EDITORIAL COMMENT

Postmenopausal Hormone Therapy—Good for Smokers?*

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In premenopausal women, estrogen therapy has different effects in smokers and nonsmokers. Studies of oral contraceptive pills consistently find that hormone use results in a much higher relative risk for cardiovascular events in smokers than in nonsmokers. For example, in the World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, use of oral contraceptives increased risk for myocardial infarction about four-fold among nonsmokers, but more than 20-fold among smokers (1).

In this issue of the Journal, Teede et al. (2) present data from a cross-sectional study of 140 postmenopausal women showing better arterial structure (intimal medial thickness of the carotid artery) and function (systemic arterial compliance) among postmenopausal hormone users compared to nonusers (2). The apparent benefit of hormone use was observed in smokers, but not in nonsmokers. This study suggests that, like oral contraceptive pill use, postmenopausal hormone therapy affects smokers and nonsmokers differently. However, it is unclear why smokers who use postmenopausal estrogen might be at lower risk for coronary disease, when smokers who use oral contraceptive estrogen are clearly at increased risk.

Does this study suggest that we should offer postmenopausal smokers hormone therapy to offset the increased risk of coronary disease associated with smoking? It is important to keep in mind that the study by Teede et al. (2) is an observational study with surrogate outcomes. More than 40 other observational studies suggest a 35% to 50% reduction in risk of coronary heart disease in women using hormone therapy compared with nonusers (3,4). Studies of other surrogate outcomes (lipoproteins, smooth muscle cell proliferation, oxidative potential, brachial artery reactivity, coronary cross-sectional area and coronary blood flow) also suggest that postmenopausal estrogen therapy reduces risk for coronary disease (5). Why might observational studies, particularly those with surrogate outcomes, provide the wrong answer?

Women who take postmenopausal hormone therapy are healthier, wealthier and have better coronary risk profiles than nonusers (6,7). This potential selection bias might account for some of the lower risk of coronary events observed in hormone users. In addition, adherence to medications appears to be a marker for lower coronary risk. For example, in the Coronary Drug Project (8) and the Beta-blocker Heart Attack Trial (9), persons who took placebo medication as directed had a 40% to 50% lower risk of coronary events compared with those who were nonadherent. None of the usual coronary risk factors accounted for this beneficial effect of adherence. Women who are classified as “hormone users” in observational studies are, by definition, adherent.

Use of surrogate outcomes can also give the wrong answer. For example, encainide and flecainide, two drugs that clearly suppress ventricular arrhythmia (a surrogate outcome), increased mortality in trials among persons with heart failure (10). Multiple positive inotropes, despite improving ejection fraction and other hemodynamic measures (surrogate outcomes), also increased mortality among persons with heart failure in clinical trials.

Randomized trials are important to define the efficacy and safety of any intervention. Trials are particularly crucial in testing the value of estrogen, because we are proposing to treat healthy, asymptomatic women with a drug that is known to have important adverse effects, including uterine bleeding and breast tenderness, and increased risk for venous thrombosis, gallbladder disease and possibly breast cancer. To date, the only randomized clinical trial that has evaluated the effect of postmenopausal hormone therapy on coronary disease is the Heart and Estrogen/progestin Replacement Study (HERS). In this trial, 2,763 postmenopausal women with documented coronary disease and a uterus were treated with conjugated estrogen plus medroxyprogesterone acetate or a placebo for an average of four years. Despite a marked reduction in LDL cholesterol and increase in HDL cholesterol (good surrogate markers), there was no overall reduction in risk of coronary events, coronary bypass surgery, revascularization or hospitalization for unstable angina (11). Among HERS participants, 60% had smoked in the past, but only 13% were current smokers—too few to detect an effect of hormone therapy on coronary disease rates among smokers.

In summary, there is observational evidence that, among smokers, postmenopausal hormone therapy reduces risk for surrogate outcomes associated with coronary disease. This possible benefit is not seen in premenopausal women using contraceptive estrogen, and is not supported by data from a randomized trial. Given this lack of convincing evidence, medical professionals should work hard to help postmeno-

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pausal women discontinue smoking, rather than treating them with estrogen—an unproved and potentially dangerous intervention.

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REFERENCES


