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CLINICAL UPDATE

HRT and venous thromboembolism: more evidence of a link

Grady D, Wenger NK, Herrington D, Khan S, Furberg C, Hunninghake D, et al. Postmenopausal hormone therapy increases risk for venous thromboembolic disease. The Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* 2000; 132:689-96.

Background: Recent observational studies[1,2] suggest that there is an increased risk of venous thromboembolism (VTE) with postmenopausal hormone replacement therapy (HRT), but this risk has not been confirmed in clinical trials.

Question: Does HRT increase the risk of VTE among postmenopausal women?

Design: The Heart and Estrogen/progestin Replacement Study [HERS][3] was a randomized, double-blind, placebo-controlled trial conducted at 20 centres. Postmenopausal women less than 80 years of age who had not undergone hysterectomy were enrolled. All had coronary artery disease, because the original goal of the trial was to examine the secondary prevention of coronary events. No subject had a history of VTE, and none had used HRT within 3 months of randomization.

The women were randomly assigned to receive conjugated equine estrogen (0.625 mg/d) and medroxyprogesterone acetate (2.5 mg/d), or placebo. Clinical follow-up occurred every 4 months. During each visit subjects were asked if a blood clot had been diagnosed in the legs or lungs, or if they had been admitted to hospital. Medical records were then reviewed to determine whether VTE had occurred. To prevent unblinding of clinical centre staff, subjects reported gynecologic symptoms to gynecology staff, who were at a separate location.

Results: A total of 1380 women were assigned to receive HRT and 1383 placebo. The mean age was 68 years at baseline. During the follow-up period of 4.1 years on average, 34 women in the HRT group experienced VTE events (6.2 per 1000 woman-years), as compared with 13 in the placebo group (2.3 per 1000 woman-years), for a relative hazard of 2.7 (95% confidence interval [CI] 1.4–5.0, $p = 0.003$). The excess risk was 3.9 events per 1000 woman-years (95% CI 1.4–6.4), yielding a "number needed to treat for harm" (the number of subjects treated for 1 year with HRT, as opposed to placebo, per VTE event) of 256 (95% CI 157–692). The findings were similar when deep vein thrombosis and pulmonary embolism were analyzed separately. Two women died of pulmonary embolism; both had received HRT.

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Multivariate analysis showed excess risk in subjects with lower extremity fracture (relative hazard 18.1, 95% CI 5.4–60.4), cancer (relative hazard 3.9, 95% CI 1.6–9.4), inpatient surgery within 90 days (relative hazard 4.9, 95% CI 2.4–9.8) and hospital admission for nonsurgical reason within 90 days (relative hazard 5.7, 95% CI 3.0–10.8). The risk of VTE was lower among women taking ASA (relative hazard 0.5, 95% CI 0.2–0.8) or statins (relative hazard 0.5, 95% CI 0.2–0.9).

Commentary: HERS is the largest randomized controlled clinical trial to date examining the health outcomes of postmenopausal HRT. Its finding of a 3-fold increase in risk of VTE is consistent with findings of previously published observational studies. Nonrandomized observational studies, however, may have been subject to selection bias, had women taking HRT been more likely to undergo more exhaustive diagnostic evaluation for symptoms suggestive of VTE. The key strength of HERS is that its randomized, double-blind design guarded against such bias.

Practice implications: Postmenopausal women should be cautioned that HRT is independently associated with a small excess risk of VTE events, most of which are nonfatal, and that this risk should be weighed against the beneficial effects of HRT. HRT should be avoided in women whose risk of VTE is increased by cancer, lower extremity fracture or recent (within 90 days) hospital admission for medical or surgical treatment. — *Benjamin H. Chen*

The Clinical Update section is edited by Dr. Donald Farquhar, head of the Division of Internal Medicine, Queen's University, Kingston, Ont. The updates are written by members of the division.

References

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