

Clinicians' Forum

From time to time, the editors of *Menopause Management* field interesting clinical questions and dilemmas. In this forum, our Editorial Advisory Board members, experts in a range of fields related to midlife women's health, tell readers how they handle these situations.

Participants

George Gorodeski, MD, PhD
Professor of Reproductive Biology, Oncology,
and Physiology and Biophysics
Case Western Reserve University School of
Medicine
Cleveland, OH

Frederick Naftolin, MD, DPhil
Professor, Department of Obstetrics
and Gynecology
Yale University School of Medicine
New Haven, CT

Amos Pines, MD
Department of Medicine "T", Ichilov Hospital,
Tel-Aviv, Israel
President Elect, The International Menopause
Society

Karol E. Watson, MD, PhD
Co-Director, UCLA Program in Preventative
Cardiology
Director, UCLA Center for Cholesterol and
Hypertension Management
Los Angeles, CA



George Gorodeski, MD, PhD

no favorable cardiovascular (CV) effect and, in fact, increased coronary heart disease (CHD) events during initial years. In contrast, the WHI did not have the statistical power to determine or exclude such an association in younger women. Therefore, it would be wrong to extrapolate WHI conclusions to younger women who undergo bilateral oophorectomy prior to menopause. The pre-WHI cohorts and experimental data showed, in general, that estrogen is an important factor in the natural course of cardiovascular disease (CVD) in women, and estrogen "replacement" (a term presently and temporarily tabled) does control progression of CVD, and may prevent CHD events in women. The two main contributions of the WHI data within the framework of the above question, and which may affect clinical decisions, are the findings that EPT, but not ET, increased the risk of invasive breast cancer, and that ET or EPT decreases the risk of osteoporosis and fractures.

With regard to the question, three types of patients should be considered. The first is the woman with established CHD who has been ovariectomized earlier than the age of natural menopause. For this woman, estrogens are contraindicated unless new data are presented to the contrary. The rationale, based on the Heart and Estrogen/progestin Replacement Study (HERS) and WHI results, is that the mild thrombogenic effects of estrogen, even at low doses, could accelerate rupture of coronary atherosclerotic plaques. Despite the fact that HERS and the WHI studied significantly older women than this putative patient, this conclusion is advanced to highlight the severity of risk.

The second type of patient is a healthy woman without apparent CVD risk, who has been ovariectomized earli-

er than the age of natural menopause. Most of these women will be placed on ET to relieve vasomotor symptoms, and upon follow-up will usually ask, "How long do I need to take it?" and "When should I stop?". The generalization, made by the FDA and other organizations, that ET should not be considered for primary prevention of CVD in healthy, young, surgically-induced menopausal women, cannot be explained by the WHI or HERS results. For these women, the only scientific evidence on which to base clinical decisions are the pre-WHI, pre-HERS cohorts and experimental data, which imply that continued ET may be beneficial for prevention of CVD. In general, when considering CVD prevention, the first consideration should be modification of lifestyle (diet, exercise); avoidance of risk factors (obesity, cigarette smoking, stress, etc.); and aggressive screening for diabetes mellitus and hypertension. The preventive role of statins, aspirin, and beta blockers in young, surgically-induced menopausal women remains to be studied.

However, and in addition to the above, the presumed role of ET in CHD primary prevention in this patient should not be ignored. Patients should be educated about the dilemma that the WHI and HERS studies have raised, and should be educated on the pros and cons of ET. If patients choose to consider this option, the mode of administration and the lowest effective ET dose will be discussed and implemented, and the necessity for regular follow-up visits should be emphasized. Since no data are currently available to determine the length of treatment, it should be dictated by known data about ET's effect on other body systems. Thus, for instance, a low risk profile for breast cancer and a high risk profile for osteoporosis would enable patients to opt for a longer duration of ET use. Undoubtedly, ongoing and future studies will provide better understanding about the role of ET for

Question: Now that the Women's Health Initiative (WHI) data show no cardiovascular benefit for treatment with estrogen alone for hysterectomized women, what should the woman who has undergone bilateral oophorectomy prior to menopause do when the risk of heart disease is known to be increased?

Answers:

Basically, the supposition of the question is wrong. The WHI had enough statistical power to determine that estrogen therapy (ET) or estrogen plus progestogen therapy (EPT) begun about 10 years after the age of natural menopause had

prevention of CVD in women, when started at a relatively young age after surgically-induced menopause.

The most difficult decision will have to be made in regard to the third type of patient; namely, women who are ovariectomized at an age earlier than natural menopause, and who have an established risk for CVD, such as obesity, hypertension, diabetes mellitus, and family history of CVD at a relatively young age, but are otherwise asymptomatic. The dilemma is, on the one hand, that such a patient may already have subtle coronary lesions, in lieu of her epidemiologic risk profile. In that event, the ERA results would contend that ET does not reverse established coronary atherosclerosis, and the WHI and HERS results would argue that ET may increase the risk of plaque rupture. On the other hand, patients with very early coronary lesions may benefit from risk reduction, and ET could modify contributing CHD risks such as plasma lipids. Moreover, co-treatment with ET could improve statin effects. ET could also improve quality of life and enable better lifestyle modifications.

Again, and similar to the above discussion, it is the physician's responsibility (and not the media's) to educate the patient, and to present objectively all available and pertinent data. An educated patient is more likely to make the right decision for herself, and to benefit from our current state of knowledge.

— George I. Gorodeski, MD, PhD

This is a very appropriate question. Unfortunately, the answer is not as clear as one would like, or expect.

Recently ovariectomized animals starting treatment shortly after ovariectomy furnish the most frequently studied models for researching possible cardioprotective effects of estrogen. The results have almost uniformly been pos-

itive, showing a variety of protective effects. With a few notable (*and supporting*) exceptions, these studies have not tested effects on longevity; rather, they have been aimed at currently interesting indices of vascular health. Without doubt, some of the outcomes, especially on primate models, have been very encouraging and internally consistent in predicting that ET will be cardioprotective in recently ovariectomized subjects. This is well supported by laboratory data on tissues and cells subjected to estrogen treatment *in vitro*. It is, therefore, appropriate to consider whether ET will be cardioprotective for oophorectomized premenopausal women.

Unfortunately, this question is not clarified by the few published studies on early cardiovascular death or even early cardiovascular events among women undergoing ovariectomy in their premenopausal years. The reason for the shortage of data is that wide-scale surgical treatment of pelvic infection waned with the appearance of antibiotics in the last half of the 20th century, while hormone therapy (HT) was not popular until the second half of the century. That having been said, the many available studies of *indicators of cardiovascular morbidity and clinical/laboratory indices* have strongly supported the early occurrence of cardiovascular disease among surgically menopausal women, and ameliorating effects of HT.

The poor outcome of hysterectomy without early replacement may be seen in the WHI itself. The WHI estrogen-only arm was performed on women who had been oophorectomized and not treated with hormones. The average age of the subjects was similar to that of the subjects who had natural menopause, but they had more evidence of ongoing



Frederick Naftolin, MD, DPhil

cardiovascular disease. In both groups, the lack of symptoms of menopause (~10%, by WHI design) indicate that these women had already undergone whatever maladaptive compensations they would undergo in response to the loss of estrogen. We are, therefore, not surprised that ET (hormone treatment without indication, as was the case in the WHI) was not effective in forestalling adverse cardiovascular events or significantly reversing already present cardiovascular disease. The lack of a reparative function of estrogen has already been amply shown by animal and laboratory studies. The presence of vascular disease and advanced age predisposed the WHI women on ET to thrombotic episodes that were associated with cardiovascular events. In short, the WHI showed that it is unwise to treat (asymptomatic) ovariectomized women with long-term ET, but the women in the WHI did not approximate women who have recently undergone oophorectomy, and those are the only ones who should be considered for ET.

The presence of menopausal symptoms is a good indicator of whether the woman is still in this window of replacement treatment and possible prevention. There is no question that ET will be helpful in alleviating menopausal symptoms, so a trial of ET for this purpose is well warranted in women who have no contraindications. This will include almost all oophorectomized women, so, it brings us to the question of whether ET should be extended for possible cardioprotection, with or without the need for bone mass protection. The animal data and tests of indices of cardiovascular health, such as intimal-medial thickness of arteries and lipid profiles, support this treatment. But, for the reasons that were mentioned above, the few studies on mortality that have been reported have not shown clearly that the protection extends life or actually turns better laboratory findings into diminished cardiac events.

In my opinion, there is sufficient evidence of positive effects of timely HT on many systems—easily demonstrable improvement in quality of life (if, in contradistinction to the WHI, one starts ET on symptomatic women), reduced colon cancer risk, and reports of clinical cardioprotection—to encourage this patient to consider a trial of ET starting when her erythrocyte sedimentation rate falls to normal after surgery, and continuing it with a visit at 3 months for a check for intravascular clotting. The ET should be part of a program of prevention that includes appropriate lifestyle modifications. The woman must balance this program against the possibility of increased breast cancer risk (which is very low in young women taking ET and is subject to very successful early diagnosis with mammography and exams) plus an unknown and poorly understood increased risk of stroke. At annual visits the situation should be assessed and brought up to date with the progress of the field. Absent complications, the treatment may be continued under these conditions.

The lack of clear evidence in answer to this question focuses the tremendous importance of further research in this area. American women now live half of their lives after the menopause. The WHI showed that HT is not appropriate for older, often ill women, but we are still in dire need of research on woman starting prevention in the menopausal transition. Women need and deserve every measure possible to make this added longevity a rewarding and healthy time. Only through research will we reach this goal.

— Frederick Naftolin, MD, DPhD

I shall start with my final conclusion: women experiencing early menopause because of oophorectomy (with or without hysterectomy) should consider

ET, exactly as suggested in the pre-WHI era. In recent years, clinicians have begun using evidence-based medicine and, hence, we have to accept an important rule; namely, that any information obtained in a study is relevant only to its particular cohort and its specific protocol. With regard to HT, there are three major groups of women: 1) the WHI scenario of women starting HT at late menopause (beyond age 60); 2) the usual scenario at the menopause clinic of women starting HT around menopause and continuing it for several years or up to age 60 (unfortunately, women tend to stop HT within a few years); 3) women who start taking HT around menopause and continue for many years into their sixties or seventies, and even beyond.

The WHI findings have no bearing on the clinical scenario presented. It should be remembered that, despite the fact that an age group of 50 to 59 appears in all sub-analyses of the WHI, the actual number of women at early menopause (up to age 54) was not revealed. According to a WHI publication on quality of life,¹ it is estimated that there were only hundreds of women in that particular age group, which makes any analysis impossible due to the very small numbers.² Looking into the details of WHI subgroups shows that in the EPT arm there were fewer coronary events in women who used EPT for less than 10 years, though not statistically significant.³ Moreover, the ET arm of the WHI suggested cardioprotection, which was almost significant.⁴ The breast cancer data from the WHI EPT arm pointed at the importance of duration of exposure to hormones.⁵ Women who never used hormones prior to the study did not demonstrate a significant increase in risk during the 5.2 years of follow-



Amos Pines, MD

up. The ET arm provided even more favorable results, since there were less cases of invasive breast cancer compared to the placebo group, but these data did not reach significance.⁴ As for stroke, both arms of the WHI showed an increase in risk in the hormone users, but sub-analysis pointed at no risk in the EPT arm in women younger than 60.⁶ As expected, the WHI reported that HT is associated with an increase in risk for thromboembolism, however ET did not increase significantly the risk for pulmonary embolism.⁴

In view of the above, I do not see the relevance of the WHI findings in making a decision whether to use HT in women after bilateral oophorectomy. While alleviating vasomotor symptoms and preserving bone mass are proven consequences of HT in this clinical scenario, the risks, if any, seem negligible. The British health authorities recently produced a document for the public on the safety of HT (www.medicines.mhra.gov.uk, December 3, 2003). According to their calculations, there is no real cardiac risk for women aged 50 to 59, and the risk for stroke is one additional case per 1,000 in women who use HT for 5 years. The Nurses' Health Study and animal data point to the possibility that ET started early may lead to substantial cardioprotection.^{7,8} According to the "window of opportunity" theory, ET prevents atherosclerosis only when arterial walls are still intact and the endothelium functions normally; a situation that is expected before age 55. However, beyond age 55 to 60, when arterial plaques have already developed, this effect no longer exists, and the "window" is shut permanently. If this concept is further validated in high-quality clinical trials, it may support a universal recommendation to use HT in all women undergoing oophorectomy in premenopause.

— Amos Pines, MD

References

1. Hays J, Ockene JK, Brunner RL, et al. Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med* 2003;348:1839-54.
2. Naftolin F, Taylor HS, Karas R. Early initiation of hormone therapy and clinical cardioprotection: the Women's Health Initiative (WHI) could not have detected cardioprotective effects of starting hormone therapy during the menopausal transition. *Fertil Steril* 2004;81:1498-501.
3. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;349:523-34.
4. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. *JAMA* 2004; 291:1701-12.
5. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women in healthy postmenopausal women: the Women's Health Initiative randomized trial. *JAMA* 2003;289: 3243-53.
6. Wassertheil-Smoller S, Hendrix SL, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women. *JAMA* 2003;289:2673-84.
7. 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;133:933-41.
8. Grodstein F, Clarkson TB, Manson JE. Understanding the divergent data on postmenopausal hormone therapy. *N Engl J Med* 2003;348:645-50.

While recent studies have yielded inconsistent results, most authorities believe that women who undergo bilateral oophorectomy prior to menopause are at increased risk for CHD. Observational data from the 1980s suggested that this risk could be reduced by ET; however, no randomized, controlled clinical trials have been performed in this population. In light of the WHI data showing no cardiovascular benefit from ET in postmenopausal women, it is prudent to search for other preventive measures in this high-risk population. All such women should pay particular attention to a healthy lifestyle consisting of smoking cessation, regular exercise and good nutrition. In addition, therapies demonstrat-



Karol Watson, MD, PhD

ed to be of cardiovascular benefit in postmenopausal women should be used when appropriate. At present we have no randomized, controlled clinical trial data showing that the risk of CHD is reduced by ET. In contrast, the statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) have been shown, in several clinical trials, to reduce the risk of CHD in both premenopausal and postmenopausal women. These, and other preventive therapies, which have been demonstrated to prolong lives and improve health, should be considered in women who have undergone bilateral oophorectomy prior to menopause.

— Karol Watson, MD, PhD

Your Chance to Be Heard: A Call for Manuscripts

Menopause Management is currently accepting manuscripts to be considered for publication in upcoming issues.

The official education publication of The North American Menopause Society, *Menopause Management* is the only controlled-circulation journal devoted exclusively to the health of midlife women.

Menopause Management is read by approximately 33,000 internists, OB/GYNs and other healthcare practitioners caring for midlife women.

Articles focus on practical information for incorporation into daily practice, and cover a wide range of topics related to women's health through menopause and beyond.

Manuscripts submitted to *Menopause Management* are reviewed by two members of the Editorial Advisory Board and Editor-in-Chief Wulf H. Utian, MD, PhD.

For more information about submitting a manuscript
for publication, please contact:

Maura Griffin, Editor, at mgriffin@menopausegmt.com

