The case for hormone replacement: New studies that should inform the debate

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ABSTRACT

The Women's Health Initiative found that the risks of hormone replacement therapy (HRT) exceeded its benefits in a large group of older postmenopausal women, but did not consider the efficacy of HRT in relieving vasomotor symptoms. Another recent study found that low-dose HRT was as effective as standard-dose HRT while causing fewer side effects. Smaller studies suggest that HRT may improve depression. HRT is not to be used for cardiovascular risk reduction. Genetic testing may point the way to more rational use of HRT.

The HRT debate is far from over

MANY WOMEN who might benefit from hormone replacement therapy (HRT) may decide to forgo it after hearing about the recent report of the Women's Health Initiative,[1] a large randomized trial that found that the risks of taking HRT exceeded the benefits.

Nevertheless, hormone replacement is still the best therapy available for menopausal symptoms, and the case is far from closed on its effects on the vasculature and other conditions. Furthermore, lower doses of hormones may well provide the same benefits while reducing side effects.

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THE WOMEN'S HEALTH INITIATIVE: EXCESS RISK IN OLDER WOMEN

The Women's Health Initiative[1] compared the use of conjugated equine estrogens (CEE; 0.625 mg) combined with medroxyprogesterone acetate (MPA; 2.5 mg)—the same combination used in the popular HRT formulation Prempro 2.5—vs placebo in 16,608 postmenopausal women, all of whom had a uterus at baseline.

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This arm of the trial was stopped early when the data and safety monitoring board detected an excess of cases of invasive breast cancer in the HRT group. The investigators calculated that, per 10,000 woman-years, the attributable risk for invasive breast cancer diagnosis was 38 cases among HRT users vs 30 cases among placebo users, for coronary events 37 vs 30 cases, and for venous thromboembolism 34 vs 16 cases. On the benefit side, per 10,000 women-years, the rates of colon cancer were 10 vs 16 cases and of hip fracture 10 vs 15 cases.

Comments. What do these findings mean for a woman with symptoms of early menopause who is contemplating going on HRT, or someone already on HRT? Several observations:

The women in the study were older: the mean age was 63. Thus, they were past the age of menopausal symptoms, and were willing to be randomized to a 50% chance of receiving placebo. The study was not an efficacy trial, but rather a preventive trial. It did not exam-

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ine the benefit of relieving vasomotor symptoms or halting genitourinary atrophy; rather, it was designed to examine the risks of cardiovascular disease, breast cancer, hip fracture, colon cancer, and overall mortality. Thus the bar for adverse effects was set very low.

Furthermore, the risks of serious adverse effects were fairly low in both absolute and relative numbers. For example, at 4 years of therapy, the hazard ratio for breast cancer in the HRT group was 1.26 (95% confidence interval 1.00–1.59). There was no overall difference in total mortality in the 0.625/2.5 mg HRT users vs placebo users.

Thus, for the indications for using HRT previously approved by the US Food and Drug Administration—relieving vasomotor symptoms, halting genitourinary atrophy, and preventing osteoporosis—the benefits of HRT may still outweigh the risks for many women.

WOMEN'S HOPE STUDY: LOW DOSES ARE EFFECTIVE, BETTER TOLERATED

Low-dose HRT was as effective as standard-dose HRT, and better tolerated

Many women stop taking HRT because of side effects. Would lower doses be better tolerated than standard doses? And would they be as effective?

The study. The Women's HOPE (Health, Osteoporosis, Progestin, Estrogen) study[2–5] enrolled more than 2,600 healthy but symptomatic postmenopausal women who had an intact uterus and randomly assigned them to receive one of eight regimens:

- CEE 0.3 mg alone
- CEE 0.3 mg plus MPA 1.5 mg
- CEE 0.45 mg alone
- CEE 0.45 mg plus MPA 1.5 mg
- CEE 0.45 mg plus MPA 2.5 mg
- CEE 0.625 mg alone
- CEE 0.625 mg plus MPA 2.5 mg (the same combination used in the Women's Health Initiative)
- Placebo.

Outcomes measured were vasomotor symptoms, vaginal atrophy, metabolic profiles, and endometrial hyperplasia. At 2 years, bone density and metabolic profiles were reassessed.

Findings. Vasomotor symptoms improved with all of the CEE regimens compared with placebo within the first 3 weeks. Data suggested that the addition of MPA to the lower doses of CEE was actually beneficial in relieving vasomotor symptoms. Complaints of adverse effects such as breast tenderness were less frequent in the low-dose groups.

Importantly, no increase in venous thromboembolism was seen in this large group of relatively healthy postmenopausal women.

The lower doses of continuous combined CEE/MPA regimens provided endometrial protection similar to that of standard doses. Also, subjects in the lower-dose CEE/MPA groups had higher rates of amenorrhea than those in the standard-dose group.

Lipid profiles were similar in the CEE 0.45/MPA 1.5 mg group compared with the CEE 0.625/2.5 mg group. There were improvements in measures of coagulation and fibrinolysis in all the active-treatment groups.

Findings show that the lower-dose regimens maintained skeletal health among early postmenopausal women.[5]

Comment. Lower doses of CEE/MPA appear effective for relieving vasomotor symptoms and for protecting the endometrium. The lower dose favorably affects the lipid profile, does not adversely affect carbohydrate metabolism, and appears to maintain skeletal health. The hope is that these lower doses will lead to higher rates of initiation and continuation of HRT and, especially, less risk.

DOES HORMONE REPLACEMENT PROTECT THE HEART?

One would expect hormone replacement to prevent coronary artery disease after observational studies such as the Nurses' Health study[6] showed a lower incidence of heart disease in women who took hormone replacement, and other studies found that HRT favorably affects lipid levels.[7]

However, in the Heart and Estrogen/progestin Replacement Study (HERS),[8,9] postmenopausal women with coronary artery disease at baseline did not have a lower rate of cardiac events if they took HRT; in fact, in the first year the event rate was higher in the HRT group than in the placebo group.

In 2001, the American Heart Association[10,11] issued guidelines stating that HRT is not to be used as secondary cardiovascular prevention; however, women with coronary

artery disease who are taking HRT for other reasons can continue taking it. Statin therapy is the first choice for treating hyperlipidemia in women at risk for heart disease or who already have coronary artery disease. Based on the findings of the Women's Health Initiative,[1] estrogen-progestin will not be recommended for primary cardiovascular prevention either.

Comments. I agree with the guidelines. Nevertheless, I would point out that the women in the HERS had coronary disease to begin with, and we should not jump to the conclusion that HRT *causes* atherogenesis, although we know that it increases the risk of clots in some women.

Furthermore, the National Registry of Myocardial Infarction recently reported data from 114,724 women age 55 or older with myocardial infarction (MI). Women with MI who had used postmenopausal HRT had a lower mortality rate: 7.4% vs 16.2% in nonusers. After adjustment for prior clinical history, clinical characteristics, and treatment, HRT remained associated with improved survival, with an odds ratio of 0.65 (95% confidence interval 0.59–0.72).[12]

These observations may be related to therapeutic effects of HRT, selection or adherence bias, or both.

Hormone replacement and blood pressure

Scuteri et al[13] examined data from 226 healthy, normotensive postmenopausal women in the Baltimore Longitudinal Study of Aging to look at the relationship between HRT and blood pressure.

Seventy-seven women used HRT, 149 did not. Lifestyle variables, blood pressure, and traditional cardiovascular risk factors were measured at baseline and approximately every 2 years thereafter. Systolic blood pressure at baseline was similar in HRT users and nonusers.

Findings. Over time, the average systolic blood pressure increased in both groups, but increased less in HRT users than nonusers, independent of other cardiovascular risk factors, physical activity, and alcohol use. The lesser increase in systolic blood pressure in HRT users was more evident at an older age, when it is potentially more important.

Comment. The mechanisms of this finding may be related to arterial stiffness and nitric oxide production. Structural changes in the endothelial wall may be a mechanism through which HRT exerts a beneficial effect.[14,15]

DOES HORMONE REPLACEMENT IMPROVE DEPRESSION?

Previous studies suggested that estrogen improves somatic and mild depressive symptoms in women. Three new studies, although small, were elegantly done and examined the question further.

Soares et al,[16] in a study in Brazil, randomized 50 perimenopausal women to wear a 100-µg estradiol patch vs a placebo patch for 12 weeks. Depression improved dramatically within 1 week in the estradiol group, and the mean Montgomery-Asberg Depression Rating Scale (MADRS) score dropped from 40 to 11 by the end of the study. Remission of depression was observed in 17 (68%) of the women treated with estradiol compared with 5 (20%) in the placebo group ($P \leq .001$).

The study was limited by brevity, self-selection from a menopause clinic, and no assessment of the endometrium.

HRT should not be used for primary or secondary cardiovascular prevention

Ahokas et al[17] looked at 23 women with postpartum depression in a study using sublingual 1-mg estradiol tablets. MADRS scores were obtained at baseline and each week through 8 weeks. All subjects started with low serum estradiol levels; it took some women 3 to 8 weeks to reach a follicular level. The results were significant, with remission of depression in more than 80% of these women.

Schmidt et al[18] observed a full or partial therapeutic response in 80% of 34 women who received estradiol for 3 weeks in a placebo-controlled crossover study, compared with 22% of those receiving placebo.

Comment. Estrogen seems to influence neuronal function via serotonergic, noradrenergic, dopaminergic, and GABA-mediated systems, but we still don't know the exact mechanism of the antidepressant effect.

Of interest, estradiol appears to reduce the symptoms of depression in perimenopausal women who do not have hot flashes, reinforcing the concept that the effects of estrogen on

mood may be independent of vasomotor symptom relief. The vasomotor symptoms returned when the HRT ended, but the depression did not.

DOES HORMONE REPLACEMENT PRESERVE COGNITIVE FUNCTION?

Controversy continues regarding whether HRT preserves cognitive function, and, if so, by how much. Small studies in women with existing dementia showed no benefit in cognitive scores. On the other hand, epidemiologic studies[19] show a lower risk of dementia and better cognitive function in long-term users of HRT than in nonusers.

CAN BREAST CANCER SURVIVORS USE HORMONE REPLACEMENT?

Standard dogma holds that women with a history of breast cancer must not take HRT, which might increase the risk of recurrence.[20] However, short-term use of HRT (< 4 years for menopausal symptom control) is not associated with any increase in breast cancer diagnosis risk.

O'Meara et al,[21] in a 17-year observational cohort study, evaluated data from 2,755 breast cancer survivors, of whom 174 had used HRT after diagnosis.

Fewer women died who used HRT than who did not. The adjusted relative risk of death for users compared with nonusers was 0.5 (95% confidence interval 0.3–0.85). The total mortality rates were 16 per 1,000 woman-years in HRT users and 30 per 1,000 woman-years in the nonusers.

The results suggest that HRT use in self-selected women breast cancer survivors has no adverse impact on breast cancer recurrence or mortality.

CAN WE PREDICT WHO WILL BENEFIT OR BE HARMED BY HRT?

We expect that in the future we will be able to use genetic testing to determine who would most benefit from long-term HRT and, conversely, identify the small but significant subset of women who may be harmed by it.

Predicting fracture risk. A genetic study examining *COLIA1* genotyping in both sexes was able to predict fractures independently of bone mass.[22] The genotyping results, coupled with the data from bone mineral density, helped identify women who were at high risk and low risk for osteoporotic fractures.

Tamoxifen reduces breast cancer risk among *BRCA2* carriers. Tamoxifen has been shown to reduce the incidence of breast cancer by half in women at high risk. Until recently, it was not known whether women who were carriers of the *BRCA1* or *BRCA2* mutation genes had the same benefit with tamoxifen chemoprevention.

Recently, King et al[23] found that tamoxifen reduced breast cancer incidence among healthy *BRCA2* carriers by 62%, similar to the reduction in incidence among all the women in the Breast Cancer Prevention Trial. However, tamoxifen use beginning at age 35 or older did not reduce breast cancer incidence among healthy women with inherited *BRCA1* mutations.

Breast ductoscopy and ductal lavage are emerging procedures that may further help to risk-stratify women who are at increased risk for breast cancer and monitor those on chemoprevention.

Predicting thrombotic and cardiovascular risk. The factor V Leiden mutation substantially increases the risk of thromboembolism. On the other hand, it is relatively rare; an estimated 188 women would need to be screened for the factor V Leiden mutation for one case of venous thromboembolism to be prevented by withholding HRT.[24]

The prothrombin *G20210A* mutation, carried by approximately 5% of people, also increases the risk of thromboembolism. Psaty et al[25] performed a case-control study to investigate the interaction between the prothrombin *G20210A* mutation and myocardial infarction in HRT users with hypertension. The investigators estimated that women who carry the *G20210A* mutation and use HRT have a nearly 11-fold increased risk of MI if they are 80% compliant with their HRT regimen, and a 20-fold increased risk if they are 100% compliant.

Elevated HDL is not always good. Generally, the serum level of high-density lipoprotein (HDL) is inversely related to the

HRT seems to improve depression independent of its effect on vasomotor symptoms

ischemic heart disease. However, Agerholm-Larsen et al[26] recently found that women who were heterozygous or homozygous for the Ile404Val mutation in the cholesteryl ester transfer protein gene had both elevated HDL levels and a 1.4-fold to 2.1-fold increased risk of ischemic heart disease.

Comment. Such studies may point the way to more rational use of long-term HRT. The use of short-term HRT (≤ 4 years) should not change based on the Women's Health Initiative study. Conceivably, women should avoid long-term HRT use if they carry a mutation that increases their risk of thrombosis, cancer, or ischemic heart disease with HRT. Conversely, they might be good candidates for utilizing tailored HRT if they carry a mutation that increases their risk of osteoporosis or derive skin benefits, neuropsychological benefits, or genitourinary benefits from HRT.

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