WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 5, 534-557. Review Article ISSN 2277– 7105

RECENT PHARMACOLOGY THERAPY FOR HYPERTENSION IN PREGNANCY

Dinesh Kawade*, Payal Bahadurkar, Nikhil Shahu, Payal Hiradewe and Nidhi Dhote

Priyadarshini J. L. College of Pharmacy, Electronic Zone Building, MIDC, Hingna Road, Nagpur-440016, MS, India.

Article Received on
28 Feb. 2020,

Revised on 19 March 2020,
Accepted on 10 April 2020,

DOI: 10.20959/wjpr20205-17312

***Corresponding Author**
Dr. Dinesh Kawade
Priyadarshini J. L. College of Pharmacy, Electronic Zone Building, MIDC, Hingna Road, Nagpur-440016, MS, India.

ABSTRACT

Hypertensive issue speak to significant reasons for pregnancy related maternal mortality around the world. Like the non-pregnant populace, hypertension is the most widely recognized clinical issue experienced during pregnancy and is evaluated to happen in around 6–8% of pregnancies. There has been for all intents and purposes no change for three decades in the treatment of hypertension in pregnancy and it's numerous namesakes: Pre-eclampsia, gestational hypertension, superimposed pre-eclampsia, gestosis, and so on. The ideal planning and decision of treatment for hypertensive pregnancy issue includes cautiously gauging the hazard versus-advantage proportion for every individual patient, with a general objective of improving maternal and fetal results. Right now have thoroughly analyzed the suggestions in various treatment rules and we have sketched out some more up to date points of view on the board. We have meant to give a clinically orientated manual for the medication treatment of hypertension in pregnancy.

KEYWORDS: Hypertension, Pregenancy, Pre-eclampsia, Pharmacotherapy, Management.

INTRODUCTION

Elevated arterial blood pressure is seen in 6% to 8% of all pregnancies and is a major contributor to maternal, fetal, and neonatal morbidity (American College of Obstetricians and Gynecologists 1996). Hypertension (arterial pressure >140/90 mmHg) in pregnancy is classified into one of four conditions: (1) chronic hypertension that precedes pregnancy; (2) preeclampsia-eclampsia, a systemic syndrome of elevated arterial pressure, proteinuria (> 300

mg protein/24 h) and other findings (seizures or coma in the case of eclampsia); (3) preeclampsia superimposed upon chronic hypertension; and (4) gestational hypertension, or nonproteinuric hypertension of pregnancy where arterial pressure returns to normal by 12 weeks postpartum.[1]

As perinatal mortality or the use of a placebo as control is no longer realistic or ethical in most trials of antihypertensive drugs in pregnancy, practitioners may find themselves armed with data favoring the use of older and potentially safer medications over newer medications with possibly more approved indications.

Table 1: Classification of antihypertensive drugs used to treat hypertension in pregnancy.

Category	Basis for classification
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	Animal studies have revealed no evidence of harm to the fetus. However, there are no adequate and well-controlled studies in pregnant women or animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women or no animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Studies;adequate, well-controlled, or observational in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.
X	Studies; adequate, well-controlled, or observational in animal or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.

Although antihypertensive therapy for mild-to-moderate hypertension in pregnancy may reduce the risk for severe hypertension, it does not seem to decrease the incidence of preeclampsia nor affect maternal or perinatal outcomes.[2] Avoidance of drug therapy is, therefore, suggested in mild hypertension where nonpharmacological therapies may suffice and the benefits from short-term therapy may be lacking (table 2). Because no interventions have been proven to decrease the risk of development of preeclampsia, delivery of the fetus and placenta remains the only effective treatment.[3] Chronic hypertension therapy can be

stopped during pregnancy under close observation, or alternatively, a woman whose arterial pressure was well controlled by antihypertensives before pregnancy may continue with the same agents (if not contraindicated). The National Institutes of Health-sponsored Working Group on High Blood Pressure in Pregnancy recommend antihypertensive therapy for blood pressures exceeding a threshold of 150 to 160 mmHg systolic or 100 to 110 mmHg diastolic or in the presence of target organ damage, such as left ventricular hypertrophy or renal insufficiency.[1]

Table 2: Therapy of hypertension in pregnancy.

Mildhypertension	**Moderate-to-severe hypertension**	
	Commonly used drugs	**Daily dose range (mg)**
Drugs, bed rest, and hospitalization are not routinely recommended. The evidence for use of fish oils, or other prostaglandin precursor supplements is insufficient. Salt restriction is not helpful for pre-eclampsia prevention. Calcium supplementation may lead to reduction in arterial blood pressure and pre-eclampsia. Alcohol and smoking cessation always advised.	Methyldopa Clonidine Prazosin Propranolol Labetalol Nifedipine Hydrochlorothiazide	250–1000 t.i.d. 0.1–1.2 b.i.d. 1–10 b.i.d. 40–120 b.i.d .or t.i.d. 100–1200 b.i.d. 10-30 t.i.d. or q.i.d. 12.5–50 q.d.

q.d., once daily; b.i.d., twice daily;t.i.d., three times daily;q.i.d, four times daily.

EPIDEMIOLOGY

There are three types of hypertensive disorders of pregnancy: chronic hypertension, gestational hypertension and pre-eclampsia. Pre-eclampsia is a leading cause of pre-term birth and cesarean delivery.[4] Chronic hypertension is defined as a BP ≥140/90 mmHg, recorded before pregnancy and before 20 weeks of gestation. The incidence of this disorder is higher in women who are older, obese or black.[5] Chronic hypertension is associated with an increased risk of pre-eclampsia, growth restriction and congenital heart diseases. Even in the absence of superimposed pre-eclampsia, women with chronic hypertension have a higher risk

of adverse outcomes.[6] Chronic hypertension complicates 3–5% of pregnancies,but the number is rising over time, along with the trend of women postponing childbirth into their 30s or 40sas well as obesity.[7] A systematic review reported chronic hypertension associated with many adverse outcomes, including superimposed pre-eclampsia, cesarean delivery, pre-term delivery (<37 weeks), low birth weight (<2500 g), neonatal intensive care and perinatal death.[8]

The presence of mild-to-moderate pre-existing hypertension(systolic blood pressure (SBP) 140–159mmHgor diastolic blood pressure (DBP) of 90–99 mmHg)increases the risk of pre-eclampsia, placental abruption and growth restriction in the fetus. However, when chronic hypertension is severe(>170/110 mmHg), the risk of pre-eclampsia is as high as 46%, with resulting raised maternal and fetal risk.[9] Thus, the management of prepregnancy blood pressure is of great importance to achieve an optimal pregnancy outcome.

PATHOPHYSIOLOGY

There are clinically determinable risk factors that increase the risk of a particular patient developing PIH. Old or young maternal age, nulliparity, a history of high blood pressure, obesity, first degree relative(s) who developed PIH, family history of early heart disease, histories of diabetes or insulin resistance, kidney disease, lupus, rheumatoid arthritis, thyroid disease, African descent and multiple gestation. All of these except multiple gestation are also known risk factors for later development of heart disease. The only major missing risk factor for heart disease is smoking which actually reduces the risk of developing PIH.[10]

Any hypertensive disorder of pregnancy can result in preeclampsia. It occurs in up to 35% of women with gestational hypertension and up to 25% of those with chronic hypertension.[11] The underlying pathophysiology that upholds this transition to, or superposition of, preeclampsia is not well understood; however, it is thought to be related to a mechanism of reduced placental perfusion inducing systemic vascular endothelial dysfunction. This arises due to a less effective cytotrophoblastic invasion of the uterine spiral arteries. The resultant placental hypoxia induces a cascade of inflammatory events, disrupting the balance of angiogenic factors, and inducing platelet aggregation, all of which result in endothelial dysfunction manifested clinically as the preeclampsia syndrome.[12] Angiogenic imbalances associated with the development of preeclampsia include decreased concentrations of angiogenic factors such as the vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) and increased concentration of their antagonist, the placental soluble

fms-like tyrosine kinase 1 (sFlt-1).[13] Impeding the binding of VEGF and PIGF to their receptors is a factor in the reduction of nitric oxide synthesis, a crucial factor in vascular remodeling and vasodilation, which may otherwise be able to ameliorate placental ischemia. Early onset preeclampsia (EOPE), occurring before 34 weeks of gestation, is thought to be primarily caused by the syncytiotrophoblast stress leading to poor placentation, whereas late onset preeclampsia (LOPE), occurring at or after 34 weeks, is understood to be secondary to the placenta outgrowing its own circulation.[14] It is worth mentioning that EOPE is more frequently associated with fetal growth restriction than LOPE, due to a longer duration of placental dysfunction. During the postpartum period, up to 27.5% of the women may develop de novo hypertension. This is due to several factors, including mobilization of fluid from the interstitial to intravascular space, administration of fluids and vasoactive agents. The shift of fluids increases the stroke volume and cardiac output up to 80%, followed by a compensatory mechanism of diuresis and vasodilation, which softens the rise in blood pressure.[12]

The pathophysiology of hypertension in pregnancy becomes particularly relevant when reviewing the current state of adjunct therapies to antihypertensives that may help prevent preeclampsia.

Figure 1 summarizes the pathophysiology of the disease.

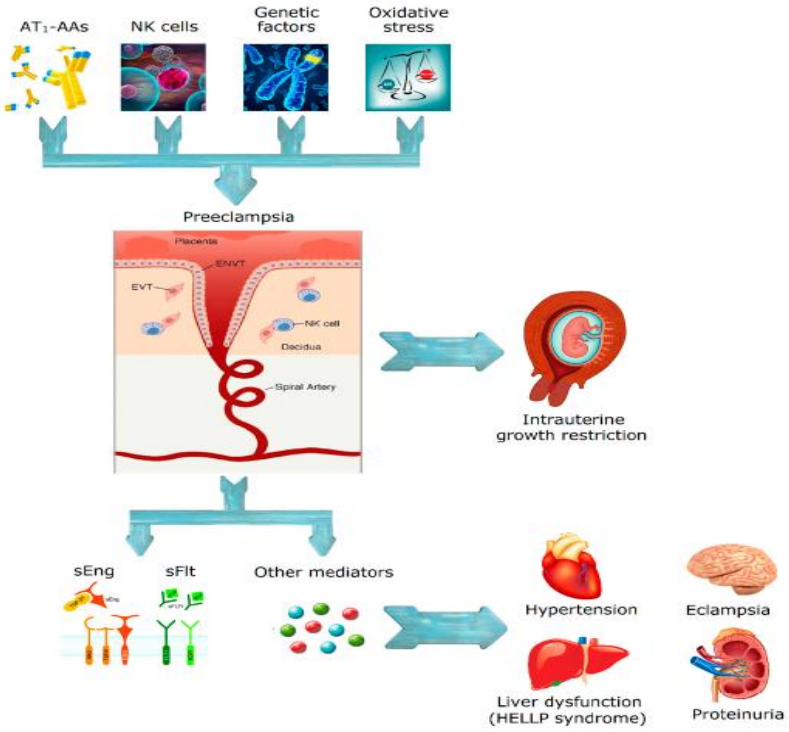

Figure 1: Proposed mechanism for pre-eclampsia and eclampsia.

MEASURING BLOOD PRESSURE IN PREGNANCY

The woman should be seated comfortably with her legs resting on a flat surface. In labour, the blood pressure may be measured in the left arm in lateral recumbency. The supine posture should be avoided because of the supine hypotension syndrome. Measurement of blood pressure should be undertaken in both arms at the initial visit to exclude rare vascular abnormalities such as aortic coarctation, subclavian stenosis and aortic dissection. Generally the variation in blood pressure between the upper limbs should be less than 10 mmHg.

The systolic blood pressure is accepted as the first sound heard (K1) and the diastolic blood pressure the disappearance of sounds completely (K5).[15] Where K5 is absent, K4 (muffling) should be accepted. Correct cuff size is important for accurate blood pressure recording. A large cuff with an inflatable bladder covering 80% of the arm circumference should be used if the upper arm circumference is greater than 33 cm. This helps to minimize over-diagnosis of hypertension during pregnancy.

1. Measurement devices

Mercury sphygmomanometers remain the gold standard for measurement of blood pressure in pregnancy however occupational health concerns are limiting their availability. Automated blood pressure recorders have provided major advantages for treatment and diagnosis of hypertension in the general community and they have been advocated for use in pregnant women. Few studies have compared these self-initiated devices with mercury sphygmomanometry inpregnant women. While such automated devices may give similar mean blood pressure values to those obtained with mercury sphygmomanometry, there is wide intra-individual error and their accuracy may be further compromised in pre-eclamptic women.[16] Aneroid sphygmomanometers are also prone to error. Each unit should maintain a mercury sphygmomanometer for validation of automated and aneroid devices. All devices should be calibrated on a regular basis (ideally monthly), as recommended by the British Hypertension Society.

2. Twenty four hour Ambulatory Blood Pressure Monitoring (ABPM)

Normal blood pressure values recorded by ABPM have been established for different stages of pregnancy. ABPM is useful in the evaluation of early (< 20 wks gestation) hypertension where approximately one third of these women will be shown to have “white coat” or “office” hypertension.[17] About half of these women will not require antihypertensive medication in pregnancy, while the other half develops true (ABPM confirmed) hypertension.

ABPM is less useful in screening for white coat hypertension in the second half of pregnancy. Twenty four hour ABPM has also been shown to predict those women at risk of developing hypertension later in pregnancy but its sensitivity and specificity for this purpose is low.[18]

CLASSIFICATION OF HYPERTENSIVE DISORDERS IN PREGNANCY

This classification of the hypertensive disorders in pregnancy reflects the pathophysiology of the constituent conditions as well as the risks and potential outcomes for both mother and baby. The following clinical classification modifies only slightly that proposed in the ASSHP consensus statement of 2000. It has subsequently been adopted by the International Society for the Study of Hypertension in Pregnancy (ISSHP). In endorsing this classification the ISSHP committee examined the classifications proposed by the ASSHP, the National High Blood Pressure Education Programme (NHBPEP) in the United States as well as earlier published criteria.[19]

I. Preeclampsia

Preeclampsia is a multi-system disorder unique to human pregnancy characterised by hypertension and involvement of one or more other organ systems and/or the fetus. Raised blood pressure is commonly but not always the first manifestation. Proteinuria is the most commonly recognised additional feature after hypertension but should not be considered mandatory to make the clinical diagnosis. As this classification is based on clinical data, it is possible that women with another condition will sometimes be classified incorrectly as having preeclampsia during pregnancy. This is not usually a clinical problem as the diagnosis of preeclampsia should lead to increased observation and vigilance which is appropriate for conditions which may mimic preeclampsia. A diagnosis of preeclampsia can be made when hypertension arises after 20 weeks gestation and is accompanied by one or more of the following.

1. Renal involvement

• Significant proteinuria – dipstick proteinuria subsequently confirmed by spot urine protein/creatinine ratio≥ 30mg/mmol. In view of the close correlation between spot urine protein/creatinine ratio and 24 hour urine excretion, the latter is rarely required.[20]

• Serum or plasma creatinine > 90 µmol/L

• Oliguria

2. Haematological involvement

• Thrombocytopenia

• Haemolysis

• Disseminated intravascular coagulation

3. Liver involvement

• Raised serum transaminases

• Severe epigastric or right upper quadrant pain.

4. Neurological involvement

• Convulsions (eclampsia)

• Hyperreflexia with sustained clonus

• Severe headache

• Persistent visual disturbances (photopsia, scotomata, cortical blindness, retinal vasospasm)

• Stroke

5. Pulmonary oedema

6. Fetal growth restriction

7. Placental abruption

II. Gestational Hypertension

Gestational hypertension is characterised by the new onset of hypertension after 20 weeks gestation without any maternal or fetal features of preeclampsia, followed by return of blood pressure to normal within 3 months post-partum. At first presentation this diagnosis will include some women (up to 25%) who are in the process of developing preeclampsia but have not yet developed proteinuria or other manifestations. Some women initially diagnosed in this category will manifest persistent blood pressure elevation beyond 12 weeks post-partum and eventually be classified as having chronic hypertension.

Gestational hypertension near term is associated with little increase in the risk of adverse pregnancy outcomes. The earlier the gestation at presentation and the more severe the hypertension, the higher is the likelihood that the woman with gestational hypertension will progress to develop preeclampsia or an adverse pregnancy outcome. Severe hypertension(≥ 170/110mmHg) is associated with increased risk of adverse outcomes in pregnancy.[21]

III Chronic Hypertension

Essential hypertension is defined by a blood pressure > 140 mmHg systolic and/or > 90mmdiastolic confirmed before pregnancy or before 20 completed weeks gestation without a known cause. It may also be diagnosed in women presenting early in pregnancy taking

antihypertensive medications where no secondary cause for hypertension has been determined. Some women with apparent essential hypertension may have white coat hypertension (raised blood pressure in the presence of a clinical attendant but normal blood pressure otherwise as assessed by ambulatory or home blood pressure monitoring). These women appear to have a lower risk of superimposed preeclampsia than women with true essential hypertension but are still at an increased risk compared with normotensive women.[17] Important *secondary* causes of chronic hypertension in pregnancy include.

• Chronic kidney disease e.g. glomerulonephritis, reflux nephropathy, and adult polycystic kidney disease.

• Renal artery stenosis

• Systemic disease with renal involvement e.g. diabetes mellitus, systemic lupus erythematosus.

• Endocrine disorders e.g. phaeochromocytoma, Cushing's syndrome and primary hyperaldosteronism.

• Coarctation of the aorta.

In the absence of any of the above conditions it is likely that a woman with high blood pressure in the first half of pregnancy has essential hypertension. It is not possible to investigate these disorders fully during pregnancy, and complete appraisal may need to be deferred until after delivery.

IV Preeclampsia Superimposed on Chronic Hypertension

Pre-existing hypertension is a strong risk factor for the development of preeclampsia.[22] Superimposed preeclampsia is diagnosed when one or more of the systemic features of preeclampsia develop after 20 weeks gestation in a woman with chronic hypertension. In women with pre-existing proteinuria, the diagnosis of superimposed preeclampsia is often difficult as preexisting proteinuria normally increases during pregnancy. In such women substantial increases in proteinuria and hypertension should raise suspicion of preeclampsia but the diagnosis is not secure without the development of other systemic features or fetal growth restriction.

TREATMENT

Non-pharmacologic management

In women with PIH, a normal diet without salt restriction is advised, particularly close to delivery. Salt restriction may lead to small intravascular volume. Calcium supplementation (≥

1 g/day) is associated with a significant reduction in preeclampsia risk, particularly for women on low-calcium diets. Fish-oil supplementation and supplementation with vitamins and nutrients have no role in the prevention of hypertensive disorders.[23] Clinical trials have not shown a beneficial effect of vitamin D supplementation on preeclampsia prevention, but the dose, timing, and duration of supplementation should be investigated in future research. Aerobic exercise for 30–60 minutes twice a week during pregnancy can reduce PIH risk significantly.[24]

Pharmacologic management

The drugs methyldopa, labetalol, beta blockers (other than atenolol), slow release nifedipine, and a diuretic in pre-existing hypertension are considered as appropriate treatment. If a woman's blood pressure is well controlled on an agent pre-pregnancy she may continue it during pregnancy, with the exception of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. If restarting drug therapy in women with chronic hypertension, methyldopa is recommended as first line therapy. For emergency treatment in preeclampsia, IV hydralazine, labetalol and oral nifedipine can be used.[25] The ACOG Practice Bulletins also recommend that methyldopa and labetalol are appropriate first-line agents and beta-blockers and angiotensin-converting enzyme inhibitors are not recommended.[26]

In current practice, antihypertensive medications other than methyldopa and hydralazine are being used more often in pregnancy (Table 3), and particularly in patients for whom BP control cannot be achieved with these agents, or in the presence of intolerable side effects.

The drug treatments for severe acute hypertension in preeclampsia are highlighted in figure 1.[25] Severe hypertension in preeclampsia being defined as ≥160 mm Hg systolic, ≥105 mm Hg diastolic, or both.

Table 3: Recommended management options for treating hypertension in pregnancy.

Drug Treatment	Dose	FDAClass	Safety	Side Effects	Breast feeding
First-line agents Methyldopa (F), (I–A) Drug of choice according to all groups.	0.5-3 gm/day in 2divided doses.	B	Proven safety and efficacy.	Some concern with depression, hepatic disturbances, hemolyticanemia - may not lower BP adequately.	Compatible with breast milk.
Labetalol (M), (I–	200–1200	C	Safety similar	May be associated	Usually

A)	mg/day p.o. in 2–3 divided doses 20–40mg iv (max 220mg total).		to methyldopa may be more efficacious than methyldopa.	with fetal growth restriction. Neonatal hypoglycemia with larger doses.	compatible with breast milk.
Second-line agents Nifedipine Long-acting (Ra), (I–A)	10–30 mg p.o.	C	Widely used	May inhibit labor; Rarely, profound hypotension if shortacting agent is used with magnesium.	Usually compatible with breast milk.
Verapamil	80mg tds p.o.	C	Similar efficacy to other oral agents.	Risk of interaction with magnesium – bradycardia.	Usually compatible with breast milk.
Clonidine Alternative option	0.1-0.6 mg/day in 2 divided doses	C	Safety similar to methyldopa Limited data regarding fetal safety.	Efficacy similar to methyldopa.	Possible breast .milk effects.
Hydrochlorothiazide Useful in chronic hypertension	12.5–25 mg/day	B		Volume contraction, electrolyte abnormalitiesrare with small doses.	May reduce breast milk production.
Hydralazine (F, Re) Not recommended by ESH	50-300 mg/d in 2–4 divided doses	D	Efficacious intraveno us agent	Possible maternal polyneuropathy, drug-induced lupus, neonatal lupusand thrombocytopenia; Tachyphylaxis.	Usually compatible with breast milk.
Atenolol	(Atenolol not recommended) (I–D) Atenolol has risk of growth restriction when started in first or second trimester and is not recommended if breast feeding.				
Diazoxide	30–50 mg iv every 5–15 min; iv bolus for acute BP lowering in severe hypertension.				
Prazosin	0.5–5mg tds; consider as a second line agent by SOMANZ Not recommended by SOGC (I–D) Associated with postural hypotension and palpitations.				
Oxprenolol (beta blocker with ISA)	20–160mg tds; a first line agent by SOMANZ Contraindicated in heart block.				
Nitroprusside	Only considered for life-threatening severe hypertension Cyanide and thiocyanate toxicity, must be carefully monitored. Also risk of cardio-neurogenic syncope.				
Contraindicated	ACE inhibitors, angiotensin II receptor blockers (Pr, Re), (II-2E), FDA Class D.				
	Direct renin inhibitors.				
	Spironolactone not recommended due to potential foetal antiandrogen effects.				
Other Management Strategies Low dose aspirin	Use advised in women at high risk Used prophylactically in women with a history of preeclampsia at <28 Weeks.				
Fishoil supplementation	Not recommended.				

Calcium supplementation	May have role in decreasing incidence of preeclampsia Role in low calcium intake populations.
Vitamin C and E	Not recommended.
Steroid therapy	Only for fetal lung maturation.

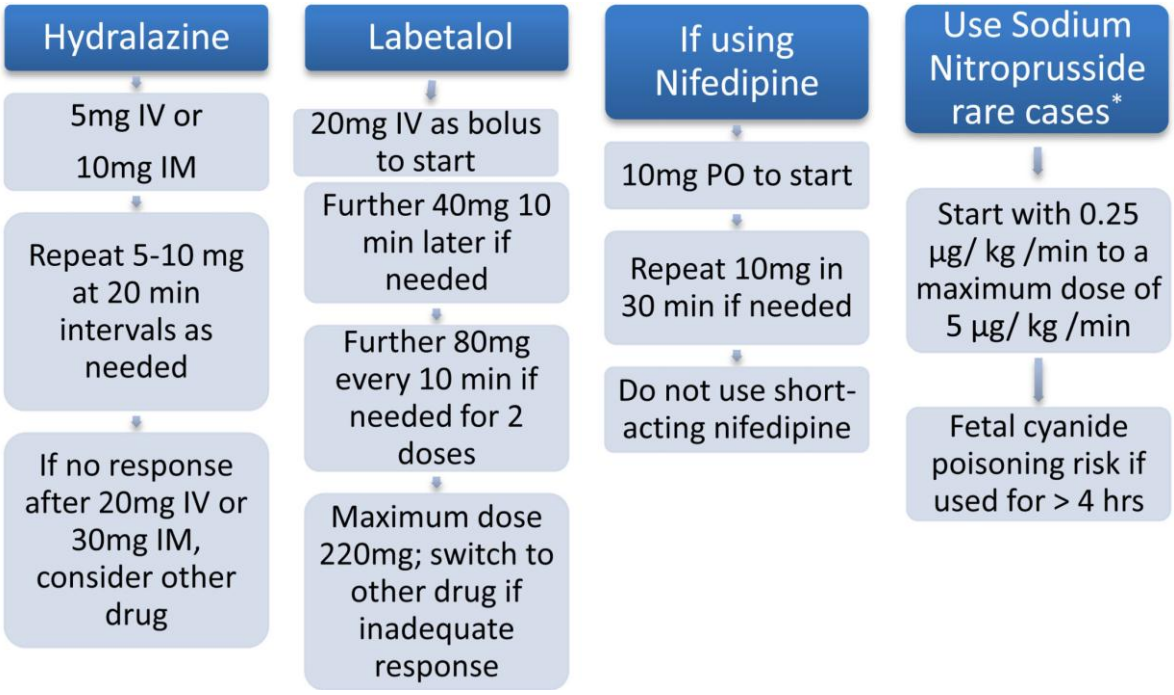

Figure 2: Drug treatments and regimens for severe hypertension in preeclampsia.

Profiles of recommended drug therapies

1. Centrally acting α2-adrenergic agonists

Methyldopa

Methyldopa is a centrally acting α2-adrenergic receptor agonist. It inhibits vasoconstriction via a central mechanism by reducing catecholamine release. It decreases central sympathetic outflow, decreasing systemic vascular resistance without decreasing cardiac output. The side effects of methyldopa include fatigue, depression, poor sleep and decreased salivation. Dose independent adverse effects include elevated liver enzymes in up to 5% of women and some patients can develop a positive antinuclear antigen or antiglobulin (Coombs') test although a clinical haemolytic anaemia is rare.[27] It has been suggested that methyldopa should be avoided in women with a prior history of depression, because of the possible increased risk of postnatal depression.[28] Methyldopa has a long history of use in pregnancy and does not appear teratogenic.[27] Methyldopa has a record of safety in pregnancy, as established by follow-up studies in the 1980's of children exposed to the drug in utero.[29] More recent studies indicate that in hypertensive pregnancy disorders, treatment with methyldopa does not

affect the maternal uterine artery Doppler pulsatility and resistance indices, suggesting that it does not impair uteroplacental circulation and consequent fetal growth. The doses of methyldopa recommended in pregnancy are similar to those used in non-pregnant patients.[30]

Clonidine

Clonidine is a centrally acting adrenergic agonist. It works as an antihypertensive agent by stimulating α-2 adrenergic receptors in the brainstem thereby decreasing central adrenergic output.[31] It acts on both peripheral and central α-2 adrenergic receptors to decrease the cardiac output, systemic vascular resistance, systolic blood pressure and heart rate. Clonidine is similar to methyldopa with regards to safety and efficacy.[32] It is generally used as a third-line agent for multidrug control of refractory hypertension.

According to the Food and Drug Administration (FDA) methyldopa is a Class B drug and clonidine is a Class C drug. According to either the World Health Organization and/or Thomson lactation ratings methyldopa is usually compatible with breast milk and clonidine has possible breast milk effects.

2. Peripherally acting adrenergic-receptor antagonists

Labetalol

Labetalol a non-selective β-blocking agent with vascular α-1-receptor blocking capabilities is widely used in pregnancy.[33] Fetal growth restriction and low placental weight in patients (with essential hypertension) have been associated with the use of atenolol during the second trimester, but not with other β-blocking agents, such as labetalol (an α and βblocker), which is used frequently for the treatment of severe acute hypertension during pregnancy, and has shown equivalent efficacy and better tolerability compared to hydralazine.[34] Side effects include fatigue, lethargy, exercise intolerance, sleep disturbance and bronchoconstriction have been reported.[33] β-blockers are not associated with teratogenicity.[33]

Prazosin

Prazosin is an α 1-blocker that selectively blocks post-synaptic α 1-adrenoceptors, producing a decrease in total peripheral resistance (and a reflex increase in sympathetic tone).[35] It is considered as a second-line agent. Prazosin has a useful role in chronic renal disease complicating pregnancy. It is associated with postural hypotension and palpitations.

Fetal growth restriction and low placental weight in patients (with essential hypertension) have been associated with the use of atenolol during the second trimester, but not with other β-blocking agents, such as labetalol (an alpha and beta blocker), which is used frequently for the treatment of severe acute hypertension during pregnancy, and has shown equivalent efficacy and better tolerability compared to hydralazine.[34] The benefits and concerns of antihypertensive agents are outlines in table 2.

According to FDA labetalol is a Class C drug. It may be associated with a risk of fetal bradycardia and neonatal hypoglycemia. According to either the World Health Organization and/or Thomson lactation ratings methyldopa is usually compatible with breast milk. Atenolol is an FDA Class D drug. It is not recommended due to risk of IUGR and is not recommended if breast-feeding.

3. Calcium Channel Antagonists

Calcium channel antagonists (CCAs) prevent the opening of voltage-gated calcium channels and reduce calcium entry into cardiac or vascular smooth muscle cells during phase 2 of an action potential exhibiting different selectivity for cardiac versus vascular calcium channels.[36] Animal studies dealing with some CCAs have shown a decrease in uteroplacental blood flow, IUGR, fetal death, and skeletal and cardiovascular malformations; yet a prospective, multicenter cohort study following 78 women with first-trimester exposure to CCAs showed no increase in major malformations. They may, however, cause cessation of uterine contraction and limited information is available on their use in the first trimester.[37]

A prospective cohort showed minimal teratogenicity when mothers are exposed to calcium channel blockers in the first trimester.[37] Furthermore, they have been shown superior to methyldopa in regard to controlling blood pressureand are possibly safer than labetalol in regard to controlling blood pressure to a safely low diastolic pressure.[38] One randomized controlled clinical trial compared oral nifedipine and labetalol in pregnant women with chronic hypertension. A central aortic pressure drop of mean 7.4 mmHg was seen in the nifedipine arm, but peripheral blood pressures were effectively the same in both arms. There was a slight increase in neonatal intensive care unit (ICU) and neonatal adverse effects in the nifedipine arm.[39]

Data for amlodipine, another commonly prescribed dihydropyridine calcium channel blocker, appear to be very limited. Three case series concluded that amlodipine does not appear to be

teratogenic[40], and a small pilot study comparing amlodipine to aspirin and furosemide for the treatment of chronic hypertension revealed no differences between the two antihypertensives in maternal or perinatal outcomes.[41]

Oral nifedipine and verapamil are frequently seen as second line agents used for the treatment of hypertension in pregnancy. They do not appear to be teratogenic. Calcium channel blockers (CCBs) inhibit the influx of calcium ions to vascular smooth muscle, resulting in arterial vasodilation; nifedipine act predominantly on the vasculature and verapamil acts primarily on the heart.[35] Side effects of CCB use in the mother include tachycardia, palpitations, peripheral edema, headaches and facial flushing.

According to FDA nifedipine and verapamil are Class C drugs. With all CCBs, there is a risk of interactions with magnesium, resulting in profound hypotension. Nifedipine and verapamil are usually compatible with breast milk.

4. Vasodilators

Hydralazine

Hydralazine is now predominantly used intravenously for the treatment of severe hypertension in pregnancy. Hydralazine selectively relaxes arteriolar smooth muscle. Adverse effects include headache, nausea, flushing, and palpitations. It does not appear teratogenic. There have been reports of neonatal thrombocytopenia, rare cases of a pyridoxine-responsive polyneuropathy with chronic use, and drug-induced lupus.[42]

However, there is evidence that intravenous labetalol or oral nifedipine are preferable firstline agents compared to intravenous hydralazine in severe hypertension in pregnancy.[34]

Sodium nitroprusside

Sodium nitroprusside is rarely used in pregnancy and is reserved for life-threatening severe hypertension.[43] Adverse effects include cyanide and thiocyanate toxicity and also the risk of cardio-neurogenic syncope.

Hydralazine is an FDA Class C drug. It is usually compatible with breast-feeding.

5. Diuretics

Diuretics can lead to reductions in the pre-eclampsiaassociated volume of: (i) circulating plasma; (ii) placental blood flow. Therefore, diuretics should be avoided in patients with pre-

eclampsia. Diuretics can be used if pulmonary edema or heart-failure signs are absent.[44] For patients with chronic hypertension who take diuretics before pregnancy, the effect of reduction in placental blood flow is not apparent if the drug is continued after pregnancy. A commonly used diuretic is hydrochlorothiazide at a daily dose of 12.5–25 mg. Spironolactone is not recommended because it has been found to have an anti-androgenic effect during fetal development in animal models, though it does not seem to induce adverse outcomes in small cohorts of human participants.[45] We do not suggest spironolactone use in pregnant women, but it can be used only if a potassium-sparing diuretic is needed.

Thiazides are FDA Class B drugs. They may cause volume contraction and electrolyte abnormalities but rare with small doses. Diuretics may reduce milk production.[46] Spironolactone is not recommended due to potential fetal antiandrogen effects.

6. Renin Angiotensin System drugs

Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) are contraindicated in pregnancy due to their association with adverse fetal effects.[47] ACE inhibitors are labelled FDA class C for the first trimester of pregnancy, and FDA class D for the second and third trimesters.

Management of Hypertension Postpartum

In the postpartum period, previously normotensive women have been noted to have a rise in BP, which reaches a maximum on the fifth postpartum day, and in 1 study 12% of patients had a diastolic BP exceeding 100 mm Hg.[48] This is thought to be a consequence of physiological volume expansion and fluid mobilization in the postpartum period. The natural history of gestational hypertension and preeclampsia in the postpartum period and the maximum time to normalization (beyond which chronic hypertension should be diagnosed) are not known. As such, and noted in a recent Cochrane analysis, the need for treatment, the management of antihypertensive medication, and patient counseling have been unguided by the literature.[49] Postpartum, no guidelines currently exist, but Tan and de Swiet have suggested that antihypertensive drugs should be given if the BP exceeds 150 mm Hg systolic or 100 mm Hg diastolic in the first 4 days of the puerperium. Choice of antihypertensive agent in the postpartum period is often influenced by breast feeding[50], but in general the agents commonly used in the antepartum period may be continued postpartum (Table 4). The medication may then be discontinued when BP normalizes. This may occur days to several weeks postpartum, and home BP monitoring by the patient may be helpful in this regard. In

select cases of women with severe preeclampsia, there seems to be some benefit to a brief course of furosemide diuresis in the days postpartum, particularly for patients with hypertension accompanied by symptomatic pulmonary or peripheral edema. A few case reports have suggested that nonsteroidal anti-inflammatories may contribute to BP elevation postpartum[51], and the effects on BP in nonpregnant individuals are well documented. Thus, in postpartum patients who are already hypertensive, these drugs should be used cautiously or should perhaps be avoided.

Table 4: Maternal Antihypertensive Medications Usually Compatible With Breastfeeding.

Captopril
Diltiazem
Enalapril
Hydralazine
Hydrochlorothiazide
Labetalol
Methyldopa
Minoxidil
Nadolol
Nifedipine
Oxprenolol
Propranolol
Spironolactone
Timolol
Verapamil

Novel therapeutic targets and emerging treatments

Angiogenesis

Dysregulation of angiogenesis appears to play a key role in the pathogenesis of preeclampsia. Placental cystathionine γ-lyse (CSE) expression is reduced in preeclampsia, leading to reduced plasma levels of the pro-angiogenic gaseous vasodilator, hydrogen sulfide (H2S) and increased sFlt-1. Targeting CSE/H2S activity may be a potential therapy pending additional studies.

Aminopeptidases

Aminopeptidases, such as placental leucine aminopeptidase (P-LAP) and aminopeptidase A (APA) do not cross the placental barrier. In the pregnant, spontaneously hypertensive rat, APA acts as an antihypertensive agent, degrading vasoactive peptides, and as a result, normalizes blood pressure. The role of aminopeptidases as potential therapeutic agents is being investigated.

Heme oxygenase 1

A recent study examined heme oxygenase 1 (HO-1) induction in a rat model of placental ischemia. George et al, suggest two potential pathways through which HO-1 acts, namely, normalization of angiogenic balance in the placenta, and reduction in oxidative stress. Both pathways are potential targets for treatment in preeclampsia.

Marinobufagenin

Uddin et al, and others, have investigated the role of marinobufagenin (MBG), a cardiotonic steroid, and its antagonist resibufogenin (RBG), in experimental animal models of preeclampsia. This group has demonstrated that in a rat model of preeclampsia, MBG inhibits first trimester cytotrophoblast cell function and that urinary excretion of MBG is elevated prior to the development of hypertension and proteinuria. MBG also causes hypoxia and ischemia leading to an imbalance of pro- and anti-angiogenic factors. RBG, when given early in pregnancy, prevented the development of hypertension, proteinuria, and intrauterine growth restriction.

G protein-coupled receptor (GPCR) targets

There is potential for investigation of novel GPCR-based therapies in preeclampsia, including calcitonin receptor-like receptor / receptor activity modifying protein 1 complexes, the angiotensin AT1, 2 and Mas receptors, and the relaxin receptor RXFP1.

Inhibitors of the enzyme poly ADP ribose polymerase (PARP)

In states of increased oxidative stress, such as diabetes, overstimulation of PARP leads to endothelial dysfunction and PARP inhibitors have been shown to be of benefit. A recent investigation has demonstrated a protective effect of a PARP inhibitor, preventing the development of both endothelial dysfunction and hypertension, in a rat model of preeclampsia.

Gasotransmitters

Nitric oxide, a potent vasodilator that mediates endothelium-dependent relaxation, has been linked to endothelial dysfunction in preeclampsia. Carbon monoxide, nitric oxide and hydrogen sulphide are endogenously generated gaseous transmitters known as, gasotransmitters. In preclinical animal models, the therapeutic use of CO gas and COreleasing molecules demonstrated anti-inflammatory properties and cardiovascular protective effects. These gaseous molecules may have a potential role in the therapeutics for

several diseases, including cardiovascular disease and preeclampsia, although their instability and potential toxicity are significant drawbacks.

Podocytes

Derangements of podocytes and podocyte-specific proteins are implicated in preeclampsia. There is evidence of an association between dysregulated pro-angiogenic factors, hypertension, and podocyte injury. Further investigation focusing on the mechanism of podocyte injury and detachment may identify novel therapeutic targets.

These are only a few of the more recent potential therapeutic targets under investigation.

Perspectives in Management

Over the last decade, new evidence has emerged, both with respect to the pathophysiology of preeclampsia and the benefits of early hypertension treatment in the general population, which may affect the management of hypertensive pregnant patients. The notion that pregnant women with chronic hypertension are at low risk for cardiovascular complications within the short duration of pregnancy may be in question given the current trend towards advanced maternal age at first pregnancy. These women may have other cardiovascular risk factors, such as obesity or hyperlipidemia, and/or signs of target organ hypertensive damage. In addition, modern methods of assisted reproduction (such as in vitro fertilization) have enabled women with CVD risk factors that are associated with decreased fertility (such as diabetes mellitus and renal disease) to conceive. In these women, treatment of hypertension of even a short duration, may improve their cardiovascular risks, especially in view of recent studies in the general population showing an important correlation between the time taken to achieve goal BP and clinical outcomes, namely better outcome with earlier and more effective treatment. Finally, recent studies have indicated that cerebral vascular events in women with severe preeclampsia and eclampsia may occur when SBP exceeds 150 mm Hg, and called for a paradigm shift, by recommending antihypertensive therapy when the SBP reaches or exceeds 155–160 mm Hg. Indeed, most investigators agree that antihypertensive therapy in the peripartum period should be initiated when the DBP approaches 100 mm Hg, or for a blood pressure ≥ 150/100 mm Hg. As abrupt decreases in BP may adversely affect uteroplacental perfusion, treatment of hypertension mandates close maternal and fetal monitoring as the BP is lowered. The ultimate therapeutic goal is to prevent maternal complications without compromising fetal wellbeing.[52]

CONCLUSION

Drug therapy to lower arterial pressure in pregnancy should be used mainly for maternal safety due to lack of data to support an improvement in fetal outcome. Drug therapy is usually indicated if arterial pressures exceeds 150 to 160 mmHg systolic or 100 to 110 mmHg diastolic or in the presence of target organ damage. Multiple drug classes have demonstrated efficacy as well as maternal and fetal safety in the treatment of hypertension in pregnancy with overall insufficient first-trimester data. Methyldopa remains the first drug of choice in the treatment of chronic hypertension. β-Adrenoceptor antagonists, especially those with vasodilating properties (labetalol, pindolol), are gradually becoming a standard therapy. ACE inhibitors, ARBs, and direct renin inhibitors should not be used in pregnancy or in females planning to conceive. Diuretic therapy is inappropriate in preeclempsia because plasma volume is reduced. In severeuncontrolled hypertension, intravenous labetalol or oral nifedipine can be used. Due to excessive adverse perinatal effects, intravenous hydralazine is less frequently used. During lactation no adverse effects have been reported from exposure to methyldopa or hydralazine. Among βadrenoceptor antagonists propranolol and labetalol are preferred. ACEIs, ARBs, and renin inhibitors should be avoided. Diuretics may suppress lactation and should be used with caution.

REFERENCES

1. Lenfant C, Working group report on high blood pressure in pregnancy, J Clin Hypertens(Greenwich), 2001; 3: 75–88.
2. Abalos E, Duley L, Steyn DW, Henderson-Smart DJ, Antihypertensive drug therapy for mild to moderate hypertension during pregnancy, Cochrane Database Syst Rev, 2002; 24: CD002252.
3. Longo SA, Dola CP, Pridjian G, Preeclampsia and eclampsia revisited, South Med Journal, 2003; 96: 891–899.
4. Brown CM, Garovic VD, Mechanisms and management of hypertension in pregnant women, Curr Hypertens Rep, 2011; 13: 46–338.
5. Sibai BM, Diagnosis and management of chronic hypertension in pregnancy, Obstet Gynecol, 1991; 78: 61-451.
6. Seely EW, Ecker J, Clinical practice, Chronic hypertension in pregnancy, N Engl J Med, 2011; 365: 46-439.
7. Knight M, Kurinczuk JJ, Spark P, et al, Extreme obesity in pregnancy in the United Kingdom, Obstet Gynecol, 2010; 115: 97-989.

8. Bramham K, Parnell B, Nelson-Piercy C, et al, Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis, BMJ, 2014; 348: 2301.
9. Chappell LC, Enye S, Seed P, et al, Adverse perinatal outcomes and risk factors for preeclampsia in women with chronic hypertension: a prospective study, Hypertension, 2008; 51: 9-1002.
10. Byrne TJ, New Pharmacologic Therapy for Hypertension in Pregnancy, J Hypertens Manag, 2019; 5(2): 041.
11. Magee LA and von Dadelszen P, State-of-the-art diagnosis and treatment of hypertension in pregnancy, Mayo Clin Proc, 2018; 93(11): 1664–1677.
12. Ngene NC and Moodley J, Role of angiogenic factors in the pathogenesis and management of pre-eclampsia, Int J Gynaecol Obstet, 2018; 141(1): 5–13.
13. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia, N Engl J Med, 2004; 350: 672–683.
14. Redman CW and Staff AC, Preeclampsia, biomarkers, syncytiotrophoblast stress, and placental capacity, Am J Obstet Gynecol 2015; 213(4 Suppl.): S9.e1, S9–S11.
15. Brown MA, Reiter L, Smith B, Buddle ML, Morris R, Whitworth JA, Measuring blood pressure in pregnant women: a comparison of direct and indirect methods, Am Journal Obstet Gynecol, 1994; 171: 7-661.
16. Brown MA, Robinson A, Buddle ML, Accuracy of automated blood pressure recorders in pregnancy, Aust NZ Journal Obstet Gynaecol, 1998; 38: 5-262.
17. Brown MA, Mangos G, Davis G, Homer C, The natural history of white coat hypertension during pregnancy, BJOG An internnational journal of obstetrics and gynaecology, 2005; 112(5): 6-601.
18. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM, The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP), (Review), Hypertens pregnancy, 2001; 20(1): 9-14.
19. Cote AM, Brown MA, Lam E, von Dadelszen P, Firoz T, Liston RM, Magee LA, Diagnostic accuracy of urinary spot protein: creatinine ratio for proteinuria in hypertensive pregnant women: systematic review BMJ, 2008; 336(7651): 6-1003.
20. Sibai BMM, Imitators of severe preeclampsia, Obstetrics & Gynecology, 2007; 109(4): 66-956.
21. Nelson-Piercy C, Pre-eclampsia: the women at risk, In: Critchley H, Maclean A, Poston L, Walker J, editors. Pre-eclampsia, London: RCOG Press, 2003: 342-353.

22. Witlin AG, Saade GR, Mattar F, Sibai BM, Risk factors for abruptio placentae and eclampsia: analysis of 445 consecutively managed women with severe preeclampsia and eclampsia, American Journal of Obstetrics & Gynecology, 1999; 180(6 Pt 1): 9-1322.
23. Olsen SF, Osterdal ML, Salvig JD, Weber T, Tabor A, Secher NJ, Duration of pregnancy in relation to fish oil supplementation and habitual fish intake: a randomised clinical trial with fish oil, Eur J Clin Nutr, 2007; 61: 976-985.
24. Purswani JM, Gala P, Dwarkanath P, Larkin HM, Kurpad A, Mehta S, The role of vitamin D in pre-eclampsia: a systematic review, BMC Pregnancy Childbirth, 2017; 17: 231.
25. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, American journal of obstetrics and gynecology, 2000; 183(1): S1–S22.
26. ACOG Practice Bulletin, Chronic hypertension in pregnancy, ACOG Committee on Practice Bulletins, Obstetrics and gynecology, 2001; 98 suppl(1): 177–185.
27. Magee LA, Drugs in pregnancy, Antihypertensives, Best practice & research Clinical obstetrics & gynaecology, 2001; 15(6): 827–845.
28. James PR, Nelson-Piercy C, Management of hypertension before, during, and after pregnancy, Heart, 2004; 90(12): 1499–1504.
29. Cockburn J, Moar VA, Ounsted M, Redman CW, Final report of study on hypertension during pregnancy: the effects of specific treatment on the growth and development of the children, Lancet, 1982; 1(8273): 647–649.
30. Magee LA, Treating hypertension in women of child-bearing age and during pregnancy, Drug safety : an international journal of medical toxicology and drug experience, 2001; 24(6): 457–474.
31. Rothberger S, Carr D, Brateng D, Hebert M, Easterling TR, Pharmacodynamics of clonidine therapy in pregnancy: a heterogeneous maternal response impacts fetal growth. American journal of hypertension, 2010; 23(11): 1234–1240.
32. Horvath JS, Phippard A, Korda A, Henderson-Smart DJ, Child A, Tiller DJ, Clonidine hydrochloride--a safe and effective antihypertensive agent in pregnancy, Obstetrics and gynecology, 1985; 66(5): 634–638.
33. Podymow T, August P, Antihypertensive drugs in pregnancy, Seminars in nephrology, 2011; 31(1): 70–85.

34. Magee LA, Cham C, Waterman EJ, Ohlsson A, von Dadelszen P, Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis, Bmj, 2003; 327(7421): 955–960.
35. Magee LA, Drugs in pregnancy, Antihypertensives, Best practice & research Clinical obstetrics & gynaecology, 2001; 15(6): 827–845.
36. Salhanick S, Shannon M, Management of calcium channel antagonist overdose, Drug Saf, 2003; 26: 65–79.
37. Magee LA, Schick B, Donnenfeld AE, Sage SR, Conover B, Cook L, McElhatton PR, Schmidt MA, Koren G, The safety of calcium channel blockers in human pregnancy: A prospective, multicenter cohort study, Am J ObstetGynecol, 1996; 174: 823–828.
38. Shawkat E, Mistry H, Chmiel C, et al, The effect of labetalol and nifedipine MR on blood pressure in women with chronic hypertension in pregnancy, Pregnancy Hypertens, 2018; 11: 92–98.
39. Webster LM, Myers JE, Nelson-Piercy C, et al, Labetalol versus nifedipine as antihypertensive treatment for chronic hypertension in pregnancy: a randomized controlled trial, Hypertension, 2017; 70(5): 915–922.
40. Ahn HK, Nava-Ocampo AA, Han JY, et al. Exposure to amlodipine in the first trimester of pregnancy and during breastfeeding, Hypertens Pregnancy, 2007; 26(2): 179–187.
41. Vigil-De GraciaP, Dominguez L and Solis A, Management of chronic hypertension during pregnancy with furosemide, amlodipine or aspirin: a pilot clinical trial, J Matern Fetal Neonatal Med, 2014; 27: 1291–1294.
42. Widerlov E, Karlman I, Storsater J, Hydralazine-induced neonatal thrombocytopenia, The New England journal of medicine, 1980; 303(21): 1235.
43. Shoemaker CT, Meyers M, Sodium nitroprusside for control of severe hypertensive disease of pregnancy: a case report and discussion of potential toxicity, American journal of obstetrics and gynecology, 1984; 149(2): 171–173.
44. Collins R, Yusuf S, Peto R, Overview of randomised trials of diuretics in pregnancy, Br Med J (Clin Res Ed), 1985; 290: 17-23.
45. Riester A, Reincke M, Progress in primary aldosteronism: mineralocorticoid receptor antagonists and management of primary aldosteronism in pregnancy, Eur J Endocrinol, 2015; 172: R23-30.
46. Podymow T, August P, Update on the use of antihypertensive drugs in pregnancy, Hypertension, 2008; 51(4): 960–969.

47. Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, et al, Major congenital malformations after first-trimester exposure to ACE inhibitors, The New England journal of medicine, 2006; 354(23): 2443–2451.
48. Walters BN, Thompson ME, Lee A, de Swiet M, Blood pressure in the puerperium. Clin Sci (Lond), 1986; 71: 589–594.
49. Magee L, Sadeghi S, Prevention and treatment of postpartum hypertension, Cochrane Database Syst Rev, 2005; CD004351.
50. Beardmore KS, Morris JM, Gallery ED, Excretion of antihypertensive medication into human breast milk: a systematic review, Hypertens Pregnancy, 2002; 21: 85–95.
51. Makris A, Thornton C, Hennessy A, Postpartum hypertension and nonsteroidal analgesia, Am J Obstet Gynecol, 2004; 190: 577–578.
52. Catherine M. Brown, Vesna D.Garovic, Drug Treatment of Hypertension in Pregnancy, PMC, 2015; 74(3): 283-296.