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A Review On: "Uses of Antihypertensive Drugs during Preeclampsia"

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ABSTRACT:
The treatment of hypertension related to pregnancy, such as preeclampsia (PE), remains a difficult problem in obstetrics.Preeclampsia is a disorder that causes a sudden increase in blood pressure and swelling, especially in the face, hands, and feet, during pregnancy.Preeclampsia is a complication that occurs most frequently during pregnancy. It usually occurs in the third trimester and affects about 1 in 20 pregnancies. Generally, aggressive hypertensive therapies are avoided to prevent pharmacologically induced hypotension. Another important risk with using antihypertensive medications during pregnancy is the possibility of poor fetal outcomes. Furthermore, the treatment of hypertension during pregnancy in chronic hypertensive individuals or those with previous renal issues is carefully examined.Recent studies suggest that preeclampsia patients are at increased cardiovascular risk postpartum.As such, these patients need to be monitored after delivery for further development of other cardiovascular diseases. In this review study, we look at the antihypertensive medicines that are currently being used to treat pre-eclampsia patients, as well as the benefits and drawbacks of utilizing them during pregnancy.

KEYWORDS: Hypertension, pregnancy, preeclampsia and the kidney, antihypertensive drugs, preeclampsia, Cardiovascular.

INTRODUCTION:

Preeclampsia is a pregnancy disorder with high blood pressure and often a high amount of protein in the urine.The problem usually appears after 20 weeks of pregnancy.In severe cases of the disease there may be red blood platelet count, impaired liver function, kidney dysfunction, swelling, shortness of breath due to fluid in the lungs, or visual disturbances. Preeclampsia increases the risk of adverse effects for both the mother and the unborn child.If left untreated, it might lead to seizures, which is referred to as eclampsia.Other clinical signs and symptoms include headaches, vision problems, epigastric pain, thrombocytopenia, and liver function abnormalities.Mild to severe microangiopathy of the target organs, such as the brain, liver, kidneys, and placenta, causes several clinical symptoms. Pulmonary edema, cerebral hemorrhage, hepatic failure, and even death are all possible maternal consequences.Possible fetal complications are caused byhypoperfusion of the placenta or the need to give birth prematurely.

Historically, the clinical diagnosis of preeclampsia is established when new hypertension in the second half of pregnancy is associated with a new onsetproteinuria. However, because some individuals show indications of multiorgan damage without proteinuria, preeclampsia can be diagnosed without proteinuria in specific conditions.If any of the following symptoms are present in the absence of proteinuria: abnormal liver function, thrombocytopenia, renal insufficiency, pulmonary edema, visual impairment, or cerebral symptoms, the diagnosis can be made.According to the 2013 report of the American College of Obstetricians and Gynecologists preeclampsia can be diagnosed when either:

1) In a previously normotensive patient, systolic blood pressure is greater than or equal to 140 mmHg or diastolic blood pressure is greater than or equal to 90 mmHg on two occasions at least 4 hours apart. (Is called Mild Preeclampsia).

or

2) systolic blood pressure is greater than or equal to 160 mmHg or diastolic blood pressure is greater than or equal to 110 mmHg and hypertension can be confirmed within minutes to facilitate timely antihypertensive therapy(is called Severe Preeclampsia).

Proteinuria must be measured as greater than or equal to 300 mg per 24-hour urine samples, as a protein ratio greater than or equal to 0.3, and as a protein ratio greater than or equal to 0.4or as a urine dipstick protein of +1 (if a quantitative measurement is unavailable).

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In India, the incidence of preeclampsia is reported to be 8-10% among the pregnant women. According to a study, hypertensive disorders of pregnancy affect 7.8% of pregnant women in India, with preeclampsia affecting 5.4 percent of the population.Preeclampsia and eclampsia cause roughly 63,000 maternal fatalities per year across the world.In developed countries, the maternal mortality rate is expected to be 0-1.8%.In the United States and the United Kingdom, the perinatal mortality rate from eclampsia ranges from 5.6 percent to 11.8 percent.Occurrence of hypertensive issues in India is observed to be 10.08% as seen through the information gathered by the Public Eclampsia Library (NER) (11,266 out of 1,11,725 conveyances) in the year 2011-2014 with 2,554 patients out of this giving eclampsia.

Table 1- Characteristics of the subgroups of preeclampsia.

Preeclampsia (PE) Subgroup	**Comment**
1. Early onset PE (Before 34 weeks of gestation)	Consist of about 10% of total cases of PE. Placental dysfunction is more likely to occur; increase intrauterine growth retardation (IUGR), maternal and perinatal mortalities. Renal function indicates serum creatinine (Cr), blood urea nitrogen (BUN) and uric acid were significantly higher, but alkaline phosphatase levels are lower, in early onset PE.
2. Late onset PE (After 34 weeks of gestation/during labor)	Majority of cases of PE. Normal or big for gestational age fetus at delivery at term.

PE was previously categorized as mild, moderate, or severe in terms of severity. Because morbidity and mortality can be considerable for PE without severe symptoms, the American College of Obstetricians and Gynecologists recommends that this categorization be avoided in a 2013 report. Instead, the term preeclampsia without severe features should be used to differentiate from on the basis of gestational age at delivery, PE has been broadly classified into early-onset, with signs and symptoms developing at 34 weeks of gestation, and late-onset, with signs and symptoms developing at 34 weeks of gestation, and sometimes during labor.

PREECLAMPSIA AND THE KIDNEY:

Patients with pre-existing chronic hypertension or chronic kidney disease may have complications from PE (CKD). Preexisting chronic hypertension is a major risk factor for PE, and it normally means the patient and the fetus have a low survival rate. When a woman with chronic/preexisting hypertension experiences new onset proteinuria and end organ failure after 20 weeks of pregnancy, a diagnosis can be made.

Preeclampsia and CKD have a phenotype of hypertension, proteinuria, impaired excretory kidney function, and increased cardiovascular risk, as well as an increased incidence of preeclampsia in women with previous AKI and underlying kidney disease, and an elevated lifetime risk of CKD in women with preeclampsia. Both preeclampsia and CKD have a same pathophysiologic mechanism: endothelial dysfunction.

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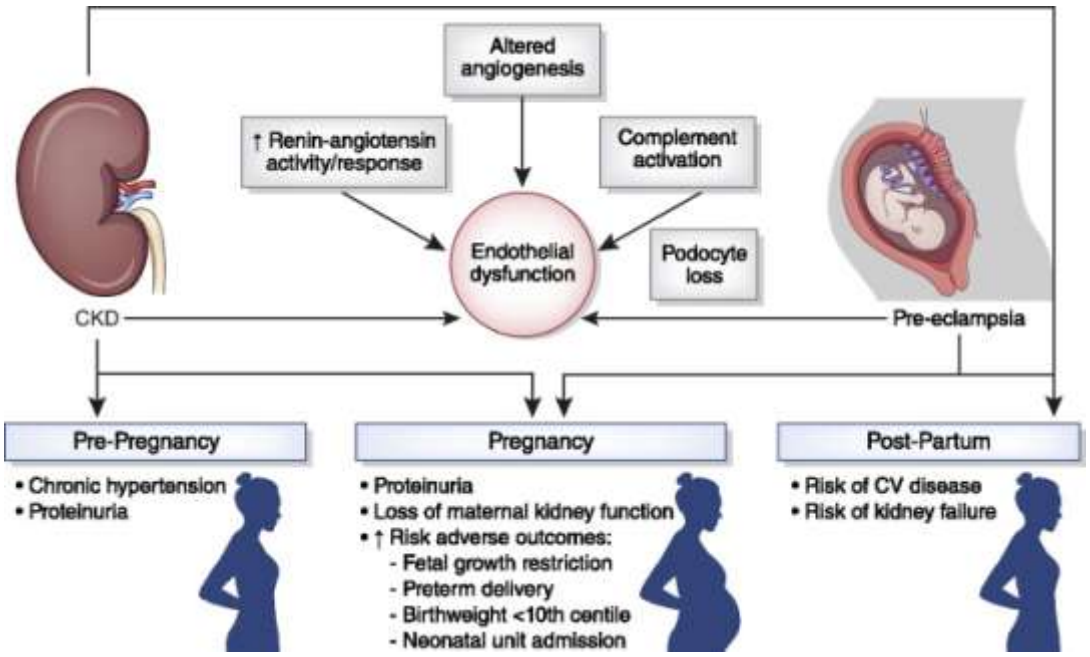
Figure 1:



Pathologic mechanisms that may contribute to endothelial dysfunction include altered angiogenesis, renin-angiotensin system activation, complement activation, and podocyte loss. Affecting 3-5 percent of pregnancies, preeclampsia is a major cause of glomerular disease that can be diagnosed and managed without the support of a nephrologist. Despite the presence of pathognomonic glomerular alterations in preeclampsia, the diagnosis is determined clinically, and a biopsy is not indicated.

Drugs	Indication	Dose	Comment
First line 1. Methyldopa	PE with severe symptoms Hypertension in pregnancy	0.5-3 g/day per oral in 2 divided doses	Established long term safety. Breast milk compatible. As a result of the mild hypertensive impact and the sluggish beginning of action, it should not be used alone.

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2. Labetalol	PE with severe symptoms, usually IV formulation	Start with 20 mg IV bolus May require double dose 10 min later	Rapid onset of action Studies confirm safety in pregnancy May cause maternal hepatotoxicity.
3. Hydralazine	PE with severe symptoms, usually IV formulation. Long acting nifedipine	5 mg IV slowly over 1 to 2 min 30-90 mg once daily. May be increased at 7 to 14 days intervals, to maximum dose of 120 mg a day.	Usually, breast milk compatible. More adverse effect than labetalol Hypotensive effect is less predictable.
4. Nifedipine	PE with severe symptoms, immediate release oral formulation	Start with 10 mg PO May repeat dose 30 min later	Use particularly when IV access is not available. May cause rapid drops in BP. When taken in conjunction with magnesium sulphate, there is a risk of major adverse effects.
Second line **5**. Nicardipine	Resistant acute onset severe hypertension when first line has failed	Give as IV infusion of 3 to 9 mg/hr.	Delay onset of action (5-15 min) Titrate slowly to avoid overdose.
6. Sodium Nitroprusside	Acute life-threatening hypertension associated with PE	Start with 0.24 µg/kg/min. May titrate to maximum dose of 5 µg/kg/min.	Rarely used in dire emergency. Give for shortest amount of time to avoid toxicity (cyanide & thiocyanate).

MANAGEMENT OF HYPERTENSION:

Aside from delivering the fetus, the major treatment for PE is hypertension management with medication when the above-mentioned drugs are used. Various antihypertensive drugs, as mentioned below, have been used in the treatment of severe PE. Salt restriction, bed rest, and physical activity restriction are not suggested for the prevention or treatment of PE without severe symptoms.

All antihypertensive drugs have the ability to pass the placenta. There are currently no randomized controlled studies on which to make a recommendation for the use of one antihypertensive medication over another. Certain medicines, on the other hand, are helpful in reducing blood pressure while maintaining an acceptable safety profile during pregnancy.

1. Methyldopa:

Methyldopa activates central alpha-adrenergic receptors via a fake neurotransmitter (-methyl norepinephrine), resulting in a reduction in sympathetic norepinephrine outflow to the heart, kidneys, and peripheral vasculature. Methyldopa has been widely used in the treatment of high blood pressure in pregnant women. It has been proven that it is safe for the child over the long term. Preeclamptic women treated with methyldopa may have had better results than those treated with labetalol in the CHIPS (Control of Hypertension in Pregnancy Study) study. Methyldopa has a mild antihypertensive effect that takes 3 to 6 hours to take effect.

2. Labetalol:

This medication reduces blood pressure by blocking and adrenergic receptors. When compared to other -blockers, it can better protect uteroplacental blood flow. As compared to methyldopa, it has a faster onset of action (2 hours). Some clinical studies comparing labetalol to methyldopa or nifedipine have indicated that labetalol is safe to use during pregnancy. Labetalol has been linked to maternal hepatotoxicity. It is critical to detect this adverse effect since it might

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be mistaken with HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count). The majority of labetalol-induced hepatotoxicity cases are reversible.

3. Nifedipine:

It is a calcium channel blocker that has been used safely during pregnancy. Long acting nifedipine is preferred over short acting nifedipine because those can cause a significant drop in blood pressure, possibly resulting in a reduction in uteroplacental perfusion. As previously stated, new data suggests that under some situations, quick release oral nifedipine may be considered for safe blood pressure lowering. Long-acting nifedipine is available as a sustained release tablet in dosages ranging from 30-90 mg once day. The dose can be raised every 7 to 14 days, up to a maximum of 120 mg per day.

4. Hydralazine:

It works as a direct vasodilator of the arterioles. Intravenous hydralazine has been widely utilized in the treatment of severe hypertension caused by pregnancy. Although a meta-analysis found that hydralazine had a slightly higher risk of adverse events than labetalol, the data was insufficient to suggest one drug over the other. When compared to other parenteral medications, the hypotensive action of hydralazine is less predictable.

As previously stated, no consensus has been established on the therapy of PE in patients with chronic hypertension or CKD who do not have severe hypertension. As first-line treatment, labetalol, nifedipine, or methyldopa are suggested. Recent research suggests that the calcium blocker nifedipine, in its quick oral release version, might potentially be used as first-line treatment.

It is generally understood that antihypertensive medications do not prevent eclampsia (seizure). Although magnesium sulphate is not indicated as an antihypertensive medication, it has been used in preeclamptic women to avoid seizures.

CONCLUSION:

Based on the review study, I conclude that when hypertensive therapy in PE is needed, management is typically dependent on the acuity and severity of the hypertension. The availability of an agent and the provider's experience are the two most important factors in selecting an agent. Some experts have suggested that labetalol combined with calcium channel blockers be used as first-line therapy in PE people with severe hypertension. As first-line medicines for acute onset severe hypertension, intravenous labetalol, hydralazine, or oral nifedipine are suggested.Recognizing PE as a risk factor for future renal and cardiovascular illness will allow researchers to identify a population of young women who are at high risk for getting cardiovascular and renal disease. Current recommendations suggest cardiovascular screening and therapy for women who were previously preeclamptic. Due to a lack of studies on screening and prevention in previously preeclamptic women, these recommendations are based on low levels of evidence.As a result, research on the causes of late illness presentations, as well as effective screening and treatment methods targeted at decreasing the late disease burden in previously preeclamptic women, is required.

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