REVIEW ARTICLE

Menopausal hormone therapy for the primary prevention of chronic conditions

U.S. Preventive Services Task Force Recommendation Statement

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KEY WORDS

cardiovascular disease, chronic disease, hormone replacement therapy, menopause

ABSTRACT

Since the early 20th century, scientists have been tantalized with the hypothesis that premenopausal health benefits in women can be preserved in postmenopausal women with the supplementation of exogenous hormone replacement therapy (HRT) of estrogen (alone/with progesterone). This hypothesis was shattered when the results of 2 large randomized controlled trials (RCTs), the Heart Estrogen/Progesterone Replacement Study (HERS) and Women's Health Initiative (WHI), reported an increased risk of adverse clinical outcomes including coronary heart disease, thromboembolic events, stroke, dementia, urinary incontinence, gallbladder disease, and breast cancer. However, since the WHI was published, firestorms of critique, controversy, and multiple subgroup analyses have populated the medical literature, predominantly focused around the analysis of the age of women at entry into the trials (hypothesized as an effect modifier) and suggesting lower-dose preparations including using bioidentical hormones. Recently, the U.S. Preventive Services Task Force (USPSTF) along with other professional groups have issued recommendations against the use of HRT to prevent chronic conditions. In this review, we review the most recent evidence, including the long-term follow-up data from RCTs along a multitude of health outcomes.

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Introduction Coronary heart disease (CHD) is the leading cause of death among women in the Western world, and it is a rising cause of death among economies in transition. It is well known that the incidence of CHD among women increases approximately a decade later than in men, and approximates that in men by the 7th decade of life.[1] Historically, this perceived "benefit" has been largely attributed to the protective effects of endogenous estrogen, which is significantly reduced when women experience menopause, at the age of 50 years, on average. With this in mind, randomized controlled trials (RCTs) of estrogen replacement have been conducted in men and women with the hope of mimicking the nature's secret and reducing the incidence of CHD. Unfortunately, most of these trials have failed. Below we provide a brief review of the evidence of estrogen replacement among peri- and postmenopausal women.

There has been a long and tumultuous history of the role of estrogen therapy to avert the aging process in women's health, including Dr. Wilson's 1966 best-selling book *Feminine Forever*, in which he claimed that the premenopausal health benefits of women could be persevered with estrogen therapy.[2] Even the Framingham investigators claimed that premenopausal women "enjoyed immunity" from heart disease, and that this had implications for "retarding the disease in the male".[3] For over half a century, scientists have been captivated with the hypothesis that hormone replacement therapy (HRT) (estrogen and/or progesterone) can extend the life course of women, despite malignancies observed in the 1930s among HRT users.[4,5] Small studies were beginning to accumulate and, in 1991, Stampfer and Coldwitz conducted a nonsystematic quantitative review of 31 observational studies and concluded that there was "strong evidence" for the protective cardiovascular

effects of HRT.[6] This controversial study inspired the need to test the hypothesis using a more compelling study design and, shortly after, several RCTs were underway. In 1998, the Heart Estrogen/Progesterone Replacement Study (HERS), which recruited 2763 women participants, examined the effect of estrogen on numerous surrogate outcomes and clinical events among women with established CHD.[7] In 2002, the Women's Health Initiative (WHI) study examined the effects of estrogen and estrogen plus progesterone among postmenopausal women without a prior history of CHD. The WHI was the definitive large randomized trial, and the results from this study have guided the use of HRT in the prevention of chronic disease in women ever since.[8] The WHI recruited a total of 27,347 women divided between those with and without prior hysterectomy, testing estrogen only vs. placebo, and estrogen plus progesterone vs. placebo, respectively. The WHI results shattered the HRT prevention therapy hypothesis, with both trial strata reporting an increased risk of adverse clinical outcomes including thromboembolic events, CHD, stroke, gallbladder disease, and breast cancer.[8] While there has been a post-hoc analysis examining whether the time since menopause of the women enrolled in the WHI may influence the RCT effects, these are mostly subgroup analyses and cannot override the main effects of the trial. After these results were published, the U.S. Preventive Services Task Force (USPSTF) along with other professional groups issued recommendations against the use of HRT to prevent chronic conditions.[9-11]

Currently, the U.S. Food and Drug Administration (FDA) approves the use of HRT, estrogen alone or in combination with progestin, for the treatment of menopausal symptoms including vasomotor hot flashes, urogenital atrophy, and for the prevention of osteoporosis, and most recommendations posit it only be used in women with severe symptoms for "the lowest dose for the shortest period of time."[12,13]

However, since the WHI has been published, firestorms of critique, controversy, and multiple subgroup analyses have populated the medical literature. These include the analysis of the age of women at entry into the trials as an effect modifier (suggesting a more positive effect among perimenopausal rather than postmenopausal women) and studies suggesting lower-dose preparations including bioidentical hormones (a marketing term) are safe.

Recently, the Dutch group conducted an open-label RCT among 1000 women aged from 45 to 58 years (women, who were recently postmenopausal or had perimenopausal symptoms in combination with recorded postmenopausal serum follicle-stimulating hormone values) testing HRT (17-β-estradiol, Estrofem; Novo Nordisk, Denmark) vs. no treatment. The randomized part of the treatment arm was stopped early[14] (median follow-up, 11 years) after the results from the WHI trial showed harm, but the Dutch investigators continued follow-up for 16 years. They reported that cardiovascular events were lower in the treatment arm compared to no treatment, and cancer was not increased; however, this study was terminated early and was not adequately powered to make any definitive conclusions.[14] Moreover, the treatment group in this study was not compared to placebo, and the study was not blinded, also affecting the rigor of the results.[15] In our opinion, the overall evidence does not change the current recommendations by the USPSTF.[11]

To evaluate the long-term effectiveness of HRT as primary prevention in reducing the risk of chronic disease and adverse events among postmenopausal women, the USPSTF conducted a systematic review evaluating 9 RCT's of fair quality, published since 2002 focusing on evidence gaps that were unresolved at the time of the previous recommendations.[11] The results of 9 placebo-controlled RCTs include the results from the 2 WHI trials,[8,16] Women's Health Initiative Memory Study (WHIMS)[17-19] and Women's Health Initiative Study of Cognitive Aging (WHISCA),[20-22] Estrogen Memory Study (EMS),[23] HERS,[7,24-29] Estrogen in the Prevention of Reinfarction Trial (ESPRIT),[30] Ultra-low Dose Transdermal Estrogen Assessment (ULTRA),[31-33] and Women's International Study of Long-Duration Oestrogen After Menopause (WISDOM).[34] A formal meta-analysis was not performed due to two main concerns; first, that the substantial sample size from the WHI studies, including WHIMS and WHISCA, would dominate the overall findings, and second, the studies are too heterogeneous. As a result, the main estimates for each outcome were used.[11] The results were generally analyzed according to 2 treatment regiments: 1) estrogen alone (conjugated equine estrogen, 0.625 mg/d) vs. placebo and 2) estrogen plus progestin (conjugated equine estrogen 0.625 mg/d plus medroxyprogesterone acetate 2.5 mg/d) vs. placebo.[11] Women assigned to estrogen plus progestin in the WHI trials had fewer fractures (46 fewer per 10,000 woman-years) and fewer cases of diabetes (15 per 10,000 woman-years), although the investigators used strict criteria to determine fractures and relied on a post-hoc analysis of self-report to analyse the incidence of diabetes. Among the estrogen-only group, women had fewer fractures (56 fewer per 10,000 woman-years) and surprisingly fewer cases of invasive breast cancer (8 fewer per 10,000 woman-years) and breast cancer deaths (2 fewer per 10,000 woman-years). Despite some benefits, there were several harms. Women randomly allocated to the estrogen-plus-progestin group had a higher incidence of invasive breast cancer (8 more per 10,000 woman-years) (despite fewer cases in the estrogen-only group), stroke (9 more per 10,000 woman-years), pulmonary emboli (9 more per 10,000 woman-years), deep vein thrombosis (12 more per 10,000 woman years), gallbladder disease (20 more per 10,000 woman years), probable dementia (22 more per 10,000 woman-years), urinary incontinence (872 more

per 10,000 woman-years), and more lung cancer deaths (5 more per 10,000 woman years).[11] Women randomly allocated to the estrogen-only group had more stroke (11 more per 10,000 woman-years), deep vein thrombosis (7 more per 10,000 woman years), gallbladder disease (33 more per 10,000 woman years), and urinary incontinence (1271 per 10,000 woman years).[11]

Of note, although there are not extensive differences from the initial results of the WHI trials on most outcomes, there is a notable increase in the estimated risk of breast cancer in the estrogen-plus-progestin group, and no increase or possibly a protective effect among the estrogen-only group. However, this finding may be due to the play of chance as it is inconsistent with other observational and clinical studies, or due to the increased length of follow-up data (11 years) currently available, allowing opportunity for the disease to manifest itself in the estrogen-plus-progestin group. Also, it appears that the risk of stroke, thromboembolism, and fractures did not have lasting effects once the HRT was stopped.[11]

As the majority of women enrolled in the studies were postmenopausal between the ages of 60 to 69 years, much of the criticism has been centered around age, since this age group does not represent the majority of current HRT users who use it for menopausal symptoms.[11,12,35-37] Subgroup analyses were undertaken and relationships in specific subgroups of women (previous smokers, age groups, early contraceptive use, high high-density lipoprotein levels, high C-reactive protein levels, obesity status, age since menopause) in the individual studies and in the meta-analysis was sought. We believe, however, that all subgroup effects should be interpreted with great caution, due to the inherent limitations of this analytical approach. The primary outcome of interest in the WHI study was the rate of CHD (a composite outcome consisting of CHD death and myocardial infarction rate), and the study results indicated an increased risk for CHD in the estrogen-plus-progestin group after 5 years of follow-up, persisting at 8.6 years (hazard ratio [HR], 1.22; 95% confidence interval [CI], 0.99–1.50) and no benefit for the estrogen-only group (HR, 0.95; 95% CI, 0.78–1.15). The subgroup effects that do not support the direction of the main study effects for which the study is powered are particularly troublesome to interpret. This is because for the subgroup effects to be considered, they should be outlined in the design stage with an a priori hypothesis and indicate the hypothesized direction and magnitude of the treatment effect, stratifying on the subgroup characteristic of interest prior to randomization and then randomizing within the subgroup[38,39] – a practice which was not undertaken in any of the 9 individual RCTs. Another issue requiring cautionary interpretation is the fact that despite the large number of total patients, there were high attrition rates in the studies (42% in active the treatment arm in WHI), low adherence to medication, (11% crossover to placebo), and few HRT regimes (i.e., in the main WHI trial, they could not separate the effects of estrogen from progesterone because patients were randomized to either estrogen-plus-progesterone or placebo).[8] Thus, the estimated main effects are likely an underestimate of the magnitude of adverse effects.

The recent recommendations by the USPSTF recognize that although there is a moderate benefit in estrogen-plus-progestin therapy in reducing the risk for fractures, this benefit is outweighed by the harms associated with this therapy that include increased risk for stroke, dementia, gallbladder disease, urinary incontinence, deep vein thrombosis, pulmonary embolism, invasive breast cancer, and cardiovascular disease.[40] For this reason, the USPSTF assigned a Grade D rating, which translated to "The USPSTF recommends against this service. There is moderate or high certainty that the service has no benefit or that the harms outweigh the benefits."[40]

Similarly, estrogen-only therapy has previously been restricted to women who have had a hysterectomy and has been shown to only have a moderate benefit in reducing fractures and a small reduction in the risk of invasive breast cancer and breast cancer death. However, the estrogen-only arm of the WHI trial was stopped early as it was found to be associated with an increased risk for stroke, gallbladder disease, urinary incontinence, deep vein thrombosis, and cardiovascular disease,[8,16] and, in consequence, the USPSTF also assigned a Grade D rating for the use of estrogen for the protection of chronic disease.[40]

Based on the USPSTF's review of the evidence, "the USPSTF concludes with high certainty that there is zero-to-negative net benefit for the use of combined estrogen and progestin therapy for the prevention of chronic conditions and concludes with moderate certainty that there is no net benefit for the use of estrogen alone."[40]

The conclusive evidence from multiple RCTs indicates that the use of HRT therapy poses more harm than benefit when considering the benefit-to-harm ratio. However, we are left with the paradoxical finding that estrogen-plus-progestin therapy poses an increased risk for developing and dying from breast cancer, while estrogen-only therapy (in women with a previous hysterectomy) seems to reduce this risk. The current hypothesis, supported by preclinical studies, suggests that some cases of breast cancer in postmenopausal women are responsive only to a limited range of estrogen exposure, and exogenous estrogen use may inhibit breast cancer growth.[41,42] Even considering this finding, the USPSTF recommends against the use of estrogen-only or estrogen-plus-progestin therapy for the primary prevention of chronic conditions such as CHD or fractures. This recommendation is not directed towards the use of HRT to treat the symptoms of menopause, for which the lowest dose for the shortest period time may be considered in women with refractory menopausal symptoms,

and is FDA-approved for this use.[13] The European agencies allow more liberal use of HRT, allowing it for vasomotor menopausal symptoms and osteoporosis fracture prevention.[12,36] This is at odds with the USPSTF recommendations but because the USPSTF meta-analysis appears to be sound and robust (collating the results of over 35,000 women) and represents the most prudent recommendations to minimize harm, we support its conclusions.

In summary, the USPSTF recommends against the use of HRT therapy (estrogen alone or estrogen plus progestin) for the prevention of chronic conditions in postmenopausal women. Individual risk assessment and proven strategies should be utilized to help guide care in women at risk for chronic conditions.

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ARTYKUŁ POGLĄDOWY

Pomenopauzalna terapia hormonalna w prewencji pierwotnej chorób przewlekłych

Zalecenia US Preventive Services Task Force

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SŁOWA KLUCZOWE

choroby przewlekłe, choroby sercowo-naczyniowe, hormonalna terapia zastępcza, menopauza

STRESZCZENIE

Od początku XX w. uczeni usiłowali udowodnić zwodniczą hipotezę, że korzyści zdrowotne obserwowane u kobiet przed menopauzą można zachować i po menopauzie dzięki hormonalnej terapii zastępczej (HTZ) z wykorzystaniem estrogenów (samych lub z progesteronem). Hipoteza ta legła w gruzach, gdy wyniki dwóch dużych badań z randomizacją (*randomized controlled trials* – RCT) – Heart Estrogen/Progesterone Replacement Study (HERS) i Women's Health Initiative (WHI) – wykazały zwiększone ryzyko niekorzystnych skutków klinicznych, w tym choroby wieńcowej, incydentów zakrzepowo-zatorowych, udaru mózgu, otępienia, nietrzymania moczu, chorób pęcherzyka żółciowego i raka piersi. Mimo to, od chwili opublikowania badania WHI, w literaturze przedmiotu nie milknie krytyka, mnożą się kontrowersje i kolejne analizy podgrup, głównie skupione na zagadnieniu wieku kobiet kwalifikowanych do badań (który miałby wpływać na efekty kliniczne), oraz sugestie stosowania preparatów zawierających mniejsze dawki hormonów bioidentycznych. W ostatnim czasie US Preventive Services Task Force oraz inne grupy zawodowe wydały zalecenia niestosowania HTZ w celu zapobiegania chorobom przewlekłym. W niniejszym przeglądzie podsumowano najnowsze dane na temat różnorodnych efektów zdrowotnych, w tym dane z przedłużonej obserwacji pacjentek uczestniczących w RCT.

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