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Hypertension Across a Woman's Life Cycle

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Abstract

Purpose of Review—We reviewed the effects of hypertension and the means to prevent and treat it across the spectrum of a woman's lifespan and identified gaps in sex-specific mechanisms contributing to hypertension in women that need to be addressed.

Recent Findings—Hypertension continues to be an important public health problem for women across all life stages from adolescence through pregnancy, menopause, and older age. There remain racial, ethnic, and socioeconomic differences in hypertension rates not only overall but also between the sexes. Blood pressure cutoffs during pregnancy have not been updated to reflect the 2017 ACC/AHA changes due to a lack of data. Additionally, the mechanisms behind hypertension development in menopause, including sex hormones and genetic factors, are not well understood.

Summary—In the setting of increasing inactivity and obesity, along with an aging population, hypertension rates are increasing in women. Screening and management of hypertension throughout a women's lifespan are necessary to reduce the burden of cardiovascular disease, and further research to understand sex-specific hypertension mechanisms is needed.

Keywords

Hypertension; Women; Sex differences; Life cycle

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Introduction

Hypertension is the most common modifiable risk factor for cardiovascular disease (CVD) and is highly prevalent worldwide, affecting 1.3 billion people [1, 2]. In the USA, 116 million adults (47.5%) have hypertension, defined as having a systolic blood pressure (SBP) > 130 mmHg or diastolic BP (DBP) > 80 mmHg or taking any antihypertensive medication [3]. Furthermore, hypertension prevalence, control rates, and subsequent outcomes are not universal and differ based on several factors, such as social inequities, environmental factors, historical factors, access to healthcare, and sex [4–6]. Hypertension is less prevalent in women than in men until 60 years of age, after which this pattern is reversed [7–9]. The pattern could be related to the longer life expectancy among women, postmenopausal hypertension, and lower response rate to treatment [10, 11]. Understanding sex differences in BP across the life course is important for the future diagnosis and treatment of hypertension. This is especially true, as effectively treating hypertension in women was found to have the greatest effect on CVD mortality and saved lives of any present preventive strategy, as evidenced by a cross-sectional study of the National Health and Nutrition Examination Survey (NHANES) data [12].

This review focuses on providing the reader with a look at the effects of hypertension and the means to prevent and treat it across the spectrum of a woman's life course, starting with adolescence and going through pregnancy, menopause, and ending with a look at its role in the elderly (Fig. 1). Attention will also be given to the pathophysiology and biological underpinnings of hypertension in women. The goal is to identify the most up-to-date, evidence-based recommendations for treating hypertension across these periods. This review will also elucidate areas of ongoing research and questions that have yet to be answered in the fight against hypertension in women. For the purposes of this review, we will focus on the effects of hypertension in individuals born biologically female. There are limitations in epidemiological data where the differences between sex and gender are not identified. The word "women" will be used, as epidemiological studies generally include individuals who self-identify as women.

Hypertension in Female Children

BP trends in childhood can lead to an increased risk of hypertension and CVD [13, 14]. The Centers for Disease Control and Prevention (CDC), using the updated 2017 American Academy of Pediatrics (AAP) clinical practice guideline, found that roughly 1.3 million or approximately 1 in 25 children between the ages of 10 and 19 have high BP [15, 16]. Obesity, which is known to be a significant risk factor for developing high BP, was a major driving force in the increasing prevalence of high BP in children and adolescents [17].

Risk factor modification is key to preventing the development of high BP in children and adolescents and thus preventing further CVD in adulthood. In addition to obesity, abdominal circumference has also been associated with an increased incidence of high BP in this demographic [18]. Disrupted sleep, especially obstructive sleep apnea and primary snoring disorders, has also been associated with increased hypertension rates [19]. Moreover, a family history of hypertension is a strong predictor of the development of hypertension in

children [20–22]. Studies have shown that Hispanic and Black children have the highest overall prevalence of hypertension at 3.1% and 2.7%, respectively [23]. However, race and ethnicity are social, cultural, and political constructs and efforts to reduce disparities should also target the underlying structural differences between groups [24].

Hypertension in Teenage and Young Adult Women

Unlike in adults where 90 to 95% of hypertension cases are deemed primary or essential, hypertension in young women is often due to a secondary cause [25, 26]. Most secondary causes are related to intrinsic renal disease. Congenital malformations of the kidneys, such as autosomal recessive polycystic kidney disease, can cause hypertension in children [27]. Fibromuscular dysplasia (FMD) is a well-known cause of secondary hypertension in teenage girls. FMD is a non-inflammatory, non-atherosclerotic arteriopathy that most often affects the renal, vertebral, and, extracranial carotid arteries and may lead to hypertension [28]. The exact prevalence of this condition is unknown, as estimates suggest a prevalence of 12 per 100,000, but the prevailing belief is that it is underdiagnosed [29]. While the underlying pathophysiology has not been elucidated, there is a strong genetic predominance; one referral center estimates that 10% of cases are inherited [30].

There are conditions other than FMD that can cause hypertension in this demographic. Menarche, for instance, plays a role in the development of hypertension. A systematic review and meta-analysis of 17 studies showed that early menarche (defined as the onset of menses before age 12) was associated with an increased likelihood of developing hypertension in adulthood [31]. Polycystic ovarian syndrome (PCOS) has been thought to be associated with the development of hypertension in young women, though the results to date are inconclusive. A recent population-based cohort study from Taiwan showed that young women, most notably those of reproductive age, with PCOS had an increased risk of developing hypertension [32]. Hypertensive patients with hypokalemia who are not on diuretics may have primary aldosteronism or Cushing’s syndrome due to excess endogenous glucocorticoid secretion. Pheochromocytoma is a rare neuroendocrine tumor in the adrenal medulla capable of secreting large amounts of catecholamines, resulting in periodic episodes of tachycardia diaphoresis, and hypertension [33, 34]. Congenital vascular abnormalities, such as aortic coarctation, can also result in hypertension [35, 36]. Coarctation of the aorta is the most common cardiac lesion found in Turner syndrome [37]. Other secondary causes of hypertension include endocrine disorders (e.g., hyperthyroidism, diabetes), psychological disorders (e.g., mental stress, anxiety), and pharmacological causes (e.g., corticosteroids, antidepressants) [38–42].

Hormonal Contraception and Hypertension in Reproductive Aged Women

Hormonal contraceptives have been associated with hypertension [43]. This association is of particular importance, as many women of reproductive age who are on contraceptives have hypertension or are at risk of developing the condition. The American College of Obstetricians and Gynecologists (ACOG) has noted that hormonal contraceptives increase SBP and DBP by as much as 8 mm Hg and 6 mm Hg, respectively [44]. Per a 2019 ACOG Practice Bulletin, women with a BP < 140/90 mm Hg can use any form of hormonal

contraception. In women who have hypertension with SBP 140–159 mm Hg or DBP 90–99 mm Hg, ACOG recommends that combined hormonal contraceptives not be used unless there are absolutely no other appropriate or acceptable options. Finally, for women with SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg or with concomitant vascular disease, no combined hormonal contraceptives should be used. The use of progestin-only contraceptives appears to be safe as they do not appear to have a significant effect on BP [44].

Hypertension in Pregnancy

Hypertension in pregnancy can be deleterious for both the mother and the developing fetus. Therefore, it is of the utmost importance for clinicians and caregivers to promptly recognize, diagnose, and treat hypertension early in pregnancy to prevent the development of any lasting complications. The prevalence of hypertension in pregnancy is significant and is increasing. A recent epidemiological study estimated the annual global incidence of hypertensive disorders in pregnancy as 18.08 million globally, a 10.92% increase since 1990 [45]. Hypertension in pregnancy is currently defined as SBP ≥ 140 mmHg and DBP ≥ 90 mmHg. This definition comes from the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy from 2000 and the more recent ACOG guidelines [46, 47]. Hypertension in pregnancy is further broken down into two categories: (1) non-severe hypertension, SBP between 140 and 159 mmHg and/or a DBP between 90 and 109 mmHg [48]; and (2) severe hypertension, SBP ≥ 160 mmHg and/or DBP ≥ 110 mmHg [49].

The latest recommendations from the ACOG concerning the diagnostic criteria for hypertension in pregnancy differ from the most recent updates from the American College of Cardiology and American Heart Association (ACC/AHA) [47, 50]. The ACC/AHA guidelines define hypertension into two stages. Stage 1 hypertension is defined as a SBP between 130 and 139 mmHg and/or a DBP between 80 and 89 mmHg. Stage 2 hypertension is defined as a SBP ≥ 140 mmHg and/or a DBP ≥ 90 mmHg [51]. Other international guidelines also have different criteria regarding hypertension in pregnancy [52, 53]. Specific types of hypertensive disorders of pregnancy, including chronic hypertension, gestational, preeclampsia/eclampsia, and chronic hypertension with superimposed preeclampsia/eclampsia, have been expanded upon by ACOG and are beyond the scope of this review [47, 50, 54]. Regarding the treatment of hypertension in pregnancy, it should be noted that all antihypertensive medications cross the placenta to some degree.

To further complicate things, there are no large-scale, randomized controlled trials comparing the efficacy and safety of antihypertensive drug classes to one another in pregnancy hypertension [55, 56]. However, based on clinical data, certain antihypertensives have been determined to be efficacious and safe to use during pregnancy. ACOG and the 2017 ACC/AHA Hypertension guidelines recommend that the following antihypertensives be used as first-line agents for patients with non-severe hypertension during pregnancy: labetalol, nifedipine extended release, and methyldopa. Hypertensive women who are treated for hypertension and are planning to become pregnant should be transitioned to one of these first-line agents. Some antihypertensive agents, most notably angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), are contraindicated

during pregnancy due to their teratogenic effects, especially when women are exposed to them during the second or third trimester [57].

Treatment of preeclampsia is primarily based on prevention. Low-dose aspirin has been associated with a 1 to 5% reduction in the incidence of preeclampsia [58]. The United States Preventive Services Task Force (USPSTF) recommends initiating low-dose aspirin at 12 weeks of pregnancy in women deemed high risk for developing preeclampsia [59].

In eclampsia, intravenous magnesium sulfate has been shown to effectively prevent convulsions [60]. Furthermore, lowering BP with parenteral labetalol, parenteral hydralazine, or oral nifedipine is also a mainstay of treatment. However, the only definitive treatment for both preeclampsia and eclampsia is delivery of the fetus.

The Chronic Hypertension and Pregnancy (CHAP) study was a recent open-label, multicenter, randomized trial that sought to determine whether a strategy of targeting a BP < 140/90 mm Hg in pregnant women with mild chronic hypertension (< 160/100 mm Hg) decreased adverse pregnancy outcomes (composite of preeclampsia with severe features, medically indicated preterm birth at less than 35 weeks of gestation, placental abruption, or fetal or neonatal death) more than treating severe hypertension in pregnancy (SBP ≥ 160 mmHg and/or a DBP ≥ 105 mmHg). The primary outcome of the trial was a composite outcome of fetal or neonatal death, preeclampsia with severe features, medically indicated preterm birth, and placental abruption. CHAP randomized 2408 women and showed that a strategy of targeting a BP of < 140/90 mm Hg resulted in a statistically significant decrease in the primary outcome (30.2% vs. 37.0%). Achieving the lower treatment target also significantly reduced the incidence of preeclampsia. Overall, the results of CHAP show that treatment of mild chronic hypertension in pregnancy is associated with better outcomes then reserving treatment for severe hypertension [61••].

Long-Term Implications of Hypertensive Disorders of Pregnancy

Hypertension in pregnancy results in an increased lifetime risk of adverse cardiovascular events in women. Guidelines now include a history of hypertension in pregnancy and other adverse pregnancy outcomes as risk enhancers that should be taken into account in the healthcare of women [62, 63]. It has been shown that women with a history of severe preeclampsia are at increased risk of cardiovascular death within the first 10 years after their pregnancy [64]. Endothelial dysfunction plays a central role in the pathogenesis of preeclampsia, and may persist for years after the affected pregnancy, conferring increased lifetime risk for CVD.

Menopause and Hypertension

Postmenopausal women have a higher prevalence of hypertension than aged matched men [65]. Sex differences in hypertension, specifically with aging, have led to increased interest in studying the role of hormones on hypertension development over the life course [66]. The evidence supporting a positive relationship between menopause and the development of hypertension is unclear. A study from the 1990s that followed women prospectively for 5 years found that peri- and postmenopausal women had a rise in SBP compared to

premenopausal women and men. Importantly, postmenopausal women had higher SBPs at baseline, and these women saw a statistically significant increase in their SBPs throughout the 5-year follow-up period [67]. Although the above study used body mass index (BMI)-matched women, other studies have posited that the rise in SBP and the development of hypertension with menopause are better explained by BMI and age. A cross-sectional Italian study that spanned 16 years saw no difference in the rates of hypertension between pre- and postmenopausal women when data were corrected for age [68]. Other factors such as stiffening of arterial walls, obesity, and genetics affect BP in menopausal women [69]. Importantly, these discordant findings do not mean that sex hormones and the changes seen in the menopausal period do not affect BP [70].

Factors Influencing HTN in Menopause

While genetics appear to play a role in the development of hypertension in postmenopausal women, the precise genetic contribution is not well understood [71]. Menopause per se appears to activate a cluster of genes that lead to hypertension [72], while polymorphisms in certain adrenergic receptors appear to play a role in development of hypertension in both genders [73].

Menopause is associated with decreases in sex hormones, particularly estrogens, and these reductions are associated with vascular endothelial dysfunction [74]. These hormonal changes also result in upregulation of the renin–angiotensin–aldosterone system, leading to increased vasoconstriction [75] and increased salt sensitivity [76]. It has also been hypothesized that a continuation of androgen production in postmenopausal women may result in increased arterial stiffness and vascular inflammation, resulting in endothelial dysfunction and resultant hypertension [77, 78]. However, this association between menopause and subsequent hormonal changes with endothelial dysfunction leading to hypertension is far from definitive. Menopausal women with normal BP also experience endothelial dysfunction that appears to be age-related [74]. Therefore, the association between BP elevation and increased BMI and aging may better explain BP elevation in menopausal women [79, 80].

Menopausal Hormone Therapy

Menopausal hormonal therapy (MHT) or hormone replacement therapy is used to treat the signs and symptoms of menopause [81]. Evidence of the effect of MHT on BP is mixed. An observational cohort study of 43,405 previously normotensive, postmenopausal women in Australia found that MHT was associated with significantly higher odds of elevated BP. These odds increased with the duration of MHT use [82]. A recent French observational study showed a slight but significant increase in hypertension risk in postmenopausal women using oral estrogen and progesterone combination therapies [83•]. However, the Kronos Early Estrogen Prevention Study (KEEPS) showed that MHT use, regardless of formulation (oral conjugated estrogen or weekly transdermal estradiol, each with intermittent progesterone administration) did not affect BP in normotensive postmenopausal women. Other studies have shown that estrogen replacement therapy is associated with a decrease in ambulatory BP [84•]. Thus, women starting MHT should be counseled on its

varied effects on BP with the understanding that there is no consensus to the underlying association between the two, and that MHT has not been shown to reduce CVD risk [85, 86].

Hypertension in Elderly Women

Hypertension occurs in up to 80% of older adults, and hypertension control rates are lower in older patients [51, 87, 88]. Moreover, hypertension rates in women are greater than in men that are 65 years of age or older [89]. Among US adults ≥ 75 years of age, 81.2% of women and 73.4% of men have hypertension. This trend may be due to a greater decline in endothelial function later in life in women than men due to decreased nitric oxide synthesis after menopause [90, 91]. Furthermore, older women, compared to middle aged and young women, have more severe and uncontrolled hypertension [89]. BP increase is associated with cognitive decline in both younger and older women [92, 93]. Therefore, it is important to control hypertension in order to reduce both mortality and incident dementia [94, 95].

Current guidelines recommend a BP goal of < 130/80 mmHg for all non-pregnant adults [51]. In the USA, 76% and 82% of adults aged 65–74 and ≥ 75 years had a SBP/DBP ≥ 130/80 mmHg, respectively [51]. Additionally, only 46% and 33% of US adults taking antihypertensives aged 65–74 and ≥ 75 had a SBP/DBP < 130/80 mmHg. The cardiovascular benefit of intensive BP control in older adults has been shown in major clinical trials [96–99]. In SPRINT (36% women), the cardiovascular benefit of a lower BP target was shown among those 75 years or older regardless of sex [97, 100]. Intensive BP lowering did not result in a greater number of injurious falls or prevalence of orthostatic hypotension. Additionally, in a recent randomized controlled trial (STEP: Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients) of Chinese patients 60–80 years of age (53% women), the SBP target 110 to < 130 mmHg resulted in a lower incidence of cardiovascular events compared to an SBP target of 130 to 150 mmHg [99]. The incidence of hypotension was higher in the intensive treatment group; but, there was no difference in the incidence of syncope, fractures, or dizziness. Most trials included only fit non-frail adults; therefore, future studies are needed to assess the effect of intensive BP lowering in older frail adults and whether sex differences exist in this population.

Disparities in Hypertension

Racial and Ethnic Disparities by Sex

BP prevalence and control rates vary by race, ethnicity, and sex [87, 101]. Non-Hispanic Black individuals have higher hypertension rates and lower control rates than non-Hispanic White individuals. In Northern California, a survey found that hypertension rates varied from 59.9 in Filipino men to 30% in Chinese women. They also found that Asian Americans and non-Hispanic Black individuals compared to non-Hispanic White individuals were more likely to be treated for hypertension. However, control rates were lowest for Filipino women and non-Hispanic Black men [5]. Socioeconomic factors, such as poor insurance coverage and limited healthcare access, contribute to disparities in hypertension control, with lower use of antihypertensive therapies observed in Hispanic individuals compared to non-Hispanic White individuals [102]. These differences are in part driven by cultural

and historical underpinnings, including genetic and social differences in potassium and sodium intake, nocturnal diuresis, and fat distribution [103–107]. Future interventions should consider sex, racial, and ethnic differences to quantify risk and improve healthcare delivery. For instance, in Europe, unlike the USA, the atherosclerotic cardiovascular risk calculator accounts for ethnic group-based differences (SCORE or QRISK 2–2017). While the prevalence of hypertension is greater among aging women than men and an increase in the age-related decline in hypertension control has been shown among women, hypertension control rates differ between women of different ethnicities and races, and there have been no sex or race/ethnic-specific efforts to address these differences [89, 101, 108–110]. Importantly, race is a sociopolitical construct, and race per se should not be used to direct treatment. Rather, the underpinnings of these apparent racial differences, including socioeconomic differences, should be addressed in future studies aimed at improving hypertension control [111].

Socioeconomic Disparities

Low socioeconomic status, including low educational status and low income, are risk factors for hypertension [51, 112, 113]. Adults with an income > 400% above the US government poverty line, i.e., have higher socioeconomic status, have better BP control than adults below this line (43.2% vs. 30.2% respectively) [114]. Low socioeconomic status makes it challenging for people to adopt a healthy lifestyle (e.g., exercise, healthy food) and access healthcare and medications [89, 101, 115]. Providing BP treatment initiatives and free medications has been shown to improve BP control [100, 116, 117]. Additional barriers affecting BP control include poor language proficiency and social support. People with limited English proficiency have lower hypertension control rates than those with adequate English proficiency [118]. Providers are also less likely to engage in participatory decision-making and to be more verbally dominant with Black patients [119]. This translates into shorter visit times and less biomedical and psychosocial support provided to Black patients with uncontrolled hypertension than Whites with controlled hypertension [120]. A study of Black patients with uncontrolled hypertension found that most were not receiving a diuretic, even though it was recommended [121]. Area-level socioeconomic status also affects hypertension rates. Findings from the 2011 Behavioral Risk Factor Surveillance System showed that states with low median household income and high percentages of the population living below the poverty line had a greater prevalence of hypertension, irrespective of individual socioeconomic status [122]. In sum, the socioeconomic and racial/ethnic disparities in hypertension reflect deeper structural issues that have long persisted in the USA [123].

Primary Prevention of Hypertension in Women

The prevalence of hypertension varies across a woman’s life cycle and cardiovascular risk profiles differ between hypertensive women and men [124]. Hypertensive women are older and have more non-traditional risk factors such as kidney disease and abdominal obesity. However, there are no sex-specific strategies to screen or prevent hypertension in women.

Screening

The 2021 Unites States Preventive Task Force (USPSTF) recommends screening for hypertension in the office in adults ≥ 18 years with confirmation by an out-of-office BP measurement (home BP monitor or ambulatory BP monitor). For adults ≥ 40 years and those with risk factors for hypertension, yearly evaluation is recommended. BP evaluation is recommended every 3 to 5 years for younger adults with no risk factors and previously normal BP. Risk factors for hypertension include older age, Black race, family history, obesity or excess weight, dietary factors, and other lifestyle factors [89, 125]. The 2017 ACC/AHA guidelines, 2018 European Society of Cardiology, European Society of Hypertension (ECC/ESH) guidelines, and the Canadian Hypertension Education Program (CHEP) recommend that all adults ≥ 18 years should be evaluated with appropriate technique in the office and/or other clinical setting [51, 126–128]. Specifically, screening for hypertension should occur in pregnancy, as discussed in the previous “Hypertension in Pregnancy” section.

Irrespective of sex or age, the following are modifiable risk factors for hypertension: diabetes mellitus, dyslipidemia/hypercholesterolemia, excess weight or obesity, lack of physical fitness or low fitness activities, unhealthy diet (diet high in sodium, diet low in potassium, excessive alcohol intake), cigarette smoking or secondhand smoking [51, 89, 125]. Treating these risk factors might reduce BP and decrease the global risk factor burden. These include weight loss, following the DASH (Dietary Approaches to Stop Hypertension) diet, sodium reduction, potassium supplementation, increasing physical activity, and decreasing alcohol consumption [51, 129–136]. Other modifiable risk factors though challenging to change include chronic kidney disease, obstructive sleep apnea, and low socioeconomic and/or educational status. Additionally, the following medications can affect BP: over-the-counter medications (nonsteroidal anti-inflammatory drugs, decongestants), recreational drugs, prescription medications (e.g., corticosteroids, atypical antipsychotics), herbal supplements (e.g., St. John’s wort). Specifically, in women, combined oral hormonal contraceptives may contribute to an increase in BP [137–140]. These drugs, when possible, should be reduced, discontinued, or replaced with an alternative agent. For pregnant women, ACOG recommends that in women with a medical history of early-onset preeclampsia and preterm delivery (<34 weeks of gestation) or preeclampsia in more than one prior pregnancy to begin taking aspirin (60–80 mg) in the third trimester to prevent recurrence of preeclampsia [141].

Women in Clinical Trials of Hypertension

The National Institute of Health (NIH) encourages the inclusion of women and minorities as research participants to be consistent with the epidemiology of the disease being studied [142]. In addition, as of 2019, the NIH has an Inclusion Across the Lifespan policy to ensure the broadest age range to be included in clinical trials. Specifically, the National Heart, Lung, and Blood Institute (NHLBI) are committed to these decisions and funding studies to improve all patients. Effective strategies to ensure women’s representation in hypertension and cardiovascular clinical trials are important to improve women’s health. Women’s representation in hypertension trials is comparable to men’s, with a participation

prevalence ratio of 0.82 (42.4% out of 136 trials). In the latest hypertension clinical trial, SPRINT, of those randomized to the intensive (SBP < 120 mmHg) and standard (SBP < 140 mmHg) treatment arm, 36% and 35.2% were women, respectively [143]. Women are also well represented in trials for hypertension drugs with a participation prevalence ratio of 0.9 [144]. However, among cardiovascular clinical trials between 2010 and 2017, women represented only 38.2% of trial participants despite making up 51% of the population [145].

Key Knowledge Gaps

Several areas would benefit from further research: (1) studying the effect of lower BP targets in women with gestational hypertension and those that develop preeclampsia; (2) development of new therapies to treat hypertension in pregnancy; (3) understanding the roles of genetic factors and sex hormones on hypertension development throughout a women's lifespan; and (4) further research aimed at developing actionable interventions to reduce racial, ethnic, and social disparities in hypertension control and management in women.

Conclusion

Hypertension affects women at all stages of life and contributes to cardiovascular morbidity and mortality. Several knowledge gaps exist in understanding sex-specific prevention, detection, and management of hypertension across the life stages, including menarche, pregnancy, menopause, and old age. It is critical to include women at all stages of life in future research to guide individualized care and improve quality of life.

Conflict of Interest

Lama Ghazi receives grant funding from American Heart Association Postdoctoral Fellowship award (829804). Natalie A. Bello receives grant funding from the NIH/NHLBI (K23-HL136853, R01-HL153382) and is a member of a CEC for a GSK trial. Bharathi Upadhya reported receiving honoraria from Novartis. Rahul V. Annabathula, Li Zhou, and Richard Brandon Stacey declare that they have no conflict of interest.

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• Of importance

•• Of major importance

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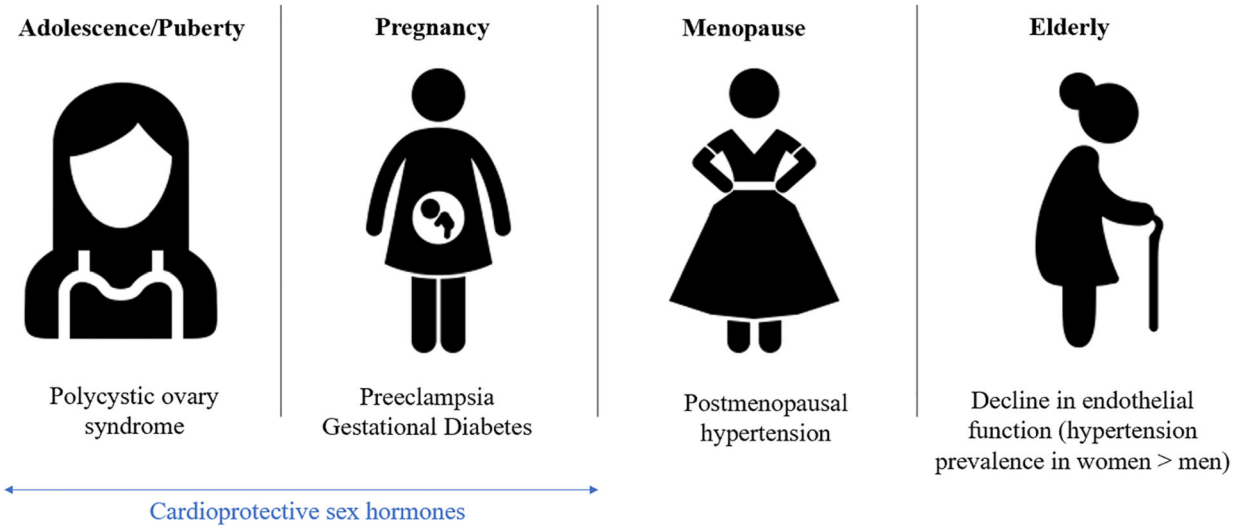

Fig. 1.
Main causes of blood pressure changes across a woman's life cycle