

Hormone Therapy for the Prevention of Chronic Conditions in Postmenopausal Women

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The contents of this course are taken from the Agency for Healthcare Research and Quality. Learning objectives and post test have been prepared by Dr. Ratnakar P. Kini.

Objectives

Upon completion of this course, the learner will be able to:

1. Explain the present considerations for hormone replacement therapy in Postmenopausal women
2. Discuss about the benefits involved in hormone replacement therapy (HRT)
3. Discuss about the harmful effects of hormone replacement therapy
4. Compare and analyze observations in preventing chronic diseases

Clinical Considerations

- The balance of benefits and harms for a woman will be influenced by her personal preferences, her risks for specific chronic diseases, and the presence of menopausal symptoms. A shared decision-making approach to preventing chronic diseases in perimenopausal and postmenopausal women involves consideration of individual risk factors and preferences in selecting effective interventions for reducing the risks for fracture, heart disease, and cancer. Other USPSTF recommendations for prevention of chronic diseases (screening for osteoporosis, high blood pressure, lipid disorders, breast cancer, and colorectal cancer; and counseling to prevent tobacco use) are available at: www.preventiveservices.ahrq.gov.
- The USPSTF did not consider the use of hormone therapy for the management of menopausal symptoms, which is the subject of recommendations by other expert groups. Women and their clinicians should discuss the balance of risks and benefits before deciding to initiate or continue hormone therapy for menopausal symptoms. For example, for combined estrogen and progestin, some risks (such as the risks for venous thromboembolism, coronary heart disease [CHD], and stroke) arise within the first 1 to 2 years of therapy, and other risks (such as the risk for breast cancer) appear to increase with longer-term hormone therapy. The

populations of women using hormone therapy for symptom relief may differ from those who would use hormone therapy for prevention of chronic disease (e.g., age differences). Other expert groups have recommended that women who decide to take hormone therapy to relieve menopausal symptoms use the lowest effective dose for the shortest possible time.

- Although estrogen alone or in combination with progestin reduces the risk for fractures in women, other effective medications (e.g., bisphosphonates and calcitonin) are available for treating women with low bone density to prevent fractures. The role of chemopreventive agents in preventing fractures in women without low bone density is unclear. The USPSTF addressed screening for osteoporosis in postmenopausal women in 2002.²
- Unopposed estrogen increases the risk for endometrial cancer in women who have an intact uterus. Clinicians should use a shared decision-making approach when discussing the possibility of using unopposed estrogen in women who have not had a hysterectomy.³

Discussion

The median age of menopause in women in the United States is 51 years (range 41-59 years), but ovarian production of estrogen and progestin begins to decrease years before the cessation of menses. The average woman in the United States who reaches menopause has a life expectancy of nearly 30 years. The probability that a menopausal woman will develop various chronic diseases during her lifetime has been estimated to be:

- 46% for CHD.
- 20% for stroke.
- 15% for hip fracture.
- 10% for breast cancer.
- 2.6% for endometrial cancer.⁴

In North America, an estimated 7 to 8 percent of people 75 to 84 years of age have dementia, and more than 90 percent of cases of colorectal cancer occur after the age of 50.⁵

Benefits of Hormone Therapy

Osteoporosis and Fractures

Good evidence from observational studies and randomized clinical trials demonstrates that estrogen therapy increases bone density and reduces the risk for fractures. The combined estrogen-progestin arm of the Women's Health Initiative (WHI) trial,⁶ a fair-

quality study, found significant reductions in total fracture risk (hazard ratio [HR], 0.76; adjusted 95% confidence interval [CI], 0.63-0.92) among healthy women taking estrogen and progestin. This arm of the WHI trial also showed reductions for hip and vertebral fracture, although these did not achieve statistical significance.⁶ (In its analysis, the USPSTF used nominal 95% CIs for the primary outcomes and adjusted 95% CIs for all secondary outcomes.)

The estrogen-only arm of the WHI trial also reported decreased risk for hip and vertebral fracture, which also did not reach statistical significance.⁷ A meta-analysis of 22 trials of estrogen reported an overall 27-percent reduction in non-vertebral fractures (relative risk [RR], 0.73; [95% CI, 0.56-0.94]), although the quality of individual studies varied.⁸ The Heart and Estrogen/progestin Replacement Study (HERS) and its unblinded followup study, HERS II,⁹ a fair-quality trial of combined estrogen-progestin 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, 0.87-1.25). Overall, a good-quality body of evidence supports the efficacy of hormone therapy in increasing bone density and decreasing fracture risk.

Colorectal Cancer

Results from the WHI study⁶ and HERS⁹ showed a trend toward reduced incidence of colon cancer (HR, 0.63; adjusted 95% CI, 0.32-1.24 and RH, 0.81; 95% CI, 0.46-1.45, respectively), but the trend did not reach statistical significance. The estrogen-only arm of the WHI trial showed neither benefit nor harm for colorectal cancer risk (HR, 1.08; adjusted 95% CI, 0.63-1.86).⁷ A meta-analysis of 18 observational studies of postmenopausal women reported a 20-percent reduction in colon cancer (RR, 0.80; 95% CI, 0.74-0.86) and a 19-percent reduction in rectal cancer (RR, 0.81; 95% CI, 0.72-0.92) among women who had ever used combined estrogen-progestin or estrogen alone compared with women who had never used hormone therapy.¹⁰ This decrease in risk was more apparent when current users were compared with those who had never used hormone therapy (RR, 0.66; 95% CI, 0.59-0.74). Overall, the evidence suggesting a trend toward reduction of colorectal cancer risk with combined hormone therapy should be interpreted cautiously until controlled trials clarify whether therapy has either no benefit or modest benefit.

Harms of Hormone Therapy

Breast Cancer

The estrogen-progestin arm of the WHI study was terminated after an average of 5.2 years of followup because "evidence for breast cancer harm, along with evidence for some increase in CHD, stroke, and pulmonary embolism, outweighed the evidence of benefit for fractures and possible benefit for colon cancer."⁶ This study showed an increased invasive breast cancer incidence (HR, 1.26; nominal 95% CI, 1.00-1.59).

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 followup in HERS.⁹

The U.K. Million Women Study, a fair-quality study, showed an increased risk for breast cancer in current users of combined estrogen-progestin (RR, 2.00; 95% CI, 1.91-2.09) compared with those who had never used hormone therapy.¹¹ Results from two good-quality cohort studies conflict on the effects of long-term hormone therapy on breast cancer mortality.^{12,13} Overall, there is a good-quality body of evidence indicating that combined estrogen-progestin increases breast cancer risk. It is unclear whether the combination of estrogen-progestin confers a greater breast cancer risk than estrogen alone. In studies of estrogen alone, the results are conflicting: the Million Women Study showed an increased risk for breast cancer in current users of estrogen only (RR, 1.30; 95% CI, 1.22-1.38) compared with those who had never used it¹¹; but the estrogen-only arm of the WHI trial showed a trend toward breast cancer prevention (HR, 0.77; nominal 95% CI, 0.59-1.01).⁷

Coronary Heart Disease

In the WHI study, women who took combined estrogen-progestin daily, compared with women taking placebo, had an increased risk for CHD (fatal and non-fatal myocardial infarctions), which became evident shortly after initiation of the study (HR, 1.29; nominal 95% CI, 1.02-1.63).⁶ However, mortality from CHD was not significantly increased among the women taking combined hormone therapy daily. One meta-analysis of observational studies showed a statistically significant reduction in CHD (RR, 0.80; 95% CI, 0.68-0.95) among current hormone therapy users, but not among those who had used hormone therapy in the past or among those who had never used it.¹⁴ This meta-analysis also showed that CHD mortality in observational studies was reduced among current hormone therapy users (RR, 0.62; 95% CI, 0.40-0.90) but was not reduced among those who had used hormone therapy in the past. However, among studies that controlled for socioeconomic status (social class, education, or income), no CHD benefit was seen among current hormone therapy users, suggesting that the observed difference may be due to confounding by socioeconomic status and other lifestyle factors (e.g., exercise or alcohol use) rather than use of hormone therapy. Thus, selection bias (in this case, the tendency of healthier women to use hormone therapy) appears to explain the apparent protective effect of estrogen against CHD seen in observational studies. The estrogen-only arm of the WHI trial showed no decreased risk for CHD.⁷

Stroke

A meta-analysis of 9 observational primary prevention studies suggests that hormone therapy is associated with a small increase in stroke incidence (RR, 1.12; 95% CI, 1.01-1.23), due primarily to an increase in thromboembolic stroke (RR, 1.20; 95% CI, 1.01-1.40).^{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, 0.71-0.92). These results are consistent with findings from the WHI, which reported increased

incidence of stroke in women taking combined estrogen-progestin daily (HR, 1.41; adjusted 95% CI, 0.86-2.31).⁶ The estrogen-only arm of the WHI trial, which was terminated after an average of 6.8 years of followup, showed a trend toward increased stroke risk with unopposed estrogen use (HR, 1.39; adjusted 95% CI, 0.97-1.99).⁷

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), hormone therapy (estrogen alone or in combination with progestin) was associated with an increased risk for venous thromboembolism (RR, 2.14; 95% CI, 1.64-2.81).^{16,17} Five of 6 studies that examined the effects of hormone therapy over time reported that the risk was highest within the first year of use (RR, 3.49; 95% CI, 2.33-5.59). These results are consistent with the findings in the estrogen-progestin arm of the WHI,⁶ which reported a 2-fold increased rate of venous thromboembolic disease, including deep venous thrombosis and pulmonary embolism, in women taking combined estrogen-progestin daily. The estrogen-only arm of the WHI trial showed a trend toward increased risk for venous thromboembolism with unopposed estrogen use (HR, 1.33; adjusted 95% CI, 0.86-2.08).⁷

Cognition and Dementia

While earlier studies showed a beneficial effect of hormone therapy on cognition, these studies had marked heterogeneity and variation in assessment of outcomes. For example, 9 randomized controlled trials examining the effect of hormone therapy on cognition in women showed improvement in verbal memory, vigilance, reasoning, and motor speed; however, these trials may have biased results, since they were conducted with women experiencing menopausal symptoms at baseline. 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 hormone therapy (RR, 0.66; 95% CI, 0.53-0.82).¹⁸

Because of issues of internal and external validity from these previous studies, the more recent, fair-quality WHI memory studies are more likely to represent the effects of hormone therapy use in the healthy postmenopausal population. The WHI memory study showed decreased global cognitive function (measured by the modified Mini-Mental State Examination) in women taking estrogen alone and in the pooled group of women taking estrogen alone or estrogen-progestin.¹⁹ The WHI memory study also showed an increased risk for probable dementia or mild cognitive impairment in both the estrogen-alone (HR, 1.38; 95% CI, 1.01-1.89) and estrogen-progestin (HR, 1.44; 95% CI, 1.04-1.99) arms of the trial.²⁰ The overall evidence supports harmful effects of hormone therapy on cognitive function, although the clinical relevance of this difference in cognitive function is unclear.

Endometrial and Ovarian Cancer

Results of a meta-analysis of 29 good-quality observational studies of endometrial cancer reported a relative risk of 2.3 for users of unopposed estrogen compared with nonusers.²¹ Risks increased with increasing duration of use (RR, 9.5 for 10 years of use), and the risk for endometrial cancer remained elevated 5 or more years after discontinuation of unopposed estrogen therapy. Estrogen and progestin did not increase the risk for endometrial cancer in HERS⁵ or in the WHI.⁶

Data on the association between the use of hormone therapy and the risk for ovarian cancer are inconsistent. Two good-quality cohort studies reported increased risks for ovarian cancer or ovarian cancer mortality among women who had taken hormone therapy for 10 years or more.^{22,23} However, a third study found no effect of hormone therapy on ovarian cancer mortality.²⁴ One study suggested higher risk with unopposed estrogen than with estrogen-progestin therapy,²² but data are insufficient to resolve the effects of different formulations or doses of hormone therapy on ovarian cancer risk. Neither the WHI nor HERS reported risk for ovarian cancer.

Cholecystitis

Results from the Nurses' Health Study, a good-quality cohort study, reported an increased risk for cholecystitis among current hormone therapy users and long-term users (>5 years) compared with nonusers.²⁵ Risk for cholecystitis remained elevated among past users. An increase in biliary tract surgery during 6.8 years of followup was reported among women taking estrogen plus progestin compared with those taking placebo in HERS.^{9,26} The WHI has not reported on outcomes for biliary tract disease among women taking hormone therapy.

Conclusion

Combined estrogen-progestin may reduce the risk for fractures and colorectal cancer but has no beneficial effect on CHD. The use of combined estrogen-progestin may lead to increased risk for breast cancer, venous thromboembolism, stroke, cholecystitis, dementia, and lower global cognitive function. The excess absolute combined risks for CHD and breast cancer that can be attributed to hormone therapy are low; for example, according to WHI results, there would be 7 more CHD events, 8 more strokes, 8 more pulmonary embolisms, and 8 more cases of invasive breast cancer each year for every 10,000 women taking hormone therapy. The absolute risk reduction for every 10,000 women would be 6 fewer colorectal cancers and 5 fewer hip fractures. The evidence is insufficient to determine the effects of hormone therapy on the incidence of ovarian cancer, mortality from breast cancer or CHD, or all-cause mortality. Evidence about the effects of different dosages, types, and delivery modes of hormone therapy remains insufficient. Overall, the harmful effects of combined estrogen and progestin are likely to exceed the benefits of chronic disease prevention for most women.

Since unopposed estrogen increases a woman's risk for endometrial cancer, it has been used in postmenopausal women without a uterus to prevent chronic disease. While estrogen alone may decrease a woman's risk for fractures, it has no beneficial effect on CHD. The use of estrogen alone may lead to increased risk for thromboembolism, stroke, dementia, and lower global cognitive function. The evidence is insufficient to determine the effects of unopposed estrogen on the incidence of breast cancer, ovarian cancer, or colorectal cancer as well as breast cancer mortality or all-cause mortality. Overall, the harmful effects of unopposed estrogen are likely to exceed the chronic disease prevention benefits in most women.

Recommendations of Other Groups

The American College of Obstetricians and Gynecologists,²⁷ American Heart Association,²⁸ North American Menopause Society,²⁹ and Canadian Task Force on Preventive Health Care,^{30,31} recommend against use of HT for the prevention of chronic diseases in postmenopausal women.

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