Estrogen therapy: Is oral superior to transdermal for endothelial function?

Zegura B, Keber I, Sebestjen M, Borko E. Orally and transdermally replaced estradiol improves endothelial function equally in middle-aged women after surgical menopause. *Am J Obstet Gynecol*. 2003; 188:1291–1296.

OBJECTIVE To explore whether estradiol's vascular effects depend on route of administration.

RESULTS Both oral and transdermal estradiol led to improved endothelial function over 28 weeks in surgically menopausal women.

METHODS Six weeks after surgically induced menopause, 43 healthy women were randomized to 28 weeks of oral or transdermal estradiol. Endothelium-dependent and endothelium-independent dilation were calculated by measuring the diameter of the brachial artery at rest using high-resolution ultrasound after reactive hyperemia, and again after sublingual glyceryl trinitrate.

OUTCOME Endothelium-dependent dilation increased after both oral (from 6% ± 3.9% to 13.2% ± 4.4%, $P<.0001$) and transdermal estradiol (from 7% ± 4.9% to 14.9% ± 5.6% ($P<.0001$). Improvements were independent of changes in blood lipids and lipoproteins. Endothelium-independent dilation did not change significantly in either group.

EXPERT COMMENTARY Both the estrogen-progestin and estrogen-only arms of the Women's Health Initiative found no reduction in heart-disease risk among participants.[1,2] This differed from findings of many observational studies, such as the Nurses' Health Study, which reported a 40% to 50% reduction in heart-disease risk in menopausal women taking estrogen for vasomotor symptoms.[3] Age and progestin use have been suggested as possible explanations for the differing results.

No clear cause of reduced risk of heart disease. Some experts argue that the cardioprotective effect of menopausal hormone therapy is mediated by alterations in the lipid profile, with an elevation in high-density lipoprotein (HDL) cholesterol and a decline in low-density lipoprotein (LDL) cholesterol.[4] This presumably results from the "first-pass effect" of oral estrogen on the liver, an activity that could be antagonized by progestin or not observed if estrogen is given by another route. Others claim the cardiac benefit stems from a direct effect of estrogen on the endothelium of blood vessels.[5] Zegura et al provide interesting data supporting both theories.

Both oral and transdermal estrogen caused a rise in HDL cholesterol, but the increase in women taking the oral hormone (15.8%) was double that of women given estrogen transdermally (8.9%). LDL cholesterol and lipoprotein (a) levels declined significantly (13.4% and 18.1%, respectively), but only with oral estrogen. Blood-flow–mediated dilation rose significantly in both groups, jumping from 6% to 13.2% in women given oral estrogen, versus 7% to 14.9% with transdermal use.

Study limitations. The authors were unable to ensure equivalency of the estradiol concentrations within subjects' systemic circulations. Even if they had measured estradiol concentrations, the expected variation following oral administration would have made interpretation nearly impossible. Thus, it remains unclear whether comparable changes in lipid parameters would be observed by lowering the oral estrogen dose or raising the transdermal

dose. It is also unclear whether lower estrogen doses given orally or transdermally would result in improved blood-flow changes.

Since study subjects became menopausal due to surgery, they were relatively young (mean age: 49.2 years, oral group; 47.8 years, transdermal group). Thus, this study does not reveal whether older women who undergo menopause "naturally" and who might have subclinical atherosclerotic heart disease would respond similarly. Finally, the impact of progestin exposure was not addressed.

While Zegura et al provide important data, their finding of equivalency in improved endothelial function for both oral and transdermal estrogen pertains only to younger menopausal women using estrogen for a relatively short time. It remains unknown whether, after years of therapy, the more beneficial lipid alterations induced by oral estrogen would lead to greater improvement in endothelial function than that observed after transdermal estrogen for a similar time.

BOTTOM LINE Given orally or transdermally, hormone therapy is FDA-approved for the treatment of menopausal symptoms, but not prevention or treatment of cardiovascular disease. The decision to give estrogen orally or transdermally should be based on patient preference or the desire to diminish side effects such as skin irritation or headaches. ■

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REFERENCES

1. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA*. 2002;288:321–333.
2. Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. *JAMA*. 2004;291:1701–1712.
3. Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease. *N Engl J Med*. 1991;325:756–762.
4. Bush TL, Barrett-Conner E, Cowen LD, et al. Results from the Lipid Research Clinics Program Follow-Up Study. *Circulation*. 1987;75:1102.
5. Clarkson TB, Anthony MS. Effects on the cardiovascular system. Basic aspects. In: Lindsay R, Dempster DW, Jordon VC, eds. *Estrogen and Anti-estrogens. Basic and Clinical Aspects.* Philadelphia: Lippincott-Raven; 1997:89–118.