Estrogen use lowered one risk factor for heart disease among some younger postmenopausal women

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A follow-up study to the federally funded Women's Health Initiative should help allay one concern in a subset of women in their 50s who are considering taking estrogen to relieve hot flashes. The study shows that among women who have had hysterectomies, estrogen use was associated with a significantly reduced risk for one predictor of future heart attacks.

However, a Stanford University School of Medicine researcher who is the senior author of the follow-up study reminded women that hormone therapy still carries other health risks, such as the increased likelihood of blood clots and stroke, and stressed that the latest findings shouldn't be interpreted to mean that estrogen should be used to prevent heart disease.

"Heart disease is complex, and the effect of estrogen on one risk factor does not adequately predict the risk of having a heart attack," said Marcia Stefanick, PhD, professor of medicine at the Stanford Prevention Research Center and chair of the national steering committee for the overall WHI study. "But this study offers some reassurance for women of menopausal age that it's not unsafe, in terms of the risk of heart attack, to take estrogen, at least for a few years."

The latest study, which will be published in the June 21 issue of the New England Journal of Medicine, shows that women who took estrogen during the WHI study had lower levels of calcified plaque in their

coronary arteries than did women who took placebo pills. The result adds yet another nuance to the complicated picture of hormone therapy that has emerged over the last five years.

Hormones relieve hot flashes and other symptoms of menopause. Until WHI was undertaken, observational studies over the years had been interpreted to suggest that hormones also protected women against heart disease, weak bones and dementia.

But WHI - the largest-ever study of postmenopausal women's health - published findings in 2002 that essentially blew up the conventional wisdom about hormone therapy and raised concerns among a few medical organizations that remain critical of the findings.

The hormone therapy portion of the WHI study had two placebo-controlled trials: one (for women who still had their uteruses) in which half of the women were assigned to take a combination of estrogen and progestin, and a similar trial for women who had undergone hysterectomies in which half the participants took estrogen alone. The estrogen-progestin arm was called to an early halt in 2002 when evidence showed that women taking the combined therapy faced a greater risk of breast cancer, stroke, blood clots and, in the first year of treatment, heart attack.

The estrogen-alone arm of the study involved women who had previously undergone a hysterectomy. Half of the women were given a form of estrogen known as conjugated equine estrogens, while the other half were given a placebo. It was stopped in 2004, one year before its scheduled conclusion, because of concerns that estrogen increased the risk of stroke and blood clots, with no benefit in terms of heart disease.

Since the end of both trials, Stefanick and the other WHI investigators have continued to analyze the data for a more detailed understanding of

hormone therapy's effects.

Although the initial analysis of the WHI data found that estrogen had no effect on the risk of heart attack among all the women, who ranged in age from 50 to 79, secondary analyses suggested that there might be some benefit for women in their 50s and those within 10 years of menopause. However, the evidence showed no heart health benefit for older women or for those who began taking estrogen more than 10 years after menopause.

To delve into the possible benefit of estrogen in the younger age group, Stefanick and her WHI colleagues at 28 of the 40 original WHI clinical centers across the United States, including Stanford, invited participants who were in the 50-59 age group at the time they were accepted into the estrogen-only trial to have cardiac computed tomography scans to assess one indicator of heart disease, their levels of coronary artery calcium. If a buildup of calcified plaque ruptures, it could block the flow of blood through the arteries, possibly causing a heart attack or stroke.

These scans were completed an average of 1.3 years after the estrogen-only arm was halted in 2004, by which time an average of 8.7 years had elapsed since the women were randomly assigned to either placebo or active estrogen. At the time of the scans, calcified artery plaque was 20 to 40 percent lower in women who had taken estrogen compared with the women assigned to placebo pills. When the researchers narrowed the focus to those women who took 80 percent of their study pills during the trial, the coronary artery calcium score was 50 to 60 percent lower for those on estrogen compared with those on placebo.

But Stefanick noted that there was no way to know whether the reduced plaque levels will continue to be a reliable indicator of the progression of coronary artery disease in these women as they age. She also noted that other researchers have begun exploring whether heart disease in women,

particularly those in their 50s, is linked to a more diffuse type of disease involving the small vessels of the heart. It is unclear how the scans for coronary artery calcification account for this disease, she added.

"Regardless, we have to keep in mind that heart disease is only one potential health risk of hormone therapy," Stefanick said. "When women are thinking about taking estrogen, they should consider the overall risk/benefit balance, which includes an increased risk of stroke and blood clots, regardless of age."

A related editorial that will appear in the same issue of the New England Journal of Medicine says the latest findings support the "timing hypothesis," meaning that estrogen use may have beneficial effects on heart health if initiated as "replacement therapy" before ovarian estrogen levels have been low for an extended period. The same hypothesis holds that if the therapy is initiated after a period of estrogen deprivation, it may be harmful.

However, Stefanick said the study data don't address the "timing hypothesis" because "only younger women were studied, so we don't know whether coronary artery calcium was higher or lower in the older women assigned to estrogen vs. placebo. Furthermore, without a baseline CT scan, we have no data about changes over time."

Stefanick said the medical advice for women experiencing hot flashes and other menopausal discomforts remains unchanged: If they choose to start estrogen, they should take the lowest dose that relieves their symptoms and limit the duration of the therapy.

Source: Stanford University Medical Center