



The ASRM is pleased to acknowledge the generous contribution of Pfizer towards publication of this e-newsletter.



Menopausal MEDICINE

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

SEPTEMBER 2011

FOR CLINICIANS WHO PROVIDE CARE FOR WOMEN



Cynthia K. Sites, MD

Division Chief, Reproductive Endocrinology and Infertility
Professor, Department of Obstetrics and Gynecology
Tufts University School of Medicine
Baystate Medical Center
Springfield, Massachusetts

FROM THE EDITOR

“So does estrogen therapy help or hurt my heart, doc?”

Such a simple question, but not such a simple answer. We thought the answer was a resounding “yes, of course it helps prevent cardiovascular disease” when asked 10 years ago following publication of numerous epidemiologic investigations and primate studies, but now we are more cautious with our reply. The Women’s Health Initiative (WHI) original report in 2002 raised this uncertainty in our mind, and subgroup analyses of WHI data in more recent publications have also raised concerns. The jury is still out, but the final verdict ultimately may be “it depends.”

In this special e-newsletter edition of *Menopausal Medicine*, Hugh S. Taylor, MD, reviews the progress of an ongoing multicenter trial, the Kronos Early Estrogen Replacement Study (KEEPS), that will be completed in 2012. This large, prospective, randomized trial asks the question: “Does estradiol, either transdermal or oral, prevent atherosclerosis in women if initiated early in menopause?” Women are recruited for this study only if they are within 3 years of menopause onset. This makes KEEPS unique among large randomized trials. The women are also given cyclic progesterone if they have a uterus.

Timing is everything. And the timing of starting menopausal hormone therapy may be as critical as the decision to take it. We eagerly wait with our patients for the KEEPS results.

MENOPAUSAL ESTROGEN THERAPY AND HEART DISEASE:

Will early intervention make a difference?

Overview of the Kronos Early Estrogen Prevention Study (KEEPS)

Hugh S. Taylor, MD

Professor and Director
Division of Reproductive Endocrinology and Infertility
Yale University School of Medicine
New Haven, Connecticut

Disclosures

Dr Taylor reports that he has served as a consultant to Pfizer and Abbott and on the speakers bureau of Abbott.

A decade ago it was widely believed that menopausal hormone treatment protected against atherosclerosis and resultant heart disease. Multiple large-scale observational studies showed a nearly 50% lower risk of coronary heart disease in women receiving menopausal hormone therapy.¹⁻³ In 2002, however, the primary results of the Women’s Health Initiative (WHI) estrogen-plus-progestin trial did not confirm the expected reduction in heart disease; further, the increase in coronary heart disease, breast cancer, and thromboembolic events led some to conclude that menopausal hormone therapy produced net harm.⁴ The results of the WHI estrogen-alone trial also showed no coronary heart disease benefit and an increased risk of stroke, although without an increase in breast cancer.⁵ The WHI results and the extensive publicity that followed the study’s publication caused widespread cessation of hormone therapy use.

WHI VS OBSERVATIONAL STUDIES

There are distinct differences between the WHI and the observational trials that preceded it. The women in the WHI had an average age of 63 years; thus, menopausal hormone therapy was begun in women who were more than a decade beyond the onset of menopause. In the observational studies, hormone therapy was used in symptomatic women at or near the time of the menopausal transition. The women in the WHI were therefore older and further from the menopausal transition than were those in whom we would typically initiate hormone therapy.

The differences in outcome may have been due to the timing of hormone therapy initiation. Atherosclerotic lesions typically accrue over many years, while clinical events occur years or decades after the initial accumulation of atherosclerotic plaques. The women in the WHI trials likely harbored significant subclinical coronary heart disease. The women in the observational studies, who were near the menopausal transition, were much less likely to have subclinical heart disease.

ORIGINS OF THE TIMING HYPOTHESIS

These differences led to development of a theory known as the “timing hypothesis.”^{6,7} The timing hypothesis suggests that when women do not have pre-existing heart disease, estrogen therapy may be beneficial, but when there is pre-existing coronary heart disease, the opposite effect may be observed. Hormone therapy may prevent or retard atherosclerosis when started early; however, it may lead to harm when initiated in women who already have established atherosclerosis.

The timing hypothesis is supported by evidence from animal models, including those developed by Clarkson.^{8,9} In the Clarkson model, monkeys were rendered menopausal by ovariectomy. When fed a high-fat diet, the monkeys developed atherosclerosis. Treatment with estrogen at the time of castration, however, reduced coronary atherosclerosis by approximately 70%. No beneficial effect was noted when estrogen therapy was delayed by 2 years, which corresponds to 6 years in a human life span. These results are similar to those of the observational studies in which newly menopausal women—presumably without a significant atherosclerosis burden—benefited from estrogen therapy.

More recent subgroup analyses of the WHI data also favor the timing hypothesis.¹⁰ In the WHI estrogen-alone study, women who were 50 to 59 years old showed a significant decrease in the risk of all adverse cardiac outcomes when data were pooled. In the estrogen-alone arm, women aged 50 to 59 years had a hazard ratio for coronary heart disease of 0.56, compared with women receiving placebo.⁵ Additionally, coronary calcium deposits (a marker for the presence of atherosclerosis) were measured by computed tomography. The 50- to 59-year-old women in the WHI who received estrogen alone had significantly lower coronary calcium scores at the trial completion than those who received placebo.¹¹

The observational studies, the primate studies, and a subgroup analysis that included the younger women in the WHI all support the timing hypothesis. It is likely that the net results of the WHI were due to the harmful cardiovascular effects of menopausal hormone therapy in older women who started treatment well beyond the average onset of menopause, while younger women may receive benefit.

KEEPS INVESTIGATES THE EARLY INTERVENTION QUESTION

The timing hypothesis is now undergoing rigorous testing in a large, randomized controlled trial, the Kronos Early Estrogen Prevention Study (KEEPS).^{12,13} This trial is comparing two hormone regimens with placebo, one using oral conjugated estrogens and the other, transdermal estradiol. Each treatment regimen includes cyclic oral progesterone. The KEEPS trial enrolled only women who were less than 3 years from menopause. As mentioned, the timing hypothesis suggests that the window of opportunity to reduce the risk for heart disease is early after the onset of menopause—precisely the time when women seek relief from vasomotor symptoms.

It is essential to determine whether estrogen provides cardioprotective effects. Coronary heart disease is the most common cause of morbidity and mortality among women. Cardiovascular disease accounts for approximately 40% of mortality in women. Although breast cancer is a devastating disease even when not fatal, the cardiovascular disease mortality is far greater than the approximately 5% of women who die of breast cancer. Not only is the incidence of cardiovascular disease great, the opportunities to prevent or reduce it may be readily available.

The KEEPS trial will provide the opportunity to identify crucial differences between the observational trials and the WHI study. KEEPS tests the hypothesis that beginning hormone therapy at the average age of menopause (ie, approximately 51 years) will retard the progression of atherosclerosis. Because atherosclerosis progresses gradually over years or decades before culminating in a clinical event, significant potential may exist for altering the course of this disease.

STUDY OBJECTIVES AND DESIGN

The KEEPS trial is a prospective, randomized, placebo-controlled, double-blinded investigation. The KEEPS investigators are evaluating the effects of menopausal hormone therapy on the progression of atherosclerosis, specifically in the coronary and carotid arteries. Coronary artery calcification (CAC) is used as a marker for coronary atherosclerosis. Similarly, carotid intima-media thickness (CIMT) is used as a measure of carotid atherosclerosis.

The inclusion criteria for KEEPS required that women be 40 to 58 years of age and at least 6 months, but no more than 3 years, from their last menstrual period. Inclusion criteria for laboratory values were a plasma follicle-stimulating hormone (FSH) level of 35 ng/mL or greater and an estradiol level of less than 40 pg/mL. Of course, given the high rates of obesity, metabolic syndrome, and diabetes in the United States, some women in midlife may already have significant pre-existing atherosclerosis. Exclusion criteria included a history of clinical cardiovascular disease, morbid obesity (body mass index [BMI] > 35 kg/m²), heavy smoking, dyslipidemia (low-density lipoprotein [LDL] cholesterol > 190 mg/dL), hypertriglyceridemia (> 400 mg/dL), and uncontrolled hypertension or diabetes. All women were screened for CAC, and those with significant pre-existing CAC were excluded.

Subjects were recruited through 9 sites throughout the United States: Brigham and Women’s Hospital; Columbia University College of Physicians and Surgeons; Mayo Clinic; Albert Einstein College of Medicine; Kronos Longevity Research Institute; University of California, San Francisco; University of Utah School of Medicine; University of Washington School of Medicine; and Yale University School of Medicine. A total of 728 participants were randomized to 1 of the 3 treatment groups.¹² Women who were enrolled in KEEPS had a similar ethnic mix as those enrolled in the WHI.¹³ However, the 3 women enrolled in KEEPS had higher levels of education. The women in KEEPS, being near menopause, were more likely to be symptomatic with significant menopausal vasomotor symptoms.

PROMISES OF KEEPS

While observational studies may be subject to healthy user bias, KEEPS is a randomized prospective trial and will therefore avoid such bias. Another advantage of KEEPS is that the study participants more closely represent the typical patient who would normally begin hormone therapy at the time of the menopausal transition.

Women in KEEPS are treated for 3 years, and repeat measurements of CAC, CIMT, and numerous cardiovascular surrogate markers are assessed. In addition to looking at cardiovascular disease, KEEPS is also examining cognitive and affective changes. It is the first randomized clinical trial that directly examines the effects of early intervention with estrogens.

One limitation of KEEPS is that the end points are all not clinical outcomes. Measurement of such end points would be impossible in younger women near the menopausal transition, where the incidence of such events is quite low; the number of subjects needed to adequately power such a study would make it prohibitively expensive. The end points used in KEEPS (CAC and CIMT), however, are not simply surrogate markers or risk factors. CIMT and CAC measure actual progression of atherosclerosis. They are a measure of disease burden rather than risk of disease.

While many subjects have already completed the KEEPS trial, the final participants are scheduled to finish the study in the first quarter of 2012. Hence, within 6 months, we should have collected all the data required to determine if early intervention with hormone therapy will lead to reduction in cardiovascular disease. It is anticipated that the initial analysis of KEEPS data will be completed late in 2012.

IN CONCLUSION

As the KEEPS trial draws to a close, we hope to obtain a definitive answer on whether early intervention with hormone therapy in menopausal women benefits the heart. The timing hypothesis suggests that early intervention is profoundly different from late intervention. The KEEPS trial may show results that are similar to those reported in animal models, observational trials, and even the subgroup analysis of data from younger women in the WHI. Low-dose estrogen plus cyclic progesterone initiated near the onset of menopause may alter the course of atherosclerosis. In addition, we will have the first direct head-to-head comparison of oral versus transdermal estrogen therapy.

The KEEPS trial results will certainly prove to be interesting and may represent a paradigm shift in our approach to cardiovascular disease.

References

- Bush TL, Cowan LD, Barrett-Connor E, et al. Estrogen use and all-cause mortality. Preliminary results from the Lipid Research Clinics Program Follow-Up Study. *JAMA*. 1983;249(7):903-906.
- Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the Nurses’ Health Study. *N Engl J Med*. 1991;325(11):756-762.
- Grodstein F, Manson JE, Colditz GA, et al. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med*. 2000;133(12):933-941.
- Rossouw JE, Anderson GL, Prentice RL, et al; Writing Group for the Women’s Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women’s Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321-333.
- Anderson GL, Limacher M, Assaf AR, et al; Women’s Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women’s Health Initiative randomized controlled trial. *JAMA*. 2004;291(14):1701-1712.
- Harman SM, Brinton EA. Biphase effects of hormone treatment on risk of cardiovascular disease: resolving the paradox in postmenopausal women. *Menopausal Medicine*. August 2009;17(3):S1-S10.
- Naftolin F, Taylor HS, Karas R, et al; Women’s Health Initiative. The Women’s Health Initiative could not have detected cardioprotective effects of starting hormone therapy during the menopausal transition. *Fertil Steril*. 2004;81(6):1498-1501.
- Williams JK, Anthony MS, Honoré EK, et al. Regression of atherosclerosis in female monkeys. *Arterioscler Thromb Vasc Biol*. 1995;15(7):827-836.
- Clarkson TB, Anthony MS, Morgan TM. Inhibition of postmenopausal atherosclerosis progression: a comparison of the effects of conjugated equine estrogens and soy phytoestrogens. *J Clin Endocrinol Metab*. 2001;86(1):41-47.
- Taylor HS, Manson JE. Update in hormone therapy use in menopause. *J Clin Endocrinol Metab*. 2011;96(2):255-264.
- Manson JE, Allison MA, Rossouw JE, et al; WHI and WHI-CACS Investigators. Estrogen therapy and coronary-artery calcification. *N Engl J Med*. 2007;356(25):2591-2602.
- Harman SM, Brinton EA, Cedars M, et al. KEEPS: The Kronos Early Estrogen Prevention Study. *Climacteric*. 2005; 8(1):3-12.
- Miller VM, Black DM, Brinton EA, et al. Using basic science to design a clinical trial: baseline characteristics of women enrolled in the Kronos Early Estrogen Prevention Study (KEEPS). *J Cardiovasc Transl Res*. 2009;2(3):228-239.