TRANSACTIONS OF THE AMERICAN CLINICAL AND CLIMATOLOGICAL ASSOCIATION, VOL. 113, 2002

HORMONES AND HEART DISEASE: WHAT WE THOUGHT, WHAT WE HAVE LEARNED, WHAT WE STILL NEED TO KNOW

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ABSTRACT

Hormone replacement therapy has previously been recommended for the prevention and treatment of many conditions affecting women as they age. Decades of research have determined many beneficial biologic effects of hormones on the direct and indirect mechanisms of atherosclerosis. Observational studies have furthered the enthusiasm for hormone use with estimates of 35–50% reduction in risk for future cardiovascular events in women who took estrogens at menopause. However, there may be inherent selection and compliance biases in the non-randomized cohort methodology. The last decade has produced important randomized clinical trial results which now question whether estrogen replacement will reduce risks or even potentially increase cardiovascular event rates, particularly in women with known coronary disease within the first 1–2 years of initiating treatment. Conclusive evidence of the true risk:benefit ratio for hormone use after menopause awaits the completion of ongoing clinical trials. Until those results are available, each decision for postmenopausal hormone use must be made on a case-by-case basis weighing individual risks with the positive and negative aspects of therapy.

INTRODUCTION

Enthusiasm for the use of postmenopausal hormone replacement has waxed and waned over the years. In the earliest phases of the history of hormone replacement therapy (HRT), popular proponents recommended that essentially all women should take hormones with little recognition of the possibility of side effects. In fact, it was recommended that HRT be started before menopause and continued life-long (1). Additionally, the benefits of hormone replacement were purported to include, not only relief of menopausal symptoms but prevention of

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bone and muscle weakening, heart trouble, hardening of the arteries, atrophy of the breasts, and wrinkling of the skin (2). The implications were that many of the attributes of aging would be attenuated in women who took HRT throughout their postmenopausal years. Women could remain healthy and youthful without developing many of the chronic conditions of old age, merely by taking HRT. The reality, of course, is that postmenopausal women are at increasing risk for CVD. Eventually, more women than men actually die of CVD (3). Women experience increased risk approximately 10 years after men begin experiencing CVD events, and do not approach the same risk as men until over age 80, if ever.

The potential link between loss of ovarian estrogen at menopause and increasing risk for coronary heart disease after menopause, has been supported by substantial evidence from observational and experimental research. Yet, recent reports from clinical trials have raised questions about the true impact of HRT on cardiovascular events. This summary will review the biological effects, animal experiments, epidemiological and observational findings, and clinical trial results regarding HRT and cardiovascular disease.

Biological Effects of Estrogen: Benefits and Discrepancies

Estrogen reduces LDL cholesterol, raises HDL cholesterol and raises triglycerides. In a randomized trial designed to determine the dose response of cholesterol levels to estrogen replacement, Walsh et al found that 0.625 mg of conjugated equine estrogen (CEE) lowered LDL levels by 15% and 1.25 mg CEE lowered LDL by 19% (4). In the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial CEE reduced LDL levels by 10–12% over 3 years (5). The addition of progestin agents (medroxyprogesterone acetate [MPA] or micronized progesterone) does not alter the level of LDL reduction (6). Walsh also found that HDL levels were increased by 16–18% by two levels of CEE dosing (.625 mg or 1.25 mg) (4). In the PEPI trial, HDL rose by 10–12% with .625 mg CEE over the first 12 months, remaining 7% higher than baseline after 3 years. Adding MPA to CEE was found to reduce the HDL increase with CEE. However, micronized progesterone did not (5). While estradiol administered orally has similar LDL and HDL effects as CEE (14% LDL lowering with 2 mg/day and 15% HDL increase), transdermal estradiol (0.1 mg twice a week) does not have either of the cholesterol benefits of lowering LDL or raising HDL (4).

The study by Walsh demonstrated that .625 mg and 1.25 mg CEE increased triglyceride levels by 24% and 38% respectively while oral estradiol (2 mg/day) increased triglycerides by 24% and transdermal

estradiol had no effect (4). The importance of triglycerides as a risk factor for cardiovascular morbidity and mortality has been debated. A recent analysis found that elevated triglycerides imposed a 14% increase in CV risk for men, but a 37% increase for women (7). Earlier studies have also suggested that triglyceride elevation was of particular importance for women (8,9) raising a concern that the estrogen effect on triglycerides may contribute to any overall impact of postmenopausal hormone use on CV risk.

It has been noted that elevations of lipoprotein (a) [Lp(a)] are associated with increased coronary artery disease and with thrombotic stroke (10). It may be that the homology between apo A, which is a portion of the Lp(a) molecule, and plasminogen explains this risk through interference with fibrinolysis (11). Estrogen replacement appears to reduce Lp(a) levels by 10%–32%, with the greater reductions produced by CEE, with or without progestins, than oral estradiol (12,13,14).

One mechanism for estrogen to potentially reduce atherosclerosis is by inhibiting cholesterol ester hydrolysis or lowering the LDL oxidation in the arterial wall (15). However, reports from clinical studies have had variable results. O'Sullivan et al found that CEE but not transdermal estradiol had measurable antioxidant activity in postmenopausal women (16). While another found no impact on LDL oxidation using CEE, transdermal estradiol or oral estradiol. Still another study reported that adding a progestin to CEE reversed the antioxidant activity found with CEE alone (17). It is not clear why some of these studies have discrepant results.

Studies have also found that estrogen has effects on endothelial function, including improving coronary blood flow with ethinyl estradiol (18), blocking or reversing the coronary vasoconstrictor response to acetyl choline with intravenous or transdermal estradiol (19), and improving vasodilatory ischemic response of the peripheral arteries (20,21). Although others have found no differences in forearm blood flow with HRT (22). Another vascular effect of estrogen is to stimulate endothelial production of prostacyclin which inhibits platelet aggregation and causes vasodilator (23). Additionally, ERT appears to reduce plasma viscosity (24), and has been reported to down-regulate inflammatory cell adhesion molecules, interfere with cytokine and growth factors, reduce vascular smooth muscle cell migration and proliferation and inhibit extracellular matrix formation, although there are also contradictory reports about these effects (25). Recently, HRT has been shown to increase levels of C-reactive protein (26) which may eventu-

ally prove to be an important observation in the explanation of unexpected clinical trial results outlined below.

Animal Experiments: Estrogen Helps, Progesterone May Not

Experiments in chicks, rabbits and cynomolgus monkeys have demonstrated reductions in atherosclerosis formation by 17β-estradiol (27,28,29). The addition of progestins to estrogen in the animal model has shown variable results which may be secondary to differences in the selected agent, route of administration and dose (30). In one study, continuous oral MPA appeared to oppose estrogen's inhibition of atherosclerosis (31) while another demonstrated no change in estradiol's reduction in plaque when progesterone was administered cyclically (28). The same group has also reported that neither CEE nor CEE plus MPA enhanced the benefit from a lipid-lowering diet in monkeys with established coronary atherosclerotic lesions (32).

Epidemiological Results: Beware the Biases

Numerous epidemiological studies have reported that HRT use (almost exclusively in the form of CEE) is associated with a reduction in the incidence of coronary artery disease events and mortality (33,34). The magnitude of effect has been estimated between 35%–50% reduction in risk with the benefit thought to reside in the biological and vascular effects of estrogen. However, it is very important to consider the possibility of selection and compliance bias in contributing to the beneficial outcomes. Women who chose to and have the ability to take estrogens are different from women who do not in terms of other risk behaviors, socioeconomic and educational status (35,36). Women in the non-randomized cohort studies have been younger, leaner, achieved a higher educational status, more likely to use alcohol, more physically active, at lower cardiac risk from their family history, less likely to smoke cigarettes, and less likely to have diabetes than women who were not taking postmenopausal hormones (35). Thus, conclusions from the epidemiological cohort studies cannot be considered proof that the differences in cardiovascular outcomes were due to HRT and not to pre-existing differences in risk level.

Another consideration with the epidemiological studies is that women were included who generally had begun hormone therapy at the onset of menopausal symptoms and not at later years for other health benefits. As will be seen from the description of the clinical trials of HRT, the populations enrolled for randomized assignment to HRT were approximately 10 years older than the average age of

menopause onset. Thus, direct comparisons of epidemiological studies with clinical trial results is difficult.

Observational Studies: Interesting But Not Definitive

In addition to cohort studies of women not known to have cardiovascular disease, several reports have evaluated outcomes in women on HRT who were enrolled in studies evaluating coronary or carotid atherosclerosis. Sullivan followed over two thousand women with angiographic coronary artery disease for 10 years and found that women who used estrogen replacement (primarily CEE without progesterones) had a significantly reduced risk of mortality compared with women who did not use hormones (although only 69 women had "ever used" estrogen compared with 377 who had never used hormones) (37). Women using estrogen who participated in the Asymptomatic Carotid Atherosclerotic Progression Study (ACAPS) were found to have less progression and possible reversal of carotid plaque assessed by ultrasound (38).

Clinical Trials

The first randomized study of estrogen and coronary heart disease was actually performed in men in the Coronary Drug Project (39,40). The hormone arms of the study were stopped early because of excess adverse thrombotic and cardiovascular effects (40). The first randomized clinical trial of hormone replacement and cardiovascular outcomes in women was not carried out until the 1990's and was designed as a secondary prevention trial in women with known symptomatic or angiographic coronary artery disease. The Heart and Estrogen/Progestin Replacement Study (HERS) found no differences between combination HRT (CEE plus MPA) and placebo in 2763 postmenopausal women (less than 80 years old with a mean age of 66.7) with regard to nonfatal MI or coronary heart disease death at over 4 years follow-up (41). There were 179 women in the hormone group and 182 women in the placebo group who experienced either a nonfatal myocardial infarction or death due to coronary heart disease. When the timing of adverse events was analyzed, the hormone group experienced an increase in cardiovascular events within the first year of therapy, but fewer events in each of the final two years. While caution must be exercised in interpreting subgroup information, the possibility that HRT may be detrimental early after initiation and beneficial late has been raised. It has been suggested that these findings may be due to opposing effects of the treatment regimen lending particular risk to an as yet unidentified susceptible group of women while providing re-

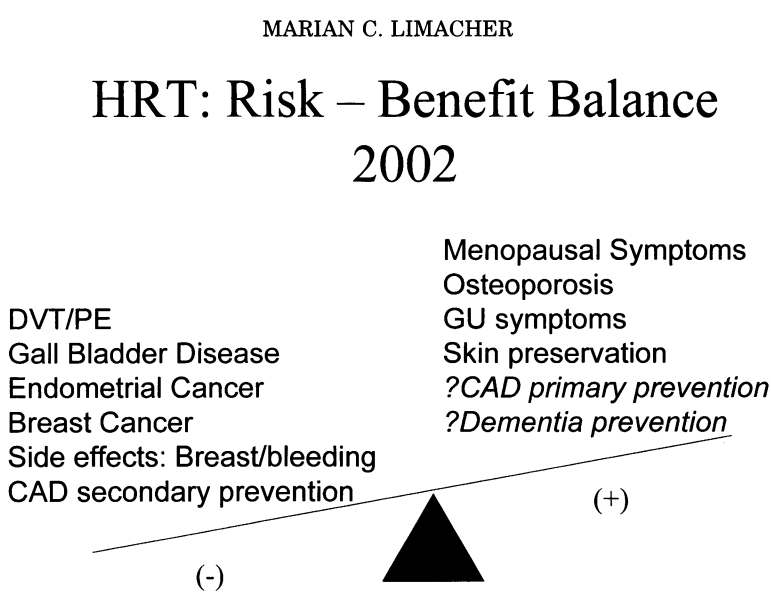

FIG. 1. The balance of positive (+) and negative (−) effects of postmenopausal hormone replacement therapy (HRT) based on the state of knowledge in 2002. Detrimental adverse effects of HRT include deep venous thrombosis (DVT) and pulmonary embolus (PE), an increase in the incidence of gall bladder disease, endometrial cancer (for unopposed estrogen) and a small increase in the risk of breast cancer. There are also predictable side effect such as breast tenderness and vaginal bleeding that limit use in many women. The latest clinical trials demonstrate no efficacy for HRT as a means to reduce recurrent cardiovascular events in women with known coronary artery disease (CAD). The remaining benefits from HRT are relief of menopausal symptoms, such as hot flushes, prevention of osteoporosis, relief of genitourinary (GU) symptoms associated with menopause, and reduction in skin changes with aging. Still unknown but potentially beneficial are the possible effects of HRT on the primary prevention of CAD and on the development of dementia, but both require confirmation through ongoing clinical trials. The overall balance currently tips more negatively than positively and a woman's decision for HRT use should be based on balancing the individual risks and benefits on a case-by-case basis.

duced risk for other women over time. Alternatively, it may also be true that there is essentially no effect on risk for coronary disease with HRT. Additionally, the Estrogen Replacement and Atherosclerosis (ERA) study has also reported no change in existing or new lesion progression with estrogen alone or estrogen plus progesterone compared with placebo in women with angiographically demonstrated coronary artery narrowings (42).

It is important to note that the ongoing Women's Health Initiative Hormone Replacement Trial (43), with over 27,000 women enrolled in both an estrogen only (10,739) or estrogen plus MPA (16,608) arm, has recently reported that risk for cardiovascular events was higher in the

treatment arms than placebo for the first 1–2 years of the study. The WHI Data Safety Monitoring Board (DSMB) did not feel the early increase in events exceeded the pre-determined stopping rules for the study and unanimously recommended the Hormone Replacement Trial continue. Data continue to be reviewed at 6 month intervals. The implications of the HERS and ERA results are that postmenopausal women should not have HRT recommended purely for cardiovascular benefit. The WHI preliminary advisories, although not available for full peer review, raise caution about early risk for cardiovascular events after initiating HRT in women without existing CAD.

Conclusions

While there is broad evidence for important cardiovascular effects of estrogen and progesterone, many questions have recently been raised about the existence of a beneficial clinical effect at all. The current weight of evidence may have shifted from overwhelmingly positive benefit from HRT to the potential for detrimental effects (Figure 1). Fortunately, clinical trials are now in progress and will continue to be undertaken to attempt to identify the true risk:benefit ratio for long term use of postmenopausal hormone replacement. Women with existing CHD should probably not begin HRT and consideration should be given for withdrawal of HRT after a cardiovascular event occurs. However, as outlined in an AHA/ACC consensus panel statement (44), the initiation or continuation of HRT in any woman must be weighed by individually considering the indications, likely benefit and potential risk. The current evidence from randomized clinical trials of women with coronary artery disease does not warrant initiation of hormone replacement for the purpose of preventing further cardiovascular events (45). Ongoing studies, particularly the Women's Health Initiative, will provide much needed additional information to guide the decision about HRT for women in the future.

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DISCUSSION

Colwell, Charleston: I enjoyed it very much. I know that you probably don't have the data here today, but you must have the breakdown of the 27,000 individuals in this study. How many of these may have been people with Type 2 diabetes? Because of the very high risk that the women with Type 2 diabetes have for coronary events, this may be the sub-group that is causing the problem.

Limacher, Gainesville: It is certainly being looked at. The proportion of women in the Women's Health Initiative Hormone Study with diabetes, was only 6% at baseline. We don't yet have the analysis available to determine if diabetics were at greater risk than any other group for the increase in cardiovascular events identified in the first several years of treatment.

Gavin, Chevy Chase: Dr. Colwell and I are, of course, interested in the same concern. Given the fact that people with Type 2 diabetes are now considered as having coronary heart disease risk equivalent status by the ATP III, I wonder whether or not there is a clinical recommendation to avoid HRT in women with diabetes. Have they been lifted to the status equivalent to acute coronary syndrome?

Limacher: That's a very important question, and one that nobody has addressed yet. As I pointed out we certainly have the large database in the Women's Health Initiative to be looking at not only diabetes and traditional risk factors, but novel risk factors and genetic markers in this study population to try to tease out this risk association. While it's a very important question, it is not yet at the evidence level to offer treatment guidelines. I think it's worth being very cautious about any recommendations for HRT in diabetic women until the research findings are available.

Hutter, Boston: As usual a superb presentation. In the meantime, while we're waiting for the answers, what would you as a clinical cardiologist recommend when a woman comes in for bypass surgery or angioplasty? Should we stop their HRT as we start the statins?

Limacher: A very important question. My response is non-endorsed, non-anything-but-personal-opinion at this time and subject to change. With all those caveats I actually do recommend discontinuing active hormone replacement at the time of an acute cardiovascular event if the woman is willing. We have other well-proven treatments that are effective in reducing secondary risk which can be strongly recommended, such as aggressive statin therapy for all who are appropriate candidates. These need to be recommended first.

Santen, Charlottesville: A question about the biology? The ovary, of course, delivers estrogen directly into the venous circulation. The usual way of replacing hormones is with premarin or with other estrogens that are taken orally. These exert a first pass effect on the liver. Is it possible that the adverse effects of estrogens occur because of alterations of prothrombotic proteins synthesized in the liver. On the other hand, estrogens can be given by transdermal patch to avoid the first pass effects on liver. Do

we have data comparing transdermal delivery systems of estrogen with oral delivery systems to try to dissect out this first pass liver effect? Is it possible that the prothrombotic effects could be avoided by transdermally delivered estradiol while still maintaining the potential protective effects on vascular endothelium?

Limacher: That's an excellent question. There are studies comparing transdermal versus oral estrogens for their effects on lipids. There is only one small study, the Papworth HRT and Atherosclerosis Survival Enquiry (PHASE) which tested transdermal estradiol in women with CAD but was stopped early because of a higher number of events in the active treatment group. So we don't yet have a full answer for this question. Certainly we know that the beneficial lipid effects of the oral estrogens are attenuated by the transdermal application, so there may be a rationale for the results of the PHASE study.

Calia, Baltimore: Similar comment to the question of the Type II diabetes, and I know it may be difficult to know this now, but I wonder are there blood pressure differences between the two groups?

Limacher: Actually, there are no differences in average blood pressure between treatment groups in the WHI HRT study. The PEPI study also showed there were essentially no differences in blood pressure on four different treatment regimens of hormones.