Cardiovascular Disease in Women (VIII)

Menopausal Hormone Therapy and Cardiovascular Disease

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Despite biologically plausible mechanisms for cardiac protection and compelling evidence from observational studies suggesting that menopausal hormone therapy confers cardiovascular benefit, results of well-designed and conducted randomized clinical trials in healthy women and in women with established coronary heart disease displayed that menopausal hormone therapy failed to prevent clinical cardiovascular events and rather was associated with harms. Clinical trial of the SERM raloxifene also did not demonstrate a decrease in coronary events.

It is unknown whether the earlier initiation of such therapies, i.e., at menopause, would result in favorable outcomes; or whether different hormonal preparations, lower doses, or alternate routes of administration would confer benefit.

At present, proved coronary risk reduction strategies are requisite (albeit underutilized) for menopausal women; these include lifestyle and pharmacologic coronary preventive interventions. The baseline characteristics of menopausal women with coronary heart disease who were participants in cardiovascular outcome trials of menopausal hormone therapy or raloxifene were remarkably similar; globally, cardiovascular risk factors were not optimally controlled at entry into these trials, suggesting that more aggressive cardiovascular risk interventions are appropriate to achieve optimal target goals for menopausal women with documented coronary heart disease.[1]

Key words: *Hormones. Cardiovascular disease. Coronary disease. Women.*

Tratamiento hormonal menopáusico y enfermedades cardiovasculares

A pesar de los mecanismos verosímiles desde un punto de vista biológico de la protección cardíaca y de las pruebas convincentes procedentes de los estudios observacionales realizados, que sugieren que el tratamiento hormonal posmenopáusico confiere un beneficio cardiovascular, los resultados de ensayos clínicos aleatorizados, bien diseñados y desarrollados, que han incluido a mujeres sanas y a otras con coronariopatía establecida, revelan que el tratamiento no previno los episodios cardiovasculares clínicos y se asoció con acontecimientos adversos. Los resultados del ensayo clínico efectuado con raloxifeno, modulador selectivo del receptor de estrógenos, tampoco han demostrado una disminución del número de episodios coronarios adversos.

Se desconoce si el inicio más precoz de estos tratamientos, es decir, en el momento de la menopausia, se traduciría en un resultado favorable, o si diferentes preparados hormonales, dosis más bajas o vías alternativas de administración proporcionarían algún beneficio.

En la actualidad, las estrategias terapéuticas demostradas de reducción del riesgo coronario son un requisito esencial —aunque infrautilizado— para mujeres menopáusicas; dichas estrategias incluyen intervenciones en el estilo de vida y tratamientos farmacológicos coronarios. Las características basales de las mujeres menopáusicas con coronariopatía que participaron en ensayos sobre variables cardiovasculares y tratamiento hormonal menopáusico o con raloxifeno fueron muy similares; en conjunto, los factores de riesgo cardiovascular no se controlaron de forma óptima en el momento de la inclusión de las mujeres en estos ensayos, lo que sugiere que sería apropiado aplicar intervenciones más agresivas dirigidas a reducir el riesgo cardiovascular, con el objetivo de obtener resultados óptimos para mujeres menopáusicas con coronariopatía documentada[1].

Palabras clave: *Hormonas. Enfermedad cardiovascular. Coronariopatía. Mujeres.*

INTRODUCTION

Despite observational data suggesting that menopausal hormone therapy confers substantial cardiovascular benefit and a number of biologically plausible mechanisms for coronary protection from

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ABREVIATIONS

apo A-1: apolipoprotein A1.
CHD: coronary heart disease.
CRP: C-reactive protein.
EBCT: electron beam computed tomography.
HDL-C: high-density lipoprotein cholesterol.
LDL-C: low-density lipoprotein cholesterol.
mMMSE: Modified Mini Mental State Examination.
PAI-1: plasminogen activator inhibitor type-1.
SERM: selective estrogen receptor modulator.
VDLD: very low-density lipoprotein.

estrogen, results of well-designed and conducted primary and secondary prevention randomized clinical trials of hormone therapy documented cardiovascular risk rather than protection. Menopausal hormone therapy failed to prevent clinical cardiovascular events both in healthy women and in women with established coronary heart disease (CHD),[2-4] and to the contrary, conferred an excess of harm relative to benefit.

NEW PIVOTAL CLINICAL TRIALS

The Heart and Estrogen Replacement Study (HERS)[2] randomized 2763 menopausal women, mean age 67 years, with established CHD to conjugated equine estrogen plus medroxyprogesterone acetate daily compared with placebo and followed these women for more than 4 years. Despite the anticipated changes in lipid levels, there was no significant difference in the primary trial outcome of total coronary events, nor in its 2 subsets, nonfatal myocardial infarction and coronary death. The concern within the null result, raised by a post hoc analysis, was the significant time trend suggesting an excess of coronary events among hormone-treated women during the first year of the study (risk hazard [RH], 1.52), with a trend to fewer events at 3-5 years of follow-up. To ascertain whether this trend to coronary risk reduction in the later years of HERS would persist and result in an overall benefit from hormone therapy on the risk of coronary events with further follow-up, 93% of the surviving HERS women were followed for an additional 2.7 years in an open-label, event surveillance study, HERS II.[3] The women were encouraged to remain on their original drug assignment, and about half of the women did so; importantly, few women initially assigned to placebo initiated hormone therapy during the open label phase of follow-up. At study end, with a mean observational period of 6.8 years, even after adjustment for potential confounders and for other factors such as aspirin use, statin use, smoking, etc, this hormone regimen failed to reduce the risk of coronary events in women with established CHD, with an overall RH=0.99. Comparable data were evident among women who did and did not adhere to their original randomized treatment assignment. Given the lack of benefit for coronary events or any secondary cardiovascular event, important potential harms were identified; these included a 2-fold increase in the risk of venous thromboembolism, predominantly in the initial years of hormone therapy, and a nearly 50% increase in the rate of gallbladder disease requiring surgery. Thus, this estrogen/progestin regimen did not provide cardiovascular benefit and caused significant harm. HERS was a challenge to conventional thinking, in that the results failed to validate the findings of observational studies, but the random allocation to hormone versus placebo was its unique strength. A fascinating observation in HERS, warranting examination in subsequent clinical trials, is the reduced incidence of diabetes in women with established CHD randomized to estrogen/progestin.[5] Data for primary prevention derive from the randomized placebo controlled hormone trial of the Women's Health Initiative (WHI), which enrolled predominantly healthy women aged 50-79 years, with one-third of the women in their 50s. Approximately 17 000 women with an intact uterus were randomly assigned to receive conjugated equine estrogen plus medroxyprogesterone acetate compared with placebo, and approximately 10 000 women who had hysterectomy were assigned to conjugated equine estrogen daily compared with placebo. In 2002, after an average follow-up of 5.2 years, the estrogen/progestin arm of the WHI hormone trial was halted prematurely because of an unanticipated increased risk of invasive breast cancer that exceeded the preset trial stopping boundaries, in association with a lack of global risk benefit, again based on a pre-established global risk score[4] that demonstrated a disproportionate increase in risk compared with benefit in the hormone-treated women. The health risks of this hormone regimen included a 26% increased risk of invasive breast cancer, a 29% increased risk of coronary events which were predominantly nonfatal myocardial infarction, a 41% increased risk of stroke, and a doubled risk of venous thromboembolism. Benefits included a 37% decreased risk for colorectal cancer, a 33% decreased risk for hip fracture, and a 24% decreased risk for total fracture, without effect on total mortality. It is relevant that coronary events, stroke, pulmonary embolism, and invasive breast cancer contributed equally to harm. The increased risk of myocardial infarction began within the initial year of therapy, and that of stroke in the initial 2 years.

Importantly, most WHI women had no adverse events, i.e., there was a low absolute excess risk of harm for an individual women. However, based on

trial data, 1 adverse event can be anticipated to occur among each 100 such women treated with estrogen/progestin for 5 years.

Limitations of the WHI include significant noncompliance and/or dropout rates; e.g., 42% dropout rates in the estrogen/progestin group and 38% in the placebo group.

A subsequently reported WHI health-related quality of life study[6] showed no clinically meaningful effect of hormone therapy on measures of general health, vitality, mental health, depressive symptoms, or sexual satisfaction. Only among the youngest women, those aged 50-54 years who had moderate-to-severe baseline vasomotor symptoms, was there improvement in these symptoms and in sleep disturbance, but no improvement in other health-related quality of life outcomes. Health-related quality of life was assessed in all WHI women at baseline and at 1 year and in a subgroup at 3 years. An ancillary study of WHI in the estrogen/progestin cohort involved 4532 WHI women ≥65 years of age free of dementia at baseline,[7,8] the Women's Health Initiative Memory Study (WHIMS). Although the absolute risk of developing dementia was low, there was a doubled likelihood of developing dementia among hormone-treated women, 66% versus 34%. Also, a small percentage of these hormone-treated women had clinically important declines in cognition; there were more statistically significant and clinically important declines in the modified Mini Mental State Examination (mMMSE) scores in the hormone-treated women. In February 2004, based on the WHI Memory Study data, the Food and Drug Administration (FDA) required a warning of the increased risk of probable dementia in women older than 65 years of age taking conjugated equine estrogen plus medroxyprogesterone acetate.[9] Further, again based on WHI data, was the FDA identification that estrogen plus progestin therapy may increase the risk of an abnormal mammogram, which will lead to further evaluation. There was also a requirement for the manufacturer to specify the lowest effective hormone dose or to state that the lowest effective dose of the hormone preparation had not been determined. Based on this information, the U.S. Preventive Services Task Force recommended that hormone therapy should not routinely be used to prevent chronic conditions in menopausal women, because the harms of estrogen/progestin therapy were likely to exceed the benefits for most women. The emphasis was to redirect focus to proved coronary risk reduction interventions for menopausal women, such as smoking cessation, a heart-healthy diet, physical activity, weight management, and pharmacologic control of hypertension and hypercholesterolemia.[10,11] Emphasis of the FDA notification in 2003 was that estrogen and estrogen/progestin products are not approved for heart disease prevention and carry an increased risk of heart disease, heart attack, stroke, and breast cancer. FDA recommendations for the approved indication for hormone therapy, moderate-to-severe menopausal symptoms, were that hormones should be prescribed at the lowest effective dose for the shortest possible duration. The FDA highlighted that research was requisite for unanswered questions, specifically, the effects of lower-dose estrogens or progestins, other types of estrogens or progestins, and other methods of hormone administration (e.g. transdermal) as potentially altering these risks. Similar recommendations derive from regulatory bodies in the United Kingdom and Europe.[12,13]

WHAT HAS BEEN LEARNED SINCE 2002?

Subsequent to publication of the WHI, a sizeable number of U.S. women discontinued menopausal hormone therapy, both with and without consultation with their physicians. This also occurred in European countries where hormone use was less prevalent than in the U.S. Women using such therapy for health promotion were more likely to discontinue use than were women who used hormone therapy for the relief of menopausal symptoms.[14] The conjugated equine estrogen arm of the WHI[15] was discontinued in 2004 after an average follow-up of almost 7 years, due to lack of improvement in the pre-set global risk score. There was an increase in stroke risk with unopposed estrogen similar to that demonstrated in the estrogen/progestin arm, with 12 more strokes anticipated annually for every 10 000 women treated with 0.625 mg daily of conjugated equine estrogen. There was no effect on heart disease risk. There was decrease in the risk of hip fracture, a nonsignificant decrease in the risk for breast cancer, and no decrease in the risk for colon cancer. A preliminary analysis of the Memory Study in the estrogen-only arm demonstrated a trend toward an increased risk of probable dementia and/or mild cognitive impairment in hormone-treated women.

Menopausal women with angiographic evidence of CHD were randomized in a 2×2 factorial design to unopposed conjugated equine estrogen or conjugated equine estrogen plus medroxyprogesterone acetate daily (dependent on the hysterectomy status) compared with placebo and to an antioxidant vitamin supplement versus placebo in the Women's Angiographic Vitamin and Estrogen (WAVE) trial. After a mean followup of 2.8 years, neither hormone therapy nor antioxidant vitamin supplements provided angiographic or clinical cardiovascular benefit, with a potential for harm suggested for each treatment.[16] Hormone-treated women had an increased risk of death and nonfatal myocardial infarction. A substudy of the WAVE trial examined endothelial vasodilator function in these women with established CHD.

Hormone therapy did not improve the baseline impaired flow-mediated vasodilation of the brachial artery.[17] Menopausal hormone therapy in WAVE was associated with a worsening of coronary atherosclerosis and exacerbation of the profile of inflammatory markers (C-reactive protein and fibrinogen) in women with abnormal glucose tolerance.[18]

One thousand and seventy menopausal women who survived an initial myocardial infarction were randomized to estradiol or placebo in the United Kingdom on EStrogen and the Prevention of ReInfarction Trial (ESPRIT). There was no reduction in the overall risk of further cardiac events and no difference in the frequency of reinfarction or cardiac death at 24 months. However, because of the low adherence to therapy (50%) in the intervention group and the substantial randomization to hormone therapy in the control population (37%), there is limited ability to extrapolate these results to other populations.[19]

Comparison of baseline and follow-up angiography at a mean of 3.3 years was undertaken in 226 menopausal women with documented CHD, 50% of whom were diabetic and 70% of whom were of racial or ethnic minorities in the Women's Estrogen-progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELLHART).[20] Randomization was to 17β estradiol, estradiol plus sequential mexdroxyprogesterone acetate, or placebo. There was no significant hormone effect on the angiographic progression of coronary atherosclerosis when added to lipid-lowering therapy; LDL-C levels were reduced to <130 mg/dL with a combination of diet and statin therapy. There was no increase in coronary events during the first year, although the statistical power to detect this was limited.

The American Heart Association Guidelines for Cardiovascular Disease Prevention in Women[21] designated menopausal hormone therapy as a class III intervention, i.e., lacking in benefit and with the potential for harm. The Guidelines indicated that combined estrogen plus progestin should not be initiated or continued to prevent cardiovascular disease in menopausal women. At the time of the report, it was also recommended that other forms of menopausal hormone therapy such as unopposed estrogen should not be initiated or continued to prevent cardiovascular disease in menopausal women, pending the results of ongoing trials. Only weeks later, the estrogen-only arm of WHI was reported, and elevated this class III recommendation to a level A, i.e. based on randomized controlled clinical trial data, rather than level C, expert opinion.

Because the above-cited studies were predominantly U.S. trials, questions arose about the generalizability of these data to other populations. Nonetheless, the Cochrane Data Base of Systematic Reviews, addressing hormone replacement therapy for preventing cardiovascular disease in postmenopausal women[22] found no protective effect on the cardiovascular outcomes assessed: all-cause mortality, cardiovascular death, nonfatal infarction, venous thromboembolism, or stroke. An increased occurrence of venous thromboembolism, pulmonary embolus and stroke were found in women randomized to hormone therapy compared with placebo, resulting in the recommendation that initiation of hormone therapy to prevent cardiovascular events in menopausal women with and without established cardiovascular disease should not be undertaken.

ADDITIONAL RESEARCH FINDINGS

Pathophysiology

Time of Initiation of Hormone Therapy

Much emphasis has been placed on the time of initiation of hormone therapy relative to menopause. In a comparison of hormone users randomized to hormone therapy vs placebo by time since menopause, women who began treatment within 5 years of menopause showed a decrease in both systolic and diastolic blood pressures, likely related to reduction in circulating levels of norepinephrine and reduction in systemic vascular resistance.[23] The duration of time since menopause might represent a different stage of atherosclerosis and a consequent differential effect of estrogen, i.e., a "window of opportunity" for estrogen. Further, baseline characteristics, both recognized and unascertained, play an important role. Lower levels of risk factors for cardiovascular disease and higher educational levels were associated with hormone use in a population-based study of Swedish women, even after adjustment by multiple logistic regression.[24]

A recent review emphasizes the importance of age-dependent changes in vascular pathology and the pharmacology of different estrogens in an effort to explore the importance of timing and type of estrogen in regard to reduction of cardiovascular risk. In an attempt to reconcile the discrepancies between observational data and the results of randomized controlled trials, the authors postulate that the timing of initiation of hormone therapy following menopause may influence therapeutic efficacy, with improved cardiovascular health at initiation of therapy potentially enhancing cardioprotection; they further suggest that transdermal estradiol rather than oral conjugated equine estrogen may be more effective. Genetic differences are also highlighted.[25]

In 2 large trials involving younger menopausal women, the HOPE Study and the Menopause Study Group, a combined cohort of 4065 women, subsequent combined analysis suggested that there was a low

incidence of coronary and other vascular events within the first year of hormone use among the healthy younger women. The rate of pulmonary embolism was slightly increased. The author suggests that adverse coronary events are less likely to occur in younger healthy asymptomatic women.[26]

The early increase in cardiovascular events after hormone therapy initiation in older menopausal women is likely related to pro-inflammatory and/or thrombogenic hormonal effects. However, the data are conflicting. Although initiation of hormone therapy following myocardial infarction significantly increased the risk of unstable angina, death, and reinfarction, chronic hormone therapy was associated with improved survival in women who underwent coronary artery bypass graft surgery; some have suggested improved outcomes in current hormone users with elective angioplasty and stenting. Whether the latter reflects other characteristics of these hormone users remains uncertain. In a prospective study of women using menopausal hormone therapy, such therapy before coronary artery bypass graft surgery did not increase the risk of adverse outcomes.[27]

A recent review raises a challenging question. Acknowledging that randomized trials have not supported the observational data indicating cardiovascular benefit of hormone therapy in older menopausal women, what is the benefit: risk equation in younger women who use hormone therapy for menopausal symptoms? Does cardiovascular hormone benefit in the perimenopausal years offset its risks for these women?[28]

Vascular Effects

A randomized comparative study of conjugated equine estrogen plus medroxyprogesterone acetate versus the selective estrogen receptor modulator raloxifene in menopausal women was designed to evaluate endothelium-dependent flow-mediated vasodilation. Hormone therapy increased flow-mediated vasodilation by 67%, with no change from baseline seen with raloxifene ($P<.01$). Although endothelin-1 levels decreased from baseline with both treatments, it was statistically significant only in the hormone group.[29] By contrast, a randomized comparison of transdermal estradiol plus norethisterone compared with oral raloxifene showed that both therapies decreased blood pressure and carotid-femoral pulse velocity, with the effect of raloxifene on vascular compliance independent of the effect on blood pressure.[30]

Lipid/Lipoprotein Effects

A randomized study in Taiwan of conjugated equine estrogen with 2 different progestogens examined the effect on lipoprotein profiles with dydrogesterone vs medroxyprogesterone acetate. Both regimens decreased total cholesterol, LDL-C, and increased triglyceride concentrations comparably, but the conjugated equine estrogen plus dydrogesterone had a more favorable effect on HDL-C.[31]

The increase in protective HDL-C levels with estrogen therapy and its blunting with a progestin is explained by postmenopausal estrogen therapy increasing apo A-1 levels and production rate, with reduction in apo A-1 production when a progestin is added.[32]

Blood Pressure Effects

Blood pressure was studied in hypertensive menopausal women who received hormone therapy to attenuate the effect of menopausal symptoms. This therapy was not associated with change in systolic blood pressure, whereas diastolic blood pressure was slightly reduced; nonetheless, this was associated with an increased need for antihypertensive medication throughout the entire follow-up period.[33]

Hormone therapy altered cardiovascular responses to laboratory stressors, with estrogen plus progestin decreasing the systolic and diastolic blood pressure responses during a speech stressor. This was not present with other hormonal regimens.[34]

Other Laboratory Findings

Self-reported hormone use in the WHI observational study was associated with unfavorable levels of CRP and triglycerides and favorable effects on tPA antigen, homocysteine, and HDL.[35]

Angiographic Coronary Disease

Retrospective examination of initial cardiac catheterization data showed that both estrogen and estrogen/progestin users were significantly less likely to have angiographic coronary disease than nonusers. After adjustment for demographic and coronary risk factors and comorbidities, there was no apparent protective effect of combination hormone therapy; the association with unopposed estrogen persisted even after adjustment for patient characteristics, suggesting that unopposed estrogen therapy may have a protective effect.[36]

Stroke

Although premenopausal women have a lower stroke risk than similarly aged men, stroke occurrence in women increases prominently following menopause. Stroke is the third leading cause of death in women. A metaanalysis of 28 clinical trials

involving 39 769 women examined the association between menopausal hormone therapy and subsequent stroke. Menopausal hormone therapy was significantly associated with total stroke, nonfatal stroke, stroke leading to death or disability, and ischemic stroke, with a trend to more fatal stroke. There was no association with hemorrhagic stroke or transient ischemic attack. The association with ischemic stroke was particularly prominent and, among women who sustained a stroke, current hormone users appeared to have a worse outcome. There was no difference between trials of unopposed estrogen and estrogen/progestin combinations.[37]

There was suggestion of a higher risk of ischemic stroke associated with conjugated equine estrogen than with a esterified estrogen alone in a computerized pharmacy database, suggesting that the effects of esterified estrogen on the risk of cardiovascular endpoints warrant examination.

Although estradiol increased stroke risk in the randomized double blind Women's Estrogen for Stroke Trial (WEST), estradiol therapy did not significantly affect cognitive measures after an average of 3.5 years. Among women with a normal Mini-Mental State Examination (MMSE) at baseline, estradiol may in reduce the risk for cognitive decline.[38]

Statin use was associated with a reduction in CHD outcomes, all-cause mortality and venous thrombosis in women assigned to hormone therapy in the HERS cohort; however, statin use did not alter the risk of all fatal stroke, fatal ischemic stroke, or fatal hemorrhagic stroke.[39]

There is lack of understanding of the mechanisms whereby hormone therapy increases stroke risk.[40,41] Inflammatory responses, activation of the coagulation system, possible adverse effects on endothelial function in the setting of advanced age, hypertension, and diabetes may be contributory; nonetheless, these are contrasted with estrogen-related improvement in lipid profiles, increased endothelial blood flow, and the potential to attenuate the secondary mechanisms of brain injury after stroke. Sex differences in the brain independent of hormones may also explain why women and men respond differently to aspirin for stroke prevention.

Venous Thromboembolism

Both menopausal hormone therapy and selective estrogen receptor modulators (SERMs) are associated with a 2- to 3-fold increased risk of venous thromboembolism. A systematic review and metaanalysis for the U.S. Preventive Services Task Force[42] concluded that the risk for venous thromboembolism may be highest in the first year of use. The association of estrogen plus progestin with venous thromboembolism was examined in detail in the Women's Health Initiative and the relationship to baseline gene variants explored. Estrogen plus progestin compared with placebo doubled the risk of venous thrombosis, which was greater among women who were overweight and obese. Factor V Leiden enhanced the hormone-associated risk of thrombosis 6.69-fold, but other genetic variants did not modify the association.[43] In contrast to oral estrogen, transdermal estrogen did not confer additional risk on women who had a prothrombotic mutation, further suggesting the need to assess the safety of transdermal estrogen in randomized clinical trials.[44]

In menopausal women with suspected deep vein thrombosis, the type of hormone therapy was explored in a prospective-case controlled study after adjustment for other factors that might confound the association. The increased risk with unopposed estrogen was not statistically significant, but estrogen/progestin was associated with a >2-fold increased risk of deep vein thrombosis.[45] Data from a large health maintenance organization suggested that conjugated equine estrogen, but not esterified estrogen, was associated with venous thrombotic risk.[46]

A review of the risk for venous thromboembolism with menopausal hormone therapy[47] offered implications for clinical management. The risk of venous thromboembolism is less likely in estrogen-only users than in users of estrogen/progestin therapy, with no apparent venous thromboembolism risk with transdermal hormone use. There was no compelling evidence that discontinuation of hormone therapy was required in the perioperative period in women who undergo elective surgery.

Acute Coronary Syndromes

The effect of menopausal hormone use in women with acute coronary syndromes was investigated in the SYMPHONY and 2nd SYMPHONY trials. Hormone use was low and was predominantly estrogen only. There was no association with improved intermediate-term outcomes (90-day and 1-year); mortality rates, stroke, myocardial infarction, and the composite endpoints did not differ between hormone users and nonusers.[48]

Peripheral Arterial Disease

Detailed analysis in the WHI estrogen/progestin versus placebo randomized clinical trial showed that clinical peripheral arterial events did not differ between treatment groups. In this study, a peripheral arterial event required an overnight hospitalization for classification.[49]

In the HERS cohort of menopausal women with documented CHD, renal insufficiency was independently associated with future peripheral

arterial disease events. Renal insufficiency is a coronary risk equivalent and predicts CHD and stroke–validation is required of its independent association with future peripheral arterial disease events.[50]

Psychological Health

Hormone therapy in the NHLBI-sponsored WISE (Women's Ischemia Syndrome Evaluation) study was consistently associated with better psychological health in white women, who had fewer symptoms of depression and lower aggression and cynicism scores. Black women had lower hostility and cynicism scores. Both white and black women with menopausal symptoms had better psychological health with hormone use.[51]

Physical Performance

There was no advantage of hormone use in peak exercise performance after 3 months of therapy in a small randomized study of estradiol and micronized progesterone.[52]

The effect of hormone therapy on physical performance was assessed in community dwelling elderly women in a prespecified subanalysis. There was no statistically significant effect on cognition or balance, nor was there prevention of the age-related decline in physical measures of mobility, ability to rise from a chair, self-reported activities of daily living, physical activity scores or falls.[53]

Miscellaneous Findings

Coronary Artery Calcium

Asymptomatic menopausal women in the Rancho Bernardo cohort who were current menopausal hormone therapy users had a striking decrease in coronary artery calcium score as evaluated by electron beam computed tomography (EBCT), suggesting an antiatherogenic effect of such therapy. Results did not differ between estrogen and estrogen/progestin users and were strongly associated with the duration of use.[54] Current users had a 60% reduced odds of severe coronary artery calcification, and past users a nonsignificant 30% reduced odds, with the reduced risk independent of CHD risk factors. Other reports of the relationship of hormone therapy and coronary artery calcium have been inconclusive or inconsistent. The Healthy Women Study showed that the distribution of coronary artery calcium did not differ significantly between hormone users and nonusers among 443 women who were about 8 years postmenopausal. Coronary calcium was determined by EBCT. Hormone users had lower LDL levels, but higher levels of large VLDL.[55]

Heart Rate Variability and QT Interval

Twenty-four hour heart rate variability was not affected either by estradiol alone or by estradiol plus norethisterone. The authors considered these findings consistent with the lack of protective cardiovascular effect of hormone therapy as described in the randomized controlled trials.[56] In a small trial of cessation of estrogen/progestin therapy, there was no adverse effect on the integrity of autonomic control of heart rate variability, suggesting that such hormone therapy has a limited role in the autonomic modulation of heart rate variability and that asymptomatic menopausal women who wish to discontinue hormone therapy may safely do so.[57]

Data from the WHI dietary intervention study (34 378 women) compared the EKG QT interval based on the current use of unopposed estrogen or combined estrogen/progestin. Unopposed estrogen mildly prolonged myocardial repolarization (as measured by the QT interval), with the effect reversed by progestin. The clinical significance is unknown.[58]

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Selective estrogen receptor modulators (SERMs) are nonsteroidal agents that bind with high affinity to estrogen receptors and promote specific effects in different tissues. The SERM raloxifene, a nonsteroidal benzothiophene derivative, exerts estrogen agonist-like effects on bone and cardiovascular risk factors, but estrogen antagonist-like effects on the breast and uterus. Raloxifene was studied in clinical trial to investigate its cardioprotective effects and its effects on the prevention of invasive breast cancer in the Raloxifene Use for The Heart (RUTH) trial. In this trial in menopausal women with documented CHD or at high risk for major coronary events. 10 101 women aged 55 years and older were randomized to raloxifene versus placebo, with an estimated follow-up of 5-7 years.[59] Selective estrogen receptor modulators are not appropriate to treat menopausal symptoms, but are effective in the prevention and treatment of osteoporosis.

Raloxine had no effect on coronary events (CHD death, myocardial infarction, or hospitalized acute coronary syndrome) but significantly reduced the risk of invasive breast cancer by 44%. There was a reduced risk of clinical vertebral fractures and an increased risk of venous thromboembolism. There was no difference in all strokes or total mortality but an increase in fatal stroke risk with raloxifene. Thus raloxifene was not cardioprotective in menopausal women at increased risk for CHD events.[60]

OTHER HORMONE PREPARATIONS, REGIMENS, DELIVERY SYSTEMS

The type of hormone preparation used is probably important, with questions raised as to how and why some progestin preparations abrogate the vascular benefits of estrogen. Differences in outcome may also relate to the route of administration, oral versus transdermal.

As an example, a small randomized study of lower versus conventional doses of hormone therapy showed comparable effects on lipoproteins, flow-mediated vasodilation, and PAI-1 antigen levels; low-dose therapy did not increase hsCRP or levels of prothrombin fragment 1+2.[61] This study, among others, provides a rationale to undertake a randomized clinical trial to investigate whether low-dose hormone therapy is cardioprotective.

A small randomized trial of transdermal estradiol and norethisterone compared with placebo showed beneficial effects on vascular function and coronary risk markers.[62]

Genistein, a phytoestrogen with selective estrogen receptor modulator properties, was compared with placebo in 60 menopausal women for its effect on cardiovascular risk markers. Genistein significantly decreased fasting glucose, fasting insulin, and fibrinogen levels, as well as levels of sex hormone binding globulin and osteoprotegerin.[63] A review of the plant-derived estrogens, known as phytoestrogens, either in dietary or supplemental form, to replace traditional forms of estrogen therapy concluded that there was insufficient evidence to recommend the use of phytoestrogens in place of traditional estrogen therapy or to make recommendations to women about specific phytoestrogen products.[64]

In a small randomized study comparing lower doses of hormone therapy (micronized progesterone plus conjugated equine estrogen) with tibolone, both therapies comparably improved flow-mediated response without a significant increase in high sensitivity C-reactive protein. Tibolone is a synthetic steroid with estrogenic, androgenic, and progestogenic properties used for relief of menopausal symptoms and prevention of menopausal bone loss.[65]

UNANSWERED QUESTIONS

It remains uncertain whether exposure to endogenous estrogen plays a significant role in the delayed manifestations of coronary atherosclerotic heart disease in women and provides an explanation for the differences in CHD rates between women and men. In contrast, it has been postulated that exogenous hormone therapy in general or specific exogenous hormones might fail to provide such benefit because of inflammatory or prothrombotic effects. The potential cardioprotective effects of endogenous estrogen underlie the premise of preventive hormonal strategies in the menopausal years.

Although, in most observational studies, hormone therapy was initiated for menopausal symptoms at the time of menopause, randomized controlled trials of hormone therapy typically initiated such therapy 10-20 years after menopause. The role of this interval remains unproved. The basic science literature suggests that the time since menopause and the extent of atherosclerosis may influence the cardiovascular actions of estrogen-this requires rigorous testing. In the interim, there is need to further explore the potential for cardioprotection and assess cardiovascular safety/risk for women who use hormone therapy for menopausal symptoms. Among the pivotal questions is whether hormone therapy initiated earlier in the menopause transition, the usual times when it is used to ease menopausal symptoms, might provide cardioprotection or lessen cardiovascular risk. These investigations should address different dosages, formulations, and delivery mechanisms of menopausal hormone therapy.

Because of discrepancy between observational studies and the WHI clinical trials, investigators analyzed corresponding data from 53 054 women in the WHI observational study, a third of whom used estrogen/progestin at baseline. Estrogen/progestin hazard ratio estimates for CHD, stroke, and venous thromboembolism in the observational study were 39%-48% lower than in the clinical trial, after age adjustment. Hazard ratios with estrogen/progestin tended to decrease with time, such that the observational study hazard ratio estimates predominantly reflect longer term use, while the clinical trial hazard ratio estimates reflect shorter term use. The authors suggest that adjustment for the time from hormone therapy initiation and confounding brings the estrogen/progestin hazard ratio from the observational studies into close agreement with that from the clinical trials. This analysis reinforces the early increase in cardiovascular risk in estrogen/progestin in WHI, consonant with that in HERS. This emphasis and the differences in the distribution of time from estrogen/progrestin initiation may explain some discrepancies, but cannot provide a full explanation for differences between the stroke hazard ratios.[66]

The data from the observational self-report Nurse's Health Study[67] identified that women beginning hormone therapy near menopause had a significantly reduced coronary risk, 0.66 for unopposed estrogen and 0.72 for estrogen/progestin. By contrast, in women who initiated therapy at least 10 years after menopause, the relative risk was 0.87 for unopposed estrogen and 0.90 for estrogen/progestin. Although these data suggest that the timing of the initiation of

hormone therapy related to menopause and/or age might influence coronary risk, the authors note that most newly menopausal women are appropriate candidates for hormone therapy because of their vasomotor symptoms; the risks of stroke, pulmonary embolism and possible breast cancer, both in randomized clinical trials and observational studies, mitigate against the general indication for long-term use for chronic disease prevention.

In the Kronos Early Estrogen Prevention Study (KEEPS) trial,[68] women 40-55 years will be randomized to oral conjugated equine estrogen, transdermal estrogen, or placebo to examine menopausal hormone therapy in the younger perimenopausal population.

The role of genetic variants remains incompletely understood, and may represent an area for fruitful research.

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