Menopausal hormone treatment cardiovascular disease: another look at an unresolved conundrum

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Cardiovascular disease (CVD) is the most common cause of death in women. Before the Women's Health Initiative (WHI) hormone trials, evidence favored the concept that menopausal hormone treatment (MHT) protects against CVD. WHI studies failed to demonstrate CVD benefit, with worse net outcomes for MHT versus placebo in the population studied. We review evidence regarding the relationship between MHT and CVD with consideration of mechanisms and risk factors for atherogenesis and cardiac events, results of observational case-control and cohort studies, and outcomes of randomized trials. Estrogen effects on CVD risk factors favor delay or amelioration of atherosclerotic plaque development but may increase risk of acute events when at-risk plaque is present. Long-term observational studies have shown ~40% reductions in risk of myocardial infarction and all-cause mortality. Analyses of data from randomized control trials other than the WHI show a ~30% cardioprotective effect in recently menopausal women. Review of the literature as well as WHI data suggests that younger and/or more recently menopausal women may have a better risk-benefit ratio than older or remotely menopausal women and that CVD protection may only occur after >5 years; WHI women averaged 63 years of age (12 years postmenopausal) and few were studied for >6 years. Thus, a beneficial effect of long-term MHT on CVD and mortality is still an open question and is likely to remain controversial for the foreseeable future. (Fertil Steril® 2014;101:887–97. ©2014 by American Society for Reproductive Medicine.)

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Atherosclerotic cardiovascular disease (CVD) remains the leading cause of death in women >50 years of age, accounting for ~40% of mortality versus about 5% for breast cancer (1, 2). This remains the case despite trends for improvement in CVD incidence rates and reductions in CVD death rates in the population overall and women in particular (3–5). Risk for new-onset CVD increases after menopause (6), and considerable evidence suggests that the decrease in estrogen experienced by menopausal women contributes to this increase. Nonetheless, after >50 years of research on female sex steroid hormones and atherosclerosis, the questions of whether estrogen deficiency accelerates development of CVD and whether menopausal hormone treatment (MHT) can ameliorate CVD risk remain controversial.

Because the numbers of postmenopausal women in the United States population is large and growing (7), CVD risk assessment and prevention in middle-aged and elderly women is of increasing clinical importance. In this review, we first examine reports of the effects of estrogens and progestogens on factors known or thought to influence development of atherosclerosis and risk of CVD events, then examine the epidemiologic evidence derived from a studies reporting rates of CVD events in menopausal women using and not using MHT, and finally provide a critique of results of recent clinical trials of MHT in which CVD outcomes were primary or secondary endpoints.

PATHOGENESIS OF ATHEROSCLEROSIS

As outlined in a review by Mendelsohn and Karas (8), atherogenesis is a progressive sequence of overlapping stages with characteristic factors influencing each stage. Estrogens and, to a lesser extent, progestogens have been shown to influence factors involved at every stage of the atherogenic process.

Stage 1: Endothelial Injury

The initial step in atherosclerosis involves injury to endothelial cells, most

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often at sites made vulnerable by disruption of laminar flow (e.g., branch points) or increased blood pressure. Arterial flexibility and vasodilation response may be impaired at such sites owing to reduced production and action of nitric oxide (NO). Lipids, such as oxidized low-density lipoprotein (LDL) cholesterol and lipoprotein (Lp) (a), may also cause endothelial injury.

Flow-mediated vasodilation (FMD) is a reflex relaxation of arterial smooth muscle after a period of arterial occlusion with reduced or absent blood flow. FMD is mediated by endothelial NO production. FMD can be quantified after compression of the brachial artery for several minutes with a blood pressure cuff with the use of Doppler ultrasound or detection systems that respond to blood flow in the digits. Impaired FMD is an indicator of endothelial dysfunction and is associated with increased CVD risk (9). Estrogens have been reported to improve FMD (10–13) and arterial compliance (14–16) in a number of studies, whereas progestogens may oppose this effect (17). Higher levels of endogenous E_2 are associated with better FMD response (18), and estrogen treatment increases NO synthase activity (19, 20). This may be due to a direct action of estrogens to induce endothelial NO synthase, but estrogens may also act indirectly via effects on asymmetric dimethyl arginine (ADMA), blood pressure, or Lp(a).

ADMA, an amino acid derivative produced by endothelial cell injury (21, 22), is an NO synthase inhibitor. ADMA is increased in hypertension (23) and CVD (24–26). It is an independent predictor of CVD mortality (27) and worsening of congestive heart failure (28). Estradiol inhibits endothelial cell ADMA production (21, 22, 29). Postmenopausal women have increased ADMA levels (30) and reduced FMD (31), and estrogen treatment decreases ADMA levels (18, 32). Oral estrogen may be more potent than transdermal estrogen in lowering circulating ADMA (33).

Blood pressure (BP) is a major factor in inducing endothelial injury and plays a role in arterial smooth muscle proliferation and thus arterial wall thickening. Oral MHT has been reported to increase BP in younger but not older menopausal women (34) as well as to have neutral effects or even to improve BP (35–37). In one study, transdermal MHT decreased BP in postmenopausal women without altering angiotensin II, and oral HRT increased angiotensin II but did not affect BP (38). Further studies comparing route of administration showed reduction in BP during MHT with transdermal but not with oral estrogen (39). In a longitudinal study, average systolic BP increased less in MHT users than in nonusers (40). However, data from the largest clinical trial of MHT to date show no overall effect of oral conjugated estrogens with constant low-dose medroxyprogesterone acetate on BP (41) and elevations on the order of 1 mm Hg in women on oral conjugated estrogen alone (42).

Lipoprotein(a) is a lipid fraction that contributes to CVD risk independently from LDL and high-density lipoprotein (HDL) cholesterol levels (43–46). High Lp(a) levels are associated with reduced FMD, suggesting that Lp(a) mediates endothelial injury (47). In a prospective study, Lp(a) levels were more predictive of CVD events in women than in men (48). MHT has been reported to reduce levels of Lp(a) (49), with a greater decrease with oral than with transdermal estrogen (50). Also, oral MHT appears to reduce CVD events more in women who have high initial Lp(a) levels than in those who do not (44).

Stage 2: Plaque Initiation

The second stage is plaque formation due to lipid deposition in the arterial wall. During this stage, microcrystals of cholesterol and cholesterol esters from circulating Lp particles accumulate at sites of endothelial injury and are phagocytosed by macrophages. These then form clumps of lipid-engorged foam cells in the arterial intima. Factors contributing to this stage include levels of circulating Lps and endothelial adhesion factors that recruit macrophages to transit the endothelium from the arterial lumen. Plaque progression may be reduced by HDL cholesterol via reverse transport of lipid from the arterial wall to the liver (51). As plaques enlarge, increasing numbers of inflammatory cells and fibroblasts are attracted, leading to formation of a fibrous cap over the lipid deposits.

In numerous studies, high total and LDL cholesterol and triglyceride levels and low levels of HDL cholesterol have been associated with increased CVD risk (52, 53). Agents that lower LDL cholesterol have been shown to decrease CVD events in persons with (54, 55) and without (56–59) prevalent CVD. However, secondary prevention may depend in part on non–lipid-lowering (antiinflammatory and plaque stabilizing) effects of these agents (60–63). Whether interventions that increase HDL cholesterol are also protective remains an unanswered question, because recent large-scale studies examining this issue have been either negative or equivocal (51, 64, 65).

As reviewed by Tikkanen (66), estrogens lower both total and LDL cholesterol and raise HDL cholesterol levels (67–73), although the transdermal route may have less effect on HDL cholesterol (72, 74, 75). Estrogen-induced increases in HDL appear to be due mainly to elevation of the cardioprotective HDL-2 subfraction (67, 74).

Stage 3: Inflammation

The third stage of atherogenesis is characterized by increasing inflammation. As plaques reach a critical size, necrosis of foam cells, invasion by inflammatory cells, and neovascularization with invasion and smooth muscle proliferation in the arterial media occur. The end stage of this phase is the "at risk" plaque partially occluding the arterial lumen containing a core of necrotic material and infiltrated with inflammatory cells. Investigations in the past 10 years have provided strong evidence that inflammatory processes are important contributors to atherosclerosis (76–78).

Inflammatory cells and activated platelets amplify the atherosclerotic process by releasing cytokines, including interleukin (IL) 6 and tumor necrosis factor (TNF) α, which attract and activate additional cells as well as stimulate smooth muscle hyperplasia (79). A variety of circulating cytokines, including IL-6 and C-reactive protein (CRP), have been shown to predict CVD event risk independently from lipids (80–82). High CRP predicts CVD event risk in both men