September 2, 2002

Workshop
Women and Ischemia Syndrome Evaluation (WISE)
Diagnosis and Pathophysiology of Ischemic Heart Disease
October 2-4, 2002

Session 4

1. Topic and Author

Effects of HRT on Hemostasis and Inflammation
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2. Where we stand in 2002. Overview/rationale for inclusion of topic.

Estrogen and hormone replacement preparations have numerous biological effects that might be expected to be beneficial or deleterious with regard to atherogenesis. Before publication of HERS, the beneficial properties were commonly reported in publications (reduction in LDL cholesterol, increased in HDL cholesterol, enhanced nitric oxide bioactivity, augmented fibrinolysis, diminished neointimal response to arterial injury in animal models). After HERS, emphasis has shifted to procoagulant and pro-inflammatory effects of hormone therapy.

HRT and Hemostasis. Levels of several coagulation factors increase following menopause, including factors VII and VIII in addition to fibrinogen, although effects of aging independent of estrogen status likely contribute to these changes. In this regard, the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial[1] reported that placebo-treated postmenopausal women had an average increase in fibrinogen levels of 0.10 g/L (baseline 2.88± 0.03 g/L, correlating positively with body mass index) over 3 years; no significant changes in fibrinogen levels were seen in groups receiving hormone therapy that included conjugated equine estrogens. In addition, levels of a critical inhibitor of fibrinolysis, plasminogen activator inhibitor-1 (PAI-1), are higher in postmenopausal women than premenopausal women, approaching PAI-1 levels present in men of any age, as reported in the Framingham Offspring Study[2]. Several studies have shown that estrogen activates coagulation pathways, as evidenced by increased factor VII antigen and activity, increased indices of thrombin generation and activity, and decreased levels of inhibitors of thrombin generation and activity.[3,4] We and others have reported that oral estrogen increases fibrinolytic activity by reducing levels and activity of PAI-1, and that this effect of oral (but not transdermal) HRT is independent of coagulation activation.[5-7] Nonetheless, the net effect of oral hormone therapy appears to be procoagulant, likely accounting for the approximately 3-fold increased risk of venous thromboemboli in healthy postmenopausal women and women with CAD.[8-11] Further, the coexistence of other risk factors for hypercoagulability (e.g., immobility, smoking, obesity, diabetes, advanced age, heart failure, malignancy,or inherited traits) may tip this balance adversely. Procoagulant effects of hormone therapy could also contribute to arterial thrombus formation, especially in the vicinity of plaques with inflammation-mediated release of the coagulation activator tissue factor.

HRT and Inflammation. Considerable pathological and experimental evidence indicates that inflammation within large arteries contributes importantly to the development, progression, and clinical expression of atherosclerosis.[12] In cohort studies of healthy men and women, serum levels of a marker of inflammation --C-reactive protein (CRP)-- were positively correlated with cardiovascular risk.[13-15] CRP may be released from the liver upon stimulation by cytokines such as interleukin-6 and from macrophages and smooth muscle cells of atherosclerotic plaques.[16] In experimental preparations, CRP induces the synthesis of cytokines, cell adhesion molecules and tissue factor in monocytes and endothelial cells and may further contribute to atherogensis by facilitating uptake of LDL by macrophages, thus accelerating foam cell formation.[17-19] Accordingly, a plausible mechanism for adverse effects of estrogen could be potentiation of vascular inflammation and thrombosis by increased CRP associated with oral hormone therapy in postmenopausal women.[20] Increases in CRP with oral hormone therapy may result in part from a direct stimulatory effect of estrogen on hepatic CRP synthesis or

release during the first pass through the liver, as transdermal application of estrogen does not increase CRP levels.[21]

HMG-CoA reductase inhibitor (statin) therapy, which reduces cardiovascular risk, may diminish arterial inflammation as suggested by reduction in levels of CRP in serum that appear to be independent of reduction in LDL cholesterol levels.[22] We recently reported that the addition of statin attenuates the stimulatory effect of hormone therapy on CRP in postmenopausal women.[23] This modulating effect of statins on the potential proinflammatory effect of hormone therapy may account for the observation in HERS that statin use was associated with lower rates of cardiovascular and venous thromboembolic events and total mortality, even in women randomized to hormone therapy.[24]

3. Current challenges and the most important issues for future research

Are the apparent deleterious effects of hormone therapy used in HERS and WHI shared by all forms of hormone therapy, whether oral or transdermal, as well as by estrogen-only preparations? Are pro-coagulant and pro-inflammatory effects of hormone therapy dose-dependent, such that lower doses might shift the balance towards net cardiovascular benefit? Is there cardiovascular benefit to estrogens from plant sources (phytoestrogens)? Does concomitant use of statins make hormone therapy “safe” from a cardiovascular perspective?

4. Current challenges in the areas of communicating messages to health care community, patients and the public

Emphasis must be placed on lifestyle choices that importantly impact cardiovascular risk (smoking, diet, sedentary lifestyle) and the need for greater personal participation in risk reduction. For women (and men) at risk for cardiovascular disease or have established disease, drugs shown in clinical trials to reduce risk must be used more frequently (statins and other lipid-lowering therapies, aspirin, ACE-I/ARBs, beta blockers).

5. Translating new findings to improved diagnosis and treatment/saving lives.

The results of large scale clinical trials with hormone therapy and statins should improve treatment and reduce risk of cardiovascular disease by shifting emphasis from hormonal approaches to lifestyle modification and greater use of statins in clinical practice.

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