American Journal of Epidemiology

Vol. 166, No. 5
DOI: 10.1093/aje/kwm214
Advance Access publication July 23, 2007

Commentary

Hormones and Heart Disease in Women: The Timing Hypothesis

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Received for publication September 28, 2006; accepted for publication December 21, 2006.

Largely on the basis of results from meta-analyses of observational studies, postmenopausal estrogen was widely prescribed to prevent coronary heart disease. However, epidemiologic studies, no matter how consistent and coherent, are not sufficient to recommend mass preventive therapy to healthy women. In fact, all three large clinical trials failed to confirm estrogen's expected cardiac protection. The most persistent explanatory hypothesis for the "trial failure" was the age of the participants, based on the thesis that estrogen in recently menopausal women could prevent the development of coronary artery plaque but, given to older women with vulnerable plaque, would have a null or even harmful effect. The timing hypothesis is plausible, but the prespecified subgroup analyses in both Women's Health Initiative trials showed no significant interaction with age or years since menopause. The best opportunity to test the timing hypothesis was lost when 1,000 Women's Health Initiative women younger than 60 years had coronary artery calcium scans to evaluate the effect of estrogen on plaque burden, but no women 60 years or over were similarly examined. Therefore, this ancillary study can examine the effect of estrogen treatment on coronary calcium in women younger than 60 years but will not be able to determine if the effect is different in older women. In the meantime, publicized statements in multiple venues have promoted the timing hypothesis as fact, confusing patients and physicians who do not realize that the hypothesis is stronger than the evidence.

coronary disease; estrogen replacement therapy; health planning guidelines; hormones; women

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HERS, Heart and Estrogen/progestin Replacement Study; WHI, Women's Health Initiative.

Editor's note: *An invited commentary on this commentary appears on page 511.*

EPIDEMIOLOGY

As reviewed elsewhere (1), women in every country are at lower risk of fatal coronary heart disease (CHD) compared with men, despite diverse socioeconomic status, lifestyle, and diet. Within countries, women have less heart disease than men when stratified by similar heart disease risk factor levels. These consistent results between and within populations support the long-held hypothesis that women are protected by a universal intrinsic attribute, believed to be estrogen. By 1991, 11 of 22 published epidemiologic studies showed a significantly reduced risk of CHD associated with postmenopausal hormone therapy, supporting the hypothesis that estrogen prevents heart disease (2).

A 1992 meta-analysis compared the benefit of estrogen therapy for reducing the risk of CHD and hip fracture versus the increased risk of breast and uterine cancer: In the pooled analysis, CHD risk was reduced by about one third in estrogen-using women, and this benefit outweighed the increased risk

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of both cancers combined (3). Another meta-analysis of 25 observational studies published through mid-1997 compared cardioprotection for estrogen alone and in combination with a progestin (4). The summary risk estimate for CHD in women who had ever used estrogen—mostly unopposed conjugated equine estrogen—compared with never users was 0.70 (95 percent confidence interval (CI): 0.65, 0.75). A similar risk estimate of 0.66 (95 percent CI: 0.53, 0.84) was observed in the seven studies that specifically reported treatment with estrogen plus a progestin, usually cyclic medroxyprogesterone acetate (4).

On the basis of the strong and consistent findings of the observational studies, it was widely accepted that postmenopausal estrogen would prevent CHD. The major estrogen manufacturers in the United States requested an indication from the Food and Drug Administration (permission to claim that their product would prevent heart disease), and most professional organizations recommended that all postmenopausal women consider estrogen to prevent heart disease. Documentation that all postmenopausal patients had been offered estrogen was one criterion used to evaluate the quality of medical practice (5).

Epidemiologic data, however consistent and coherent, are not sufficient to recommend mass therapy to healthy women. In 1991, the late Trudy Bush and I wrote the following: ''Clearly, the weight of the evidence at this time points toward a substantial reduction in CHD risk among women using estrogens. Nevertheless, it is important to recognize the limitations of the data on which this statement is based. All but one small study are observational. There is no information on why women were prescribed estrogen and no ability to contrast these women with others who may have never been offered or refused or stopped hormone replacement therapy. Overall, women who take estrogen after the menopause are more likely to be white, educated, upper middle class, and lean, thereby at lower risk of heart disease than women without estrogen replacement therapy'' (2, p. 1865).

Because estrogen therapy was being proposed for every postmenopausal woman on the basis of presumed cardiovascular benefit, it was critical to determine by clinical trial whether women would benefit (or be harmed). Only randomized controlled clinical trials can control for known and unknown differences between women who use hormone therapy and those who do not. Just in the nick of time, three large clinical trials were initiated.

RANDOMIZED PLACEBO-CONTROLLED CLINICAL TRIALS

The Heart and Estrogen/progestin Replacement Study (HERS) was a secondary prevention trial studying the effect of a single daily tablet containing conjugated equine estrogen (0.625 mg) and medroxyprogesterone acetate (2.5 mg) on the risk of CHD events in 2,763 postmenopausal women who had established CHD (6). In the first year, there was an excess risk of CHD events; for the overall 4.2 years of the trial, there was no difference in CHD events between the hormone therapy and placebo groups (relative hazard = 0.99, 95 percent CI: 0.81, 1.22). Another 2.7 years of follow-up still showed no cardiovascular benefit (7).

The Women's Health Initiative (WHI) included two primary prevention trials to evaluate the effect of hormone therapy on CHD in healthy postmenopausal women. In one WHI trial, 16,608 women who had an intact uterus were randomly assigned to a single daily tablet containing conjugated equine estrogen (0.625 mg) and medroxyprogesterone acetate (2.5 mg) or placebo, the same regimen used in HERS. There were an excess risk of CHD in the first year and a nearly 30 percent increased risk of coronary events after 5.2 years; the hazard ratio for CHD was 1.29 (95 percent CI: 1.02, 1.63) (8). A subgroup analysis of the 400 women who had a history of heart attack or coronary revascularization showed a similar risk (hazard ratio = 1.28). In the second WHI trial, 10,739 women without a uterus were randomly assigned to placebo or conjugated equine estrogen (0.625 mg/d) without a progestin; there was no overall effect on coronary risk (hazard ratio = 0.91, 95 percent CI: 0.75, 1.12) (9).

Thus, none of the only three clinical trials powered to show a reduced risk of cardiac events showed benefit.

SUBGROUP ANALYSIS

Subgroup analyses in clinical trials are often performed to determine whether overall benefits extend to several subgroup characteristics, such as age, sex, and ethnicity. Ideally, these analyses are based on a priori hypotheses that are prespecified before results are known. Most of the subgroup analyses in HERS and the WHI were not done to show generalizability but to determine whether there were subgroups of women who might have benefited (or been harmed) even when the overall results were null.

Furberg et al. (10) published an extensive search for subgroups that might explain the early harm or overall null effect in HERS. Nine of the 172 tests for interactions were statistically significant—about the number expected by chance alone. There is no way to determine which, if any, of these nine associations are not due to chance.

In an updated report from the WHI estrogen-plus-progestin trial, only one of 36 subgroup analyses was statistically significant: a higher relative risk for coronary events among women with a high level of low-density lipoprotein cholesterol compared with those with a lower level. The other nonsignificant subgroup analyses included age and years since menopause (11). In an updated report from the WHI unopposed estrogen trial, 26 subgroup analyses were performed. The only significant interaction showed that women with elevated C-reactive protein levels at baseline were at significantly greater risk of CHD with estrogen therapy than women with lower levels. One of the other nonsignificant subgroup analyses was age (12).

THE TIMING HYPOTHESIS

The currently favored explanation for the null WHI results is that the women were ''too old.'' This thesis has recently been transformed into a more positive statement: ''Younger

women would benefit." This emphasis is now called the "timing hypothesis."

The timing hypothesis is based on the thesis that the HERS and WHI trials failed to show cardioprotection because these older women already had atherosclerosis. This thesis supposes that estrogen therapy is bad for atherosclerotic arteries (i.e., causes events when vulnerable plaque is present) but prevents atherosclerosis if begun early enough. On the basis of this theory, estrogen to prevent atherosclerosis should be initiated as soon as possible after menopause, certainly within 10 years. The thesis fits with results in the Clarkson nonhuman primate model, where conjugated equine estrogen prevented atherosclerosis only in animals treated early after castration (within the calculated equivalent of 6 human postmenopausal years) before the onset of diet-induced atherosclerosis (13). It is plausible that an estrogen effect differs with the stage in the natural history of the disease and the severity of subclinical disease.

How good is WHI trial evidence for the timing hypothesis? In WHI, CHD events were uncommon in women less than 60 years of age, and the power to detect treatment effects was limited. In the WHI estrogen-plus-progestin trial with 5,522 women aged 50–59 years, there was no significant interaction of treatment effect on age or years since menopause ($p = 0.36$): The hazard ratios for heart disease were 1.27 in women aged 50–59 years and 1.24 for the trial cohort as a whole (11).

The WHI unopposed estrogen arm with 2,310 women aged less than 60 years also showed no significant interaction for the primary CHD outcome ($p_{\text{interaction}} = 0.35$) among adherent participants aged 50–59 years, and although the hazard ratio was 0.6, the nominal 95 percent confidence interval was 0.25, 1.50. Despite the wide confidence interval, the abstract states that the results suggest heart protection in younger women (12). This statement is apparently based on other subgroup analyses, one showing less revascularization surgery, and the other showing protection against a composite outcome. Because data on the age at menopause (hysterectomy in 100 percent) or oophorectomy (in 40 percent) were not obtained for the women in the unopposed estrogen trial, the treatment effect was assessed by proximity to menopause estimated in four different ways: Only one of several subgroup analyses ($\geq$20 years since hysterectomy) showed a nearly significant test for interaction ($p = 0.06$).

Clinical trials have sample sizes powered to test the primary hypothesis and are apt to be underpowered for subgroup analyses, one reason why decisions about the validity of subgroup analyses should not be based entirely on p values. Nevertheless, studies suggest that significant subgroup treatment effect interactions are necessary for reliable results and are robust to differences in the size of subgroups (14).

With or without significant interaction, replication of results is necessary to confirm the validity of results from subgroup analysis. The only other clinical trial data of estrogen therapy in young women with cardiovascular event outcomes (recorded as an adverse event or a reason for dropout) come from an analysis of 22 small clinical trials with 4,124 women, most conducted in women with menopause symptoms (15). In this pooled analysis, the calculated odds ratio in women taking estrogen versus those who were not taking estrogen was 1.39 (95 percent CI: 0.48, 3.95). This result is unlikely if the true odds ratio was 0.7 or less. These results offer no support for the timing hypothesis.

Other evidence for the timing hypothesis could have been obtained by using electron beam computed tomography to measure coronary artery calcium; the calcium score mirrors the plaque burden (as shown at autopsy) and predicts future coronary events (16). Although coronary calcium was not measured at baseline, the WHI sample is large, and the probability of baseline differences in the treatment versus placebo arms is therefore small. If the timing hypothesis is correct, this test in younger WHI women would be expected to show less calcium in the estrogen than the placebo group in the younger women and little or no difference in the older women.

This hypothesis was not tested in the WHI. Coronary artery calcium was measured at the end of the estrogen-only trial in 1,000 women less than 60 years of age and not in older women. At the time of this writing, the coronary artery calcium scores for the younger women have not been reported, and it is unknown whether women assigned to unopposed estrogen had less, more, or no difference in the amount of coronary artery calcium or had too little coronary calcium to decide. If the results show meaningful differences in the estrogen group as assessed by less coronary artery calcium, the WHI coronary artery calcium study will suggest that estrogen reduces calcified plaque burden. The WHI study cannot test the hypothesis that estrogen is good for younger but not older menopausal women because women 60 years or older were not studied.

The decision not to study coronary artery calcium in older women was apparently based on cost, feasibility, and clinical relevance.

- The cost for studying an additional 1,000 older women was estimated at 1.5 million US dollars, which seems expensive to me but is a pittance compared with the cost of the WHI overall.
- It is not clear to me why heart scans were feasible only for women younger than 60 years at baseline. Many of the women aged 60–70 years at baseline were well enough to participate; older women have been successfully included in other long clinical trials and are often eager to have these evaluations.
- The clinical relevance of the coronary artery calcium outcome in younger women is not clear. Estrogen to prevent heart disease in young women still seems inappropriate, on the basis of the null effect on clinical heart disease, the absence of information about how long to continue postmenopausal estrogen given that the risk of thromboembolic disease and stroke increases with duration of use, and the availability of other proven medications to prevent heart disease in women.
- Finally, based on data from the WHI observational study, the rate of CHD events in women aged 50–54 years is 8/10,000 women per year (17). Given the low disease rates, the absolute risk reduction would be small, and the number needed to treat would be very large.

THE PROMOTION OF A HYPOTHESIS

I find the marketing of the timing hypothesis troublesome. Despite the nonsignificant results in both WHI trials, the timing hypothesis continues to be the subject of overstated conclusions in the medical literature (18–21), newsprint (22, 23), and an article for women subscribing to the *Harvard Women's Health Watch* (24). The message is that "age at initiation and duration of hormone therapy use are sufficient to explain the ostensibly discordant findings for hormone therapy use and coronary heart disease between the WHI trial and observational studies; . . ." and "The WHI findings, taking into account the age of initiation and duration of hormone therapy use, support the validity of findings from observational studies relating hormone therapy use to reduced coronary heart disease risk" (20, p. 1067). Even as I finish writing this commentary, my local newspaper quotes a famous gynecologist as saying, "Later studies showed that hormone therapy actually prevents heart attacks in women who start close to menopause, rather than years later" (25, p. E4).

Current evidence does not support these conclusions. Unfortunately, many patients and physicians do not understand that the opinion that hormones prevent heart disease in recently postmenopausal women is only a hypothesis, without significant evidence from any randomized controlled clinical trials.

CONCLUSION

It seems to me that "flaws" in the WHI clinical trials' design or execution have been sought in order to allow a continuation of old, familiar, health-benefit concepts advanced by epidemiologists and to avoid a painful paradigm shift in limiting long-term use of postmenopausal hormone therapy. Too old and too late is a plausible thesis, but the enthusiasm for the timing hypothesis far exceeds the science. The current Food and Drug Administration proscription that health-care providers prescribe hormone therapy only for symptomatic women, and in as small a dose for as short a time as possible, seems entirely reasonable. No WHI results to date change this situation.

ACKNOWLEDGMENTS

Conflict of interest: none declared.

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