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ANTIHYPERTENSIVES THERAPY AND MONITORING IN PRE-ECLAMPSIA: ROLE OF THE PHARMACIST

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ABSTRACT

Pre-eclampsia is an obstetric disorder that affects the prognosis of pregnancy, resulting in complications or mortalities. It is typically associated with hypertension which should be managed pharmacologically to protect the health of the mother and the fetus. Yet, not much is known about pharmacists' roles and commitment to pre-eclampsia management. In this review, we update pharmacists on antihypertensives indicated in pre-eclampsia as well as parameters they have to monitor during pharmacotherapy in line with their duty of care to women with preeclampsia. Using recent evidence from 16 national/international guidelines (2014-2022), we compared antihypertensives approved for use in pregnancy and highlighted major drug information that pharmacists require to optimize the use of these medications in pre-eclampsia. Intravenous labetalol, hydralazine or oral nifedipine agents are mostly indicated in pre-eclampsia with severe hypertension. In mild-moderate hypertension, oral agents such as methyldopa, labetalol, sustained released nifedipine and hydralazine are the commonest recommendations. While monitoring for maternal bronchoconstriction, neonatal bradycardia or hypoglycemia is required with the administration of intravenous labetalol; intravenous hydralazine is observed for maternal shock; nifedipine for tachycardia, headache, ankle edema and methyldopa for depression if use is extended to the postpartum period. Controlled hypertension in pre-eclampsia mitigates maternal vascular complications. Apart from early referral and counselling of pregnant women at risk, pharmacists with sound knowledge of the pharmacotherapy of pre-eclampsia could advise on appropriate antihypertensive therapy and follow on to ensure that these medicines are responsibly used for optimal outcomes. These roles by pharmacists, may reduce adverse maternal outcomes associated with pre-eclampsia.

Keywords: antihypertensives in pre-eclampsia, obstetrics, hypertension in pregnancy, monitoring, pharmacists' role

INTRODUCTION

Pharmacists offer essential services that impact maternal health.[1] However, most have not demonstrated their commitment and active participation in managing major obstetric conditions like pre-eclampsia (PE), probably because of their disinterest or lack of insight in PE.[2] PE is one of the vascular disorders of pregnancy that typically presents as new onset hypertension or organ dysfunction around mid-gestation in previously normotensive women.[3-5] It is suspected when blood pressure (BP) increases from 140-159 mmHg systolic or 90-109 mmHg diastolic, with minimal to moderate proteinuria.[3-5] In the absence of proteinuria, some PE cases manifest as acutely elevated BPs that injure the liver or kidneys. In some pregnancies, PE occurs early ($<34^{+0}$ weeks of gestation), demanding preterm delivery ($<37^{+0}$ weeks' gestation) or late-onset, where the baby may be delivered at or after 37^{+0} weeks.[3] Besides, PE could be complicated with severe features such as an acute hypertension (BP $\geq$ 160/110 mmHg), remarkable proteinuria, markedly elevated liver enzymes, creatinine or uric acid in maternal serum. Again, hemolysis, thrombocytopenia and neurological signs such as frontal headaches, visual blurring, nausea etc, are suggestive of PE with severe features.[3, 5, 6] Other pregnant women develop gestational hypertension (GH) instead of PE when their BPs increase (140/90-159/109 mmHg) after midgestation without proteinuria or end-organ dysfunction. In those with established hypertension before conception, chronic hypertension (CH) in pregnancy is diagnosed. If this progresses to any of the systemic features of PE, the woman is said to have developed superimposed PE.[4] Together with eclampsia, GH and CH, these diseases affect about 3-10% of pregnancies globally and contribute significantly to poor pregnancy outcomes.[5, 7, 8] More than a tenth (14%) of global maternal deaths between 2015 and 2018 was caused by these disorders, with worse fatalities in sub-Saharan Africa and Southern Asia.[9, 10] In Ghana, mortalities due to PE/eclampsia doubled from 9% to 18% over the past decade.[11] Many fetuses exposed to these conditions suffered stillbirth, prematurity, low birth weight or neonatal deaths.[12-15]

In Canada, community pharmacists' surveillance of gestational hypertensives lacked commitment and was sub-optimally executed.[2] Besides, in spite of the burden of PE in Bangladesh, the knowledge of antihypertensives for its treatment was poorly demonstrated among pharmacy staff.[16, 17] Although PE and GH continue to be negatively impactful in Ghana and other low-middle income countries, there is a paucity of studies regarding pharmacists' engagements in mitigating same in these countries. The overarching need for a greater understanding and active participation of pharmacists of our time in demonstrating their support for PE management cannot be overemphasized. Helping to manage the hypertensive phase of PE is life-saving. Even though a controlled BP does not cure PE or avert eclampsia, it minimizes maternal target organ damages, avoids emergency preterm deliveries which ultimately curbs neonatal complications.[18]

This review was conducted to crave the attention of pharmacists about the woes of PE, equip them competently so that they could contribute toward its management. To achieve this goal, we sought to update pharmacists' knowledge of antihypertensives for BP control in PE and expose them to the monitoring parameters of these medicines when treatment is initiated in pregnancy. By offering their support to obstetricians, pharmacists could help avoid the untimely death of pregnant women who because of PE/eclampsia lose their lives or babies.

METHODOLOGY

Data search was conducted on PubMed, Cochrane library, World Health Organization (WHO) database and Google scholar/Google (first 150 publications), for published guidelines on hypertension in pregnancy and its management from January 2014 and October 2022. Search terms included "hypertension guidelines", "pregnancy hypertension guidelines", "hypertensive disorders of pregnancy", "gestational hypertension", "antihypertensives and pre-eclampsia", "pharmacokinetics of antihypertensives and pregnancy". Preferred literature included guidelines published in English language, national, international or professional in character and the most recent document that was

accessible. Publications carved out of national guidelines for local use by hospitals were excluded, as well as those that did not address antihypertensives in pregnancy or PE.

Seventy-eight publications were extracted and exported into Endnote reference manager with 16 duplicates identified and deleted. Further screening by title and abstract led to the exclusion of 30 documents which did not meet the inclusion criteria and additional eight, for restricted access, non-recognition as national, international or obstetric-gynecological guidelines. Finally, 23 documents were reviewed. Of these, 16 were composite guidelines on hypertension or obstetricgynecological publications, while seven were either systematic reviews of antihypertensives in pregnancy/PE or their pharmacokinetics studies in pregnancy (Figure 1).

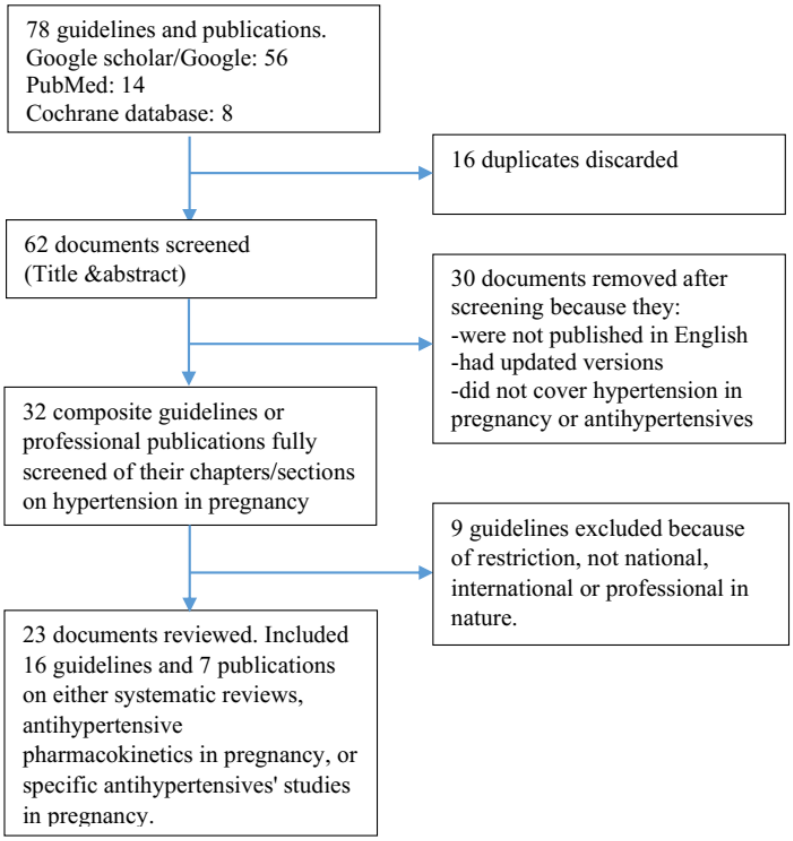

Figure 1: Flow chart of search results

PRE-ECLAMPSIA DIAGNOSIS AND COMPLICATIONS

Pregnant women are usually diagnosed with PE if their symptoms or clinical findings correspond with the features listed in Table 1. Advanced maternal age (≥35 years), a history of CH or PE in preceding pregnancies, diabetes, chronic renal disease or autoreactive disease like systemic lupus confer an increased risk.[3, 5, 6] Nulliparity, maternal obesity (pre-conception BMI ≥35 kg m^{-2}), a family history of PE, short and long interpregnancy intervals (<12 months or >10 years) and twin gestation confer a moderate risk. Again, black ethnic origin, poverty, pregnant women in resource-limited countries and conception by assisted reproductive techniques, increase the risk of PE on a pregnancy.[5, 6, 19] PE induces acute organ injuries presenting as seizures (eclampsia), stroke, encephalopathy, myocardial ischemia, placental abruption, pulmonary edema and death.[5, 6] Moreover, exposed fetuses grow poorly, usually delivered prematurely with low birth weight, poor APGAR scores or die.[3]

Table1: Features suggestive of pre-eclampsia

Pre-eclampsia without severe features:
Hypertension (systolic BP 140-159 mmHg or diastolic, 90-109 mmHg) mostly at or after 20 weeks' of pregnancy plus urine dipstick proteinuria measuring up to 2+.
Pre-eclampsia with severe features:
Severe BP elevation (BP ≥ 160/110 mmHg)

Severe proteinuria (≥3+)
Thrombocytopenia, hemolysis with increased bedside clotting time
Elevated serum alanine transaminases (≥2 fold of normal upper limit)
Serum creatinine surge (≥ 1.1 mg dL^{-1})
High serum uric acid level (based on gestational corrected range)
Severe persistent frontal headaches
Right upper quadrant pain or palpitations
Pulmonary edema
New or recurring visual disturbances
Hyperreflexia
Fetal growth failure
Abnormal Doppler findings

Adapted from American College of Obstetricians and Gynecologists (ACOG) 2020, and National Institute for Health and Care Excellence (NICE) (2019).

MANAGING SEVERE HYPERTENSION IN PRE-ECLAMPSIA

While some authorities consider a BP of ≥160/110 mmHg as severe hypertension in PE, others have a higher threshold, ≥170/110 mmHg, before emergency treatment is initiated.[3, 5, 6, 20-22] BP control is recommended within an hour of detecting an acute spike to avert maternal organ dysfunctions.[6] Treatment is not targeted at normalizing BP but usually, decreasing it to levels that minimize the occurrence of stroke and other complications.[3] In most guidelines, dipping the BP below 160/110 mmHg using first line antihypertensives is the initial concern.[5, 6]

CHOICE OF ANTIHYPERTENSIVE IN PRE-ECLAMPSIA

A range of antihypertensives are available for severe hypertension, yet, not all have safety profiles in pregnancy. Table 2 identifies examples of agents considered effective, safe for the fetus, and recommended by international guidelines for treatment in pregnancy.[23, 24] WHO in 2018 recommended hydralazine, labetalol, nifedipine or methyldopa in their appropriate dosage forms for severe hypertension in pregnancy/PE.[23] In an update (2020), medicines for same indication did not vary except the recommendation of methyldopa and other beta-blockers for non-severe hypertension in pregnancy.[24] In hypertension Canada and the Brazilian 2020 guidelines, hydralazine was relegated, leaving labetalol, nifedipine and methyldopa as first choice drugs for obstetric emergencies. However, in the 2020 updates by the American College of Obstetricians and Gynecologists (ACOG), intravenous (IV) hydralazine is still considered a first line agent.[6] In United Kingdom, the National Institute for Health and Care Excellence (NICE) publication (2019) also recommends venous labetalol, hydralazine or oral nifedipine.[5] South Africans (2019); IV labetalol, hydralazine/dihydralazine or nifedipine; International Federation of Gynecology and Obstetrics (FIGO); nifedipine, labetalol, hydralazine, methyldopa and the Japanese Society of Hypertension (JSH), IV glyceryl trinitrate, nicardipine or hydralazine for acute hypertension in pregnancy.[21, 25, 26] The Ghanaian Standard Treatment Guideline (2017) accepts IV labetalol, hydralazine or nifedipine.[20] For the same purpose, while the 2018 International Society for the Study of Hypertension in Pregnancy (ISSHP) publication prefers nifedipine, labetalol, methyldopa and oxprenolol as first choices, the European Society of Cardiology (ESC, 2018) also recommends IV labetalol, nifedipine or methyldopa.[27, 28] In addition, IV urapidil is indicated in the ESC and Polish guidelines for acute cases, whereas IV diazoxide is an alternative in Society of Obstetric Medicine of Australia and New Zealand (SOMANZ, 2014).[28-30] Although not favored due to toxicities, nitroprusside is a second choice in the Korean and ESC publications.[28, 31]

Table 2: Antihypertensives listed in some international guidelines for hypertension in pregnancy

Guideline	Antihypertensive

WHO (2018); International	Nifedipine, labetalol, hydralazine and methyldopa
WHO (2020 updates: non-severe hypertension)	Methyldopa and beta-blockers (e.g. labetalol in particular, others are atenolol, mepindolol, metoprolol etc.)
Hypertension Canada's 2020 Guidelines	Nifedipine, labetalol, methyldopa, metoprolol, pindolol, propranolol etc.
BGH (2020); Brazil	Nifedipine, beta-blockers except atenolol, methyldopa etc.
ACOG (2020); Professional, USA	Nifedipine, labetalol and hydralazine.
NICE (2019); UK	Nifedipine, labetalol, hydralazine and methyldopa.
NG (2019); South Africa	Nifedipine, labetalol, hydralazine, methyldopa.
FIGO (2019); Professional	Nifedipine, labetalol, hydralazine, methyldopa, clonidine (not in lactation), captopril (postpartum only) etc.
JSH (2019); Japan	Nifedipine, labetalol, hydralazine, methyldopa etc.
ISSHP (2018); International	Nifedipine, labetalol, methyldopa (Second line agents: hydralazine etc.
ESC (2018); Europe	Nifedipine, labetalol, hydralazine*, methyldopa, urapidil etc.
KSH (2018); Korea	Nifedipine, labetalol, methyldopa, nitroprusside etc.
STG (2017); Ghana	Nifedipine, labetalol, hydralazine and methyldopa.
PSH (2015); Poland	Nifedipine, labetalol, hydralazine, methyldopa, metoprolol, nitrendipine, urapidil etc.
SOMANZ (2014); Australia & New Zealand	Nifedipine, labetalol, hydralazine, methyldopa, diaxozide etc.
EHS (2014); Egypt	Nifedipine, labetalol, methyldopa, hydralazine*.

ACOG, American College of Obstetricians and Gynecologists; BGH, Brazilian Guidelines of Hypertension; EHS, Egyptian Hypertension Society; ESC, European Society of Cardiology; FIGO, International Federation of Gynecology and Obstetrics; HCG, Hypertension Canada 2020 Guideline; ISSHP, International Society for the Study of Hypertension in Pregnancy; JSH, Japanese Society of Hypertension; KSH, Korean Society of Hypertension; NG, National Guideline; NICE, National Institute for Health and Care Excellence; PSH, Polish Society of Hypertension; SOMANZ, Society of Obstetric Medicine of Australia and New Zealand; STG, Standard Treatment Guidelines; WHO, World Health Organization.*Not a drug of choice

In a systematic review of obstetric practice guidelines (2014), IV labetalol and oral nifedipine were the preferred agents for hypertensive emergencies in pregnancy.[32] In 2021, a statement by the American Heart Association mentioned labetalol, methyldopa and in some cases, nifedipine.[33]. According to a 2021 systematic review and meta-analysis that weighed the clinical effectiveness of venous labetalol, hydralazine and nifedipine for severe hypertension in pregnancy, nifedipine was considered superior, or at least, comparable to IV labetalol.[34] The Brazilian guideline (2020) also cited a study where nifedipine outperformed labetalol and methyldopa.[35] Compared to IV hydralazine, immediate acting nifedipine (buccal) was safer and faster when a quicker response was needed in an emergency.[31, 36, 37] In this current write-up, it is also noted that for guidelines that chose between IV hydralazine and IV labetalol for acute case management, many (Brazilian Guidelines of Hypertension [BGH], Egyptian Hypertension Society [EHS], ESC, ISSHP and HCG) opted for labetalol instead of hydralazine; probably due to the unpredictable antihypotensive effect of hydralazine.[22, 27, 28, 35, 38] Besides, IV labetalol is faster in onset and less reflex tachycardic relative to IV hydralazine.[36]

Contrarily, the ACOG based on the evidence of a Cochrane review does not have significant safety or efficacy concerns regarding the use of IV hydralazine over IV labetalol nor the use of oral nifedipine over these parenterals in PE.[6] It advocates that medications for acutely elevated BP in PE should be chosen based on patient's condition, co-morbidities or obstetrician's familiarity with antihypertensives, which is consistent with WHO recommendations.[6, 23] For instance, IV hydralazine could be initiated instead of labetalol in patients with a bronchospastic diseases or heart failure whereas IV glyceryl trinitrate is suitable when PE is complicated by pulmonary edema.[21, 28, 38, 39] In patients with glucose-6-phosphate dehydrogenase (G6PD) deficiencies, labetalol, instead of hydralazine or methyldopa is recommended.

After initial attainment of BP below 160/110 mmHg, any quick acting or parenteral medication used would have to be substituted with an oral agent for further management. Oral antihypertensives that cut across most national/international guidelines include: labetalol, nifedipine, methyldopa, and hydralazine.[5, 6, 20, 23, 26, 28, 29] The NICE prefers the order of choice: labetalol, nifedipine then methyldopa whereas the ESC guideline chooses nifedipine ahead of labetalol because of fetal bradycardia and hypoglycemia associated with the use of the latter.[5, 28] From the JSH, methyldopa and labetalol are preferred in gestations < 20 weeks, and nifedipine, ≥ 20 weeks.[21] However, a 2020 WHO release advocates the use of methyldopa or beta blockers in non-severe hypertension in pregnancy but not calcium channel blockers because they could accelerate disease progression to PE.[24]

All guidelines accept pharmacotherapy during severe hypertension in PE but they vary when it is mild-moderate (BP not >159/109 mmHg) and devoid of severe features. Some evidence disassociates good fetal outcomes with drug treatment to much lower BP values.[33] The Ghanaian and Egyptian treatment policies are therefore reluctant to initiate therapy until the BP >150/100 mmHg.[20, 38] Nonetheless, the NICE and ESC guidelines recommend antihypertensives at BPs persistently >140/90 mmHg.[5, 28] When indicated, oral antihypertensives are used singly or in appropriate combinations depending on the level of difficulty in maintaining a controlled BP and if combination therapy is necessary, the JSH recommends a sympatholytic agent to be combined with a vasodilator instead of drugs from the same class.[21] Dipping the BP <140/90 mmHg in expectant management is unrecommended by some authorities because of fetal hypoperfusion or distress associated with acutely lowered maternal BP.[20, 28, 33, 40] To others, a tight BP control to
135/85 mmHg could prevent complications and preterm delivery.[33]

Angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and direct renin inhibitors (RIs) are still avoided in pregnancy due to their unsafety profiles.[41] Diuretics are unsuitable in PE because they may worsen an already contracted plasma volume, except in pulmonary edema or volume overload where they are appropriate.[28, 41-43] However, in a chronic hypertensive initiated on a diuretic therapy before conception, continued usage may not seriously impact placental perfusion.[21, 22]

MONITORING PARAMETERS OF ANTIHYPERTENSIVES FOR PRE-ECLAMPSIA

Understanding of the basic pharmacodynamics and pharmacokinetics of commonly used obstetric antihypertensives is important in order to successfully monitor and optimize their therapy in PE. The basic knowledge required of pharmacists to efficiently monitor the safe use of labetalol, methyldopa, hydralazine and nifedipine in PE is highlighted in the subsections below and in Table 3, their dosage forms, administration and actions required of pharmacists during their application have been displayed.

Table 3: Antihypertensives for controlling blood pressure in pre-eclampsia

Drug & dosage form	Indication & Dose	Pharmacists' action/attention
Injectable labetalol:	Severe hypertension Give 10-20 mg IV stat over 1 minute, then 40mg after 30 minutes if BP is still > 160/110 mmHg, and subsequently,	Ask about lung function and G6PD status of patient.

	80 mg every 30 minutes to a total cumulative dose of 220 mg.	
	Or IV infusion of 1-2 mg min^{-1} until a satisfactory BP.	Calculate flow rate. Ensure patient receives correct dose.
Oral labetalol:	Mild-moderate hypertension 100-800 mg 12 hourly.	To be taken with meals
Oral methyldopa	Mild-moderate hypertension 250-500 mg 8-12 hourly Max: 2 g.	Ask about G6PD status of patient. Avoid if positive.
Injectable hydralazine:	Severe hypertension Give 5 mg IV slowly over 10 minutes; repeat after 30 minutes if BP is still >160/110 mmHg. Then, 5 mg IV every 30 minutes if required to a cumulative dose of 20 mg by IV or 30 mg by IM.	Ask about G6PD status. Ensure drug is diluted properly and administered slowly.
	Or, infuse drug at 0.5-10 mg hr^{-1}	Calculate flow rate. Ensure patient receives correct dose.
Oral hydralazine:	Mild-moderate hypertension 25-50 mg 8 hourly.	
Oral nifedipine Immediate release:	Severe hypertension Give 10-20 mg, repeat after 30 minutes if BP still >160/110 mmHg, then, every 2-6 hours (Max daily dose: 180 mg).	Supply buccal formulation, verify dose, avoid sublingual product. May cause reflex tachycardia
Extended release:	Mild-moderate hypertension 30-60 mg daily.	Could cause GI obstruction. Be sure patient has no intestinal strictures or narrowing.
Retard:	10-40 mg 12 hourly (Max daily dose: 90 mg-120 mg)	Formulation causes reflex tachycardia.

IV, intravenous; IM, intramuscular; G6PD, Glucose-6-phosphate dehydrogenase; GI, gastrointestinal.

Labetalol

Oral absorption of labetalol is almost 100%, but for extensive first-pass effect, bioavailability is reduced to almost a quarter.[44] It is moderately lipophilic and distributes widely, but clearance is amplified in pregnancy due to increased expression and activity of liver enzymes mediated by pregnancy-related hormones.[44-47]

Labetalol antagonizes alpha-1 adrenergic receptors on peripheral vessels to cause vasodilation, block myocardial beta-1 receptors to lower heart rate and blocks beta-2 receptors on vasculature of skeletal muscles.[44, 45, 48] It has differential inhibitory effects on beta and alpha receptors depending on its route of administration and the selectivity of its stereo isomers.[45, 47] In pregnancy, when venous labetalol is administered, beta and alpha effects are attenuated equally due to their similar rates of clearance.[47, 49] However, given orally, alpha-1 effects dominate because of increased elimination of the beta-1 isomer resulting in minimal deceleration of maternal heart rate.44, 45, 47, 49

Labetalol's antihypertensive effect begins in 2-5 minutes after IV administration, lasting up to 4 hours. The effect after oral intake is seen in 20-120 minutes.[44] It crosses the placenta and enters breast milk marginally but safe in pregnancy and lactation. Renal elimination is extensive, mostly as inactive conjugates and some, through biliary excretion.[44]

With IV dosing, orthostatic hypotension, dizziness or syncope may occur.[44] Lowering maternal BP suddenly with 50 mg IV labetalol from 170/110 to 115/85 mmHg caused a stillbirth in pregnancy.[40] Intravenous start doses ranging from 10-20 mg should be recommended before upward titration and BP monitored not to drop sharply to minimize episodes of these adverse effects. For patients lying supine during IV administration, advising against sudden upright positioning is important and patients should be helped to do so securely if required.[40, 45] Due to labetalol's bronchoconstrictive effect, respiratory rate needs to be checked when treatment is started and therapy avoided if the pregnant woman has a history of asthma, obstructive airway disease or bradycardia (Table 3).[36, 50] Liver injury has been reported after short term use of labetalol. A sign of jaundice observed in patients on labetalol is an indication for drug withdrawal.[44] Further, a unit dose of labetalol (30 mg IV) administered 20 minutes before caesarean delivery for severe maternal hypertension was associated with neonatal hypoglycemia, hypotension and bradycardia.[51] Pharmacists ought to prompt obstetricians to check blood glucose levels of babies born to pregnant women who received labetalol injection a few minutes before their delivery.

Methyldopa

A prodrug to alpha-methyl-noradrenaline, methyldopa acts as a central agonist on alpha-2 adrenoceptors, inhibiting noradrenaline outflow, decreasing its effects on the heart, kidneys and peripheral vessels; causing a dip in BP.[41, 44] About 50% of the oral dose of methyldopa is absorbed with average bioavailability of 25%. When administered concomitantly with ferrous sulfate tablets, oral absorption is impaired.[52] It is lipophilic, weakly bound to plasma proteins and distributes widely, crossing into cerebrospinal fluids.[44, 53] Blood pressure begins to drop after 11½ hours following oral administration and persists for up to 12 hours in pregnancy.[41] Methyldopa crosses the placenta, enters breast milk but unharmful to the fetus and breast feeding babies.[44] Renal clearance and excretion are extensive and further maximized in gestation, except where PE impairs kidney function severely and causes active metabolite accumulation.[44] In PE with oliguria, increased methyldopa sensitivity is possible.[44, 53]

Few hours after initiating therapy, patient's BP is monitored for drug response. Medication charts are to be assessed for appropriateness and patients should be asked whether they have experienced any untoward effect after drug intake. These effects may include dry mouth, transient sedation, weakness, drowsiness and dizziness[44] Advice on bed time administration may lessen drowsiness and sedation if these are troublesome. Ice chips or gums may be recommended for patients experiencing troublesome dryness in the mouth. Orthostatic hypotension may occur with high doses and patients need to be cautioned when rising from recumbency and sitting positions after the first doses.[44] Tolerance to the antihypertensive effect of methyldopa is possible after months of monotherapy which requires advice for dose optimization.[44]

Methyldopa may occasionally provoke hemolysis, leucopenia and thrombocytopenia.[44, 53] Monitoring of patients' urine color is necessary and if cola-like, a full blood count (FBC) should be recommended. If anemia and pancytopenia are present from the FBC, comb's test would be needed to rule out drug-induced hemolysis. It should be noted that hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome in PE may present similar features and confusion may arise.[44, 53] If hemolytic anemia is confirmed, drug withdrawal is advisable and corticosteroid therapy is recommended.[53] Equally, in G6PD deficient patients, hemolysis may be worse. Patient screening for this defect is important before therapy initiation and if positive, methyldopa should be avoided (Table 3).

In chronic hypertensives started on methyldopa before conception, usage of the drug continuously for 6 weeks may cause hepatotoxicity. Therefore, a rise in bilirubin and liver enzymes need correct interpretation to differentiate PE with liver dysfunction from methyldopainduced liver toxicity in a patient.[44, 53] Moreover, pharmacists and obstetricians should note that, although rare, antenatal methyldopa therapy may predispose pregnant women to postpartum depression.[44, 50, 54] The drug decreases dopamine, serotonin and noradrenaline levels centrally, thereby altering the brain reward system.[54, 55] Postpartum PE patients on methyldopa are to be observed closely for mood swings while consideration for drug substitution is required.[5, 50]

Hydralazine

Hydralazine interferes with calcium ions' movement in peripheral vascular smooth muscles, relaxing peripheral arterioles and lowering systemic resistance to blood flow.[56] It is rapidly absorbed after oral intake with food enhancing its absorption but poorly bioavailable due to firstpass effect.[41]. Bioavailability varies; ranging from 26% for rapid acetylators and 50% for slow acetylators.[41, 56]. Oral hydralazine distributes extensively, highly bound to plasma proteins in normal patients but binding may be less in pregnancy due to low plasma albumin. After oral dosing, its effect occurs after 20-40 minutes and 5-20 minutes following IV application.[44, 56] Maximum activity occurs in 1½ hours when used orally and 15-30 minutes by the IV route; persisting for 2-6 hours.[56] Hydralazine crosses the placenta, secrets into breast milk but fetal friendly.[44] Due to variations in its metabolism, patients less sensitive to its effects may require shorter dosing intervals. Hydralazine's metabolites are excreted mostly in urine and if the estimated glomerular filtration rate (eGFR) is < 30 $mLmin^{-1}$, maintenance doses should be limited to 5mg because GFR would be poor resulting in drug accumulation.[50, 56]

Hydralazine commonly causes headache, dizziness, palpitation and tachycardia, which may be confused with severe features of PE. Patients are informed of drug-induced headaches and palpitations which usually resolve spontaneously but therapy should be tapered and withdrawn if heart rate (HR) ≥120bpm.[57] Besides, patients could develop shock when dose limits are inadvertently exceeded. This is especially possible in PE with hypovolemia, where drug induced vasodilation may sharply drop BP, compromising maternal and fetal perfusion.[41] It is therefore appropriate to recommend preloading with about 300-500 mL of Ringer's lactate or normal saline when IV hydralazine is the choice for PE with severe features. To avoid inadvertent administration of higher doses when giving IV boluses, pharmacists may advice for injectable hydralazine dilution; e.g., a 20 mg mL^{-1} ampoule to be diluted 20 mg per 10mL or 20mg per 20mL using normal saline for ease of injecting smaller doses (Table 3). After an IV bolus, monitoring of patient's BP every 5-10 minutes is required to ensure circulatory stability and subsequently, every 15-20 minutes until the patient's condition is satisfactory. This enables early detection of a rapid fall in BP when IV boluses are administered rapidly or when doses are exceeded.

Unusually, few patients receiving hydralazine may experience lupus-like syndrome induced by extreme drug doses. Obstetricians are to be prompted to run titers for antinuclear antibodies (ANA) and direct Comb's test, especially in patients who complain of sore throat, arthralgia, fever, dyspnea, edema, pleurisy, malaise and for patients testing positive, therapy should be withdrawn and trial of corticosteroid recommended.[44, 56]

On routine medication checks, hematological reports of patients on long term hydralazine therapy ought to be assessed for neutropenia and anemia.[58] Moreover, in slow acetylators on higher doses, the drug may complex with pyridoxine, causing its deficiency, resulting in peripheral neuritis.[56, 59] Treated patients who complain of numbness and tingling sensations may require pyridoxine supplementation.[56]

It is important to advice against sudden withdrawal of the drug to avoid rebound hypertension. Orthostatic hypotension may occur, especially with IV application. Patients should be informed to avoid sudden changes in position a few minutes after receiving medication. PE patients on hydralazine therapy need monitoring for rare but serious effects like arthralgia, sore throat, rash and fever, which may signify lupus-like symptoms, calling for drug discontinuation.[60]

Nifedipine (Immediate acting and long acting)

On vascular smooth muscles, nifedipine aborts calcium-mediated contractions; consequently, it dilates systemic arteries and reduces peripheral resistance to blood flow.[44, 61] In pregnancy, the time to onset of action is similar to nonpregnant hypertensives.[62] In 10-15 minutes after oral administration of the quick-acting buccal formulation, BP begins to drop, but with the standard long-acting product, the effect manifests in 30-45 minutes.[62, 63] Metabolism and clearance of nifedipine are increased in pregnancy with a shorter half-life.[62, 64] This may reduce the duration of action, requiring dose repetition.[62, 64] The immediate acting product could be repeated after 30 minutes and subsequently every 2-6 hours.[6, 62] While the standard formulations could be used once daily in nonpregnant individuals, twice-daily administration in pregnancy may be necessary to ensure effective 24 hour BP

control because of rapid inactivation and clearance.[44, 61, 63] Nifedipine has tocolytic effects, crosses the placenta but unassociated with known malformations. It is compatible with lactation.[23, 44]
During drug application, medication charts, dose and dosing frequency are verified to ensure conformity with prescriber's intent. Nifedipine causes dose-related ankle edema, headache and tachycardia which require patient's prior notification to allay fears and noncompliance.[44, 61] However, when HR is ≥120bpm, nifedipine needs to be withheld.[57] Before therapy, a patient is assessed for pre-formed pedal edema so that it does not confound drug-induced ankle swelling. If the patient experiences severe hypotension, adrenaline could be recommended to reverse vasodilation, while crystalloids are administered cautiously, guarding against pulmonary congestion.
With extended-release formulations, nifedipine is embedded in a nondeformable matrix which is shed in feces. It is possible that this matrix could cause intestinal obstruction in patients with strictures or gastrointestinal tract (GIT) narrowing (Table 3).[44] Patients to be initiated on such formulations should be free from GIT strictures and monitored for obstructive signs.[44] Extended release or retarded nifedipine formulations are swallowed whole without crushing or breaking tablets to preserve drug release technology.

STUDY LIMITATION

Due to language barrier, only English Language publications were consulted; a potential source of bias against non-English publications. Some national/international clinical practice guidelines consulted had not been updated for more than 5 years, thus might not be in tandem with current global practice. There was limited access to the Obstetrics and Gynecology practice guidelines of some countries, resulting in the use of composite national hypertension documents which may have resulted in the omission of some relevant information in this review.

CONCLUSION

Controlled hypertension in PE mitigates vascular complications and saves lives of mothers and unborn fetuses. Apart from counselling of pregnant women at risk of PE and referring to specialists, pharmacists in health care settings should have sufficient knowledge of PE and its effective drug management, so they could advice on appropriate antihypertensives during pharmacotherapy and follow up to ensure their responsible use for optimal outcomes. This requires commitment, high sense of professionalism and evidence-based PE therapeutic outcomes monitoring. By playing these roles actively as pharmacists in obstetric care teams, maternal or fetal mortalities associated with PE in parts of the world could be averted or reduced.

CONFLICTS OF INTEREST

The Authors declare that there is no conflict of interest.

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AUTHORS' CONTRIBUTIONS

FF, ETD and KOB conceptualized the idea; FF and ETD designed the methodology; FF and KBM did the literature search; ETD, KOB, AAK, PA and KAD analyzed the literature for appropriateness and inclusion in the review. FF and PA prepared the first draft. ETD, KBM, AAK, KAD and KOB reviewed and edited the drafts until the final version. Mentorship and supervision was provided by KOB and ETD. All authors read the final manuscript and consented to its submission.

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