 48 hours, birth weight lower than the 10th percentile, and preterm delivery (16).

Laboratory and ultrasound examinations

A general laboratory examination consists of the following: complete blood count, urine analysis, liver enzymes, seric creatinine, and uric acid in serum (1). Proteinuria can detect the impact of the disease on the kidney. A dipstic test > 1+ is an indication to do a further investigation like albumin-creatinine ratio which can be measured by a single specimen of urine. The lower limit for the albumin-creatine ratio to identify proteinuria

is 30 mg/mmol. When secondary hypertension is suspected, additional tests should be performed. Hyperuricemia in pregnancy hypertension is considered a negative clue for the prognosis of the mother and fetus (16).

Echo Doppler of uterine arteries can detect pregnancies at high risk for pregnancy hypertension, preeclampsia and intrauterine growth restriction (17).

Preeclampsia and eclampsia syndrome

Preeclampsia is a specific syndrome in pregnancy characterized by hypertension, BP ≥ 140/90 mmHg, and proteinuria over 3 grams per 24 hours after the 20th week of pregnancy.

The disease in 75% of cases is developed in mild form and 25% of cases in severe form. Even though proteinuria can be a late manifestation of preeclampsia, it should highly be suspected when hypertension is accompanied by symptoms (i.e. headache, visual disturbance, abdominal pain or abnormal laboratory findings) (18). Proteinuria happens initially because of growing of glomerular permeability and later on because of its damaged function, which remains an integral part of diagnosing preeclampsia. Edema is no longer included in diagnostic criteria because it is a normal pregnancy symptom. The severe form of preeclampsia is diagnosed in cases for which BP > 160/110 mmHg, with or without signs that affect other systems or organs. Eclampsia is a severe form of preeclampsia accompanied by tonic-clonic generalized seizures (19). Other symptoms are headache, visual disturbances, confusion, and epigastric pain but in extreme cases there can be a liver failure and renal failure, disseminated intravascular coagulopathy (DIC), and damage of the brain. Maternal complications include eclamptic seizures, cerebral edema, cerebral hemorrhagic insults, and pulmonary edema as the result of capillary hyperpermeability and myocardial dysfunction. Women suffering from preeclampsia have a reduction of glomerular filtration and a reduction of blood flow in kidneys as the result of vasospasm and glomerular endothelial edema which leads often to non-functional glomeruli. Oliguria defined as less urine amount than 500 ml in 24 hours can happen from haemoconcentration and lower blood flow on kidneys. This can lead also to tubular renal necrosis and acute renal insufficiency as the result of vasospasm, tubular acute necrosis and cortical necrosis. Fetal complications include HELLP (hemolysis, coagulopathy, thrombocytopaenia, liver and spleen dysfunction, high liver enzymes) syndrome and DIC. In the world ranking preeclampsia and eclampsia are responsible for 14% of maternal deaths per year, while in the USA they cause 17.6% of maternal deaths in a year (20).

Risk factors

Women with high risk for preeclampsia include those with chronic preexisting hypertension, previous pregnancy hypertension, history of preeclampsia in a previous pregnancy, diabetes mellitus, renal disease, and autoimmune diseases (like systematic erythematosus lupus, and antiphospholipid syndrome). Women who

develop preeclampsia are 18% more likely to have the same situation in subsequent pregnancies. Women who are primigravida, in older age, have multiple pregnancies, obesity (BMI > 35 kg/m2), and women with a known familiar history of preeclampsia are at moderate risk of developing preeclampsia (21).

Pathophysiology

The mechanisms underlying preeclampsia pathogenesis are still unclear, dividing scientists and doctors. Hypertension, which is the most prevalent symptom is not the beginning of the process. This remains unclear, but many theories propose that on the basis of the process, there is vascular insufficiency of the placenta because of endothelial dysfunction, vasocontraction, and microthrombosis. Oxidative stress of syncytiotrophoblast (epithelial cover of placental villi in contact with mother's blood) is one of the explanations. When under stress, syncytiotrophoblast releases factors that include pro-inflammatory cytokines, antiangiogenetic agents, ectosomes, and fetal DNA without cells in mother blood circulation. These factors damage the endothelial function of the mother resulting in a systemic inflammatory response and causing hypertension and other symptoms of the disease (hematologic dysfunction, cardiac dysfunction, cerebral dysfunction, pulmonary dysfunction, renal dysfunction and liver dysfunction) (9). Genetics can play an important role also (22). Preeclampsia as a complication of pregnancy has been well known for a long time as a dysfunction related mainly to placental dysfunction, which is the cause of a non-normal invasion of trophoblast. Despite that proof from the previous two decades has changed the overview of preeclampsia as a condition which can be caused by cardiovascular dysfunction of the mother, maybe completely independent from the placenta. Arterial functional anomalies and cardiac anomalies are quite visible in the subclinical early stages of preeclampsia even before conception. By studying the central hemodynamic system for women, we can detect two different mechanisms of cardiovascular dysfunction which are thought to create two phenotypes of preeclampsia with completely different phenotypes: early preeclampsia and late preeclampsia (23).

Complications

Preeclampsia is a multisystem disease that is complicated in average in 3-8% of all pregnant women and almost 10% of primigravida (24). In the United States, the incidence of preeclampsia ranged from 2 to 6% in healthy pregnancies, while the range varies from 4 to 18% in developing countries (25). The risk is higher in 50% of women who have severe forms of preeclampsia before the 27th week of pregnancy. In 10% of cases, the development of preeclampsia happens in pregnancies less than 34 weeks (26). Intrauterine fetal growth restriction because of placental insufficiency is a common cause for preterm delivery (26). Preeclampsia accompanied by hemolysis, rising of liver enzymes, and low platelet is known as HELLP syndrome and is a life-threatening condition that

can be fatal if it's not diagnosed from the beginning. The worldwide incidence of mortality of HELLP syndrome is reported to be around 25% (27).

TREATMENT

Nowadays there is no sure way to prevent hypertension and there is no evidence of lifestyle changes that have an impact on hypertension reduction during pregnancy. However safe physical activity can continue with obstetrical control. Obese women (BMI >35 kg/m20) are recommended to control the gain weight at no more than 6.8 kg. Women at risk of developing pre-eclampsia should take 100-150 mg aspirin per day from the 12th to 36th week of pregnancy (12). Aspirine can reduce the risk of pre-eclampsia by 12% and the risk of premature labor by 14%.

Calcium supplements 1.5 – 2 gram per day are recommended for all patients that do not consume more than 600 mg of calcium per day. Many strategies, such as vitamin C and E intake, have no benefit and have even been shown to increase the risk of delivering low-weight infants (12). The purpose of antihypertensive medications is to prevent the progression of the disease and to contribute to full-term labor (29). For patients with severe hypertension BP>160/110 mm Hg hospitalization is needed (12). Antihypertensive medications should be started when the BP≥150/95 mmHg in patients with pre-existing persistent hypertension and when the BP>140/90 mmHg in patients with pregnancy hypertension (with or without proteinuria), in patients with pre-existing hypertension that have coexisting pregnancy hypertension and in patients with organ dysfunction and symptoms caused by hypertension. When they discover that they are pregnant, many women with chronic hypertension are already taking antihypertensive medications. Fortunately, the antihypertensive effect of the pregnancy in several cases allows the interruption of medications until the second trimester. The restart of antihypertensive therapy in pregnancy is necessary when the blood pressure increases with the ongoing pregnancy, especially after the 28th week. Most of the women with chronic hypertension have uncomplicated pregnancy for the mother but there is a risk for the fetus (growth retardation, small placenta, small for gestational age babies) (30). Some women can stop taking antihypertensive medications as a result of physiological blood pressure decrease during pregnancy. That is the reason why patients should be observed carefully before starting antihypertensive therapy during pregnancy (30,31,32).

DRUG THERAPY FOR MILD TO MODERATE CASES

Alpha-Methyldopa, beta-blockers and calcium channel blockers are the selected drugs for the treatment of hypertension during pregnancy (12, 31).

Alpha-Methyldopa

It is one of the most secure drugs during pregnancy, it is used for more than 40 years, without severe side effects for the mother or the fetus. This is an alpha2-adrenergic agonist that affects the central nervous system and peripheral nervous system. The recommended daily dose of methyldopa is 0,5-3,0 g divided into 2-4 doses. Side effects include sleepiness, dry mouth, tiredness, hemolytic anemia, and hepatopathy (30,31).

Beta-blockers

Even if beta-blockers are one of the first line drugs used during pregnancy and lactation they are less effective than calcium channel blockers. Labetalol is one of the most used drugs during pregnancy hypertension. It can be used in a parenteral administration in severe cases. Beta-blockers can cause fetal bradycardia, hypoglycaemia, or intrauterine growth retardation, that's why is very important to decide which drug to use, the dosage and careful fetal monitoring. Atenolol should be avoided during pregnancy (12,31).

Calcium channel blockers

Calcium channel blockers are recommended for hypertension during pregnancy but there is sufficient evidence only for nifedipine (12).

Diuretics

If there is not a strong indication for the use of diuretics (for example cardiac insufficiency), then they are not recommended. The use of diuretics during pregnancy holds a potential risk of oligohydramnios. Diuretic therapy should be avoided, especially in pre-eclampsia, because it reduces plasma volume (12). Loop diuretics are allowed in pregnancy, while thiazides and potassium sparing diuretics are contraindicated (31).

Renin-angiotensin-aldosteron system inhibitors

Renin-angiotensin-aldosteron system inhibitors (RAAS) include angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), renin inhibitors, nonselective aldosterone receptor antagonist (spironolactone) and selective (eplerenone) (31). Approximately 19% of pregnant women with chronic hypertension use ACE-Is or ARBs during the first trimester, and approximately one-third do not discontinue use. However, the studies show that taking these medications during pregnancy increases the risk of central nervous system disease and congenital heart diseases like, pulmonary valve stenosis, secundum atrial septal defect, ventricular septal defect and aortic coarctation from 3% to 7% (33,34,35). Pregnant women with hypertension who were treated with these medications during pregnancy had a higher risk than untreated women (33). Other studies suggest that taking RAAS inhibitors during the second and third trimesters has a higher risk for other fetal complications like renal dysplasia, pulmonary hypoplasia and growth restriction (31,33). Beta-blockers are used as an alternative for ACE-I and ARB in hypertensive young women who are planning a pregnancy (1,31).

Drugs in severe cases

BP≥170/110 mmHg is considered an emergency during pregnancy and should be done the immediate hospitalization and should be started the therapy with parenteral antihypertensive drugs (12). Intravenous labetalol and oral methyldopa or nifedipine are recommended. It can also be used urapidil which is an α1-adrenoreceptor with central and peripheral effects. Hydralazine is used only when other drugs can not control hypertension because of its side effects (17). In cases of pre-eclampsia complicated by pulmonary edema, intravenous nitro-glycerine is recommended. The aim is to reduce the blood pressure in values lower than 160/105 mmHg. Intravenous magnesium sulfate is the preferred treatment for eclampsia, but it should be used with caution when combined with calcium channel blockers (12). The delivery of fetus is the only therapy for pre-eclampsia, but in asymptomatic patients the delivery can be done in the 37th week of pregnancy.

Antenatal corticosteroid therapy

Glucocorticoids are widely accepted to be the most effective therapy to reduce neonatal morbidity and mortality in preterm infants born between 24 and 34 weeks gestation. Antenatal corticosteroids reduce the incidence of neonatal death and the incidence and severity of respiratory distress syndrome, cerebral hemorrhage, and necrotizing enterocolitis. In high-income countries, and increasingly in low- and middle-income countries, antenatal corticosteroids (24 mg betamethasone or dexamethasone, administered over 48 h) are routinely administered to women considered at imminent risk of preterm delivery (birth before 37 weeks gestation and before the natural increase in endogenous glucocorticoid concentrations would be expected). Thus, in high-income settings, antenatal corticosteroids are undoubtedly life-saving in preterm infants delivered at 24–34 weeks of gestation within a 2- to 7-day window following initiation of a single course of antenatal corticosteroid therapy (36). Antenatal corticosteroid therapy is an established and effective therapy to improve lung function in preterm infants, to reduce neonatal morbidity and mortality. However, increasing evidence suggests that it is not always without risk, particularly in infants delivered at or near term (37). More knowledge is urgently needed to inform future refinements to ACT. Current treatment protocols were developed decades ago and are based on limited knowledge about optimal formulation, dosage timing, and efficacy at various gestational ages (38).

THE TIME AND TYPE OF DELIVERY

It is preferred vaginal delivery if there are no obstetrical or medical contraindications.

The delivery in the 37th week is recommended in uncomplicated patients. Women diagnosed with pre-eclampsia should be hospitalized and begin antihypertensive therapy if they have not previously done so. Women with pre-eclampsia who have visual or hemostatic disorders or suffer

from HELLP syndrome should deliver as soon as possible (12).

THE MANAGEMENT OF PREGNANCY HYPERTENSION AFTER DELIVERY

After delivery, the blood pressure decreases rapidly in the first three weeks and can be stabilized at the end of the sixth week. When the hypertension persists after the delivery, antihypertensive drugs should be continued. Almost every drug is secreted in the breast milk, but in different amounts (20). Because of the lack of evidence, most of doctors use during the breastfeeding the same therapy rules that are used during pregnancy. Methyldopa should be avoided because of the risk of postpartum depression. Labetalol and propranolol concentrations are seen to be low in breast milk, atenolol and metoprolol are found in concentrations that can affect the newborn. Diuretics concentrations are low and are considered safe but diuretics can reduce the amount of breast milk in the breast feeding mothers. Calcium channel blockers can pass through breast milk but have no side effects and can be used during lactation. There is not enough evidence for the use of ACE-I and no published evidence exists on the safe use of ARBs. Breast milk concentrations of enalapril are low, 1.16% and breast milk concentrations of captopril are also low, only 1% but only 0.03% will pass at the newborn. Based on these findings American Paediatric Association allows their use during lactation (39).

CONCLUSION

Pregnancy hypertension represents a serious condition that increases the risk of maternal and fetal morbidity and mortality. Nowadays there is no efective way to prevent pregnancy hypertension. Early detection and management are guaranteed by the regular monitoring of blood pressure during antenatal visits. The management of hypertension during pregnancy needs further explorations in high-risk pregnancies and cardiovascular diseases, which is why it needs teamwork between obstetricians and cardiologists. Before prescribing antihypertensive drugs for pregnant women the physician should carefully look at the possible side effects during pregnancy and lactation.

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