Rev Colomb Cardiol. 2018;25(S1):30–33

SOCIEDAD COLOMBIANA DE CARDIOLOGÍA & CIRUGIA CARDIOVASCULAR

Revista Colombiana de Cardiología

www.elsevier.es/revcolcar

ARTÍCULO ESPECIAL

Menopause and menopausal hormone therapy in women: cardiovascular benefits and risks

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Received 19 October 2017; accepted 12 December 2017
Available online 9 January 2018

KEYWORDS
Menopause;
Menopausal hormone therapy;
Women;
Cardiovascular prevention

Abstract The last decade has brought many challenges and uncertainties regarding the use of menopausal hormone therapy in women. Two early key studies, the Heart and Estrogen/Progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) failed to prove beneficial effects of exogenous estrogen, and estrogen combined with progestin, in cardiovascular prevention. More recent studies, however, introduced the concept of a possible ''window-of-opportunity'' for hormonal therapy, in which menopausal hormone therapy is used early after the onset of menopause, and may lead to more favorable, cardio-protective outcomes. Despite the increasing wealth of clinical data, menopausal hormone therapy is not currently recommended for primary or secondary prevention of coronary heart disease in women. Further research is needed to understand the risk-benefit balance of menopausal hormone therapy.

PALABRAS CLAVE
Menopausia;
Terapia hormonal en la menopausia;
Mujeres;
Prevención cardiovascular

La menopausia y la terapia hormonal en la menopausia en mujeres: beneficios y riesgos cardiovasculares

Resumen La última década ha traído muchos retos e incertidumbres respecto al uso de la terapia hormonal en la menopausia en mujeres. Dos estudios tempranos clave, el *Heart and Estrogen/Progestin Replacement Study* (HERS) [Estudio del Corazón y Reemplazo de Estrógeno/Progestina] y la *Womenś Health Initiative* (WHI) [Iniciativa de Salud de la Mujer] no pudieron demostrar los efectos benéficos del estrógeno exógeno y el estrógeno combinado con la progestina, en la prevención cardiovascular. Sin embargo, estudios más recientes han introducido el concepto de una posible ''ventana de oportunidad'' para la terapia hormonal, en donde la terapia hormonal en la menopausia se emplea tempranamente luego del inicio de la

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https://doi.org/10.1016/j.rccar.2017.12.004

menopausia, y que puede llevar a resultados más favorables y cardioprotectores. A pesar de la creciente riqueza en datos clínicos, en la actualidad no se recomienda la terapia hormonal en la menopausia para la prevención primaria o secundaria de la enfermedad coronaria en mujeres. Se requiere más investigación para entender el balance riesgo-beneficio de la terapia hormonal en la menopausia.

Cardiovascular disease is the leading cause of morbidity and mortality in the United States. The risk for heart disease increases exponentially with age for both men and women. For women, however, the risk is delayed by about 10 years, and becomes even more prominent after the onset of menopause.[1] Endogenous estrogen during women's reproductive years has many beneficial and protective effects.[2] Estrogen has anti-atherosclerotic and anti-inflammatory properties,[3] and may protect women from cardiovascular disease through halting the process of plaque formation and through modification of the lipid profile.[2] Premenopausal women have higher HDL cholesterol and lower LDL cholesterol levels compared to men, which significantly reverses after menopause.[4] Estrogen also has beneficial effects on the vascular endothelium and smooth muscle cells.[2] Following menopause, impaired endothelium-mediated vasodilation contributes to increased cardiovascular risk.

A progressive decline in endogenous estrogen levels may therefore contribute to the development of heart disease in post-menopausal women. Menopause (usually around the age of 50 years), and the postmenopausal period, may be risk factors for developing coronary heart disease in women, independent of increasing age. Specifically, following menopause, the loss of estrogen contributes to an increased development of hypertension, coronary artery disease, congestive heart failure and cerebrovascular disease.[5] Early menopause (women younger than 40-45 years of age) and lower than average premenopausal levels of endogenous estrogen carry an even higher risk of cardiovascular disease, independent of other risk factors. The cardiac effects of surgical menopause with unilateral or bilateral oophorectomy remain unclear. The Nurses' Health Study showed that surgical menopause increased cardiac risk, but natural menopause did not.[6] Another research study which enrolled women who underwent bilateral oophorectomy also confirmed enhanced subclinical atherosclerosis, when assessed by the carotid artery intima media thickness, which carries an increased risk of cardiac events.[7]

Because the risk of heart disease in women increases after menopause, it was hypothesized that exogenous hormones (estrogen with or without progesterone) would have a protective role and would reduce the risk of heart disease. Although initial observational data[8] supported this hypothesis, larger randomized clinical trials did not demonstrate that the use of menopausal hormone therapy would be beneficial for primary or secondary prevention of heart disease.

In 1998, the Heart and Estrogen/Progestin Replacement Study (HERS) enrolled over 2,760 post-menopausal women (average age 66.7 years old) with established coronary heart disease in a randomized, blinded, placebo-controlled clinical trial.[9,10] Unexpectedly, the study failed to show cardio-protective benefits of hormone replacement therapy with estrogen and progesterone. There was no reduction in overall risk for myocardial infarction, coronary heart disease, death or other cardiovascular outcomes during an average of 4.1 years of follow up.[9] Therefore, in women with established obstructive coronary artery disease enrolled in the HERS trial, hormone replacement therapy showed no benefit for secondary prevention of heart disease. The rate of coronary events increased in the first two years with the use of hormone replacement therapy, while in the subsequent two years the risk decreased, with no net benefit.[9,11]

Similarly to HERS Heart and Estrogen/Progestin Replacement Study, the Women's Health Initiative (WHI), a large, prospective, randomized clinical trial, failed to show cardioprotective benefits of hormone replacement therapy in women without a prior history of coronary heart disease.[12] The study, which recruited more than 16,000 healthy, post-menopausal women 50 to 79 years old, showed no benefit of hormonal therapy for primary prevention of heart disease, for an average 5.2-year follow up.[12] On the contrary, this study showed that the combination of estrogen and progesterone leads to an increased risk of adverse clinical outcomes, with a greater risk of coronary disease, stroke and thromboembolic disease, as well as breast cancer. Overall health risks outweighed the benefits of combined estrogen/progestin therapy. Subsequent subgroup analysis revealed that the risk is particularly evident in women over the age of 60 years who have been on menopausal hormone therapy for many years.

Based on the clinical trials described above, it has been postulated that estrogen-progesterone replacement therapy may be harmful in older women. Currently, the U.S. Preventive Services Task Force (USPSTF) does not recommend hormone replacement therapy for primary or secondary prevention of cardiovascular disease, and it is a Class III recommendation with a Level of Evidence A. In addition, current treatment guidelines do not recommend menopausal hormone therapy for stroke prevention or for stroke recurrence.[13]

Following the HERS and WHI Heart and Estrogen/Progestin Replacement Study and the Women's Health Initiative publications, multiple subgroup analyses

have been performed to further understand the controversy regarding the cardiovascular outcomes of menopausal hormone therapy in women, particularly as it pertains to the combination of hormones administered. The type of progesterone used, however, may be another important variable in predicting coronary heart disease in women. Not all progesterone formulations are the same in terms of cardiovascular effects, and may have differential effects on lipid metabolism, clotting, or inflammation. It has been postulated that natural progesterone may have beneficial cardiovascular effects, while synthetic progestins may not, due to their vasoconstrictive properties.[14] Further studies on the role of natural progesterone versus synthetic progestins on cardiovascular outcome are warranted.

Several studies have suggested a ''timing hypothesis'' or a ''window-of-opportunity'' for the initiation of menopausal hormone therapy, which is early after menopause. The Danish Osteoporosis Prevention Study (DOPS), a recent open label, randomized controlled trial demonstrated a beneficial effect of menopausal hormone therapy on the reduction of coronary artery disease.[15] The study included more than 1,000 healthy, post-menopausal women (mean age 50 years) and hormonal therapy was initiated early after menopause (on average, seven months post-menopause). With 10 years of intervention, menopausal hormone therapy led to a significant reduction of mortality, heart failure and myocardial infarction. There was no increased risk of thromboembolic events, stroke or cancer. Additionally, the Kronos Early Estrogen Study (KEEPS) investigated approximately 720 women (mean age 50 years) within six to 36 months of menopause and found that the use of menopausal hormone therapy did not lead to progression of carotid intima media thickness or progression of atherosclerosis, assessed by the coronary artery calcium score.[16] Therefore, the cardiovascular risk-lowering effects of menopause hormone therapy appear to depend on the duration and timing of hormonal therapy. To maximize the beneficial effects of hormonal therapy, it has been postulated that the ''window-of-opportunity''for reducing coronary heart disease and overall mortality in women is initiating hormonal therapy within six years of menopause and/or before 60 years of age, and for a short duration of time.[17,18]

However, despite the favorable results from the above studies, at the current time the overall evidence does not support the use of postmenopausal hormone therapy for prevention of heart disease. The USPSTF does not recommend the use of estrogen-only or estrogen with progestin therapy for primary or secondary prevention of coronary heart disease.[19] The U.S. Food and Drug Administration, however, does approve the use of estrogen with or without progesterone for treatment of moderately severe, or severe, refractory menopausal symptoms, such as vasomotor hot flashes, night sweats or vulvo-vaginal atrophy, but at the lowest possible dose and for the shortest period of time. Further randomized clinical trials are needed to clarify the cardiovascular effects of menopausal hormone therapy.

Conclusions

Overall, an individualized, patient-focused risk assessment should be used when assessing the risks and benefits of hormonal therapy in post-menopausal women.[20] The decision of whether or not to initiate or continue menopause hormone therapy requires a personalized discussion between the patient and the physician. Important factors in the decision making are the age of the woman, the age at the onset of menopause, and an assessment of overall cardiovascular health. Hormonal therapy may be harmful and is not advised in the setting of pre-existing coronary disease, cerebrovascular disease, or a history of thromboembolic disease. The presence or absence of menopausal symptoms, quality of life and the patient's individual preferences are also key in the decision making process. Women need to be aware of the non-hormonal therapies available for both management of vasomotor symptoms associated with peri-menopause and early menopause, and for reducing cardiovascular risk, including maintaining a healthy lifestyle.

Recommended articles

1. Manson JE, Aragaki AK, Rossouw JE, et al. Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials. JAMA 2017; 318:927 2. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of North American Menopause Society. Menopause 2017; 24: 728 3. Marjoribanks J, Farquhar C, Roberts H. et al. Long-term hormone therapy for perimenopausal and postmenopausal women. Chochrane Database Syst Rev 2017; 1: CD004143

Conflict of interest

Authors declare that they don't have any conflict of interests.

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