

NEWS & Commentary

Oral Estriol Not Associated With Significant Histopathologic Changes in the Endometrium

Granberg S, Eurenus K, Lindgren R, Wilhelmsson L. The effects of oral estriol on the endometrium in postmenopausal women. *Maturitas* 2002;42:149-56.

Oral estriol, available as a custom-compounded agent in the United States, does not increase endometrial histology, although estriol is associated with a non-significant increase in polyps, according to this cross-sectional, parallel-group study conducted between October 1994 and March 1995. Postmenopausal women (n = 125) receiving estriol (either 1 or 2 mg/day) were compared with a control group of postmenopausal women who had not received any estrogen therapy for at least 1 year (n = 116). Both endometrial histology and thickness were assessed. No statistically significant differences between the groups were found for endometrial histology.

In women with an atrophic endometrium, the mean endometrial thickness among estriol recipients was 3.0 mm compared with 2.4 mm in the control group, a significant difference ($p = 0.01$). The number of women with polyps was higher among estriol recipients (n = 14) than controls (n = 3); however, the histopathologic diagnosis was not significantly different between the groups.

Comment. In the study, it is not surprising that endometrial histology and thickness were not different between postmenopausal women using estriol and those who had not used estrogen for a year. It is known that dosages of estriol

such as the 1 to 2 mg/day used in this trial have little proliferative effect on the endometrium. However, unlike other estrogen preparations, 1 or 2 mg of estriol will not conserve bone mass, and estriol is no better than placebo at relieving vasomotor symptoms. When given as a single daily dose, estriol does not induce endometrial proliferation, even at dosages of up to 8 mg daily (Tzingounis et al, *Acta Endocrinol Suppl* 1980).

The intended 5-year Scandinavian Long-Cycle Study (1-2 mg/day 17 β -estradiol) was stopped after 3 years because of increasing hyperplasia, including atypia, and one case of endometrial cancer (Bjarnason et al, *Maturitas* 1999). So this 6-month study is certainly not long enough to show endometrial safety. Even with a 3- to 5-year study of ultralow dose estriol, it is doubtful that this estrogen would produce hyperplasia or cancer, since it is such a weak estrogen. The increase in endometrial polyps in the estriol users is an interesting finding.

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Cognition in Elderly Not Improved by Ginkgo

Solomon PR, Adams F, Silver A, et al. Ginkgo for memory enhancement: a randomized controlled trial. *JAMA* 2002;288:835-40.

Ginkgo, a supplement available over the counter (OTC), does not improve learning, memory, attention, concentration, or naming and verbal fluency in elderly adults who do not have cognitive impairment, according to the results of this randomized, double-blind, placebo-controlled, parallel-group trial. A total of 132 women and 98 men were randomly assigned to receive ginkgo (40 mg, 3 times per day) or placebo for 6 weeks. Standardized neuropsychologic tests (verbal

and nonverbal learning and memory, attention and concentration, naming and expressive language), a self-report questionnaire and a caregiver clinical global impression report were used to evaluate changes in cognition. At study end, the ginkgo recipients did not differ from the placebo recipients on any outcome measured by the neuropsychologic tests. Also, no significant differences between the groups were seen for any self-reported memory function or global ratings by caregivers.

Comment. This trial adds important information to our understanding of the benefits, or lack of benefits, of herbal supplements. It also serves as a model for randomized, controlled trials of such products—it was double-blinded, selection criteria were clearly specified, men and women were included, compliance with study drugs was carefully monitored, medication dosing and duration had clear rationale, there was breadth in the outcomes studies, and the study was well-powered to find statistical significance. Two limitations are worth mentioning. First, adverse events were not monitored. If this study were conducted today, it is likely that a data safety and monitoring board would be required, and adverse events would be ascertained. This is particularly important as the assumed safety of herbal supplements is increasingly being questioned. Second, as the authors point out, they did not use quality control tests to analyze the content of the ginkgo used in the trial. This standard is gaining acceptance because of the variability found when OTC supplements are tested for quality control. It is hoped that similar well-designed studies of ginkgo use for memory enhancement, perhaps in different populations or with a longer duration of therapy, will build on these results.

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Estrogen Slows Calcification of Atherosclerotic Plaque

Christian RC, Harrington S, Edwards WD, et al. Estrogen status correlates with the calcium content of coronary atherosclerotic plaques in women. *J Clin Endocrinol Metab* 2002;87:1062-7.

Women's estrogen levels are associated with the amount of coronary artery calcium, a radiographic marker for atherosclerosis, independent of age and coronary heart disease (CHD) risk factors, indicating that estrogen may modulate the calcium content of atherosclerotic plaque and, thus, slow the progression of atherosclerosis in women, according to this study of 56 deceased white women aged 18 to 98 years: 10 were premenopausal, 13 were postmenopausal taking either estrogen or hormone replacement therapy (ERT/HRT), and 33 were postmenopausal and not taking ERT/HRT. Use of ERT/HRT and menopausal status were identified by medical record review. Medical records were also reviewed for CHD risk factors (i.e., age, smoking, diabetes mellitus status, hypertension, obesity and family history of heart disease). The extent of calcification and atherosclerotic plaque were identified at autopsy. In postmenopausal women, those receiving ERT had lower mean coronary calcium content, mean plaque area and mean calcium-to-plaque area ratio than those who had not received ERT. Mean calcium area, but not atherosclerotic plaque area, was significantly greater in postmenopausal women who had received ERT than in premenopausal women. A woman's estrogen level related to menopause was found to be a significant predictor of both calcium and atherosclerotic plaque area, even after adjustment for CHD risk factors. Coronary calcium and plaque area increased significantly with age in untreated postmenopausal women but not in ERT-treated postmenopausal women.

Comment. Coronary artery calcification (CAC) identified by ultrafast electron beam CT scan parallels coronary artery plaque burden and has been used to predict future risk of cardiovascular events. This study differs in that CAC and plaque were measured at autopsy. The authors report less CAC and plaque in premenopausal women and in postmenopausal women using ERT/HRT when compared with nonusers.

Things to consider when interpreting this paper: (1) Autopsy studies are plagued by unknown differences between women who died and or survived, women who are autopsied or not and women who are excluded by design. In this study, women were excluded if their death was associated with cardiac surgery or acute myocardial infarction, although HERS and WHI clinical trial results suggest that such women might have been more likely to be taking estrogen. (2) All observational studies of HRT suffer from differences between women who do or do not begin and continue HRT. In this study, hormone users were less likely to be obese or diabetic than hormone nonusers. Only controlled clinical trials can control for both known and unknown biases. (3) Only 13 women were taking estrogen for 6 or more months.

Data on duration of use would have helped to support causality. A trial of 13 women is too small a number to support the authors' statement that plaque does not increase with age in estrogen-replete women. (4) Apparently some women had zero CAC, yet the authors use statistical means for comparisons. Categories of increasing plaque burden would be preferred statistically, which would make the results more clinically relevant.

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