Effect of Transdermal Estradiol and Oral Conjugated Equine Estradiol on C-Reactive Protein in Retinoid-Placebo Trial in Healthy Women

To the Editor:

In their interesting study, Decensi et al demonstrated that oral conjugated equine estrogen caused an increase in plasma C-reactive protein (CRP), whereas transdermal estradiol (E2) did not elevate CRP levels. The Heart and Estrogen/Progestin Replacement Study (HERS) and Women’s Health Initiative (WHI) trials demonstrated that oral hormone replacement therapy (HRT) did not reduce the risk of coronary artery disease (CAD) in postmenopausal women with or without coronary disease. Because elevated CRP is an independent risk factor for cardiovascular disease, a proinflammatory effect of oral estrogen might explain the increased risk of CAD during the first year of these recent trials. Accordingly, neutral effect of transdermal E2 on CRP might possibly be associated with a safer profile on early CAD risk. However, it is not clear whether oral estrogen stimulates systemic inflammatory responses or whether it simply stimulates hepatic synthesis of CRP without activation of inflammatory cytokines such as interleukin-6 (IL-6), which regulate hepatic CRP production. According to the WHI observational study, HRT-associated increases in CRP are due to a direct hepatic pass effect of oral estrogen and not to an effect of systemic inflammation because HRT did not increase plasma IL-6 concentrations. However, these data in this study are observational. A prospective randomized study by Herrington et al demonstrated that HRT increased plasma levels of CRP and IL-6 in postmenopausal women. Thus, oral estrogen replacement therapy (ERT) may exert a proinflammatory effect that could partially offset estrogen’s favorable effects and may lead to the increased risk of CAD. In contrast to oral ERT, transdermal E2 has been reported to depress IL-6 secretion in postmenopausal women. Accordingly, transdermal ERT can eliminate the adverse effects of oral ERT on inflammatory markers and could have a favorable effect on clinical outcome. Studies are needed to investigate whether transdermal ERT is effective for the risk of CAD in postmenopausal women with or without CAD.

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Reply

We agree with the comment by Wakatsuki and colleagues, who support our contention that transdermal estradiol may have safer cardiovascular effects than oral conjugated equine estrogen (CEE), on the basis of the different modulation of ultrasensitive C-reactive protein (CRP). As Wakatsuki et al correctly point out, there are conflicting data as to whether the increase during oral CEE is caused by a proinflammatory effect on vessels and atherogenesis through the upstream cytokine interleukin-6 or is simply the result of a metabolic aberration due to increased liver synthesis. In clinical terms, however, this distinction may not be so important, as recent data suggest a direct effect of CRP on amplification of vascular inflammation regardless of the mechanism for this elevation.

Although long-term oral CEE use is associated with increased CRP, hormone replacement therapy (HRT) users were at a similar risk to that of nonusers for all levels of baseline CRP or interleukin-6 levels in the Women’s Health Initiative (WHI) observational study. A more definitive answer on the role of CRP as a potential surrogate end point biomarker of coronary heart disease (CHD) risk while on oral CEE can only be obtained through randomized clinical trials.

In our study, body mass index had a positive effect on the CRP increase over and above the effect of oral CEE. This observation may offer additional clues as to the results of the WHI trial, in which an excess of CHD during oral CEE occurred in a predominantly overweight or obese population. Women with high body mass index or other CHD risk factors might thus be at further increased risk for CHD compared with lean women, as a result of their persistently elevated CRP levels during oral CEE therapy. In contrast, most epidemiological evidence for a beneficial effect of oral CEE is based on studies in healthier and leaner women, who more frequently use HRT in real life and may benefit from its use in terms of CHD mortality. In contrast to those in the WHI trial, subjects in our study received HRT for menopausal symptom relief and were much younger and leaner. They also had no prior CHD or related risk factors.

If confirmed in larger trials, our observation on CRP supports the notion that transdermal estradiol should be the preferred form of estrogen replacement therapy to control menopausal symptoms in heavier women with high CRP values or other cardiovascular risk factors.

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