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Nifedipine Effectiveness in Treating Hypertension Disorders of Pregnancy: A Literature Review

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ABSTRACT

Hypertension Disorders of Pregnancy (HDP), defined by systolic blood pressure ≥140 mmHg or diastolic ≥90 mmHg, is a leading cause of maternal and fetal mortality, with severe cases marked by systolic ≥160 mmHg or diastolic ≥110 mmHg. HDP leads to significant complications such as preeclampsia, HELLP syndrome, and long-term cardiovascular risks for mothers. Management of HDP is crucial, and nifedipine, a calcium channel blocker, is commonly used as a first-line treatment due to its rapid onset and effectiveness in reducing blood pressure. Studies show nifedipine lowers blood pressure faster and is more tolerable than other antihypertensives like labetalol and hydralazine. However, it can cause side effects such as tachycardia, headache, and potential fetal complications, including lower birth weight. Despite these risks, nifedipine remains a preferred treatment option for managing HDP.

Keywords: nifedipine; hypertension disorders of pregnancy; management; effectiveness; side effects.

INTRODUCTION

Hypertension Disorders of Pregnancy (HDP) is defined as a condition where the systolic blood pressure is ≥ 140 mmHg or the diastolic blood pressure is ≥ 90 mmHg, with severe HDP being characterized by systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg[19]. HDP is one of the leading causes of maternal and fetal mortality worldwide, with an estimated mortality rate of 14% globally[26]. The prevalence of HDP occurs in 116 out of every 100,000 women of reproductive age each year globally, with Southeast Asia ranking second in the world, with a prevalence of 136.8 per 100,000 women of reproductive age[12]. HDP affects both developed and developing countries. However, developing countries have a higher prevalence of HDP compared to developed countries, including a mortality rate that accounts for up to 99% of all deaths from HDP worldwide[28].

Hypertension Disorders of Pregnancy (HDP) can lead to complications in 5-10% of pregnancies, resulting in morbidity and mortality for both mothers and fetuses. These complications can have immediate effects or cause long-term consequences for both mother and fetus[2].

One syndrome that can occur alongside HDP is severe preeclampsia, which can lead to HELLP syndrome (Hemolysis, Elevated Liver Enzymes, and Low Platelets Syndrome) and contributes to 24% of maternal deaths and 37% of fetal deaths[16],[23]. Additionally, HDP poses a high risk for cardiovascular and cerebrovascular health issues, with these risks extending up to 24 months[1],[24]. For the fetus, HDP can cause growth and developmental disorders, including neurological conditions such as autism and ADHD[24].

Management of Hypertension Disorders of Pregnancy is essential to prevent complications and reduce maternal and fetal mortality[7]. Management approaches include both pharmacological and non-pharmacological treatments[19]. This review focuses on the pharmacological management of HDP, particularly the use of nifedipine and its effectiveness in treating the condition.

REVIEW OF CONTENT

Classification of HDP

Hypertension Disorders of Pregnancy (HDP) is classified into four types according to the American Heart Association[9].

TABLE 1: Classification of Hypertensive Disorders of Pregnancy.

< 20 gestational weeks	
Chronic hypertension	Hypertension detected in: - Before conception (Wilkerson, 2019) or 20 weeks of pregnancy - After 12 weeks of delivery
Chronic hypertension with superimposed preeclampsia	Hypertension detected in: - Before 20 weeks of pregnancy - After 12 weeks of delivery Involvement of target organ (Table 2)
>20 gestational weeks	
Gestational hypertension	Hypertension detected in: - After 20 weeks of pregnancy with a history of normotensive
Preeclampsia	Hypertension detected in: - After 20 weeks of pregnancy Involvement of target organ

Hypertension disorders in pregnancy are generally classified based on the timing of onset, divided into two categories: before and after 20 weeks of pregnancy. Chronic hypertension can also be identified based on a history of antihypertensive medication use before pregnancy or before the 20th week of gestation[15]. Around 3-5% of pregnant women with Hypertension Disorders of Pregnancy (HDP) experience chronic hypertension[15],[29]. The risk of a woman with chronic hypertension developing chronic hypertension with superimposed preeclampsia is 20-50%, which is 5-6 times higher compared to gestational hypertension. In cases of severe hypertension, this risk can rise to 78%. Chronic hypertension with superimposed preeclampsia increases the risk of complications and morbidity for both the mother and fetus compared to preeclampsia [14],[29].

Gestational hypertension is defined as new-onset hypertension after 20 weeks of pregnancy and typically improves within 12 weeks postpartum. However, if blood pressure remains elevated beyond 12 weeks after delivery, the diagnosis may change to chronic hypertension[15],[29]. The prevalence of gestational hypertension is 6-17% in nulliparous women and 2-4% in multiparous women[29]. Gestational hypertension may progress to preeclampsia or eclampsia in 15-46% of cases. Preeclampsia is defined as new-onset hypertension accompanied by proteinuria or target organ dysfunction[15],[29]. However, recent guidelines no longer require proteinuria as a diagnostic criterion for preeclampsia. Preeclampsia can progress to severe forms, manifesting as target organ damage (Table 2). Eclampsia is preeclampsia with convulsions, which may be tonic-clonic, focal, or multifocal, occurring during pregnancy, labor, or shortly after delivery, without an underlying neurological disorder[19].

TABLE 2: Target organ involvement.

Organ	Symptoms
Cardiovascular	Elevated blood pressure (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg)
Central Nervous System	Headache, visual disturbance
Thrombocyte	Platelet<100.000/mL
Renal	Creatinine >1.1 mg/dL
Liver	Transaminase serum > 2x normal level
Pulmonary	Oedema

Pathophysiology of HDP

In a normal pregnancy, blood pressure decreases during the first trimester due to reduced vascular resistance, reaching its lowest point at around the 18th week, and then increases again between weeks 28-36 as the blood vessels return to pre-conception conditions[2],[15]. The decrease in blood pressure during the first trimester can be as much as 10% and is influenced by hormones such as estrogen and progesterone[15]. Factors such as hormones, blood vessels, and metabolism contribute to changes in blood pressure during pregnancy[2].

The pathophysiology of hypertension in pregnancy is not yet fully understood, but the complex interaction between the mother and fetus plays a crucial role[2]. Disruption can begin as early as the first week of pregnancy when placentation is impaired due to failure in the remodelling of spiral arteries. Normally, spiral artery remodelling increases the diameter of blood vessels, but in patients with HDP, vasodilation does not occur. This results in ischemia and hypoxia in the tissue, leading to systemic endothelial dysfunction[25]. In addition to tissue hypoxia, abnormal placentation causes an imbalance in inflammatory factors, which increases oxidative stress and reduces pro-angiogenic factors, such as PIGF[9].

Diagnosis of HDP

Hypertension in pregnant women is diagnosed through blood pressure measurement, either while sitting or lying on the left side, with the cuff positioned at heart level, using Korotkoff V sounds to measure diastolic blood pressure[2]. To screen for preeclampsia, pregnant women are advised to have routine blood pressure checks. Chronic hypertension is identified during the first visit or even before pregnancy. Hypertension is diagnosed with at least two blood pressure measurements taken within 4 hours, initially measured in both arms, but the arm with the higher reading will be used for subsequent measurements[2],[19],[27]. If the difference between the readings is more than 10 mmHg, a third test should be conducted[2].

Common laboratory tests include urine analysis, complete blood count, liver enzymes, serum creatinine, and urea levels. Urine testing for proteinuria is essential to detect preeclampsia and kidney disorders. Doppler ultrasound of the uterine arteries after the 20th week of pregnancy can detect fetal growth disturbances. Additionally, biomarker tests, such as measuring sFlt-1 and PIGF levels, can help detect preeclampsia and can be performed until the 37th week of pregnancy[2],[5],[29],[30].

Management of HDP

The management of hypertension in pregnancy aims to prevent complications, reduce the risk of preeclampsia, and decrease the risk of maternal and fetal mortality. According to the ISSHP 2021, several management strategies for Hypertensive Disorders of Pregnancy (HDP) include:

TABLE 3: Management of HDP.

Antihypertensive therapy	• Non-severe hypertension: First-line treatment includes nifedipine, methyldopa, or labetalol[15],[19],[30]. • Severe hypertension: Emergency treatment with nifedipine, oral labetalol, IV labetalol, or IV hydralazine [15],[29]. • Systolic blood pressure target: Maintain between 110-140 mmHg[27]. • Diastolic blood pressure target: Maintain <85 mmHg. If diastolic pressure ≤80 mmHg, antihypertensive dosage should be reduced or stopped [27],[19]. • If systolic blood pressure ≥160 mmHg, the dosage of medication should be increased or a new medication should be prescribed[19].
Corticosteroid administration	For pregnant women with severe preeclampsia, corticosteroid treatment is recommended if administered before 34 weeks or between 34-36 weeks with the risk of delivery within 24 hours to 7 days [11],[19].
Timing of delivery	In severe preeclampsia, delivery may be performed earlier if the life of the mother or fetus is at risk, and delaying delivery for 1-2 weeks would worsen the condition. However, delivery can be postponed until the condition of the mother and fetus deteriorates when the gestational age is <34 weeks[19],[27].
Magnesium Sulphate (MgSO4) admission	Indications for the use of anticonvulsant therapy in eclampsia, severe preeclampsia with proteinuria, and severe hypertension include preventing neurological complications in pregnant women during and after pregnancy, including the prevention of seizures. This treatment can be administered during labor and up to 24 hours postpartum[10],[19],[30]
Bedrest	Bedrest is not recommended, except in cases of gestational hypertension and severe preeclampsia where exercise is contraindicated[5],[19].
Aspirin administration	Aspirin administration can be used to prevent preeclampsia. The recommended dose is low-dose aspirin (81 mg-150 mg), which can be given from the 12th week to the 28th week of pregnancy[6],[10],[27].

Nifedipine

Nifedipine is an antihypertensive medication, a calcium channel blocker class, specifically the dihydropyridine subclass. It works by inhibiting calcium channels, which reduces the influx of calcium into the muscles, leading to the relaxation of the smooth muscles in blood vessels, resulting in vasodilation and a decrease in peripheral vascular resistance[17].

Nifedipine is the first-line treatment for acute and severe hypertension, especially when intravenous access is difficult[5],[8],[10],[19],[30]. Nifedipine is available both as an emergency medication and as a maintenance therapy, making it a preferred treatment option for hypertension disorders of pregnancy[5].

Effectiveness of nifedipine in lowering blood pressure

Nifedipine has a rapid onset of action, with effects occurring within the first 20 minutes [8],[17]. This was demonstrated in a randomized controlled trial by Donel (2023), which showed the most significant reductions in systolic blood pressure, diastolic blood pressure, and mean arterial pressure (MAP) within the first 20 minutes, with a p-value of <0.0001, indicating a significant difference in blood pressure changes following nifedipine intervention[8]. With a single dose, nifedipine can achieve maximum blood pressure reduction within the first 20 minutes, although after 4 hours, blood pressure gradually begins to rise again[8]. In cases of severe hypertension and severe preeclampsia, oral nifedipine has been found to be more effective than intravenous labetalol in lowering blood pressure more rapidly[13],[22]. Additionally, nifedipine and intravenous hydralazine show similar effectiveness, but nifedipine is better tolerated[13]. A meta-analysis by Awaludin (2022) also concluded that nifedipine is more effective in reducing the risk of persistent hypertension disorders in pregnancy compared to intravenous hydralazine and labetalol[4]. Alavifard (2019) in a meta-analysis concluded that oral nifedipine had the highest therapeutic success rate compared to intravenous hydralazine and labetalol[3].

Adverse effect

Nifedipine can cause reflex tachycardia due to rapid vasodilation, which is followed by sympathetic reflex activation. In addition to tachycardia, side effects of nifedipine include headache and facial flushing[17]. Other reported side effects include hypotension, fatigue, nausea, diarrhea, peripheral edema, and skin rash. Nifedipine can also lead to increased serum aminotransferase levels, although these typically improve after discontinuation of the drug[18]. In a randomized controlled trial, patients treated with nifedipine experienced the most headaches compared to those treated with methyldopa and labetalol. Nifedipine may also have side effects on the fetus. The intervention with nifedipine resulted in more infants being referred to the intensive care unit compared to the two comparator drugs, with a p-value <0.05, indicating a significant difference. This may be due to lower birth weight[7].

CONCLUSION

Hypertension disorders of pregnancy (HDP) are one of the leading causes of maternal mortality worldwide, making management, including the administration of antihypertensive medication, crucial. Nifedipine, a calcium channel blocker from the dihydropyridine subclass, is chosen as the first-line antihypertensive treatment due to its oral administration, which is considered easier and available in both rapid onset and maintenance formulations. Nifedipine is regarded as more effective compared to other first-line antihypertensives for HDP, as it can lower blood pressure quickly and is better tolerated by patients. However, on the downside, nifedipine can cause side effects such as tachycardia and may have adverse effects on the fetus.

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