Statin Attenuates Increase in C-Reactive Protein During Estrogen Replacement Therapy in Postmenopausal Women

To the Editor:

In their interesting study, Koh et al. demonstrated that 0.625 mg of conjugated equine estrogen (CEE) daily for 6 weeks caused an increase in plasma C-reactive protein (CRP), whereas the combination of simvastatin 10 mg daily with CEE for 6 weeks reduces the estrogen-induced increase in CRP. The antiinflammatory effect of HMG-CoA reductase inhibitors (statins) may reduce the estrogen-induced increase in plasma concentrations of CRP. The Heart and Estrogen/Progestin Replacement Study (HERS) demonstrated that estrogen and progestin therapy did not reduce the overall rate of coronary events in postmenopausal women with established coronary disease. Because elevated CRP may be associated with plaque destabilization and rupture, a proinflammatory effect of estrogen might explain the increased number of cardiovascular events demonstrated in women with existing cardiovascular disease during the first year of the HERS trial. Accordingly, a combination of statin therapy may lead to a reduction in the occurrence of coronary events in women with coronary artery disease. However, combination therapy did not completely reverse the increase in CRP concentrations. In contrast to oral estrogen replacement therapy (ERT), transdermal ERT has been reported to decrease CRP concentrations. Because estrogen directly passes hepatic circulation when administered orally, estrogen’s hepatic stimulation may result in an increased production of CRP. Because of less hepatic stimulation, transdermal ERT may decrease CRP concentrations.

We previously demonstrated that the addition of clinically determined doses of medroxyprogesterone acetate (MPA) to estrogen inhibited the increase in CRP to the baseline level. Because androgens have been reported to have antiinflammatory effects and because synthetic progestins such as MPA also have androgenic effects, MPA may reduce CRP concentrations. Thus, transdermal administration of estrogen or the addition of MPA to estrogen decreases CRP concentrations effectively. Further studies are needed to investigate whether CRP reduction can prevent early increases in coronary events in women with coronary artery disease, as demonstrated in the HERS trial.

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Response

Wakatsuki et al raise two issues about hormone therapy relative to changes in C-reactive protein (CRP) levels that may relate to the route of administration and the composition of therapy. Thus, they claim that transdermal administration of estrogen reduces levels of CRP in postmenopausal women, referring to observations made in adult-onset diabetics treated for 6 months with transdermal estradiol in combination with oral norethisterone. However, other groups have not found transdermal estrogen to lower levels of CRP in nondiabetic postmenopausal women.1,2 This is likely because of the absence of a significant stimulatory effect of transdermally applied estrogen on hepatic synthesis of CRP, in contrast to oral administration of estrogen with increased levels of hormone in the portal circulation. Effects of transdermal estrogen on other markers of inflammation (cell adhesion molecules) are also a matter of dispute, with some groups reporting reductions in levels1,3 and others finding no change.2 Whether transdermal estrogen use affects cardiovascular risk is unknown.

Wakatsuki et al also quote their recently published experience with oral combination hormone therapy, in which addition of medroxyprogesterone acetate (MPA) to conjugated equine estrogens (CEE) attenuated the increase in CRP compared with CEE alone. Although this finding is contrary to the observation of Cushman et al4 in the Postmenopausal Estrogen/Progestin Interventions (PEPI) study, similar data have been reported by another group,5 suggesting to these investigators that the addition of a progestin might attenuate otherwise proinflammatory effects of estrogen and thus provide a more atheroprotective form of hormone therapy. However, this combination hormone therapy did not reduce cardiovascular risk in the Heart Estrogen/progestin Replacement Study (HERS). Furthermore, in the Estrogen Replacement in Atherosclerosis (ERA) trial, women randomized to MPA combined with CEE had similar coronary events as the group randomized to unopposed CEE; neither treatment reduced atherosclerosis progression compared with placebo-treated patients. And on July 9, 2002, Dr Claude Lenfant, Director of the National Heart, Lung, and Blood Institute, announced the early termination of the estrogen plus progestin (CEE and MPA) treatment component of the Women’s Health Initiative because of increases in cardiovascular events (as well as pulmonary embolism and invasive breast cancer) in healthy postmenopausal women randomized to this treatment compared with placebo-treated women. Whether unopposed estrogen will be of cardiovascular benefit to women who had prior hysterectomy remains to be determined in this clinical trial.

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