Austin Hypertension

Open Access

Austin Publishing Group

Review Article

Hypertension in Pregnancy-Treatment

Gasnier R*
Hospital De Clinicas De Porto Alegre, Federal University of Rio Grande Do Sul, Brazil

***Corresponding author:** Gasnier R, Hospital De Clinicas De Porto Alegre, Federal University of Rio Grande Do Sul, Brazil

Received: September 19, 2016; **Accepted:** October 01, 2016; **Published:** October 14, 2016

Abstract

Chronic hypertension complicates 3-5% of pregnancies, with 25-30% of superimposed preeclampsia. Antihypertensive medication is used for severe hypertension cases, but there is no consensus about the treatment of mild-to-moderate hypertension in pregnancy. Agents used normally include methyldopa, labetalol and nifedipine. In cases of severe hypertension, intravenous labetalol and oral nifedipine are as effective as intravenous hydralazine. The objective of the treatment is to protect the mother and to permite continuation of the pregnancy. Treatment of hypertension is not related to prevention of preeclampsia, only can previne severe hypertension development.

Keywords: Chronic hypertension; Nifedipine; Hypertension treatment; Gestational arterial hypertension

Hypertension in Pregnancy

The American College of Obstetricians and Gynecologists (ACOG) had proposed in 1972 and revised in 2000 a classification for hypertension in pregnancy, with no changes during the Task Force in 2013 [1].

1. Preeclampsia-eclampsia.
2. Arterial chronic hypertension (of any etiology).
3. Arterial chronic hypertension with superimposed preeclampsia.
4. Gestational arterial hypertension.

Chronic hypertension is diagnosed before pregnancy or in the 20 weeks of gestation, or persists more than 42 days after delivery, complicating 3-5% of pregnancies [2]. In gestational hypertension cases, occurring in 6% of pregnancies, hypertension occurs after 20 weeks of pregnancy and is not associated to proteinuria or other systemic features of preeclampsia, with normalization during the 12 weeks following delivery [3]. Preeclampsia is characterized by hypertension and proteinuria or other systemic features. Eclampsia is described as convulsions associated to preeclampsia and not caused by epilepsy or other convulsive disorders. Preeclampsia superimposed on chronic hypertension is defined as a condition of hypertension with onset of proteinuria, complicating 25% of the pregnancies with chronic hypertension [4].

Hypertension is increasingly diagnosed in the childbearing age and this mainly due to the combination of obesity and older maternal age at pregnancy. Chronic hypertension often improves in the second trimester and early third trimester because of the reduction in the systemic vascular resistance, to be restored in late pregnancy. In some cases, women with gestational hypertension remain hypertensive after delivery. They most likely have preexisting chronic hypertension masked in early pregnancy by physiological vasodilatation. After delivery blood pressure usually falls, then increases over the first 5 postpartum days. Even women whose Blood Pressure (BP) was normal during pregnancy may experience transient hypertension in the early postpartum period, reflecting a degree of vasomotor instability [5,6].

Treatment of Hypertension

The control of severe hypertension is uncontroversial, preventing complications as intracranial hemorrhage, hypertensive encephalopathy, pulmonary edema, stroke and other cardiovascular complications. In addition, it is related to pregnancy prolongation and better perinatal outcomes, avoiding fetal distress. It is important to remember that cerebral hemorrhage is the commonest cause of maternal death in preeclampsia and eclampsia. Severe hypertension in pregnancy (systolic BP 170 mm Hg, diastolic BP 110 mm Hg) represents a very serious risk, but mild-to-moderate hypertension is associated to lower risk [7]. Those with hypertensive encephalopathy, hemorrhage or eclampsia require treatment with parenteral agents to lower MAP (Mean Arterial Pressure) by 25% over minutes to hours and then lower BP to 160/110 mm Hg over subsequent hours [8], avoiding hypotension. Lower doses should be initiated in preeclampsia, because of volume depletion and attention is needed for hypotension during treatment. The velocity of BP raise may be more important than the actual level of BP. The utero-placental circulation and the cerebrovascular circulation both do not auto regulate blood flow in this setting. The basic principle is always starting low and going slow.

Most women with chronic hypertension during pregnancy present with mild essential uncomplicated hypertension and are at minimal risk for cardiovascular complications within the short time of pregnancy. Women with mild, uncomplicated chronic hypertension, without target organ damage, have good perinatal outcomes regardless of the use of antihypertensive therapy [4]. Clinical trials indicate non-consistent data concerning antihypertensive treatment on antenatal rate of hospitalization, proteinuria at delivery and preeclampsia, perinatal outcomes, preterm labor or Small for Gestational Age (SGA) [9,10]. *Prevention of preeclampsia is desirable, but either specific BP targets or antihypertensive agents modify the risk.* Aspirin is related to risk reduction of preeclampsia in high risk groups as chronic hypertension [11]. Antihypertensive drugs, therefore, are not related to modification in the placentation process and do not reduce chance of preeclampsia progression.

Citation: Gasnier R. Hypertension in Pregnancy-Treatment. Austin Hypertens. 2016; 1(2): 1007.

Preeclampsia is a pregnancy-specific syndrome of reduced organ perfusion secondary to vasospasm and endothelial activation, occurring in 7-10% of pregnancies and it can be associated with significant maternal and fetal morbidity-mortality. Hypertension is due to generalized arteriolar vasospasm and decreased plasma volume. The pathological process in the placenta results in dissemination of abnormal substances throughout circulation, leading to disturbed endothelial function with multiorgan systemic clinical features. Maternal and perinatal morbidities significantly increased with severe preeclampsia, causing seizures, pulmonary edema, acute renal and liver failure, Disseminated Intravascular Coagulopathy (DIC), stroke. According to the Task force in 2013, proteinuria is not a necessary feature and the emphasis is the multiorgan system involvement, as previous described by Australasian Consensus [12].

Chronic hypertension therapy can be stopped during pregnancy under close observation, or a women whose arterial pressure was well controlled before pregnancy may continue with the same agents, if not contraindicated. *The National Institutes of Health recommend antihypertensive therapy for blood pressures exceeding a threshold of 150 to 160 mm Hg systolic or 100 to 110 mm Hg diastolic or in the presence of target organ damage* [2,8]. In women with renal dysfunction, it is better to choose a slightly lower threshold for treatment [13]. The focus of treatment is the pregnancy, during which untreated mild-to-moderate hypertension is unlikely to lead to unfavorable long-term maternal outcomes.

There are still no definitive and complete data about safe BP treatment targets for women with hypertension in pregnancy, however guidelines and reviews generally recommend the BP values of 140-155/90-105 mm Hg [14]. In contrast to hypertension guidelines in general clinical practice, which emphasize the systolic BP, much of the obstetric literature focuses on diastolic BP, in part because of the lack of clinical trials to support one approach versus another. Review of women who suffered stroke in the setting of preeclampsia had demonstrated systolic hypertension more prevalent that diastolic hypertension (most women did not reach diastolic BP of 110 mm Hg) [15]. *The literature suggests that the degree of systolic hypertension may be more associated with significant morbidity.*

There are two approaches for hypertensive pregnant with Chronic Kidney Disease (CKD): the same guidelines for chronic hypertension in pregnancy or transferring the "lowest the best" approach suggested in non-pregnant CKD patients (normally BP less than 120/80 mm Hg) [16]. The effect of stricter BP control in preventing placental damage is more important in CKD with normal placentation as compared to cases in which the placenta itself is the origin of hypertension (preeclampsia superimposed on CKD). In the same way that it is possible to see different forms of preeclampsia, also there are different presentations of chronic kidney disease. Control of hypertension related to renal disease is important to prevent severe hypertension and renal damage during pregnancy, sometimes irreversible.

Antihypertensive Drugs

The question has been raised whether treatment is necessary in mild-to-moderate hypertension, especially in the absence of proteinuria. Drugs used are mainly to prevent and treat severe hypertension. One concern is that hypertension or iatrogenic hypotension might cause cardiovascular malformations and reduction of birth weight by altering perfusion in the placenta and/or fetus [17]. Because of the circulating plasma volume contraction in preeclampsia, women may be very sensitive to relatively small doses of antihypertensive agents, risking abrupt reductions in blood pressure.

Fetal growth restriction secondary to placental insufficiency can occurs in pregnancy complicated by hypertension. Reduction in maternal BP may lead to decrease in uterine perfusion pressure and consequently in fetal oxygen supply. Decreased blood volume in preeclampsia may exacerbate this effect. *In cases of mild chronic hypertension, ACOG recommends withholding or discontinuing therapy because of concern about fetal growth.*

Benefits and risks of antihypertensive treatment for mild-to-moderate hypertension are not completely defined in recent reviews, including a Cochrane meta-analysis [7,18]. Antihypertensive treatments for mild-to-moderate hypertension seem to be beneficial for the mother, but without better pregnancy outcome. Treatment is based on control of severe rise in BP and the fact that arteriolar vasodilatation may help to improve organ perfusion.

International societies have differed in their recommendations for the BP which should initiate therapy. The US professional bodies recommend starting with the therapy at BP 160/105 mm Hg, not defining the target values [8]. The Canadian Hypertension Society recommends BP of 140-150/90-95 mm Hg, targeting dBP 80-89 mm Hg [19]. The Australasian professional bodies recommend BP 160/90 mm Hg and target value of 140-110/80-90 mm Hg. In cases of co-morbidities as pre-gestational diabettes and renal diseases, the values should be more restrict, but is necessary to avoid excessive lower BP to prevent placental hypoperfusion and fetal growth abnormalities [20]. The National Institute of Health and Clinical Excellence recommends BP lower than 150/100 mm Hg in pregnant women with uncomplicated chronic hypertension and that lowering diastolic pressure below 80 mm Hg should be avoided. Blood pressure should be lower than 140/90 mm Hg in cases of target-organ damage.

During the Control of Hypertension in Pregnancy Study (CHIPS), comparing less-tight vs. tight control, it was shown that less-tight control was not superior to tight control for the fetus but was associated with more severe hypertension for the mother [21]. The composite primary outcome was pregnancy loss or high-level neonatal care for more than 48 hours in the first 28 days of life and the secondary serious maternal complications before 6 weeks postpartum. It is important to remember that failure to identify and treat it has been recognized as the most important failing in the care of women with pregnancy hypertension. It was a randomized trial-987 women-allocated to a target diastolic BP of 100 mm Hg or 85 mm Hg. There were few differences in key baseline characteristics between less tight versus tight control among women on either labetalol or methyldopa [22], but women who switched from labetalol or methyldopa to an agent other than these two had worse outcomes. Severe hypertension was not a primary or secondary outcome and was already a known risk associated with less-tight control. The power was insufficient to assess pregnancy outcomes that are influenced by antihypertensive therapy as SGA.

In a second analysis of this trial it was concluded that at the time that a pregnant women with chronic hypertension becomes hypertensive, or a normotensive women develops gestational hypertension, it is not possible to use maternal or pregnancy clinical characteristics including BP level to predict adverse outcomes [23]. In the same way, outcomes for less tight *versus* tight control were not dependent on use of methyldopa or labetalol [24]. The medications were considered at or after randomization.

Centrally acting alfa-2-adrenergic agonists

Methyldopa: It is the most common treatment for hypertension in pregnancy. There is extensively experience with the drug and long-term follow-up data regarding children whose mothers received methyldopa during pregnancy [14,25]. In a follow-up study of a large clinical trial on the effectiveness of methyldopa versus no treatment, no differences were found in the functional development of children a 4 and 7.5 years of age [26,27]. During the long term treatment, the drug does not alter cardiac output or blood flow to the uterus or kidneys [28]. BP control is gradual, over 6 to 8 hours, because of the indirect mechanism of action. It was tested in several trials compared to placebo or other hypertensive treatments.

Adverse effects are consequence of central alfa-2-agonism or decreased peripheral sympathetic tonus. These drugs act in sites in brain stem to decrease mental alertness and impair sleep, leading to fatigue, depression, poor sleep. Decreasing salivation leading to xerostomia is experienced. Elevated transaminases (5%), hepatitis and hepatic necrosis have also been reported. Some patients will develop a positive antinuclear antigen or antiglobulin (Coombs) test with chronic use and this is occasionally associated with clinical hemolytic anemia. In these cases, medications of other classes are used [29].

Clonidine: It is a selective alfa-2-agonist, acts similarly and is comparable to methyldopa with respect to safety and efficacy. Sleeping disturbances after prenatal exposure have been reported in a cohort study. It is used as third agent line for multidrug control of refractory hypertension [30].

Peripherally acting adrenergic-receptor antagonists

Beta-blockers have been used extensively in pregnancy. Small studies had suggested an association with lower Birth Weight Infants (LBW); however, in a recent meta-analysis of published data from randomized trials, the presence of SGA appeared not to be related to the antihypertensive used [31].

Labetalol: It is a non-selective beta-blocker with vascular alfa1-receptor-blocking effects and produces its hypotensive effects without compromising the maternal cardiovascular system, with immediate and prolonged effect and uteroplacental flow increase. In a trial which has included 263 patients with mild-to-moderate hypertension, randomly separated to methyldopa, labetalol and no treatment, patients with therapy had significantly lower maternal blood pressures compared to the non-medication group and were no differences among the groups concerning gestational age at delivery, birth weight, incidence of fetal growth restriction, neonatal head circumference or uteroplacental circulation [32]. *In some centers methyldopa was substituted for labetalol as the first choice of treatment because of central side effects of methyldopa*. Others otherwise concluded that labetalol as other beta blockers is related to fetal growth abnormalities.

It is considered safe and effective treatment, although neonatal hypoglycemia with higher doses has been reported and one placebo controlled study reported an association with fetal growth restriction in the management of preeclampsia remote from term [33]. It is used parentally to treat severe hypertension: because of a lower incidence of maternal hypotension and other adverse effects, its use now supplants that of hydralazine [34], which was previously the most commonly used agent for the treatment of severe hypertension. There is wide interpatient variability in the dose of labetalol required to control BP, an event that is not predictable by any clinical item before therapy. Another problem is the variable duration of action, particularly in patients who require higher doses. Congestive heart failure, asthma, sinus bradycardia and first-degree atrial-ventricular block contra-indicate its use.

Atenolol: It is a commonly used cardio selective beta-blocker in non-pregnant patients, but its use especially in early pregnancy should be avoided. Placebo-controlled study demonstrated that atenolol in early pregnancy for chronic hypertension treatment is associated with significantly LBW and higher proportion of SGA, compared to the placebo group [35]. Bayliss concluded that LBW was associated to atenolol taken at the time of conception or during the first trimester of pregnancy [36]. Studies with atenolol in preeclampsia failed to find differences, maybe because of the late starting therapy.

In a meta-analysis and Cochrane review in 2000, individual agents were not different in their perinatal effect with the exception of atenolol, which in one small study was started at 12 to 24 weeks and resulted in significant fetal growth restriction and decreased placental weight compared to placebo: these findings were supported in subsequent retrospective review comparing atenolol with alternative therapies. Oral beta-blockers for mild-to-moderate hypertension during pregnancy have specifically been estimated in the Cochrane database [37].

Maternal outcomes are improved with the use of beta-blockers, with effective control of BP, decreased incidence of severe hypertension and decreased rate of preterm admission [2]. They have been found to be more effective in lowering BP compared with methyldopa in 10 trials in a recent Cochrane analysis [7].

Peripherally acting alfa-adrenergic antagonists are second line antihypertensive drugs in non-pregnant adults. Those are indicated during pregnancy in the management of hypertension because of suspected pheochromocytoma and both prazosin and phenoxybenzamine have been used, with beta-blockers used as adjunctive agents after alfa-blockade is accomplished [38]. Because there is limited experience with these drugs in pregnancy, their routine use cannot be advocated.

Methyldopa *versus* labetalol was associated with fewer adverse perinatal and maternal outcomes during CHIPS trial: pregnancy loss or high-level neonatal care for more than 48 hours (CHIPS primary outcome), birth weight<10th centile, severe maternal hypertension, preeclampsia and delivery at <37 weeks or <34 weeks of gestation.

Methyldopa also was of particular benefit among women with preexisting hypertension for perinatal outcomes and preterm delivery [24]. These results are consistent with a recent historical cohort from Canada: women with chronic hypertension taking methyldopa and

not labetalol had fewer SGA and/or with necessity of hospitalization (respiratory distress, sepsis, seizures) [39]. The findings are not consistent with the results of previous studies: methyldopa may have had better outcomes, particularly among women with preexisting hypertension.

Severe hypertension was more common in the higher BP arm whether labetalol was the recommended drug or methyldopa was used exclusively. *There is no evidence that the results of CHIPS are dependent on the choice of labetalol or methyldopa therapy used to achieve less tight or tight control of maternal BP.*

Otherwise, meta-analysis of 22 trials did not find a significant difference in outcomes for methyldopa compared with beta-blockers [40]. Analyzing methyldopa *versus* beta-blockers and methyldopa *versus* calcium-channel blockers, methyldopa was associated with more adverse maternal outcomes (without impact on perinatal outcomes) with more severe hypertension (RR 1.85 95% CI 1.05-3.33) and progression to proteinuria preeclampsia (RR 1.33 95% CI 1.01-1.85).

Calcium Channel Blockers (CCB)

Calcium channel blockers have been used to treat chronic hypertension, mild preeclampsia presenting late in gestation and urgent hypertension associated with preeclampsia. The papers have focused on the use of nifedipine. Amlodipine has been used in pregnancy but safety data are lacking. Over the last decades its favorable characteristics have resulted in its efficacy and safety being assessed in pregnancy. Its application both as a treatment for acute severe hypertension, as well as for long term use for hypertension in pregnancy, have been explored. It has minimal effect on the cardiac conducting system. It causes a decrease in arterial vascular resistance but with minimal effect on the venous system. It results in a 20% lowering of the systolic, diastolic and arterial blood pressures [41].

Due to the differences in the metabolism and clearance in pregnancy, the recommended starting dose is 10 to 20 mg, six hourly. The efficacy and safety of long acting oral nifedipine, with less risk of hypotension and fetal distress was proven for severe hypertension in pregnancy, advocating its use [42,43]. The mode of action of nifedipine reducing systemic vascular resistance and its ability to improve renal blood flow make it a highly appropriate drug for use in hypertension in pregnancy [44]. If rapid BP control is desired, the use of parenteral labetalol or hydralazine is recommended, until the desired target is achieved. *The Canadian Hypertension Society as well as the Australasian Society for Study of Hypertension has both recommended its use as one of the first line drugs in severe hypertension in pregnancy.*

Nifedipine also causes an increase in blood flow to the liver which may alter the metabolism of other drugs. Maternal side effects with nifedipine seldom occur and there is rarely a need to stop the drug. Side effects are related to the dose and include flushing, headaches, sweaty palms, peripheral edema [45]; rarely constipation, diarrhea, heartburn, dyspnea and chest pain have been described. Tachycardia occurs commonly but is seldom associated with palpitations and appears to have no adverse effects.

Nifedipine does not seem to cause decrease in uterine blood flow. It has been compared with methyldopa for the treatment of pregnancy-induced hypertension and been shown to be comparable in its antihypertensive action but achieved no improvement in prolongation of pregnancy or fetal outcome. It appears to be as good as hydralazine in its antihypertensive effect, but its onset of action is less likely to be precipitous. Both drugs seem to reduce blood pressure to acceptable levels due to a significant reduction in systemic vascular resistance, accompanied by similar increases in cardiac output and heart rate. Nifedipine is also associated with fewer episodes of acute fetal distress, as suggested by non-reassuring fetal heart rate changes in pregnancies with and without intrauterine growth restriction. Different units have their preferences for either parenteral labetalol or hydralazine and some use oral nifedipine.

A recent large study from the Agency for Healthcare Research and Quality-funded Health Maintenance Organization Research Network's Center for Education and Research on Therapeutics program have concluded that third trimester exposition to calcium channel blockers was associated with markedly increased risk of neonatal seizures in term neonates, related to a decrease in fetal intracellular calcium [46]. Bateman, et al. otherwise, did not observe that increase [47].

A systematic review by Shekhar, et al. based on the results of seven trials and 363 women with severe hypertension has concluded that nifedipine is more effective that intravenous labetalol: less persistent severe hypertension 3.3% *vs.* 8.3% RR 0.42 95% CI 0.18-0.96 [48]. Nifedipine was associated with fewer maternal adverse effects as headache, nausea, vomiting and palpitations.

Direct vasodilators

Dihydralazine: Dihydralazine selectively relaxes arteriolar smooth muscle by an unknown mechanism. It has been commonly used in the acute emergency or as a third line agent for multidrug control of refractory hypertension. Its ability to cause too rapid a fall in blood pressure is well described, due to excessive vasodilatation or sympathetic activation. It is possible that hypotensive episodes may be a reflection of underlying intravascular volume status rather than any property of the drug itself. Also oral hydralazine it can be used for chronic hypertension in the second and third trimesters, but its use has been supplanted by agents with more favorable adverse effects [49]. Chronic use can lead in rare cases to a pyridoxine-responsive polyneurophaty or to immunologic reactions, including a drug-induced lupus syndrome. It has been used in all trimesters of pregnancy and data have not shown an association with teratogenicity, although neonatal thrombocytopenia and lupus have been reported [50] (Tables 1 & 2).

A recent meta-analysis of intravenous hydralazine for severe hypertension in pregnancy has concluded that parenteral labetalol or oral nifedipine were preferable first-line agents in accordance with association of intravenous hydralazine with more maternal and perinatal adverse effects, such as maternal hypotension, maternal oliguria, cesarean section, placental abruption, adverse effects on fetal heart rate and low Apgar scores at one minute [34,51].

Isosorbide nitrate: It is a Nitric Oxide (NO) donor, has been investigated in a small study of gestational hypertensive and preeclamptic pregnant patients. It was found that cerebral perfusion pressure is unaltered by isosorbide dinitrate, despite significant

Table 1: Hypertension treatment.

Medication	Recommended Dose
First line therapy	
Methyldopa	0.5 to 3 g/day in 2 to 3 times
Labetalol	200 to 1200 mg/day in 2 to 3 times
Second/Third line therapy	
Hydralazine	50 to 300 mg/day in 2 to 4 times
Atenolol	50 to 100 mg/day in 2 to 3 times
Nifedipine	30 to 120 mg/day in 3 to 4 times
Verapamil	240 to 320 mg/day in 3 times
Hydroclorotiazide	12.5 to 50 mg/day in the morning

Adapted from Umans, Lindheimer 1998 and NHBPEP 2000.

changes in maternal BP, thus decreasing the risk for ischemia and infarction when BP is lowered [52]. Besides, some papers had tested your use in form of patch medication for meliorating Doppler measurements and consequently with best pregnancy outcomes [53].

Sodium nitroprusside and diazoxide: These are known to produce precipitous falls in blood pressure, often with adverse effects in an already compromised fetus [54]. Sodium nitroprusside, a direct NO donor, which non selectively relaxes both arteriolar and venular vascular smooth muscle, is potent, rapid-acting and short-lasting drug which is used in pregnancy for the treatment of an acute hypertensive crisis not responding to other agents. Administered only by continuous titrated because it has a near-immediate onset of action and duration of effect of 3 minutes. Considering that utilization of this medication may cause fetus cyanide poisoning, transient fetal bradycardia, metabolic acidosis and maternal hypotension, it must be given under continuous surveillance and with caution. When control of acute crisis is attained, the fetus should be delivered as soon as possible. It is a drug of last choice for the treatment of acute hypertension in pregnancy.

Diuretics

Diuretics are common antihypertensive drugs used in non-pregnant patients because of low cost and suitable impact on major cardiovascular events as shown in randomized controlled trials. Although diuretics reducing maternal plasma volume have been reported to be connected with poor perinatal outcome, negative effect on fetal growth has not been completely proven. It does not seem to increase neonatal thrombocytopenia or other adverse effect among newborns. Hydrochlorotiazide, triamterene and amiloride are not considered teratogenic [55,56]. The use of spironolactone is not advised because of its antiandrogenic effects during fetal development [57,58]. The National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy concluded that they may be continued through gestation (with an attempt made to lower the dose) or used in combination with other agents, especially for women deemed likely to have salt-sensitive hypertension.

The side effects of diuretics are expected in situation of volume depletion as preeclampsia, despite salt and water retention, but volume overload is usually the main cause of CKD hypertension for which the use of diuretics has been reevaluated. Diuretic are the basis of the supportive management of the nephrotic syndrome in non-pregnant patients and it may difficult to control edema without diuretics.

In the postpartum period, with the return of liquid from the interstitial and extravascular compartment to the intravascular, rise in BP is common. In preeclampsia cases, also is noted inadequate secretion of sodium due to reduced glomerular filtration. Loop diuretic can act in patients with fluid overload, eliminating the intravascular fluid that has been mobilized in the postpartum period and reducing the need of antihypertensive therapy. Also it acts maintaining low central venous pressure and pulmonary capillary wedge pressures, raising colloid osmotic pressure and preventing development of pulmonary edema and congestive heart failure.

Angiotensin-converting-enzyme inhibitors and Angiotensin receptor antagonists

Angiotensin-Converting-Enzyme (ACE) inhibitors are contraindicated in second and third trimesters because of toxicity associated with reduced fetal renal perfusion. It is proved that may cause oligohydramnios as a result of fetal oliguria, fetal growth restriction, calvarial and pulmonary hypoplasia, joint contractures and renal dysgenesis, neonatal anuric renal failure, hypotension and death [59,60]. Similar fetal anomalies have been reported with angiotensin II receptor antagonists [61], attributed primarily to renal failure [62,63].

Some studies have reported fetal abnormalities among women who have taken ACE inhibitors only during the first trimester of pregnancy. Several studies have shown that the expression of the type II angiotensin receptor peaks early in gestation and then gradually declines, with a role in the early embryologic development of the heart, kidney and brain. These drugs also have been shown to inhibit the proliferation of fetal smooth-muscle cells in the ductus arteriosus,

Table 2: Acute hypertension treatment (BP>155/105 mm Hg).

Woman lying on her left side		
Venous access with dextrose 5%		
Options of treatment		
1	**Nifedipine**	10-20 mg, repeat every 30 minutes if necessary, in a total of 30 mg.
2	**Hydralazine**	5 mg (diluting 1 ampoule-2 ml 20 mg) in 3 ml of distilled water, each 1 ml is 5 mg of hydralazine). If blood pressure is not controlled, repeat 5 to 10 mg every 20 minutes. Repeat the medication if necessary until 20-30 mg for each drug (BP>155/105 mm Hg).
3	**Labetalol**	It is an option: 20 mg in bolus and if necessary, repeat 40 mg in 10 minutes and more two doses of 80 mg every 10 minutes (total dose 220-300 mg). Maternal blood pressure measurement every 5 minutes for 20 minutes after medication. Fetal heart pattern evaluation by at least 20 minutes after the medication. BP targets<160/110 and >135/85 mm Hg.

Adapted from NHBPEP 2000.

which may lead to patent ductus [64,65]. Cooper, et al. conducted a study to assess the association between exposure to ACE inhibitors during the first trimester and risk of congenital malformations: the risk of major malformations was higher in infants who had been exposed to ACE inhibitors, compared with infants who had not been exposed to antihypertensives (OR 2.71), while exposition to other antihypertensive medications did not increase the risk of major malformations. Among infants with exposure to ACE inhibitors in the first trimester alone, the adjusted proportion with any major congenital malformation was 7.1 percent. ACE inhibitors increased risk of malformations of the cardiovascular system and the central nervous system [66]. *Also has been suggested that these agents should be avoided by women who attempt to conceive* [67]. Whether adverse outcomes are because of a hemodynamic effect in the fetus or specific requirements for angiotensin II as a fetal growth factor is unknown: first trimester use of these drugs should be avoided. Because angiotensin II receptors are widely expressed in fetal tissues and could have an important role in fetal development, it is possible that first trimester exposition to ACE inhibitors increases the risk of congenital malformations.

Because exposure to ACE inhibitors during first trimester is not considered safe, it may be best to counsel women to switch to alternative agents while attempting to conceive. In those who inadvertently become pregnant, the risk of birth defects rises from 3 to 7%: it is not recommended pregnancy termination.

Currently, all ACE inhibitors, Angiotensin Receptor Blockers (ARBs) and renin inhibitors are considered pregnancy category C (FDA Pregnancy Category to indicate the potential of a drug to cause birth defects) in the first trimester and category D in the second and third trimesters. Considering the importance of renal protection and following the hypothesis that starting pregnancy with low levels of proteinuria has a positive effect on the outcomes, it is possible to do a course of treatment previous a new pregnancy.

Serotonin$_2$ receptor blockers

Serotonin-induced vasodilatation is mediated by S_1 receptors and release of prostacyclin and NO. Endothelial dysfunction and loss of endothelial S_1 receptors allows serotonin, of which the levels are greatly increased in pregnancy, to react only with S_2 receptors, resulting in vasoconstriction and platelet aggregation. **Ketanserin** is a selective S_2 receptor-blocking drug that decreases systolic and diastolic BP in non-pregnant patients with acute or chronic hypertension. It has not be found to be teratogen in animals or humans and has been studied in small trials, which suggest that may be safe and useful in the treatment of chronic hypertension in pregnancy, preeclampsia and HELLP syndrome [68,69]. Ketanserin has not been FDA approved for pregnancy in the United States.

Management of Hypertension Postpartum

No guidelines exist to post-partum, but it was suggested that treatment should be initiated if the BP exceeds 150 mm Hg of systolic or 100 mm Hg of diastolic in the first 4 days of the puerperium [70,71]. Choice of antihypertensive agent in the postpartum period is often influenced by breastfeeding, but in general the agents commonly used in the antepartum period may be continued postpartum. The medication may be discontinued when BP normalizes, which occurs days to several weeks postpartum and home BP monitoring may be helpful. Up 20% of women with hypertensive pregnancy disorders might persist with high BP levels after 6 weeks postpartum, thus developing chronic hypertension.

In cases of severe preeclampsia, seems to be benefiting a brief course of oral furosemide course in the days postpartum, particularly in cases of hypertension with symptomatic pulmonary or peripheral edema [72,73]. It is related to better control of hypertension and a less prolonged hospitalization. Case reports have suggested that nonsteroidal anti-inflammatories may contribute to BP elevation postpartum and the effects on non-pregnant individuals are well documented [74]. These drugs should be used with caution or perhaps be avoided in postpartum patients already hypertensives.

There are no well-designed studies assessing neonatal effects of maternally administered antihypertensive drugs delivered via breast milk. Satisfactory drugs include metyldopa, beta-blockers with high protein binding, ACE inhibitors and some CCB, as nifedipine. Neonatal exposure to methyldopa is likely low and it is generally considered safe. Atenolol and metoprolol are concentrated in breast milk, possibly to levels that could affect the infant; by contrast, exposure to labetalol and propranolol seems low. Although milk concentrations of diuretics are low and considered safe, these agents can decrease milk production significantly. There are reports of calcium channel blockers transfer into breast milk, apparently without significant adverse effects. Sufficient data exist for the safety of captopril and enalapril [75].

References

1. Hypertension in pregnancy: report of the American College of Obstetricians and Gynecologists' Task force on Hypertension in Pregnancy. Obstet Gynecol. 2013; 122: 1122-1131.
2. Magee LA, Ornstein MP, Dadelszen VP. Management of hypertension in pregnancy. BMJ. 1999; 318: 1332-1336.
3. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. Obstet Gynecol. 2003; 102: 181-192.
4. Sibai BM. Chronic hypertension in pregnancy. Clin Perinatol. 1991; 833-844.
5. Folic M, Folic N, Varjacic M, Jakovijevic M, Jankovic S. Antihypertensive drug therapy for hypertensive disorders in pregnancy. Acta Medica Medianae. 2008; 47; 65-72.
6. James PR, Nelson-Piercy P. Management of hypertension before, during and after pregnancy. Heart. 2004; 90: 1499-1504.
7. Abalos E, Duley L, Steyn D and Henderson-Smart D. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev. 2014; 2252.
8. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol. 2000; 183: 1-22.
9. Montan S. Drugs used in hypertensive diseases in pregnancy. Current Opinion in Obstet Gynecol. 2004; 16: 111-115.
10. Lubano K, Qureshi Z. Antihypertensive drug therapy for mild-to-moderate hypertension during pregnancy. RHL commentary, The WHO Reproductive Health Library; Geneva: World Health Organization. 2007.
11. Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Buyold E. The role of aspirin on the prevention of preeclampsia and fetal growth restriction: systemic review and meta-analysis. Am J Obstet Gynecol. 2016.
12. Brown MA, Lindheimer M, De Swiet, Assche VA, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy:

statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy. 2001; 20: IX-XIV.

13. Sibai BM. Chronic hypertension in pregnancy. Obstet Gynecol. 2002; 100: 369-377.

14. Sibai BM, Barton JR. Expectant management of severe preeclampsia remote from term: patient selection, treatment and delivery indications. Am J Obstet Gynecol. 2007; 196: 511-519.

15. Martin JN, Thigpen BD, Moore RC, Rose CH, Cushman J, May W. Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure. Obstet Gynecol. 2005; 105: 246-254.

16. Piccoli GB, Cabiddu G, Attini R, Parisi S, Fassio F, Loi V, et al. Hypertension in CKD pregnancy: a question of cause and effect (cause or effect? This is the question). Curr Hypertens Rep. 2016; 18: 35-46.

17. Schardein JL. Chemically induced birth defects. 3rd ed. New York, NY: Marcel Dekker, Inc. 2000; 517-557.

18. Dadelszen VP, Magee LA. Antihypertensive medications in management of gestational hypertension-preeclampsia. Clin Obstet Gynecol. 2005; 48: 441-459.

19. Rey E, Lorier LJ, Burgess E, Lange IR, Leduc L. Report of the Canadian Hypertension Society consensus conference. Pharmacologic treatment of hypertensive disorders in pregnancy. Canadian Medical Association Journal. 1997; 157: 1245-1254.

20. Brown MA, Hague WM, Higgins J, Lowe S, McCowan L, Oats J. The detection, investigation and management of hypertension in pregnancy: full consensus statement. Aust N Z J Obstet Gynaecol. 2000; 40: 139-155.

21. Magee LA, Dadelszen VP, Rey E, Susan Ross, Elizabeth Asztalos, KE Murphy, et al. Less-tight *versus* tight control of hypertension in pregnancy. NEJM. 2015; 372: 407-417.

22. Magee LA, Dadelszen VP, Singer J, Lee T, Rey E, Ross S, et al. Control of Hypertension in Pregnancy Study randomized controlled trial-are the results dependent on the choice of labetalol or methyldopa? BJOG. 2016; 123: 1135-1141.

23. Magee LA, Dadelszen VP, Singer J, Lee T, Rey E, Ross S, et al. Can adverse maternal and perinatal outcomes be predicted when blood pressure becomes elevated? Secondary analyses from the CHIPS (Control of Hypertension in Pregnancy Study) randomized controlled trial. Acta Obstet Gynecol Scand. 2016; 2: 1-13.

24. Magee LA, Dadelszen VP, Singer J, Lee T, Rey E, Ross S, et al. Do labetalol and methyldopa have different effects on pregnancy outcome? Analysis of data from the Control of Hypertension in Pregnancy Study (CHIPS) trial. BJOG. 2016; 123: 1143-1151.

25. Fidler J, Smith V, Fayers P. Randomized controlled comparative study of methyldopa and oxprenolol in treatment of hypertension in pregnancy. Br Med J. 1983; 286: 1927-1930.

26. Ounsted MK, Moar VA, Good FJ, Redman CW. Hypertension during pregnancy with and without specific treatment; the development of the children at the age of four years. BJOG. 1980; 87: 19-24.

27. Podymow T, August P. Update on the use of antihypertensive drugs in pregnancy. Hypertension. 2008; 51: 960-969.

28. Khedun S, Maharaj B, Moodley J. Effects of antihypertensive drugs on the unborn child. Paediatr Drugs. 2000; 2: 419-436.

29. Redman CW, Beilin LJ, Bonnar J. Treatment of hypertension with methyldopa blood pressure control and side effects. BJOG. 1977; 84: 419-426.

30. Cockburn J, Moar VA, Ounsted M, Redman CW. Final report of study on hypertension during pregnancy: the effects of specific treatment on the growth and development of the children. Lancet. 1982; 647-649.

31. Dadelszen VP, Ornstein MP, Bull S, Logan AG, Koren G, Magee LA. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension. Lancet. 2000; 335: 87-92.

32. Sibai BA, Mabie WC, Shamsa F, Villar MA, Anderson GD. A comparison of no medication *versus* methyldopa or labetalol in chronic hypertension during pregnancy. Am J Obstet Gynecol. 1990; 162: 960-967.

33. Sibai BM, Gonzalez AR, Mabie WC, Moretti M. A comparison of labetalol plus hospitalization *versus* hospitalization alone in the management of preeclampsia remote from term. Obstet Gynecol. 1987; 70: 323-327.

34. Magee LA, Cham C, Waterman EJ, Ohlsson A, Dadelszen V. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. BMJ. 2003; 327: 955-960.

35. Butters L, Kennedy s, Rubin PC. Atenolol in essential hypertension in pregnancy. BMJ. 1990; 301: 587-589.

36. Bayliss H, Churchill D, Beevers M, Beevers DG. Antihypertensive drugs in pregnancy and fetal growth: evidence for "pharmacological programming" in the first trimester? Hypertens. Pregnancy. 2002; 21: 161-174.

37. Magee LA, Duley D. Oral beta-blockers for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev. 2000; 2863.

38. Grodski S, Jung C, Kertes P, Davies M, Banting S. Phaeochromocytoma in pregnancy. Intern Med J. 2006; 36: 604-606.

39. Xie RH, Guo Y, Krewski D, Mattison D, walker MC, Nerenberg K, et al. Beta-blockers increase the risk of being born small for gestational age or of being institutionalized during infancy. BJOG. 2014; 121: 1090-1096.

40. Abalos E, Duley L, Steyn DW. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev. 2014; 2252.

41. Gasnier R, Valerio EG, Ramos JGL. Antihypertensive drugs in pregnancy. Family Med and Community Health. 2013; 37-50.

42. Brown MA, Buddle ML, Farrel T, Davis GK. Efficacy and safety of nifedipine tablets for the acute treatment of severe hypertension in pregnancy. Am J Obstet Gynecol. 2002; 187: 1046-1050.

43. Prevost RR, Pharm D, Sherif A, Whybrew DW, Sibai BM. Oral nifedipine: pharmacokinetics in pregnancy induced hypertension. Pharmacotherapy. 1992; 12: 174-177.

44. Smith P, Anthony J and Johanson R. Nifedipine in pregnancy. BJOG. 2000; 107: 299-307.

45. Papatsonis DN, Lok CA, Bos JM, Geijn HP, Dekker GA. Calcium channel blockers in the management of preterm labor and hypertension in pregnancy. Eur. J Obstet Gynecol Reprod Biol. 2001; 97: 122-140.

46. Davis RL, Eastman D, McPhillips H, Raebel MA, Andrade SE, Smith D, et al. Risks of congenital malformations and perinatal events among infants exposed to calcium channel blockers during pregnancy. Pharmacoepidemol Drug Saf. 2011; 20: 138-145.

47. Bateman BT, Huybrechts KF, Ayumi M, Desai R, Patorno E, Seely EW, et al. Calcium channel blocker exposure in late pregnancy and the risk of neonatal seizures. Obst Gynecol. 2015; 126: 271-278.

48. Shekhar S, Gupta N, Kirubakaran R, Pareek P. Oral nifedipine *versus* intravenous labetalol for severe hypertension during pregnancy: a systematic review and meta-analysis. BJOG. 2016; 123: 40-47.

49. Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European society of Cardiology. Expert consensus document on management of cardiovascular diseases during pregnancy. Eur Heart J. 2003; 24: 761-781.

50. Widerlov E, Karlman I, Storsaret J. Hydralazine-induced neonatal thrombocytopenia. NEJM 1980; 303: 1235.

51. Magee LA, Abalos E, Dadelszen VP, Sibai B, Walkinshaw SA. CHIPS Study Group. Control of hypertension in pregnancy. Curr Hypertens Rep. 2009; 11: 429-436.

52. Nevo O, Thaler I, Shik V, Vortman T, Soustiel JF. The effect of isosorbide dinitrate, a donor of nitric oxide, on maternal cerebral blood flow in gestational hypertension and preeclampsia. Am J Obstet Gynecol. 2003; 188: 1360-1365.

53. Kalidindi M, Velauthar L, Khan K, Aquilina J. The role of nitrates in the prevention of preeclampsia: an update. Curr Opin Obstet Gynecol. 2012; 24: 361-367.

54. Godlin RC. Fetal and maternal effects of sodium nitroprusside. Am J Obst Gynaecol. 1983; 146: 350-351.

55. Sibai BM, Grossman RA, Grossman HG. Effects of diuretics on plasma volume in pregnancies with long-term hypertension. Am J Obstet Gynaecol. 1984; 150: 831-835.

56. Collins R, Yusuf S, Peto R. Overview of randomized trials of diuretics in pregnancy. BMJ. 1985; 290: 17-23.

57. Psaty BM, Smith NL, Siscovick DS, Koepsell TD, Weiss NS, Heckbert SR, et al. Health outcomes associated with antihypertensive therapies used as first-line agents: a systematic review and meta-analysis. JAMA. 1997; 277: 739-745.

58. Groves TD, Corenblum B. Spironolactone therapy during human pregnancy. Am J Obstet Gynecol. 1995; 172: 1655-1656.

59. Gress TW, Nieto J, Shahar E, Wofford MR, Brancati FL. Atherosclerosis Risk in Communities Study Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. NEJM. 2000; 342: 905-912.

60. Quan A. Fetophaty associated with exposure to angiotensine converting enzyme inhibitors and angiotensin receptor antagonists. Early Hum Dev. 2006; 82: 23-28.

61. Pryde PG, Sedman AB, Nugent CE, Barr M. Angiotensin-converting enzyme inhibitor fetopathy. J Am Soc Nephrol. 1993; 3: 1575-1582.

62. Alwan S, Polifka JE, Friedman JM. Angiotensin II receptor antagonist treatment during pregnancy. Birth Defects Res A Clin Mol Teratol. 2005; 73: 123-130.

63. Briggs GG, Nageotte MP. Fatal outcome with the combined use of valsartan and atenolol. Ann Pharmacolther. 2001; 35: 859-861.

64. Lambot MA, Vermeylen D, Noel JC. Angiotensin-II-receptor inhibitors in pregnancy. Lancet. 2001; 357: 1619-1620.

65. Steffensen FH, Nielsen GL, Sorensen HT, harlotte Olesen, Jorn Olsen. Pregnancy outcome with ACE-inhibitors use in early pregnancy. Lancet. 1998; 351: 596.

66. Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. NEJM. 2006; 354: 2433-2451.

67. Bos-Thompson MA, Hillaire-Buys D, Muller F, Dechaud H, Mazurier E, Boulot P, et al. Fetal toxic affects of angiotensin II receptor antagonists: case report and follow-up after birth. Ann Pharmacother. 2005; 39: 157-161.

68. Bolte AC, Geijn VHP, Dekker GA. Pharmacological treatment of severe hypertension in pregnancy and the role of serotonine(2)-receptor blockers. Eur J Obstet Gynecol Reprod Biol. 2001; 95: 22-36.

69. Steyn DW, Odendaal HJ. Serotonin antagonism and serotonin antagonists in pregnancy: role of ketanserin. Obstet Gynecol Surv. 2000; 55: 582-589.

70. Magee L, Sadeghi S. Prevention and treatment of postpartum hypertension. Cochrane Database Syst Rev. 2005; 4351.

71. Tan LK, de Swiet M. The management of postpartum hypertension. BJOG. 2002; 109: 733-736.

72. Ascarelli MH, Johnson V, McCreary H, Cushman J, May WL, Martin JN. Postpartum preeclampsia management with furosemide: a randomized clinical trial. Obstet Gynecol. 2005; 105: 29-33.

73. Cursino T, Katz L, Coutinho I, Amorim M. Diuretics *vs.* Placebo for postpartum blood pressure control in preeclampsia (DIUPRE): a randomized clinical trial. Reprod Health. 2015; 12: 66.

74. Makris A, Thornton C, Hennessy A. Postpartum hypertension and non-steroidal analgesia. Am J Obstet Gynecol. 2004; 190: 577-578.

75. American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. Pediatrics. 2001; 108: 776-789.

Austin Hypertens - Volume 1 Issue 2 - 2016
Submit your Manuscript | www.austinpublishinggroup.com

Citation: Gasnier R. Hypertension in Pregnancy-Treatment. Austin Hypertens. 2016; 1(2): 1007.