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Estrogen treatment: Safe and effective in early menopause

But many unanswered questions persist

CASE "Doctor, for how long is it safe to continue my estrogen?"

A 50-year-old G3P3 presents with menorrhagia and a 16-week size pelvic mass consistent with a myomatous uterus, by both physical examination and pelvic sonogram. Her endometrial biopsy demonstrated secretory endometrium. She tried a course of progestin treatment, but this did not adequately relieve her bleeding. Her physician recommended either uterine artery embolization or hysterectomy.

The patient chose hysterectomy and bilateral salpingo-oophorectomy because of a family history of ovarian cancer. Immediately postoperatively she was started on conjugated equine estrogen 0.625 mg daily to treat vasomotor symptoms. Four weeks later she reports that she feels very well. She is sleeping well and has no vasomotor symptoms.

She would like to continue to take her estrogen treatment, and asks: "For how many years would it be safe to take the estrogen treatment?"

***FAST** TRACK*

How many years would you be willing to continue estrogen treatment for this patient?

When contemplating any treatment recommendation, physicians and patients must balance potential benefits and risks. In many situations few data are available to fully inform the decision; clinical experience and judgment play a major role. In other situations, overwhelming data from high-quality trials endow the decision with strong evidence for or against a particular strategy.

For women who have just become menopausal, estrogen treatment is clearly both safe and effective. Estrogen treatment is highly effective in the treatment of vasomotor symptoms experienced by hypoestrogenic women. In newly menopausal women, estrogen also appears to reduce the risk of cardiovascular disease and bone loss, and does not increase the risk of breast cancer during the first 8 years of use. Given the benefits and risks, estrogen is a good option for treatment of vasomotor symptoms in early menopause.

Cardioprotective effects

The latest data support the idea that among recently menopausal women, estrogen treatment does not increase, and may decrease, the risk of cardiovascular disease. In the Women's Health Initiative (WHI), 3,310 menopausal women 50 to 59 years old who had a hysterectomy were randomly assigned to treatment with conjugated equine estrogen (0.625 mg daily) or a placebo. Over 6.8 years of follow-up, estrogen treatment demonstrated:

- **a trend for reduced myocardial infarction and death** from coronary disease (hazard ratio 0.63, nominal 95% confidence interval [CI], 0.36–1.08).
- **a statistically significant decrease in coronary artery bypass surgery or percutaneous coronary artery intervention** rates (hazard ratio 0.55, nominal 95% CI, 0.35–0.86).

This protective effect of estrogen was not observed among the menopausal hys-

terectomized women in the WHI who were 60 to 79 years of age.

These findings suggest that the cardioprotective effect of estrogen is most easily observed in women who are immediately menopausal, such as women who recently had a bilateral salpingo-oophorectomy. Estrogen initiated in women 60 to 79 years of age does not appear to have a cardioprotective effect.[1]

Recent epidemiologic studies also support the idea that the cardioprotective effect of estrogen is probably limited to women who are recently menopausal.[2] The recent WHI findings are consistent with the observation in monkeys that estrogen therapy initiated immediately after oophorectomy reduced the extent of coronary artery plaque, but initiation of estrogen 2 years after oophorectomy did not.[3]

Other effects of estrogen

Breast cancer. Previous reports from the WHI found that conjugated equine estrogen 0.625 mg daily did not increase the risk of breast cancer[4]—a sharp contrast from the finding that the combination of conjugated equine estrogen plus medroxyprogesterone was associated with a small increase in the risk of breast cancer after about 5 years of use.[5]

Bone fracture. The WHI clearly indicated that estrogen treatment reduced the risk of bone fracture to a greater degree than either placebo or vitamin D and calcium treatment.[6]

Stroke. Among hysterectomized women in the WHI, the main risk of estrogen treatment was a small increase in the risk of stroke.[4]

Hot flashes. Estrogen treatment is clearly effective in reducing vasomotor symptoms.

Unanswered questions

Given the relative safety of estrogen with regards to breast cancer risk, and the positive effect of estrogen on cardiovascular risk (when started soon after menopause) and bone health, it is clear that estrogen treatment is both effective and safe in women who are recently menopausal. This interim conclusion should be balanced with the knowledge that many unanswered questions remain, including:

- How long should estrogen be continued before tapering?
- What is the lowest effective dose of estrogen that will provide maximal benefits and minimal risks?
- Is non-oral estrogen superior to oral?
- Does a mixture of estrogen agonists and estrogen antagonists have a superior risk-benefit profile than an estrogen agonist alone?
- Are there interventions that will reduce the risk of deep venous thrombosis or stroke associated with estrogen treatment?

We value your opinion. How many years would you be willing to continue estrogen treatment for this patient?

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