


## REVIEW ARTICLE

# The role of antihypertensive drugs in patients with preeclampsia and how to prevent it

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Article Info	ABSTRACT
<p>Received Oct 22, 2021 Revised Feb 17, 2022 Accepted Mar 20, 2022 Published Dec 1, 2022</p> <p><b>Corresponding author:</b> I Gde Sastra Winata sastra@unud.ac.id</p> <p><b>Keywords:</b> Preeclampsia Antihypertensive Methyldopa Nifedipine Maternal health</p> <p>This is an open access article under the CC BY-NC-SA license (<a href="https://creativecommons.org/licenses/by-nc-sa/4.0/">https://creativecommons.org/licenses/by-nc-sa/4.0/</a>)</p> 	<p>Treatment of hypertension in pregnancy, such as preeclampsia (PE), is still a difficult issue with negative short and long-term consequences for both the mother and the baby. Screening for preeclampsia at 11-13 weeks' gestation using a combination of maternal demographic characteristics and medical history with biomarker measurements can identify approximately 75% of women who develop premature preeclampsia with delivery at 37 weeks gestation and 90% of those with early preeclampsia. Preeclampsia has a 10% positive screen rate at 32 weeks. Another important worry on the use of antihypertensive medications during pregnancy is the potential harm to the fetus. Methyldopa, hydralazine, labetalol, and nifedipine are some common antihypertensive medications. Aspirin use is frequently related to a decrease in the prevention of early preeclampsia, but it must be accompanied by medication adherence. Aspirin can be coupled with heparin. Recent investigations on the use of furosemide and nifedipine in preeclampsia have also revealed a new combination.</p>
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## INTRODUCTION

Severe hypertension in pregnancy is defined as systolic blood pressure  $\geq 160$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg. The most common cause of severe hypertension in pregnancy is pre-eclampsia (PE), which is presenting after 20 weeks' gestation. Severe hypertension happened before 20 weeks' gestation is rare, usually due to chronic hypertension and need a rapid control of blood pressure due to risk of hemorrhagic stroke, and other target organ damage.<sup>1</sup>

PE is a condition resulting in hypertension, proteinuria, and end-organ damage. One of the most typical cases of pregnancy-related hypertension might develop after giving delivery. Other clinical signs and symptoms include thrombocytopenia, epigastric discomfort, altered eyesight, headache, and reduced liver function.<sup>2</sup> These clinical symptoms are brought on by mild to severe microangiopathy in target organs like the brain, liver, kidneys, and placenta. The effects on the mother could include pneumoedema, cerebral hemorrhage, hepatic failure, renal failure, and even death. Fetal issues

brought on by placental hypoperfusion or the need for an early birth.<sup>3</sup>

In affluent countries, preeclampsia affects 3 to 5 percent of pregnancies and is characterized by hypertension, the onset of proteinuria, or organ failure after 20 weeks of pregnancy.<sup>4,5</sup> The signs and symptoms of severe preeclampsia include organ damage or restricted prenatal development.<sup>6</sup>

Delivery of the fetus was the definite therapy for PE, but the mainstay of the treatment is the use of antihypertensive drug to control the blood pressure when indicated. Many antihypertensive drugs have been used in the management of severe PE and have an acceptable safety profile in pregnancy. The choice of therapy also depends on the severity of the hypertension. However, there was no clear recommendation for the use of combined antihypertensive drugs.<sup>4</sup>

Preeclampsia also increases the risk of cardiovascular disease over the long run in addition to the short-term risks of morbidity and mother and child deaths (CVD). Future CVD is up to seven times more likely to affect severe preeclamptic women than normotensive pregnant women. PE patients had an elevated postpartum cardiovascular risk, according to recent research. As a result, people with hypertension during pregnancy should be watched for the development of additional cardiovascular problems postpartum.

In this review article, we discuss the antihypertensive medicines that are currently used to treat patients with PE, as well as the benefits and drawbacks of utilizing these drugs during pregnancy.

## DIAGNOSIS

According to International Society for the Study of Hypertension in Pregnancy (ISSHP)<sup>7</sup> in 2018, hypertension is defined as systolic blood pressure (SBP) of  $\geq 140$  mmHg and/or diastolic blood pressure (DBP) of  $\geq 90$  mmHg; and severe Hypertension defined as SBP of  $\geq 160$  mmHg and/or DBP of  $\geq 110$  mmHg. Hypertension arising de novo minimum at 20 weeks' of gestation was classified into Transient Gestational Hypertension (TGH), Gestational Hypertension (GH), and Preeclampsia—de novo or superimposed on chronic hypertension.

TGH is a de novo hypertension that develops at any gestation and resolves without any treatment during pregnancy. GH is a persistent de novo hypertension in the absence of features of pre-eclampsia. Meanwhile, PE is defined as a GH which is accompanied by one or

more of the following onset conditions minimum at 20 weeks' of gestation: proteinuria (positive if  $\geq 1+$  or 30 mg/dL), maternal organ dysfunction – such as acute kidney injury (creatinine  $\geq 90$   $\mu\text{mol/L}$  or 1 mg/dL), liver involvement (elevated ALT or AST  $>40$  IU/L) with or without right upper quadrant or epigastric abdominal pain, neurological complications (eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, persistent visual scotomata), hematological complication (thrombocytopenia  $<150.000/\mu\text{L}$ , DIC, hemolysis); and uteroplacental dysfunction – such as fetal growth restriction, abnormal umbilical artery Doppler wave form analysis or stillbirth. In certain circumstances, PE can be diagnosed without proteinuria. However, some people showed signs of multiorgan disease without it.<sup>8</sup>

According to a 2013 report from the American College of Obstetricians and Gynecologists (ACOG) Task Force on Hypertension in Pregnancy, PE can be identified when, in previously normotensive patients, either the systolic blood pressure is greater than or equal to 160 mm or the diastolic blood pressure is greater than or equal to 90 mmHg on two separate assessments at least 4 hours apart.<sup>2,9</sup> A protein ratio more than or equal to 0.3, a urine dipstick protein level of greater than 1, or more than 300 mg of protein per 24-hour urine samples should be considered proteinuria in addition to hypertension (if quantitative measurement is not available).<sup>3</sup>

## CLASSIFICATION

PE used to be classified as either mild, moderate, or severe. Both ISSHP and ACOG Task Force on Hypertension in Pregnancy recently recommended against using this categorization because to the substantial morbidity and mortality associated with severe asymptomatic PE.<sup>3</sup> They also agree that PE may become a major threat to both mother and fetus at any stage of pregnancy, and so classification of PE into mild or severe disease might be misleading to less experienced clinician. They recommended to use PE with or without severe features as a more practical approach rather than using severe PE as a diagnosis.

Generally speaking, PE can be divided into two groups: those with symptoms appearing before 34 weeks of pregnancy (early-onset PE) and those with symptoms appearing later in pregnancy (late-onset PE), such as new-onset hypertension and proteinuria before 34 weeks of pregnancy (late-onset PE), and sometimes after labor (Table 1). Despite the lack of evidence, it has been hypothesized that preeclampsia subgroups have different rates of maternal and perinatal death.<sup>10,11</sup> Ten



percent of all PE cases are classified as having an early onset, and placental dysfunction is more prevalent in this group than in the more common late onset PE group.

The effects of PE might be compounded in patients with preexisting conditions such chronic hypertension or chronic renal failure. Both the mother and the unborn child have a dismal prognosis when chronic hypertension is present.<sup>12</sup> Diagnosis is made when a pregnant woman who has chronic hypertension or who has been previously diagnosed develops proteinuria and/or end-organ failure after 20 weeks of pregnancy.

Women with chronic preexisting hypertension/ previously diagnosed who have proteinuria before or in early pregnancy are at increased risk of being misdiagnosed with preeclampsia if their hypertension worsens suddenly or if they need to increase their antihypertensives.

Despite the well-established association between preeclampsia and renal disease, distinguishing between CKD and PE during pregnancy can be challenging due to the fact that both conditions can coexist with hypertension and proteinuria. Uteroplacental flow and tyrosine kinase-1, such as the soluble tyrosine kinase-1 in maternal circulation to placental growth factor ratio, are two of the methods being explored to differentiate CKD from PE.<sup>13</sup> Protection of high-risk individuals and, in the event of PE, stabilization of the mother and fetus before timely delivery are the cornerstones of care.<sup>14</sup>

**TREATMENT**

All antihypertensive drugs are able to cross the placenta safely. To yet, no randomized controlled trials have shown any clear benefit from one antihypertensive over another. However, there are drugs that can reduce blood pressure while still being safe for the mother and unborn child. The severity of hypertension is a major factor in

deciding the course of treatment. Additionally, the question of whether a patient would prefer parenteral or oral treatment needs to be addressed before a medication can be selected.

**Methyldopa**

The neurotransmitter (-methylnorepinephrine) decreases sympathetic outflow of norepinephrine to the heart, kidneys, and peripheral blood vessels by stimulating central alpha-adrenergic receptors. Methyldopa is commonly prescribed to manage hypertension in pregnant women. Additionally, its safety for the developing baby over time has been demonstrated. Women with preeclampsia who were given methyldopa in the CHIPS (Control of Hypertension in Pregnancy Study) trial may have fared better than those given Labetalol.<sup>15</sup> In contrast, methyldopa's antihypertensive effects are mild and gradual in onset (3 to 6 hours). It is unlikely that the majority of preeclamptic women will be able to achieve the desired blood pressure levels using only oral drugs.

**Labetalol**

Specifically, labetalol blocks alpha-1 and alpha-2 adrenergic receptors, which results in a decrease in blood pressure. The blood flow between the uterus and the placenta can be maintained for a longer period of time than with other blockers. It starts working more quickly than methyldopa (2 hours). Safe labetalol during pregnancy has been demonstrated in randomized clinical trials where the drug was compared to methyldopa and nifedipine.<sup>16,17</sup> Maternal hepatotoxicity from labetalol has been described. This adverse effect warrants close attention because it can be easily mistaken for HELLP syndrome. However, there have been fatalities associated with labetalol, despite the fact that hepatotoxicity is usually reversible.<sup>18</sup>

Table 1. Characteristics of the preeclampsia subgroup

Preeclampsia Subgroup	Signs and Symptoms
Early-onset PE (<34 weeks of gestation)	Only ± PE case Often due to placental dysfunction, increased IUGR, and maternal and perinatal mortality. Renal function indicators (Cr, BUN, and Uric Acid) increased significantly, but alkaline phosphate was low
Late-onset PE (>34 weeks gestation)	Most cases of PE Severe during normal or large-term labor



## Nifedipine

Nifedipine, a kind of calcium channel blocker, has been used successfully during pregnancy. Since short-acting nifedipine can cause a significant reduction in blood pressure, long-acting nifedipine is recommended. Short-acting oral nifedipine may be investigated for safely decreasing blood pressure, according to the findings of certain recent trials. Once daily dosing of 30-90 mg is appropriate for long-acting nifedipine. The highest recommended daily dose is 120 mg, and it can be raised by 20 mg every 7 to 14 days.<sup>19</sup>

## Hydralazine

The arteriolar vasculature is immediately dilated by hydralazine. Hydralazine is commonly used intravenously to treat severe hypertension related to pregnancy. Although meta-analyses showed that the risk of adverse events was somewhat greater with hydralazine than with labetalol, there is not enough information to recommend one drug over the other.<sup>20</sup> But the hypotensive effect of hydralazine is less predictable than that of other parenteral medications. Hypertension caused by pregnancy can be managed with oral hydralazine. However, it has several drawbacks, including edema in the lower limbs and a tachycardia reflex.<sup>19</sup>

There is less consensus on the best way to manage PE in individuals with chronic hypertension or CKD who do not have severe hypertension. Patients with PE who also have high hypertension may benefit from antihypertensives (sustained systolic blood pressure of at least 160 mmHg or diastolic blood pressure of at least 110 mmHg).<sup>3</sup> Medications including labetalol, nifedipine, and methyl dopa are commonly recommended as first treatments. Nifedipine, a calcium channel blocker, may also be first-line treatment, as shown by recent studies, especially in its rapid-onset oral release form.<sup>20-26</sup>

First-line treatment, especially in the absence of intravenous access, should consist of oral-rapid onset nifedipine, according to the 2017 Committee Opinion of the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. You should stay away from the renin-angiotensin-aldosterone system inhibitors such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, and mineralocorticoid receptor antagonists. A blood pressure reading between 120/80 mm Hg to 160/105 mm Hg is considered normal.

Likewise, it is not known whether or not antihypertensives can help prevent eclampsia. Magnesium sulfate has long been used to control recurrent seizures in eclampsia and prevent seizures in preeclamptic women with severe symptoms. However, it is not advised as an antihypertensive medication. In a small double-blind, placebo-controlled study, individuals with severe asymptomatic preeclampsia who were given magnesium sulfate had the same rate of eclampsia progression as those who were given a dummy treatment.<sup>27</sup>

Magnesium sulfate should not be administered to all women with preeclampsia who have systolic blood pressure less than 160 mmHg and diastolic blood pressure less than 110 mmHg and no maternal symptoms, as per 2013 recommendations from the American College of Obstetricians and Gynecologists (ACOG). Magnesium sulfate is only recommended for the prevention of eclampsia by the ACOG in patients with blood pressure of 160/110 or higher, or in patients with blood pressure of less than 160/110 who also exhibit additional severe symptoms that typically precede seizures. Compared to other common anticonvulsants like phenytoin and diazepam or lytic combinations, research shows that magnesium sulfate is more effective at avoiding recurrent seizures in eclampsia.<sup>27-28</sup>

Preventing seizures with magnesium sulfate is associated with its effects on the central nervous system, maybe through NMDA receptors, calcium channels, and acetylcholine, although the exact mechanism of action is uncertain. While there is limited information, it is safe to say that taking magnesium sulfate and nifedipine together will not result in serious side effects, including hypotension and neuromuscular inhibition.<sup>29</sup>

During the postpartum period, 108 women with severe preeclampsia had two readings of 150/100 mmHg or above within the first 24 hours after giving birth. These patients were randomly split in half (Group A: furosemide 20 mg OD plus nifedipine; Group B: nifedipine alone). Women in Group B took antihypertensives at a much higher rate than those in Group A did (26.0 percent versus 8.0 percent,  $p = 0.017$ ). There were no significant differences between the groups in terms of length of hospital and postpartum stays or the prevalence of antihypertensives prescribed upon release.<sup>30</sup>

Table 2. Antihypertensive drugs frequently used in severe preeclampsia

Drugs	Indications	Doses
First Line		
Methyldopa	PE with severe symptoms Hypertension in pregnancy	0.5-3 g/day PO in 2 divided doses
Labetalol	PE with severe symptoms, usually IV formulation	Starting with 20 mg IV bolus May require double dose 10 minutes later
Hydralazine	PE with severe symptoms, usually IV formulation. Long acting nifedipine	5 mg IV slowly over 1 to 2 minutes 30-90 mg once daily. It can increased at 7 to 14-day intervals, up to a maximum dose of 120 mg daily
Nifedipine	PE with severe symptoms, immediate release of an oral formulation	Start with 10 mg PO May repeat 30 minutes later
Second Line		
Nicardipine	Severe acute-onset hypertension that is resistant when first-line fails	Give IV infusion of 3 to 9 mg/hour
Sodium Nitroprusside	Life-threatening acute hypertension associated with PE	Start with 0.24 g/kg/min. Can be titrated until maximum dose of 5 g/kg/min

## PREVENTION

There are three levels of protection against preeclampsia, known as primary, secondary, and tertiary.<sup>8</sup> Primary prevention is taking measures to decrease disease prevalence, such as modifying one's lifestyle or dietary habits, or improving one's overall dietary intake. That is why it is quite improbable that we will be able to stop a case of PE in its tracks.<sup>31</sup>

Women who are overweight, have dyslipidemia (especially hypertriglyceridemia and hypercholesterolemia), uncontrolled diabetes mellitus, or obstructive sleep apnea are at a higher risk for developing preeclampsia (chronic hypoxemia).<sup>32,33</sup> High-risk individuals should have surgical therapy for sleep apnea in addition to weight loss, correction of an aberrant lipid profile, blood sugar management, and other lifestyle changes. While the preventive benefit of adding low molecular weight heparin to aspirin is minimal, it may be amplified when used in conjunction with other preventative medications.<sup>34</sup>

Recent studies have shown that the use of L-arginine or isosorbide mononitrate (both of which improve endothelial nitric oxide production) can lower the risk of preeclampsia and boost intrauterine growth and fetal development. Therefore, boosting nitric oxide production need to be a part of the preventive strategy.<sup>35</sup> Statins have been shown to have beneficial benefits in initiating the HO pathway and reducing the risk of preeclampsia, and, therefore, they should be included in the preventive strategy even in individuals who do not have preexisting dyslipidemia.<sup>36</sup>

Preeclampsia can be avoided by taking aspirin, according to one study. For aspirin, the odds ratio for preeclampsia was 0.24 (95% CI, 0.09-0.65) at 90% adherence and 0.59 (95% CI, 0.23-1.53) at 90% adherence. Preeclampsia prevalence increased with maternal age, and decreased with smoking, being of African-American or South Asian descent, or having a previous pregnancy complicated by preeclampsia. Benefits from medication are contingent on patients being compliant with their dosing schedules, a study found.<sup>37</sup>

Aspirin use during pregnancy reduced the need for neonatal intensive care unit admissions by nearly 70%, according to another study of high-risk pregnancies. In particular, earlier preeclampsia avoidance is responsible for the decline in 32-week birth rates. These results have implications for newborn mortality and disability, as well as immediate medical expenses.<sup>38</sup>

There were 1620 people that took part in the study, and 1571 live births occurred. Length of time spent in newborn intensive care was higher in the placebo group compared to the aspirin group (1696 vs 531 days). This is because aspirin significantly decreased the median length of stay in the neonatal intensive care unit from 31.4 days to 11.1 days (95% CI, 7.0-38.6; P =.008).<sup>39</sup>

Aspirin and heparin together have been shown to be effective in a recent study. Aspirin combined with LMWH has been shown to improve clinical efficacy, coagulation function, renal function, and blood pressure levels in patients with severe preeclampsia, and to reduce the risk of adverse pregnancy outcomes. As a result of the intervention, the overall effective rate was



94.44% in the study group and 76.00% in the control group. It was statistically proven that the overall effective rate of patients in the study group was much greater than in the control group after treatment (P 0.05).<sup>40</sup>

## CONCLUSION

Many variables complicate PE case prevention. The majority are linked to an unclear etiology, the low predictive value of current screening tools, and diverse illness presentations. Interventions that define a small risk reduction imply that a large number of women must be treated to prevent a single instance. For the time being, the definitive treatment is placental delivery and expulsion. At this time, no effective PE prophylaxis is officially suggested. However, because PE is seen as a global health issue, with relatively high maternal and newborn morbidity and mortality rates in many countries, prophylactic measures with minimal or moderate impact may be beneficial.

## DISCLOSURES

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### Conflict of interest

The authors report there are no competing interests to declare.

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### Author contribution

The authors have contributed to all processes in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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