Reflections on the Women's Health Initiative Trial of postmenopausal hormone therapy

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In the summer of 2002, the early discontinuation of one arm of the Women's Health Initiative trial of hormone replacement therapy sent shock waves through the world's medical community (1). The ripples continue to spread (2, 3). The arm stopped was continuous daily conjugated equine estrogen (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) vs. placebo in asymptomatic women. Overall, this hormone regimen caused more harm than good. Two important aspects of the trial and its aftermath merit comment: the paradoxical effect of hormone replacement therapy on women's health, and the extrapolation of the trial's results (4).

Both basic research and observational epidemiology in past decades suggested a consistent, strong protective effect of hormone replacement against coronary artery disease. The benefit seen in observational studies now appears due to residual confounding related to selection bias and other biases such as surveillance and co-treatment bias. Briefly put, women who chose to use hormone replacement therapy in the past were healthier than those who did not. Thus, the benefit seen in these studies was likely due to the better inherent health of the women and not to the hormones they took (selection bias).

Other types of biases were also likely involved. Women who took hormone replacement therapy, available only by prescription in the countries where these studies were done, likely had more frequent contacts with physicians than did other women (surveillance bias) (5). This might have translated into better health. Women who developed intercurrent illness while taking hormones often stopped these medications; such women had a markedly higher risk of death than did women who continued their hormone regimen (survivor bias) (6). In addition, women who took pills faithfully had lower rates of coronary disease than did less compliant women (7). Successful pill-taking itself is a marker for personal characteristics associated with better health (adherence bias).

A properly designed and conducted randomized controlled trial is the only way to avoid these biases. This arm of the Women's Health Initiative Trial was designed specifically to address the putative preventive benefits of hormone replacement therapy, with a focus on cardiovascular disease (1). At the time it was stopped by its Data Safety and Monitoring Board, the trial had documented that cardiovascular disease and breast cancer were increased with this treatment, whereas colorectal cancer and osteoporotic fractures were reduced.

Are these results credible? By international standards for the conduct and reporting of randomized controlled trials, the Women's Health Initiative Trial was well done (8). Thus, its internal validity is high: it measured what it set out to measure. Moreover, corroborating evidence soon emerged from systematic reviews commissioned for the U.S. Preventive Services Task Force (7, 9). An important feature of these reviews is that they excluded poor-quality observational studies. The findings were consistent

with the Women's Health Initiative Trial: hormone therapy increased the risk of coronary artery disease, stroke, and thromboembolism; the risk of breast cancer and gallbladder disease increased with longer use. In contrast, this therapy reduced the risk of osteoporotic fractures and colorectal cancer. Data on dementia were insufficient.

A second concern with any randomized controlled trial is external validity: can a clinician generalize the results to his or her patients? Volunteers in clinical experiments are different than those who choose not to participate. For example, the health of volunteers tends to be better (10). Yet another problem with external validity for the Women's Health Initiative is that it was a prevention trial focused on asymptomatic women. Many women take estrogen and progestin around the time of menopause mainly for relief of menopausal symptoms (3).

Can the results from the Women's Health Initiative Trial, whose participants had a mean age of 63 years, be extrapolated to younger, symptomatic women? The authors of the trial report found consistent results among women of different ages, including those in their 50's (10 % were 50-54 years, and 20 % were 55-59 years) (1). However, these women were not taking hormones for relief of symptoms but, rather, for prevention of illness in the future. Thus, the question of extrapolation to symptomatic women remains unresolved.

Another unsettled question relates to the possible effects of hormone therapy on the brain. Randomized controlled trials among symptomatic women have shown benefits in verbal memory, vigilance, reasoning, and motor speed, although the results have not been consistent (4). Weaker observational studies have suggested protection against Alzheimer disease. These outcomes were beyond the scope of the Women's Health Initiative trial.

Given these results, what are women and their clinicians to do? Estrogen remains the best treatment of menopausal symptoms. Other drugs and other routes of delivery, e.g., ring or transdermal patch, need evaluation. Since lower doses of estrogen than that studied in the Women's Health Initiative Trial (0.625 mg of conjugated equine estrogen) appear equally effective in relieving vasomotor symptoms, reduced doses seem advisable (4). This may be especially true for women who may need hormone replacement longer than five years. Treatment plans should probably be made for no more than a year at a time, and plans should be tailored to the woman's needs. A single, one-dose-for-all approach to hormone therapy appears inappropriate.

While other medications can be used to treat menopausal symptoms, none is as effective as estrogen. Alternative treatments for hot flushes include megestrol, venlafaxine or paroxetine, and clonidine. Selective estrogen-receptor modulators are not effective in treating hot flushes, and herbal preparations have marginal benefit at best (4).

For osteoporosis prevention, other alternatives to estrogen are available. These include raloxifene, a selective estrogen-receptor modulator, which can prevent spinal fracture. Bisphosphonates, including risedronate and alendronate, reduce the risk of fractures (4). Exercise has been shown consistently to improve bone mineral density although there is a lack of data regarding fractures (11).

In summary, the Women's Health Initiative is a landmark study that has already had a profound impact on women's health. The dominant message is that asymptomatic women should not take combined daily conjugated equine estrogen 0.625 mg plus medroxyprogesterone acetate 2.5 mg to prevent cardiovascular disease. Many clinicians have been prescribing these drugs for that purpose (12). Instead, proven approaches to prevention of cardiovascular disease deserve emphasis: maintaining normal weight, exercise, and avoidance of smoking. Antihypertensive medications and cholesterol-lowering drugs may be appropriate for women unable to reach desirable values through lifestyle modifications. For those with established cardiovascular disease, antiplatelet therapy, beta-blockers, or other drugs may be advisable.

Preventive services for women, like curative services, should be based on the best available evidence (13, 14). Large, rigorous randomized controlled trials (1) and systematic reviews (7, 9). continue to provide the best guidance for both women and their clinicians.

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