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COMMENTARY

Hypertension in Women

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Hypertension is a major cause of cardiovascular disease in the United States and an important contributor to morbidity and mortality. Men in the general population have higher diastolic blood pressures than women at all ages and also have a higher prevalence of hypertension overall. Although men have a higher incidence of total cardiovascular end points at all ages, hypertensive men and women develop strokes, left ventricular hypertrophy, and renal dysfunction at similar rates. Hypertension is particularly important in women because it is a modifiable risk factor that is extremely prevalent in older women (1).

Gender differences in blood pressure

Based on interviews and examinations of 9901 American adults 18 yr of age or older, the Third National Health and Nutrition Examination Survey determined that overall mean arterial pressure is higher in both normotensive and hypertensive men than in women (2). Gender differences in blood pressure are detectable during adolescence and persist through adulthood (3, 4). In all ethnic groups, men tend to have higher mean systolic and diastolic blood pressures than women (by 6–7 and 3–5 mm Hg, respectively), and through middle age, the prevalence of hypertension is higher among men than among women. After age 59 yr, the Third National Health and Nutrition Examination Survey found that hypertension is more prevalent among women than among men. Another large population survey, the Community Hypertension Evaluation Clinic Program, screened 1 million Americans between 1973 and 1975, and found that mean diastolic pressure was higher in men than in women at all ages, whereas mean systolic pressure was higher in men than in women until age 50 yr for blacks and age 65 yr for whites and was higher in women thereafter (5). The Hypertension Detection and Follow-up Program (HDFP) Cooperative Group screened 158,906 persons, aged 30–69 yr, in 14 communities between 1973 and 1974 and found that hypertension was more prevalent in men than in women of both races (6).

Whether there is a cross-over in the relative prevalence of hypertension in men *vs.* women, with younger men and older women having more hypertension, is a point of controversy; the cross-over has been reported in a number of cross-sectional studies (7), but was not apparent in the 30-yr longitudinal data from the Framingham study (8). Mean systolic blood pressure in older women in Framingham approached that in older men, but did not exceed it; mean diastolic blood pressure was lower in women at all ages and declined in both sexes after age 65 yr.

The reasons for gender differences in blood pressure are not known, but are being investigated by several laboratories. It has been suggested, but not proven, that estrogen is responsible for the lower blood pressure in younger women. Data on blood pressure fluctuations during the life cycle lend some support to this hypothesis, but the evidence linking changes in blood pressure throughout the life cycle to levels of endogenous sex hormones remains circumstantial. A recent study of hemodynamic changes associated with the menstrual cycle reported lower blood pressure during the luteal phase than during the follicular phase (9). However, conflicting observations have been made, with some reporting higher pressures in the luteal phase (10, 11). During normal pregnancy, both estrogen and progesterone levels are 50–100 times higher than prepregnancy levels, and blood pressure decreases dramatically. However, the time course of the maximal decrease in blood pressure does not coincide with the maximal rise in hormone levels, suggesting that the relationship between blood pressure and endogenous levels of hormones is complex and is probably influenced by other factors (12).

The influence of menopause on blood pressure is also controversial. Longitudinal studies have not documented an increase in blood pressure with menopause (13–15), whereas cross-sectional studies have reported significantly higher systolic and diastolic blood pressures in postmenopausal women (16, 17). Staessen and colleagues reported a fourfold higher prevalence of hypertension in postmenopausal women than in premenopausal women. After adjusting for age and body mass index, postmenopausal women were still more than twice as likely to have hypertension as premenopausal women. The menopause-related increase in blood pressure described in some studies has been attributed to a variety of factors, including increases in weight, decreases in activity, and increases in alcohol intake. Currently unresolved is whether reduced ovarian estrogen production

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plays a major role in the increase in blood pressure after menopause. Investigation of the biological effects of estrogen has demonstrated that exogenously administered estrogens, in the form of 17β-estradiol, promote endothelium-dependent vasodilatation (18). Further, studies of endothelial function using acetylcholine-induced changes in forearm blood flow demonstrate diminished endothelium-dependent vasodilatation in association with menopause, suggesting a role for endogenous estrogen in blood pressure regulation (19). Clinical studies have shown that estrogen may modulate blood pressure responses to stressful stimuli; postmenopausal women and men demonstrate larger stress-induced increases in blood pressure and higher ambulatory daytime blood pressure than premenopausal women (20). However, although postmenopausal women clearly have higher blood pressures than premenopausal women, the age-related increase in blood pressure in women is greatest after the age of 62 yr, suggesting that loss of estrogen is not the primary cause (2). A study from Finland, which demonstrated that women who had undergone hysterectomy with ovarian preservation had higher blood pressures than age-matched women who had not undergone hysterectomy (21), highlights the importance of studying factors in addition to estrogen in relation to the pathogenesis of postmenopausal increases in blood pressure.

Pathophysiology of primary hypertension

Essential hypertension is a heterogeneous disorder; thus, it is not surprising that few gender-specific pathogenic factors have been identified. Premenopausal hypertensive women have been shown to have higher resting heart rate, left ventricular ejection time, cardiac index, and pulse pressure compared to age-matched men and have decreased total peripheral resistance and blood volume (22). Lower plasma renin levels have been reported in both pre- and postmenopausal hypertensive women compared to those in men (23). Nordby and colleagues reported lower serum estradiol levels in hypertensive premenopausal women compared to normotensives (24).

One aspect of hypertension in women that is worthy of emphasis is obesity. Obesity is significantly more common in middle-aged women than men, and there is evidence that body weight has a greater impact on blood pressure in females than in males (25). Although the association between obesity and hypertension is firmly established, the mechanisms involved are not well understood. The relationship of hyperinsulinemia and insulin resistance (both associated with obesity) to hypertension is under investigation by several laboratories. A significant amount of hypertension in women is attributable to obesity, an observation that underscores the importance of dietary modification and exercise in treatment.

Secondary hypertension in women

The causes of secondary hypertension in women are generally the same as those in men, and similar considerations with respect to evaluation and treatment are applicable. Parenchymal renal disease should be considered and ruled out with urinalysis and serum creatinine levels. Collagen diseases, such as systemic lupus erythematosis and systemic sclerosis, are more common in women, and the presence of hypertension in patients with these disorders suggests renal involvement. Renovascular hypertension due to fibromuscular dysplasia is primarily a disease of young women. Given the excellent results reported with renal angioplasty (26), this condition should be ruled out in women under the age of 40 yr with moderate to severe hypertension. It is particularly important to diagnose this disorder before pregnancy, because women with renovascular hypertension are more likely to have complicated pregnancies. Similarly, pheochromocytoma, although rare, is associated with considerable maternal morbidity and mortality during pregnancy and should be ruled out in young hypertensive women with characteristic symptoms.

Oral contraceptive hypertension

Exogenous estrogen, particularly in the form of oral contraceptive pills, is an important cause of secondary hypertension in women. A review of 24 yr of data suggests that most women taking oral contraceptives experience a small, but detectable, increase in both systolic and diastolic blood pressure (27). The magnitude of the increase varies among populations and also with doses of estrogen and progestin. The Walnut Creek Contraceptive Drug Study, which included 11,672 women, reported an increase in pressure of 5–6 mm Hg systolic and 1–2 mm Hg diastolic in white women and a lesser rise in black women (28). A study conducted in developing countries reported similar average changes after 1 yr of oral contraceptive use (29). However, in some centers, marked elevations (10 mm Hg systolic, 6.9 mm Hg diastolic) were reported.

Hypertension is 2–3 times more common in women taking oral contraceptives than in age-matched women not taking these medications (30). The risk of hypertension increases with age, duration of use, and increased body mass. Oral contraceptives currently in use contain lower doses of ethinyl estradiol (20–35 μg) than those previously used. The available data suggest that there is a correlation between both estrogen and progestin dose and blood pressure (27). Thus, the current incidence of oral contraceptive-induced hypertension may be less than that reported by earlier studies. Nevertheless, recently published data obtained from the Nurses' Health Study suggests that even oral contraceptives with lower doses of estrogen increase the risk of hypertension, and that the risk increases with duration of use and with increased progestin potency (28).

The mechanism of the increase in blood pressure or of the development of overt hypertension due to oral contraceptives remains unclear. Increases in body weight, plasma volume, exchangeable sodium, plasma insulin, insulin resistance, and hepatic synthesis of angiotensinogen have been reported to be involved. Experimental evidence favors a role for the renin-angiotensin system in the hypertension induced by estrogen (29). In a rat model of oral contraceptive hypertension, administration of estrogen alone (ethinyl estradiol) caused hypertension and an increase in angiotensinogen and angiotensin II levels (33). The hypertension induced by estrogen responded to angiotensin-converting enzyme inhib-

itor treatment. Progestin administration alone also increased blood pressure, although the elevation in blood pressure was of lesser magnitude, of shorter duration, and associated with increased sodium retention.

In view of the above considerations, a prudent approach to oral contraceptive use is to monitor blood pressure at least every 6 months (only dispense 6 months of pills). If blood pressure rises, then a decision to discontinue the pill should be based on the degree of hypertension, the potential hazards of pregnancy, and the overall cardiovascular risk profile. Although it is preferable to avoid oral contraceptives in individuals with elevated blood pressure, this modality of contraception can be considered in carefully selected individuals when the risks of pregnancy appear greater than the risks of mild hypertension.

Hormone replacement therapy (HRT) and hypertension

The effects of HRT on blood pressure are not as clear-cut as the effects of oral contraceptive pills. An association between estrogen therapy in postmenopausal women and hypertension was first reported in the 1970s and 1980s (34–37), and until recently many physicians considered hypertension to be a contraindication to HRT. The mechanism of the increase in blood pressure was attributed to increased angiotensinogen generation as well as increased sodium retention (38). In fact, estrogen preparations (*e.g.* Premarin and ethinyl estradiol) with a greater ability to stimulate hepatic synthesis of angiotensinogen have been shown to raise blood pressure to a greater extent than those preparations that have a modest effect on angiotensinogen (natural estradiol and transdermal estrogen) (39, 40). However, the hypertensive effect of postmenopausal estrogen therapy is not as consistently observed as that of oral contraceptive pills. One difference that may account for the more common association of increases in blood pressure with oral contraceptive pills is the dose. The dose of ethinyl estradiol in contraceptive pills is more potent than the doses of conjugated estrogens that are given to postmenopausal women. The effects of synthetic progestins on blood pressure have not been extensively studied in postmenopausal women. Preliminary evidence suggests that they cause increases in blood pressure by increasing sodium retention (41).

Data from recently published prospective clinical trials suggest that the risk of hypertension due to HRT is low, and some studies have even documented a decrease in blood pressure in patients treated with HRT (42–44). The Postmenopausal Estrogen/Progestin Interventions Trial evaluated cardiovascular risk factors in 875 normotensive postmenopausal women, aged 45–64 yr, randomly assigned to treatment with a variety of different regimens of HRT. At 3 yr of follow-up, there were no differences in systolic or diastolic blood pressure in any of the treatment groups compared to that in the placebo group. The patients in this clinical trial were normotensive to start, and it is not known whether hypertensive women would be more likely to develop increases in blood pressure while taking HRT. A recent prospective study of 75 hypertensive women treated with HRT failed to demonstrate an increase in blood pressure after 12 months of follow-up (45), but data on larger numbers of patients are needed to determine whether HRT is a risk factor for blood pressure elevation in hypertensive postmenopausal women. A concern with respect to the existing data is that reporting mean changes in blood pressure in a population may mask individuals who have a blood pressure increase with HRT. This was demonstrated by a recent study of ambulatory blood pressure monitoring in normotensive women receiving either transdermal or oral estrogen, which showed that although the group as a whole did not have a rise in blood pressure, as many as one third of the individuals had a 4-mm Hg increase in diastolic blood pressure after 6 months of therapy (40).

In summary, currently available data suggest that HRT is an uncommon cause of worsening hypertension in postmenopausal women. However, very few hypertensive subjects have been followed prospectively during HRT; thus, the incidence of HRT-induced increases in blood pressure in individuals with preexisting hypertension is not known. Subtle increases in blood pressure attributable to HRT might be difficult to detect in women already receiving treatment for hypertension, whose blood pressures may fluctuate with changes in body weight, level of activity, and diet. It is prudent to follow blood pressure closely in hypertensive women receiving HRT and to consider using preparations with minimal effects on hepatic production of angiotensinogen (transdermal estrogen) if blood pressure control becomes difficult.

Gender issues and treatment of hypertension

Lifestyle modifications. The Treatment of Mild Hypertension Study demonstrated that women are less likely than men to have their blood pressure controlled with lifestyle interventions alone, perhaps because they are less successful in losing weight (46). Weight reduction is of particular importance for blood pressure control in women, given the high prevalence of obesity, particularly in African-Americans. The effects of weight reduction on blood pressure have not been studied extensively in women; however, small clinical trials clearly demonstrate the expected benefits (47). Decreased levels of physical activity have been associated with higher blood pressures in women, but prospective trials of the effects of exercise on blood pressure in women have not been performed. However, given the beneficial effects of exercise on weight control, prevention of osteoporosis, and insulin and glucose metabolism, it is justified to recommend increased activity for hypertensive women in the absence of unstable coronary artery disease.

Dietary recommendations for hypertensive women are similar to those for hypertensive men. Preliminary studies have suggested a greater depressor response to sodium restriction in women than in men (48). Thus, sodium restriction should be encouraged in women who are likely to be salt sensitive (African-Americans, elderly women, and those with low PRA), and all patients should be encouraged to eat a diet with abundant fruits, vegetables, and low fat dairy products.

Excessive (more than two or three drinks per day) alcohol intake is associated with increases in blood pressure. Thus,

all hypertensive women should be advised to limit alcohol intake.

Drug therapy. The effects of antihypertensive therapy on the cardiovascular complications of hypertension (heart attack, stroke, and death) have not been studied separately in women. The large clinical trials of antihypertensive therapy (*e.g.* HDFP, Medical Research Council and Australian Therapeutic Trial) have included variable proportions of women, and as certain subgroups (*e.g.* younger white women) have a low incidence of cardiovascular complications, there was insufficient power to detect a treatment effect in all groups (reviewed in Ref. 49). The HDFP trial did demonstrate a reduction in stroke in all women receiving stepped care treatment; the effects on nonstroke outcome were less clear-cut. The benefits of treatment have been most clearly shown in African-American women and in elderly women. Analysis of the large clinical trials with respect to mortality in women has yielded conflicting results. The HDFP and Medical Research Council trials did not demonstrate a decrease in mortality in the active or stepped care treatment groups, whereas the Australian Therapeutic Trail did. Nevertheless, at present, the evidence is insufficient to warrant less aggressive treatment of hypertension in women, and it should be emphasized that African-American women require particularly aggressive treatment. This view is supported by a recent meta-analysis of the effects of antihypertensive treatment on cardiovascular outcomes in women and men (50). Antihypertensive treatment clearly reduced the incidence of stroke in women. A reduction in coronary events was not as apparent in women, a finding that the investigators attributed to the lower risk of coronary disease in untreated women.

Side-effects. Adverse effects of antihypertensive medication are a major obstacle to treatment. A growing body of evidence suggests that there may be gender-specific side-effect profiles (reviewed in Refs. 23 and 51). In the Treatment of Mild Hypertension Study, in which 902 men and women received nonpharmacological treatment plus treatment with a drug from each class of antihypertensive agents, women reported twice as many side-effects as men, although the incidence of side-effects in women was similar in placebo- and drug-treated individuals. Biochemical responses to drugs may be gender dependent; women are more likely to develop hyponatremia associated with diuretic therapy, whereas men are more likely to develop gout. Hypokalemia is more common in women taking diuretics. Angiotensin-converting enzyme inhibitor-induced cough has been reported to be twice as common in women as in men (52). The effect of antihypertensive agents on lipid profiles has not been investigated extensively in women, although this is an important consideration with respect to cardiovascular risk. Preliminary evidence suggests that menopausal status may influence the effect of drugs on lipid profiles: high doses of diuretics have been shown to raise total cholesterol in both men and postmenopausal women, but not in premenopausal women (52).

Another area of relevance to drug treatment of hypertension is the effect of antihypertensive therapy on sexual function. This is a major obstacle to successful therapy of hypertension in men, and there is evidence that sexual dysfunction is a problem in hypertensive women as well. However, information regarding sexual dysfunction in women is seldom obtained in clinical trials or in clinical practice. Thus, this is an area clearly in need of further investigation.

Summary

Hypertension is an important risk factor for cardiovascular disease in women. Although younger, premenopausal women have lower blood pressures than age-matched men, population blood pressure rises with age, and the prevalence of hypertension is higher in older women. Oral contraceptive use increases the risk of hypertension in women, and women using this therapy should have blood pressure monitored twice yearly. The risk of hypertension is low in normotensive women receiving HRT. Few studies of HRT in hypertensive women have been performed, and more information is needed to assess the risk of worsening hypertension in hypertensive postmenopausal receiving this therapy. Investigations of gender differences in pathophysiology and response to treatment of essential hypertension have not been extensive, and current evidence does not support gender-specific treatment of hypertension at the present time.

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