

# Antihypertensive Choices during Pregnancy in Limited Setting

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## ABSTRACT

**Background:** Antihypertensive agents used during pregnancy may vary from institution to institution and depend on resource availability. **Objective:** This study aimed to determine the profile of antihypertensive drugs used in pregnancy in low-middle-income countries and the impact of these drugs on maternal and fetal outcomes. **Materials and Methods:** This is a retrospective study on hypertensive pregnant patients admitted to the emergency unit at a tertiary referral Hospital in Indonesia. The type of hypertension during pregnancy, antihypertensive drugs, side effect, and maternal and perinatal outcomes was extracted from medical hospital records. **Results:** A total of 762 hypertensive pregnant women were recruited; 61 were diagnosed with preeclampsia, 491 were preeclampsia with severe features and 174 were chronic hypertension superimposed preeclampsia, and 81.54% of them received antihypertension therapy. The most commonly prescribed antihypertensive drugs were combination therapy of nifedipine and methyldopa (96.7%), followed by monotherapy of methyldopa (2.3%), nicardipine (1.1%), and nifedipine (0.2%). Most of the patients successfully attained a Systolic blood pressure <160mmHg. Tachycardia was reported in 47 (7.9%) pregnant women who received antihypertensive medication; none reported hypotension and arrhythmia. **Conclusion:** Nifedipine and methyldopa are choices for an antihypertensive agent in limited resources, either monotherapy or combined. Nifedipine's immediate release can be used with a low risk of hypotension.

**Key words:** Hypertension during pregnancy, Preeclampsia, Chronic hypertension, Antihypertensive agent, Side effect.

## INTRODUCTION

Hypertension is one of the most prevalent medical disorders in pregnancy and constitutes an enormous global public healthcare concern. Hypertension is considered the second most common cause of direct maternal death and causes complications in approximately 7% of pregnancies, of which 3% of whom have pre-existing hypertension before pregnancy and 4% develop hypertension during pregnancy, with the latter raising the risk of preeclampsia.<sup>1</sup> In pregnancy, there are numerous broad groups of hypertensive disorders, including chronic hypertension, preeclampsia and eclampsia, chronic hypertension with superimposed pre-eclampsia, and gestational hypertension. According to a 2013 WHO international hospital survey on maternity and newborn health, the incidence of pre-eclampsia and eclampsia were 2.5% and 0.3% respectively among 314,623 women from Asia, Africa, and Latin America.<sup>2</sup> Owing to the irreversible vascular and metabolic changes that may persist after the complicated pregnancy, women with hypertensive disorders of pregnancy are at greater risk for the development of cardiovascular diseases later in life.<sup>3</sup> Therefore, managing hypertension in pregnancy does not only improve the immediately affected pregnancy but also the long-term maternal cardiovascular health.<sup>4</sup>

In terms of treatment, the clinical management of hypertensive disorders in pregnancy is challenging. Unlike the standard of care in non-pregnant individuals, the use of antihypertensive medications to normalize blood pressure in pregnancy is crucial due to the major adverse perinatal outcomes that hypertension can cause.<sup>1</sup> Although treatment with

medication might be beneficial for maternal health, it may carry potential risks to the fetus from both impaired uteroplacental perfusion and fetal exposure to the medications; thus, it must be considered carefully in the context of possible teratogenicity of medications if taken in early pregnancy.<sup>5</sup> As pregnancy progresses, the impact of drugs on blood flow and placental perfusion must be addressed. Previous studies have shown the use of methyldopa and labetalol to control blood pressure in pregnancy may significantly reduce the incidence of preterm deliveries, small for gestational age, and admissions to the neonatal unit.<sup>6</sup> Labetalol is recommended as first-line therapy for gestational hypertension and preeclampsia, yet intravenous hydralazine and oral nifedipine alternatively can also be used. Moreover, methyldopa is recommended as first-line therapy in managing pre-existing hypertension in pregnancy in addition to labetalol, nifedipine, and a diuretic.<sup>7</sup> However, some studies have linked these antihypertensive medications used in pregnancy to potential fetal adverse outcomes, such as decreased birth weight, cognitive development delay, neonatal seizures, and hematological disorders.<sup>1,8</sup> Nonetheless, there is still no strong evidence supporting and confirming these associations, and the potential adverse effects of these antihypertensive drugs on pregnancy and the newborn are debatable.<sup>9</sup>

Given the various guidelines and results from previous studies, the prescribing patterns for blood pressure control during pregnancy may vary from institution to institution and depend on resource availability. This study aimed to determine the profile of antihypertensive drugs used in pregnancy in low-middle-income country and the impact of these drugs on maternal and fetal outcomes.

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## 6 METHODS

This retrospective study was conducted at Dr. Soetomo General Academic Hospital in Surabaya, Indonesia. The sample was a hypertensive pregnant patient admitted to the hospital emergency unit during 2019-2020. Data were extracted from existing medical records. The inclusion criteria included pregnant women diagnosed with hypertension with complete medical record data. The electronic medical records of the eligible patients were then reviewed, and data regarding the type of hypertension during pregnancy (HDP), antihypertensive drugs used, side effects, and maternal and perinatal outcomes were collected. Ethical approval of the study was granted by the institutional ethics board of Dr. Soetomo General Academic Hospital.

Patients were diagnosed according to the American College of Obstetricians and Gynecologists guidelines.<sup>10</sup> Gestational hypertension was defined as new-onset hypertension (blood pressure  $\geq$  140/90 mmHg) after 20 weeks gestation. Preeclampsia was new-onset gestational hypertension accompanied by proteinuria. Chronic hypertension (pre-existing hypertension) was hypertension detected before 20 weeks gestation. Chronic hypertension with superimposed

preeclampsia is chronic hypertension with proteinuria, whereas eclampsia was preeclampsia combined with seizures.

Descriptive statistics were used to obtain frequencies, means, medians, standard deviations (SD), and minimum and maximum of the different variables. The values of the normally distributed continuous variables were presented as mean $\pm$ SD. The associations of the categorized variables were assessed using the Chi-square test, whereas one-way analysis of variance and post hoc analysis were used to compare means of continuous variables and assess their associations with categorized variables. *P*-values < 0.05 were considered significant for all used statistical tests. All statistical analyses were performed on IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA).

## 24 RESULTS

Between January 1, 2019, and December 31, 2020, a total of 762 hypertensive pregnant women were analysed. We excluded 36 (4.72%) women who were ineligible due to lack of data. The mean age of 726 hypertensive pregnant women was 31.01 years; with a minimum age of 15 years and maximum 49 years. Among 726 included pregnant women, 33.3% were primigravida whereas 66.7% multigravida. Among

32 **Table 1: Baseline characteristics of hypertensive pregnant women in the studied population.**

Variables	PE (n = 61)	PE with severe features (n = 491)	Chronic HT superimposed PE (n = 174)	P
<b>Maternal demographics</b>				
Maternal age, year, median (IQR)	29 (10)	30 (10)	34 (9)	<0.001 <sup>a</sup>
Obesity, n (%)	32 (52.5)	235 (47.9)	109 (62.6)	0.004 <sup>b</sup>
Renal disorder, n (%)	1 (1.6)	34 (6.9)	13 (7.5)	0.256 <sup>b</sup>
<b>Pregnancy characteristics</b>				
Gestational age, week, median (IQR)	38 (4)	34 (5)	33 (7)	<0.001 <sup>a</sup>
Multiple pregnancy, n (%)	35 (57.4)	302 (61.5)	147 (84.5)	<0.001 <sup>b</sup>
<b>Clinical measurements</b>				
Systolic BP, mmHg, median (IQR)				
Admission	142 (8)	160 (17)	165 (20)	<0.001 <sup>a</sup>
In ward	130 (10)	140 (12)	140 (13)	<0.001 <sup>a</sup>
Diastolic BP, mmHg, median (IQR)				
Admission	90 (7)	100 (20)	100 (17)	<0.001 <sup>a</sup>
In ward	84 (10)	87 (10)	90 (10)	0.028 <sup>a</sup>
Highest BP at admission, mmHg				
Systolic BP	170	260	260	
Diastolic BP	104	159	149	
Heart rate at admission, bpm, median (IQR)	88 (10)	98 (18)	96 (14)	<0.001 <sup>a</sup>
Anti hypertension received, n (%)				
Nifedipine	0	1 (0.2)	0	
Methyldopa	1 (1.6)	6 (1.2)	5 (2.9)	<0.001 <sup>b</sup>
Nifedipine + Methyldopa	13 (21.3)	423 (86.2)	137 (78.7)	<0.001 <sup>b</sup>
Captopril	0	0	0	
Amlodipine	0	0	0	
Nicardipine (IV)	0	4 (0.8)	2 (1.1)	0.546 <sup>b</sup>
MgSO <sub>4</sub> administration, n (%)	10 (16.4)	336 (68.4)	113 (64.9)	<0.001 <sup>b</sup>
Complication, n (%)				
CVA	0	3 (0.6)	5 (2.9)	0.047 <sup>b</sup>
HELLP syndrome	0	85 (17.3)	31 (17.8)	0.002 <sup>b</sup>
Heart failure	0	37 (7.5)	10 (5.7)	0.071 <sup>b</sup>
Maternal death	1 (1.6)	13 (2.6)	8 (4.6)	0.350 <sup>b</sup>
IUGR	2 (3.3)	39 (7.9)	12 (6.9)	0.407 <sup>b</sup>
Fetal death	3 (4.9)	49 (10)	27 (15.5)	0.023 <sup>b</sup>
Fetal outcome (n = 47) (n = 418) (n = 139)				
Fetal weight, g, median (IQR)	3,100 (1,100)	2,200 (1,185)	2,000 (1,330)	<0.001 <sup>a</sup>

Abbreviations: PE, preeclampsia; HT, hypertension; IQR, interquartile range; BP, blood pressure; bpm, beat per minute; IV, intravenous; CVA, cerebrovascular accident; HELLP, hemolysis, elevated liver enzyme and low platelets; IUGR, intrauterine growth restriction; <sup>a</sup>Kruskal-Wallis test; <sup>b</sup>Chi-square test.

**Table 2: Outcomes in the studied population according to antihypertension.**

Variables	Nifedipine (n = 1)	Methyldopa (n = 12)	Nifedipine + Methyldopa (n = 573)	Nicardipine (n = 6)	p
Systolic BP <160mmHg, n (%)	1 (100)	12 (100)	553 (96.5)	5 (83.3)	0.186 <sup>a</sup>
Diastolic BP <85mmHg, n (%)	0	5 (41.7)	236 (41.2)	1 (16.7)	0.030 <sup>a</sup>
Dosage, n (%)					
3x10mg	1 (100)	0	0	0	
3x250mg	0	1 (8.3)	0	0	
3x500mg	0	11 (91.7)	0	0	
3x10mg + 3x250mg	0	0	3 (0.5)	0	
3x10mg + 3x500mg	0	0	570 (99.5)	0	
0.5µg	0	0	0	6 (100)	
Adverse events, n (%)					
Tachycardia	0	3 (25)	43 (7.5)	1 (16.7)	
Hypotension	0	0	0	0	
Arrhythmia	0	0	0	0	

<sup>a</sup>Chi-square test.

the pregnant women associated with hypertension, 61 were diagnosed as preeclampsia, 491 were preeclampsia with severe features and 174 were diagnosed as chronic hypertension superimposed preeclampsia (Table 1). When timing of diagnosis of hypertension was analysed, the average of gestational age was more than 33 weeks. About 51.8% hypertensive pregnant women were having obesity, whereas 6.6% were having other comorbid illness, namely renal disorder.

On clinical measurements, the mean systolic blood pressure of the patients on admission was 162.53 (80-260) mmHg while mean diastolic blood pressure was 100.98 (50-159) mmHg. Of 726 hypertensive pregnant women, 81.54% of them received antihypertension medication on admission; monotherapy was used in 19 (3.6%) pregnant women whereas combination therapy was used in 573 (96.7%) (Table 2). In this study, the most commonly prescribed antihypertensive drugs were combination therapy of nifedipine and methyldopa (96.7%), followed by monotherapy of methyldopa (2.3%), nicardipine (1.1%), and nifedipine (0.2%). In term of eclampsia prophylaxis, a total of 16.4% pregnant women with preeclampsia were administered with MgSO<sub>4</sub>, whereas in groups of preeclampsia with severe features and chronic hypertension superimposed preeclampsia were 68.4% and 64.9%, respectively. Among reported complications, HELLP syndrome dominated with the prevalence of 17.3% and 17.8% in PE with severe features and chronic HT superimposed PE, respectively. On analysis of neonatal outcome, the current study found that a total of 530 (73%) were live births followed by 79 (10.9%) were born dead. Detailed information was summarized in Table 1.

Of 592 hypertensive pregnant women received antihypertension medication, 96.5% of patients were successfully attained the SBP<160mmHg whereas 40.9% were successfully attained DBP<85mmHg. In term of adverse events, tachycardia was reported in 47 (7.9%) of pregnant woman that received antihypertensive medication. In addition, none reported hypotension and arrhythmia. Detailed information was summarized in Table 2.

## DISCUSSION

Hypertensive disorders of pregnancy (HDP), including preexisting and gestational hypertension, preeclampsia, and eclampsia, complicate up to 10% of pregnancies and represent a significant cause of maternal and perinatal morbidity and mortality.<sup>10</sup> In low- and middle-income countries (LMICs), including Indonesia, HDP remains a major cause of maternal mortality with approximately three maternal daily, which may soon replace postpartum hemorrhage as the most common cause of direct maternal mortality by its current increasing trend.<sup>11</sup>

Albeit research demonstrated that maternal mortality from HDP is preventable if the pregnant woman receives appropriate management, many maternal mortality from HDP in our country are not well anticipated due to lack of practice guidelines in primary care.<sup>12</sup> The goals of therapy and treatment agents for hypertension in pregnancy have been long debated and remain controversial; thus, the current study aimed to determine the pattern of antihypertensive medication prescription during pregnancy in one of tertiary hospital in LMIC.

In this study, central alpha agonist (methyldopa) and calcium channel blockers (nifedipine) are the first choices of oral antihypertensive agents used in HDP. Nicardipine is IV agent used. The American College of Obstetrics and Gynecology Practice Bulletin recommends methyldopa and Labetalol as first-line agents for treating HDP.<sup>13</sup> Other randomized controlled trials (RCT) also suggested that all three oral medications, namely nifedipine, hydralazine, and Labetalol, are viable as initial options for treating severe hypertension, as well as the use of methyldopa.<sup>14</sup> There was no significant difference between nifedipine, hydralazine, and Labetalol in the risk of maternal hypotension, adverse effects, and maternal and fetal outcomes.<sup>15</sup> However, if only a single drug were available, nifedipine or labetalol would be preferential to methyldopa. Nevertheless, the findings should reassure providers to use the available drugs, especially given the supply chain and licensing variability between clinical settings.<sup>16</sup> In our study, labetalol was not used because it was unavailable in Indonesia.

Combination therapy of nifedipine and methyldopa was the most prescribed antihypertensive drug, followed by monotherapy using methyldopa, nicardipine, and nifedipine. Most patients successfully attained the SBP target (<160mmHg), whereas less than 50% successfully attained the DBP target (<85mmHg) with oral antihypertensive management. Even though monotherapy is the first choice for non severe antihypertensive therapy,<sup>17</sup> combination therapy (nifedipine and methyldopa) was chosen because a single agent did not achieve the target of reducing hypertension. Additional antihypertensives from a different drug class should choose from the first-line or second-line agent available.<sup>18</sup> The same report was stated in Al Ismaili *et al.* and Subki *et al.* studies which presented that most pregnant women who had HDP were on combination therapy.<sup>9,19</sup>

The side effect noted in using antihypertensives in this study was increased heart rate (tachycardia). Highest in patients receiving combination therapy of nifedipine and methyldopa. However, the highest prevalence of tachycardia was presented in methyldopa monotherapy. No hypotension or arrhythmia was noted in this study.

Various guidelines recommend that cases other than the urgency of hypertension should use extended release nifedipine. However, due to limited facilities, nifedipine immediate release is the first choice in our hospital. Nifedipine extended release is not widely used because of its relatively high price, not available in generic preparations, and only one brand circulating in the Indonesian market. The immediate release type of nifedipine is feared to cause a too-sharp decrease in blood pressure, thereby disrupting the mother's hemodynamics and the risk of disruption to uteroplacental blood flow. However, the data in this study did not record a decrease in blood pressure too quickly and even still required additional therapy from another type, namely methyldopa. This is possible because pregnant women are still in the relatively young age range (<40 years), so the vascular response is still quite good.

The high maternal complication and mortality reported in the present study mainly were obtained from pregnant women on combination therapy than women who received single medication only. Besides, higher fetal death was also significantly more prevalent in newborns of women who received combination therapy than newborns who were given a single medication. These women are more likely to have more severe uncontrolled hypertension that requires more antihypertensive medications, which may lead to higher adverse perinatal, maternal, and fetal outcomes. However, this does not exclude the effect of medications that could have contributed to the increased adverse outcomes in these women. Moreover, coexisting comorbidities might also contribute to higher adverse outcomes; however, our study showed no significant difference between those on single and combined therapy regarding the renal disorder.

The current study was conducted at a tertiary healthcare center that provides specialized consultative care and referral center in east Indonesia, so it had an adequate sample size. Even though this study was conducted in a single-center institution, the results may be representative of the general Indonesian population. Consequently, the overall prevalence of maternal complications and mortality associated with HDP might have been underestimated and is a limitation of this study. However, this study's result shall enhance the physicians' knowledge of the maternal and perinatal outcomes associated with hypertension and antihypertensive medications and be more cautious when selecting and using antihypertensive medication in pregnant women. They should be more vigilant to the commonly reported outcomes during the antenatal and postnatal follow-up.

## CONCLUSION

Calcium channel blockers (nifedipine) and central alpha agonists (methyldopa) are choices for an anti-hypertensive agent in limited resources, either monotherapy or combined. Nifedipine's immediate release can be an alternative if the extended release nifedipine is unavailable, with a low risk of hypotension.

## ACKNOWLEDGEMENT

None

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