NAMS Practice Pearl

Hypertension in Menopausal Women: The Effect and Role of Estrogen

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States of estrogen imbalance or deprivation are associated with higher risks of hypertension and cardiovascular disease in women; however, the effects of estrogen on hypertension are multifactorial, complex, and not completely understood. Although controversial, hormone therapy may improve cardiovascular outcomes when initiated by recently menopausal women. Improved screening for hypertension, especially in specific groups of younger women at higher risk, is recommended. Further study is needed to determine whether sex-specific differences exist in therapeutic response to pharmacologic management of hypertension.

Hypertension (HTN) is a major risk factor for cardiovascular disease (CVD) and cerebrovascular disease and results in significant global health and economic burdens.[1] Estimates suggest that elimination of HTN can lead to a 38% reduction in CVD mortality in women. Women without HTN live approximately 5 years longer than those with hypertension.

The prevalence of HTN is less than 10% for women aged 20 to 34 years. This prevalence increases with age, reaching 56% at ages 55 to 64 years.[1] However, recent changes to HTN guidelines with lower diagnostic thresholds (stage 1 HTN defined as systolic blood pressure [SBP] 130-139 mm Hg; diastolic blood pressure [DBP] 80-89 mm Hg) could significantly increase this number.[2] A higher percentage of women aged 65 years and older have HTN than men. Specifically, 65.8% of women aged 65 to 74 years and 81.2% of women aged 75 years and older have HTN versus 63.6% and 73.4%, respectively, in men.[1]

Cardioprotective role of estrogen. Seventy-five percent of postmenopausal US women have HTN, with a similar prevalence globally.[1,3] Women tend to be protected from HTN until midlife and menopause, when endogenous estrogen falls.[3] Most observational data show that menopause is associated with a 2-fold increase in risk of HTN, adjusting for age and body mass index. Estrogen may therefore play a role in women's HTN risk.

The vascular protective role of estrogen is complex and not completely understood. Estrogen plays a significant role in endothelial homeostasis through its actions on vascular and cardiomyocyte estrogen receptors (ERs), namely ERα, ERβ, and G protein-coupled ER. Proposed mechanisms include upregulation of the nitric oxide pathway, reduction of reactive oxygen species and increased antioxidant production, reduction of fibrosis via inhibitory effects on profibrotic genes, and stimulation of neoangiogenesis. Estrogen also regulates renin-

angiotensin-aldosterone system and endothelin levels.[4] Loss of these mechanisms with menopause may explain lower arterial compliance in postmenopausal women and greater future risk of HTN and CVD.

Postmenopause hypertension and the role of hormone therapy. There are insufficient and conflicting data on the effects of hormone therapy (HT) on HTN in postmenopausal women.[5] Hormone therapy has overall neutral effects on blood pressure (BP) and is likely safe to use in postmenopausal women with controlled HTN. In the Women's Health Initiative (WHI), one-third of women enrolled had a preexisting diagnosis of HTN, and subgroup analysis did not show significant interaction between HTN and HT use on CVD outcomes. However, there was a hazard ratio of 1.29 for stroke in women using estrogen alone. This should be considered when starting a woman with HTN on exogenous estrogen therapy. Moreover, a recent subsample analysis of the WHI suggests an 18% higher risk of incident HTN in women on HT versus placebo, with reversibility postintervention. Further study is warranted to determine the effects on HTN of different doses, formulations, and routes of administration.[6]

Cardiovascular safety of HT is most favorable when initiated by recently menopausal women.[7] Although data support a "timing hypothesis," which proposes that starting HT early in the postmenopause period may be beneficial and risk of CVD increases when started later, practice guidelines do not recommend initiating HT for CVD prevention. Long-term mortality data from the WHI suggest that HT is not associated with excess cardiovascular (CV) harm when initiated by recently menopausal women.[8]

Estrogen balance in younger, premenopausal women. Use of estrogen-progestin oral contraceptive pills (OCPs) in premenopausal women may reversibly increase BP.[4] Renin-angiotensin-aldosterone system and sympathetic activation may be implicated in this response to OCPs and is felt to be driven by estrogen. Limited studies on progesterone suggest no increase in risk of HTN or short-term CV outcomes. Therefore, current guidelines suggest the use of progestin-only contraception in older women with HTN.

Further insight into the role of estrogen in CVD is obtained from women with primary ovarian insufficiency (POI) and hypertensive disorders of pregnancy. Primary ovarian insufficiency affects approximately 1% of women and is associated with a modest increase in CVD risk.[9] Early surgical menopause can be a secondary cause of POI. A retrospective study of 113,679 women aged 35 to 45 years found that surgical menopause is associated with greater hospital admissions for and death from ischemic heart disease compared with ovarian conservation. In women with POI, physiologic HT lowers 24-hour SBP and DBP and plasma angiotensin II levels. Hypertensive disorders of pregnancy, and specifically preeclampsia, increase future risk of HTN by 2- to 4-fold, with a persistent risk even 20 years later.[10] Pathophysiology is unclear but is likely related to endothelial dysfunction and sex-hormone effects.

Practical tips for screening, diagnosis, and management of hypertension in women. Unfortunately, BP awareness does not necessarily translate to better BP control.[1] National Health and Nutrition Examination Survey data suggest that only 54.4% of persons had HTN under control, with this number dropping to less than 40% in those aged 80 years and older.[1] Sex-specific data are limited; however, women seem to be more aware of, on treatment for, and have better control of HTN than men.

Screening and diagnosis. Women should be screened at all appropriate clinical visits to assess CV risk or response to treatment. Blood pressure greater than 130/80 mm Hg on two or more readings over two or more occasions confirms a diagnosis of HTN.[11] Accurate measurement of BP is essential to establishing a diagnosis. Automated BP devices are recommended, with the patient seated comfortably, back supported, and feet flat. The arm should be at heart level and supported on a surface. Proper BP cuff size should be chosen. Blood pressure should be checked in both arms on the first visit. An average of at least three readings should be obtained. Screening for other modifiable CV risk factors, such as dyslipidemia, diabetes, smoking, and obesity, also should be performed.

Nonpharmacologic management. Nonpharmacologic therapies can reduce BP and may result in 5 mm Hg to 10 mm Hg improvement.[11] Proven strategies include weight loss in patients with HTN who are overweight or obese (estimated 1 mm Hg reduction for each 1 kg weight loss), sodium reduction (goal, <1,500 mg/d), increased potassium intake, increased physical activity (goal, 150 min/wk of moderate-level exertion), and moderation of alcohol intake, with one or fewer drinks daily recommended for women. In order to reduce future risk of HTN in specific groups of women at higher risk, focused intervention aimed at weight loss after gain in pregnancy and in those with obesity at midlife is recommended.

Pharmacologic management. Sex differences exist in pharmacokinetic and pharmacodynamic properties of antihypertensive medications but do not appear to alter therapeutic response. First-line therapy as dictated in current guidelines for management of HTN in adults is suggested.[11] Target SBP less than 130 mm Hg is recommended. This is in contrast to previous guidelines that advocated for an SBP goal of less than 150 mm Hg in older persons. Women using combination OCPs should be monitored for HTN; combination contraception should be avoided in women with HTN aged older than 35 years. In women with early or induced menopause, HT should be considered at least until the normal age of menopause for CV protection. In spontaneously menopausal women aged 50 years and older, use of HT solely to prevent CVD is not recommended.

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Disclosures

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