

**Review Article****ANTI-HYPERTENSIVE DRUGS USED DURING PREGNANCY**Sushobhan Bhandari^{1*}, Sanju Kharel¹, Deepak Bhatt¹, Saugat Dahal¹¹Pharm.D, Krupanidhi College of Pharmacy, Carmelaram Post, Varthur Hobli, Bangalore, Karnataka.

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ABSTRACT

Hypertension is a major cause of maternal and fetal mortality during pregnancy. Estimated to cause complications in around 15% pregnancies, hypertension is the most commonly encountered medical complication during pregnancy. The use of antihypertensive therapy during pregnancy is validated by weighing risks and benefits of the therapy. This review comprises of various antihypertensive drugs used as a treatment guideline for treating different types of hypertension during pregnancy. Severe hypertension during pregnancy poses enormous risk to both mother and fetus and should be treated immediately. Treatment can drastically decrease the risk and can result in an uncomplicated pregnancy. This review comprises the use of methyldopa, clonidine, β -adrenoceptor antagonists (labetalol), prazosin, vasodilators (hydralazine), calcium channel blockers (nifedipine, nicardipine), loop diuretic, thiazide diuretic, and its safety and efficacy for treating hypertension during pregnancy.

Keywords: Hypertension in pregnancy, preeclampsia, antihypertensive drugs and fetus, teratogenicity, fetotoxicity.

INTRODUCTION:

Hypertension is a medical condition where there is rise in arterial blood pressure greater than 140/90mmHg. Hypertension during pregnancy is a common medical condition accounting for around 15% cases of preeclampsia which leads to direct maternal deaths^[1]. High blood pressure during pregnancy leads to preeclampsia, formerly known as toxemia, which is regarded as one of the leading causes of maternal deaths in developed countries like US and the UK. Eclampsia which is a condition in which one or more convulsions occur in a pregnant woman appears after preeclampsia, risking the life of both mother and baby. The choice of antihypertensive drugs during pregnancy is done by weighing down the risks and benefits enacted to both the mother and fetus at risk. This review links various antihypertensive drugs suggested during different treatment guidelines for managing hypertension during pregnancy. Our main goal is to provide a clinical guide for treatment of hypertension during pregnancy.

Measurement of hypertension during pregnancy

Hypertension during pregnancy is defined as a condition where the systolic blood pressure is above 130mmHg and the diastolic blood pressure is above 90mmHg. Rise in blood pressure during pregnancy is gestation related. However, risk arises when systolic blood pressure >30mmHg and diastolic >15mmHg from the time of admission. Pre-eclampsia, a condition of high blood pressure during pregnancy and is dangerous to both mother and fetus. Pregnancy related hypertension is associated with a high number of maternal mortality, as well as other complications such as thromboembolism, non-obstetric injuries and hemorrhage.

Measurement of blood pressure for pregnant woman should be done in a seated position. Proper size cuff should be used. During the period of gestation, the end of second trimester and from the beginning of third trimester, venous bloods flow maybe obstructed by gravid uterus. In such case blood pressure should be measured with the woman lying on her side, instead of supine position. Also, the arm used for measuring blood pressure should be at the level of the heart. Korotkoff phase 1 and 5 measurements should be

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used to measure the diastolic pressure ^[3]. If not phase 4 measurement should be used.

Physiological changes in blood pressure during pregnancy

During the course of pregnancy, active vasodilation is achieved by mediators such as prostaglandin and nitric acid. This causes fall in blood pressure during the first trimester of pregnancy. It is normal for the diastolic blood pressure to fall 10mmHg during the first 13-20 weeks of pregnancy ^[17]. Although blood pressure decreases, blood volume and plasma volume increases due to increase in aldosterone. Also sodium and water retention increases causing blood volume expansion. This results in increased heart rate, stroke volume and cardiac output. Blood pressure continues to fall up to 22-24 weeks ^[1]. After 24 weeks the blood pressure slowly increases until it reaches pre-pregnancy levels. After delivery however, blood pressure gradually increases and post - partum women may experience transient hypertension even though she has had no history of hypertension. This increase in blood pressure after delivery is normal and a woman may experience hypertension until 5 days after delivery.

Classification of Hypertension during pregnancy

There are 3 types of hypertension classified during pregnancy:-

- Pre-eclampsia
- Gestational hypertension
- Chronic hypertension

Pre-eclampsia and Eclampsia:

Pre-eclampsia is a condition of high blood pressure and proteinuria during pregnancy. Pre-eclampsia is identified if the gestational blood increases above 130/90mmHg and proteinuria >0.3gm per 24 hours ^[2]. Pre-eclampsia causes narrowing of spiral arteries and in turn leads to reduced uteroplacental perfusion subsequently leading to endothelial activation/dysfunction^[4]. This flow of events is followed by endothelin and thromboxane formation, decreased formation of nitric oxide and prostacyclin and vascular sensitivity to angiotensin 2. Pre-eclampsia usually persists after 20 weeks of gestation ^[1]. If pre-eclampsia is not identified and treated in time it may lead to a condition known as eclampsia where the patient suffers from grand mal seizure. 1 in 10 women suffer from pre-

eclampsia condition, which is around 5-6% of pregnancy and the chances increase to 25% amongst women with pre-existing hypertension ^[5]. The main complication that arises from pre-eclampsia includes cardiac failure, placental abruption, cerebral hemorrhage^[7], intra-abdominal hemorrhage and multi organ failure. Maternal symptoms of pre-eclampsia include intrauterine growth retardation (IUGR), premature delivery, and placental insufficiency. Undiagnosed pre-eclampsia if persists for a long time, leads to eclampsia which is a serious condition that can put the baby at risk, and in rare cases death. An estimated 50,000 women die each year from pre-eclampsia ^[6]. Around average, 25% of very low infant birth weight of less than 1500g accounts to pre-eclampsia.

Table 1: Symptoms and signs of severe pre-eclampsia

Left upper quadrant/epigastric pain due liver edema + hepatic hemorrhage
Headache + visual disturbance (cerebral edema)
Occipital lobe blindness
Hyperreflexia + clonus
Convulsions (cerebral edema)

Gestational Hypertension:

Gestational hypertension is defined as hypertension that develops during the second half of the pregnancy or after 20 weeks gestation in a normal pregnancy with no proteinuria observed. Gestational hypertension is also known as transient hypertension of pregnancy. Around 6-7% of all pregnancy is complicated by gestational hypertension ^[8]. 15-45% women diagnosed with gestational hypertension will ultimately develop pre-eclampsia. Women with a previous history of high BP, hypertensive pregnancy, as well previous miscarriages are at risk of developing pre-eclampsia. The goal of therapy during gestational hypertension is to prevent the risk of severe hypertension. Gestational hypertension usually normalizes after 6 weeks of post-partum^[1] in most cases. However, if blood pressure does not normalize after 3 months of pregnancy it denotes that the woman is most likely having pre-existing hypertension which was masked by pregnancy. In such case, a diagnosis of chronic hypertension is made. However, the maximum time for the BP to

normalize post-partum, after which chronic hypertension is diagnosed are not known. Gestational hypertension >140/90mmHg is dangerous and one in three women with gestational hypertension develop pre-eclampsia.

Chronic Hypertension:

Chronic hypertension which accounts to obesity and delayed pregnancy affects around 3-5% of pregnancies^[9] around the world and the number is increasing day by day. Delay in childbearing age is associated with chronic hypertension. Chronic hypertension is defined as a condition where the blood pressure exceeds 140/90mmHg before 20 weeks of gestation^[10]. Chronic hypertension is primary or secondary in its etiology.

The etiology of chronic hypertension shows a primary etiology in 90-95% of cases and secondary in cases of underlying conditions such as renal parenchymal disease, renal vascular disease, endocrine disorders, aortic coarctation, and or contraceptive use.^[18]

Chronic hypertension may go undiagnosed as the woman may seem normotensive during early pregnancy because blood pressure falls during the first trimester and hypertension may go unnoticed. Also, when hypertension is later diagnosed during pregnancy it may be misinterpreted as gestational hypertension. The diagnosis is sometimes made after post-partum when blood pressure fails to fall back to normal. Chronic hypertension is a serious condition and should be treated immediately to prevent maternal cardiovascular and cerebral injuries. 20-25% of chronic hypertensive women develop pre-eclampsia.^[18] The presence of mild hypertension doubles the chances of developing pre-eclampsia and also increases the possibility of fetal growth restriction and placental abruption. In retrospect, women who get early treatment for chronic hypertension have a better chance for normal pregnancy with fewer complications. However, there is no predefined level of hypertension or any antihypertensive medications that can minimize the risk of pre-eclampsia in women with preexisting hypertension.

Pathogenesis of Pre-eclampsia

The exact pathophysiology of pre-eclampsia and its mechanism is rather unknown. However, there are many underlying factors that suggest the development of pre-eclampsia. Factors such as

family history, age, parity as well as concomitant disease can precipitate pre-eclampsia. The pathogenesis of pre-eclampsia can be put into two factors. The primary factor for pre-eclampsia is placental. During pregnancy the trophoblast cells invade the uterine decidua and reach the myometrium. This invasion of trophoblast cells around the spiral arteries during the first trimester result in four fold increase in diameter of the artery causing low resistance, high capacity blood supply to the myometrium^[11]. The formation of thromboxane and endothelin causes sensitivity to angiotensin 2, which results in decreased formation of nitric acid and prostacyclin. The overall increment in peripheral vascular resistance results in platelets formation and coagulation. The invasion is completed during the second trimester when a series of trophoblast cell invades the arteries of the myometrium causing limited blood supply in the vessels of the decidua. Furthermore, the inability of vasomotor activities by the arteries increases the buildup of atherosclerotic plaque which impairs perfusion to the myometrium.

The secondary factor involved during pre-eclampsia is the maladaptation of uteroplacenta which manifest to systemic syndrome. Failure of the cardiovascular system to adapt during pregnancy causes hypertension, reduced plasma volume, and impaired perfusion to every organ of the body. Vasospasm is produced as a result, which activates the coagulation system and platelets formation cascade and forms micro thrombi. Endothelial dysfunction and oxidative stress¹²⁻¹³ shows a link with placental disorder and systemic disorder. Preeclamptic women sometimes show lesser side effects. So women should be regularly screened and women with higher risk should have increased screening and intensive monitoring.

Risk factors for pre-eclampsia^[2]

- Nulliparity
- Multiple pregnancy
- Chronic hypertension
- Family history of pre-eclampsia
- Increased insulin resistance
- Hypercoagulability
- Increased body mass index
- Renal disease
- Antiphospholipid syndrome
- Hydatidiform mole

- Black race
- Renal disease even without severe impairment
- Low socioeconomic condition
- Previous pre-eclampsia

Management of Hypertension during Pregnancy

Hypertension during pregnancy can complicate the pregnancy which can become life threatening to both mother and fetus. Women with Chronic hypertension can avoid secondary complications such as renal and endocrine. Pre-pregnancy counselling can help plan pregnancy with hypertension and majority of the women with chronic hypertension can have a successful pregnancy with positive outcome. People with increased risk of pre-eclampsia can be educated about the changes in drug regimen during the first trimester. Medications such as ACE (Angiotensin Converting Enzyme) inhibitors and ARBs (Angiotensin Receptor Blockers) should be stopped during the first trimester because it causes fetotoxicity. During the course of counselling hypertensive women, it should be emphasized that antihypertensive drugs used during pregnancy can be safe, produce no teratogenic effect and people can have a normal pregnancy during the course of this treatment. New studies suggest that endothelial dysfunction and oxidative stress which causes pre-eclampsia during pregnancy can be improved by antioxidant vitamin C and E supplementation during the second trimester.^[14]

Maternal and Fetal care during pre-eclampsia:

Diagnosis of pre-eclampsia during the early stages of pregnancy is essential for a successful treatment of hypertension during pregnancy. Proteinuria is an important marker in screening pre-eclampsia in women. Women who show significant proteinuria in the absence of renal disease are a best indicator of superimposed pre-eclampsia. Another surveillance tool used to detect pre-eclampsia is Doppler ultrasound evaluation of the uterine arteries which is done during 20-22 weeks of pregnancy^[1]. Depending upon the symptoms and clinical findings of fetal growth pattern the assessment can be completed by outpatient program, otherwise the patient is admitted. Doppler ultrasound of the uterine arteries can demonstrate the placental vascular resistance^[15] and tell whether there is complete or partial invasion of trophoblast in the spiral arteries. Doppler test is done for women with high risk at

around 20-22 weeks pregnancy. The Doppler test is very useful and effective because of its predictive nature and low risk and a positive Doppler test increases the likelihood of developing preeclampsia by 20%.^[16]

Fetal monitoring and assessment is necessary for a successful pregnancy. Women with pre-eclampsia and chronic hypertension are at increased risk of IUGR. Fetal ultrasound scan can help assess fetal growth rate, amniotic fluid volume, and umbilical blood flow. Severe pre-eclampsia in some cases requires early delivery at around 34 weeks. In such cases intramuscular corticosteroids are given for fetal lung maturity.

Drug treatment during Hypertension in Pregnancy

Most antihypertensive drugs are known to cross the placental barrier and reach the fetal circulation. This is dangerous during pregnancy because it causes fetal toxicity and can cause developmental disorders. Early studies of ARBs and ACE inhibitors have shown to produce teratogenic effects to the fetus such as oligohydramnios, IUGR, pulmonary hypoplasia, hypocalvaria, joint contractures, neonatal renal failure and fetal renal tubular dysplasia. Antihypertensive drugs used during pregnancy are put into "category C" which means that human studies are lacking, animal studies shows fetal risk and the drug is only used when potential benefits outweigh potential risk. In this regard antihypertensive drugs should be carefully selected during pregnancy.

Methyldopa:

A study report based on fetal hemodynamics and uteroplacental blood flow shows that methyldopa is the preferred first line treatment during the first trimester of pregnancy. Methyldopa has been studied the most among all other antihypertensive drugs and is regarded as the most safest and efficacious drug therapy for the treatment of hypertension during pregnancy. A study conducted on methyldopa^[19] showed a decreased head circumference after first trimester use of Methyldopa, however, a follow up study after 4 years showed a less developmental delay amongst babies whose mother were treated with methyldopa rather than women who were untreated^[20]. Other studies also back up this claim saying that methyldopa used during pregnancy

neither causes short-term nor long-term effects^[17]. Also, methyldopa used during the last trimester has shown to reduce maternal blood pressure and heart rate without any adverse effects. Methyldopa is a weak antihypertensive drug and should be given four times a day and requires titration, which can cause maternal adverse effects. Methyldopa studies have shown that it increased the risk of postnatal depression amongst women with a history of depression and should be avoided. Methyldopa has been linked to elevated liver transaminase in up to 5% women or a positive Coomb's test, although hemolytic anemia is rare.

Clonidine:

Clonidine, a centrally acting adrenergic agonist, is an antihypertensive agent which works by stimulating alpha-2 adrenergic receptors in the brain. This causes a decrease in central adrenergic output. Clonidine decreases the cardiac output, systemic vascular resistance, systolic blood pressure and heart rate by acting on both central and peripheral alpha-2 adrenergic receptors. Clonidine, like methyldopa is very safe and efficacious and is used mainly during the third trimester. There is no report of adverse outcome or rebound hypertension with clonidine use^[21]. Generally, clonidine is used as a third-line agent for multidrug control of refractory hypertension. Clonidine is excreted twice in human milk than in maternal serum and hence should be used carefully in lactating mother^[22].

β -Adrenoceptor Antagonist:

β -adrenoceptor antagonist blocks β 1 and β 2 adrenoceptors in the body. β 1 adrenoceptors reduces heart rate, blood pressure, myocardial contractility and myocardial oxygen consumption whereas beta 2 adrenoceptors works by inhibiting relaxation of smooth muscles in blood vessels, bronchi, gastrointestinal system, and genitourinary tract. Metoprolol and atenolol are β adrenoceptors and is regarded as a safe and efficacious drug during late gestation. However, these drugs have shown to cause fetal complications when given in early and mid-gestation. β -adrenoceptor antagonists are considered safe during pregnancy as we can see from labetalol and oxprenolol. Evidence shows that β -blockers are more effective at managing

mild to severe hypertension during pregnancy than methyldopa. However, concerns are shown regarding the produce of adverse effects such as IUGR, bradycardia, hypoglycemia, cardio-respiratory depression and hypothermia. However, concerns as such are overexpressed and drugs under this category are just the same from other hypertensive drugs.^[9 23]

Labetalol:

Labetalol is one of the most widely used antihypertensive during pregnancy. It is a nonselective beta blocking agent with vascular alpha-1 blocking capabilities. Labetalol is used frequently for the treatment of severe acute hypertension during pregnancy and is not associated with fetal growth restriction and low placental weight in patients. Labetalol has shown to reduce blood pressure during pregnancy without changing uteroplacental blood flow^[24]. A recent trial conducted to test the efficacy between labetalol and methyldopa showed that labetalol showed faster blood pressure control, better renal functions and was better tolerated when compared to methyldopa. In a placebo-controlled study for the treatment of mild to moderate gestational hypertension using labetalol showed reduced preterm delivery, neonatal respiratory distress syndrome, and jaundice in labetalol treated group^[25]. Labetalol is secreted in breast milk, however, is compatible with breastfeeding.

Prazosin:

Prazosin, a sympatholytic drug is an α 1-blocker which blocks post synaptic α 1-adrenoreceptors and decreases total peripheral resistance and increases reflex in sympathetic tone. It is used in treating chronic renal disease complicated pregnancy. Prazosin is considered safe during the last trimester^[26] although it increases the half-life and bioavailability during pregnancy. Prazosin produces better result against severe gestational hypertension when used with oxprenolol. Data regarding prazosin use and breastfeeding are not available^[27].

Calcium Channel Blocker:

Calcium channel blockers are drugs which are used to reduce the amount of calcium entering smooth muscles or vascular smooth muscle cells by preventing the opening of voltage gated calcium

channels within these cells. Calcium contracts the muscular lining of blood vessels and by blocking calcium from entering the cells these blood vessels can be relaxed. A cohort study done on 78 women during the first trimester showed no sign of major malformation.

Nifedipine:

Nifedipine belongs to the class of calcium channel blockers and is used for the treatment of hypertension during pregnancy. A study done to compare nifedipine 20mg with placebo, showed nifedipine to be efficacious without adverse fetal consequence as well as improvement in serum urea and creatinine levels. Nifedipine is considered safe during any stage of pregnancy and do not cause teratogenicity^[28]. Sublingual nifedipine use is not considered safe as it may cause hypotension resulting in hypo perfusion of the placenta, causing fetal distress^[29]. Nifedipine is compared with methyldopa for its antihypertensive action during pregnancy; although there is not many evidence to back up this claim. Nifedipine is also used during pregnancy for preterm contraction and unwanted early labor.

Nicardipine:

Nicardipine is used to treat hypertension during pregnancy. A study carried out shows the use of oral nicardipine to treat 40 patients with mild to moderate hypertension from the 28th week of pregnancy to the seventh day postpartum^[30]. Intravenous nicardipine was used for 20 patients with severe preeclampsia. No neonatal or fetal adverse effects were seen and both regimens significantly decreased blood pressure in both groups. In a study which compares nicardipine with metoprolol showed nicardipine to be more effective in controlling maternal BP. Nicardipine also showed higher birth weight in this study.

Vasodilators:

Hydralazine:

Hydralazine is a direct vasodilator which relaxes the arteriolar smooth muscles and is used as an antihypertensive drug during pregnancy. Hydralazine is a choice of drug used for rapid control of severe hypertension and multi drug control refractory hypertension. Adverse effect includes palpitation, excessive vasodilation, headache, flushing and nausea. No teratogenic

effect is seen with hydralazine use and can be used in all trimesters of pregnancy. However, neonatal thrombocytopenia and lupus has been associated with its use^[30].

Thiazide Diuretic:

The use of thiazide therapy during pregnancy is debatable as it can reduce plasma volume. In a randomized trail conducted among women with chronic hypertension showed reduced plasma volume, but no adverse effect was observed^[31]. The ability of diuretics to control edema has been associated with its use during pregnancy, which was previously used in the diagnosis criteria of preeclampsia. Collins et al. 1985 compared thiazide therapy (hydrochlorothiazide, chlorthalidone, chlorothiazide, bendroflumethiazide, dihydrochlorothiazide) with no treatment result in 7000 pregnant women. Hypovolemia and volume contraction is expected to cause growth limitation in fetus. However, teratogenic effect is not observed with thiazide use^[32].

Loop Diuretics:

Loop diuretic such as spironolactone is used for the treatment of severe hypertension in the presence of congestive heart failure, or chronic kidney disease^[33]. However, there is potential risk of hyperbilirubinemia is present. There is no sufficient data that can verify safety of loop diuretics during pregnancy.

Conclusion:

The above review about antihypertensive drugs during pregnancy suggests that during pregnancy if the arterial blood pressure exceeds above 150 to 160mmHg systolic or diastolic pressure above 100 to 110mmHg, that indicates the use of antihypertensive drugs. Many antihypertensive classes of drugs have shown potential in treating hypertension with efficacy and decreasing maternal and fetal risks. The first choice of drug regimen to treat chronic hypertension during pregnancy is methyldopa. Methyldopa is extensively studied among all other antihypertensive drug and provides the most reliable data for safety and efficacy when used during pregnancy. Labetalol a β -blocker has also shown efficacy in treating hypertensive pregnancy and is being used as a standard therapy. Calcium channel blocker such as nifedipine is also an

emerging antihypertensive drug known to be safe and efficacious. Nifedipine is compared with methyl dopa in the treatment of hypertension. Loop diuretic such as hydralazine is also used in rapid treatment of severe hypertension during pregnancy. Hydralazine is not associated with teratogenic effect but can cause fetal thrombocytopenia and lupus, therefore should be carefully used. When it comes to ACE inhibitors or ARBs, these drugs should be avoided during pregnancy because of its ability to cause fetotoxicity. The drugs under this class should be discontinued during the first trimester of pregnancy; however, greatest risk is associated with the use of ACE inhibitors and ARBs during the third trimester. Patient education can be therefore beneficial for patients using ARBs or ACE inhibitors because early discontinuation lessens the chances of fetotoxicity.

Conflict of Interest:

The authors have no conflict of interest.

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