Hypertension Curriculum Review

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Hypertension in Women: Part I

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The basis for the treatment of hypertension in women has evolved in step with the inclusion of women in studies of treatment in hypertension. Recent outcome trials comparing angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or calcium antagonists with diuretics and β-blockers in older, high-risk patients have generally shown similar benefits for women and men. The current evidence therefore indicates that sex should not play a role in decisions about whether to treat hypertension or about the choice of agents. J Clin Hypertens (Greenwich). *2008;10:406–410.* ©*2008 Le Jacq*

The prevalence of hypertension increases with age across all race and sex groups. Women have lower systolic blood pressure (SBP) levels than men during early adulthood, while the opposite is true after the sixth decade of life. Diastolic blood pressure (DBP) tends to be just marginally lower in women than men regardless of age. Similarly, in early adulthood, hypertension is less common among women than men. However, after the fifth decade of life, the incidence of hypertension increases more rapidly in women; thus, women older than 60 years have higher rates of hypertension compared with men. The highest prevalence rates of hypertension are observed in elderly black women, with hypertension occurring in >75% of black women older than 75 years.

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AWARENESS, TREATMENT, AND CONTROL OF HYPERTENSION IN WOMEN

Women are more likely than men to know that they have hypertension and to seek treatment. However, recent analysis of the data from the National Health and Nutrition Examination Survey (NHANES) show a lag in control rates among women compared with men. In NHANES 1999–2004, approximately 68% of hypertensive women were aware of their high blood pressure (BP) in contrast with 67% of hypertensive men. Overall, 58% of hypertensive women but only 52% of hypertensive men were being treated with antihypertensive medication. The higher treatment rates in women have been attributed to increased numbers of physician contacts. Control rates for treated male hypertensive patients is 66% compared with 62.5% among women, which represents a reversal of the observation from 2001 and 2002 when 65.2% of women vs 62.6% of men had controlled BP. This difference in control rates did not reach statistical significance.

ETIOLOGY AND PATHOPHYSIOLOGY OF HYPERTENSION IN WOMEN

Most (90%–95%) hypertension in the United States is essential hypertension; however, 5% to 10% of hypertension has a well-defined etiology. Most secondary hypertension generally occurs with equal frequency in women and men. Exceptions include hypertension caused by renal artery stenosis due to fibromuscular dysplasia, which occurs more commonly in women than men, and secondary hypertension due to the use of oral contraceptives, preeclampsia, and vasculitides.

Although there are exceptions in individual patients, hypertensive women tend to have lower plasma renin activity (PRA) than hypertensive men. PRA, intravascular volume, and BP vary during the menstrual cycle in normotensive women. The increase in intravascular volume

during the luteal phase of the menstrual cycle may play a role in hypertension in some women and may account in part for hypertension associated with use of oral contraceptives. Karpanou and colleagues demonstrated that premenopausal hypertensive women have increased testosterone levels during ovulation and increased testosterone and PRA during the luteal phase of the menstrual cycle. In this study, hypertensive women with high PRA exhibited no change in BP during the cycle (much like normotensive patients), whereas hypertensive women with relatively low PRA had a nighttime increase in BP during ovulation. The authors speculate that BP may be regulated mainly by the renin-angiotensin-aldosterone system in hypertensive persons with high PRA, whereas sex steroids may play a more important role in those with low PRA.

In premenopausal women, hypertension is often characterized by a higher resting heart rate, left ventricular ejection time, cardiac index, and pulse pressure and a lower total peripheral resistance and total blood volume compared with age-matched men with the same BP level. Hypertension in older women tends to be characterized by elevated peripheral vascular resistance, low or normal plasma volume, and a tendency toward low PRA.

ORAL CONTRACEPTIVES AND BP

Many women taking oral contraceptives experience a small but detectable increase in BP; a small percentage experience the onset of frank hypertension. This is true even with modern preparations that contain only 30 μg estrogen. The Nurses' Health Study found that persons currently using oral contraceptives had a significantly increased risk of hypertension compared with those who had never used oral contraceptives (relative risk, 1.8; 95% confidence interval, 1.5–2.3). Absolute risk was small: only 41.5 cases of hypertension per 10,000 person-years could be attributed to oral contraceptive use. Controlled prospective studies have demonstrated a return of BP to pretreatment levels within 3 months of discontinuing oral contraceptives, indicating that their BP effect is readily reversible.

Oral contraceptives occasionally may precipitate accelerated or malignant hypertension. Family history of hypertension, including preexisting pregnancy-induced hypertension, occult renal disease, obesity, middle age (>35 years), and duration of oral contraceptive use increase susceptibility to hypertension. Contraceptive-induced hypertension appears to be related to the progestogenic, not the estrogenic, potency of the preparation.

Regular monitoring of BP throughout contraceptive therapy is recommended, and it has been suggested that the duration of prescription contraceptive use be limited to 6 months to ensure at least semiannual reevaluations. Withdrawal of the offending contraceptive agent is generally desirable in cases of contraceptive-induced hypertension, but such therapy may have to be continued in some women (eg, if other contraceptive methods are not suitable) and combined with antihypertensive therapy.

MENOPAUSE AND BP

The effect of menopause on BP is controversial. Longitudinal studies have not documented a rise in BP with menopause, while cross-sectional studies have found significantly higher SBP and DBP in postmenopausal vs premenopausal women. In NHANES III, the rate of rise in SBP tended to be steeper in postmenopausal compared with premenopausal women until the sixth decade, when the rate of increase tended to slow. Staessen and associates reported that even after adjustment for age and body mass index, postmenopausal women are more than twice as likely to have hypertension as premenopausal women. In a prospective study of conventional and ambulatory BP levels, postmenopausal women had higher SBP (4–5 mm Hg) than premenopausal and perimenopausal controls. The increase in SBP per decade was 5 mm Hg greater in the perimenopausal and postmenopausal women than in the premenopausal group. Thus, there is evidence that at least part of the rise in BP (particularly SBP) seen later in life in women is due to menopause. A menopause-related increase in BP has been attributed to a variety of factors, including estrogen withdrawal, overproduction of pituitary hormones, weight gain, or a combination of these and other yet-undefined neurohumoral influences.

POSTMENOPAUSAL HORMONE THERAPY AND BP

Results of studies evaluating the effects of hormone replacement therapy (HRT) on BP have been inconsistent. Overall, HRT-related changes in BP are likely to be modest and should not preclude hormone use in normotensive or hypertensive women. All hypertensive women receiving HRT should have their BP monitored closely.

CHOICE OF ANTIHYPERTENSIVE DRUGS FOR WOMEN

While women generally respond to antihypertensive drugs similarly to men, some special considerations may dictate treatment choices for women.

Table I. Hypertension in Pregnancy	
Chronic hypertension	Blood pressure (BP) ≥140/90 mm Hg before pregnancy or before 20 weeks' gestation. Persists >12 weeks postpartum.
Preeclampsia	BP ≥140/90 mm Hg with proteinuria (>300 mg/24h) after 20 weeks' gestation. Can progress to eclampsia. More common in nulliparous women, multiple gestation, women with hypertension ≥4 years, family history of preeclampsia, preeclampsia in a previous pregnancy, and renal disease.
Chronic hypertension with superimposed preeclampsia	New-onset proteinuria after 20 weeks' gestation in a woman with hypertension. In a woman with hypertension and proteinuria before 20 weeks' gestation: Sudden 2- to 3-fold increase in proteinuria Sudden increase in BP Thrombocytopenia Elevated aspartate aminotransferase or alanine transaminase
Gestational hypertension	Hypertension without proteinuria occurring after 20 weeks' gestation. Temporary diagnosis. May represent preproteinuric phase of preeclampsia or recurrent chronic hypertension abated in midpregnancy. May evolve to eclampsia. If severe, may result in higher rates of premature delivery and growth retardation than mild preeclampsia.
Transient hypertension	Retrospective diagnosis. BP normal by 12 weeks postpartum. May recur in subsequent pregnancies. Predictive of future primary hypertension.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are contraindicated for women who are or intend to become pregnant because of the risk of fetal developmental abnormalities. Diuretics are particularly useful in elderly individuals because of a decreased risk of hip fracture. Some antihypertensive drugs have sex-specific adverse effect profiles. For example, in the Treatment of Mild Hypertension Study (TOMHS), women reported twice as many adverse effects as men. Women are more likely to develop diuretic-induced hyponatremia, and men are more likely to develop gout. Hypokalemia is more common in women taking a diuretic. ACEI-induced cough is twice as common in women as in men, and women are more likely to complain of calcium channel blocker–related peripheral edema and minoxidil-induced hirsutism.

Clinical trial evidence supports the effectiveness of algorithm-driven therapy as a means of reaching BP goals. To get the individual patient to goal BP, addition of a second drug from a different class should be initiated when use of a single agent in adequate doses fails to achieve the goal. When BP is >20 mm Hg above systolic goal or 10 mm Hg above diastolic goal, consideration should be given to initiate therapy with 2 drugs, either as separate prescriptions or in fixed-dose combinations. The initiation of therapy with >1 drug increases the likelihood of achieving BP goal in a more timely fashion.

NONPHARMACOLOGIC TREATMENT OF HYPERTENSION

Adoption of healthy lifestyles by all persons is critical for the prevention of high BP and is an indispensable part of the management of those with hypertension. Weight loss of as little as 10 lb (4.5 kg) reduces BP and/or prevents hypertension in a large proportion of overweight persons, although maintenance of normal body weight is ideal. BP is also benefited by adoption of the Dietary Approaches to Stop Hypertension (DASH) eating plan, which is a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of dietary cholesterol as well as saturated and total fat (modification of whole diet). It is rich in potassium and calcium. Dietary sodium should be reduced to no more than 100 mmol/d (2.4 g of sodium). Additional measures include regular aerobic physical activity such as brisk walking at least 45 minutes per day most days of the week. Alcohol intake should be limited to no more than 1 drink per day in women. A drink is 12 oz of beer, 5 oz of wine, or 1.5 oz of 80-proof liquor. For overall cardiovascular risk reduction, patients should be strongly counseled to quit smoking.

HYPERTENSION IN PREGNANCY

Hypertensive disorders in pregnancy are a major cause of maternal, fetal, and neonatal morbidity and mortality. Hypertension in pregnancy is classified

Table II. Treatment of Chronic Hypertension in Pregnancy

Agent	Comments
Methyldopa	Preferred on basis of long-term follow-up studies supporting safety.
β-blockers	Reports of intrauterine growth retardation (atenolol). Generally safe.
Labetalol	Increasingly preferred to methyldopa because of reduced adverse effects.
Clonidine	Limited data.
Calcium antagonists	Limited data. No increase in major teratogenicity with exposure.
Diuretics	Not first-line agents. Probably safe.
Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists	Contraindicated. Reported fetal toxicity and death.

into 1 of 5 categories, and it is critical to differentiate preeclampsia, a pregnancy-specific syndrome of exaggerated vasoconstriction and reduced organ perfusion, from preexisting chronic hypertension.

PREPREGNANCY ASSESSMENT

Women should be evaluated before conception to define their BP status, and, if hypertensive, to assess its severity, possible secondary causes, and presence of target organ damage and to plan treatment strategies. Many hypertensive women who plan to become pregnant should be screened for pheochromocytoma because of the high morbidity and mortality of this condition if not diagnosed antepartum.

In hypertensive women planning to become pregnant, it may be prudent before conception to change to antihypertensive medications known to be safe during pregnancy, such as methyldopa or β-blockers. ACEI and ARB use should be discontinued before attempts at conception or as soon as pregnancy is confirmed. Those with progressive renal disease should be encouraged to complete their childbearing while their renal function is relatively well preserved. Mild renal disease (serum creatinine <1.4 mg/dL) has a minimal effect on fetal survival, and the underlying renal disease does not generally worsen during pregnancy. However, moderate or severe renal insufficiency in pregnancy may accelerate both hypertension and the underlying disease and markedly reduce fetal survival.

TREATMENT OF CHRONIC HYPERTENSION DURING PREGNANCY

Women with stage 1 hypertension are at low risk for cardiovascular complications during pregnancy and are candidates for lifestyle modification therapy only, as there is no evidence that pharmacologic treatment improves neonatal outcomes. Further, BP usually falls during the first half of pregnancy; therefore, hypertension may be easier to control with reduced or no medications. With lifestyle modification, aerobic exercise should be restricted on the basis of theoretical concerns that inadequate placental blood flow may increase the risk of preeclampsia, and weight reduction should not be attempted, even in obese pregnant women. Although the data on pregnant women are sparse, many experts recommend restriction of sodium intake to the same 2.4 g of sodium intake recommended for those with primary hypertension. Use of alcohol and tobacco must be strongly discouraged.

Use of antihypertensive drugs in pregnant women with chronic hypertension varies greatly among centers. Some clinicians prefer to stop antihypertensive medications while maintaining close observation, including use of home BP monitoring. This approach reflects concern about the safety of antihypertensive drug treatment in pregnancy. A meta-analysis of 45 randomized controlled studies of treatment with several classes of antihypertensive drugs in stage 1 and 2 hypertension in pregnancy showed a direct linear relationship between treatment-induced fall in mean arterial pressure and the proportion of small-for-gestational-age infants. This relationship was independent of type of hypertension, type of antihypertensive agent, and duration of therapy.

For pregnant women with target organ damage or a prior requirement for multiple antihypertensive agents for BP control, however, antihypertensive medication should be continued as needed to control BP. In all cases, treatment should be reinstituted once BP reaches 150 to 160 mm Hg systolic or 100 to 110 mm Hg diastolic to prevent increases in BP to very high levels during pregnancy. Aggressive treatment of severe chronic

hypertension in the first trimester is critical because fetal loss rates of 50% and significant maternal mortality have been reported in these patients. Most of the poor outcomes are related to superimposed preeclampsia. Further, women with chronic hypertension are also at higher risk for adverse neonatal outcomes if proteinuria is present early in pregnancy. Fetal loss and acceleration of maternal renal disease increase when serum creatinine levels exceed 1.4 mg/dL at conception.

ANTIHYPERTENSIVE DRUG SELECTION

The primary goal of treating chronic hypertension in pregnancy is to reduce maternal risk, but the choice of antihypertensive agent(s) is largely driven by the safety of the fetus. Methyldopa is preferred by many as first-line therapy, based on reports of stable uteroplacental blood flow and fetal hemodynamics and the absence of long-term (7.5-year follow-up) adverse effects on development of children exposed to methyldopa in utero. Other treatment options are summarized in Table II.

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