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Hormone replacement therapy: Applying the results of the Women's Health Initiative

THE GROUND RULES have changed for the way we prescribe combined hormone replacement therapy (HRT), thanks to findings from the estrogen-progestin arm of the landmark Women's Health Initiative (WHI).[1] And although some of the findings were disappointing, we should be glad we finally have answers to some of the most controversial questions affecting the health of older women.

EXPECTED AND UNEXPECTED RESULTS

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In this issue of the *Cleveland Clinic Journal of Medicine*, Dr. Holly Thacker[2] summarizes the major results of the WHI, which was designed primarily to determine if HRT prevents coronary artery disease in healthy older women.

It doesn't. In fact, compared with placebo, combined HRT (conjugated equine estrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day) was associated with small but statistically significant increases in the risk of coronary events, invasive breast cancer, strokes, and pulmonary embolism. On the other hand, it protected against colorectal cancer and hip fractures.

Most of these results are very similar to the findings of earlier, observational studies. Thus, while the increases in breast cancer and venous thromboembolism and the decreases in colon cancer and fractures were expected, this is the first randomized trial to confirm these effects in a healthy population.

The cardiovascular results were the major surprise, since nearly all observational studies have shown both unopposed estrogen and estrogen combined with a progestin to have a cardioprotective effect.

As most commentators have pointed out, the absolute level of risk for any of the outcomes in the WHI was quite small. Nonetheless, the overall level of risks exceeded the benefits—not a desirable profile for a drug intended to prevent disease in a healthy population.

Thus, the WHI investigators concluded that HRT should not be started or continued for prevention of cardiovascular disease, and that its long-term use to prevent osteoporosis must be very carefully considered.

MY RECOMMENDATIONS

As evidenced by the lively debate that has emerged since the findings were released on July 9, 2002, there is not yet consensus on how these results should affect clinical practice. Here is my current approach to this issue.

Women on estrogen-only need not change

Although the combined estrogen-progestin arm of the WHI was stopped early because of the increased risk of breast cancer, the WHI also includes an estrogen-only arm (among women with a hysterectomy), and this is continuing. The only information available so far is that there was no difference in breast cancer risk between the placebo and the active-treatment groups at the 5.2-year mark.

We can keep giving long-term HRT to women younger than age 50

Women in the WHI were between 50 and 79 years old at the start of the trial, and the risks identified can be generalized only to that age group. Healthy women under 50 years of age will have much smaller baseline risks for car-

diovascular events and for breast cancer, and so even the increases seen in this study will have very little effect on the real risk to individual women.

We can keep offering HRT to healthy women with vasomotor symptoms

For these relatively young women (almost all under 60 years of age), the risk for cardiovascular disease is extremely low, so that a slight increase makes little real difference. Most women will need therapy for 5 years or less, so breast cancer is not a significant issue, and the benefit in this situation is clear.

I have made three changes in my approach to vasomotor symptoms in light of the WHI results:

- I now start at a lower dose (for example, 0.3 mg of conjugated estrogens), but I still increase the dose if needed.
- I suggest that women try stopping their combined HRT periodically, perhaps annually, to better determine when they can reasonably discontinue the hormones.
- I will be more careful in prescribing combined HRT in this situation to women who are at very high immediate risk for either myocardial infarction or stroke, since the risk of these events appears to go up soon after beginning hormone treatment.

Women over 50 taking HRT solely to prevent chronic disease should consider stopping

For these women, other methods for preventing cardiovascular disease and osteoporosis are available that appear to have a more favorable risk-benefit ratio. In particular, even though estrogen prevents bone loss and now has been shown in the WHI to reduce the risk of fractures, the other methods of preventing bone loss and fractures appear to have fewer risks. Thus, in my view, long-term combined HRT is not a first-line option for these purposes.

Other regimens may not be better

We should not assume that other estrogen-progestin combinations, different progestin frequencies, or lower doses of either drug would give different results than the regimen used in the WHI trial. Although it is true that the results cannot be directly applied to other drugs and combinations, it would be foolish in my view to assume that these other regimens are different.

Women who stop HRT should be assessed for osteoporosis risk

My advice depends on the woman's risk.

- For women with normal bone density, I recommend exercise combined with adequate intake of calcium and vitamin D.
- For women with osteopenia and no risk factors (smoking, low body weight, or personal or family history of a fracture), I suggest monitoring bone mineral density, and prescribing exercise, calcium, and vitamin D, and perhaps antiresorptive therapy, but I explain that antiresorptive therapy has not been shown to be cost-effective in this situation.
- For osteopenic women with risk factors, antiresorptive therapy is more likely to be of clear benefit. My current first-line choice is raloxifene, as it appears to also reduce breast cancer risk. My second choice is a bisphosphonate (alendronate or risedronate).
- For women with osteoporosis as evidenced by either a vertebral fracture or low bone density, I recommend either raloxifene or a bisphosphonate, according to the woman's individual health situation.
- For women who are frail or have multiple fractures, I recommend a bisphosphonate.

No consensus yet on HRT, but here is my approach

MORE TO COME

Stay tuned! Over the next 3 to 5 years, additional analyses from the combined-treatment arm of the WHI will be performed, the estrogen-only trial results will appear, and other randomized trials of other drugs for postmenopausal health will be completed.

REFERENCES

1. **Writing Group for the Women's Health Initiative Investigators.** Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative Randomized Controlled Trial. JAMA 2002; 288:321–333.
2. **Thacker HL.** The case for hormone replacement: new studies that should inform the debate. Cleve Clin J Med 2002; 69:670–678.

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