Current Hypertension Reports (2019) 21:74
https://doi.org/10.1007/s11906-019-0979-y

PEDIATRIC HYPERTENSION (B FALKNER, SECTION EDITOR)

Hypertension in Premenopausal and Postmenopausal Women

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Abstract

Purpose of Review To examine available clinical data on the differences between premenopausal and postmenopausal women with hypertension (HTN). Clinical conditions related to HTN and reproductive status differ in younger women compared with older women. Due to recent changes in the definition of HTN, the prevalence of HTN has increased significantly in all women. Rising rates of obesity among women of all ages increase the risk for HTN.

Recent Findings Among younger women, long-term vascular consequences of preeclampsia, the under-reported prevalence of fibromuscular dysplasia, and widespread use of oral contraceptive pills in women with contraindications confer unique risks for HTN-related cardiovascular risk. For older women, insights on vascular aging and hormonal changes with menopause are shown to be gender-specific causal factors for HTN.

Summary Assessment of risk factors unique to premenopausal and postmenopausal women can facilitate the management of HTN and improve long-term outcomes. Further studies in women are needed to accurately stratify women risk based on these risk factors.

Keywords Hypertension · Premenopause · Postmenopause · Women · Risk factors

Introduction

Hypertension (HTN) is the main modifiable risk factor for cardiovascular disease (CVD). With the growing obesity epidemic in developed and developing nations, the prevalence of HTN is increasing and deserves a greater focus on prevention and management. HTN in women warrants special attention due to the conditions unique to women throughout life. It is well known that conditions like pregnancy and postmenopause can be associated with HTN. Other conditions unique to women including the menstrual cycle, polycystic ovarian syndrome (PCOS), perimenopause, and menopause to name a few have been associated with changes in blood pressure (BP) through several hormonal pathways. This review focuses on the causes and management of HTN across the lifetime of women and discusses how changes in hormones may affect the onset of HTN.

This article is part of the Topical Collection on *Pediatric Hypertension*

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Prevalence of Hypertension in Premenopausal and Postmenopausal Women

The most recent 2017 ACA/AHA guidelines for HTN [1••] define stage I HTN as BP 130–139/80–89 mmHg and stage II HTN as BP greater than 140/90 mmHg. BP between 120 and 129/< 80 mmHg is defined as "elevated BP" and replaces the term "pre-hypertension." Normal BP is now defined as less than 120/80. These guidelines are aligned with the 2017 pediatric HTN guidelines for adolescents > 13 years of age [2]. Therefore, the same definitions of elevated BP and HTN apply to all individuals aged 13 years and above regardless of age, sex, or height.

The prevalence of HTN in men and women, based on NHANES data according to the previous definition compared with the 2017 ACA/AHA guidelines, is provided in Table 1. With the new guidelines, the prevalence of HTN in premenopausal women has increased to 19%, in perimenopausal women it is now 44%, and in postmenopausal women between 65 and 74 years old it is now 75%. The prevalence of HTN in women over aged 75 years is now 85% which is higher than men of the same age. Interestingly,

Published online: 26 August 2019

Table 1 Prevalence of HTN based on two BP thresholds, NHANES 2010–2014 data set

	BP > 130/80 or self-reported antihypertensive medication		BP > 140/90 or self-reported antihypertensive medication	
	Men ($n = 4717$)	Women ($n = 4906$)	Men ($n = 4717$)	Women ($n = 4906$)
Overall, age-sex adjusted	48%	43%	31%	32%
Age group, y				
20–44	30%	19%	11%	10%
45–54	50%	44%	33%	27%
55–64	70%	63%	53%	52%
65–74	77%	75%	64%	63%
75+	79%	85%	71%	78%

[5] Whelton, R. Carey et al.; 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Journal of the American College of Cardiology vol 71, no 19, 2018, table 7

women between ages 45–54 years (perimenopausal years) seem to have the greatest increase in the prevalence of HTN with the new guidelines (from 27 to 44%). HTN was detected in this entire cohort of 4906 women by (1) office BP greater than 130/80 mmHg and (2) self-reported antihypertensive medication. Because HTN is more correctly diagnosed with an average of 3 readings after 5 min of quiet rest, these data may have over-estimated true HTN prevalence.

The prevalence of HTN is lower in young women than in men until about the fifth decade but increases later in life [3]. Furthermore, BP control is more difficult to achieve in older women [4]. The pathophysiology of this age-related decline in BP control among women remains unclear, though biological aging seems to be of significant importance. Despite these age- and sex-related differences in the prevalence of HTN, women are under-represented in many clinical trials. This is more significant for women in the premenopausal and perimenopausal (less than 60 years) age group.

Despite the increasing prevalence of HTN, the recommendations to treat HTN with medications according to the new AHA/ACA guidelines are recommended when:

1) Average SBP > 130 or average DBP > 80 with the clinical presence of CVD or ASCVD score > 10% OR
2) Average SBP > 140 or average DBP > 90 without CVD or with ASVD less than 10%

The ASCVD risk score has been validated in Caucasian and African-American women and men aged between 40 and 59 without co-existing comorbidities, and it does not account for the postmenopausal state, or other chronic conditions such as autoimmune disorders or chronic kidney diseases (CKD), which are more common in younger women and are associated with HTN.

Mortality Outcomes in Women with HTN Compared with Men

HTN is still the main risk factor for cardiovascular disease which is the leading cause of death. The 5th leading cause of death is stroke, and the 6th leading cause of death is now Alzheimer's disease [6]. The number of deaths in the USA in 2015 for men with heart disease totaled 335,002 compared with 298,840 for women. Deaths from cerebrovascular disease for men totaled 58,288 compared with 82,035 for women. Deaths from Alzheimer's disease in men totaled 33,690 compared with 76,871 for women [7]. It is interesting to note that deaths from cerebrovascular diseases and Alzheimer's disease are far greater in women compared with men despite the greater prevalence of controlled HTN in women compared with men and the overall greater prevalence of HTN in men compared with women. This difference may be due to multiple factors such as women living longer than men and postmenopausal women having more difficult to control HTN than men [5].

Hypertension in Premenopausal Women

Obesity-Related Hypertension

The prevalence of obesity is increasing in all age groups especially in women. Center for Disease Control (CDC) data [8•] indicate that the prevalence of grade II obesity (BMI 35.0–39.9) in premenopausal women aged 20–34 years old, between 2013 and 2016, was 10.7%, and that of aged between 35 and 44 years old was 11%. The prevalence of grade II obesity has doubled compared with the data 10 years prior. HTN is strongly associated with being overweight (OR 2.1) and obese (OR 5.2) in women, and weight loss has been

proven to reduce BP [9]. The accumulation of adipose tissue results in a cascade of events that cause obesity-related HTN. The exact mechanisms are unclear, but mainly involve the development of metabolic syndrome; greater insulin resistance leading to increased sympathetic activity, renal sodium retention, and endothelial dysfunction leading to vasoconstriction [10]. A recent population-based cross-sectional study from China suggested that adverse menstrual cycle characteristics (specifically longer menstrual cycle, irregular bleeding, and heavy bleeding) are associated with increased risk of stage II HTN in overweight and obese women compared with women of normal weight [11]. However, other menstrual abnormalities like dysmenorrhea and longer duration of bleeding were associated with stage II HTN independent of BMI [11]. Bariatric surgery has a sustained antihypertensive effect [12] and could be considered in obese women with resistant HTN.

Premenstrual Syndrome

Clinically significant premenstrual syndrome (PMS) affects up to 15% of women and substantially interferes with quality of life. Emerging data reveal that the renin-angiotensin-aldosterone pathway that contributes to HTN may also influence PMS by causing symptoms of premenstrual edema, abdominal bloating, and breast tenderness. Whether women with PMS have a higher risk of developing HTN was evaluated prospectively in the Nurses' Health Study II [13]. After adjustment for age, smoking, BMI, and other risk factors, women with PMS had a hazard ratio for HTN of 1.4 (95% CI 1.2, 1.6) compared with women without PMS. Among the small number of women who developed HTN prior to the age of 40 years, PMS was associated with a tripling of the risk (adjusted hazard ratio 1.4; 95% CI 1.5–6.5). This risk was not modified by the use of the oral contraceptive pill (OCP) or antidepressants but seemed to be attenuated among women with high intakes of riboflavin and thiamine (p value < 0.05). The study suggests PMS may be associated with future development of HTN and this risk may be modifiable. The study showed that women with moderate to severe PMS had a 40% higher risk of developing HTN in the following 20 years compared with women with fewer menstrual symptoms. Based on this data, regular screening for HTN is warranted in women with a history of moderate to severe PMS.

Hormonal Contraceptive Use

Use of estrogen-containing oral contraception is independently associated with an increased risk of ischemic stroke in women with certain medical conditions: (1) HTN, (2) smokers older than 35, (3) diabetes with complications, (4) coronary artery disease, (5) history of venous thromboembolism, and (6) migraine with aura. Therefore, evidence-based guidelines from the World Health Organization (WHO) and CDC recommend avoidance of the combined OCP (COC) in the presence of these medical conditions. Despite this recommendation, a recent study reported a high rate of COC use in women with a medical contraindication to estrogen use [14]. Small effects of HTN can have considerable overall consequences given the large numbers of women taking the OCP. A recent metanalysis containing 24 studies with 27,084 participants demonstrated that for every 5-year increment in oral contraceptive use, the risk of HTN increased by 13% [15]. These studies highlight the need for safe and effective forms of contraception among women at increased risk for cardiovascular events.

Increased BP associated with OCP use may lead to HTN possibly through activation of the renin-angiotensin-aldosterone system (RAAS) [16]. The "traditional" vasoconstrictor ACE/AngII/Ang type I receptor pathway appears to be balanced by a vasodepressor arm of the RAAS named the ACE 2/Ang [1–7]/MAS receptor. Blood pressure is stable during the menstrual cycle possibly due to the vasodepressor arm. A recent study [16] investigated levels of the vasoconstrictor RAAS enzymes and vasodilator ACE 2/Ang [1–7] in normally menstruating women compared with women taking the combined OCP. They found women taking OCPs have a higher Ang II/Ang [1–7] ratio associated with their BP elevation, although no causal relationship could be found. This suggests OCP-mediated HTN effects may be related to RAAS pathways. Giribela et al. [17] investigated the effect of a COC containing drospirenone (an anti-androgenic progestogen related to 17 alpha spironolactone that exhibits potent anti-mineralocorticoid activity) in 81 women without cardiovascular risk factors. They found that a COC containing low-dose ethinyl estradiol (20 mcg) and drosperenone did not negatively influence risk factors for cardiovascular disease. In view of the global prevalence of oral contraceptive use, careful BP monitoring of women who take oral contraceptives is important.

Polycystic Ovarian Syndrome

Polycystic ovarian syndrome (PCOS) is a common endocrinopathy affecting women of reproductive age, with a prevalence of 6–15% based on diagnostic criteria applied. Diagnosis is based on the presence of 2 of the 3 criteria: oligo/anovulation, hyperandrogenism, and polycystic ovaries on ultrasound. Not only do women with PCOS have increased risks for infertility, they also have increased risks for developing metabolic syndrome, non-alcoholic fatty liver disease, visceral obesity (a consequence of hyperandrogenemia), diabetes (due to increased insulin resistance), HTN, obstructive sleep apnea, depression, and anxiety at an earlier age than women without PCOS [18]. A cross-sectional analysis of data from the Australian Longitudinal Study on Women's Health found that the prevalence of HTN was higher in women reporting

PCOS compared with women not reporting PCOS (5.5% vs. 2%, $p < 0.001$) [19]. Although PCOS is an independent risk factor for CVD, evidence on cardiovascular outcomes in women with PCOS is limited. The most commonly prescribed treatments recommended for women with PCOS not seeking immediate fertility are the COC (for endometrial protection and hyperandrogenic symptoms) and the combination with metformin may provide an additional benefit on BMI and glucose tolerance [20]. The negative impact of cardiovascular risk factors of COCs in women with PCOS is currently unknown.

Hypertension in Pregnancy

Hypertensive disorders occur in 6–8% of pregnancies and are defined as follows [21]:

- Chronic hypertension in pregnancy is defined as a known history of HTN before pregnancy or a BP greater than 140/90 mmHg before 20 weeks of gestation. BP normally declines during the first trimester of pregnancy physiologically and then slowly rises. Thus, BPs in the normal range in the first and second trimesters and elevated BPs later in pregnancy may lead to the erroneous assumption of gestational HTN, rather than masked chronic HTN. Chronic HTN is then ultimately confirmed in the post-partum period due to the persistence of elevated BP. Women with chronic HTN seeking to get pregnant should achieve optimal control of their BP prior to conceiving to optimize a healthy pregnancy and healthy offspring. Avoiding ACE inhibitors and ARBs during pregnancy is imperative due to the risk of fetal toxicity.
- Gestational HTN is defined as newly diagnosed BP elevation in the second half of pregnancy and has an incidence of 6–7%.
- Preeclampsia is defined as two BP readings greater than 140/90 mmHg, measured on two separate occasions, after 20 weeks gestation in a previously normotensive pregnant woman, plus proteinuria > 300 mg/day. The diagnosis can also be made in the absence of proteinuria when there are clinical features of severity: thrombocytopenia (< 100,000/μl), serum creatinine > 1.1 mg/dl or doubling of creatinine in the absence of other kidney disease, liver transaminases two times the upper limit of normal, pulmonary edema, and cerebral or visual symptoms.

The placenta is considered to be the root cause of preeclampsia. With the delivery of the placenta, preeclampsia begins to resolve. Immunologically mediated insults to the trophoblasts within the placenta result in failed vascular remodeling of the maternal spiral arteries that perfuse the placenta. Reduced placental perfusion alters placental function which subsequently leads to maternal disease via oxidative stress, inflammation, impaired endothelial function, and angiogenesis. Serial BP measurements during pregnancy are the only reliable screening approach to detect preeclampsia. A meta-analysis of more than 30,000 women indicated that low-dose aspirin beginning in the late first trimester may reduce risk of preeclampsia and adverse perinatal outcomes among women with prior history of preeclampsia and preterm delivery (< 34 weeks) and those with preeclampsia in two or more pregnancies [21]. There is no evidence that low-salt diet, bed rest, and vitamin C or E are effective in preventing preeclampsia.

The goal of antihypertensive treatment during pregnancy is the prevention of severe HTN and prolonging gestation to facilitate fetal growth and development before delivery. Uncontrolled HTN increases the risk for maternal stroke; alternatively, tight BP control has been linked to placental hypoperfusion and fetal compromise. The American College of Obstetrics and Gynecology (ACOG) provides guidelines for the treatment of hypertension in pregnancy based on available evidence [21, 22•, 23••, 24]. Drugs to avoid in pregnancy include ACE inhibitors, angiotensin receptor blockers, direct renin inhibitors, and nitroprusside because of risk of fetal toxicity and malformations. Weight loss and extremely low-sodium diet < 100 meq/d are not recommended for managing chronic hypertension in pregnancy. Up to one-third of women with a hypertensive disorder during pregnancy may develop hypertension within a decade of an affected pregnancy, indicating that cardiovascular disease prevention in these women should include blood pressure monitoring initiated soon after pregnancy [25].

Renovascular Disease (Fibromuscular Dysplasia)

In 10% of patients with renovascular HTN in the Western population, narrowing of the lumen is due to fibromuscular dysplasia, and not atherosclerosis. Fibromuscular dysplasia (FMD) is generally thought of as a disease that occurs in young women less than 30 years of age. The First International Consensus Report on FMD [26••] estimates that 80–90% of patients with fibromuscular dysplasia (FMD) are women and the mean age at diagnosis is over 50 years. Therefore, it is suspected that age at a clinical diagnosis of FMD has been substantially delayed. In a recent study of 2420 patients with FMD, 86.2% were female [27]. FMD is a nonatherosclerotic arterial disease that is characterized by abnormal cellular proliferation and distorted architecture of the arterial wall. FMD manifests primarily as beaded (multifocal) or focal lesions in medium- or small-sized arteries, though the clinical phenotype of FMD has recently been expanded to include arterial dissection, aneurysm, and tortuosity [26••, 28].

Screening for renal fibromuscular dysplasia should be considered in the following settings:

- Hypertensive patients < 30 years of age, especially women. European guidelines recommend screening between 20 and 50 years of age.
- Severe or resistant HTN
- Unilateral small kidney without a causative urologic abnormality
- Abdominal bruit in the absence of atherosclerotic disease or risk factors
- Renal artery dissection/infarction
- Screening for cervical cephalic FMD is indicated in case of pulsatile tinnitus cervical or intracranial, carotid aneurysms and dissections, subarachnoid hemorrhage, or retinal cerebral ischemic events.

Diagnosis can be confirmed by computed tomographic angiography (CTA). Magnetic resonance angiography is an option if CTA is contraindicated. FMD has 2 types of angiographic appearance, which is how FMD is now classified: multifocal FMD with alternating areas of stenosis in dilation "string of beads" occurring in mid and distal portions of the artery and focal FMD (less common) which may occur in any part of the artery.

Treatment of patients with renal FMD may include endovascular therapy angioplasty (without stenting) or surgery or medical therapy with surveillance. The decision depends on the nature and location of vascular lesions, presence and severity of symptoms, prior vascular events related to FMD, and comorbid conditions. HTN cure after revascularization varies between 30 and 50% and is more favorable in younger patients with recent HTN. Medical therapy includes antihypertensive drugs and antiplatelet treatment after angioplasty. ACE inhibitors or ARBs have been recommended. The observation that FMD is predominantly a disease of women raises a theoretical concern for exogenous hormone therapy. However, no data exists to support safety or harm.

Autoimmune Disorders: Hypothyroidism, SLE, DM

Optimal BP control is favored in patients with chronic conditions such as type 1 diabetes, systemic lupus erythematosus (SLE), and hypothyroidism to reduce risk of CVD. Hypothyroidism which is 5–8 times more common in women than men is associated with increasing peripheral resistance which can lead to diastolic hypertension. SLE, also more common in women, especially of childbearing age, can lead to HTN secondary to renal manifestations of lupus.

The presence of diabetes eliminates any gender advantage that premenopausal women may have at risk for cardiovascular disease. Diabetes is characterized by systemic and vascular inflammation and endothelial dysfunction. These mechanisms may link type 1 diabetes to increased pulse pressure. Inflammatory markers such as cell adhesion molecules (CAMs) and C-reactive protein (CRP) have been proposed as possible determinants of arterial stiffness/pulse pressure and hypertension. A recent study [29] investigating inflammatory markers (CRP, soluble intracellular CAM [sICAM-1], soluble vascular CAM [sVCAM-1], and soluble E-selectin [sE-selectin]) in patients with type 1 diabetes over 20 years found that higher levels of sICAM and sVAM-1 at baseline and during follow-up predicted the prevalence and incidence of HTN. No differences in gender were noted. Increased expression of non-coding RNAs and micro-RNAs triggers pathways that mediate endothelial dysfunction and subsequent atherosclerosis and are also involved in the pathogenesis of HTN in diabetes [30].

The Effect of Hormonal Changes on Hypertension in Women

The menopause transition goes through several adaptations: normal ovarian activity, through a stage with prolonged follicular phase and no luteal activity. There is a stage with normal follicular activity and insufficient luteal phase, and finally the menopause with low estrogens and progesterone. During the transition, cycles become longer due to delayed ovulation or anovulatory cycles. As the process moves on, follicle-stimulating hormone (FSH) levels are higher and inhibins are lower than in the follicular phases [31]. Once menstruation has ceased, estradiol and progesterone concentrations are low. Hormone measurements other than FSH are of little diagnostic value. The transition can take up to 4 years. Hot flushes, night sweats, and vaginal dryness are common symptoms of the menopause from estrogen withdrawal.

Experimental studies in mice determined that estrogen receptors (ERs) are expressed in vascular endothelial and smooth muscle cells and estradiol can cause vasodilation by both ER-dependent and ER-independent mechanisms. Estradiol induces an increase in intracellular free calcium concentration in endothelial cells which could contribute to the increase in endothelial-derived nitric oxide (NO). Since inhibition of NO synthesis favors arterial HTN, it is conceivable that estradiol protects against HTN by increasing NO synthesis. Progestins inhibit the estradiol-induced synthesis of endothelium-derived NO and may contribute to the diminished vasodilator effects of estrogen observed in postmenopausal women receiving estradiol plus progestins. Additionally, estradiol activates adenyl cyclase activity and increases the synthesis of cyclic AMP, a vasodilator second messenger. Estradiol also reduces the synthesis of potent vasoconstrictors such as angiotensin II, endothelin-1, and catecholamines [32]. Experimental mouse models suggest that ovarian hormones may be responsible for lower BP in premenopausal women and for the increase in BP in postmenopausal women.

A recent review by Sylvester and Brooks [33] examined the role of T cells in immune-mediated HTN in animals and

discovered that premenopausal females were resistant to immune-mediated HTN. This protective effect of estrogen was lost in postmenopausal animals [33••].

Hypertension in Postmenopausal Women

Obesity-Related HTN

In addition to an increased prevalence of metabolic syndrome and obesity in women, sex-related differences in fat distribution have been implicated in ischemic heart disease (IHD) and HTN. Excess visceral fat and pericardial fat are independent risk factors for IHD. Women who have more subcutaneous fat are thought to be at lower risk than men who have more visceral fat. Abdominal visceral fat increases sympathetic nerve activity in muscles. Visceral fat also serves as an endocrine organ releasing adipocytokines such as leptin, resistin, TNF-alpha, and IL-6 [34]. These factors contribute to vascular inflammation and atherosclerosis. Adrenal androgen levels are 50% lower in postmenopausal women compared with premenopausal women. Ovarian androgens are about 30% lower in postmenopausal women. Therefore, the concept of relative hyperandrogenism in postmenopausal women has been challenged. When the protective effect of estrogen is reduced, androgen deficiency contributes to enlarge the size of visceral fat because of increased lipid accumulation in adipocytes, which in turn causes cellular death followed by macrophage activation, cytokine production, and endothelial dysfunction. The NF-kB signaling pathway may play an important role in enlarging visceral adipocytes. Androgen deficiency, by increasing visceral obesity and contributing to adipocyte and endothelial dysfunction, may be a major determinant of increased prevalence of HTN in men and postmenopausal women when protective effects of estrogen have ended [35].

Korean investigators have proposed that menopause is closely associated with an increased incidence of HTN, but the increase may not be attributable to menopause itself but to the increased prevalence of metabolic syndrome [36]. They retrospectively studied over 1500 women aged 42–53. Menopause was defined as 3 months or more without menstruation; and women were followed for 4 years. Among nonhypertensive subjects at baseline, the prevalence of HTN at 4-year follow-up was 9.4%, 19.7%, and 13.1% for nonmenopausal women, those who became postmenopausal during follow-up, and those who were menopause at baseline, respectively. Development of HTN was positively correlated with metabolic syndrome (hazard ratio 3.9, 95% CI 2.51–6.07) and increase in BMI (HR 1.09, 95% CI 1.03–1.16), while the association with menopause was not significant. However, this study had several limitations such as self-reported menopause rather than measuring FSH levels to determine the menopausal state, possible selection bias, and confounding variables of the perimenopausal state which can also lead to metabolic syndrome.

Interestingly, a large population-based study from the UK [37] involving 471,998 participants (56% women with mean age 56.2), who were followed for 7 years, revealed that the risk for MI increased with BMI in both men and women, with no sex difference in MI risk. However, other risk factors were more strongly associated with MI in women compared with men including type 1 DM (HR 8.2 in women, HR 2.8 in men), HTN on medications (HR 3.65 in women, HR 1.75 in men), and smoking (HR 3.46 in women, HR 2.23 in men). Despite these increased risk factors for women, the incidence of MI per 10,000 person years was 7.76 for women and 24.3 for men. This difference could be due to the age range of female patients which included pre, peri, and postmenopausal women.

Adverse Pregnancy Outcomes

A past history of preeclampsia quadruples the risk of developing HTN later in life and increases the risk of future heart disease. Gestational diabetes, preeclampsia, eclampsia, and preterm delivery all increase the risk of future heart disease. In a study from Norway, gestational HTN was found to be associated with increased risk of subsequent cardiovascular disease with a hazard ratio of 1.8 (95% CI 1.7–2.0), and the highest risk was observed when gestational hypertension was combined with small-for-gestational-age infants and/or preterm delivery (hazard ratio 2.6 [95% CI 2.3–3.0]) [42]. Recent studies also reveal that a history of preeclampsia increases the risk for stroke later in life, due to changes in microvascular remodeling and angiogenesis that occur during preeclampsia [38•]. These pregnancy conditions could contribute to the significantly greater risk of cerebrovascular disease in women compared with men.

Vascular Aging in Postmenopausal Women

Increases in aortic stiffness are associated with increased CV risk. Arterial compliance is the change in arterial blood volume attributed to a given change in pulsatile BP. Arterial compliance (AC) has been shown to be lower in women than in men. AC is associated with a greater burden of coronary artery plaque and calcification in older women, but not men [39] and may contribute to greater CV risk in postmenopausal women compared with men. Women, nevertheless, develop a higher degree of pulsatality than men with advancing age. This is likely due to smaller physical characteristics and is independent of the hormonal effects of menopause [40•].

Postmenopausal changes in estrogen/androgen ratio that induce a relative androgen excess have been proposed as important factors in the higher prevalence of HTN in older

women. However, observational studies examining the associations between sex hormone levels and CVD events in postmenopausal women have yielded conflicting results. Both low and high androgen levels have been linked to CVD in women. Estradiol levels have been inversely associated with CVD events or not at all. As a result, the relationship of sex hormones with CVD events in postmenopausal women is still unclear. A recent multi-center prospective study followed 2834 postmenopausal women for 12 years. Sex hormones were measured at baseline. Investigators reported that a higher testosterone/estradiol ratio was associated with an elevated risk for incident CVD, CHD, and HF events [41]. However, women who developed CV events were also more likely to have diabetes and hypertension.

Side Effects of Antihypertensive Medications in Women

Foy et al. [42] analyzed data in the Systolic Blood Pressure Intervention Trial (SPRINT) to investigate the effects of intensive treatment on cardiovascular and renal outcomes based on gender. There was no statistically significant difference in specific side effects in women compared with men in this study. Thomas et al. [43] further investigated the SPRINT data set to assess differences in sexual activity based on the class of drug. They found no statistical difference in sexual activity in women on medications versus those not on medications. In another report, increased sexual activity was reported in women on ACE inhibitors or ARBs compared with women not taking HTN medications. There was also a statistical difference in increased sexual *dysfunction* in women on HTN medications compared with women not taking medications, but there did not seem to be a difference between classes of drug. However, there is increasing evidence that women have more drug-related side effects like ACEi-induced cough, calcium channel blocker–related peripheral edema, or diuretic-associated hyponatremia or hypokalemia [44].

It is a common belief that antihypertensive medications are linked with an increased risk of falls and fractures. However, there are little data supporting this belief. The 2015 SPRINT trial [45••] found no increase in injurious falls with mean SBP 121 mmHg in the intensive treatment group compared with 136 mmHg in the standard treatment group. Other observational studies also reveal no increased risk of falls or fractures [46, 47]. A recent prospective study on 5971 women, mean age 79 years, reported that hypertensive women had a lower risk of falls compared with non-hypertensive women. Lower DBP was weakly associated with increased fall risk in women on antihypertensive treatment [48].

Outcomes of Women in Major Hypertension Clinical Trials

In general, there is no evidence that the BP threshold for initiating drug treatment, the treatment target, or the choice of initial antihypertensive medication for lowering BP differs for women versus men. The only exception is special recommendations for the management of HTN during pregnancy. Observational studies show that lower BP is associated with lower CVD risk in both men and women [49]. Major clinical trials of antihypertensive treatment have shown comparable benefit in both men and women [44, 45••, 50–56]. However, initial data are not presented by sex and women enrolled in these trials are older women. Therefore, it is difficult to draw gender-specific conclusions regarding the relative effectiveness of antihypertensive agents in controlling BP and impact on CV outcomes in women. The average age of participants was above 60 years, and women represented less than 50% of the participants (Table 2). However, subgroup analyses of some trials reported gender differences in both beneficial and adverse effects of treatment. The VALUE study [50] revealed that SBP and DBP reduction was more pronounced with the amlodipine-based regimen by 2.2/1.6 mmHg throughout the trial and 4.0/2.1 mmHg after the first month in women compared with men. The ALLHAT trial [51] revealed the mean reduction in systolic BP from baseline was 2–3 mmHg greater with chlorthalidone than that with lisinopril, and 0.4–1 mmHg greater with chlorthalidone than that with amlodipine in women compared with men. The mean attained SBP in women was 2–3 mmHg lower on chlorthalidone versus lisinopril and differed by < 1 mmHg on chlorthalidone versus amlodipine. These findings were associated with a lower primary endpoint of cardiac mortality and morbidity and a more pronounced reduction in stroke respectively overall.

In a large meta-analysis that included 31 randomized control trials (RCTs) with about 100,000 men and 90,000 women with HTN, there was no convincing evidence that different antihypertensive drug classes exerted sex-related differences in BP-lowering and CVD outcomes (stroke, coronary heart disease events, heart failure, and other CV death) [44]. The average proportion of women in all trials was 46.8% (range 10.9–67.2%). The mean age for women was 63.0 years and for men 61.7 years. Overall, there were 6586 stroke, 9400 coronary heart disease (CHD), and 3522 heart failure events included in the analyses. Forty-one percent of CHD and heart failure events and 32% of stroke events occurred in women. The CV mortality rate was 4.4% for men and 3.4% for women. There was no difference in the effects of BP-lowering treatment regimens between men and women for the outcome of major CV events except for stroke. Women derived borderline greater protection from regimens based on calcium antagonists than ACE inhibitors compared with males ($p = 0.05$). Treatment

Table 2 Women enrolled in major HTN trials

Trial	% female	Mean age (years old)	Treatment comparison	Primary endpoint	Result
SYS-EUR (52) 1997	66.8	70 (> 60)	Nitrendipine vs. placebo	Fatal and non-fatal stroke	Nitrendipine reduces the rate of CV complications among elderly with isolated systolic HTN.
HOPE [53] 2000	26.7	66 (> 55)	Ramipril vs. placebo	Composite of MI, stroke, or death from CV causes	Ramipril significantly reduces the rates of high-risk patients.
RENAAL [54](2001)	36.8	60 (31–70)	Losartan vs. placebo	Doubling of the baseline Cr, ESRD or death	Losartan conferred significant renal benefits in patients with DM2 and nephropathy.
AASK [55] 2002	39	54.6 (18–70)	3 × 2 factorial trial102–107 mmHg or < 92 of metoprolol or ramipril or amlodipine	Reduction in GFR by > 50% from baseline, ESRD, or death	Lower BP goal had no additional benefit of slowing progression of hypertensive nephrosclerosis.
ALLHAT [51] 2002	47	67	Compared lisinopril, doxazosin, and amlodipine with chlorthalidone	Fatal CHD or non-fatal MI	Neither lisinopril nor amlodipine is superior to chlorthalidone for initial treatment of HTN in either women or men.
VALUE [50] 2004	42.5	67 (> 50)	Valsartan vs. amlodipine	Composite of cardiac M&M	The main outcome of cardiac disease did not differ between the treatment groups.
ACCOMPLISH [56] 2008	39.5	68.4	Benazepril + amlodipine or benazepril + HCTZ	Composite of death from CV causes, non-fatal MI, non-fatal stroke, hospitalization for angina, resuscitation after SCD, and coronary revascularization	Benazepril-amlodipine combination was superior to the benazepril-HCTZ
SPRINT [45••] 2015	36	67.9	BP target of < 120 mmHg vs. < 140 mmHg	MI, other ACS, stroke, HF, or death from CV causes	Intensive BP target resulted in lower rates of fatal and non-fatal major CV events and death from any cause

ACS, acute coronary syndrome; *BP*, blood pressure; *CHD*, coronary heart disease; *Cr*, creatinine; *CV*, cardiovascular; *DM*, diabetes mellitus; *ESRD*, end-stage renal disease; *GFR*, glomerular filtration rate; *HCTZ*, hydrochlorothiazide; *HF*, heart failure; *HTN*: hypertension; *MI*, myocardial infarct; *M&M*, morbidity and mortality; *SCD*, sudden cardiac death

with beta-blockers or diuretics showed similar benefit to other drug classes for either gender. This meta-analysis provides evidence that a broad range of different BP-lowering regimens will provide comparable protection against CV events in both men and women. There is currently no evidence of an interaction between sex and the effectiveness of treatment. However, RCTs are underpowered to determine the value of intensive BP reduction in subgroups, including women, specifically in the case of the SPRINT.

Whether efficacy of treatments differs for essential HTN in premenopausal women compared with postmenopausal women remains unanswered. This limitation is due to the low statistical power of RCTs for subgroup analysis, differences in the population studied, methods of measuring BP, and most clinical trials have not conducted subgroup analysis in patients of different sex and age. Based on current data, HTN guidelines make no specific recommendations for different BP targets, or for management with particular classes of a drug on the basis of sex.

Conclusion

The prevalence of HTN in premenopausal and postmenopausal women is increasing. High-quality evidence to provide guidelines on optimal management is more limited in younger women. Assessing women's unique risk factors for CVD could improve medical decision-making. Future research in this area is essential and should focus on recruiting more young women in HTN clinical trials. In women, menopausal state and presence of chronic conditions should be included in the determination of CVD risk.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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