Review Article

Adverse Drug Reactions of Antihypertensive Drugs in Pregnancy: A Comprehensive Study - A Review

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ABSTRACT

Antihypertensive medication-related adverse drug reactions (ADRs) during pregnancy are a serious concern since they may have an impact on the development of the fetus as well as the health of the mother. A considerable percentage of pregnancies are complicated by hypertensive conditions such gestational hypertension, preeclampsia, and chronic hypertension, which frequently call for pharmacological treatment. Labetalol, methyldopa, nifedipine, and hydralazine are common antihypertensive medications; however, their safety profiles varies depending on the stage of pregnancy. While some medications are thought to be reasonably safe, others may cause fetal problems such intrauterine growth restriction, preterm birth, and congenital abnormalities, as well as negative maternal effects like hypotension, exhaustion, and electrolyte imbalance. Notably, because of their link to severe fetal toxicity, some classes, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), are prohibited. The purpose of this research is to critically assess the prevalence, mechanisms, and risk factors related to adverse drug reactions (ADRs) of antihypertensive medications during pregnancy. In order to reduce possible hazards, it also emphasizes the significance of careful medication selection, dose adjustment, and ongoing monitoring. To give a thorough understanding of drug safety in this population, evidence from clinical research, pharmacovigilance databases, and treatment guidelines is reviewed. In order to effectively manage hypertension during pregnancy and enhance mother and fetal outcomes, the review highlights the necessity of tailored therapy and greater knowledge among healthcare professionals.

Keywords: Adverse Drug Reactions (ADR), Antihypertensive drugs, Pregnancy, preeclampsia, Drug Safety, Fetal outcome, Maternal Health.

INTRODUCTION

Any negative or unexpected consequence that arises when a medication is taken at standard, advised dosages during routine clinical use is referred to as an adverse drug response (ADR). ADRs are rather common in routine healthcare settings and can significantly affect patients. They may lower one's quality of life and, in certain situations, result in fatalities or major health issues. Recognizing and controlling adverse drug reactions (ADRs) is crucial to providing safe and efficient patient care due to their prevalence and potential severity.[1]

About 5–10% of pregnancies result in hypertension, the most common cardiovascular illness. It plays a major role in the morbidity and mortality of both mothers and fetuses. [2,3] Pregnant women who suffer from hypertension disorders are also more likely to have cardiovascular ailments in the future.[4,5] Systolic blood pressure (SBP) of ≥160 mmHg or diastolic blood pressure (DBP) of ≥110 mmHg are indicative of severe hypertension in pregnancy.

Antihypertensive drugs must be used as soon as possible in order to quickly control blood pressure and avoid consequences because this condition is regarded as a medical emergency.[6-8]

Antihypertensive medication-related adverse drug reactions (ADRs) during pregnancy are a serious therapeutic concern since they can impact both the growing fetus and the mother. Pregnancy issues include prenatal hypertension, preeclampsia, and persistent hypertension frequently need medical attention to avoid dangerous consequences. Although medications including hydralazine, labetalol, methyldopa, and nifedipine are frequently used in clinical practice, their safety may vary based on the patient's condition and the stage of pregnancy.

Even though many of these drugs are thought to be reasonably safe when taken as directed, there is still some risk involved. Side effects that pregnant women may have include low blood pressure, fatigue, or imbalances in electrolytes. In addition, the fetus may be at risk for congenital defects, early delivery, or limited growth. Because they are known to seriously impair fetal development, some medication types, especially angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), are rigorously avoided during pregnancy.

Understanding the frequency of these adverse events, their underlying mechanisms, and potential risk factors are the main goals of this research. It also emphasizes how crucial it is to choose the right drugs, properly modify dosages, and keep a close eye on the mother and fetus during therapy. This article attempts to give a clear and impartial summary of medication safety in pregnant patients with hypertension by utilizing information from clinical research, pharmacovigilance data, and established treatment guidelines. In the end, it emphasizes how crucial individualized treatment plans and increased knowledge

among medical experts are to guaranteeing safer results for both mother and child.[9]

Types of ADR:

Based on their features, adverse drug reactions (ADRs) are typically classified into two primary groups.

Type A reaction:

often called augmented reactions, which are dose-related. These reactions are foreseeable and typically happen when patients are extremely sensitive to the medicine's effects or when the drug concentration in the body is higher than anticipated.

Type B reactions:

also referred to as weird reactions are rare and unrelated to the drug's established pharmacological effect. They are unpredictable, often include odd or extreme reactions, and may be related to specific patient characteristics like immune systems or genetic predispositions.[10]

Table 1: Comparison of Type A and Type B Adverse Drug Reactions (ADRs)

Characteristics	Type A	Type B
Dose dependency	Usually shows a good relationship	No simple relationship
Predictable from known pharmacology	Yes	Not usually
Host factor	Genetic factors might be important	Dependent on host Factor
Frequency	Common	Uncommon
Severity	Variable but usually mild	Variable proportionately sever
Clinical Burden	High morbidity and low mortality	High morbidity and mortality
Overall proportion of adverse drug Reaction	80%	20%
First detection	Phase Ⅰ - III	Usually phase IV
Animal model	Usually reproducible in animals	No known animal models

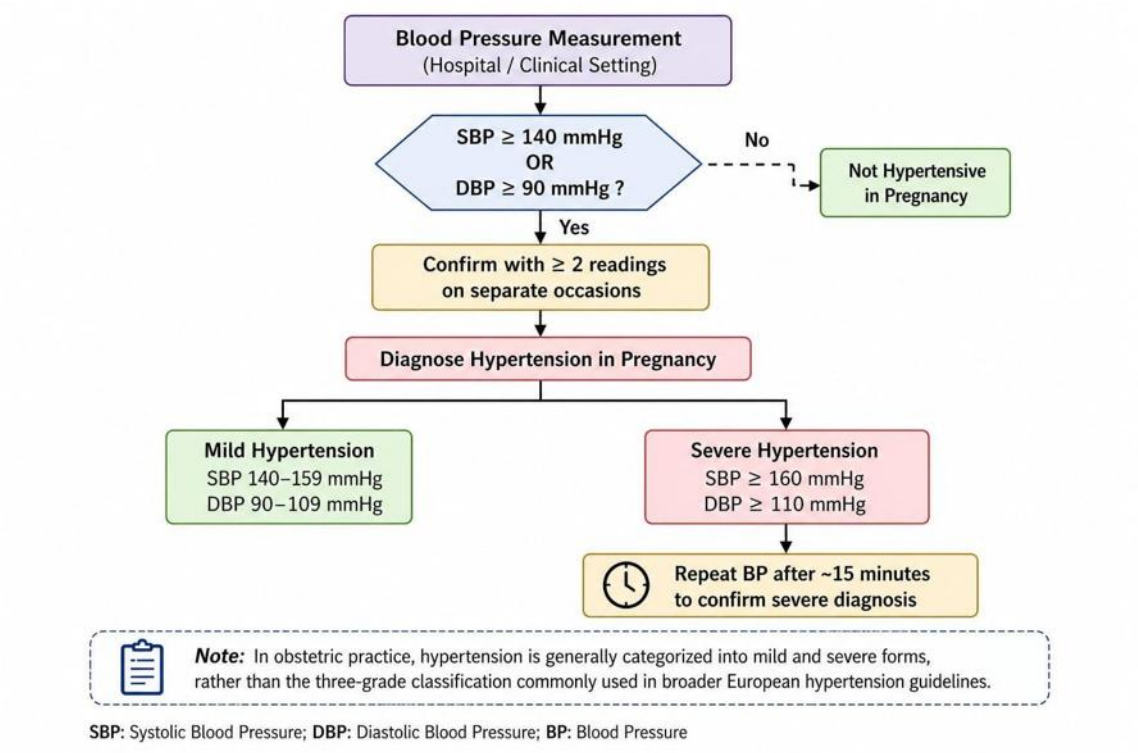

Figure 1: Diagnosis of Hypertension in pregnancy

Diagnosis of Hypertension in Pregnancy:

In a clinical context, such as a hospital or doctor's office, a woman is diagnosed with hypertension during pregnancy if her systolic blood pressure (SBP) is 140 mmHg or higher and/or her diastolic blood pressure (DBP) is 90 mmHg or higher. These readings should be verified at least twice to guarantee accuracy. Measurements may be repeated after a brief delay of roughly 15 minutes to confirm the diagnosis in situations of severe hypertension, which is defined as blood pressure levels of 160/110 mmHg or higher. In contrast to the three-grade classification frequently seen in more general European hypertension recommendations, hypertension in obstetric practice is typically divided into moderate and severe types.[11]

Classification of Hypertension in pregnancy:

The National Heart, Lung, and Blood Institute's (NHLBI) National High Blood Pressure Education Program typically divides pregnancy-related hypertensive disorders into four

major categories: gestational hypertension, chronic hypertension, preeclampsia, and preeclampsia superimposed on preexisting hypertension.[12]When the diastolic blood pressure is 90 mm Hg or higher, or the systolic blood pressure is 140 mm Hg or higher, hypertension in pregnancy is diagnosed in clinical practice. A correctly fitted cuff should be used to take the patient's blood pressure from their upper arm while they are comfortably seated. To achieve accurate findings, it's also critical that the patient has been peacefully resting for a few minutes prior to the reading.[13]

Gestational Hypertension:

High blood pressure that initially appears in the latter stages of pregnancy, usually after mid- pregnancy, and happens without the presence of protein in the urine is known as gestational hypertension. This group comprises women who just have increased blood pressure and those who may later develop preeclampsia (but have not yet demonstrated proteinuria). It is frequently only after delivery that the differences between these two states become apparent.

This syndrome, once known as transitory hypertension, may go away on its own within 12 weeks following childbirth. Blood pressure is then classed as chronic hypertension if it does not return to normal within this time frame. Although it may reoccur in subsequent pregnancies, transitory hypertension often has a very mild course and is linked to a favorable overall outcome. Women who suffer prenatal hypertension are more likely to have hypertension later in life, even though blood pressure usually stabilizes shortly after delivery.[14]

Preeclampsia:

High blood pressure and protein in the urine are the primary indicators of preeclampsia, a complicated condition that affects several organ systems. If there is no urinary tract infection, it is usually identified when urine protein levels in a 24-hour sample reach 300 mg or greater, which roughly translates to a dipstick reading of 1+ (around 30 mg/dL).[15]This illness has historically been linked to first-time pregnancies and typically manifests after 20 weeks of pregnancy. However, preeclampsia is more likely to recur in subsequent pregnancies among women who have already experienced it. A family history of preeclampsia, extremely young or elderly mothers, multiple pregnancies, including twins, and underlying medical conditions like chronic hypertension, diabetes, kidney disease, connective tissue disorders, or trophoblastic disease can all raise the risk. Preeclampsia is linked to significant alterations in circulation from a physiological standpoint. These include a decrease in cardiac output relative to a typical pregnancy, an increase in blood vessel resistance, and a disruption of the typical day-night blood pressure rhythm, which frequently results in higher readings at night.[16]

Chronic Hypertension:

When a woman's blood pressure is 140/90 mm Hg or above before getting pregnant or before 20 weeks of gestation, it is considered chronic hypertension in pregnancy.[17]When the diastolic blood pressure (DBP) hits 90 mm Hg or above, antihypertensive drug treatment is typically initiated. Pregnancy problems, particularly the development of preeclampsia, are more likely to occur in women with pre-existing hypertension. This risk increases if the hypertension is brought on by an underlying (secondary) ailment or if their blood pressure does not exhibit the usual drop throughout the middle of pregnancy.[18] Preeclampsia exacerbates persistent hypertension, making the condition more dangerous and raising the risk of complications such placental abruption and cerebral hemorrhage. It is currently unclear if beginning treatment early in pregnancy will successfully avoid the onset of preeclampsia, despite the fact that controlling chronic hypertension is crucial for maternal health.[19]

Antenatally unclassified hypertension

High blood pressure that is initially identified after 20 weeks of pregnancy in women whose prior blood pressure records are unavailable is referred to as antenatally unclassified

hypertension. It is impossible to identify the kind of hypertension right away because there is no information regarding their blood pressure condition prior to or during the early stages of pregnancy. Following delivery, a follow-up assessment is therefore crucial, typically at or after 42 days postpartum. During this time, the disease is referred to as gestational hypertension if the blood pressure returns to normal. However, the condition is classed as chronic (pre-existing) hypertension if the hypertension continues.[20]

Table 2: Classification of hypertension in pregnancy

Gestational hypertension	(i) transient hypertension appearing after mid- pregnancy (ii) confirmed by return to normal BP postpartum no proteinuria
Chronic hypertension	(i) increased BP before week 20 (or known to exist prior to pregnancy) hypertension persistent for more than 12 weeks after pregnancy
Preeclampsia	(i) de novo appearance of hypertension after mid-pregnancy
Antenatally unclassified hypertension	(i) new onset proteinuria

Signs and Symptoms of High Blood Pressure During Pregnancy:

Gestational Hypertension Symptoms:

Symptoms of gestational hypertension include persistent headaches, impaired vision, nausea, High blood pressure and proteinuria (protein in the urine) are signs of preeclampsia, a more dangerous condition. It is also frequently seen that the hands, feet, or face swell. These characteristics are especially crucial since preeclampsia can worsen quickly and endanger both the mother and the unborn child if treatment is not received.[21]

Preeclampsia Hypertension symptoms:

High blood pressure and proteinuria (protein in the urine) are signs of preeclampsia, a more dangerous condition. It is also frequently seen that the hands, feet, or face swell. These characteristics are especially crucial since preeclampsia can worsen quickly and endanger both the mother and the unborn child if treatment is not received.[22]

Chronic Hypertension symptoms:

High blood pressure that either preexists or develops early in pregnancy is referred to as chronic hypertension. Chest pain, nausea, dyspnea, headaches that don't go away, blurred vision, and swelling in the limbs are some of the symptoms. In contrast to other hypertension conditions, these symptoms typically persist during pregnancy and require ongoing medical attention.[23]

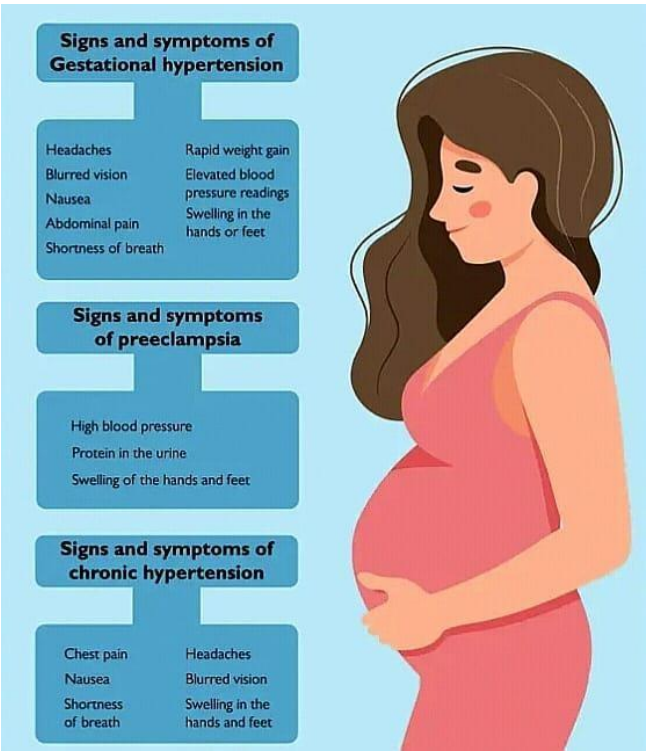

Figure 2: Hypertensive Disorders in Pregnancy: Signs & Symptoms

Adverse Drug Reactions of Antihypertensive Therapy in Pregnancy

Careful drug selection is necessary for the treatment of hypertension during pregnancy in order to protect both the mother and the fetus. The National High Blood Pressure Education Program (NHBPEP) states that methyldopa, labetalol, beta-blockers (apart from atenolol), sustained-release nifedipine, and several diuretics are frequently advised antihypertensive medications. With the exception of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers, which are contraindicated due to possible fetal hazards, women whose blood pressure was successfully controlled with medication prior to pregnancy may typically maintain the same therapy**.** Methyldopa is usually recommended as the first-line medication when treatment for women with persistent hypertension needs to be restarted. Oral nifedipine, labetalol, and intravenous hydralazine are often used treatments for severe hypertension, especially in pregnancy.[24]

Centrally acting α2-adrenergic agonists

Methyldopa is a centrally acting α_2-adrenergic receptor agonist that reduces catecholamine release in the brain to lower blood pressure.[25] As a result, there is less sympathetic outflow, which lowers systemic vascular resistance while preserving cardiac output.[26]Fatigue, depression, insomnia, and decreased salivation are typical adverse effects. Some side effects, like slight increases in liver enzymes (seen in up to 5% of patients), are unrelated to dosage. Although clinically significant hemolytic anemia is rare, some patients may also get a positive Coombs test or antinuclear antibodies. Methyldopa is typically avoided in women with a history of depression because it may exacerbate mood and raise the likelihood of postpartum depression. [27,28]

Another centrally acting antihypertensive medication that acts as an agonist of the α_2-adrenergic receptor is clonidine. By activating brainstem receptors that decrease sympathetic (adrenergic) output, it lowers blood pressure.[29]Clonidine reduces heart rate, systolic blood pressure, cardiac output, and systemic vascular resistance via acting on both central and peripheral α_2 receptors.[30]

Calcium channel blockers

Pregnancy-related hypertension is frequently treated with oral nifedipine and verapamil as second-line drugs. According on available data, these medications do not appear to have teratogenic effects.[31]Calcium channel blockers (CCBs) relax blood arteries and lower blood pressure by preventing calcium ions from entering vascular smooth muscle cells. While verapamil predominantly affects the heart by lowering cardiac activity, nifedipine primarily acts on the blood vessels, causing vasodilation. Pregnant women who use CCBs may experience adverse effects include elevated heart rate, palpitations, extremity swelling, headaches, and flushing of the face.[32]

Direct vasodilators

Intravenous hydralazine is most frequently used to treat severe hypertension during pregnancy. It causes vasodilation and a drop in blood pressure by directly relaxing the smooth muscles of the arterioles. However, adverse symptoms like headache, nausea, flushing, and palpitations may be linked to its use.

Sodium nitroprusside is usually saved for life-threatening, critical cases of severe hypertension when all other treatments have failed. It is rarely used in pregnant patients. Because of the serious hazards associated with its usage, such as cyanide and thiocyanate toxicity and the possibility of cardio-neurogenic syncope, its regular use during pregnancy is restricted.[33]

Angiotensin-Converting Enzyme Inhibitors

Due to their detrimental effects on the growing baby, angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors are not advised during pregnancy, especially in the second and third trimesters. These medications have the potential to cause major problems by decreasing blood supply to the developing kidneys. Their use has been associated with a pattern of abnormalities that resemble Potter's syndrome, such as poorly developed kidneys (renal dysgenesis), low amniotic fluid levels (oligohydramnios) due to decreased fetal urine production, underdeveloped skull and lungs, restricted fetal growth, and severe kidney failure in the newborn. These issues frequently have the potential to cause fetal mortality.[34-36]

Angiotensin Receptor Antagonists

Pregnancy-related ARB use has also been linked to fetal death, primarily from renal failure. [37,38]Exposure during the first trimester is also regarded as dangerous, even though the dangers are greatest in the latter stages of pregnancy. The risk of birth abnormalities rises from roughly 3% to roughly 7% if a woman falls pregnant while using ARBs or ACE inhibitors. As a result, these drugs should be avoided as much as possible during pregnancy.[39]

Diuretics

Before becoming pregnant, essential hypertension is frequently treated with diuretics. The National High Blood Pressure Education Program Working Group has stated that although these drugs can be taken during pregnancy, the dosage should ideally be lowered or combined with other antihypertensive medications when necessary, based on the evidence that they are generally safe.[40]

In instance, hydrochlorothiazide may be sustained, particularly at modest doses (12.5–25 mg daily), which helps lower the risk of adverse effects like low potassium levels and impaired glucose tolerance.[41]In the few case studies that are currently available, other diuretics like triamterene and amiloride have not demonstrated teratogenic consequences. Although this danger has not been consistently detected in all reported cases, spironolactone is generally avoided during pregnancy due to its antiandrogenic effects, which may potentially disrupt fetal development.[42]

Serotonin 2 Receptor Blockers

Vasodilators like prostacyclin and nitric oxide are released when serotonin acts on S1 receptors in the endothelium, causing blood vessels to relax. However, the S1 receptors may be diminished or eliminated in cases of endothelial dysfunction, such as those associated with pregnancy. In this case, S2 receptors are mostly stimulated by serotonin, which is more abundant during pregnancy. Vasoconstriction and enhanced platelet aggregation result from this change.

One medication that specifically inhibits S2 receptors is ketanserin. It has been demonstrated to reduce both systolic and diastolic blood pressure in nonpregnant people with hypertension. Research on humans and animals indicates that ketanserin is not teratogenic. It may be a safe and potentially helpful choice for treating disorders like preeclampsia and HELLP syndrome (hemolysis, high liver enzymes, and low platelets), according to small clinical trials mostly carried out in Australia and South Africa. Nevertheless, the US Food and Drug Administration has not authorized ketanserin for use in clinical settings.[43,44]

β-Blockers

By inhibiting β-adrenergic receptors, β-blockers lower blood pressure by slowing heart rate, lowering cardiac output, and reducing renin release from the kidneys. These medications may affect embryonic development because they can pass through the placenta.[45]Intrauterine growth restriction (IUGR), fetal bradycardia, neonatal hypoglycemia, and respiratory depression are among the reported consequences on the fetus and newborn. More lipophilic β-blockers and those with longer half-lives, like atenolol, typically have more hazards. Bradycardia, exhaustion, and the possibility of masking hypoglycemic symptoms are typical adverse effects in mothers. Additionally, some data points to a potential connection between premature delivery and low birth weight.[46]

Direct Renin Inhibitors (e.g. aliskiren)

By directly inhibiting renin, the enzyme that transforms angiotensinogen into angiotensin I, direct renin inhibitors reduce blood pressure. They depress the entire renin-angiotensin-aldosterone system (RAAS) by stopping this initial phase.[47]Like other medications that interfere with the RAAS, their use during pregnancy is generally discouraged due to significant dangers to the fetus. Complications include diminished amniotic fluid (oligohydramnios), compromised embryonic kidney function, underdeveloped skull and lungs, and even fetal mortality have all been linked to exposure. Reduced blood supply to the fetal kidneys and disturbance of normal RAAS development are the main causes of these detrimental effects. The mother may experience less severe side effects, such as low blood pressure and hyperkalemia (high potassium).[48]

Neonatal ADR via Breast Milk

Breast milk exposes newborns to very little methyldopa and is generally thought to be safe. On the other hand, beta-blockers like metoprolol and atenolol tend to build up in breast milk and may reach levels that could have an impact on the infant. Propranolol and labetalol, on the other hand, are thought to be safer substitutes and exhibit far less transfer into breast milk.[49]

Diuretics are generally harmless and found in small levels in breast milk, although they can lower milk production by making the mother lose fluid. While medications like nifedipine, verapamil, and diltiazem have a low relative baby dose and are thought to be compatible with breastfeeding, calcium channel blockers do seep into breast milk.[50]

The American Academy of Pediatrics considers captopril, enalapril, and quinapril to be safe ACE inhibitors that can be used during nursing. However, there is currently little information available about angiotensin II receptor blockers, and using them during nursing is not advised.[51]

DISCUSSION

Selecting the appropriate medicine is crucial since high blood pressure during pregnancy still poses serious hazards to the mother and the developing fetus. Medications like methyldopa, labetalol, and nifedipine are frequently chosen among the possibilities since they have been thoroughly researched and are seen to be quite safe. Even though methyldopa can have minor side effects like drowsiness, it is frequently utilized as a first-line treatment. Although it might cause symptoms like headaches and flushing, nifedipine is also useful in lowering blood pressure. Although hydralazine may cause some adverse effects in mothers, it is usually saved for more serious circumstances, particularly emergencies.

However, drugs that affect the renin-angiotensin-aldosterone system, such as renin inhibitors, ACE inhibitors, and angiotensin receptor blockers, should not be taken while pregnant since they might seriously injure the fetus, potentially leading to renal issues or even fetal death. Diuretics are typically not the primary option, though they may be taken into consideration in some circumstances. Since no antihypertensive medication is completely risk-free, treatment choices should be customized for each patient and closely monitored to provide the greatest results for mother and child.

CONCLUSION

Overall, optimal management of hypertension in pregnancy requires individualized treatment strategies, careful drug selection, dose adjustment, and continuous monitoring of both mother and fetus. Healthcare professionals must balance the benefits of blood pressure control against potential risks, while also considering patient-specific factors and disease severity. Increased awareness, adherence to clinical guidelines, and ongoing pharmacovigilance are essential to minimize adverse drug reactions and improve pregnancy outcomes. Future research and stronger clinical evidence will further enhance the safe use of antihypertensive medications in this sensitive population. In general, customized treatment plans, cautious medication selection, dose modification, and ongoing monitoring of the mother and fetus are necessary for the best management of hypertension during pregnancy. In addition to taking patient-specific characteristics and illness severity into account, healthcare professionals must weigh the advantages of blood pressure regulation against potential hazards. To reduce adverse medication responses and enhance pregnancy outcomes, increased awareness, adherence to clinical recommendations, and continuous pharmacovigilance are crucial. The safe administration of antihypertensive drugs in this vulnerable population will be substantially improved by future studies and more solid clinical data.

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