Clinical Take-Home Points From the WHI Hormone Therapy Trials

JoAnn E. Manson, MD, DrPH

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Hello. This is Dr. JoAnn Manson, Professor of Medicine at Harvard Medical School and Brigham and Women's Hospital in Boston, Massachusetts. Today I want to talk about an update on the Women's Health Initiative (WHI) hormone therapy trials recently published in *JAMA*.[1] I am principal investigator at the Boston site of the WHI and first author of the *JAMA* article. This is a comprehensive report on the 2 trials -- the trial of estrogen plus progestin in women with an intact uterus and the trial of estrogen alone in women with hysterectomy. Overall, more than 27,000 women participated.

This report provides detailed findings on primary, secondary, and quality-of-life outcomes with a full breakdown of the results by age, time since menopause onset, and other clinical characteristics, and with follow-up to 13 years. The main goal of this comprehensive report is to provide as much information as possible to help women and clinicians make informed decisions about hormone therapy and to provide individualized care.

The key findings of the WHI trials are that the balance of benefits and risks seems to be more favorable for estrogen alone than for estrogen plus progestin, but the pattern of benefits and risks was complex in both trials. Overall, the results appear to be more favorable for younger women than for older women in both trials.

Some of the risks associated with hormone therapy included increased risk for stroke, venous thrombosis, gallstones, and urinary incontinence. Benefits included a lower incidence of hip and other fractures, less diabetes, and reductions in vasomotor and other menopausal symptoms. With regard to cognitive function in women 65 and older, there was an increased risk for dementia but neutral results for cognitive symptoms in younger women (in their early 50s). Again, this was a complex balance of benefits and risks overall.

After stopping hormone therapy, most of the benefits and risks did dissipate. A significant reduction in endometrial cancer emerged after stopping therapy, and the results for all-cause mortality and for cancer mortality were neutral in both trials.

No Benefit for Chronic Disease Prevention

The main conclusion from these trials is that hormone therapy remains appropriate for the management of moderate to severe hot flashes, night sweats, and other menopausal symptoms in early menopause. The findings do not support long-term use for chronic disease prevention.

Clearly, the bar is set very high for the long-term use of a medication for chronic disease prevention; the risks of treatment have to be extremely low. Very few medications have met that standard; however, the absolute risks are certainly lower in younger women, and menopausal symptoms and impaired quality of life related to vasomotor and other symptoms are much more likely in younger than in older women. Overall, the quality-of-life benefits that would be derived from treating symptomatic women are likely to outweigh the risks in those younger age groups; however, long-term use for chronic disease prevention would not be recommended on the basis of these findings.

Additional research on other formulations of estrogen and progestin, using different, lower doses and different routes of delivery such as the transdermal route will be very important to assess whether some of these risks can be avoided, as has been suggested by some observational studies. In conclusion, the findings suggest that hormone therapy remains appropriate for management of menopausal symptoms in early menopause, but they do not support long-term use for chronic disease prevention.

Thank you very much for your attention. This is JoAnn Manson.