Treatment of arterial hypertension in pregnant women

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Abstract

Pregnant women especially have an increased risk for arterial hypertension, which can lead to maternal and fetal complications. Preeclampsia and severe arterial hypertension are associated with the highest risk. In pregnancy, there are four major hypertensive disorders: chronic (preexisting) hypertension, preeclampsia-eclampsia, gestational hypertension and preeclampsia-eclampsia superimposed on chronic hypertension. The therapeutic approach of hypertension in pregnant women should balance the risks and benefits for both mother and fetus. The factors that should be taken into consideration are: the level of blood pressure, the etiology of the hypertension, and timing of delivery.

Keywords: *arterial hypertension, pregnancy, preeclampsia*

Introduction

Arterial hypertension is an important cardiovascular risk factor. It is defined as a systolic blood pressure ≥140 mm Hg and/or diastolic ≥90 mm Hg and/or receiving antihypertensive medications (Table 1). Women have often multiple cardiovascular risk factors, including central obesity, elevated total cholesterol, low density lipoprotein and higher systolic blood pressure that independently predict cardiovascular events. Pregnant women especially have an increased risk for arterial hypertension, which can lead to maternal and fetal complications[1]. As etiology is largely unknown, preventive measures are lacking and management is directed to control of clinical manifestations. Delivery remains the only definitive treatment in a vast majority of cases. Preeclampsia and severe arterial hypertension are associated with the highest risk. In pregnancy, there are four major hypertensive disorders: chronic (preexisting) hypertension, preeclampsia - eclampsia, gestational hypertension and preeclampsia-eclampsia superimposed on chronic hypertension. If persisting >3 months after delivery, postpartum hypertension is reclassified as chronic hypertension[2].

Preeclampsia-eclampsia is the syndrome of new onset of hypertension and either proteinuria or end-organ dysfunction, most often after 20 weeks of gestation in a previously normotensive woman. The term of eclampsia is used when seizures occur[3]. Gestational hypertension is hypertension first diagnosed after 20 weeks of gestation in the absence of proteinuria or other diagnostic elements of preeclampsia. A percentage of patients with gestational hypertension will develop proteinuria or end-organ dysfunction specific to preeclampsia and will be categorized as preeclampsia, while others will be diagnosed with chronic hypertension due to persistent hypertension postpartum. Preeclampsia-eclampsia superimposed upon chronic hypertension is diagnosed when a woman with chronic hypertension develops worsening hypertension with new onset proteinuria or other features of preeclampsia[3]. Hypertensive pregnant women may develop complications such as placenta abruption, accelerated hypertension requiring hospitalization and acute target organ damage. The fetus has also risks associated with mother hypertension: growth restriction and preterm birth[4].

Placental Ischemia

Placental ischemia is a key factor in pregnancy-induced hypertension. Placenta becomes increasingly ischemic as gestation progresses, with increased frequency of placental infarcts and altered morphology. It has been suggested that release of factors from the placenta in response to ischemia leads to appearance of endothelial dysfunction of the maternal circulation[3]. The endothelial dysfunction is an early event in preeclampsia, not a result of preeclampsia. Furthermore, in women who will develop preeclampsia, other preexisting factors such as diabetes, dyslipidemia, obesity, chronic hypertension may predispose the women endothelium to further lesions. The ischemic placenta releases vasopressor substances. The management of patients with hypertensive disorders of pregnancy should begin with pre-conception measures. As the risks of pre-eclampsia and gestational hypertension increase with raised body mass index, weight loss should be encouraged in overweight women prior to pregnancy. Women with chronic hypertension should be assessed to exclude secondary causes of hypertension and to ensure optimal control. The therapeutic approach of hypertension in pregnant women should balance the risks and benefits for both mother and fetus. The factors that should be taken into consideration are: the level of blood pressure, the etiology of the hypertension, and timing of delivery. If the hypertension is severe, the major benefit for woman is decreasing the stroke risk. Regarding the etiology, women with chronic preexisting hypertension may tolerate higher values of blood pressure better than normotensive women with acute increase in blood pressure due to preeclampsia[4].

Antihypertensive Therapy

The American College of Obstetricians and Gynecologists recommends starting antihypertensive therapy in pregnant

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Table 1 Grades of hypertension according to severity

TERMINOLOGY	BLOOD PRESSURE (mmHg)
Mild hypertension	140-149 / 90-99
Moderate hypertension	150-159 / 100-109
Severe hypertension	>160 / >110

women with a blood pressure of 150-160/100-110 mm Hg[4]. In mild hypertension, antihypertensive therapy may be reduced or withheld unless complicating factors exist (like cardiovascular or renal disease) or if the body pressure is ≥150/100 mm Hg. Furthermore, there is evidence that, in some cases, aggressive lowering of the blood pressure can inhibit fetal growth or increase the fetus risk due to secondary effects of antihypertensive drugs. If chronic severe hypertension exists (i.e. ≥160/110 mmHg) treatment should be started immediately to reduce the risk of maternal stroke[5].

A meta-analysis published in 2014 evaluated 49 randomized trials of treatment versus no treatment of pregnant women with mild to moderate hypertension (i.e. any category of pregnancy hypertension). Mild to moderate hypertension was defined as 140-169/90-109 mmHg. Women with cerebral symptoms or cardiac decompensation should be treated. Severe hypertension requires parenteral therapy, usually with labetalol or hydralazine. Labetalol should be used in the following doses: 20 mg i.v. over 2 minutes, followed by doses of 20-80 mg at 10 minutes intervals, up to the maximum cumulative dose of 300 mg. If possible, a constant infusion of 1-2 mg/min can be a better option. The blood pressure should be monitorized. Labetalol iv has a rapid effect on hypertension, the blood pressure begins to decrease in 5-10 minutes and the duration of the effect is 3-6 hours. Hydralazine should be started 5 mg i.v. over 1-2 minutes, with increasing doses up to the maximum bolus dose of 20 mg. Its antihypertensive effect starts within 10-30 minutes and the duration is 2-4 hours. Calcium channel blockers are another antihypertensive class that can be used in preeclampsia, without significant side effects. In pregnant women, sustained release nifedipine and immediate release nicardipine are used; immediate release nifedipine should be avoided, due to the risk of acute fall in blood pressure and myocardial ischemia or even infarction. In hypertensive pulmonary edema, intravenous infusion of nitroglycerin 5 mcg/min, gradually increased every 3-5 minutes to a maximum dose of 100 mcg/min, can be used. All antihypertensive drugs are assumed to cross the placenta and enter the fetal circulation. Most of the drugs commonly used have not been found to be teratogenic, although angiotensin-converting-enzyme (ACE) inhibitors and angiotensin receptor blockers are fetotoxic and may lead to oligohydramnios, joint contractures, pulmonary hypoplasia, renal tubular dysplasia in the fetus. The drugs commonly used to treat hypertension in pregnancy are listed in Table 2.

Evidence-based guidelines from the American Association of Clinical Endocrinologists recommend methyldopa or nifedipine as preferable antihypertensive medications in pregnancy, with magnesium sulphate for women with preeclampsia who are at high risk for seizures, but they recommend all major antihypertensive agents with the exception of ACE inhibitors and angiotensin II receptor blockers[6]. ACE inhibitors should be avoided during pregnancy, due to the risk of fetal renal dysgenesis or death when used in the second or third trimesters, as well as with increased risk of cardiovascular and central nervous system malformations when used in the first trimester[7]. Chronic preexistent hypertension increases the risk for maternal and fetal complications: preterm delivery, preeclampsia, cesarean delivery, birth weight <2500 g, neonatal intensive care, perinatal death[8]. If preeclampsia appears in women with chronic hypertension, iatrogenic preterm delivery is necessary. Severe hypertension, on the other hand, may have a serious consequences on mother and fetus[9].

After delivery, women with chronic hypertension should be treated with the same drugs or the treatment may be switched to pre-pregnancy drugs[10]. Antihypertensive medication may need to be stopped, changed or reduced in dose. Post-partum antihypertensive treatment may be necessary for 2-6 weeks after which it may be stopped. Women who experienced hypertension during their first pregnancy are at increased recurrence risk of 19% for gestational hypertension, 32% for pre-eclampsia and 46% for pre-eclampsia superimposed on pre-existing chronic hypertension[11].

The European Society of Cardiology Guidelines on the Management of Cardiovascular Diseases during Pregnancy recommend nonpharmacological management for pregnant women with systolic blood pressure of 140-150 mm Hg or diastolic blood pressure of 90-99 mm Hg(12). In women with gestational hypertension or preexisting hypertension superimposed by gestational hypertension or with hypertension and subclinical organ damage or symptoms at any time during pregnancy, initiation of drug treatment is recommended at blood pressure of 140/90 mmHg. In any other circumstances, initiation of drug treatment is recommended if systolic blood pressure is ≥150 mmHg or diastolic blood pressure is ≥95 mmHg. Systolic blood pressure ≥170 mmHg or diastolic blood pressure ≥110 mmHg in a pregnant woman is an emergency, and hospitalization is indicated[12,13].

The majority of women with gestational hypertension become normotensive after delivery[14]. The mean time to normalization of blood pressure postpartum after preeclamptic pregnancies is about two weeks. Regarding the long term prognosis, women with gestational hypertension have a greater risk of development of hypertension later in life and should be monitored[15-19].

Table 2 Drugs commonly used in the treatment of pregnancy hypertension[11]

Methyldopa *Dose:* 250 mg - 3 g/day orally *Mode of action:* false neurotransmitter to norepinephrine *Side effects:* orthostatic hypotension, depression, bradycardia, headache *Contraindications:* liver diseases, increased risk of postnatal depression
Labetalol *Dose:* 200-1600 mg/day orally; 50 mg bolus iv then titrated infusion *Mode of action:* alpha1 and non-specific betablocker *Side effects:* bradycardia, bronchospasm, gastrointestinal effects *Contraindications:* asthma, cardiac diseases, feochromocytoma
Hydralazine *Dose:* 5 mg slow bolus iv, then 5 mg/hr *Mode of action:* vasodilator *Side effects:* fluid retention, palpitations, flushing, headache, tachycardia, systemic lupus like syndrome *Contraindications:* severe tachycardia
Nifedipine *Dose:* 20-90 mg od orally (avoid sublingual route) *Mode of action:* calcium channel antagonist *Side effects:* headachem dizziness, tachycardia, flushing *Contraindication:* aortic stenosis, liver disease
Magnesium sulphate *Dose:* 4 g bolus iv over 10 min then 1 g/hr infusion for 24 hours or 0.5 g/hr if oliguric *Mode of action:* calcium channel antagonist, N-methyl D-aspartate receptor antagonist - anticonvulsant action *Side effects:* therapeutic range (2-4 mmol/L) - loss of deep tendon reflexes, >5 mmol/L - blurred vision, >7 mmol/L - respiratory depression, >10 mmol/L - cardiac arrest *Contraindications:* neonatal hypotonia and respiratory depression in fetus (magnesium crosses the placenta); in case of cardiac arrest - stop infusion, give 10 ml of 10% calcium gluconate iv.

Conclusions

The only curative treatment for eclampsia is delivery. Until delivery, the pregnant woman has increased risk for seizures, placental abruption, thrombocytopenia, pulmonary edema, liver insufficiency or acute kidney injury. Women with gestational hypertension have the same treatment options as those with preeclampsia. Education and counseling are important in the management of these patients, because they are at increased risk for preeclampsia. They must be educated to self-monitor and report the symptoms. If systolic blood pressure is <160 mmHg or diastolic blood pressure is <110 mmHg, the drug treatment usually is not recommended. Severe gestational hypertension imposes preterm delivery and treatment with antihypertensive agents. ■

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