Commentary

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

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Abstract

The observational studies of hormone users are compromised by systematic biases that lead to an overestimation of benefit and an underestimation of risk. Studies of mechanism could support either benefit or harm. The results of clinical trials of oral hormone therapy in women with existing coronary heart disease (CHD) have been uniformly disappointing. The largest trial found an early increased risk for CHD and for venous thromboembolism. Postmenopausal hormone therapy should not be considered for CHD prevention until methods for excluding high-risk women have been established, and until the results of the long-term trials have shown benefit. There is a need for clinical trials of nonoral estrogens.

Keywords: clinical trials, coronary heart disease, epidemiology, postmenopausal hormone therapy

Introduction

The conventional wisdom that postmenopausal hormone therapy reduces the risk for CHD is being questioned, following reports from clinical trials that have failed to show benefit, or have even produced evidence of increased risk during the first years of treatment. The Heart and Estrogen/progestin Replacement Study [1] was a 4.1-year secondary prevention trial of conjugated equine estrogens plus medroxyprogesterone in 2763 women with an intact uterus, and its finding of increased risk during the first year with possible subsequent benefit is consistent with an cohort study of women with prior heart disease from the Nurses' Health Study [2]. The Estrogen Replacement and Atherosclerosis trial [3] was an angiographic trial of 309 women who were randomized to conjugated equine estrogens, conjugated equine estrogens plus medroxyprogesterone, or placebo. At the end of 3 years there was no difference in angiographic progression between the study groups. Despite these findings, it remains possible that longer term treatment will reduce the risk for CHD. Even if that is so, the apparent excess early risk needs to be explained and methods found to avoid it, if postmenopausal hormone therapy is to regain its position as a recommended preventive treatment for CHD.

The most convincing strands of evidence in humans that estrogen may prevent CHD comes from observational epidemiology and from studies of mechanism. Each type of evidence has strengths and weaknesses, and is subject to varying interpretations.

CHD = coronary heart disease; HDL = high-density lipoprotein.

Observational epidemiology

The later onset of CHD in women than in men may be due to higher endogenous estrogen levels (and consequently higher high-density lipoprotein [HDL]-cholesterol levels) in premenopausal women than in men. However, the HDL-cholesterol difference between women and men is an androgen effect, not an estrogen effect. Up to puberty, young men and women have similar HDL-cholesterol levels. At puberty, concurrent with the rise in endogenous testosterone levels, the HDL-cholesterol levels in young men decline to the lower adult level [4,5]. A 20% difference in HDL-cholesterol levels predicts at least a 20% difference in CHD rates in the short term, and may predict even larger differences in CHD rates over a lifetime [6]. Thus, the entire sex difference in CHD risk may be due to the lifelong difference in HDL-cholesterol levels.

It is often stated that CHD rates in women rise steeply after the menopausal age, and that this is again due to the relatively lower levels of estrogen in postmenopausal women. However, there is actually no evidence for an increase in the year-on-year incidence of CHD around the age of menopause. The linear relationship between age and CHD incidence as seen on a semilogarithmic plot shows that there is a constant proportional increase in CHD incidence with age, with no inflection upward at the average age of menopause [7]. This is strong evidence for an age effect, and evidence against an effect of menopause. The Nurses' Health Study investigators [8] reported that, after controlling for age and smoking status, the natural menopause is not associated with an increased risk for CHD. Those investigators also reported that, in contrast to the natural menopause, bilateral oophorectomy is associated with an increased risk for CHD in women who had never taken estrogen after menopause. However, that study had very few cases of CHD in women with oophorectomy, and the increased risk was no longer significant in the multivariate analysis. The use of estrogens appeared to eliminate this increased risk. Even if these findings were real, it is possible that women who have a hysterectomy and bilateral oophorectomy are at higher risk because of a higher prevalence of metabolic risk factors such as central obesity, high blood pressure, lipid disorders, and glucose intolerance. The finding of an apparently lower risk in women who subsequently used estrogen would be subject to a number of biases (discussed below).

By far the most persuasive evidence in favor of a protective effect for estrogen comes from the large number of cohort studies that compared CHD risk in postmenopausal women currently using estrogen with that in those who had never used estrogen. These studies have shown consistently that CHD risk is 35–50% lower in estrogen users, after adjusting for other risk factors [9]. The lower risk has been found in studies of estrogen alone, as well as in studies of estrogen used in combination with a progestin. For healthy women, the lower risk is found in those who have recently started estrogen, as well as in long-term users [10].

These findings from observational epidemiology provide the rationale for clinical trials testing whether and to what degree current use of postmenopausal hormone therapy prevents a first heart attack. However, observational epidemiology is not sufficient to prove the case, because even the best studies may be subject to a variety of systematic biases that could lead to an overestimation of benefit and an underestimation of harm from hormone therapy, hence the need for an unbiased estimate from clinical trials. These biases in observational studies are summarized below.

Biases in observational studies

In combination, the biases summarized below will lead to a systematic overestimation of benefit, and an underestimation of risk. Adjusting for baseline differences in risk factors will mitigate only one kind of bias (healthy user selection bias), but will not affect compliance, surveillance, or survivor bias. Thus, the real benefit for CHD may be much less than that predicted by the observational studies, or there may be no benefit at all. The clinical trials to date have failed to show overall benefit for CHD over the short term (although longer term trials are ongoing to ascertain the long-term effects, particularly in women without prevalent CHD).

Healthy user selection bias

Some, but not all studies have shown that women who elect to use hormone therapy are healthier than those who elect not to. Health differences may be present before they commence therapy, and thus the more favorable health outcome in hormone users may be due to the characteristics of the women who take hormones, rather than due to the intrinsic effects of hormones [11]. The differences in risk factors may be large, and in themselves could explain a large part of the lower risk in hormone users. The better observational studies adjusted for some of these variables, but could not adjust for variables that either were not measured at all, or were not measured before the commencement of the hormone therapy.

Compliance bias

Women who use hormone therapy for a number of years are a highly select group with good compliance. Clinical trials of other preventive treatments (e.g. β-blockers) have demonstrated that patients who are good adherers to the study treatment (irrespective of whether they are in the active or placebo arms) have up to 60% reduced risk for death compared with poor adherers [12]. This remarkable finding is due to the characteristics of good adherers, who are likely to be

more aware of their health than are poor adherers, and therefore will be taking a number of health-promoting steps (either consciously or unconsciously), resulting in a lower mortality. Compliance bias is very powerful, and is impossible to correct for in an observational study. The very definition of the index group of hormone users in an observational study, especially in the case of long-term current users, ensures that a very special group is selected for study.

Surveillance bias

Since hormones are prescription drugs, women who use them are more likely to be in contact with the medical care system than are other women. This leads to a greater likelihood that risk factors and early disease will be identified and treated, thus lowering mortality from CHD. Reports from the Nurses' Health Study illustrate this surveillance bias phenomenon. For each of CHD and stroke, current hormone users have greater apparent risk reductions for mortality than for incidence [10,13].

Survivor bias

Another type of bias that will ascribe a lower mortality to current hormone users is the fact that women who stop hormones often do so because of intercurrent illness. Women who have recently stopped taking hormones have a markedly higher total mortality, as well as cause-specific mortality from cardiovascular disease and cancer [14]. Thus, the women who remain on hormones are survivors with a lower mortality than women in the general population. Like compliance bias, it is very difficult to correct for survivor bias in an observational study.

Studies of mechanisms

The possibility that estrogen may reduce CHD risk has stimulated a wide variety of studies that have attempted to explain the presumed benefit. Because it was unexpected, fewer studies have been done to explain the apparent excess risk early during the course of treatment. Mechanisms that may contribute to benefit include lowered low-density lipoprotein cholesterol and lipoprotein(a) levels, raised HDL-cholesterol levels, reduced fibrinogen levels and enhanced fibrinolysis (reduced plasminogen activator-inhibitor 1 and increased D-dimer levels), reduced homocysteine levels, antioxidant properties, and improved endothelial function (reduced E-selectin levels and improved flow-mediated dilatation) [15]. On the other hand, several mechanisms that might increase risk have been found, including increases in triglycerides, in some coagulation markers (eg factor VII, prothrombin fragments 1+2, activated protein C resistance), and in the inflammatory marker C-reactive protein [16–18]. Particularly with regard to coagulation and inflammation, laboratory measurements do not predict whether the predominant effect will be favorable or unfavorable. On the other hand, studies of venous thromboembolism (including clinical trials) provide unequivocal evidence that the overall effect is indeed procoagulant [1,19].

Compounding this difficulty in interpreting laboratory measurements is the fact that progestins counteract some of the effects of estrogens, and that the clinical expression of metabolic changes may be time dependent. The early excess risk for arterial disease observed in Heart and Estrogen/progestin Replacement Study [1] might have been due to an initial procoagulant or inflammatory effect on susceptible plaques, whereas the favorable effects in the survivors might have been due to the later assertion of the generally favorable lipid effects. The role of the direct vascular effect of estrogen is unclear, because impaired endothelial function has not yet been established as a risk factor for CHD. Interestingly, current estrogen users do not appear to have a lower risk for angina, as one would expect if direct vascular effects were important [10]. Overall, the studies of mechanisms have not resolved the core issue of whether estrogens protect against CHD.

It is important to realize that almost all of the studies of mechanism were done using oral estrogen preparations, and thus may have little relevance in explaining the sex difference in CHD. Ovarian estrogen directly enters the systemic circulation, unlike oral estrogens, which undergo first-pass hepatic circulation and which need to be given at 10 times the dose of nonoral estrogen in order to achieve similar blood levels. These doses of estrogens cause changes in the hepatic metabolism of a variety of proteins, including lipid apoproteins, coagulation proteins, and (probably) C-reactive protein [20,21]. The large effects on lipids and coagulation proteins described for oral estrogens are greatly attenuated, absent, or in the opposite direction with nonoral estrogens. Nonoral estrogens have very modest effects on lowering low-density lipoprotein cholesterol and lipoprotein(a), they lower rather than raise triglycerides, they have no effect on HDL-cholesterol, and they have a modest or no effect on coagulation protein levels [22–24]. Nonoral estrogens retain the ability to improve endothelial function [25]. Additional mechanistic studies, as well as epidemiologic studies and clinical trials, that focus on the role of nonoral estrogen preparations are needed.

Conclusion

Despite the substantial evidence suggesting benefit for CHD, the trials of oral estrogens have failed thus far to show benefit, and there are some suggestions of early harm. These findings may be related to the new knowledge that oral estrogens are prothrombotic. It is not known whether the failure to show benefit in the short term is due to the particular estrogen and estrogen/progestin combination used in these trials, or will apply also to other dosages and forms of oral estrogen and progestin, and in particular whether it will apply to nonoral routes of

administration. Postmenopausal hormone use should not be considered for the prevention or treatment of CHD until strategies to exclude women who are at high risk for early events have been devised, and until the long-term clinical trials have shown benefit for CHD. Hormones have multiple effects on several organ systems, and the overall risk and benefit depends greatly on whether a reduction in the risk for CHD is realized. Therefore, it is critically important that this issue is settled before recommending the use of postmenopausal hormones for this indication.

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