EDITORIAL COMMENT

Estrogens, Lipids and Cardiovascular Disease: No Easy Answers*

Vera Bittner, MD, MSPH, FACC
Birmingham, Alabama

Postmenopausal hormone therapy as a means of cardiovascular risk reduction remains highly controversial. Advocates point to the numerous experimental studies that show beneficial vascular effects and favorable effects on lipoprotein profiles and to the myriad of observational epidemiologic studies showing improved cardiovascular disease morbidity and mortality among hormone users (1–3). Opponents of such therapy point out that reductions in cardiovascular morbidity and mortality have yet to be proven in randomized clinical trials and that the only trials published to date have not shown any benefit of hormone replacement therapy on clinical end points or angiographic coronary disease progression (4,5) and may have even resulted in an increase in cardiovascular events early after initiation of therapy (4). The Adult Treatment Panel II of the National Cholesterol Education Program suggested in 1993 that oral estrogens be considered as an alternative to standard lipid-lowering therapy among postmenopausal women (6). More recent American Heart Association/American College of Cardiology guidelines instead recommend standard pharmacologic lipid-lowering therapy for coronary heart disease risk reduction in hyperlipidemic postmenopausal women and endorse the recommendation by the Heart and Estrogen/progestin Replacement Study (HERS) investigators not to initiate hormone replacement therapy among postmenopausal women with established coronary artery disease (7). Clearly more research is needed to disentangle potential beneficial and potential detrimental effects of hormone therapy after menopause.

Menopause and therapy with oral estrogens: Effects on lipoprotein profiles in postmenopausal women. After menopause (natural or surgical), total cholesterol rises, low density lipoprotein (LDL) cholesterol rises, and high density lipoprotein (HDL) cholesterol does not change or decreases slightly (8,9). There is a decrease in the HDL-2 subfraction and a shift in LDL particle size toward smaller and denser LDL particles (9,10). Does postmenopausal hormone therapy reverse these potentially atherogenic changes? In cross-sectional studies, postmenopausal women taking estrogens tend to have more favorable coronary heart disease risk factor profiles than those who are not, including higher HDL cholesterol levels and lower LDL cholesterol levels (11). These seemingly beneficial lipid effects of oral estrogens have been confirmed in prospective, randomized controlled trials. In the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial (12), for example, women randomized to oral conjugated equine estrogen increased their HDL-cholesterol by 5.6 mg/dl (9%) and reduced their total cholesterol and LDL cholesterol by 7.6 mg/dl (3.4%) and 14.5 mg/dl (10.3%), respectively. The beneficial effect of estrogen on HDL cholesterol was attenuated when medroxyprogesterone acetate, a commonly used progestin, was added, while the degree of LDL lowering was similar with all regimens tested. Oral estrogens also reduce plasma levels of lipoprotein (a) (Lp[a]) (13). Conversely, oral estrogens tend to increase plasma triglyceride levels: in the PEPI trial, triglycerides increased 13.7 mg/dl (13.9%) among women treated with conjugated equine estrogen (12). Women who are hypertriglyceridemic at baseline may experience much larger increases in plasma triglycerides.

Why do these changes in lipoprotein profiles occur? The available kinetic data have been summarized by Sacks et al. (14). Exogenously administered oral estrogen increases apolipoprotein B gene transcription and increases production of very low density lipoprotein (VLDL) particles in the liver. Clearance of these VLDL particles is accelerated, reducing residence time and thus reducing the potential for cholesteryl ester enrichment and oxidative modification, changes believed to be atherogenic. Hypertriglyceridemia in the setting of estrogen therapy may thus not have the same atherogenic consequences as hypertriglyceridemia due to obesity or diabetes where particle clearance is diminished. Estrogen therapy also enhances LDL catabolism, presumably due to increased expression of LDL receptors. The rise in HDL and apo A-I is primarily attributable to increased synthesis with decreased clearance of HDL particles through diminished hepatic lipase activity playing a lesser role. Prior studies have documented a shift toward smaller LDL particles after oral estrogen therapy, but this shift appeared to be due to a decrease in the LDL subfraction with the largest particles rather than to an increase in the number of small, dense LDL particles, and none of the women changed from pattern A to pattern B (14).

Estrogen as an antioxidant. Oxidative modification of LDL particles is believed to be a significant contributor to atherogenesis (15). Susceptibility to oxidation varies from LDL particle to LDL particle and is determined by, among other factors, particle size (small, dense LDL particles are more easily oxidized than are larger particles), particle composition (e.g., high content of polyunsaturated fatty acids increases susceptibility to oxidation), and level of antioxidants such as vitamin E within the particle (16).
High density lipoprotein protects LDL from oxidation, but is itself susceptible to oxidation. Such oxidation has been shown to increase HDL clearance and could be pro-atherogenic.

Estrogens share structural similarities with vitamin E and other lipophilic antioxidants and are thus able to function as scavengers for lipid peroxyl radicals and interrupt the chain reaction of lipid peroxidation. Estrogens vary in their antioxidant potency: equine estrogens appear to have greater antioxidant effects than do estradiol and estrone, at least in vitro (17). Several studies in postmenopausal women have shown decreased susceptibility of LDL particles to oxidation in women who have been treated with oral and transdermal estrogens, an effect that is independent of the lipid-lowering effects (18–20). Estrogens also protect HDL from oxidation, an effect that should preserve the beneficial functions of HDL, including the protection of LDL from oxidation (21). To date, however, there are no controlled studies to show that such antioxidant effects translate into a slowing of atherosclerosis progression or a decrease in clinical cardiovascular events.

Clinical trials addressing this question are in progress. The current study. In this issue of the Journal, Wakatsuki et al. (22) add to the complexity of the existing data. They treated 24 lean, healthy, naturally postmenopausal Japanese women, mean age 53 years and without coronary heart disease risk factors, with 0.625 mg of oral conjugated equine estrogen daily for three months and determined plasma lipoprotein concentrations, LDL particle size, and susceptibility of LDL particles to oxidation before and after hormone therapy. Treatment with estrogen decreased LDL cholesterol (−17.7%) and apo B concentrations (−8.4%), increased HDL cholesterol (3.96%) and apo A1 concentrations (6.3%), and increased triglyceride concentration (16.5%). The LDL particle size decreased during treatment, and 6 of 16 subjects (38%) converted from LDL pattern A to pattern B. The investigators observed a negative correlation between LDL particle size and plasma triglyceride concentration pre- and posttherapy, and a decrease in LDL particle size during therapy was significantly correlated with an increase in triglyceride concentration. Regression analysis suggested a threshold of 15 mg/dl increase in triglyceride levels beyond which LDL particle size decreased and beyond which LDL particles became more susceptible to oxidation. Among women who did not experience an increase in triglycerides, estrogen therapy reduced the susceptibility of LDL particles to oxidation. The investigators concluded that the estrogen-induced increase in plasma triglycerides could be atherogenic via a decrease in LDL particle size and could partially offset the otherwise beneficial changes in LDL and HDL cholesterol and the antioxidant effects of estrogen.

The current study in perspective. Wakatsuki et al. (22) equate small, dense LDL particles with increased atherogenicity. Although there is certainly substantial evidence to support this contention, there is also data to the contrary (23,24). In primate models of atherosclerosis, the group at Wake Forest has shown that larger LDL particles were more atherogenic than were the smaller particles, and some human studies have had similar findings (24). Rudel and Kesäniemi (25) thus concluded that no one particle is inherently more atherogenic than another, but that any LDL particle can contribute to atherogenesis depending on the surrounding milieu in the body and that lowering of LDL concentration overall thus remains the most appropriate therapeutic target. Without outcome data we cannot conclude that the estrogen-induced LDL particle changes observed in the current study were necessarily detrimental, but further studies relating LDL subfractions and modification of LDL subfractions by hormone therapy to cardiovascular outcomes in women are clearly needed.

Can the changes in LDL subfractions and LDL oxidation observed in this study be generalized to other populations of postmenopausal women? The current study was performed in Japanese women. Wakatsuki et al. (22) do not provide information on their subjects’ diets. Because the Japanese diet differs significantly from Western diets, it is likely that fatty acid composition of LDL particles also differs between Japanese and Western women and could modify the impact of estrogen therapy on oxidative susceptibility and atherogenic potential. Whether phytoestrogen intake (which is also greater among Japanese women than women in Western societies) may have further modified the results is also unknown, but it should at least be considered (26).

All subjects in the current study had undergone natural menopause. Postmenopauusally, ovaries secrete androgens, some of which are converted to estrogen in the periphery. The impact of exogenous estrogen is likely to vary depending on the baseline hormonal milieu—women who have undergone surgical menopause may well show different responses from those who have undergone natural menopause, and those with relatively high estrogen levels due to peripheral conversion may show different responses from those with low baseline levels. Although Wakatsuki et al. (22) measured estrone and estradiol plasma levels before and after treatment, they did not report on the relationship between circulating estrogen levels and lipoprotein profiles including LDL subclass patterns at baseline and during therapy.

Women in the current study were also carefully selected not to have any coronary disease risk factors. Obesity and diabetes, for example, have been associated with secondary dyslipidemias and potentially more atherogenic LDL subclass patterns. Whether introduction of exogenous estrogens into a dyslipidemic environment would have similar effects as those described in the current study is unknown, but, given that many such dyslipidemic individuals appear to be more prone to the triglyceride raising effects of oral estrogens, caution in the use of such therapy may be warranted among high-risk individuals until more definitive results are available.

Can we predict which women will have a potentially adverse impact of estrogen therapy and which women are likely to benefit? Baseline lipid profiles were similar among the 11 women who did and the 13 women who did not experience a triglyceride increase in this study, but there was a suggestion that women who increased their triglycerides
during therapy had lower HDL cholesterol levels at baseline (22) (Table 3). Low HDL cholesterol is believed to be a marker for abnormal metabolism of triglyceride-rich lipoproteins. It is thus possible that the increase in VLDL production induced by oral estrogen therapy unmasked a latent defect in the catabolism and clearance of apo B-containing lipoproteins among these women with lower baseline HDL cholesterol levels. Whether women with lower HDL cholesterol levels are more susceptible to adverse effects of estrogen therapy should be determined in larger samples of postmenopausal women.

Although the small sample size and highly selected population in the current study limit its generalizability, Watsuki et al. (22) have made a significant contribution to the current knowledge base by pointing out that lipoprotein responses to estrogen therapy are heterogeneous and that an increase in triglycerides after initiation of oral estrogen therapy may not be a benign phenomenon.

Current recommendations and future directions. The relationship between menopause, estrogens, lipids and cardiovascular risk is complex and there are no easy answers. Rather than recommending oral estrogen therapy across the board for most if not all postmenopausal women as has been advocated in the past, therapy must be individualized, and potential risks and benefits should be assessed on an individual basis. Such individual counseling, if it is to be successful, requires a much more comprehensive research database than is currently available. In addition to mechanistic studies at the bench, larger and more detailed clinical studies of the impact of estrogen therapy on coronary disease risk factors and cardiovascular disease outcomes in different subsets of postmenopausal women are clearly needed. When discussing options for modification of cardiovascular risk with postmenopausal women, evidence-based interventions such as lifestyle modifications (e.g., smoking cessation, consumption of a low-fat diet and maintenance of normal weight, increase in physical activity) and, when indicated, pharmacologic treatment of hypertension and hyperlipidemia should be emphasized. Until further data are available, a cautious approach to the use of postmenopausal hormone therapy appears to be advisable.

Reprint requests and correspondence: Dr. Vera Bittner, University of Alabama at Birmingham, LHRB 310-UAB Station, Birmingham, Alabama 35294. E-mail: VBITTNER@UAB.EDU.

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