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Review Article

Hypertension in Women

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Abstract

Hypertension (HTN) in women has generated more focus in view of reports of increased prevalence. Women compared with men exhibit a steeper increase in blood pressure (BP) as early as in the third decade and continue in a linear time course thereafter. HTN is the most common medical disorder during pregnancy. Pre-existing HTN is defined as HTN diagnosis before pregnancy, early in pregnancy (before 20 weeks of gestation), or HTN continues after 6 weeks postpartum. Gestational hypertension (GH) is defined as HTN first diagnosis during pregnancy after 20 weeks of gestation. Antihypertensive medications should be initiated at BP ≥150/95 mmHg for patients with pre-existing HTN and >140/90 mmHg for patients with gestational HTN with or without proteinuria. BP target should be <140/90 for all hypertensive pregnant women. Women who take antihypertensive treatments other than ACE inhibitors, ARBs, thiazide or thiazide-like diuretics, and limited evidence available have not shown an increased risk of congenital malformation with such treatments. Labetalol is first-line medication during pregnancy and lactation. Antihypertensives should be restarted after delivery and tapered slowly only after days 3–6 postpartum. Most antihypertensive medicines taken while breastfeeding is safe. Women with established strong clinical risk factors for preeclampsia should be treated ideally before 16 weeks with low-dose aspirin 75–162 mg/day. Women with GH or preeclampsia have increased risks of cardiovascular disease and recurrence of preeclampsia and GH in future pregnancies.

Key words: Gestational hypertension, hypertension during pregnancy, hypertension, labetalol, preeclampsia, proteinuria

Introduction

The prevalence of hypertension (HTN) in women is an increasing concern. Data from 5,26,336 participants aged 40–79 years in the high-income countries have shown a prevalence of HTN across all women participants aged 40–79 years from 33% to 52%. In the age group of 40–49 years, HTN prevalence ranged from 12% to 20% and in 70–79 years from 61% to 82%.[1]

Blood pressure (BP) was recorded for 180,335 participants with a mean age 40.6 ± 14.9 years in India which included 33.2% of women. The prevalence among women was 23.7%. Higher predisposition was noted during the menopausal age. In the age group of 45–54 years, the prevalence of HTN was 34.6% with systolic blood pressure (SBP) of 126.7 ± 18.0 mmHg and diastolic blood pressure (DBP) of 80.3 ± 10.9 mmHg.[2,3]

HTN in Women

Sympathetic activity, increased arterial stiffness may play an important role in the increased prevalence of HTN after menopause.[4,5] Women with HTN are noted to develop more heart failure with preserved ejection fraction (HFpEF), atrial fibrillation, and dementia compared to men.[6,7]

Gender-specific analysis of existing data of four community cohort studies in 32,833 individuals over four decades and inclusive of 54% of women done recently has brought forth some important information on the trajectories of BP elevation. Women compared with men exhibited a steeper increase in BP that began as early as in the third decade and continued through the life course (likelihood ratio test $\chi^2 = 531$ for systolic BP; $\chi^2 = 123$ for diastolic BP; $\chi^2 = 325$ for mean arterial pressure [MAP]; and $\chi^2 = 572$ for PP; for all $P < 0.001$). MAP which is a vascular marker of small artery function also had a greater increase in women as they aged.[8]

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Considering the assumption that vascular physiology may or may not fundamentally differ between women and men, these data revealed the early onset and more rapid progress of high BP in women and the manifestations of cardiovascular diseases in their later life.

Underlying genetic expression at the cellular level is a plausible hypothesis.[9]

Hypertensive Disease of Pregnancy (HDP)

HTN is the most common medical disorder during pregnancy, with a prevalence of 5–10% of all pregnancies worldwide.[10]

The discussion in the further text is based on the guidelines of American College of Obstetricians and Gynecologists, ESC/ESH guidelines, ISHHP guidelines, and the NICE guidelines[11-14] for the benefits of healthcare professionals. The discussion is mainly pertinent to HTN and BP lowering drugs and not on other pregnancy-related complications including eclampsia, which is beyond the purview of this article.

Classification of HDP

European guidelines have classified the severity of hypertension as mild HTN (SBP 140–159 mmHg and/or DBP 90–109 mmHg) and severe HTN (BP ≥160/110 mmHg). Classification of hypertension during pregnancy is described in Table 1.

Aneroid devices are used commonly for BP measurement, but they may be inaccurate and need to be regularly calibrated. In a smaller study, 50% of aneroid devices had at least 1 BP reading >10 mmHg out of range compared with the same error in only 10% of mercury devices.[15]

Diagnosis of HTN during pregnancy is based on the standard office BP measurements. Standard procedure for measurement of BP in pregnancy is described in Table 2. Ambulatory blood pressure monitoring (ABPM) which is an important tool in diagnosis and outcome studies in clinical practice[16] is not recommended because they may record lower BP readings and are unreliable in preeclampsia.[17] Also, the diagnosis of hypertension in the ambulatory phase relies on the non–outcome-derived cutoffs from normotensive pregnancies, or the defined threshold values in non-pregnant adults. Paucity of prospective multi-centric studies in different ethnicities of adequate sample size and ABPM outcome-derived thresholds makes ABPM recommendations difficult in HDP. With ongoing studies and data generation ABPM role in pregnancy should not be undermined.

Twenty-four hours ABPM or home BP monitoring has a utility in confirming office or clinic HTN after repeated measurements over hours at the same visit or on two consecutive antenatal visits to eliminate a diagnosis of white coat HTN. Normal values for 24 h ABPM in pregnancy have been determined.[18] Before 22 weeks, BP values should be below: 24 h average 126/76 mmHg; awake average BP 132/79 mmHg; and sleep average BP 114/66 mmHg. These values are slightly lower than those used as thresholds for diagnosing HTN in non-pregnant women.

ISSHP does not recommend routine testing for any secondary cause of HTN in the absence of clinical clues to these conditions as they are less common.

Complications of Hypertension during Pregnancy are described in Table 3. Eclampsia is a severe form of preeclampsia associated with generalized tonic-clonic seizures. Preeclampsia may develop in the early postpartum period in few cases. If women with chronic HTN are suspected of developing preeclampsia,

Table 1: Classification of hypertension

Preexisting hypertension
HTN diagnosis before pregnancy, early in pregnancy (before 20 weeks of gestation), or HTN continues after 6 weeks postpartum.
Gestational hypertension
HTN first diagnosis during pregnancy, after 20 weeks of gestation; it usually resolves within 6 weeks postpartum. Gestational HTN is considered a form of secondary HTN
Preexisting hypertension plus superimposed gestational hypertension with proteinuria
Preeclampsia
Antenatally unclassifiable hypertension
HTN is first diagnosed after 20 weeks of gestation and it is unclear if hypertension was preexisting and reassessed after 6 weeks postpartum

HTN: Hypertension

Table 2: Blood pressure measurement and HDP

Defined as systolic BP ≥140 and/or diastolic BP ≥90 mmHg. BP should be repeated to confirm true hypertension
BP should be confirmed within 15 min if systolic BP ≥160 and/or diastolic BP ≥110 mmHg
BP to be measured with a liquid crystal sphygmomanometer and if unavailable, validated and appropriately calibrated automated device
Correct cuff size is important, large cuff to be used if the mid upper arm circumference is >33 cm

HDP: Hypertensive disease of pregnancy, BP: Blood pressure

Table 3: Complications of hypertension during pregnancy

Preeclampsia
HELLP syndrome (hemolysis, elevated liver enzymes, and a low platelet count)
Placental abruption
Disseminated intravascular coagulation.
Intrauterine growth retardation (25% cases of preeclampsia)
Prematurity (27% cases of preeclampsia)
Intrauterine death (4% cases of preeclampsia)
Chronic hypertension (4-fold higher risk)
Stroke and ischemic heart diseases (2-fold higher risk)
Preterm delivery (12.5% in women with gestational hypertension)

placental growth factor-based testing is recommended to help rule out preeclampsia between 20 weeks and up to 35 weeks of pregnancy.

Principles of antihypertensive therapy

Antihypertensive medications should be initiated at BP ≥150/95 mmHg for patients with preexisting HTN and >140/90 mmHg for patients with gestational HTN (with or without proteinuria) and patients with subclinical HTN-mediated organ damage.

BP target should be <140/90 for all hypertensive pregnant women. Physiological drop of BP is noted in the second trimester and some pregnant women may require reduction of dose or sometimes withdrawal of their antihypertensive medication. It is desirable to maintain BP 110–140/85 mmHg.

CHIPS trial (control of HTN in pregnancy study) studied the effects of tight control of BP (DBP <85 mmHg and SBP <160 mmHg). Diastolic BP of 85 mmHg was associated with reduced likelihood of developing accelerated maternal HTN and no demonstrable adverse outcome for babies compared with targeting higher diastolic BP in the CHIPS trial in chronic hypertensive women.[19]

Development of severe HTN was associated with significantly greater likelihood of adverse outcomes in the mother (thrombocytopenia, abnormal liver enzymes with symptoms, and longer hospital stay) and neonate (low birth weight, prematurity, death, and morbidity requiring neonatal unit care) in the follow-up of women in the CHIPS trial. Severe HTN in the less tight control was associated with significantly more serious maternal complications.[20]

Cochrane review on antihypertensive therapy for mild-to-moderate HTN during pregnancy (BP 140–169 mmHg/90–109 mmHg) found that initiating treatment halved the risk of progression to severe HTN but had no effect on the risk of preeclampsia.[21]

Drug therapy for mild HTN

Rigorous salt restriction and weight loss are not recommended during pregnancy due to the risk of volume contraction and neonatal growth restriction, respectively.[22,23] Recent reexamination of the high-risk aspirin trial data during pregnancy reported that the newly identified Stage 1 HTN in pregnancy was associated with increased risk of preeclampsia compared with normotensive women (39% vs. 15%) and that randomization to aspirin reduced this risk (24% vs. 39%).[24]

ISSHP recommends that women with established strong clinical risk factors for preeclampsia (i.e., prior preeclampsia, chronic HTN, pregestational diabetes mellitus, maternal body mass index >30 kg/m^2, antiphospholipid syndrome, and receipt of assisted reproduction) be treated, ideally before 16 weeks but definitely before 20 weeks, with low-dose aspirin (defined as 75–162 mg/day, as studied in randomized controlled trials). Pre-pregnancy advice for BP lowering drugs in women is described in Table 4.

Table 4: Pre-pregnancy advice for blood pressure lowering drugs

ACE inhibitors or ARBs are associated with an increased risk of congenital abnormalities if taken during pregnancy
ACE inhibitors or ARBs should be stopped preferably within 2 working days of notification of pregnancy
Thiazide or thiazide-like diuretics may have an increased risk of congenital abnormalities and neonatal complications
Antihypertensive treatments other than ACE inhibitors, ARBs, thiazide, or thiazide-like diuretics have not been shown to have an increased risk of congenital malformation

Pregnancy and lactation labeling rule system must be checked before prescribing any drugs to pregnant women. BP lowering drugs and drugs for urgent BP control are described in Tables 5 and 6 respectively. Acceptable initial antihypertensives include labetalol, oxprenolol, methyldopa, nifedipine, diltiazem, prazosin, and hydralazine are usually used as the second- or third-line agents. Atenolol should be avoided in pregnancy as it is associated with fetal growth impairment and this effect is related to duration of therapy. Recent studies suggest that exposure to ACEI early in pregnancy during the period of organogenesis does not confer an increase in the risk of malformations.[25]

Timing of birth and intrapartum antihypertensive treatment

Women with preeclampsia should be delivered if they have reached 37 weeks' (and 0 days) gestation or if they develop repeated episodes of severe HTN despite maintenance treatment with three classes of antihypertensive agents (ISSHP). Planned early birth before 37 weeks is not recommended to women with chronic HTN whose BP is lower than 160/110 mmHg, with or without antihypertensive treatment, unless there are other medical indications. For women with chronic HTN, whose BP is lower than 160/110 mmHg after 37 weeks, with or without antihypertensive treatment, timing of birth, and maternal and fetal indications for birth should be agreed between the woman and the senior obstetrician. If planned early birth is necessary, antenatal corticosteroids and magnesium sulfate, if indicated, may be given in line with the NICE guideline on preterm labor and birth.

Oral antihypertensives should be given at the start of labor. HTN should be treated urgently with oral nifedipine or either intravenous labetalol or hydralazine if BP rises ≥160/110 mmHg. Total fluid intake should be limited to 60–80 mL/h. Absorption of antihypertensives after oral administration can be hampered because of reduced gastrointestinal motility. Intravenous antihypertensives may be needed to control severe HTN. Short term and long term measures in the post partum phase are described in Table 7.

Antihypertensive treatment during lactation

Antihypertensive medicines can pass into breast milk. Most antihypertensive medicines taken while breastfeeding only lead to very low levels in breast milk, so the amounts taken in by babies are very small and would be unlikely to have any

Table 5: Antihypertensive drugs during pregnancy

Drug	Recommended	Dose	Side effects/concerns
Labetalol	Yes (first choice)	100–200 mg bid, maximum 1200 mg in four doses	Fetal bradycardia or intrauterine growth retardation
Alpha methyldopa	Yes	0.5–3.0 g in 2–4 doses	Sleepiness, dry mouth, general malaise, hemolytic anemia, and hepatopathy[26]
Calcium channel blockers, for example, nifedipine	Yes	20–120 mg long-acting single dose	Headache, pedal edema, dizziness
Hydralazine	Yes	40–200 mg/day in up to four doses	Fetal thrombocytopenia Reflex sympathetic activation
Thiazide and potassium-sparing diuretics	No	--	Potential risk of oligohydramnios
ACEIs and ARBs	No	--	Renal dysplasia, pulmonary hypoplasia, growth restriction[27]

Table 6: Drug therapy for urgent BP control[13]

Drug	Dose	Side effects
Labetalol	10–20 mg IV, then 20–80 mg every 10–30 min to a maximum cumulative dosage of 300 mg; or constant infusion 1–2 mg/min IV; onset of action 1–2 min	Bradycardia
Hydralazine	5 mg IV or IM, then 5–10 mg IV every 20–40 min maximum dose 20 mg; or constant infusion of 0.5–10 mg/h; onset of action 10–20 min	Maternal hypotension, headaches, and abnormal fetal heart rate tracings
Nifedipine immediate release	10–20 mg orally, repeat in 20 min if needed; then 10–20 mg every 2–6 h; maximum daily dose is 180 mg; onset of action 5–10 min	Tachycardia, headache

Table 7: Postpartum follow-up – short term and long term

Blood pressure should be monitored at least every 4 h while awake in view of high risk for preeclamptic complications for the first 3 days.
Antihypertensives administered antenatally should be continued and withdrawn slowly over 3–6 days
Antihypertensive therapy may be given for any hypertension before day 6 postpartum
Review recommended at 3 months postpartum by which time BP, urinalysis, and all laboratory tests should have normalized
Women with gestational hypertension should be advised that they have approximately a 4% risk for developing preeclampsia[28]

clinical effect.[29,30] Most medicines are not tested in pregnant or breastfeeding women, so disclaimers in the manufacturer's information are not because of any specific safety concerns or evidence of harm.

Methyldopa, labetalol, and propranolol are considered safe. Beta-blockers such as metoprolol and atenolol can achieve high levels in breast milk and therefore should be avoided. Methyldopa should be avoided because of the risk of postpartum depression.

Angiotensin-converting enzyme inhibitors captopril and enalapril are considered safe given their low concentrations in breast milk. Enalapril can be offered to treat HTN in women during the postnatal period, with appropriate monitoring of maternal renal function and maternal serum potassium. Calcium channel blockers have a limited data and nifedipine is commonly used during breastfeeding. Diuretics are discouraged because of the risk of reducing breast milk production.

HTN in Pregnancy – Future Cardiovascular Implications

Progression to chronic HTN postpartum has been reported in 42% of women with preeclampsia and 39% of women with gestational hypertension (GH) after mean follow-up of 2.5 years as compared to 1% among women with normotensive pregnancies.[31] Women with GH or preeclampsia should be advised that they have increased risks of cardiovascular disease, death, stroke, diabetes mellitus, venous thromboembolic disease, and CKD compared with women who have had normotensive pregnancies.[32,33]

Women with a history of preeclampsia have 71% increased risk of CV mortality, a 2.5-fold increase in risk of coronary artery disease (CAD), and a 4-fold increase in the development of heart failure when compared to normal cohorts as shown in a recent meta-analysis.[34,35] Nurse's Health Study II reported that women with GH and pre-eclampsia had a 3-fold and 6-fold increased rate of chronic HTN. Women with HTN during their first pregnancy had 70% increased risk of type 2 diabetes and 30% increased prevalence of hypercholesterolemia later in life.[36] Norwegian study with a mean follow-up of 17.2 years found that women with preeclampsia alone had a 2-fold increased risk of a major CV event.[37]

Conclusions

High-income countries have reported prevalence of HTN in women aged 40–79 years from 33% to 52% and in India of 23.7%. Higher predisposition is noted during the menopausal age. Vascular physiology may or may not fundamentally differ between women and men but recent evidence has focused on the early onset and more rapid progress of high BP in women and the manifestations of cardiovascular diseases in their later life. HDP which includes all the entities preeclampsia, GH, and chronic HTN is associated with significantly increased risk of CVD in the first decade postpartum and in the long term.

HTN is the most common medical disorder during pregnancy, with a prevalence of 5–10% of all pregnancies worldwide. Progression to chronic HTN postpartum has been reported in close to half of women with preeclampsia and substantial number of women with GH. Women with a history of preeclampsia have a high risk of CV mortality, a 2.5-fold increase in risk of CAD, and a 4-fold increase in the development of heart failure. Labetalol, CCB's, and methyldopa are safe drugs in HDP and ACE inhibitors, ARBs, thiazide, or thiazide-like diuretics are to be avoided. Women with HTN who need to take antihypertensive medication can be adapted to accommodate breastfeeding without any harm.

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