Hormone replacement therapy: the final frontier

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Gebbie A. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative randomized controlled trial. Writing Group for the Women's Health Initiative #10 Investigators. *JAMA* **2002;288(3):321-33.**

Research question

Is combined estrogen and progestin hormone replacement therapy (HRT) effective as primary prevention for disease in healthy postmenopausal women?

Type of article and design

Randomized, double-blind, placebo-controlled, multicentre primary prevention trial that began enrolling 16 608 postmenopausal women aged 50 to 79 years in 1993 and is expected to be completed by March 2005.

Relevance to family physicians

In 1998, results of the Heart and Estrogen/progestin Replacement Study (HERS), a double-blind, randomized controlled trial (RCT) lasting 4.2 years, were released.[1] Unfortunately, the HERS trial followed only women with established heart disease and primarily examined outcomes of coronary artery disease (CAD). The Women's Health Initiative (WHI) trial is important because it followed healthy postmenopausal women for a variety of outcomes of interest to family physicians: CAD, risk of breast cancer, stroke, colorectal cancer, and fractures. All these outcomes greatly interested women, but risk of breast cancer was of particular concern to physicians counseling women about HRT because increased risk of breast cancer was "a possibility but not a certainty."

Before the HERS study, most of us prescribed HRT to perimenopausal and postmenopausal women, especially if they had heart disease. After the HERS study, we generally took a "don't start, don't stop" stance (ie, we did not start HRT in postmenopausal women, but we did not stop it because it might have a long-term advantage in reducing CAD after initially increasing risk of thromboembolic events).

An estimated 38% of postmenopausal women in Canada currently take HRT, according to an Angus Reid survey in 2000. Even before the HERS results, only 22% of women at high risk of CAD at a Canadian cardiac centre were using HRT, despite evidence for its efficacy at the time.[2] It seems that women's concerns were warranted.

Overview of study and outcomes

Participants were postmenopausal women 50 to 79 years old with intact uteri. Postmenopausal was defined as no vaginal bleeding for 6 months (12 months for 50- to 54-year-olds) or previous use of postmenopausal hormones. Women were excluded if they had medical conditions predicting less than 3 years' survival (acute myocardial infarction [MI], stroke, or transient ischemic attack in the past 6 months); previous breast cancer or suspicion of breast cancer at baseline or any other invasive cancer in the last 10 years; and a femoral neck bone mineral density reading of more than three standard deviations below the corresponding age-specific mean on any of three assigned scans. Also, women were excluded for safety and adherence concerns (low blood count, severe hypertension, chronic active hepatitis, severe cirrhosis, and current use of oral corticosteroids).

Of the 16 608 women recruited, 8506 were randomized to one tablet containing 0.625 mg of conjugated equine estrogens and 2.5 mg of medroxyprogesterone acetate daily, and 8102 were randomized to placebo of identical appearance. Follow-up time averaged 5.2 (range 3.5 to 8.5) years.

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Primary outcome measured was CAD defined as acute MI requiring overnight hospitalization, silent MI determined from serial electrocardiograms, or death from CAD. Invasive breast cancer was designated a primary adverse outcome. Secondary outcomes included hip fracture, stroke, venous thromboembolism, deep vein thrombosis, pulmonary embolism (PE), endometrial and colorectal cancer, and other fractures. The effect of hormones on overall health was measured using a global index that represented a summary measure of the overall balance of risks and benefits.

Results

In absolute terms, during 1 year, 10 000 women receiving daily combined estrogen and progestin will experience 20 more harmful events than women not taking this therapy: seven more CAD events and eight more each of invasive breast cancers, strokes, and PE. Hormone replacement therapy is also protective: there were six fewer colorectal cancers and five fewer hip fractures in the treatment group. This translates into a 1% risk of one of these adverse events occurring with each year of hormone use.

The global index showed a 15% increase in overall harm to the women receiving HRT that occurred gradually over 5 years. No statistically significant difference in mortality was seen between the groups (2.7% deaths in the HRT group; 2.6% in the placebo group). Most deaths were attributable to cancers other than breast (45% and 39%, respectively) and CAD (25% and 28%, respectively). Few women died of breast cancer (two and three, respectively).

Interestingly, subgroup analysis demonstrated that the only significant risk factor for invasive breast cancer was previous postmenopausal hormone use, which resulted in elevated risk ratios. Risk factors, such as family history, parity, and ethnicity, were not significant.

Analysis of methodology

This double-blind RCT conducted at 40 centres across the United States began in 1993 and is slated to end by March 2005. The WHI planned to enrol 161 809 women into several clinical trials: studies of low-fat dietary patterns, and calcium and vitamin D supplementation; an observational study; and two studies of HRT, estrogen plus progestin, and estrogen alone.

Investigators and patients were blinded to group assignment through use of unique bottle numbers and bar codes. Treatment groups were balanced at baseline for demographics and risk of breast cancer and CAD, and were assessed equally. As to adherence, 42% of women in the treatment group and 38% in the placebo group stopped taking the drugs at some point, and 10.7% women in the placebo group crossed over to the treatment group. Daily adherence was assessed with serial bottle weights, but was not reported in the study.

Although this drop-out rate was high, it would only have led the investigators to underestimate degree of harm and falsely decrease amount of benefit of HRT. Due mainly to persistent vaginal bleeding, the study investigators were unblinded to the treatment assignment of 3444 women in the treatment group and 548 women taking placebo (248 women in the treatment arm and 183 taking placebo had had hysterectomies). A remarkably low 3.5% of patients were lost to follow up.

All analyses used time-to-event methods and were based on intention to treat. Primary outcome comparisons were presented as risk ratios with both 95% nominal and adjusted confidence intervals.

Follow up was conducted semiannually by telephone and annually by clinic visits. Electrocardiography was conducted every 3 years, and mammograms and clinical breast examinations were given annually. The study does not mention how many patients omitted these safety measures, but states that study medication was withheld from these patients until follow up was established.

Application to clinical practice

This trial builds on the HERS trial and provides more data to inform our management of HRT in postmenopausal women. As with the HERS trial, these results indicate no reduction in CAD events and, in fact, increased harm soon after initiation of therapy. The 27% incidence of invasive breast cancer and no CAD benefit after 6.8 years of follow up in the HERS II trial are consistent with results of this study.[3] Results of this study are clearly generalizable to Canadian women.

Some questions and concerns remain.

- This study does not answer whether the estrogen-progestin combination or simply progestin itself is responsible for most harmful effects of HRT or whether estrogen alone has fewer harmful effects. We await results of the WHI estrogen-only study.
- The trial used a fixed, typical dose of HRT and did not indicate whether lower doses of estrogen and progestin in combination or other formulations would carry the same or fewer risks.
- Measurement of subjective parameters, such as symptoms and sequelae of menopause (vaginal dryness, dyspareunia, urinary symptoms, hot flushes, sleep disturbance, skin elasticity), common reasons for family physicians to initiate HRT, was limited.

- Whether HRT prevents or delays dementia is unproven by high-quality trials. The WHI trial did not shed further light on this topic.

Bottom line

Risks of HRT certainly outweigh benefits in the measured outcomes of the WHI trial. Results of the WHI trial support those of the HERS study and have further defined the increased risk of thromboembolic events and breast cancer and HRT's protective effect on osteoporosis and colorectal cancer. Individual assessment of patients for other symptoms of menopause that could seriously affect their lives needs to be part of this equation.

- It is reasonable to discontinue HRT in women using it to prevent disease. This is supported by the HERS II study that showed no CAD benefit after 6.8 years.
- It seems reasonable to start a short course of HRT for managing menopausal symptoms. Patients can be informed that the risk of harm while receiving HRT is approximately 2/1000 per year and is cumulative over time.
- Better solutions for preventing disease in postmenopausal women include lifestyle modification, acetylsalicylic acid, lipid-lowering medication, bisphosphonates, and selective estrogen receptor modulators.

I also learned some lessons from the HRT story.

- Experiment trumps observation. We all need to be aware of the hierarchy of medical evidence.
- Evidence changes, and communicating change is an integral part of any physician-patient relationship.

References

1. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998;280:605-13.
2. Wise MR, Stewart DE, Liu P, Abramson BL. Use of hormone replacement therapy among cardiac patients at a Canadian academic centre. *Can Med Assoc J* 1999;161(1):33-6.
3. Grady D, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, et al. Cardiovascular disease outcomes during 6.8 years of hormone replacement therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA* 2002;288:49-57.

Points saillants

Les risques de l'hormonothérapie de remplacement (HTR) excèdent certainement les avantages dans les résultats mesurés de l'essai WHI. Ces résultats corroborent ceux obtenus dans l'étude HERS et décrivent plus en détail le risque accru d'événements thromboemboliques et de cancer du sein ainsi que l'effet de protection de l'HTR contre l'ostéoporose et le cancer colorectal. Une évaluation individuelle des patientes concernant d'autres symptômes de la ménopause qui pourraient sérieusement affecter leur vie doit aussi faire partie de cette équation.

- Il est raisonnable de discontinuer l'HTR chez les femmes qui l'utilisent comme mesure de prévention des maladies. Cette suggestion est appuyée par l'étude HERS II qui a fait valoir l'absence de bienfaits protecteurs contre la coronaropathie après 6,8 ans.
- Il semble raisonnable de commencer une HTR de courte durée pour la prise en charge des symptômes ménopausiques. Les patientes peuvent être avisées que le risque de dommages survenant durant l'HTR est d'environ 2/1 000 par année et qu'il est cumulatif avec le temps.
- De meilleures solutions pour prévenir les maladies chez les femmes postménopausiques incluent une modification du mode de vie, l'acide acétylsalicylique, une médication hypolipidémiante, des biphosphonates et des œstrogènes de confection.

J'ai aussi tiré certaines leçons de l'expérience de l'HTR.

- L'expérimentation l'emporte sur l'observation. Nous devons tous être conscients de la hiérarchie des données scientifiques médicales.
- Les données scientifiques changent et la communication des changements fait partie intégrante de toute relation médecin-patient.