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(REVIEW ARTICLE)

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Management of hypertension during pregnancy: A meta-analysis

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Abstract

Gestational hypertension, chronic hypertension, preeclampsia, and preeclampsia superimposed on pre-existing hypertension are the four categories into which the National High Blood Pressure Education Program of the NHLBI divides hypertensive disorders of pregnancy. Pregnant women with hypertension are at risk for death, renal failure, heart failure, hepatic rupture, cerebral edema, and cerebrovascular accidents. The foetuses of hypertension mothers are at risk for stillbirth, intrauterine growth restriction, and preterm birth difficulties after delivery due to maternal symptoms. When the diastolic pressure is greater than 90 to 110 mm Hg or the systolic pressure is greater than 140 to 170 mm Hg, most doctors start antihypertensive medication. A pre-pregnancy assessment for women with chronic hypertension should focus on end-organ damage, medication history, possible secondary causes of hypertension, and counselling on pregnancy's hazards. Women need to be monitored during their pregnancies, as well as during the intrapartum and postpartum periods.

Keywords: Preeclampsia (PE); Ambulatory blood pressure monitoring (ABPM); Hyperbaric index (HBI); Blood Pressure (BP); Renin-Angiotensin-Aldosterone System (RAAS)

1. Introduction

Hypertension is the most common medical disorder of pregnancy and is reported to complicate up to 1 in 10 gestations and affects an estimated 240,000 women in the United States every year [1]. The National High Blood Pressure Education Program of the NHLBI classifies hypertensive disorders of pregnancy into following categories: gestational hypertension, chronic hypertension, preeclampsia, and preeclampsia superimposed on pre-existing hypertension.[2]

Hypertension in pregnancy is defined as a systolic of 140mmHg or greater or a diastolic of 90mmHg or greater. Hypertension in pregnancy includes a range of conditions, most notably preeclampsia, a form of hypertension unique to pregnancy that occurs de novo or may be superimposed on chronic hypertension. The other forms, chronic and gestational hypertension, usually have more benign courses [3]. Controversy remains as to the blood pressure criteria used to define preeclampsia. Some experts of this specialized area of medicine have argued that a rapid rise in blood pressure of 30mmHg systolic or 15mmHg diastolic should be sufficient to diagnose preeclampsia. However, the current recommendations of the 2000 working group suggest that women who experienced only this change are not yet preeclamptic but do warrant close observation, especially if this finding is accompanied by proteinuria and hyperuricemia [4].

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Hypertensive pregnant women are at risk for cerebrovascular accident, cerebral oedema, hepatic rupture, renal failure, heart failure and death. The foetuses of hypertensive women are at risk for complications of preterm birth after delivery for maternal indications, intrauterine growth restriction and stillbirth. The risk for the severest of outcomes such as maternal mortality and cerebral injury is moderated through prenatal care [5].

Preeclampsia (PE) is a clinical entity characterized by either the new onset of hypertension and proteinuria or end organ damage after 20 weeks of gestation. It is one of the major pregnancy related hypertensive disorders and can occur postpartum. Additional clinical signs and symptoms include headache, visual disturbance, epigastric pain, thrombocytopenia, and abnormal liver function[6]. Traditionally, the clinical diagnosis of PE is made when new-onset hypertension in the second half of pregnancy is associated with new-onset proteinuria. However, following the observation that some patients show evidence of multiorgan damage without proteinuria, under certain circumstances PE can be diagnosed without proteinuria. In the absence of proteinuria, the diagnosis can be made if any of the following is present: abnormal liver function, thrombocytopenia, renal insufficiency, pulmonary oedema, visual impairment, or cerebral symptoms [7]

A variety of antihypertensive medications have been used in pregnancy. (Table 2) lists those commonly used and summarizes their pathways of drug disposition, the impact of pregnancy on these pathways when known, the primary mechanism of action and the primary and secondary hemodynamic changes [5].

Treatment of pregnancy-related hypertensive disorders, such as preeclampsia (PE), remain a challenging problem in obstetrics [7]. 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 [8].

2. 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.[3] 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.[9]

2.1. When to treat hypertension during pregnancy

Significant hypertension must be treated in its own right, regardless of the assumed underlying pathology, largely to reduce the risk of maternal intracranial haemorrhage. The level at which antihypertensive treatment is initiated for non-severe hypertension remains controversial, depending on whether treatment is focused on maternal or fetal wellbeing. Most physicians commence antihypertensive medication when the systolic blood pressure > 140–170 mm Hg or diastolic pressure > 90–110 mm Hg. Treatment is mandatory for severe hypertension when the blood pressure is ⩾ 170/110 mm Hg. Once treatment is started, target blood pressure is also controversial, but many practitioners would treat to keep the mean arterial pressure < 125 mmHg—for example, a blood pressure 150/100 mm Hg. Overzealous blood pressure control may lead to placental hypoperfusion, as placental blood flow is not auto regulated, and this will compromise the fetus.

Unfortunately there is no evidence that pharmacological treatment of chronic or gestational hypertension protects against the development of pre-eclampsia. Changes in diet or bed rest have not been shown to provide maternal or fetal benefit [10].

Table 1 Classification of blood pressure in pregnancy

Condition	**Definition and management**
Preeclampsia or eclampsia	A pregnancy-specific disorder that is a multisystem disease characterized by hypertension ≥ 140/±90 mm Hg on at least two occasions at least 6 hours apart, and proteinuria ≥ 300 mg in a 24-hour urine collection, after 20 weeks gestation. Antihypertensive therapy is indicated for sustained blood pressure elevations ≥ 160 mm Hg systolic or 105 mm Hg diastolic. The goal of blood pressure reduction in emergency situations should be a gradual reduction of blood pressure to the normal range. The convulsive form of preeclampsia, eclampsia, affects 0.1% of all pregnancies.
Preeclampsia superimposed on chronic hypertension	≤ 30% of women with chronic hypertension develop preeclampsia (de novo proteinuria), usually in the third trimester; proteinuria is not seen in uncomplicated chronic hypertension.
Chronic hypertension	BP ≥ 140/± 90 mm Hg before pregnancy or before the 20th week of gestation. The NHBPEP Working Group advises that antihypertensive medication can be safely withheld in this group, provided that blood pressure remains < 150–160 mm Hg systolic and 100–110 mm Hg diastolic while the patient is off medications.
Gestational hypertension	New onset of hypertension ≥ 140/±90 mm Hg on at least two occasions at least 6 hours apart, after 20 weeks gestation in the absence of proteinuria (< 300 mg in a 24-hour urine collection). If blood pressure returns to normal by 12 weeks postpartum, the diagnosis of transient hypertension of pregnancy can be assigned. If elevated blood pressure persists, the diagnosis of chronic hypertension is made.

Table 2 Commonly used antihypertensive agents in pregnancy

Drugs by Class	**Disposition**	**Impact of Pregnancy on Disposition**	**Mechanism of Action**	**Hemodynamic Effect**
Beta-Blockers			↓heart rate	↓HR ↓CO ↑TPR ↑SV
Atenolol	renal	↑		
Metoprolol	CYP-2D6	↑↑↑		
Propranolol	CYP-2D6	↑↑↑		
Mixed Effect			↓vascular resistance ↓ HR (at higher doses)	↓TPR →HRR→CO
Labetolol	conjugation to glucuronide	↑↑↑β-isomer ↑α-isomer		
Central α-Agonists			↓central adrenergic output	↓TPR ↓HR ↓CO Individual Variability
Methyldopa	Renal conjugation	?		
Clonidine	Renal	↑		
	CYP-2D6	↑↑↑		
Vasodilators			↓ vascular resistance	↓TPR ↑↑HR ↑CO
Ca-channel Blockers	CYP-3A↑↑	↑↑		
Nifedipine	CYP-3A↑↑	↑↑		

Amlodipine Hydralazine	acetylation	?		
Diuretics			↓vascular volume	↓SV ↓CO ↑TPR ↑HR
Furosemide	conjugation to glucuronide	?		

Table 3 Antihypertensive therapy of chronic hypertension in pregnancy

Drug	Dosage	Additional comments
Methyldopa	500–3000 mg in 2–4 divided doses	Considered to be drug of choice because of extensive experience
Labetalol	200–1200 mg in 2–3 divided doses	Similar in efficacy and safety to methyldopa
Beta-blockers	Variable	Possibility of fetal bradycardia, lower birth weight (when used early in pregnancy)
Calcium channel blockers	variable	Accumulating data support maternal and fetal safety; may interact with magnesium sulfate
Alpha- blockers	Variable	Scant data for use in pregnancy
Clonidine	0.1–0.8 mg in 2–4 divided doses	Limited data
Thiazide diuretics	Variable	May be associated with diminished volume expansion in pregnancy; may be necessary in salt-sensitive hypertensives at lower doses
Angiotensin- converting enzyme inhibitors	Contraindicated	Contraindicated in pregnancy; neonatal anuric renal failure
Angiotensin receptor antagonists	Contraindicated	Contraindicated in pregnancy; neonatal anuria renal failure.

2.2. α-adrenergic agonists

One of the medications with the longest track record in pregnancy is methyldopa. A longterm follow-up study on children born to women treated with methyldopa during pregnancy could find no increased incidence of general health problems or cognitive problems. [11] This record of safety makes it the first line agent recommended by the NHBPEP working group. [3] Methyldopa acts centrally by decreasing sympathetic tone, and therefore can have many side effects, including sedation and impaired sleep patterns. One potential side effect is that it may cause mild elevations of liver enzymes, which can lead to diagnostic confusion with HELLP syndrome. Although it is relatively safe, methyldopa is not a potent BP lowering agent and side effects, which are commensurate with the dose, can limit its use. Methyldopa can be combined with other anti-hypertensives, such as a diuretic (discussed below), to achieve target blood pressure values.

Clonidine has a similar mode of action to methyldopa, but has a much stronger effect in lowering BP. Clonidine may impair fetal growth, especially if the mother has a reduction in heart rate after therapy is initiated. [12] It can cause significant rebound hypertension and does not have as strong a record of safety as methyldopa. It should be considered in cases of intolerance to methyldopa.

2.3. Beta-blockers

Beta-blockers are generally well-tolerated and safe in pregnancy. Labetalol is becoming one of the favored therapies for hypertension in pregnancy. It is a non-selective beta blocker that antagonizes both beta and alpha-1 receptors. Its side effects include fatigue, decreased exercise tolerance, as well as bronchospasm in individuals with reactive airway disease.

Labetalol has been compared to methyldopa in prospective trials and neither medication was associated with adverse maternal or feotal outcomes. [13,14] It is available in both oral and intravenous forms, so it may be used for both outpatient and inpatient management.

Atenolol has been shown to have minimal effects on systolic BP in preeclamptic women, and it is also associated with intrauterine growth retardation [15] Given the availability of other more effective medications, including labetalol, atenolol should be avoided in pregnancy.

2.4. Calcium channel blockers

Oral nifedipine and verapamil are frequently seen as second line agents used for the treatment of hypertension in pregnancy. They do not appear to be teratogenic [16].

In a small trial of preeclamptic mothers who received nifedipine versus placebo, there were significant reductions in maternal BP, serum creatinine and urea values, and 24-hour urinary protein measurements, without a reduction in umbilical artery blood flow. [17] According to a prospective, multicenter cohort study of 78 women exposed to calcium channel blockers in the first trimester, mainly nifedipine and verapamil, there was no increase in major congenital malformations. There was an increase in preterm delivery in those who received calcium channel blockers versus controls, matched for age and smoking status (28% vs. 9%, p=0.003), although this was attributed to underlying maternal disease by stepwise regression.[16] There is little data available on diltiazem, although it may be used as a rate control agent in pregnancy,[18] and has been shown to lower BP and proteinuria in pregnant patients with underlying renal disease in a small study of 7 patients.[19] Calcium channel blockers are also potent tocolytics and can affect the progression of labour. A major concern with calcium channel blockers in pregnancy is the concurrent use of magnesium sulfate for seizure prophylaxis, as co-administration of these agents has been reported to cause circulatory collapse and neuromuscular blockade.[16] Despite these issues, calcium channel blockers, nifedipine in particular, as there is more data available for it, is an effective and safe alternative to methyldopa as a first-line agent for the treatment of hypertension in pregnancy.

According to FDA nifedipine and verapamil are Class C drugs. With all CCBs, there is a risk of interactions with magnesium, resulting in profound hypotension. Nifedipine and verapamil are usually compatible with breast milk.

2.5. Direct vasodilators

Hydralazine is now predominantly used intravenously for the treatment of severe hypertension in pregnancy. Hydralazine selectively relaxes arteriolar smooth muscle. However, hydralazine has been associated with hypotension, oliguria and fetal distress. [20]It is also associated with a lupus-like syndrome and peripheral neuropathy. The lupus-like syndrome is usually seen with higher oral daily doses (> 200 mg daily)[21], though has been seen with doses as low as 50 mg daily when the exposure is prolonged (months to years)[22]. However, there is evidence that intravenous labetalol or oral nifedipine are preferable firstline agents compared to intravenous hydralazine in severe hypertension in pregnancy [20]. Hydralazine remains, however, commonly used when other treatment regimens have failed to achieve adequate BP control, as most obstetricians are quite familiar with its pharmacological actions and find its side-effect profile acceptable.

2.6. Diuretics

Diuretics are the most commonly used medication among women of childbearing age with chronic hypertension. [23] A possible side effect of any diuretic is vascular volume contraction, which may paradoxically cause further elevations of BP in preeclamptic women.

Women with preeclampsia have lower plasma volumes compared to those with normal pregnancies, and volume contraction may stimulate the renin-angiotensinaldosterone axis, causing further increases in peripheral vascular resistance, thus worsening hypertension. [24,25] However, the 2000 NHBPEP Working Group report on High BP in Pregnancy recognized that the major concern for diuretic use in pregnancy is mainly theoretical, as supporting evidence for their adverse effects is lacking. Therefore, if a woman is on a diuretic prior to pregnancy, this can be continued during pregnancy, with the exception of spironolactone, which may have fetal anti-androgen effects.

2.7. Renin-Angiotensin-Aldosterone System Blockade

Renin-Angiotensin-Aldosterone System (RAAS) blockers, including most commonly ACE inhibitors and ARBs, are extremely effective in lowering BP and have significant benefit in proteinuric diseases. Initially, these medications were considered to be relatively safe during the first trimester, and only associated with defects when taken in the second

trimester, potentially leading to oligohydramnios, anuria, and fetal renal failure. However, a study published in 2006 by Cooper and colleagues demonstrated that exposure to ACE inhibitors in the first trimester can be associated with significant congenital malformations affecting both the cardiovascular and central nervous systems. [26] The relative risk of major congenital malformations after a first trimester exposure was 2.71 (95% CI 1.72–4.27) as compared to infants with no exposure to anti-hypertensives. A 2011 study of over 400,000 women-infant pairs in the Northern California Kaiser Permanente region did find an increased risk of congenital heart defects in the offspring after exposure to ACE inhibitors in the first trimester as compared to healthy controls (OR 1.54, CI 0.9–2.62), but not as compared to women on other anti-hypertensive agents (OR 1.14, CI 0.65–1.98).[27] However, ACE inhibitors are still considered contraindicated in pregnancy, despite the controversy regarding the magnitude of the risk associated with exposure. If a woman becomes pregnant while on one of these agents, she should be switched immediately to an alternative therapy and offered an ultrasound and fetal echocardiography at 18 weeks gestation, and providers should discuss the possible risks for congenital malformations with the patient. There is little data regarding direct renin inhibitors, such as aliskerin, in pregnancy, but they are also considered category D by the US Federal Drug Administration as they block the RAAS system (see Table 4). As mentioned previously, spironolactone is contraindicated in pregnancy as it can cross the placenta and have anti-androgen effects on the fetus. There is a case report of eplerenone being used successfully for blood pressure control in a women with primary hyperaldosteronism during pregnancy.[28]

3. Management beyond Antihypertensive Therapy

3.1. Magnesium Sulphate and Other Anticonvulsants

A Cochrane review of treatment of women with preeclampsia reported that magnesium sulphate more than halves the risk of eclampsia and probably reduces maternal death [29]. In women with eclampsia, magnesium sulphate reduces the risk ratio of maternal death and of recurrence of seizures, compared with diazepam.

3.2. Antiplatelet agents

A review of 59 trials involving 37,560 women found that low doses of aspirin reduced the risk of preeclampsia by 17%, the risk of fetal or neonatal deaths by 14%, and the relative risk of preterm births by 8% [30]. Doses up to 75 mg appear to be safe.

3.3. Antioxidants to Prevent Preeclampsia

It has been demonstrated that supplementation with vitamin C (at a dose of 1000 mg daily) and vitamin E (at a dose of 400 IU daily) does not reduce the rates of either serious adverse outcomes of pregnancyassociated hypertension or preeclampsia among low-risk, nulliparous women [31].

3.4. Calcium Supplementation

A review of calcium supplementation during pregnancy for preventing hypertensive disorders concluded that calcium supplementation appears to approximately halve the risk of preeclampsia and reduces the risk of preterm birth and the rare occurrence of the composite outcome “death or serious morbidity” [32]. Of note, most women in these trials had a low-calcium diet.

3.5. Other Options

Other management options such as the use of corticosteroids, plasma volume expansion, or interventions such as rest or exercise have not been validated [33]. A suggested management paradigm can be found in the comprehensive review of preeclampsia by Steegers et al [34].

Table 4 Medication choices for pharmacologic treatment of hypertension in pregnancy

		Benefits	**Risks**	**U.S. Federal Drug Administration Pregnancy Risk Category**
Central agents				
Preferred	Methyldopa	Proven safety and efficacy	Neuro-depressant side effects	B/C in injectable form
Alternative	Clonidine	Efficacy similar to methyldopa	Unproven safety	C
Beta blockers				
Preferred	Labetalol	Safety and efficacy similar to methyldopa. May be used for hypertensive urgency.	Fetal bradycardia, neonatal hypoglycemia, decreased uteroplacental flow	C
Contraindicated	Atenolol	None compared to Labetalol	Intra-uterine growth retardation	D
Calcium channel blockers				
Preferred	Nifedipine	Lowers BP without affecting umbilical artery flow	Fetal distress, profound hypotension with magnesium	C
Alternative	Verapamil	Similar efficacy to other oral agents	Untested safety profile, risk of interaction with magnesium	C
Direct vasodilators				
Preferred	Hydralazine	Most efficacious oral agent	Maternal neuropathy, drug-induced lupus, neonatal thrombocytopenia and lupus	C
Alternative	Nitroprusside	Effective in severe hypertension	Cyanide and thiocyanate toxicityC	C
Diuretics				
Preferred	Thiazide	Useful in chronic hypertension, renal failure, congestive heart failure	Volume contraction, electrolyte abnormalities	B
Contraindicated	Spironolactone	None	Possible fetal anti-androgen effects	C
RAAS blockade				
Contraindicated	ACE inhibitors/ARBs	None	Associated with congenital heart and kidney defects	D
Contraindicated	Aliskerin	None	Oligohydramnios and other defects associated with RAAS blockade in the fetus	D

4. Conclusion

Hypertension in pregnancy is a common complication of pregnancy and one associated with significant maternal and fetal morbidity and mortality. The central issue in the management of hypertension in pregnancy is achieving a balance between the maternal benefits derived from improved BP control, and the fetal risks resulting from intrauterine medication toxicity and possible uteroplacental hypoperfusion. For the severe forms of hypertensive pregnancy disorders, including eclampsia, severe preeclampsia and HELLP syndrome, delivery remains the standard of care. Women with mild preeclampsia prior to 32 weeks gestation may be candidates for expectant management, but after 37 weeks, current evidence supports induction of labor to prevent adverse maternal and fetal outcomes.

Women with chronic hypertension should undergo a pre-pregnancy evaluation, with a focus on end-organ damage, medication profile, potential secondary causes of hypertension, and counseling on the risks of pregnancy, including the development of superimposed preeclampsia. Women must be followed carefully during pregnancy and in the intra- and post-partum settings. There is ongoing research focusing on the appropriate management of hypertension in pregnancy and the long-term consequences for the mother that may influence future recommendations in this field.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors state that this review was conducted without any conflict of interest.

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