Commentary

Debate: The potential role of estrogen in the prevention of heart disease in women after menopause

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Abstract

Large numbers of observational studies have described a decrease in the incidence of cardiovascular disease in women taking hormone replacement therapy (HRT). The potential mechanisms for this effect are numerous, including direct effects on lipid levels and lipid metabolism, cardiovascular dynamics, and endothelial reactivity. The beneficial effects of HRT are probably affected by various factors, including the age of onset of therapy, the presence of coronary artery disease, the type of estrogen and whether it is used in combination with progesterone, concurrent modification of other cardiac risk factors, and duration of therapy. Until further prospective clinical trials are done, HRT should be considered in those women for whom the potential benefits exceed the potential risks, on the basis of an individualized patient evaluation.

Keywords: coronary heart disease, estrogen replacement therapy, hormone replacement therapy, postmenopause, women's health

Introduction

At the end of the 20th century, coronary heart disease (CHD) remains the most common cause of death among both men and women in most of the westernized world. The increased relative risk for CHD death in men (2.5- to 4.5-fold) compared with women is seen in countries with high or low rates of heart disease [1]. This male surplus of CHD in diverse populations with very divergent lifestyles, eating patterns, and disease rates is only compatible with an intrinsic female advantage or a male disadvantage [2]. The female advantage has naturally been attributed to estrogen.

There are many reasons to believe that estrogen is cardioprotective. The fact that CHD is uncommon in women before 50 years of age (average age of menopause 49–51 years), that postmenopausal women demonstrate increased rates of CHD compared to premenopausal women of the same age range, and the increased risk of CHD after premature menopause lend support to the estrogen–CHD hypothesis [3]. Numerous *in vivo* and *in vitro* studies show at least a dozen estrogen effects that would be expected to prevent or delay CHD [4]. Observational studies have almost universally reported a lower risk of CHD in postmenopausal women who take estrogen

CHD = coronary heart disease; HDL = high-density lipoprotein; HRT = hormone replacement therapy; LDL = low-density lipoprotein; MPA = medroxyprogesterone acetate.

alone or with a progestin as compared with those women who do not [1–3,5]. This trend has also been demonstrated in women with established CHD [6].

Menopause

On average, women develop heart disease approximately 10 years later than men, but the largest increase in coronary mortality coincides with the menopause [7]. Estradiol levels in postmenopausal women are reduced by approximately 75% compared with premenopausal levels. The degree to which estrogen deficiency contributes to CHD risk in women has not been definitively established, and cross-sectional and prospective studies have generally failed to find an association between endogenous estrogen levels and CHD risk factors in women or men [8]. Data from vital statistics also do not support a conclusion that menopause, apart from the effects of chronological aging, increases the risk for CHD. Obviously, these studies cannot completely exclude a cardioprotective effect of endogenous estrogen since a single hormone assay may be inadequate to correctly classify individuals with regard to their usual endocrine status. It seems likely that both aging and estrogen decline contribute to increased CHD risk [9].

Data from women who undergo premature menopause – natural or surgical – indicate that CHD develops prematurely in these women, supporting the concept that menopause and CHD are linked. Autopsy studies [10] have shown a clear increase in coronary disease in women after oophorectomy or premature ovarian failure. There are many possible confounding variables in these studies, including changes in hypothalmic and pituitary hormone levels after surgery, and the antecedent disease processes that necessitated oophorectomy or caused the ovarian failure. More recent studies have yielded inconsistent results [11]. In the Nurses' Health Study [5], bilateral oophorectomy, but not natural menopause, was associated with an increased risk for CHD. No increased risk was observed in oophorectomized women who had been treated with estrogen. The fact remains, however, that after oophorectomy the incidence of CHD in women is increased.

Perhaps the most dramatic evidence suggesting that loss of endogenous estrogen increases cardiac risk is the sharp increase in low-density lipoprotein (LDL)-cholesterol that begins during the perimenopausal period and continues to at least age 60 years, with these higher levels sustained thereafter [12]. Interestingly, both cross-sectional and prospective studies show only a small decrease in high-density lipoprotein (HDL)-cholesterol levels at the time of menopause; on average, HDL-cholesterol levels in women remain higher than those in men for at least another 30 years after menopause [8].

Hormone replacement therapy and risk factors for coronary heart disease

A number of biologically plausible mechanisms exist for hormone-mediated protection from CHD. The Postmenopausal Estrogen/Progestin Intervention (PEPI) trial [13] examined the effect of HRT [conjugated equine estrogen alone or in various combinations with medroxyprogesterone acetate (MPA) or micronized progesterone] on cardiovascular risk factors. The PEPI trial and numerous observational studies have shown that oral estrogen therapy is associated with a 10–15% increase in HDL-cholesterol and a similar decrease in LDL-cholesterol. The elevation in HDL-cholesterol is due to increased production of HDL_2 and apolipoprotein A-1, whereas the decrease in LDL-cholesterol is due to increased expression of hepatic LDL receptors. All progestins are not alike, however, and the PEPI trial found differences in the effects of different HRT preparations on CHD risk factors. While all women who received estrogen had an increase in HDL-cholesterol and a decrease in LDL-cholesterol, the HDL-cholesterol effect was more pronounced with micronized progesterone than with MPA. Progestins, such as MPA, have been found to reduce the beneficial effects of estrogen on endothelial function and on atherosclerosis in several animal models [14]. The benefits and risks of cyclic versus daily progestin regimens also have not been fully determined.

Oxidation of LDL-cholesterol is believed to be an initiating event in atherogenesis, and estradiol and/or other estrogens may inhibit this process [15]. Oral conjugated estrogens are also associated with increases in very low-density lipoprotein, triglycerides, and apolipoprotein B levels, as well as with decreases in lipoprotein(a) levels. These are not large changes, however, and the effects of modest alterations in these molecules on the development of CHD are uncertain.

In addition, estrogen has multiple other effects expected to be cardioprotective. These include favorable changes in postprandial lipid metabolism, plasminogen activator inhibitor-1, fibrinogen, antithrombin III, homocysteine levels, carbohydrate metabolism, atheroma formation, cardiovascular hemodynamics, and endothelial dysfunction [4,16,17].

On the other hand, the PEPI investigators [18] found that HRT rapidly increases the level of C-reactive protein (a marker of inflammation that has been associated with increased risk of cardiovascular events) while reducing the levels of soluble E-selectin (a possible anti-inflammatory effect). As pointed out by those investigators, such data underscore the need to study the effect of HRT-mediated changes in inflammation on the risk of subsequent coronary events.

Observational evidence and randomized trials

Since the 1970s, more than 30 case–control and prospective studies have reported a decrease in risk for CHD in women on HRT. In the most recent meta-analysis, Barrett-Connor and Grady [1] estimated that estrogen therapy alone was associated with a 35–50% reduction, and estrogen–progesterone with a 33% reduction in the risk of coronary disease, as compared with women who were not on HRT. These observational data are extensive and largely consistent.

In the Lipid Research Clinic Follow-up Study [6], 2270 hyperlipidemic, Caucasian women aged 40–69 years at study entry were followed for more than 8 years. Over 60% fewer CHD deaths occurred in women who received estrogen than in those who did not. This benefit remained after adjustment for age, hypertension, and smoking, and it was most pronounced in women with known CHD.

It has been suggested that observational studies may overestimate the amount of protection attributed to estrogen. Numerous biases in the epidemiologic studies have been identified (compliance, healthy user, prescription, prevention, survivor) [19]. Only randomized trials can control for both known and unknown differences in women who do and do not elect to take medication.

The only large, randomized clinical trial testing the benefit of HRT – the Heart and Estrogen/Progestin Replacement Study (HERS) [20] – found no overall benefit of HRT on secondary prevention of CHD in 2763 postmenopausal women with established coronary disease who were treated for an average of 4.1 years (relative risk 0.99, 95% confidence interval 0.80–1.22). HRT was associated with more secondary cardiac events as compared to placebo during year 1 of treatment, and with a significant trend toward fewer events in years 4 and 5.

At face value the results of HERS are not consistent with our knowledge of estrogen's action on the cardiovascular system and the many observational studies showing estrogen's benefit, and it is premature and counterintuitive to rely only on the results of this one study. This was an older cohort of women (mean age 67 years) with significant heart disease. More than 80% of the HERS study group had revascularization within 6 months of study entry, which could have resulted in the low event rates in both the placebo and treatment arms (the event rate in the placebo group was 50% lower than that in the treatment group during the first year). The HERS selection criteria also excluded women with uncontrolled diabetes or hypertension, which also may have resulted in low event rates. Most women in observational studies began using HRT during the perimenopausal or early postmenopausal period [2]. In the HERS study, women were an average of 18 years past the cessation of menses. Only 46% of patients received cholesterol-lowering statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) and diet modification in addition to HRT, even though more than 90% had LDL-cholesterol in excess of 100 mg/dl at baseline. The majority of those taking statins did not achieve target goals for lipid reduction. Statins have been shown in clinical trials to reduce the risk of CHD in women with or without known heart disease. Another significant variable is if the choice of HRT used in the HERS (a fixed-combination estrogen and progestin) played a role in increasing CHD events. Since a comparison group taking estrogen alone was not included, and some progestins are thought to attenuate the benefits of estrogen on the cardiovascular system, the possibility exists that a different regimen may have offered greater benefits.

Conclusion

Before HERS, the real controversy over hormone therapy was whether all postmenopausal women were likely to derive cardioprotective benefit and should therefore be encouraged to use HRT. Despite the nearly universal findings from observational studies that postmenopausal estrogen therapy reduces the risk of CHD and the multiple mechanisms by which estrogen might be beneficial, hormone therapy had no benefit in the only large randomized clinical trial to date. At this time, what we have really learned from HERS is that, in older women with severe CHD, a fixed estrogen–progestin regimen should not be prescribed with the expectation that it will decrease the incidence of cardiovascular events in the short term. Women who are already on HRT should probably continue with the regimen because there appears to be a protective effect of HRT on the cardiovascular system after the first few years of use. On the basis of the results of the HERS trial, a consensus panel of the American Heart Association and the American College of Cardiology [21] has suggested that initiation or continuation of HRT should be considered in those women for whom the potential benefits of therapy may exceed the potential risks based on individualized patient history. Thus, although there is significant evidence that HRT is protective in postmenopausal women in the primary prevention of CHD, further large-scale studies of HRT in women with established CHD are warranted, especially with other HRT regimens.

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