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Review Article

PHARMACOTHERAPY OF HYPERTENSION IN PREGNANCY

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ABSTRACT

Hypertension is a common disease in general population and among pregnant women leading to rise in morbidity and mortality. Hypertension among pregnant women even causes mortality of foetus. Therefore adequate treatment should be started in time to control it. Though a big list of antihypertensive drugs are there, the selection of antihypertensive in pregnancy is important, as because some may dampen the labor process, some may have teratogenic effect on foetus. At times quick lowering of BP is required, and at times drugs are prescribed during whole pregnancy period particularly who are known hypertensive and who are gestational hypertensives. Many molecules are in pipeline e.g. Heme oxygenase 1, G protein-coupled receptor (GPCR) targets, Aminopeptidase etc. and they are showing good result.

Key words: complications, drugs, eclampsia, hypertension, pregnancy.

Hypertension:[1] Sustained increase in blood pressure >140/90 mm Hg is defined as hypertension. Hypertension is a major risk factor for stroke, myocardial infarction, cardiac failure, renal insufficiency, dissecting aneurysm of aorta, peripheral arterial diseases.

Epidemiology: This is the most common cardiovascular disease and its prevalence increases with age. In United States[2], there is a 65.4% prevalence of hypertension in people between ages of 60-69 years which further increases with age. Diastolic blood pressure also increases with age until approximately 55 years of age, after which it tends to decrease. Systolic hypertension tends to increase after 60 years further while diastolic blood pressure may decrease because of decreased compliance of blood vessels with aging and atherosclerosis.

Whereas, in India, a study[3] showed a prevalence of hypertension in India is 29.8%. About 33% urban and 25% rural Indians are hypertensive. It means one third of urban population and one fourth of rural population are suffering from hypertension in India. Genetic and environmental factors may have an important role in hypertension prevalence. Obesity, weight gain, high dietary sodium chloride intake, alcohol consumption, stress, low physical activity may play important roles in hypertension.

Stages of hypertension[2]

	Systolic blood pressure	Diastolic blood pressure
Normal	<120 mmHg	and <80 mmHg
Pre-hypertension	120-139	or 80-89
Hypertension, stage 1	140-159	or 90-99
Hypertension, stage 2	≥160	or ≥100
Isolated Systolic Hypertension	≥140	And < 90

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But very recently, blood pressure more than 130/80 mm of Hg is called as stage 1 hypertension and more than 140/90 mm of Hgis called as stage 2 hypertension.[4]

Hypertension also divided as primary hypertension also known as essential hypertension (~80-95% of all hypertensive patients) and secondary hypertension.

Primary hypertension is likely to be associated with environmental and genetic interaction.

Whereas secondary hypertension may be due to secondary causes like renal diseases (CKD, renal cysts *etc*), adrenal diseases (Primary Aldosteronism, Cushing's syndrome), preeclampsia, eclampsia, neurogenic, medications (high dose estrogens, adrenal steroids, MAO inhibitors, tricyclic antidepressants).

HYPERTENSION AND PREGNANCY[5]

During pregnancy blood pressure usually decreases in the latter half of first trimester to the mid half of second trimester due to decreased vascular resistance and start to increase in the third trimester till pre-pregnancy level.

In a cross sectional study[6] carried out in 20 sub-centers under Community Health Center (CHC) Chiri, Block Lakhanmajra prevalence of hypertension in pregnancy was found to be 6.9%.

Hypertension in pregnancy may be chronic which she already has, before she got pregnant or may be induced by pregnancy (gestational hypertension, preeclampsia, eclampsia).

Preeclampsia: It includes presence of non dependant edema, hypertension and proteinuria in a pregnant woman which is generally nulliparous and these symptoms appears in the third trimester. Generalized arteriolar constriction being the patho-physiology causing decreased blood flow to the placenta leading to IUGR in the fetus and maternal complications like severe hypertension, seizure, stroke, oliguria, renal failure, pulmonary edema, DIC etc. Patient may develop HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets).[7]

Mild preeclampsia: (BP>140/90 or increase over pre-pregnancy BP of >30/15 with proteinuria >300mg/24hr) can be treated with induction of labor for term pregnancies. Antihypertensive medication like methyl-dopa, labetalol, hydralazine, nifedipine may be used.[8]

Severe preeclampsia: Magnesium sulfate for seizure prophylaxis and hydralazine for BP control can be used. The therapeutic level of magnesium will be between 4-7 mEQ/L. If there is constant threat of eclampsia, maternal interest should always be considered. If mother completed 37 weeks of gestation delivery should be considered. Corticosteroid is given if pregnancy is less than 34 weeks.[8]

Gestational hypertension: Blood pressure > 140/90 or systolic BP >30 of prepregnancy systolic BP or diastolic BP >15 of pre-pregnancy diastolic BP on two occasions 4-6 hours apart with 24 hour total urinary protein < 300mg.

Eclampsia: Generalized tonic clonic seizures occurring in a pre-eclampsia patient. Hypertension can be managed by hydralazine. Magnesium sulfate to be started for seizure management and to be continued continued for 24 hours after last seizure or delivery whichever is later. [8]

Chronic hypertension: It is defined as hypertension before conception, before 20 weeks of gestation or persisting more than 6 weeks postpartum. Patients with hypertension of 140/90 or less are managed expectantly. Above this level medications used are labetolol, nifedipine, methyldopa. If a woman is taking an antihypertensive medication before conception and her BP is well maintained, she can continue it during her pregnancy with exception of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists. ACE inhibitors and ARBs are contraindicated in pregnancy sue to their association with adverse fetal effects.

Drugs used for severe hypertension in preeclampsia (SBP ≥ 160 or DBP > 110)[5]

Hydralazine - 5mg IV or 10 mg IM → repeat 5-10 mg at 20 min intervals as needed → if no response after 20mg IV or 30 mg IM, consider another drug

Labetolol - 20 mg IV as bolus to start → Further 40 mg 10 min later if needed → further 80 mg every 10 min if needed for 2 doses → maximum dose 220mg. switch to other drug if there is inadequate response.

If using nifedipine - 10mg PO to start → repeat 10 mg in 30 min if needed → do not use short acting calcium channel blockers.

Use sodium nitroprusside (rare cases) - Start with 0.25 µg/kg/min to maximum dose of 5µg/kg/min → fetal cyanide poisoning risk if used for > 4 hours.

Diazoxide – 30-50 mg IV bolus every 5-15 min

Commonly used antihypertensives during pregnancy

Methydopa -It is a centrally acting α2 adrenergic agonist. Methyldopa has long being used in pregnancy and doesn't appear to be teratogenic. According to FDA methydopa is a class B drug. Dose: 0.5-3 gm/day orally in divided doses.

Clonidine - It is also a centrally acting α2 adrenergic agonist and is a class C drug according to FDA. Dose: 0.1-0.6 mg/day in 2 divided doses (not commonly used)

Labetolol - It is a non selective β blocker and a vascular α1 receptor blocker. Labetolol has shown equivalent efficacy and better tolerability compared to hydralazine. It is a class C drug according to FDA and has risk of fetal bradycardia and neonatal hypoglycemia. Dose: 200-1200 mg/day orally in 2-3 divided doses.

Beta blockers can be prescribed during pregnancy except atenolol. Atenolol is an FDA Class D drug. It is not recommended due to risk of IUGR and is not recommended if breast-feeding.[9] Though another study recommend careful use of atenolol during breastfeeding because atenolol concentrations will be too low to be clinically relevant in majority of healthy, term infants. Premature infants and those with kidney disease require further study.[10]

Prazosin - It is a selective α1 blocker. Prazosin has a useful role in chronic renal disease complicating pregnancy. It is associated with postural hypotension and palpitations. Dose: 0.5-5 mg tds

Calcium channel blockers - Nifedipine and verapamil doesn't appear to be teratogenic and frequently seen as 2nd line agents. According to FDA nifedipine and verapamil are Class C drugs. Commonly used calcium channel blockers may be avoided or withdrawn before parturition because it may delay labor and also may cause PPH in full term pregnancy. Nifedipine – 10-30 mg orally, Verapamil – 80 mg tds orally (not commonly used during pregnancy).

Diuretics - Diuretics are commonly prescribed in essential hypertension before conception and are used during pregnancy for treating hypertension and cardiac disease Patients already on diuretics prior to pregnancy can continue during pregnancy. Hydrochlorothiazide, triamterene, and amiloride are not teratogenic according to a small number of case reports.[11] But diuretics are not part of the standard treatment for gestational hypertension and oedema. Use of diuretics is always limited. Methyldopa and prazosin can cause fluid retention, which can be prevented by using diuretics.[11] Furosemide may be used to manage heart or kidney failure.[9]

Drugs for prevention of preeclampsia

Aspirin - antiplatelet agent. Low dose aspirin (75mg orally daily) reduces the risk of preeclampsia by 17%, intrauterine fetal death or neonatal death by 14% and preterm delivery by 8%.[12] It should be stopped once 34 weeks completed to avoid the possibility of premature closure of patent ductus arteriosus.

Calcium - calcium supplementation (1gm orally daily) may reduce the occurrence of preeclampsia, premature delivery etc.[13] though the efficacy is doubtful.

Drugs in pipeline

Heme oxygenase 1 (*HO-1*) –In animal model HO-1 acts in 2 pathways, namely, normalization of angiogenic balance in the placenta, and reduction in oxidative stress. Both are potential pathway for treatment of preeclampsia.[14]

G protein-coupled receptor (*GPCR*) *targets* - 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 have good potential.[15]

Inhibitors of the enzyme poly ADP ribose polymerase (*PARP*) - PARP inhibitor, preventing the development of both endothelial dysfunction and hypertension have protective effect in preeclampsia in animal model.[16]

Angiogenesis - Placental cystathionine γ-lyse (CSE) expression is reduced in preeclampsia, resulting in reduction of plasma levels of the pro-angiogenic gaseous vasodilator, hydrogen sulfide (H2S) and increment of sFlt-1. Targeting CSE/H2S activity may be a potential therapy.[17]

Marinobufagenin & resibufogenin – (60-70)% of preeclampsia patients showed increased serum and urinary marinobufagenin. This changes can be prevented by the administration of resibufogenin beginning early in pregnancy.[18]

Aminopeptidase - both aminopeptidase A and placental leucine aminopeptidase could be potentially safe and effective drugs for patients and their babies in the treatment of preeclampsia and preterm labor.[19] The changes of the balance between fetal angiotensin II (A-II) and vasopressin (AVP) andA-II and AVP degrading enzymes, between aminopeptidase A (APA) and placental leucine aminopeptidase (P-LAP) - in the placenta and maternal blood due to fetal stress such as hypoxia - are the provable causes of preeclampsia or preterm labor. Estradiol benzoate (E2) and progesterone (P) from placenta can induce APA & P-LAP. Sex steroid treatment with increasing dose manner by gestational week may be a good treatment option for severe preeclampsia and preterm labor.[20]

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