Review

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The Particularities of Arterial Hypertension in Female Sex. From Pathophysiology to Therapeutic Management

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Abstract: Arterial hypertension is the most important modifiable cardiovascular risk factor and a major cause of cardiovascular mortality worldwide. In daily clinical practice, the hypertensive patient is often treated in a uniform way, thus ignoring the significant effects of sex on several aspects of hypertension including its prevalence, pathophysiology, response to antihypertensive treatment, and outcomes. The substantial hormonal changes during a woman's life cycle along with the immune response and several cardiometabolic risk factors that frequently coexist are among the main pathophysiological mechanisms driving hypertension in women. Concurrently, women exhibit increased cardiovascular risk at lower blood pressure (BP) levels compared to age-matched men and present certain disparities in the incidence of cardiovascular events and subsequent hypertension-related cardiovascular prognosis. In addition, women respond differently to antihypertensive treatment, experiencing more drug-related side effects, and exhibit lower rates of BP control compared to men. Currently, international guidelines propose the same targets and the same therapeutic algorithms for the treatment of hypertension in both sexes, without taking into account the sex differences that exist. In this review we aim to describe the certain particularities of arterial hypertension in female sex, moving from pathophysiological aspects to clinical and therapeutical management.

Keywords: hypertension; women; hormone; cardiovascular risk; antihypertensive treatment

Introduction

Arterial hypertension is the most important modifiable risk factor for cardiovascular disease worldwide and a major cause of cardiovascular mortality and disability in both sexes [1]. Notably, in recent years, a growing amount of evidence has corroborated the impact of sex on several aspects of hypertension, including its pathophysiology, prevalence, cardiovascular prognosis, and antihypertensive treatment response. In fact, multiple sex-related differences exist, which commonly arise as early as the beginning of a woman's reproductive age [2–4].

The constant change in the hormonal milieu throughout a woman's cycle represents a major factor that drives the pathophysiology of hypertension in females. Typically, several conditions that arise from that hormonal imbalance confer a significantly higher risk of developing hypertension in women compared to men, the most impactful of them being pregnancy and menopause [5]. Furthermore, various other factors that are influenced by sex contribute to hypertension in females such as the upcoming role of immune system and certain cardiometabolic risk factors that cluster with higher frequency in women, including metabolic syndrome, obesity, insulin resistance, and chronic autoimmune inflammatory diseases [4].

In addition to the pronounced pathophysiological differences that exist between the two sexes, women respond differently to cardiovascular risk in association with blood pressure (BP). In this regard, it has been demonstrated that the risk of major cardiovascular events occurs at lower BP levels

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in females compared to males [6]. Moreover, the impact of hypertension on the incidence of cardiovascular events seems to differentiate according to sex, with women suffering more frequently from heart failure and myocardial infarction [7,8].

Finally, women differ in several aspects of the antihypertensive treatment compared to men. More specifically, it has been shown that women differ in terms of drug metabolism and are also more prone to experiencing certain drug-related side effects compared to men [9,10]. At the same time, women seem to present comparable BP reductions with men upon initiating all major antihypertensive drug classes, but noticeably they present poorer BP control [11,12].

Despite all the above fundamental differences, current international guidelines do not support a sex-specific approach of the hypertensive patient, including pre- and postmenopausal women. In this review, we aim to describe the particularities of arterial hypertension in female sex, from pathophysiological aspects to its therapeutic management.

Epidemiology of Hypertension in Women

In general, the prevalence of hypertension is higher in men <50 years old compared to age-matched premenopausal women. From puberty onwards, however, certain sex differences in the BP trajectories over the life course exist, with the mean BP being approximately 10 mmHg higher in male subjects by the age of 18 [13]. This pattern begins to reverse by the third decade of life where BP exhibits a steeper incline in women. Of note, the prevalence of hypertension in women increases significantly after the age of 60 [14]. As a result, the prevalence of hypertension reaches almost 68% in postmenopausal women aged 65-74 years, exceeding the prevalence of men of the same age [14,15]. Remarkably, the prevalence of hypertension in women aged ≥75 years reaches 78% [16].

Pathophysiology of Hypertension in Women

- The role of Sex Hormones

The pathophysiology of hypertension in women is elaborate and multifactorial, including a variety of sex-related factors [4,17]. Above all, female sex hormones and their age-related changes due to declining ovarian function confer significant susceptibility to hypertension in women compared to age-matched men. It has long been established that estrogens exert several potent vasoprotective effects. Firstly, estrogens cause vasodilation through multiple estrogen receptor-dependent and independent mechanisms [18–20]. The vasodilatory effects are mediated, at least in part, by the ability of estrogens to increase the activity of endothelial nitric oxide (NO) synthase, which leads to increased NO bioavailability [18,19]. As such, it has been shown that estradiol can increase endothelium-dependent vasodilation in the forearm of hypertensive postmenopausal women [21,22]. In addition, estradiol contributes to vasodilation though opening of the calcium-activated, large conductance K^+ channels, activation of adenylyl cyclase and production of cyclic AMP, and stimulation of adenosine and prostacyclin synthesis [23]. Secondly, estrogens engage in several key cellular mechanisms of vascular remodeling by decreasing the expression adhesion molecules, inhibiting neointima formation and the mitogenic effects of several factors generated at the sites of endothelial injury, thus profoundly intercepting the vascular response to injury [24]. Thirdly, estrogens help maintain and regulate autonomic balance by decreasing basal sympathetic nervous system activity [25,26]. In this context, studies in estrogen deficient postmenopausal women have shown changes in autonomic tone, including decreased baroreflex sensitivity and vagal tone, and a preponderance of the sympathetic tone [27]. Fourthly, and most importantly, it has been demonstrated that estrogens have a substantial impact on renin-angiotensin-aldosterone system (RAAS), which is a key regulatory mechanism of hypertension. In this aspect, estradiol has been shown to down-regulate the expression of angiotensin converting enzyme (ACE) and decrease renin and angiotensin II (AngII) formation [18,28,29]. At the same time, increased plasma renin activity has been documented in estrogen-deficient postmenopausal women [30]. Furthermore, estradiol down-

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regulates the expression of AngII type 1 receptors in smooth muscle cells and blocks the AngII-mediated synthesis of endothelin-1 [31,32]. Overall, estrogen depletion results in enhanced AngII activity which causes impaired renal sodium handling and oxidative stress which contribute to high BP [33,34]. Consistent with the above, it has been demonstrated that salt-loading induces a decrease in renal plasma flow in postmenopausal women and surgical menopause has been linked to salt-sensitive hypertension [35,36].

Although estrogens appear to be one of the most important hormonal factors involved in the pathophysiology of hypertension during a woman's lifetime, the role of progestins and androgens should also be taken into account. Experimental studies have shown that progesterone, the natural progestin, prevents noradrenaline-mediated vasoconstriction by acting directly on smooth muscle cells, thereby exerting an endothelium-independent vasodilatory effect [37]. Additionally, clinical data have shown that administration of progesterone in combination with estrogens produces a greater reduction in systolic BP (SBP) than estrogens alone in postmenopausal women [38]. On the other hand, the role of androgens in the pathophysiology of hypertension in women remains controversial and under investigated. Experimental data has shown that androgens exert a rather pro-hypertensive effect by enhancing adrenergic vasoconstriction and the production of vasoconstrictor metabolites, and also by stimulating RAAS and endothelin activity [39–41]. From a clinical point of view, women who have hyperandrogenemia, such as those with polycystic ovary syndrome (PCOS) present hypertension, oxidative stress and an increased inflammatory milieu [42].

- The Role of the Immune System

Over the last years a growing amount of data has highlighted the role of immunity in the pathophysiology of hypertension. However, much remains unknown regarding the effect of sex on the immune-driven environment of hypertension and the development of vascular damage. Contemporary studies in experimental hypertension have confirmed the presence of distinct sex differences considering the adaptive immune response, mainly within the T-cell niche [43–46]. In this context, it has been shown that premenopausal female animals have a predilection for anti-inflammatory T regulatory cells and production of anti-inflammatory cytokines, such as interleukin-10, which confer a largely protective effect from hypertension. At the same time menopause abrogates this protective effect, which may be due to changes in the population of anti-inflammatory T regulatory cells [44,47,48]. On the other hand, scarce experimental data regarding sex differences in innate immune cells exists. Only recently, the sex differences in response to Toll-like receptor (TLR) 3,4,9 signaling have emerged [49,50].

- The role of cardiometabolic and other risk Factors

Various cardiometabolic risk factors that cluster throughout a woman’s life cycle also contribute to the pathophysiology of hypertension. Women, especially postmenopausal, are more prone to develop metabolic syndrome and obesity [51,52]. Furthermore, changes in weight and body fat distribution are linked to insulin resistance, diabetes mellitus (DM), fatty liver disease, and hypertension [53]. In addition, women compared to men show a higher prevalence of certain diseases that are closely related to the development of hypertension and cardiovascular disease, such as chronic inflammatory diseases (rheumatoid arthritis, systemic lupus erythematosus) and migraine [54,55].

Hormonal Related Conditions Associated with Hypertension. From Physiology to Clinical Disease

Considering the impact of sex hormones on vascular homeostasis, many physiological and pathological conditions affecting the menstrual cycle during a woman's lifetime have been associated with hypertension, usually in a bi-directional relationship [13].

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1. Menarche

Menarche or first menstruation represents the start of the menstrual life cycle of a woman, which typically occurs between the ages of 10 and 16, and signals the advent of puberty along with the onset of the reproductive capacity [56]. Of note, menarche age has been correlated with increased cardiovascular risk later in adulthood, such as incident cardiovascular disease (CVD), DM type II, obesity, and, importantly, hypertension [57,58]. More specifically, the large UK Biobank Study including more than 250,000 female participants showed that early menarche (8-11 years old) was associated to an almost 37% higher risk of hypertension [59]. Interestingly, some studies have demonstrated a rather U-shaped association between age at menarche and hypertension. In this context, the environmental and lifestyle factors in metabolic health throughout life-course trajectories (ELEFANT) study including 60,135 healthy young women showed that age of menarche ≤12 years followed by ≥16 years present the highest risk of hypertension (OR=1.46 vs OR=1.36) [60]. Similarly, a population-based cohort study including 1.2 million women with an average follow-up of 11.6 years showed a significant increased risk of hypertension when onset of menarche was ≤10 and ≥17 years, compared with menarche at 13 years of age [61].

2. Menstrual Disorders

Disorders of the menstrual cycle consisting of premenstrual syndrome, irregular, painful (dysmenorrhoea), or heavy (menorrhagia) menstruations have been also associated with hypertension. In a retrospective study of 704,743 female individuals aged 18-40 years who were followed up for 26 years, women with irregular menstrual cycles presented elevated risk of hypertension compared to those with regular menses [62]. Moreover, prospective results have shown that women who experience heavy periods, usually in the context of underlying fibroids, are at increased risk of incident chronic hypertension (RR 1.53, 1.13-2.09) [63]. Above all, premenstrual syndrome is a very disruptive menstrual irregularity consisting of emotional and physical symptoms that frequently occur shortly before the start of each menstruation [64]. Emerging data has provided support for the existence of certain abnormalities in the vascular physiology of women with premenstrual syndrome that could predispose to hypertension [65]. Relative to this, it has been shown that aortic stiffness, as indicated by carotid-to-femoral pulse wave velocity (PWV) and pulse pressure (PP), is increased in women with premenstrual syndrome during different phases of the menstrual cycle and is also linked to elevations in peripheral and central SBP and mean BP [66]. From a more clinical perspective, a prospective study by Bertone-Johnson E. et al. found that women who meet the criteria for moderate to severe premenstrual syndrome had 40% higher risk of developing hypertension over a follow up period of 20 years compared with women free of symptoms. Notably, the observed risk did not vary by body mass index (BMI) and concurrent medications and was highest for women younger than 40 years, who presented a 3-fold higher risk of developing hypertension [67].

3. Pregnancy

Many physiological changes that occur during pregnancy in order to meet the increased maternal and fetal demands are held responsible for the development of gestational hypertension, that is hypertension occurring after the 20th week of gestation. Typically, pregnancy is associated with changes in cardiac output and kidney function, including increased activation of the RAAS and subsequent salt and water retention. Additionally, progressive insulin resistance and weight gain also result in enhanced sympathetic activity, endothelial dysfunction, and increased vascular resistance, all factors predisposing to hypertension [5,68,69]. Although gestational hypertension usually resolves within 6 weeks postpartum, it can lead to significant perinatal and maternal complications during pregnancy and, significantly, it may also adversely impact maternal cardiovascular health later in life. According to this, it is now well documented that women with a history of gestational hypertension present an increased risk of developing hypertension late in life,

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which may be evident even from the first years following birth [70–73]. As such, a recent study showed that women with gestational hypertension in first pregnancy exhibited an almost 3-fold higher risk of developing hypertension compared to women with normotensive pregnancies, that was evident shortly after pregnancy. In particular, the risk was highest within the first five years post-partum, reaching a 4.3-fold increased rate [74]. Another cohort of more than one million women showed an exceptionally high rate of incident hypertension (up to 25-fold) within one-year post-partum in women with gestational hypertension compared to women with a normotensive pregnancy. Interestingly, over a period of 20 years post-partum, women with gestational hypertension consistently experienced a 2-fold risk of hypertension compared to women with normotensive pregnancies [75]. Moreover, another study adjusting for a wide range of prepregnancy risk factors found a persistent 7-fold excess risk of hypertension within 10 years of delivery in women with history of gestational hypertension [76].

Finally, pre-eclampsia, which is the most severe phenotype among the hypertensive disorders of pregnancy, is equally linked to a substantial cardiovascular risk including the risk of development of hypertension. A wealth of studies has confirmed that history of pre-eclampsia during pregnancy is associated with a 2-fold to 7-fold higher risk of developing hypertension over 10 years post-partum [72,75–79].

4. Menopause

Menopause marks a major hormonal change during a woman's life. It is characterized by a dramatic decrease in estrogen levels which has a significant impact on several physiologic pathways, ultimately leading to endothelial dysfunction, oxidative stress, impaired sodium excretion, and increased arterial stiffness [80–82]. In addition, estrogen's decline in women is associated with decreased baroreflex sensitivity and vagal stimulation, a sharper increase in autonomic sympathetic nervous activity and central sympathetic outflow and a stronger vasoconstrictor response to noradrenaline [83,84]. Typically, the prevalence of hypertension is higher in postmenopausal women compared to men and twice as high compared to premenopausal females [54]. Although menopause has been largely considered a significant contributing mechanism to the development of postmenopausal hypertension, it is nevertheless controversial whether endogenous estrogen depletion accounts, independently, for the higher prevalence of hypertension in postmenopausal women. In fact, several data from cross-sectional studies have demonstrated an increase [85], a neutral effect [86] or even a decrease in BP values [87] with the onset of menopause. Furthermore, some prospective data has shown that menopause is not associated with BP increase [88], while other prospective studies have demonstrated that onset of menopause may independently increase BP, primarily SBP [89]. This is due to the fact that aging, a major risk factor of hypertension, as well as increasing BMI coincide with the postmenopausal status and thus, take their share as crucial determinants of postmenopausal hypertension, confounding the observed results [81,90,91]. Moreover, several other conflicting results have been found due to study differences, including the sample size, age ranges, duration of postmenopausal status, self-reported menopause based on questionnaires and, finally, the inclusion of women with surgical menopause.

5. PCOS

PCOS is the most common endocrine disease affecting up to 1 in 5 women of reproductive age. It is a rather heterogenous condition whose main clinical hallmarks are polycystic ovaries, irregular ovulation, androgen excess and insulin resistance feature as [92,93]. In addition, many adverse cardiometabolic conditions cluster with increased prevalence in PCOS, including obesity, hyperglycemia, dyslipidemia, metabolic-associated fatty liver disease, and hypertension [93]. Several mechanisms have been postulated to explain the association between hypertension and PCOS including activation of the RAAS and sympathetic nervous system, hyperinsulinemia, hyperandrogenism, and endothelial dysfunction [92,94].

 doi:10.20944/preprints202502.1429.v1

So far, several studies have shown increased prevalence of hypertension in women with PCOS compared to the general population [92,95]. However, they are complicated by a failure to adjust for the presence of obesity, which is highly prevalent in women with PCOS and, at the same time, a well-established risk factor of hypertension. On the other hand, a handful of studies have included BMI in their analyses and, even though results are conflicting, a particular association between PCOS and risk of hypertension cannot be precluded [92,96–100].

Towards this direction, the Australian Longitudinal Study on Women's Health including 8,223 women of child-bearing potential (mean age 25 years) showed that PCOS was independently associated with 37% greater risk of incident hypertension over a follow up period of 15 years. Following stratification by BMI, the incidence of hypertension was higher in women across all weight categories, the rate being nearly 4-fold higher in the obese (BMI ≥30 kg/m^2) compared to the age-matched lean women with PCOS [100]. In close association, another population-based cohort found that young women with PCOS had a 62% greater risk of incident hypertension compared with controls. Notably, the above risk was increased up to 9-fold in those women suffering from comorbidities including DM and hyperlipidemia [96]. Additionally, a recent meta-analysis confirmed a greater risk of hypertension of up to 1.7-fold in women with PCOS compared to age-matched controls. However, that risk was observed only in women of reproductive age and not in menopausal/aging patients who had suffered from PCOS during their reproductive years, thus downgrading the importance of PCOS as a predisposing risk factor for hypertension later in life [97].

6. Endometriosis

Endometriosis, which affects up to 10% of women of childbearing potential, is a condition characterized by the presence of endometrium-like cells growing outside the uterus that often results in painful menstruation, chronic pelvic pain, and infertility. Ultimately, endometriosis has been linked to an elevated risk of developing hypertension, probably through systemic inflammatory-mediated pathways even though other mechanisms such as chronic nonsteroid anti-inflammatory drugs (NSAIDs) use may be involved [101]. A large prospective study including 116,430 females aged 25–42 years that were followed up for 20 years showed that endometriosis is associated with a 14% higher risk of developing hypertension compared to controls. Of note, the risk was highest among women younger than 40 years and decreased with increasing age [102]. In addition, it has been found that endometriosis is an independent risk factor of the occurrence of gestational hypertension and preeclampsia associated with an almost 2-fold higher risk compared to women without endometriosis [103–105].

7. Fibroids

Uterine fibroids are reported in up to 30% of women of reproductive age and even though they are frequently overlooked, an increasing amount of evidence has linked fibroids to a notably worse cardiovascular risk profile, including hypertension [106]. Whether this association is attributed to a common pathophysiology involving enhanced smooth muscle proliferation or to urinary tract obstruction by the expanding uterine mass, remains to be elucidated. Either way, a cross-sectional study including 5,552 women aged 20-54 years showed a significantly higher prevalence of hypertension in women with fibroids compared to controls (33.4% vs. 15.3%, respectively), with the younger ones (aged ≤35 years) being most prone to develop hypertension [107]. Moreover, a higher prevalence of asymptomatic hypertension-mediated organ damage (PP, aortic PWV, electrocardiographic left ventricular hypertrophy, ankle-brachial index, proteinuria) has been reported in women with fibroids, particularly those aged <50 years, compared to controls (66.7% vs 42.9%, respectively) [108]. Moreover, presence of fibroids in pregnant women has been associated with a significant risk of developing hypertensive disorders in pregnancy [109].

Hypertension-Related Cardiovascular Prognosis in Women

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It has been consistently demonstrated that the risk of CVD is continuously increased from the SBP level of 120 mmHg and upwards. However, studies have advocated that the association of SBP with incident CVD may be influenced by sex. As such, in women, it has been shown that the risk of major cardiovascular events such as stroke, myocardial infarction and heart failure occurs at lower BP levels, including SBP values approximately 10 mmHg lower than the corresponding values in men [6,110]. Indeed, a pooled analysis of 27,542 participants from established community-based cohort studies (Framingham Heart Study, Multi-Ethnic Study of Atherosclerosis, Atherosclerosis Risk in Communities Study, Coronary Artery Risk Development in Young Adults Study) showed that SBP levels of 100-109 mmHg relative to levels of SBP <100 mmHg were consistently associated with incident CVD in women but not men. In addition, the magnitude of risk seen in men at higher SBP thresholds was comparable to that seen in women at lower SBP thresholds [6].

Of great importance, not only cardiovascular events present at lower BP thresholds in women but also the impact of hypertension on the incidence of cardiovascular events seems to differentiate according to sex. Indeed, data from the prospective REGARDS study in 26,461 individuals aged ≥45 years showed that the association between increasing hypertension severity and incident ischemic stroke was almost twice as large in women compared with men, even after adjustment for other conventional stroke risk factors. In fact, when SBP was treated as a continuous variable, women had higher risk of stroke compared to men per each 10 mmHg increase in SBP [111]. Furthermore, it has been speculated that the association of hypertension with cognitive decline is stronger in women compared to men. In support of this, a population-based cohort including young, middle-aged and older adults spanning 20-76 years showed that incident midlife hypertension is associated with greater memory decline in late-life in women compared to men [112]. Similarly, another population-based cohort demonstrated that hypertension during mid-adulthood (overall mean age 44 years) was associated with 65% higher risk of dementia in women but not men. Interestingly, within the female group, hypertensive women with onset of hypertension during mid-adulthood presented 73% higher dementia risk compared to those who remained normotensive throughout their whole age span. On the contrary, there was no evidence that hypertension or changes in hypertension increased dementia risk among men [113].

Concerning cardiovascular system, women compared to men typically present a greater prevalence of left ventricular hypertrophy, diastolic dysfunction and heart failure as a consequence of the more frequently observed isolated systolic hypertension phenotype, with women outweighing men by around 2:1 in terms of the prevalence of heart failure with preserved ejection fraction [8,114,115]. In fact, hypertension portends a 3-fold higher risk of heart failure in women compared to a 2-fold risk in men [116,117].

Moreover, a close association between hypertension and myocardial infarction in women exists. In the UK Biobank study which included 471,998 people (56% female) aged 40 - 69 years that were free of CVD at baseline, the relative risk of myocardial infarction in hypertensive women was 83% higher compared to men and consistently higher across different hypertension stages, even though the absolute risk and incidence of myocardial infarction were clearly higher in males [7]. Noteworthy, the risk in hypertensive women remained more elevated even in those receiving antihypertensive treatment as compared to treated hypertensive men. In keeping with these findings, another study including 1,25 million patients and 11,029 myocardial infarction events demonstrated a higher relative risk of myocardial infarction with increasing SBP in women compared to men [118]. Of great interest, the relationship between hypertension and cardiovascular events in females has been observed across different hypertension phenotypes. In a sex-stratified analysis in younger women aged 20–39 years with a median follow-up of 13.2 years, the hazard ratios for CVD events (myocardial infarction, stroke, heart failure, and cardiovascular disease-related death) associated with elevated BP, including isolated systolic, isolated diastolic and systolic-diastolic hypertension were higher in women compared to men, with the women-to-men relative risk ratio ranging from 1.14 to 1.46 [119]. Finally, a meta-analysis including 9,357 subjects from 11 populations of whom 47% were women showed a steeper increase in the risk of cardiovascular events with increasing levels of 24h and

 doi:10.20944/preprints202502.1429.v1

nighttime SBP in women. Consequently, for each 1-SD decrease in 24-hour SBP (13.4 mmHg) and nighttime SBP (14.1 mmHg), the proportion of potentially preventable events was higher in women than in men regarding all cardiovascular events (35.9% vs 24.2% for 24h SBP, 35.1% vs 19.4% for nighttime SBP), therefore unveiling an extensive potential for cardiovascular prevention by lowering BP in women [120].

Antihypertensive Treatment in Women

Even though pronounced biological differences are implicated in the pathogenesis of hypertension in women, there is still no clear sex-specific treatment approach of hypertension. As a matter of fact, both the latest European Society of Hypertension and European Society of Cardiology guidelines suggest the same BP goals and the same therapeutic algorithms for the management of hypertension in males and females [15,121]. More importantly, up to now, limited data and several areas of uncertainty exist regarding the BP thresholds for initiation of antihypertensive treatment in women, the therapeutic goals, the choice of antihypertensive drugs and their effectiveness and finally, the drug-related adverse effects. This is partly related to the fact that women, including those belonging to special categories (e.g. pregnant women, pre- and postmenopausal women) are largely underrepresented in large clinical studies, including approximately 30% of the participants, and their cardiovascular risk is often underestimated [122]. Moreover, no randomized controlled trials with the necessary power to investigate BP outcomes and mortality exclusively in hypertensive women exist. Another drawback of several studies is the lack of performance of risk stratification by sex. On the other hand, wherever stratification by sex was implemented, no sex differences were found. Notably, none of those studies were designed or powered to specifically address the efficacy of antihypertensive treatment in women and men. A representative example is the SPRINT study, which investigated the benefit of intensive SBP reduction to levels <120 mmHg versus the conventional SBP goal <140 mmHg in elderly men and women ≥75 years of age. Women's participation rate was only 36%, their number of cardiovascular events was lower compared to those in the general population, while the study was terminated early because of an overall benefit of the intensive treatment in the male arm [123]. Similarly, negative results regarding the benefit of intensive antihypertensive treatment in women were demonstrated by two subsequent post hoc analyses [124,125]. Finally, it should be mentioned that the average age of women included in most large studies investigating the BP effect on cardiovascular events was approximately 50 years, which does not coincide with the highest prevalence of hypertension, hence excluding those postmenopausal women with the greatest cardiovascular risk [45].

Concerning the choice of antihypertensive treatment, it should be noted that women differ in terms of absorption, metabolism and elimination of drugs compared to men. The above differences have been generally attributed to the effects of sex hormones on certain factors, such as particular drug transporters (e.g. P-glycoprotein), the volume of distribution, cytochrome P450 activity and renal clearance [9,55,126]. At the same time, in daily clinical practice, some certain patterns of antihypertensive drug prescription in women exist. Relative to this, a large meta-analysis of 46 population-based studies, including 164,858 women and 123,143 men aged 20–59 years, showed that hypertensive women were more likely to be treated with diuretics, while men with ACE inhibitors (ACEIs), b-blockers and calcium channel blockers (CCBs). In the same line, another meta-analysis of 43 studies including 2,264,600 participants showed that women were 30% more likely to be treated with diuretics and 15% less likely to be treated with ACEIs [127]. The above differences were largely driven by the presence of side effects, since it has been shown that women are more prone to experiencing certain drug-related side effects compared to men [128]. More specifically, it has been shown that women experience more often cough as a side effect of the treatment with ACEIs [129], suffer more frequently from lower limb edema during treatment with CCBs [130] and present more frequently electrolyte disturbances (hyponatremia, hypokalemia) with diuretics [10]. Finally, another sex related factor that has an impact on pharmacological treatment is the higher prevalence of certain comorbidities in women, such as autoimmune diseases. Women are more susceptible to chronic, and

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inflammatory pain, and more often consume steroids and NSAIDs, which may counteract the efficacy of antihypertensive treatment due to potential side-effects and a higher risk of cardiovascular complications [131,132].

Paradoxically, even though certain disparities in the antihypertensive treatment of men and women are observed, their clinical significance remains unknown. Of particular importance, current evidence broadly demonstrates comparable BP reductions with all major antihypertensive drug classes in both sexes while no differences in the dosing regimens of antihypertensive drugs between the two sexes are proposed [11]. In addition to this, it is noteworthy that even upon starting antihypertensive therapy, women finally achieve lower rates of BP control [12,133]. This phenomenon exacerbates with increasing age and culminates during menopause [134]. In the largest and most well-characterized cohort of postmenopausal women in the US which included nearly 100,000 postmenopausal women of various ethnic groups, aged 50–79 years, it was found that only 36.1% of hypertensive women had their BP controlled. In fact, BP control demonstrated a progressive decline with increasing age, with the lowest rate (29.3%) observed in the older postmenopausal hypertensive women (70–79 years) [135]. Whether this result is solely due to physiological aging and the hormonal effects, or other factors are implicated, including among others therapeutic inertia, poor adherence, and side effects, remains to be further elucidated.

The Role of Hormone Replacement Therapy in the Treatment of Hypertension

While estrogen depletion is a crucial mechanism involved in the pathogenesis of hypertension in women, on the other hand, the antihypertensive effect of hormone replacement therapy (HRT) currently remains uncertain. Overall, the available results are inconsistent since some studies have shown HRT reduces BP [136,137], while others have shown a neutral [138,139] or even a BP increasing effect [140,141]. Similarly, the optimal formulation (estrogen alone or in combination with progestin), the most proper route of administration as long as the duration of administration, are all matters of concern that need to be further elucidated relative to their impact on BP and cardiovascular disease [142]. Of note, oral formulations of estrogen therapy (alone or in combination with progestins) appear to be associated with greater hypertension risk compared to other routes of administration. This association has been attributed to first-pass hepatic metabolism of oral estrogens, which has been hypothesized to result in increased RAAS activation as evidenced by enhanced hepatic angiotensinogen production and greater downstream AngII levels [143].

Considering the above, a French prospective population-based study of 49,905 normotensive menopausal women under HRT reported that oral estrogen use, particularly in combination with a progestogen, was associated with a significantly increased risk of hypertension compared to a transdermal formulation [144]. Similarly, a 18% higher risk of hypertension was confirmed in older postmenopausal women receiving conjugated equine estrogens alone or in combination with progestins [140]. Furthermore, a more recent population-based study including 112,240 postmenopausal women who used an estrogen-only form of HRT showed that women who used the oral estrogen form had 14% higher risk of developing hypertension compared to those using estrogen topically, and 19% greater risk compared to those using vaginal creams or suppositories. At the same time, duration of estrogen exposure and cumulative estrogen dose were positively associated with the risk of hypertension [145]. On the other hand, the Women's Health Initiative Observational Study including 19,986 normotensive menopausal participants demonstrated that transdermal estradiol was associated with lower odds for newly treated hypertension compared with conjugated estrogens with or without a progestin [146].

Conclusions

Hypertension is undoubtedly a major cardiovascular risk factor in women. However, there are still many controversies and unsolved questions regarding the mechanisms that lie behind its pathophysiology and impact on women. The several sex-specific factors, including the substantial

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hormonal changes during a woman's cycle, as well as the plethora of other conditions that cluster with greater prevalence in females, render women more vulnerable to adverse cardiovascular events and at lower BP levels compared to age-matched men. Also, women present certain differences considering the choice of antihypertensive agent and the response to antihypertensive treatment, with subsequent poorer BP control. Despite emerging evidence, there is still a gap regarding the proper management and treatment of female hypertensive patients which is largely reflected in the uniform approach of hypertensive women and men in all current guidelines. More studies are imperative, aimed at a deeper understanding of the pathophysiology and therapeutic approach of hypertension in women.

Future Directions

Given the several disparities that exist considering antihypertensive treatment and cardiovascular prognosis in hypertensive women including pre- and postmenopausal individuals, future research should focus on the deeper understanding of the sex-specific factors that drive the pathophysiology of hypertension in women compared to men. Optimal targeting of the several risk factors clustering in women is another compelling task. In addition, it is of utmost importance to increase participation of women in large clinical trials with the aim to explore sex-specific threshold and target BP values and improve antihypertensive regimes in order to ameliorate cardiovascular prognosis in women.

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Abbreviations

The following abbreviations are used in this manuscript:

ACEIs	angiotensin converting enzyme inhibitors
AngII	angiotensin II
ACE	angiotensin converting enzyme
BMI	body mass index
BP	blood pressure
CCBs	calcium channel blockers
CVD	cardiovascular disease
DM	diabetes mellitus
HRT	hormone replacement therapy
NSAIDs	nonsteroid anti-inflammatory drugs
NO	nitric oxide
PCOS	polycystic ovary syndrome

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PP	pulse pressure
PWV	pulse wave velocity
RAAS	renin angiotensin aldosterone system
SBP	systolic blood pressure
TLR	toll-like receptor

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