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Questions remain about safety of hormone therapy

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The picture is getting clearer about hormone therapy, but five years after a landmark study of the treatment was halted many questions are still unanswered.

In July 2002 leaders of the massive Women's Health Initiative, a randomized controlled trial that enrolled more than 100,000 women at 40 sites across the country, including UMass Medical School and Fallon Clinic, told women to stop taking their Prempro pills because early results showed the drugs raised the risk of heart attack and stroke.

Millions of women followed suit when the news broke, abandoning the estrogen-plus-progestin combination that had become standard treatment not just for the relief of menopausal symptoms but also for prevention of heart disease, based on earlier observational studies. Observational studies do not carry as much scientific weight as randomized controlled trials, so the WHI was eagerly anticipated to give the final word on hormone use.

It did and it didn't.

Five years and a slew of smaller studies later, this much is agreed on: Hormone therapy should not be used to prevent heart disease. Its use may be appropriate to relieve severe to moderate symptoms of menopause — hot flashes and night sweats that interrupt sleep and interfere with quality of life — at the lowest effective dose for the shortest amount of time.

"I think this has been a sea change in how medicine is practiced," Dr. Judith K. Ockene, chief of preventive and behavioral medicine at UMass, said last week. She was the principal investigator for the UMass site of the WHI. "It also adds to our understanding of the evidence. Observational studies are important but you can't base your guidelines purely on them."

Recent research suggests that the age at which a woman takes the hormones and how long she takes them can make a difference in how the therapy affects her. Last month Dr. JoAnn E. Manson, chief of preventive medicine at Brigham and Women's Hospital in Boston, reported in the *New England Journal of Medicine* that women ages 50 to 59 who took estrogen had a lower risk of coronary artery calcification — a marker for heart disease — than women of the same age who did not take the hormone. But older women who took estrogen had worse coronary artery calcification.

"We now have a refined understanding of the benefits and risks of hormone therapy and the evidence is now mounting that a woman's age and amount of time since onset of menopause influences her health outcomes on estrogen, particularly the risk of heart disease," Dr. Manson

said last week. But “it should not be used for the prevention of cardiovascular disease in either younger or post-menopausal women.”

The long-term risk-benefit ratio of hormone therapy is still not known, although answers may emerge from WHI participants who are still being followed, Dr. Ockene said.

WHI has made an important contribution by changing the clinical practice of starting hormone therapy in older women at higher risk of heart disease, Dr. Manson said. It was designed to address whether hormones helped prevent heart disease in women with an average age of 63.

“The clear and conclusive answer was that the risk outweighed the benefit and that it should not be used for that purpose,” she said. “What the WHI was not able to do was to address the benefits and risks of hormone therapy in younger, recently menopausal women who are starting hormone therapy for the treatment of menopausal symptoms.”

Dr. Manson is recruiting participants for a new trial, called the Kronos Early Estrogen Prevention Study, or KEEPS, that will look at women who are one to three years past menopause. The trial will study the progression of coronary artery disease, cognitive function, quality of life and breast density in women on hormone therapy as it compares different forms of hormones. Traditional hormones will be stacked against bioidentical forms; oral pills will be compared to transdermal patches.

Cognitive function and breast cancer were also studied in the WHI. Dr. Ockene was surprised when the study showed that women’s cognitive function suffered when they were on hormone therapy, exactly opposed to the received wisdom that said menopausal women had memory loss and poor concentration when their natural estrogen levels dipped.

She is also recruiting women for new trials that will look at alternatives to hormone therapy. One will test soy isoflavones, or plant-based compounds, and the other will study meditation as a method of coping with menopausal symptoms.

Dr. Ockene noted that changes in behavior — quitting smoking, eating a healthy diet, getting physical exercise, cutting down on alcohol — are all known to improve heart health, ease menopausal symptoms and lower the risk of cancer without the risks posed by hormone therapy.

“These are the kinds of things women need to think about in the overall picture,” she said.

The connection between estrogen and breast cancer had long been suspected, said Dr. Dale Magee, a gynecologist in private practice in Shrewsbury who is also president of the Massachusetts Medical Society. Research had suggested a link between hormone therapy and breast cancer, which had biological plausibility on its side. Women with early menopause have a lower risk of breast cancer and women who enter menopause later have a higher risk, he said, so it makes sense that prolonging a woman’s exposure to estrogen in pill form would also increase the risk of breast cancer.

But the increase in risk is important to understand, he said. The WHI reported a 26 percent increase in the risk of breast cancer among women on hormone therapy, but the actual

numbers were small. About 28 women out of 10,000 women per year would get breast cancer without hormone therapy. With hormone therapy the number rose to 35 women out of 10,000 women per year.

"This is a 25 percent increase, but if we say that the increase was 7 per 10,000 per year, it puts it into a more realistic perspective," he said. "We need to put risk in the context of everyday life."

Dr. Magee says his patients are less worried now than they were in 2002.

"Most are not taking (hormone therapy), but then, most didn't even back then. The percent has dropped, though," he said.

Dr. Ockene can understand why women might be confused by conflicting studies, but she counsels an individual approach based on a woman's health and concerns.

"We need to come back to what one would call personalized medicine, in the sense of what is best for that person," she said.

To find out more about the soy-isoflavone or meditation studies at UMass Medical School, send an e-mail to hotflash@umassmed.edu or call (508) 856-5691. To find out more about the KEEPS trial at Brigham and Women's Hospital, go to www.keepstudy.org

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