Postmenopausal Hormone Replacement Therapy for the Primary Prevention of Chronic Conditions

Recommendations and Rationale

U.S. Preventive Services Task Force

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This statement summarizes the U.S. Preventive Services Task Force (USPSTF) recommendations for use of hormone replacement therapy (HRT) for the primary prevention of chronic conditions in postmenopausal women, and it updates the 1996 recommendations contained in the *Guide to Clinical Preventive Services,* second edition.[1] Explanations of the ratings and of the strength of overall evidence are given in Appendix A and Appendix B, respectively. The complete information on which this statement is based, including evidence tables and references, is available in the summary of the evidence, "Postmenopausal Hormone Replacement Therapy for the Primary Prevention of Chronic Conditions."[2] The USPSTF recommendations and individual reports on hormone replacement therapy and specific disease outcomes are available on the USPSTF Web site (www.preventiveservices.ahrq.gov) and through the National Guideline Clearinghouse (www.guideline.gov).

The USPSTF reviewed the evidence on the use of postmenopausal HRT and the following outcomes: cardiovascular disease, including coronary heart disease and stroke; osteoporosis and fractures; thromboembolism; dementia and cognitive function; breast, colon, ovarian, and endometrial cancer; and cholecystitis. The USPSTF also reviewed evidence of the effects of HRT on phytoestrogens and osteoporosis and CVD. The use of HRT for relieving active symptoms of menopause, such as hot flashes, urogenital symptoms, and mood and sleep disturbances, among others, is outside the scope of these USPSTF recommendations, and literature on this topic was not reviewed. Sources for estimates of benefits and harms cited in this Recommendation statement are described in the summary of the evidence.[2]

SUMMARY OF RECOMMENDATIONS

The U.S. Preventive Services Task Force (USPSTF) recommends against the routine use of estrogen and progestin for the prevention of chronic conditions in postmenopausal women.

D recommendation.

The USPSTF found fair to good evidence that the combination of estrogen and progestin has both benefits and harms. Benefits include increased bone mineral density (good evidence), reduced risk for fracture (fair to good evidence), and reduced risk for colorectal cancer (fair evidence). Harms include increased risk for breast cancer (good evidence), venous thromboembolism (good evidence), coronary heart disease (CHD) (fair to good evidence), stroke

(fair evidence), and cholecystitis (fair evidence). Evidence was insufficient to assess the effects of HRT on other important outcomes, such as dementia and cognitive function, ovarian cancer, mortality from breast cancer or cardiovascular disease, or all-cause mortality.

The USPSTF concluded that the harmful effects of estrogen and progestin are likely to exceed the chronic disease prevention benefits in most women. The USPSTF did not evaluate the use of HRT to treat symptoms of menopause, such as vasomotor symptoms (hot flashes) or urogenital symptoms. The balance of benefits and harms for an individual woman will be influenced by her personal preferences, individual risks for specific chronic diseases, and the presence of menopausal symptoms.

The USPSTF concludes that the evidence is insufficient to recommend for or against the use of unopposed estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy. **I recommendation.**

The USPSTF found fair to good evidence that the use of unopposed estrogen has both benefits and harms. Although most current data come from observational studies, likely benefits include increased bone mineral density, reduced fracture risk, and reduced risk for colorectal cancer. Likely harms include increased risk for venous thromboembolism, cholecystitis, and stroke; in women who have not had a hysterectomy, unopposed estrogen increases the risk for endometrial cancer. Evidence is insufficient to determine the effects of unopposed estrogen on the risk for breast and ovarian cancer, CHD, dementia and cognitive function, or mortality. As a result, the USPSTF could not determine whether the benefits of unopposed estrogen outweigh the harms for women who have had a hysterectomy. Better data on benefits and harms are expected from

ongoing randomized trials, including the Women's Health Initiative (WHI) study of unopposed estrogen in women who have had a hysterectomy.[3]

CLINICAL CONSIDERATIONS

- Although the USPSTF concludes that the harms of estrogen-progestin therapy are likely to outweigh the chronic disease prevention benefits for most women, the absolute increase in risk from HRT is modest. Some women, depending on their risk characteristics and personal preferences, might decide that the benefits of taking HRT outweigh the potential harms. Based on results reported from the WHI study[3] for women aged 50 to 79 years (average age 63 years), 10,000 women taking estrogen and progestin for 1 year might experience 7 additional CHD events, 8 more strokes, 8 more pulmonary emboli, and 8 more invasive breast cancers, but would also have 6 fewer cases of colorectal cancer and 5 fewer hip fractures.

- Clinicians should develop a shared decision-making approach to preventing chronic diseases in perimenopausal and postmenopausal women. This approach should consider individual risk factors and preferences in selecting effective interventions for reducing the risks for fracture, heart disease, and cancer. Clinicians should discuss with patients other effective strategies for preventing osteoporosis and fractures (see other USPSTF recommendations available on the USPSTF Web site [www.preventiveservices.ahrq.gov]: *Screening for Postmenopausal Osteoporosis, Screening for Hypertension, Screening Adults for Lipid Disorders, Counseling To*

Prevent Tobacco Use, Counseling To Promote a Healthy Diet, Counseling to Promote Physical Activity, Screening for Breast Cancer, and Screening for Colorectal Cancer).

- The USPSTF did not consider the use of HRT for the management of menopausal symptoms. Decisions to initiate or continue HRT for menopausal symptoms should be made on the basis of discussions between a woman and her clinician. Women should be informed that there are some risks (such as the risk for venous thromboembolism, CHD, and stroke) within the first 1 to 2 years of therapy, whereas other risks (such as the risk for breast cancer) appear to increase with longer-term HRT. Other expert groups have recommended that women who decide to take HRT for the relief of menopausal symptoms use the lowest effective dose for the shortest possible time.
- The quality of evidence on the benefits and harms of HRT varies for different hormone regimens. Other than the 2 large randomized controlled trials of daily conjugated equine estrogen (CEE) and medroxyprogestrone acetate (MPA), most of the evidence on HRT comes from observational studies that did not differentiate among the effects of specific hormone preparations.[3,4] Until data indicate that other HRT regimens have a favorable balance of benefits to harms, a cautious approach would be to avoid using HRT routinely for the specific purpose of preventing chronic disease in women.
- Evidence is inconclusive to determine whether phytoestrogens (isoflavones such as iproflavone, which are found in soy milk, soy flour, tofu, and other soy products) are effective for reducing the risk for osteoporosis or cardiovascular disease (USPSTF, unpublished data, 2002).

SCIENTIFIC EVIDENCE

Epidemiology and Clinical Consequences

Hormone replacement therapy is one of the most commonly prescribed drug regimens for postmenopausal women in the United States. Many women use HRT to treat symptoms of menopause, but publicity about the possible ability of HRT to prevent chronic conditions, such as osteoporosis, CHD, Alzheimer disease, and colorectal cancer, has also contributed to the increase in HRT use over the past decade.

The median age of menopause in women in the United States is 51 years (range, 41 to 59 years), but ovarian production of estrogen and progestin begins to decrease years before the complete cessation of menses. Lower levels of circulating estrogen contribute to the accelerated bone loss and increased low-density lipoprotein levels that occur around menopause. The average woman in the U.S. who reaches menopause has a life expectancy of nearly 30 years. The probability that a menopausal woman will develop various chronic diseases over her lifetime has been estimated to be 46% for CHD, 20% for stroke, 15% for hip fracture, 10% for breast cancer, and 2.6% for endometrial cancer.[4] In North America, an estimated 7% to 8% of people 75 to 84 years of age have dementia, and postmenopausal women have a 1.4- to 3.0-fold higher risk for Alzheimer disease than do men. The lifetime risk for developing colorectal cancer for a woman in the U.S. is 6%, with more than 90% of cases occurring after 50 years of age.[5] Many of these causes of morbidity in older women appear to be influenced by estrogen or progestin.

Osteoporosis affects a large proportion of postmenopausal women in the U.S., and the prevalence of osteoporosis increases steadily with age. In the postmenopausal period, decline of estrogen production is associated with reduction of bone mineral density. Bone density is estimated to decrease by 2% each year during the first 5 years after menopause, followed by an annual loss of approximately 1% for the rest of a woman's life. On the basis of commonly used criteria, up to 70% of women older than 80 years of age have osteoporosis.

Benefits of Hormone Replacement Therapy

Osteoporosis and Fractures

Low bone density is associated with an increased risk for osteoporotic fractures. Good evidence from observational studies and randomized clinical trials demonstrate that estrogen therapy increases bone density and reduces risk for fractures. Good evidence from many randomized clinical trials has demonstrated that HRT increases bone density at the hip, the lumbar spine, and peripheral sites. A meta-analysis of 22 trials of estrogen reported an overall 27% reduction in nonvertebral fractures (relative risk [RR], 0.73; 95% CI, 0.56 to 0.94), although the quality of individual studies varied.[6] Observational studies have also demonstrated reductions in fractures of the vertebrae (RR for ever use, 0.6; 95% CI, 0.36 to 0.99), wrist (RR for current use, 0.39; 95% CI, 0.24 to 0.64), and possibly hip (RR for current use, 0.64; 95% CI, 0.32 to 1.04) among women taking HRT. The Heart and Estrogen/Progestin Replacement Study (HERS and its unblinded follow-up study, HERS II),[7] a trial of combined estrogen and progestin (CEE/MPA) for the secondary prevention of heart disease that reported many other outcomes, found no reduction in hip, wrist, vertebral, or total fractures with hormone therapy (relative hazard [RH] for total fractures, 1.04; 95% CI, 0.87 to 1.25). The WHI[3] found significant reductions in total

fracture risk (RH, 0.76; 95% CI, 0.63 to 0.92) among healthy women taking estrogen and progestin. The WHI also reported reductions for hip (RH, 0.66; 95% CI, 0.33 to 1.33) and vertebral fracture (RH, 0.66; 95% CI, 0.32 to 1.34), although these did not achieve statistical significance in adjusted analyses.[3] The WHI reported both nominal and adjusted confidence intervals. The USPSTF relied on nominal confidence intervals for the primary outcomes of breast cancer and CHD and adjusted confidence intervals for other secondary outcomes. The USPSTF concluded that there was good evidence that HRT increases bone mineral density and fair to good evidence that it reduces fractures.

Colorectal Cancer

A meta-analysis of 18 observational studies of postmenopausal women reported a 20% reduction in cancer of the colon (RR, 0.80; 95% CI, 0.74 to 0.86) and a 19% reduction in cancer of the rectum (RR, 0.81; 95% CI, 0.72 to 0.92) among women who had ever used HRT.[8] This decrease in risk was more apparent when current users were compared with those who had never used HRT (RR, 0.66; 95% CI, 0.59 to 0.74). Comparable results from the WHI study were reported for women taking CEE/MPA (RH, 0.63; 95% CI, 0.32 to 1.24), and the HERS studies also found reduced incidence of colon cancer (RH, 0.8; 95% CI, 0.46 to 1.45). The USPSTF concluded that there was fair evidence that HRT reduces colorectal cancer incidence.

Uncertain Benefits or Harms of Hormone Replacement Therapy

Cognition and Dementia

Nine randomized controlled trials examining the effect of HRT on cognition showed improvement in verbal memory, vigilance, reasoning, and motor speed among women who had

menopausal symptoms but not among women who were asymptomatic at baseline. Because of heterogeneity and variation in assessment of outcomes among studies, meta-analysis of these studies was not performed for the USPSTF.[2] A meta-analysis of 12 observational studies (1 of good quality, 3 of fair quality, and 8 of poor quality) showed a reduction in the risk for dementia among postmenopausal women taking HRT (RR, 0.66; 95% CI, 0.53 to 0.82).[9] Neither the WHI nor HERS has yet reported effects of HRT on cognition and dementia, but other ongoing trials are examining the effects of HRT on these endpoints. Given the methodologic limitations of the available studies and the potential for confounding or selection bias, the USPSTF concluded that there is insufficient evidence to determine whether HRT reduces the risk for dementia or cognitive dysfunction in otherwise healthy women.

Harms of Hormone Replacement Therapy

Breast Cancer

Because breast tissue is sensitive to reproductive hormones, there has been long-standing concern about breast cancer risk among women who take HRT. The estrogen and progestin arm of the WHI study was recently terminated because of an increased breast cancer incidence (RH, 1.26; 95% CI, 1.00 to 1.59).[3] However, no effect on breast cancer mortality was observed. Comparable increases in breast cancer incidence were observed among women taking estrogen and progestin over 6.8 years of follow-up in the HERS studies (RH, 1.27; 95% CI, 0.84 to 1.94).[7] Although many good observational studies on breast cancer and meta-analyses of these studies have been conducted, the conclusions are limited by healthy-user bias; variations in specific preparations, dose, and duration of estrogen and progestin therapy; and differences in the ways in which breast cancer end points were ascertained. In the aggregate, breast cancer incidence is

slightly increased for current (RR, 1.21 to 1.40) or long-term (>5 years) users (RR, 1.23 to 1.35) compared with nonusers.[2,10,11] However, there seems to be no effect on or decreased breast cancer mortality in ever- or short-term users (RR, 0.5 to 1.0).[11] The effects of long-term HRT use on breast cancer mortality in 2 good-quality cohort studies are conflicting.[12,13] Whether the combination of estrogen and progestin confers a greater risk than estrogen alone is unknown; WHI investigators have reported that no increase in breast cancer has been observed after 5 years of follow-up in the ongoing study of unopposed estrogen in women who have had a hysterectomy. The USPSTF concluded that there was fair to good evidence that HRT increases the incidence of breast cancer (with best evidence for estrogen plus progestin), but its effects on breast cancer mortality are uncertain.

Coronary Heart Disease

Coronary heart disease remains the leading cause of death among women. Hormone replacement therapy has diverse effects on lipid levels, endothelial wall function, blood pressure, coagulation factors, weight, and inflammation (for example, C-reactive protein). In the WHI study, women who took CEE/MPA daily had an increased risk for CHD (fatal and non-fatal myocardial infarctions), which was evident shortly after initiation of the study (RH, 1.29; 95% CI, 1.02 to 1.63). Coronary heart disease mortality was not significantly increased (RH, 1.18; 95% CI, 0.70 to 1.97). Meta-analysis of observational studies showed a statistically significant reduction in CHD (RR, 0.80; 95% CI, 0.68 to 0.95) among current HRT users, but not among ever or past users, compared with women who had never taken HRT (nonusers).[2,14] However, among studies that controlled for socioeconomic status (social class, education, or income), no benefit was seen among current HRT users (RH, 0.97; 95% CI, 0.82 to 1.16), suggesting that the

observed difference may be due to confounding by socioeconomic status and other lifestyle factors (eg, exercise, alcohol use) rather than use of HRT. Coronary heart disease mortality in observational studies is reduced among current HRT users (RR, 0.62; 95% CI, 0.40 to 0.90) but is not reduced among ever, past, or all users. Thus, selection bias (the tendency of healthier women to use HRT) appears to explain the apparent protective effect of estrogen on CHD seen in observational studies. The USPSTF concluded that HRT does not decrease, and may in fact increase, the incidence of CHD. The effects of HRT on CHD mortality, however, are less certain.

Stroke

A meta-analysis of 9 observational primary prevention studies suggests that HRT use is associated with a small increase in stroke incidence (RR, 1.12; 95% CI, 1.01 to 1.23), due primarily to an increase in thromboembolic stroke (RR, 1.20; 95% CI, 1.01 to 1.40).[14,15] The risk for subarachnoid bleeding and hemorrhagic stroke was not increased, and the overall stroke mortality was marginally reduced (RR, 0.81; 95% CI, 0.71 to 0.92). These results are consistent with findings from the estrogen and progestin arm of the WHI, which reported increased incidence of stroke in women taking CEE/MPA daily (RH, 1.41; 95% CI, 0.86 to 2.31). Two secondary prevention trials,[16,17] which were not included in the USPSTF review of HRT for primary prevention, reported no clear effect of HRT on stroke incidence, but stroke mortality was increased in women with a previous stroke.[17] The USPSTF concluded that there is fair evidence that HRT increases the risk for stroke.

Venous Thromboembolism (Deep Venous Thrombosis and Pulmonary Embolism)

In a meta-analysis of 12 studies (3 randomized, controlled trials; 8 case-control studies; and 1 cohort study), HRT was associated with an increased risk for venous thromboembolism (RR, 2.14; 95% CI, 1.64 to 2.81).[18,19] Five of 6 studies that examined the effects of HRT over time reported that the risk was highest within the first year of use (RR, 3.49; 95% CI, 2.33 to 5.59). These results are consistent with the findings in the estrogen and progestin arm of the WHI, which reported a 2-fold increased rate of venous thromboembolic disease (RH, 2.11; 95% CI, 1.26 to 3.55), including deep venous thrombosis and pulmonary embolism, in women taking CEE/MPA daily. The USPSTF concluded that there is good evidence that HRT increases the risk for venous thromboembolism.

Endometrial and Ovarian Cancer

Results of a previously published meta-analysis of 29 good-quality observational studies of endometrial cancer reported a relative risk of 2.3 (95% CI, 2.1 to 2.5) for users of unopposed estrogen compared with nonusers.[20] Risks increased with increasing duration of use (RR, 9.5 for 10 years of use). The risk for endometrial cancer remained elevated 5 or more years after discontinuation of unopposed estrogen therapy in these studies. With combined estrogen-progestin regimens, cohort studies showed a decreased risk for endometrial cancer (RR, 0.4; 95% CI, 0.2 to 0.6) compared with nonusers, but case-control studies showed an increase in risk (odds ratio [OR], 1.8; 95% CI, 1.1 to 3.1). Estrogen and progestin did not increase the risk for endometrial cancer in HERS (RH, 0.25; 95% CI, 0.05 to 1.18)[6] or in the WHI (RH, 0.83; 95% CI, 0.29 to 2.32). The USPSTF concluded that unopposed estrogen, but not combined estrogen-progestin therapy, increases risk for endometrial cancer.

Data on the association between the use of HRT and the risk for ovarian cancer are inconsistent. Results of case-control studies have been mixed, but 2 good-quality cohort studies reported increased risks (RR, 1.8 to 2.2) for ovarian cancer or ovarian cancer mortality among women who had taken HRT for 10 years or more[21,22]; a third study found no effect of HRT on ovarian cancer mortality.[23] One study suggested higher risk with unopposed estrogen than with estrogen-progestin therapy,[21] but data are insufficient to resolve the effects of different formulations or doses of HRT on ovarian cancer risk. Neither the WHI nor HERS has reported risk for ovarian cancer. The USPSTF concluded that evidence was insufficient to determine the effect of HRT on ovarian cancer.

Cholecystitis

Many but not all studies have reported an association between HRT and gallbladder disease. Results from a good-quality cohort study, the Nurses' Health Study, reported an increase in risk for cholecystitis among current HRT users (RR, 1.8; 95% CI, 1.6 to 2.0) and long-term users (>5 years) (RR, 2.5; 95% CI, 2.0 to 2.9) compared with nonusers.[24] Risk for cholecystitis remained elevated among past users. An increase in biliary tract surgery during 6.8 years of follow-up was reported among women taking estrogen plus progestin compared with those taking placebo (RR, 1.48; 95% CI, 1.12 to 1.95) in HERS[7,25]; the WHI has not reported biliary tract outcomes. The USPSTF concluded that there is fair evidence that HRT increases the risk for cholecystitis.

DISCUSSION

Most women begin HRT to relieve symptoms of menopause. Many women, however, have continued to take HRT because earlier studies indicated that HRT could prevent osteoporosis,

heart disease, and possibly other chronic diseases. More recent, higher quality studies have confirmed the benefits of HRT in preventing osteoporosis and fractures. These studies, however, demonstrated that HRT does not reduce, and may actually increase, the risk for CHD, and they confirmed previously suspected harms of HRT. Therefore, the calculus of benefits and harms has changed. Important questions about the effects of dose, duration, and specific preparations of hormone therapy remain. For an individual woman, the balance of benefits and harms may vary**.** Women considering taking HRT for prevention should make that decision with their clinician in the context of a discussion of benefits and harms of HRT and alternatives to HRT for the prevention of chronic diseases.

RECOMMENDATIONS OF OTHERS

Most organizations with guidelines on postmenopausal HRT have revised or are revising their recommendations in light of the findings of recently reported clinical trials. The American College of Obstetricians and Gynecologists[26] and the North American Menopause Society[27] recommend against the use of HRT for the primary or secondary prevention of cardiovascular disease. Both organizations recommend caution in using HRT solely to prevent osteoporosis and suggest that alternative therapies should also be considered. Both organizations consider HRT an acceptable treatment option for menopausal symptoms but advise caution about the prolonged use of HRT for the relief of symptoms. The American Heart Association now recommends against the use of HRT for primary or secondary prevention of cardiovascular disease.[28] The American College of Preventive Medicine,[29] the American Association of Clinical Endocrinologists,[30] and the American Academy of Family Physicians[31] have previously recommended counseling perimenopausal and menopausal patients about the benefits and harms

of HRT based on the individual risks for a particular patient, but these organizations have not yet revised their recommendations in light of the findings of recently reported trials. The Canadian Task Force on Preventive Health Care is updating its assessment of the effect of HRT on cardiovascular disease and cancer.[32]

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