

Failure of Estrogen Plus Progestin Therapy for Prevention

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APPROXIMATELY 38% OF POSTMENOPAUSAL WOMEN in the United States use hormone replacement therapy.¹ In 2000, 46 million prescriptions were written for Premarin (conjugated estrogens), making it the second most frequently prescribed medication in the United States and accounting for more than \$1 billion in sales, and 22.3 million prescriptions were written for Prempro (conjugated estrogens plus medroxyprogesterone acetate).² While US Food and Drug Administration–approved indications for hormone therapy include relief of menopausal symptoms and prevention of osteoporosis, long-term use has been in vogue to prevent a range of chronic conditions, especially heart disease. Estrogen alone was the dominant hormone until the increased risk of endometrial cancer led to the addition of progestins for women with an intact uterus. Since the mid-1980s, combined estrogen/progestin use has steadily increased.³

Evidence on the potential risks and benefits of combined estrogen/progestin has slowly accumulated, suggesting that the combination acts differently than estrogen alone. Several studies found a link between duration of estrogen/progestin use and breast cancer risk.⁴⁻⁸ Addition of progestins may increase risk above that observed with estrogen alone, as mitotic activity in the breast during normal menstrual cycles is greatest when progesterone levels are highest.⁹

Early evidence from studies of unopposed estrogen suggested it lowered risk of cardiovascular disease, consistent with results from studies of intermediate markers that showed beneficial changes.¹⁰ However, recent evidence from secondary prevention trials and observational studies using combined estrogen/progestin therapy showed increased risk of coronary heart disease in the first year.¹¹⁻¹³ This may reflect prothrombotic and proinflammatory effects of progestins that outweigh any effects of estrogens on atherogenesis and vasodilatation.

Now, the surprising results of the Women's Health Initiative (WHI) are reported in this issue of THE JOURNAL.¹⁴

See also p 321.

The WHI is the first randomized primary prevention trial of postmenopausal hormones, and the part of the study that compared estrogen/progestin with placebo was terminated early. The data and safety monitoring board (DSMB) recommended stopping the trial because women receiving the active drug had an increased risk of invasive breast cancer (hazard ratio [HR], 1.26; 95% confidence interval [CI], 1.00-1.59), and an overall measure suggested that the treatment was causing more harm than good (global index, 1.15; 95% CI, 1.03-1.28). The decision to stop the trial after an average follow-up of 5.2 years (planned duration, 8.5 years) was made when these results met predetermined levels of harm. However, several other outcomes also suggested harm, including increased coronary heart disease (HR, 1.29; 95% CI, 1.02-1.63), stroke (HR, 1.41; 95% CI, 1.07-1.85), and pulmonary embolism (HR, 2.13; 95% CI, 1.39-3.25). Beneficial results included decreases in colorectal cancer (HR, 0.63; 95% CI, 0.43-0.92) and hip fracture (HR, 0.66; 95% CI, 0.45-0.98). Numbers of overall deaths in the estrogen/progestin and placebo groups were statistically and clinically similar in this short-duration study. Most adverse outcomes began appearing within 1 to 2 years, but increased breast cancer risk did not begin until 3 years. Results were remarkably consistent in subgroup analyses, suggesting that there is not a subgroup that the drug benefits.

The DSMB did not recommend stopping the other portion of the hormone replacement trial, which compared estrogen alone with placebo in women with hysterectomies, so it is reasonable to assume that to date, estrogen alone may be safer than combination estrogen/progestin.

The methods of the WHI study appear strong. A total of 16608 women entered the randomized double-blind trial, and the active treatment group and the placebo group appeared to be comparable at baseline. It is interesting that such a large number of women were willing to participate in a study of a commonly used and accepted drug, and perhaps equally remarkable that only 3.5% were lost to follow-up. Clinicians were unblinded for 40.5% of women in the

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active treatment group and 6.8% of the placebo group, usually because of persistent vaginal bleeding. The types of outcomes and standardized procedures for measurements make it unlikely that this degree of unblinding affected results. During the study, 42% of women receiving active drug and 38% of those receiving placebo stopped taking their assigned medications, and 6.2% and 10.7%, respectively, initiated hormone therapy. Therefore, as the authors suggest, the reported findings of the intention-to-treat analysis may have underestimated the true effects. Also, if duration of treatment is important, as appears to be the case with breast cancer risk, and if compliance decreases over time, 5-year results may underestimate longer-term treatment effects. The investigators took into account competing risks of therapy and created a global index of major medical events to give an overall assessment of benefits and harms.

The authors present both nominal and rarely used adjusted CIs to take into account multiple testing, thus widening the CIs. Whether such adjustments should be used has been questioned,¹⁵ but nominal CIs are appropriate for breast cancer, coronary heart disease, and the global index outcomes because they were the preselected major outcomes of the trial. Also, the consistency of the results over the 5 years of the study, as shown in Table 4 of the article and in the figures, argues against spurious statistical results.

Overall, the results of the WHI study are consistent with the growing body of literature on the effects of combination estrogen/progestin. The increasing risk of breast cancer with duration of use and the reductions in risk of colon cancer and fractures are in the expected direction and magnitude. Risk for stroke and venous thromboembolism continued throughout the 5 years of therapy, whereas the elevated risk of coronary heart disease was largely limited to the first year of therapy, as occurred in the Coumadin Aspirin Reinfarction Study¹² and the Heart and Estrogen/progestin Replacement Study.^{11,16}

How should practicing clinicians and the millions of women taking an estrogen/progestin combination react to the unexpected and disquieting results of this study? First, although the trial results are reported primarily in terms of relative risk, which is appropriate for studies of cause, when applying the results to practice, they must be translated into absolute risk. The absolute risk of harm to an individual woman is very small. As the authors point out, the increased risk of the estrogen/progestin combination means that in 10000 women taking the drug for a year (10000 must be used to register risks in whole integers), there will be 7 more coronary heart disease events, 8 more invasive breast cancers, 8 more strokes, and 8 more pulmonary emboli, but 6 fewer colorectal cancers and 5 fewer hip fractures. Nevertheless, when counting all events over the 5.2 years of the trial, the excess number of events in the active drug group was 100 per 10000 (or 1 in 100 women). This is still a small risk, but it demonstrates that risks from the drug add up over time.

Second, the whole purpose of healthy women taking long-term estrogen/progestin therapy is to preserve health and prevent disease. The results of this study provide strong evidence that the opposite is happening for important aspects of women's health, even if the absolute risk is low. Given these results, we recommend that clinicians stop prescribing this combination for long-term use. *Primum non nocere* applies especially to preventive health care. The results are for a single dosing regimen (1 daily tablet containing 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate) and other regimens may have different results, but the 3 studies reported to date in the United States with other regimens have all found an increased risk of breast cancer.^{5,6,17}

How can women be protected against osteoporosis? The results from the WHI and from numerous other studies have shown protection with hormone replacement therapy. Fortunately, there are alternative preventive strategies, at least one of which also lowers the risk of breast cancer (although to date, cardiovascular effects are not clear).¹⁸ What about short-term use for managing menopausal symptoms? The WHI trial does not specifically address this question, but the results suggest short-term use (≤ 1 year) of the combination has risks for coronary heart disease and thromboembolic disease. The possibility of these small absolute risks must be balanced against the severity of symptoms and benefit of treatment.

Common preventive therapies require rigorous evaluation. For hormone replacement therapy, which is used by millions of patients, even rare adverse effects can harm substantial numbers of women. Although prevention trials are difficult and expensive (the expense often pales compared with drug expenses over time), these studies have produced important results for health care, as demonstrated by the WHI, the Breast Cancer Prevention Trial,¹⁹ and the Multiple Outcomes of Raloxifene Evaluation study.²⁰ The WHI provides an important health answer for generations of healthy postmenopausal women to come—do not use estrogen/progestin to prevent chronic disease.

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Estrogen Replacement Therapy and Risk of Ovarian Cancer

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BY THE MIDDLE OF THE 20TH CENTURY, IT WAS WELL recognized that elderly women frequently developed severe osteoporosis, resulting in a life complicated by constant back pain and repeated fractures. By the 1970s and 1980s, it became clear that use of estrogenic substances at or near the time of menopause could prevent or treat osteoporosis, and these drugs became widely prescribed and taken. Even before the bone-sparing effects of estrogen were known, these agents were used extensively for the treatment of menopausal symptoms, primarily vasomotor instability and vaginal atrophy.¹

An intriguing coincidence occurred from about 1955 to 1965. Reproductive-aged women from that generation were the first to experience substantially reduced pregnancy risks due to development of safe anesthesia and readily available transfusion, as well as the availability of antihypertensive agents and broad-spectrum antibiotics. During this time, effective oral contraception became widely available to the general population at a reasonable cost. The ability to prevent pregnancy effectively further reduced reproductive-associated risk. By the 1980s and 1990s, as a result of these and other medical advances, the US population of postmenopausal women began to increase dramatically. At the same time, the incidence of cardiovascular, neoplastic, and neurologic diseases among older persons began to soar.

For a short time, estrogen replacement was viewed as the perfect solution for many health problems in postmenopausal women. Estrogens were thought to prevent coronary artery disease² and delay the onset of Alzheimer disease.^{3,4} The benefits of preserving bone⁵ and reducing menopausal symptoms were already well-known.⁶ It is not

surprising that the pharmaceutical industry developed numerous estrogenic agents, which could be swallowed, placed in the vagina, applied with a patch, or rubbed into the skin, and that these agents have been prescribed for and are now used by millions of women. However, recent secondary prevention studies provide compelling evidence that there is no protection against further cardiovascular events for women with coronary heart disease who take hormone replacement therapy (HRT) and there may be real harm.^{7,8}

In this issue of THE JOURNAL, Lacey et al⁹ report the results of their follow-up study of a large cohort of women who were recruited in the 1970s to participate in the Breast Cancer Detection Demonstration Project. In 1979, the National Cancer Institute added questions concerning ovarian cancer and its suspected risk factors (including HRT) to follow-up questionnaires. The analyses of these data by Lacey et al show that women who used estrogen-only HRT had a significantly increased risk of later development of ovarian cancer. The fact that the association increased with longer duration of therapy, particularly with duration of use for 10 years or longer, increases the face validity of their findings.

The study by Lacey et al is not the first to examine the association between HRT and ovarian cancer. Most early studies found no association, although more recent studies have reported consistent increases in the risk ratio for ovarian cancer among women who have taken estrogen-only HRT compared with those who have not.¹⁰⁻¹² While the data from these observational studies do not establish causality, the association between estrogen use and ovarian cancer should

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