Research & Reviews on Pregnancy and Women's Health

Chapter 2

Management of Pregnancy induced Hypertension

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1. Introduction

The incidence of pregnant induced Hypertension (PIH) in Europe and the United States accounted for about 6%-10% of pregnant women. The prevalence of chronic hypertension and hypertensive disorders of pregnancy continues to increase. It is recorded that the incidence of preeclampsia was increased by 25% in the USA during the past two decades [1]. Epidemiological survey found that the incidence of peoplein China is similar to that of 5.6%-9.4% in pregnant women. After two child policy in China, the incidence is increased since the elderly pregnant women increased. About 10%-25% develop into preeclampsia in women with chronic hypertension.

2. Classification and Definitions

According to the guideline of American Congress of Obstetricians and Gynecologists (ACOG) in 2013, there are four categories of hypertension during pregnancy. (1) Preeclampsia-eclampsia, in the absence of proteinuria, preeclampsia is diagnosed as hypertension in association with thrombocytopenia (platelet count less than 100,000/microliter), impaired liver function (elevated blood levels of liver transaminases to twice the normal concentration), the new development of renal insufficiency (elevated serum creatinine greater than 1.1 mg/dl or a doubling of serum creatinine in the absence of other renal disease), pulmonary edema, or new-onset cerebral or visual disturbances; (2) chronic hypertension refers to a the systolic blood pressure is more than 140 mm Hg and (or) diastolic blood pressure greater than or equal to 90 mm Hg before pregnancy or gestational age of 20 weeks, or 12 weeks postpartum blood pres-

sure is still not normal; (3) chronic hypertension with superimposed preeclampsia is chronic hypertension in association with preeclampsia; (4) gestational hypertension is diagnosis as hypertension developing after 20 weeks without proteinuria or the afore mentioned systemic findings [2,3]. For the convenience of initiation antihypertensive medication, it is usually defined into two categories of severity: mild-moderate (SBP 140 to 159 mm Hg, DBP 90 to 109 mm Hg) and severe (≥160/110 mm Hg) [4].

3. Pathophysiological Changes in Gestational Hypertension

In physiological condition, blood pressure of pregnant women begins to reduce after the onset of pregnancy. At the same time, the cardiac output increases slightly, mean while peripheral vascular resistance decreases significantly. Moreover, the renal blood flow and glomerular filtration rate increase. These conditions peaked at week 12 of pregnancy. Peripheral vascular resistance and blood pressure also slightly increases during the whole pregnancy. These tendencies return to the pre-pregnancy levelat week 36 of pregnancy [5].The pathological changes of PIH are spasm of small arteries and retention of sodium in the whole body. This pathological change leads to target organs damage and eclampsia. In addition to the pathlogical changes, there are also a few risk factors induced eclampsia, including nulliparity, multiple gestation, family history of preeclampsia, chronic hypertension, diabetes, renal disease, history of preeclampsia, especially if early (before 34 weeks) in a previous pregnancy, history of HELLP syndrome in previous pregnancy, obesity and hydatidiform mole.

4. The Harm of Pregnancy Induced Hypertension

Pregnancy induced hypertension is a pregnancy complication that threatens maternal and child health. Fetal growth restriction and placental abruption were increased significantly in PIH patients [6]. The risk of maternal brain edema, acute heart failure, stroke, and acute renal failure are also increased due to the pathological changes of gestational hypertension. A recent large meta-analysis showed that women with a history of pre-eclampsia have approximately double the risk of subsequent ischaemic heart disease, stroke and venous thromboembolic events over the 5-15 years after pregnancy [7]. The risk of developing hypertension is almost four-fold [8].

5. Nonpharmacologic Management

A normal diet without salt restriction is advised, particularly close to delivery. Salt restriction may lead to low intravascular volume. Calcium supplementation (≥ 1 g/day) is associated with a significant reduction in the risk of pre-eclampsia, particularly for women with low calcium diets. Fish oil supplementation as well as vitamin and nutrient supplements have no role in the prevention of hypertensive disorders [9]. Till now, clinical trials do not show positive effect of vitamin D supplementation is help for preventing preeclampsia; however,

the dosage, timing, and duration of supplementation should be discussed in the future research [10]. Aerobic exercise for 30-60 min twice a week during pregnancy significantly reduced risk of gestational hypertension and cesarean delivery [11].

6.Pharmacologic Management. (Table 1)

6.1. Imitation treatment and target of the Blood Pressure

A major benefit of BP control is to reduce the incidence of severe hypertension and decrease the risk for maternal and fetal complications [12,13]. It is a common consensus among national and international guidelines to start medication BP 160/110 mmHG or higher [13-15]. Different guidelines are slightly different, such as AHA/ASA suggests considering pharmacologic therapy for BPs 150 to 159/100 to 109 mm Hg [14]. However, the European Society of Cardiology (ESC) goes even further to recommend treatment of BP 140/90 mm Hg or above in women with organ damage, symptoms or super imposed gestational hypertension on chronic hypertension [3,16].

In patients with PIH, it is necessary to reduce the risk of maternal organ damage without affecting placental blood flow. However, there isno evidence regarding the target for blood pressure control. In 2014 Japanese Society of Hypertension (JSH), a target systolic blood pressure ≤160 mm Hg, and a target diastolic blood pressure is ≤110 mm Hg or the rate of decrease in the mean blood pressure should be 15–20% is suggested [17]. A recent large clinical trial, the Control of Hypertension In Pregnancy Study (CHIPS), has demonstrated that women treated to lower blood pressure targets (130 to 140/85 mm Hg) had fewer episodes of severe hypertension in pregnancy [12]. Importantly, there were no adverse fetal effects in the lower blood pressure target group, challenging the previous concern that lowering blood pressure to 'normal' might be associated with reduced fetal growth [18]. The incidence of preeclampsia was similar in women treated to standard, less-tight control (target DBP, 100 mm Hg) or tight control (target DBP, 85 mm Hg). The ACOG recommends adjusting therapy to maintain BP in the 120 to 160/80 to 105 mm Hg range during pregnancy [2]. The target range is narrower in the Canadian guidelines and is further divided into 130 to 155/80 to 105 mm Hg for women with chronic hypertension without comorbidities and less than 140/90 if comorbidities are present [15].

6.2. Oral medication and dosages administrated in PIH

(1) Methyldopa: Methyldopa, acting as α2 adrenergic receptor agonist, is widely used as sympatholytic drug. It is a first-line agent used in the treatment of PIH [19,20]. Although there is no evidence, no serious adverse effect on maternal or fetal conditions has been reported during a 40-year history of use. A total dosage recommended is 0.5-3.0 gram (g) daily and divided into 2-4 times [21]. Side effects such as sleepiness, dry mouth, general malaise, hemolyticanemia,

and hepatopathy are observed.

(2) Hydralazine: Many years ago, hydralazine, a vasodilator, has been recommended as the first choice for severe antihypertensive medication in pregnancy [22,23]. The common side effects include headache, nausea, and vomiting. Acutely this drug is not normally used for hypertension treatment, but the guidelines recommend it as a first-choice drug, considering the fact that it is still selected by a large number of obstetricians. According to a recently reported meta-analysis, this drug was less effective than labetalol for PIH from all aspects [24]. A dosage of 50 milligram (mg) to 300 mg a day divided in 3 or 4 times is recommended. Side effects include hypotension and neonatal thrombocytopenia.

(3) Calcium channel blockers: Calcium channel blockers include two subtypes: dihydropyridine (nifedipine) and non-dihydropyridine (verapamil, diltiazem). Other than nifedipine are contraindicated for pregnant women or those who may be pregnant. Nifedipine considered safe in pregnancy [25]. When administering Calcium channel blockers other than long acting nifedipine, they should be used in accordance with the physician's evaluation and responsibility after explaining their necessity for treating the condition and obtaining informed consent, although this approach is not recommended in guidelines because of insufficient supporting evidence. The current recommended starting dose for nifedipine is10–20 mg orally three times daily, maximum does or 180 mg per day, and for nifedipine long-acting tablet formulation is usually dosed once daily starting at 30–60 mg and maximum of 120 mg per day [26].

(4) Beta-blockers: Labetalol, a third-generation β blocker, is a nonselective against β1 and β2 adrenoreceptor. It also has α1 adrenoreceptor blockade properties, which causes vasodilation. It has more β blocking effect than α blocking effect (3:1 ratio). Labetalol is considered to be firstline medication for management of hypertensive disease of pregnancy. It is widely used in Europe, United States and China, because there may few problems regarding its safety [27,28]. Furthermore, there is a meta-analysis improved that labetalol is more helpful than hydralazine with respect to adverse effects on the maternal condition [24]. Most β blockers are contraindicated for pregnant women. Therefore, if the administration of other β blockers is necessary, informed consent must be obtained after explaining the contents of treatment.

(5) Diuretics: Diuretics may lead to a reduction in the circulating plasma volume and placental blood flow which associated to pre-eclampsia. Therefore, diuretics should be avoided in patients with pre-eclampsia. It can be used when pulmonary edema or heart failure signs are absent [29]. For patients with chronic hypertension who take diuretics before pregnancy, the effect of placental blood flow reduction is not apparent when the drug is continued after pregnancy. The commonly used diuretics is hydrochlorothiazide. The dosage is 12.5 mg to 25 mg, once a day. Spironolactone is not recommended since it is found to have an antiandrogenic effect during fetal development in animal models. But it does not seem to induce adverse out-

comes in small human cohorts [30]. We do not suggestit's used in pregnant woman, only if a potassium-sparing diuretic is needed.

(6) α-blockers: These kinds of drugs are not contraindicated for pregnant women or those who may be pregnant. But they are not used, and should be avoided. Only one research has recommended using of these drugs inpregnant women with hypertension secondary to pheochromocytoma [31].

(7) Renin aldosterone system blocker: There are 3 kinds of RAS inhibitor including angiotension convert enzyme inhibitor (ACEi), angiotensin II type -1 receptor blocker (ARBs) and direct renin inhibitors. The administrations of these drugs are strictly contraindicated in women who is pregnant even who may become pregnant. All the RAS inhibitor may lead to teratogenicity and oligohydramnios during pregnancy [32,33].

7. Treatment of Hypertensive Emergencies

Although different countries have slightly different treatment strategies, the commonly used agents are: intravenous labetalol, intravenous hydralazine, and oral nifedipine [15,34]. Nitroprusside is rarely used during pregnancy. It may increase the risk of fetal cyanide intoxication. (**Table 2**)

Table 1: Oral medication and Dosages used in PIH

Drug	Dose	Comments
Methyldopa (B)	0.5-3g/day, 2-4 times	Safety after first trimester well documented, including 7-year follow-up of offspring
Labetalol (C)	200-1200 mg/day, 2-3 times	May be associated with fetal growth restriction and neonatal bradycardia.
Nifedipine (C)	30-90 mg/day of a slow-release preparation, 1-3 times	
Hydralazine (C)	50-300 mg/day, 2-4 times	Few controlled trials, but long experience with few adverse events documented; May cause neonatal thrombocytopenia.
β-Receptor blockers (C)	Depends on specific agent	May cause fetal bradycardia; May impair fetal response to hypoxic stress; possible risk for lower birth weight when started in first or second trimester (especially atenolol)
Hydrochlorothiazide (C)	25 mg/day	May cause volume depletion and electrolyte disorders. May be useful in combination with methyldopa and vasodilator to mitigate compensatory fluid retention.
ACE inhibitors and AT1 receptor antagonists (D)		Leads to fetal loss in animals; human use in second and third trimester associated with fetopathy, oligohydramnios, growth restriction, and neonatal anuric renal failure, which may be fatal.

A: No antihypertensive has been proven safe for use during the first trimester.
B: Drug therapy indicated for uncomplicated chronic hypertension when diastolic blood pressure ≥100 mm Hg (using Korotkoff V phase for diastolic measurement). Treatment at lower levels may be indicated for patients with diabetes mellitus, renal disease, or target organ damage.
C: United States Food and Drug Administration classification.
D: Some agents are omitted (e.g., clonidine, alpha blockers) as a result of limited data on use for chronic hypertension in pregnancy.

E: Authors would classify in category X during second and third trimeesters.

Table 2: Drugs of hypertensive emergencies

Drug	Dose	Comments
Labetalol (C)	20 mg IV, then 80 mg every 20-30 min, up to maximum of 300 mg; or constant infusion of 1-2 mg/min	Less risk of tachycardia and arrhythmia than with other vasodilators
Nifedipine (C)	Tablets recommended only: 10-30 mg	Safe to use in labor
Hydralazine (C)	5 mg, IV or IM, then 5-10 mg every 20-40 min; or constant infusion of 0.5-10 mg/hour	Long experience of safety and efficacy
Nitroprusside(C)	Constant infusion of 0.5-10 mcg/kg/min	Possible cyanide toxiciy

8. Conclusion

Pregnancy induced hypertension increases the risk of eclampsia and threatens maternal and fetal health. In this review were commend treatment when BPis 150/90 mm HGor higher with oral labetalol, nifedipine, or methyldopa as firstline agents. In the setting of chronic hypertension, one agent should be maxed out prior to combine with another agent. Hypertension emergencies exceeding 160/110 mm Hg may result in maternal stroke or eclampsia. When delivery is imminent, parenteral therapy with intravenous labetalol, hydralazine, or oral nifedipine are needed.

9. Reference

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