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Clinical Decision Making During the Perimenopause

Case Study and Commentary:

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In women, perimenopause is the time that ovarian function begins to change, usually preceding final menses by approximately 2 to 8 years.^{1,2} However, the transition between perimenopause and postmenopause is not distinct; the periods cannot even be defined until after menopause has occurred (ie, when menses have ceased for the previous 12 months). The median age of onset of perimenopause is between 45.5 and 47.5 years.³

Early perimenopause generally begins when neurohormonal systems governing ovulation start to become dysregulated. At this point, there usually is no evidence of overt modifications in menstrual cycle length. At middle to late perimenopause, however, irregular menstrual cycles become quite typical; shorter cycles, followed by longer periods between menstruation, are often characteristic. The clinical features of perimenopause are associated with varying serum concentrations of follicle-stimulating hormone (FSH); concentrations might reach a higher, postmenopausal range during some cycles but then return to premenopausal range during subsequent cycles. In addition, serum levels of gonadotropin and estrogen can be higher than normal during the transition from perimenopause to menopause.⁴ Such observations clearly indicate that using hormone levels to diagnose menopause while a patient is still menstruating is inappropriate.

Although the physiologic and clinical manifestations of the transition from full menses to menopause are not well defined or understood, there are certain recognizable symptoms accompanying perimenopause that can be highly distressing to the patient. Indeed, perimenopausal women self-report more symptoms associated with changes in menses than do premenopausal or postmenopausal women.⁵ For example, hot flashes (defined as sensations of warmth) are common and have a direct temporal relation with perimenopause and

menopause. Although a flush reaction and perspiration can accompany hot flashes, they need not, and so hot flashes and flushes should be noted independently. Although most women report hot flashes during perimenopause, the incidence of this symptom varies between western and Asian countries. Studies of women in western countries have reported the occurrence of hot flashes in up to 80% of the female population,⁶ whereas studies of women in Asian countries have reported an incidence as low as 10%.⁷

Another symptom sometimes associated with perimenopause and menopause is urinary incontinence. Unfortunately, the relationship between urinary incontinence and changes in menses is not clear, with some studies reporting a statistical association and others not finding one.^{8,9} The observation of a potential link might be explained in part by peri- and postmenopausal changes in the female urinary tract, such as atrophy of the bladder trigone, decreased sensitivity of the bladder neck and urethral sphincter to adrenergic receptors, and thinning of the urethral mucosa. The use of estrogens to treat urinary incontinence is consistent with this theoretical link. However, just as the relationship between urinary incontinence and change in menses is unclear, the effectiveness of estrogens in treating perimenopausal women with urinary incontinence has not been proved clearly or positively, with some studies reporting significant reductions in stress

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and urge urinary incontinence^{10,11} and others showing no or little symptomatic benefit for either.^{12,13}

Urinary tract infections, like urinary incontinence, can increase in frequency in peri- and postmenopausal women. Although there does not appear to be a direct causal relationship between such infections and the reduction or cessation of menses, physiologic changes might increase patients' risk for infection. Treatment of these urinary tract infections with vaginal estriol has been effective, resulting in significantly fewer episodes of infection and in improved conditions involving risk factors (eg, vaginal pH, vaginal flora) after treatment.¹⁴

During perimenopause, vaginal atrophy also can occur, often becoming clinically apparent after a patient reports dyspareunia, vaginal dryness, itching, and irritation; some patients, of course, can have these symptoms with no apparent atrophy. Treatment for vaginal atrophy usually involves use of systemic estrogen, although further vaginal therapy (eg, use of vaginal moisturizers) might be necessary in cases of women who refuse to take systemic estrogens.¹⁵

Finally, some women experience a reduction in sexual function and libido during peri- and postmenopause. However, the relationship between sexual drive/activity and change in menses is uncertain. Decreased sexual drive in women has been associated with vaginal dryness and friability, which can cause dyspareunia and reduced arousal during sexual relations.^{16,17} If the underlying causal factor or factors can be identified, treatment should be directed toward them. Although the effectiveness of other treatments for this symptom has yet to be rigorously proved, oral administration of low-dose methyltestosterone has been reported to increase self-stimulation but not self-reported arousal.¹⁸

Women in the perimenopausal period experience significant symptoms. Although not directly deleterious to their health, such symptoms can be worrisome and distressing to patients. Primary care providers should be sensitive to these concerns, as well as to those that present more serious health risks (eg, coronary artery disease, osteoporosis, other chronic conditions), because these health providers often are most accessible to the patient for discussion of symptoms. Consequently, knowledge of the epidemiology, etiology, and treatment of perimenopausal symptoms is essential to benefit patients in an area of their lives that they might deem most important.

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Women in the perimenopausal years experience not only physiologic changes but also major transitions

in social roles and life circumstances. An estimated 41 million women in the United States are now in or past menopause, and another 10 million or more will reach this stage of life in the next decade.¹⁹ Knowledge and research on the physiologic, psychological, and sociologic changes that come with menopause are steadily expanding.

The perimenopause is an important time for establishing preventive health goals. Coronary heart disease (CHD) is the leading cause of death in women in the United States²⁰; therefore, primary prevention of CHD is paramount. Research supports preventive strategies for other leading causes of morbidity and mortality, including cancer, alcohol abuse, depression, osteoporosis, and stroke. In addition, much of the functional loss considered as "normal aging" can be modified with lifestyle and pharmacologic intervention. A thorough understanding of the risks and benefits of hormone replacement therapy (HRT) is central to managing the menopause.

CASE STUDY

Initial Presentation

A 48-year-old woman presents to her primary care physician with a chief complaint of menstrual irregularity.

History

The patient's cycles had been regular until 8 months ago, when she noted the interval between menses was lengthening. Her normal menstrual cycle had been a 29-day interval and 5-day duration. Twice, her cycles changed to 45-day intervals, and now she reports amenorrhea for the past 5 months. She has experienced mild hot flushes, disturbed sleep, decreased libido, and emotional lability.

For the past 4 years, the patient has been the principal of a local elementary school, and for 20 years prior to becoming an administrator she was a schoolteacher. She becomes tearful when describing her job stress and difficulties managing her 3 adolescent children. Additionally, her 80-year-old mother with mild dementia recently moved in with the family. The patient states that her husband is supportive but has just become principal of the local junior high, which has significantly increased his job stress. The patient sporadically takes calcium supplementation and drinks wine to help her relax. She asks if this is what menopause is all about and if hormones will help.

Physical Examination

Physical examination reveals a blood pressure of 146/90 mm Hg, pulse of 88 bpm, respiratory rate of

18 breaths/min, and temperature of 98.2°F. The patient is 5' 5" tall and weighs 175 lb. Head, neck, lung, heart, and abdominal examinations reveal no abnormalities. Breast examination reveals a mobile smooth nodule in the right breast located in the upper outer quadrant. The nodule measures 1.5 × 1.5 cm and is nontender. There are no other abnormalities. Pelvic examination reveals normal external genitalia and dry vaginal mucosa. The cervix is parous and nontender, and the uterus is mobile and of normal size. Ovaries are nonpalpable.

QUESTION

- Is the patient menopausal?

DISCUSSION

By definition, menopause is diagnosed 12 months after the last menses. The final menses is determined retrospectively. Therefore, this patient is considered not menopausal but perimenopausal. Preceding the final menses by 2 to 8 years, the perimenopause is a period of changing ovarian function, characterized by a variety of symptoms including irregular menses, hot flashes, night sweats, urogenital atrophy, and psychological changes. Hot flashes define the onset of the perimenopause in many women.¹

QUESTION

- Are any diagnostic tests needed to confirm the diagnosis?

DISCUSSION

Laboratory Work-up

During the perimenopausal transition period, the serum levels of FSH increase at a variable rate. FSH levels may be in the postmenopause range during some cycles and then return to premenopausal concentrations during subsequent cycles. Therefore, a high concentration of FSH does not diagnose menopause in menstruating women. Gonadotropins and estrogen may be high during this transition as well.⁴ Luteinizing hormone (LH) increases later, when women are postmenopausal. Eventually, a 10- to 20-fold increase in FSH, accompanied by a 3-fold increase in LH, occurs and a peak level is reached 1 to 3 years after cessation of the last period.²¹ An FSH level greater than 40 IU/L confirms cessation of ovarian function in an amenorrheic woman.

A serum β -human chorionic gonadotropin (β -HCG) is the best diagnostic test to rule out pregnancy in sexually active women who are amenorrheic. The FSH level is suppressed during pregnancy. In women who experience hot flashes and a few months of amenorrhea, a FSH greater than 40 IU/L confirms menopause.²²

This patient is sexually active and has only been amenorrheic for 5 months; therefore, a β -HCG measurement should be done to rule out pregnancy. FSH and LH levels could be measured if the exact status of ovarian function is desired. A serum FSH should be performed prior to starting HRT in any asymptomatic woman who has had a hysterectomy. Clinicians should confirm ovarian failure in any woman who experiences early menopause (before age 40 years) by obtaining 2 elevated levels of FSH and by performing an appropriate work-up for secondary amenorrhea.²³

FURTHER HISTORY

The patient is emotional and admits to several life stressors. She has gained 20 lb in the past year and finds herself eating when she feels overwhelmed. She has been awakening at 3:00 AM and has trouble going back to sleep. Her 17-year-old daughter's grades have dropped significantly; her 15-year-old son was discovered to have marijuana at a party; but her 11-year-old daughter is doing well. The patient feels derelict as a mother and does not enjoy time with her family anymore. She reports being too tired to exercise and has difficulty with concentration, symptoms she attributes to the multiple demands in her life. She denies suicidal ideations.

QUESTION

- Is depression a symptom of menopause?

DISCUSSION

Women attending menopause clinics have an up to 45% incidence of clinical depression.²⁴ Cohort studies have identified an increased rate of perimenopausal depression primarily in women with a history of depression.^{25,26} In contrast, several longitudinal population-based studies report no association between depression and menopause.²⁷ It is extremely important to recognize that this patient is clinically depressed and will need management. The *DSM-IV* criteria for major depression are shown in **Table 1**. This patient has 7 of the 9 symptoms listed, meeting the criteria for an episode of major depression.

QUESTION

- What is the best approach to treating depression in this patient?

DISCUSSION

This patient should be medically treated for depression. Selection of an antidepressant should be based on safety, tolerability, cost, and dosing convenience. In addition, potential drug interactions and

Table 1. Criteria for Major Depressive Episode

- Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least 1 of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure
- (1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad or empty) or observation made by others (eg, appears tearful); in children and adolescents, can be irritable mood
 - (2) Markedly diminished interest or pleasure in all, or almost all, activities for most of the day, nearly every day (as indicated by either subjective account or observation made by others)
 - (3) Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day; in children, consider failure to make expected weight gains
 - (4) Insomnia or hypersomnia nearly every day
 - (5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
 - (6) Fatigue or loss of energy nearly every day
 - (7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
 - (8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
 - (9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

NOTE: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

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medical conditions should guide the selection of an appropriate antidepressant.

The selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and bupropion are equivalent in efficacy for the treatment of major depression.²⁸ SSRIs have the advantages of favorable safety profiles and once-daily dosing. Unlike the TCAs, SSRIs have no potential for lethal overdose and cause few or mild adverse effects. These activating antidepressants are typically administered in the morning to prevent insomnia, one of the potential side effects. During

Table 2. CAGE Screening Questionnaire for Alcohol Abuse

- C** Have you ever felt you should **C**ut down on your drinking?
- A** Have people **A**nnoyed you by criticizing your drinking?
- G** Have you ever felt bad or **G**uilty about your drinking?
- E** Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (ie, an **E**ye-opener)?

Adapted with permission from Mayfield D, McLeod G, Hall P. The CAGE questionnaire: validation of a new alcoholism screening instrument. *Am J Psychiatry* 1974;131:1121–3.

the first week of therapy, nausea can occur but usually subsides with tolerance. Some women experience anorgasmia as a side effect; this can be ameliorated with tolerance, a dosage reduction, or treatment with the serotonergic antihistamine cyproheptadine.

Anticholinergic effects, weight gain, sedation, and orthostatic hypotension are seen with the tertiary amine TCAs. These medications would not be a good choice for this patient because they would exacerbate her weight gain. In contrast, secondary amine TCAs cause less sedation and fewer anticholinergic effects. Side effects of bupropion include agitation, insomnia, psychosis, confusion, and weight loss. Even though the patient's insomnia may be exacerbated, it may be a good second-line agent to facilitate weight loss or as a substitution if sexual dysfunction becomes a problem when taking an SSRI.

Estrogen replacement alone can provide relief of vasomotor symptoms and minor cognitive and mood symptoms. However, HRT has limited benefit in the treatment of major depression, and this patient needs concomitant antidepressant drug therapy and/or psychotherapy.²⁹

QUESTION

- **Should the patient be screened for alcohol abuse?**

DISCUSSION

The National Institute of Alcohol Abuse and Alcoholism recommends using the CAGE questionnaire to screen every patient who drinks alcohol (**Table 2**). Two affirmative responses are a positive indication for alcoholism.³⁰ Using the *DSM-III* or *DSM-III-R* criteria as the standard, a CAGE questionnaire score of 2 or higher has a reported sensitivity of 73% to 81% for detecting alcohol abuse or dependence, while specificity ranges from 89% to 96%.^{31–33}

Screening for Alcohol Abuse

The patient's alcohol use is further assessed using the CAGE questionnaire. During evaluation, the patient admits to drinking more than she did a year ago. She drinks 2 to 3 glasses of wine each night and at parties will have as many as 4 drinks. She has never needed an eye-opener but does report feeling guilty about her drinking. Although she has considered the need to cut back on her alcohol use, she is annoyed at her husband's urging to do so.

QUESTION

- What are the health-related effects of this amount of alcohol intake?

DISCUSSION

Health Risks Associated with Alcohol Consumption

Alcohol intake of more than 6 drinks per day increases the risk of many adverse health events.^{34–36} Less is known about the effects of alcohol consumption in quantities more than 2 but fewer than 6 drinks per day. However, there have been at least 13 large prospective studies that have evaluated the relationship between alcohol consumption and all-cause mortality.^{37–49} These studies found either a U- or J-shaped association between alcohol consumption and all-cause mortality for both sexes. Six studies^{37,39,40,43,47,49} reported statistically significant risk estimates (relative risk [RR] range, 1.2 to 2.2), whereas 2 investigations^{41,42} showed that 2 or more alcoholic drinks per day significantly lowered overall mortality. Deaths from cardiovascular disease were, on average, lower across all exposure categories. In contrast, various cancers and fatal injuries were substantially increased.

The association between alcohol consumption and stroke has been examined in 5 recent large prospective studies.^{50–54} Two studies^{50,53} found increased risk of ischemic stroke among subjects who consumed 2 or more drinks per day; however, statistical significance was demonstrated in only 1 trial (RR, 2.0).⁵³ Of the remaining 3 studies, 1 found no effect,⁵¹ while 2 others^{52,54} found nonsignificant protective effects. The risk of hemorrhagic stroke may increase with alcohol consumption of 2 or more drinks per day. Statistically significant increases in risk (RR range, 3.1 to 3.9) were reported by 2 studies that examined the relationship between alcoholic intake and hemorrhagic stroke.^{52,53}

Breast cancer risk may increase with 3 or more drinks per day, as demonstrated in 5 large prospective studies.^{55–59} Two of these investigations^{56,59} showed a statistical significance (RR range, 1.6 to 3.3), whereas 3 studies^{55,57,58} found nonsignificant increases. Given the

public health importance of this cancer, women who have 3 or more drinks per day should be counseled to reduce their alcohol intake, despite the fact that a causal connection has not been definitely established between alcohol consumption and breast cancer.

Overall, these data suggest that alcohol-related morbidity and mortality may occur at doses below those typically considered diagnostic of alcohol abuse and/or dependence. Further, daily alcohol consumption of 2 drinks or more may increase the risk of developing hypertension,^{60,61} traumatic injuries,^{62,63} and adverse drug-alcohol interactions^{64,65} and may impair an individual's social and occupational functioning. The absolute magnitude of this effect can vary widely by outcome.

QUESTION

- How effective are primary care interventions for alcohol problems?

DISCUSSION

Brief Interventions

Establishing a treatment plan is very important in the management of patients with alcohol use disorders. Brief interventions for treatment of hazardous or harmful drinking have been demonstrated to be effective in the primary care setting. A brief intervention is defined as "a short counseling session focused on helping a person change a specific behavior"⁶⁶; it employs counseling strategies that are within the skill level of primary care physicians and can be performed in the course of an office visit. These techniques have been elucidated in the FRAMES acronym (Table 3).⁶⁷

QUESTION

- What laboratory studies should be considered in this patient?

DISCUSSION

Risk factors for CHD should be assessed in this patient; therefore, a lipid panel and fasting plasma glucose test should be ordered. Because the patient is depressed and fatigued and has gained weight over the past year, thyroid function should be determined by measuring thyroid-stimulating hormone (TSH) levels. Hypothyroidism can cause these symptoms and is common among women. In addition, a complete blood count (CBC) should be considered because depressed mood is often associated with iron or vitamin B₁₂ deficiencies. Liver function studies are warranted, given the patient's alcohol use. Her abnormal breast examination indicates the need for a mammography as well as a Papanicolaou smear to screen for cervical cancer.

Table 3. FRAMES Approach to Implementing a Brief Intervention

F	Giving F eedback about behaviors
R	Indicating patients' R esponsibility for changing their behavior
A	Giving patients specific A dvice on how behavior should be changed
M	Giving patients a M enu of options on how to change their behavior
E	Approaching patients with E mpathy
S	Supporting patients' S elf-efficacy

Adapted with permission from Miller WR, Rollnick S. Motivational interviewing: preparing people to change addictive behavior. New York: Guilford Press; 1991.

INITIAL TREATMENT

The physician tells the patient that her drinking puts her at risk, explaining the association of alcohol use and hypertension and the depressant effect of alcohol. The physician indicates that it is the patient's responsibility to change her behavior and advises that she stop drinking on her own or seek counseling. The patient says that she can quit on her own. The physician also prescribes an SSRI for treatment of her depression. Laboratory studies are ordered, and a follow-up visit is scheduled for 2 weeks.

2 WEEKS LATER

After 2 weeks, the patient returns for a follow-up visit. She has cut down on her alcohol consumption and reports feeling better. Further history is taken, which reveals that her father died at age 61 years from CHD and that her mother fractured her hip 2 years ago. Mammography shows a stable nodular density in the right breast. Results of a Papanicolaou smear and a serum β -HCG are normal. Fasting glucose level is 99 mg/dL. A fasting lipid panel reveals the following: total cholesterol, 251 mg/dL; low-density lipoprotein (LDL) cholesterol, 154 mg/dL; high-density lipoprotein (HDL) cholesterol, 50 mg/dL; triglycerides, 134 mg/dL. FSH level is 55.4 mIU/mL, and TSH level is 1.5 mIU/mL. Results of CBC and liver function tests are within normal limits.

QUESTIONS

- What risk factors for CHD does this patient have?
- What can be offered to modify these risk factors, and what evidence supports these treatments?

DISCUSSION

This patient presents with several CHD risk factors, including hypertension, family history of CHD, obesity, perimenopause, sedentary lifestyle, and hypercholesterolemia. She does not smoke or have a history of diabetes.

CHD Risk Factor Modification

Research on the primary prevention of CHD in women has been relatively sparse. Although many believe that heart disease is not a serious problem for women, it is estimated that 1 in 2 women will eventually die of heart disease or stroke, whereas 1 in 25 will die of breast cancer.⁶⁸ Moreover, in the Framingham Heart Study, nearly two thirds of sudden deaths in women due to CHD were in women who were previously asymptomatic.⁶⁸ Primary care providers should aggressively address modification of CHD risk factors in women.

Smoking. This patient should be commended on her nonsmoking status, as smoking is the leading preventable cause of CHD and death in women. The risk in heavy smokers (20 or more cigarettes per day) is 2 to 4 times higher than in nonsmokers.⁶⁹ Light smokers (1 to 4 cigarettes per day) double their risk compared with those who have never smoked.⁷⁰ People who quit smoking begin to reduce CHD risk within months, and after 3 to 5 years achieve the risk level of nonsmokers. In addition, smoking is the major risk factor in developing lung cancer, which is the most common malignancy seen in women.

Blood pressure. The patient's blood pressure should be lowered by decreasing her alcohol and salt consumption, encouraging weight loss and exercise, and, if necessary, initiating pharmacologic intervention. The association between hypertension and CHD in women is documented in epidemiologic⁷¹⁻⁷⁴ and prospective⁷⁵⁻⁷⁹ studies. Isolated systolic hypertension is a risk for older women and affects an estimated 30% of women older than 65 years.⁷² In the Systolic Hypertension in the Elderly Program,⁵⁷ in which women comprised 57% of the study population, any hypertensive therapy reduced the incidence of CHD by 25% and stroke by 36%. A subgroup meta-analysis of databases from 7 studies in the Individual Analyses of Antihypertensive Intervention Trials demonstrated a significant decrease in stroke and major coronary vascular disease events in women. These trials, which primarily used β -blockers and thiazide diuretics, showed an equal reduction in relative risk for both men and women.⁷⁴ A meta-analysis⁷⁴ of randomized treatment trials involving 37,000 subjects (47% women) evaluated therapy of

3 to 6 years' duration for mild to moderate hypertension. A mean decrease of 6 mm Hg in diastolic pressure significantly reduced overall mortality from vascular disease by 21%, fatal and nonfatal stroke by 42%, and fatal and nonfatal CHD by 14%. Weight reduction and dietary intervention are important in preventing and treating hypertension as well.⁷¹ Studies of non-pharmacologic treatment for hypertension in which 30% to 60% of the patients were women showed moderate success⁸⁰⁻⁸²; however, none of these trials have reported results separately for women.⁷⁹

Body mass index. Direct positive association between obesity and the risk of CHD has been demonstrated in a number of large, prospective cohort studies involving women.⁸³⁻⁸⁵ Results from the Nurses' Health Study, involving more than 120,000 middle-aged women, indicated that the risk of CHD was more than 3 times higher among women with a body mass index (BMI) of 29 or higher than among those with a BMI lower than 21.⁸⁵ A large portion of the excess risk is attributable to the influence of adiposity on blood pressure, glucose tolerance, and lipid levels after adjustment for these variables. A moderate residual effect persists that may be caused by other mechanisms.⁸⁵ This patient's current BMI is 29.2; therefore, she needs to lose 25 to 30 lb to attain a high-normal BMI of 25.

Cholesterol. Increased total serum cholesterol and LDL cholesterol levels are CHD risk factors in both women and men. From 1980 to 1991, more than 50% of women older than 55 years had serum cholesterol levels greater than or equal to 240 mg/dL.⁸⁶ In 1 meta-analysis, hyperlipidemia predicted CHD mortality in women younger than 65 but not in older women.⁸⁷ Observational studies further suggest that triglycerides may be an important risk factor for women and the elderly.⁸⁸ In contrast, an increased level of HDL cholesterol is a particularly strong predictor of decreased risk of CHD in women.⁸⁹⁻⁹¹ HDL cholesterol level was second only to age as a predictor of death from cardiovascular causes among women in the Lipid Research Clinic Follow-up Study.⁹⁰

Very few randomized trials of lipid-lowering therapy for primary prevention of CHD in women have been done. Three such trials that included women showed no evidence for reduction in CHD or total mortality.⁹² Although data from randomized trials have yet to provide definitive evidence that lowering cholesterol levels reduces women's risk of CHD, the consistency of observational data suggests that intervention to lower LDL cholesterol levels and raise HDL levels would benefit women. Secondary prevention trials of lipid-lowering therapy in women with CHD not only suggest substan-

tial treatment benefits but also point to a significant undertreatment of menopausal women with CHD.

The patient should be counseled to begin a low-fat diet, with a goal of lowering her LDL level to 130. If dietary changes are not successful after 6 months, pharmacologic intervention should be considered. Estrogen replacement therapy reduces LDL cholesterol level in postmenopausal women and should be considered. Statins may be used as first-line therapy in these women as well.

Diet. Compelling evidence from epidemiologic studies indicates that diets low in saturated fats and high in fruits, vegetables, whole grains, and fiber are associated with a reduced risk of CHD.⁹³ The Nurses' Health Study, for example, showed a significant inverse association between intake of dietary fiber and risk of CHD. The association was confined to fiber from cereal sources and demonstrated a 34% lower risk of total CHD in women in the highest quintile of cereal fiber intake than in those in the lowest quintile.⁹⁴ Recently published findings from the Iowa Women's Health Study reported a 30% to 36% reduction in risk of ischemic heart disease when comparing extreme quintiles of whole-grain food intake.⁹⁵ The reduction in CHD associated with increased cereal fiber is greater than expected from beneficial effects on serum cholesterol level alone. Plausible mechanisms include delayed absorption of macronutrients⁹⁶ leading to increased insulin sensitivity⁹⁷ and lower triglyceride levels.⁹⁸⁻¹⁰² Additionally, the Nurses' Health Study showed that frequent nut consumption was associated with a reduced risk of both fatal CHD and nonfatal myocardial infarction.¹⁰³ Other research has recently linked *trans*-fatty acids to adverse lipid profiles and increased CHD risk.¹⁰⁴

Exercise. The patient should also be advised to exercise daily for at least 30 minutes. Most of the epidemiologic studies of exercise and CHD have been conducted in men; however, studies in women suggest a comparable 50% risk reduction among active individuals compared with their sedentary counterparts. Evidence indicates that even activity of moderate intensity, such as brisk walking, is associated with a substantial reduction in CHD.¹⁰⁵

Monitoring for diabetes. Although this patient has a fasting glucose within the normal range, she should be counseled regarding diabetes symptoms and have her glucose checked annually. Diabetes mellitus appears to be an even stronger risk factor for CHD in women than in men.¹⁰⁶ It is associated with a 3- to 7-fold elevation in women's CHD risk, whereas in men the elevation is only 2- to 3-fold.¹⁰⁶

Hormone Therapy

The patient should be counseled regarding the risks and benefits of HRT. The Postmenopausal Estrogen/Progestin Trial established the effectiveness of HRT in the primary prevention of CHD. This trial showed that there was a significant lowering of LDL cholesterol level with oral equine estrogen even with the addition of medroxyprogesterone or micronized natural progesterone. Estrogen at a dose of 0.625 mg without progestin had the most favorable effect on HDL; however, the high rate of endometrial hyperplasia (at least 10%) makes this an unacceptable regimen for women with a uterus.¹⁰⁷ Observational studies in the general population have consistently shown a 50% reduction of CHD in women who used HRT.¹⁰⁸

The recent findings from the Heart and Estrogen/Progestin Replacement Study (HERS)¹⁰⁹ have challenged previous observational data regarding the role of hormones in preventing cardiovascular events. HERS was the first large-scale randomized clinical trial to test the efficacy and safety of HRT on clinical cardiovascular outcome in older postmenopausal women with confirmed coronary disease. The overall null result from HERS does not support the initiation of HRT in older postmenopausal women with confirmed CHD. The HERS trial included women with coronary disease younger than 80 years, with a mean age of 66.7 years. However, results from the HERS trial may not apply to women free of vascular disease.

Alternatives to traditional HRT include use of soy phytoestrogens and selective estrogen receptor modulators (SERMs). Due to a lack of sufficient data, no recommendation regarding their use for preventing CHD can be made at this time.

Addressing of CHD Risk Factors

The physician discusses with the patient ways to reduce her risk for heart disease. During the discussion, the patient expresses concerns about HRT and breast cancer risk; however, she has heard that HRT protects against osteoporosis, which she is also concerned about due to family history of hip fracture. The primary care physician recommends HRT based on the patient's medical and family history but expresses understanding toward the patient's concerns about breast cancer.

QUESTION

- What advice should be given to patients who are concerned about their risk for breast cancer?

DISCUSSION

Breast cancer is diagnosed in more than 170,000 wo-

men each year in the United States.¹¹⁰ Primary care physicians must become skilled at evaluating breast cancer risk and counseling women about its effect on medical decisions.¹¹¹ The most commonly used model to predict breast cancer risk was developed by Gail et al¹¹² based on findings from the Breast Cancer Detection Demonstration Project, a large mammographic screening program conducted in the 1970s. This model assigns a risk score based on number of first-degree relatives with breast cancer, age at menarche, age at first live birth, and number of breast biopsies (0, 1, or ≥ 2), as well as race or ethnicity. Risk score is then multiplied by an adjusted population risk of breast cancer to determine individual risk. Because the effects of risk factors interact and vary with age, breast cancer risk is most easily calculated with a software program available from The National Cancer Institute (<http://bcra.nci.nih.gov/brc/q1.htm>).

Observational studies suggest that HRT halves the risks of CHD and osteoporosis but increases the risk of breast cancer by 30% to 40%.^{113–115} Raloxifene, a SERM, provides less protection than HRT against CHD and osteoporosis but may reduce the risk of breast cancer.^{116–118} As a woman's risk of breast cancer increases, the relative benefit of raloxifene may increase.

Tamoxifen, another SERM, is the first drug shown to reduce the incidence of breast cancer in healthy women. The Breast Cancer Prevention Trial randomly assigned more than 13,000 women with a 5-year breast cancer risk of 1.7% or more to tamoxifen or placebo.¹¹⁹ Over a mean follow-up period of 4 years, tamoxifen had reduced the incidence of breast cancer by 49% compared with placebo.

Physical activity has been shown to modestly lower the risk of breast cancer in several studies.^{120,121} Mono-unsaturated dietary fat has been associated with a decreased risk of breast cancer and polyunsaturated dietary fat with an increased risk in some studies; however, no associations like these have been seen in other research.^{122,123} In addition, secondary prevention by mammographic screening in women 50 years of age and older reduces mortality from breast cancer.¹²⁴ All postmenopausal women should have yearly mammographic screenings.

This patient's risk of breast cancer is 1.3%, compared with 0.6% in a woman her age with no risk factors. In the Breast Cancer Prevention Trial,¹¹⁹ eligible women had a breast cancer risk of 1.7% or greater. The women in this study were selected due to their high risk of invasive cancer. With this patient's risk of 1.3%, it is acceptable to use HRT (as opposed to a SERM), which will provide protection against CHD and osteoporosis.

QUESTION

- How should risk of osteoporosis be managed in peri- and postmenopausal women?

DISCUSSION

Evaluation for Osteoporosis

The goal of evaluating women for osteoporosis is to establish a diagnosis based on bone mass measurement.¹²⁵ In perimenopausal women, assessing for fracture risk and need for therapy is also important. A history and physical examination are essential to an evaluation for any woman receiving routine care.¹²⁶ Demographic factors to consider include age, gender, and race; risk is increased in all persons with advancing age, in women, and in white women in particular. A patient's history should include family history of osteoporosis (especially maternal history of a hip fracture), cigarette smoking, caffeine and alcohol intake, evaluation of nutritional status, exercise regimen, and history of premature menopause.^{127–130} The history should also focus on diseases known to be secondary causes of osteoporosis, which can be drug-related, endocrine, gastrointestinal, neoplastic, renal, or rheumatologic.¹²⁸ Physical examination may reveal some signs of secondary diseases associated with osteoporosis. Primary osteoporosis is often not evident until a fracture occurs or until the disease is in later stages, with decreased height or kyphosis.

The most commonly used measurement to diagnose osteoporosis and predict fracture risk is based on the assessment of bone mass density (BMD), which is primarily determined by the mineral content of bone. The gold-standard diagnostic imaging test for determining a patient's BMD is dual-energy x-ray absorptiometry (DEXA).¹³¹ This technique uses 1 high-energy and 1 low-energy beam. After subtracting for soft-tissue absorption, the uptake by bone is used to calculate a BMD value. Two scores have been established by the World Health Organization: the T score, which compares BMD to that of a 25- to 30-year-old woman, and the Z score, which compares BMD to that of a same-age, same-sex individual. Each standard deviation below the normal T-score mean increases fracture risk 2- to 3-fold. The DEXA scan is noninvasive, delivers less radiation than a chest radiograph, is well tolerated by the patient, has high specificity and sensitivity, and is reproducible.¹³¹

Although guidelines for DEXA are not universal, the value of bone density in predicting fracture risk is established. The general consensus is that bone density measurement should be considered in patients on glucocorticoid therapy for 2 months or more and in pa-

tients with other conditions that place them at high risk for osteoporotic fracture.¹³² Unfortunately, the practice of universal screening—especially in perimenopausal women—has not been established. There are several unknowns in this approach. First, many women would need to be treated to prevent a single fracture. For example, in white women age 50 to 59 years, 70 DEXA tests would be required to prevent 1 hip or vertebral fracture over a 5-year period. Second, value has been not established for the common practice of beginning therapy in the perimenopausal period to prevent fractures later in life. Until there is solid evidence to support the cost-effectiveness of routine screening or the efficacy of early initiation of preventive drugs, an individualized approach is recommended. Bone density measurement should be considered when it would help the patient decide whether to institute treatment to prevent osteoporotic fracture.¹²⁵

Treatment of Osteoporosis

During perimenopause, primary prevention of osteoporosis is primarily related to lifestyle modifications. Growth in bone size and strength occurs during childhood, but bone accumulation is not complete until the third decade of life. It is during this time of bone growth that nutrition, exercise, and absence of smoking are vitally important to achieve an optimal peak bone mass.¹²⁵ However, in perimenopause, continued attention to lifestyle factors related to osteoporosis acceleration will slow the progression of decreasing bone mass.

Calcium is the specific nutrient most important for attaining peak bone mass and for preventing and treating osteoporosis. Sufficient data exist to recommend specific dietary calcium intakes at various stages of life. For perimenopausal women, calcium intake should be maintained at 1000 to 1500 mg daily. It is believed that only 50% to 60% of the population meets this requirement.¹³³ Vitamin D is required for optimal calcium absorption and thus is important for bone health. A recommended daily vitamin D intake of 400 to 600 IU has been established for adults.¹³³

Regular physical activity has been investigated as it relates to bone health. There is strong evidence that physical activity early in life contributes to higher peak bone mass. Some evidence indicates that resistance and impact exercise may be the most beneficial.¹³⁴ Exercise during the later years of life, in the presence of adequate calcium and vitamin D intake, probably has a modest effect on slowing a decline in BMD.¹³⁵ Perimenopausal women also should be counseled on the deleterious effects of smoking on bone density. Tobacco is the most

common risk factor for osteoporosis. Spinal BMD is decreased in smokers compared with nonsmokers, and menopause occurs earlier in women who smoke.¹³⁰ Nicotine accelerates bone loss and decreases intestinal calcium absorption in the elderly.^{129,130}

TRIAL OF HRT

The patient's risk factors for osteoporosis include white race, female gender, maternal history of hip fracture, and sedentary lifestyle. She has never smoked, is moderately overweight, and is perimenopausal. She decides to start HRT and agrees to lifestyle modifications. DEXA scanning is not necessary as HRT therapy will provide protection against bone loss and testing would be unlikely to result in a change in therapy. The patient should have an annual review of history, complete physical examination, and mammography while taking HRT.

6 MONTHS LATER

At 6 months' follow-up, the patient looks and feels much better. She has lost 10 lb, tries to exercise at least 4 times a week, has stopped using alcohol altogether, and reports that she is enjoying her life again. She has done well on the SSRI but has stopped and restarted her HRT. Initially, she felt better on HRT but stopped after hearing a report about breast cancer. After a telephone conversation with her primary care physician about her concerns, she reinstated HRT and now thinks she will continue taking it.

SUMMARY

The primary care physician assumes a critical role in helping women effectively transition through the perimenopausal period. Both primary and secondary prevention strategies are necessary. History, physical, and laboratory evaluation confirm hormonal status and assess for underlying disease. The physician should take this opportunity to assess stress level, mental health, alcohol use, and coping mechanisms of patients and to provide appropriate management, counseling, and referral. The physician and patient should engage in frank discussions about hormone replacement, diet, and physical activity to assure successful aging. **HP**

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