Indonesian Journal of Pharmaceutical Education (e-Journal) 2025; 5 (2): 229– 239
ISSN: 2775- 3670 (electronic)
Journal Homepage: http://ejurnal.ung.ac.id/index.php/ijpe/index
DOI: 10.37311/ijpe.v5i2.31058

Pharmacokinetics of Antihypertensive Drugs During Pregnancy: A Systematic Review

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Article Info:
Received: 27 March 2025
in revised form: 4 April 2025
Accepted: 1 June 2025
Available Online: 5 June 2025

Keywords:
Antihypertensive Drugs;
Maternal Pharmacokinetics;
Pregnancy;
Drug Metabolism;
Physiological Changes

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ABSTRACT

Hypertension during pregnancy is a serious medical condition that poses risks to both maternal and fetal health. Physiological changes associated with pregnancy can significantly alter the pharmacokinetics of antihypertensive medications, necessitating individualized dose adjustments and careful monitoring. This systematic review aims to evaluate the pharmacokinetic profiles of five commonly used antihypertensive drugs in pregnant women: amlodipine, metoprolol, magnesium sulfate, labetalol, and nifedipine. The literature search was conducted using recent articles published in the past ten years. Study selection followed the PRISMA guideline, and data were analyzed qualitatively. The findings indicate that increased plasma volume, hepatic changes, and genetic polymorphisms influence drug disposition. Amlodipine and metoprolol exhibit good bioavailability but are affected by genotype. Magnesium sulfate is effective for preeclampsia management but is frequently associated with side effects such as nausea and headache. Labetalol and nifedipine demonstrate acceptable safety profiles but require dose modifications based on lean body weight. In conclusion, although these antihypertensive agents are generally safe for use during pregnancy, their administration must be tailored to individual patient characteristics. Further research is needed to assess long-term outcomes and determine the most effective treatment strategies for hypertensive pregnant populations.

How to cite (APA 6th Style):
Trisnadewi, N.L.P.W.,Sarasmita,M.A., Setyawan,E.I.(2025). *Pharmacokinetics of Antihypertensive Drugs During Pregnancy: A Systematic Review. Indonesian Journal of Pharmaceutical Education (e-Journal), 5*(2), 229-239.

ABSTRAK

Hipertensi dalam kehamilan merupakan kondisi medis serius yang dapat membahayakan kesehatan ibu dan janin. Perubahan fisiologis yang terjadi selama kehamilan dapat secara signifikan memengaruhi farmakokinetika obat antihipertensi, sehingga diperlukan penyesuaian dosis yang bersifat individual serta pemantauan terapi secara ketat. Tinjauan sistematis ini bertujuan untuk mengevaluasi profil farmakokinetik lima obat antihipertensi yang umum digunakan pada ibu hamil, yaitu amlodipin, metoprolol, magnesium sulfat, labetalol, dan nifedipin. Pencarian literatur dilakukan terhadap artikel terkini yang diterbitkan dalam sepuluh tahun terakhir. Seleksi studi mengikuti panduan PRISMA dan data dianalisis secara kualitatif. Hasil menunjukkan bahwa peningkatan volume plasma, perubahan fungsi hati, dan variasi genetik memengaruhi proses distribusi obat dalam tubuh. Amlodipin dan metoprolol memiliki bioavailabilitas yang baik namun dipengaruhi oleh genotipe. Magnesium sulfat efektif dalam penanganan preeklampsia, tetapi sering menimbulkan efek samping seperti mual dan sakit kepala. Labetalol dan nifedipin tergolong aman, namun memerlukan penyesuaian dosis berdasarkan berat badan tanpa lemak. Sebagai kesimpulan, meskipun obat-obatan antihipertensi ini umumnya aman digunakan selama kehamilan, pemberiannya harus disesuaikan dengan karakteristik individual pasien. Penelitian lebih lanjut diperlukan untuk menilai keamanan jangka panjang dan menentukan strategi terapi paling efektif bagi ibu hamil dengan hipertensi.

Kata Kunci: Obat Antihipertensi; Farmakokinetik Ibu; Kehamilan; Metabolisme Obat; Perubahan Fisiologis

1. Introduction

Hypertension is a condition where a person experiences an increase in blood pressure above normal, namely systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg [1]. According to Riskesdas 2018, the prevalence of hypertension in Indonesia was 34.11%, the estimated number of hypertension cases in Indonesia was 63,309,620 people while the death rate in Indonesia due to hypertension was 427,218 deaths [2]. This medical condition is one of the serious conditions that increase the risk of cardiovascular disease. Hypertension in pregnancy is one of the most common and dangerous medical complications, affecting approximately 5-10% of all pregnancies worldwide [3]. The risk of maternal morbidity and mortality is elevated, and it can also lead to serious consequences for the fetus, such as stunted growth, premature birth, and even perinatal death [4].

The treatment of hypertension during pregnancy is a challenge for health practitioners, given the significant physiological changes in the body of pregnant women that can affect the pharmacokinetics of drugs. Physiological changes during pregnancy, such as increased plasma volume, changes in renal and hepatic function, and variations in plasma protein levels, can substantially alter the absorption, distribution, metabolism, and elimination of antihypertensive drugs [5]. This has the potential to alter the effectiveness and safety of a given therapy. An in-depth understanding of the pharmacokinetics of antihypertensive drugs in the pregnant population is crucial to ensure optimal management of hypertension without jeopardising maternal and foetal health [6].

Although several studies have been conducted on the pharmacokinetics of antihypertensive drugs during pregnancy, comprehensive and integrated information is limited. This systematic review aims to collect, analyse and synthesise the current evidence on changes in the pharmacokinetics of various commonly used antihypertensive drugs during pregnancy. By combining findings from various studies, it is hoped that this review can provide clearer guidance for clinicians in adjusting

treatment regimens, improving therapeutic effectiveness, and minimising the risk of adverse effects on the mother and fetus.

2. Methods

The literature search was conducted using PubMed and Google Scholar. The keywords used were "antihypertension", "pharmacokinetics", and "pregnancy". The inclusion criteria were: (1) articles describing pregnant women taking antihypertensive drugs, (2) articles written in English or Bahasa Indonesia, (3) full-text articles, and (4) articles published after 2014. Exclusion criteria were: (1) articles published before 2014, (2) not written in English or Bahasa Indonesia, (3) incomplete articles (only abstract or paywalled full text), and (4) studies not involving pregnant women.

The article selection process was carried out in October 2024 using Publish or Perish and Mendeley software. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 flow diagram was employed to ensure transparency and methodological rigor. The collected data included: author, year of publication, country of origin, study type, sample size, drug name and dosage, study location, test parameters, and pharmacokinetic outcomes. These data were tabulated and critically reviewed.

The flow of article selection is shown in **Figure 1**.

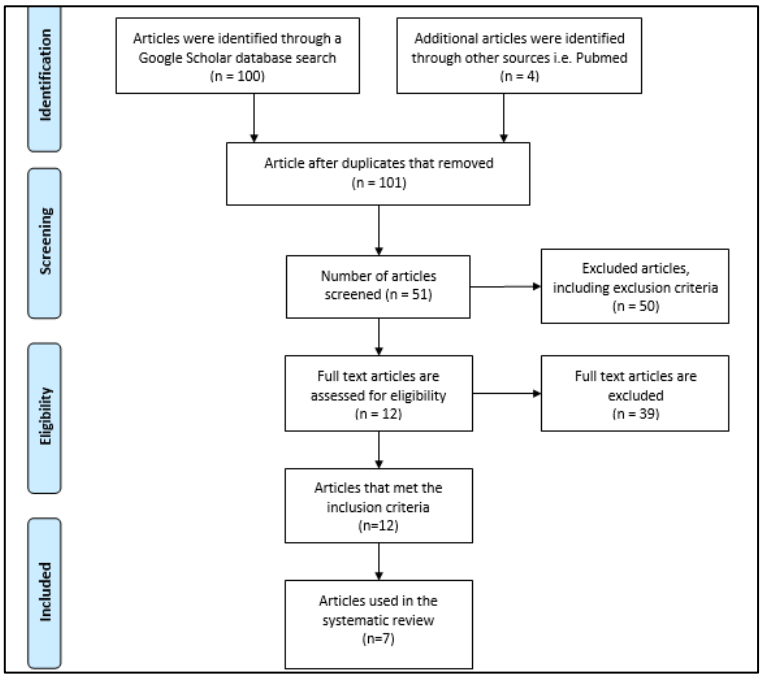

Figure 1. PRISMA Flowchart

3. Results and Discussion

A total of twelve articles were included in this systematic review after meeting the predefined inclusion and exclusion criteria. These articles provided comprehensive data on the pharmacokinetic behavior of antihypertensive drugs in pregnant women. The studies represented a variety of research approaches and clinical contexts, reflecting differences in population characteristics, sample sizes, drug types, dosages, and therapeutic indications. The reviewed drugs included amlodipine, metoprolol,

magnesium sulfate, labetalol, and nifedipine, which are commonly prescribed to manage blood pressure during pregnancy. Each drug showed distinctive pharmacokinetic patterns that were influenced by physiological changes associated with pregnancy, such as increased plasma volume, altered hepatic and renal function, and hormonal fluctuations.

Table 1. Characteristics of Included Studies on Antihypertensive Drug Pharmacokinetics During Pregnancy

Information	N samples	Type	Name of medicine	Dosage	Indications	Duration of research
Morgan *et al.*, USA, [7]	16	Perspective study / Cohort study	Amlodipine besylate	5 mg per day	Chronic hypertension	10 months (March 2015-January 2016)
Antunes *et al.* UK, [8]	35	Clinical protocol	Metoprolol	100 mg per day	Hypertension	-
Ryu *et al.*, USA, [9]	22	Observational study	Metoprolol	25-750 mg per day	Hypertension	4 weeks
Deng *et al.*, China, [10]	51	Population Pharmaco-kinetics (PPK)	Magnesium Sulphate	5 g as loading dose and continued with 10 g per day	Preeclampsia (PE)	-
Vusse *et al.*, USA, [11]	-	Systematic Review	Labetalol	50 mg single dose up to 2400 mg per day	Hypertension	-
	11		Nifedipine	20 mg per 6 hours	Preterm labour and gestational hypertension	
Filgueira *et al.*, UK, [12]	22	Observational study	Nifedipine	20 mg per 12 hours	Hypertension	3 months
Fischer *et al.*, USA, [13]	57	Prospective longitudinal design study	Labetalol	50-200 mg per day	Hypertension in pregnancy	10 months

The general characteristics of the included studies such as country of origin, number of participants, type of study, name and dose of medication, clinical indication, and duration of observation are presented in **Table 1**. Meanwhile, pharmacokinetic findings including peak plasma concentration, time to peak, half-life, drug clearance, and extent of distribution are summarized in **Table 2**. These results provide an important foundation for understanding how drug disposition is altered in pregnant individuals. The discussion that follows examines each drug in greater detail to explore

how these pharmacokinetic changes may impact safety, dosing strategies, and clinical outcomes for both mothers and their unborn children.

Table 2. Pharmacokinetic Parameters and Results of Antihypertensive Drugs in Pregnant Women

Information	Pharmacokinetic Test Parameters	Test Results
Morgan *et al.*, USA, [7]	• AUC = 53.4 h*ng/mL • Tmax = 7.5 hours • Cmax = 2.0 ng/mL • T½ = 13.7 hours • Cl (clearance rate) = 109.7 L/h	• Amlodipine penetrates the placenta and is detected in fetal cord blood, but is not detected in breast milk or infant plasma at 24-48 hours after birth. • The pharmacokinetics of amlodipine during the peripartum period (before and after labour) differ from those of non-pregnant individuals, with lower drug exposure and shorter half-life.
Antunes *et al.* UK, [8]	• Cmax and Tmax • Elimination rate	• The C max (t max) for metoprolol enantiomer R-(+)-MET was 22.89 ng/mL for 1.5 hours in the control group and 18.98 ng/mL 2.5 hours in the group with gestational diabetes (GDM). For S-(-)-MET, the C max (t max) was 41.42 ng/mL 1.5 hours in the control group and 22.90 ng/mL 2.75 hours in the GDM group. • This article investigates the effect of well-controlled gestational diabetes on the kinetic disposition, metabolism, and distribution of metoprolol and its metabolites in hypertensive pregnant women receiving a single dose of racemic metoprolol.
Ryu *et al.*, USA, [9]	• Plasma concentrations of metoprolol during late pregnancy and postpartum in EM (Extensive Metaboliser) or CYP2D6*1/*1	• In EM, metoprolol CL/F increased significantly during mid-pregnancy (432 L/h) and late pregnancy (629 L/h) compared to postpartum (238 L/h). The results showed that metoprolol was concentrated in breast milk, as indicated by the ratio of the mean AUC of milk to plasma concentrations of 2.4. This suggests pregnancy significantly increases metoprolol clearance, especially in individuals with extensive metabolizers. • Individuals with *poor metabolizers* showed significantly lower metoprolol clearance during pregnancy compared to *extensive metabolizers*. This suggests that genetic variation of CYP2D6 and individual metabolic status affect the elimination process of metoprolol during pregnancy, thus dose adjustment may be required to ensure therapeutic effectiveness and safety.
Deng *et al.*, China, [10]	• Serum magnesium concentration of pregnant women with pre-eclampsia after administration of	• The estimated population parameters were as follows: CL is 2.98 L/h, V is 25.07 L. Model predictions changed significantly with covariates (BMI, creatinine clearance, and furosemide).

	magnesium sulphate ($MgSO_4$)	• A one-compartment population pharmacokinetic (PPK) model was developed to describe the pharmacokinetics of magnesium sulphate (MgSO4) in Chinese women with preeclampsia. Creatinine clearance (CCR), body mass index (BMI), and furosemide use were identified as the main covariates affecting MgSO pharmacokinetics[4]. • The optimal dosing regimen was determined based on the KDP model, i.e: - An initial dose of 5 g combined with a maintenance dose of 10 g for patients not receiving furosemide. - An initial dose of 2.5 g combined with a maintenance dose of 10 g for patients receiving furosemide.
Vusse *et al.*, USA, [11]	• Cmax and Tmax of labetalol, and Volume of distribution • Cmax and Tmax of nifedipine	• The Cmax of labetalol is 300 ng/mL after a single dose, with a Tmax of 5-8 hours, where the volume of distribution reaches 4 L/kg. Whereas the steady-state AUC of nifedipine was estimated at 11% 237 ng*h/mL with a Cmax of 184 ng/mL. • This study is a systematic review which provides a detailed description of the pharmacokinetics of labetalol and nifedipine during pregnancy as antihypertensive drugs. The results of the *review* showed that these drugs can cross the placenta, but there is no apparent accumulation in the fetus, so further studies with a wider population are needed to understand their pharmacodynamic effects more definitively and to optimise safe doses for mother and fetus.
Filgueira *et al.*, UK, [12]	• Cmax • Tmax • AUC • T ½ • Distribution divided by bioavailability (Vd/F)	• The results of CG median pharmacokinetic parameter testing were: Cmax = 26.41 ng/mL, Tmax = 1.79 hours, AUC = 235.99 ng*h/mL, T ½ = 4.34 hours, Volume of distribution divided by bioavailability (Vd/F) = 560.96 L, CIT/F = 84.77 L/h. Parameters for the T2DM group were: Cmax 23.52 ng/mL, tmax 1.48 h, AUC(0-12) 202.23 ng*h/mL, t ½ 5.00 h, Vd/F 609.40 l, and apparent total clearance (ClT/F) 98.94 L/h. • Controlled type 2 diabetes mellitus (T2DM) does not affect the pharmacokinetics or placental transfer of nifedipine in pregnant women with hypertension. The pharmacokinetic parameters and placental transfer ratio of nifedipine showed no significant difference between pregnant women with hypertension who had T2DM and those without T2DM. Well-controlled T2DM did not affect the distribution of nifedipine in pregnant women with hypertension. These

		results suggest that the use of nifedipine in pregnant women with hypertension remains effective and safe, even if the patient has controlled T2DM.
Fischer *et al.*, USA, [13]	• Labetalol AUC • Oral clearance (CL/F) • Plasma Concentration	• When the AUC for each regimen was stratified by TBW, a striking difference was observed among the three doses, as TBW increased from≤ 70 to> 130 kg, the median AUC with 300 mg dosing (not adjusted for body size) decreased by approximately 36%, and with 300 mg TBW-adjusted dosing increased by approximately 37%. In contrast, for the LBW-adjusted dose, the median labetalol AUC remained identical across groups. • Lean body weight (LBW) and gestational age (gestational week) significantly influenced the oral clearance (CL/F) of labetalol, with CL/F ranging from 1.4 times greater than the post-partum value at 12 weeks' gestation to 1.6 times greater at 40 weeks' gestation. Doses adjusted based on LBW provided more consistent drug exposure compared to doses adjusted based on total body weight (TBW). The apparent volume of distribution in the central compartment and at steady-state was 1.9 times higher during pregnancy compared to post-partum. This suggests that labetalol dose adjustment based on LBW and gestational age may help achieve optimal drug exposure during pregnancy.

Note: AUC = area under the curve; Cmax = maximum plasma concentration; Tmax = time to reach Cmax; T½ = half-life; CL = clearance; Vd = volume of distribution.

Pharmacokinetics of Antihypertensive Drugs in Pregnancy

Based on the systematic literature review presented above, the pharmacokinetic profiles of several antihypertensive drugs, including Amlodipine, Metoprolol, Magnesium Sulphate, Labetalol, and Nifedipine, were evaluated. The results from these studies provide insights into the pharmacokinetic characteristics of these medications. According to Morgan [7], Amlodipine exhibits a favorable pharmacokinetic profile, characterized by a prolonged half-life, which enables the use of a lower daily dose of 5 mg. This drug is known for its high bioavailability and is effective in managing chronic hypertension in pregnant women [14]. Amlodipine is well absorbed when taken orally, with a bioavailability ranging from 60-80%. The time to reach peak plasma concentration (Tmax) occurs within 6-12 hours after oral administration. Although Amlodipine crosses the placenta in measurable amounts, it is not detected in breast milk or infant blood within 24-48 hours after delivery. Moreover, the pharmacokinetics of Amlodipine in pregnant and postpartum women differ from those in non-pregnant individuals [7]. These differences may result from the physiological changes that occur during pregnancy and after childbirth. Changes in blood flow, body fluid volume, and renal and hepatic function during pregnancy can influence drug metabolism and elimination, potentially leading to variations in drug concentrations within the body. Furthermore,

alterations in hormone levels and enzymes involved in drug metabolism may contribute to these pharmacokinetic variations [15].

In the studies conducted by Antunes and Ryu [8], [9], it was observed that the enantiomers of metoprolol and the genetic makeup of individual pregnant women can influence its pharmacokinetic profile. Antunes' research [8], demonstrated that the elimination rate of metoprolol is primarily affected by the activity of the CYP2D6 and CYP3A enzymes, with approximately 65% of the metoprolol dose being excreted as the metabolite O-desmethyl metoprolol (AODM). While metoprolol is efficiently absorbed through the gastrointestinal tract following oral administration, it has relatively low oral bioavailability (around 50%) due to significant first-pass metabolism in the liver. The drug is predominantly metabolized in the liver by the enzyme CYP2D6, which is significantly influenced by genetic variations within the population, particularly CYP2D6 gene polymorphisms. For instance, genotypes such as EM (Extensive Metabolizer) or CYP2D6*1/*1 indicate fast metabolism. Individuals who are rapid metabolizers of CYP2D6 may require higher doses to achieve the desired therapeutic effects, while slow metabolizers are more likely to experience side effects due to drug accumulation [5].

According to Deng [10], magnesium sulfate ($MgSO_4$) is typically administered via intravenous infusion, allowing for rapid absorption into the bloodstream. In hypertensive pregnant women, particularly those with preeclampsia and eclampsia, the use of magnesium sulfate aims to prevent and manage seizures. After administration, magnesium exhibits a high affinity for tissues, and plasma concentrations may fluctuate based on factors such as body mass index (BMI) and creatinine clearance rate (CCR). Based on research conducted by Fischer[13] , labetalol is is frequently used to manage hypertension in pregnant women. Labetalol is well absorbed following oral administration; however, its oral bioavailability is relatively low due to significant first-pass metabolism in the liver. During pregnancy, the distribution volume of labetalol tends to increase, likely due to enhanced plasma volume and other physiological changes [16]. Labetalol is considered the first-line treatment for emergency hypertension in pregnancy, including severe preeclampsia or eclampsia, because it crosses the placenta only to a small extent. The drug undergoes metabolism to form inactive metabolites [17]. This metabolic process can also be influenced by physiological changes during pregnancy, such as increased hepatic blood flow and alterations in enzyme activity that accelerate labetalol's metabolism [18]. In pregnant women, labetalol clearance tends to increase as gestational age advances, which suggests that dose adjustments may be necessary in some cases. The labetalol dose is often tailored based on lean body weight (LBW), or in some cases, without considering total body weight, in order to avoid excessive drug exposure to both the mother and fetus [10].

Nifedipine is efficiently absorbed following oral administration. It is primarily metabolized in the liver by the enzyme CYP3A4 [19]. Nifedipine is excreted through the urine, both in unchanged form and as metabolites. In the study conducted by Filgueira [12], plasma concentrations of labetalol were measured using high-performance liquid chromatography (HPLC) to assess the drug and its metabolites. The study found that no increase in the drug dose was necessary for patients in either group, and there were no reported cases of preeclampsia, suggesting that labetalol can be safely used to manage hypertension in pregnant women, including those with diabetes. This study underscores the importance of monitoring drug levels and making dose adjustments as needed to achieve optimal hypertension control in pregnant women with diabetes [12].

Safety Profile of Antihypertensive Drugs in Pregnancy

The findings from the literature review indicate that all of the antihypertensive drugs examined demonstrate a relatively favorable safety profile. However, their use should be approached with caution in pregnant individuals. Despite their generally safe profiles, close monitoring of metoprolol and amlodipine is advised due to potential fetal risks [7], [8], [9]. In contrast, the study by Deng [10], reported that 41.20% of participants experienced adverse drug reactions (ADRs) associated with magnesium sulfate ($MgSO_4$), including symptoms such as flushing, headache, dizziness, nausea, and vomiting. This highlights the importance of determining the appropriate dosage. Antihypertensive medications, including Amlodipine, Metoprolol, Magnesium Sulfate, Labetalol, and Nifedipine, have varying mechanisms of action and pharmacokinetic profiles in individuals, particularly during pregnancy, where physiological changes can affect drug absorption. Pharmacists play a critical role in monitoring and assessing the use of these medications. They are responsible for delivering clinical pharmacy services, ensuring that prescribed doses are both safe and effective, and educating patients about potential side effects and the importance of medication adherence [16].

Strengths and Weaknesses of the Study and Further Research

This review presents valuable insights into the pharmacokinetic profiles of antihypertensive drugs used in pregnancy by compiling evidence on clinically relevant dosages and safety considerations. One notable strength is the focus on literature published within the past decade, which ensures the findings remain relevant to current clinical practices. The inclusion of various study designs and populations enhances the contextual understanding of drug behavior during pregnancy, which is essential for informing individualized treatment approaches.

Despite its strengths, this review is limited by the relatively small number of studies included, which may restrict the comprehensiveness of the findings. Certain aspects, such as adverse drug reactions, interindividual variability, and specific pharmacogenetic factors, remain underexplored. Additionally, few studies offer longitudinal data that capture maternal and neonatal outcomes beyond the immediate postpartum period. Future research should aim to address these gaps by conducting larger, multicenter investigations and by comparing multiple antihypertensive agents within standardized clinical frameworks. Expanding such evidence will contribute to a more nuanced understanding of drug safety and therapeutic optimization in maternal care.

4. Conclusion

This review emphasizes the critical importance of understanding the pharmacokinetic characteristics of antihypertensive drugs commonly used in pregnant women, namely amlodipine, metoprolol, magnesium sulfate, labetalol, and nifedipine. Pregnancy-induced physiological changes significantly alter drug absorption, distribution, metabolism, and elimination, thereby necessitating individualized dosing and vigilant therapeutic monitoring to ensure optimal efficacy and safety. Although these medications generally exhibit favorable safety profiles, inappropriate dosing may pose potential risks to both mother and fetus.

Further investigations are warranted to evaluate the long-term safety outcomes and to compare the clinical efficacy of different antihypertensive therapies in pregnant

populations. Clinicians are advised to consider pharmacogenetic factors and gestational age when selecting and adjusting treatments. Moreover, pharmacists play an essential role in supporting safe pharmacotherapy by optimizing dosage regimens and providing patient education to improve adherence and outcomes in hypertension management during pregnancy. This review serves as a valuable reference for guiding evidence-based and patient-centered decision-making in maternal pharmacotherapy.

Acknowledgments:

The authors would like to express their sincere gratitude to the Faculty of Mathematics and Natural Sciences, Udayana University, for the academic support and facilities provided during the completion of this review. Appreciation is also extended to the editorial team of the Indonesian Journal of Pharmaceutical Education for the opportunity to publish this work.

Conflicts of Interest:

The authors declare no conflicts of interest.

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