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Reproductive Hormone Exposure Timing and Ischemic Heart Disease: Complicated Answers to a Simple Question

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Premenopausal women have a relatively lower risk of ischemic heart disease (IHD) compared to age matched men and this gender gap narrows after menopause. The observation that the onset of IHD occurs 10 years later in women than it does in men is said to suggest that endogenous reproductive hormones play a protective role. Indeed, animal models and human epidemiological studies suggest that oophorectomy is a risk factor for accelerated IHD. In animal models, hormone therapy (HT) has anti-atherosclerotic effects after oophorectomy, HT in the form of oral contraceptives (OCs) prevents atherosclerosis in anovulatory cycling women, and large numbers of premenopausal women taking OCs have relative safety from an IHD standpoint (1). Further, observational epidemiological studies in humans have consistently demonstrated protective effects for IHD among HT users. Such studies are typically performed on relatively younger women where HT is prescribed for vasomotor symptoms during menopausal transition or shortly following menopause. In contrast, clinical trials in older, postmenopausal and often asymptomatic women have demonstrated no overall benefit and early adverse effects when randomized to a variety of forms of HT (1). These data discrepancies have called into question the validity of the reproductive hormone estrogen protection hypothesis, and raise the alternative possibility

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that HT efficacy may differ according to the timing of exposure. Stated as a simple question, *is the effect of HT on the risk of IHD in relatively young pre- or early menopausal women with vasomotor symptoms, different than it is in older, fully menopausal women?*

Data from the Women's Ischemia Syndrome Evaluation (WISE), a prospective multi-center NHLBI-sponsored study designed to explore female-specific pathophysiology in a large sample of women undergoing coronary angiography for suspected IHD (2), may shed light on this controversy. These new data, prospectively obtained using novel methods, including detailed reproductive health questionnaires, menopausal adjudication algorithms, and quantitative coronary angiography as a measure of atherosclerosis, allow a more precise inspection of this question. However, to answer this simple question we need to first answer others. Specifically, how can we integrate and understand the findings from the available observational, animal and clinical trial data? And to interpret these data other questions become relevant: 1) How accurately was menopause assessed in prior observational HT studies? 2) Does HT in premenopausal women in the form of OC therapy confirm atherosclerosis benefit? and 3) Does HT in early menopausal women confer reduced atherosclerosis and benefit on the risk of IHD?

How accurately was menopause assessed in prior observational HT studies?

Prior epidemiological studies have often failed to distinguish surgical menopause in premenopausal women (bilateral removal of ovaries prior to the onset of natural menopause) from other forms of surgery (hysterectomy or postmenopausal oophorectomy), or to separate hysterectomy without bilateral oophorectomy (cessation of menstrual periods with persistent ovarian function) from hysterectomy with bilateral oophorectomy (cessation of ovarian function). Needless to say, determining whether ovarian function was preserved despite the absence of menstruation is important to correctly adjudicate the impact of reproductive hormones on atherosclerosis. Misclassification of "menopause", particularly among women in the early menopausal transition who represent those most often treated in practice with HT, could contribute to erroneous conclusions regarding relations atherosclerosis and IHD.

We found that inaccurate determinations of menopausal status occurred up to one-third of the time when data were obtained by single self-report measures and/or depended on the presence/absence of menstrual periods. The most common error was to categorize a non-menopausal (i.e. a pre- or peri-menopausal women with $\geq$ intact ovary) as a postmenopausal woman. This suggests that the results of prior observational studies which utilized these menopausal status classification methods are likely impacted by this error, potentially over-estimating the benefits of HT in the postmenopause. We further demonstrated that utilization of a few additional and relatively simple questions regarding reproductive function and a single blood reproductive hormone level, in a straightforward classification algorithm, could significantly improve the accuracy of menopausal status determinations for healthcare research (3).

Does HT in premenopausal women in the form of OC therapy confirm IHD benefit?

Given the animal and observational human data consistent with anti-atherosclerotic effects of OC, it is reasonable to hypothesize that, compared to non-users, women with a history of OC use in their premenopausal years may be relatively protected against IHD via an anti-atherosclerotic benefit resulting in a relatively less IHD events during the postmenopausal period.

We assessed past OC use and evidence of atherosclerotic coronary artery disease in 672 postmenopausal women in the WISE study (4). Past OC hormone use was associated with a significantly *reduced* risk (by a factor of 2.4) of atherosclerotic coronary artery disease measured by quantitative coronary analysis in a core laboratory, even after adjusting for age and coronary risk factors. However, there was no apparent relation between duration of past OC use and the coronary artery disease severity index score. Limitations of this observational study included a greater use of menopausal hormone therapy and a higher risk factor burden among past users of OCs, although these factors would have mitigated toward more adverse cardiovascular events and atherosclerosis in this group.

Does HT in early menopausal women confer reduced atherosclerosis and benefit on the risk of IHD?

Recent data suggest that the timing of initiation of HT in the peri- and postmenopause may be important. In observational studies, younger women without coronary heart disease (CHD) had a reduction in IHD events with HT use, while older women with known CHD had an initial increase in IHD events followed by a reduction after several years of treatment, similar to what was seen with older women in the WHI trials. In the combined WHI trials, women who initiated HT within 10 years of menopause had less relative risk for CHD events compared with those who initiated HT more than 10 years from menopause, and pooled data from randomized trials including WHI found that HT significantly reduced CHD events in younger but not older women (6).

Similarly, in the WISE study, we examined the relationships of total estrogen exposure time, the timing and type of menopause, and the timing of HT use with the degree of atherosclerosis measured by quantitative coronary angiography as well as the number of adverse cardiovascular events determined prospectively (5). We found that HT use, particularly with an earlier onset, was associated with less angiographic CHD and fewer adverse cardiovascular events. Adjustment for age, cardiac risk factors, and a multitude of socio-demographic and lifestyle variables consistent with a “healthy user” effect still demonstrated a significant residual beneficial effect.

Summary

The current literature, combined with improved methodology in the WISE study, suggests that there is a beneficial relation between HT use and IHD in peri- and early postmenopausal women. Our results are also consistent with recent clinical trials that have failed to show benefit of HT initiation in older postmenopausal women, either for angiographic coronary disease or cardiac events. Overall, our data suggest that the anti-atherosclerotic effect of HT, if present, may be age-dependent and primarily evident in relatively younger peri- and early postmenopausal women.

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