Testimony
Before the
Special Committee on Aging
United States Senate

The Women's Health Initiative

Statement of
Jacques Rossouw, M.D.
Chief, Women's Health Initiative Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
U.S. Department of Health and Human Services

For Release on Delivery
Expected at 10:00 a.m.
Thursday, April 19, 2007

I am pleased to appear before this Committee in my capacity as the chief of the Women's Health Initiative (WHI) branch of the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health (NIH), an agency of the Department of Health and Human Services. I am here to tell you what we have learned from the WHI about menopausal hormone therapy using conjugated equine estrogens and to briefly comment on other forms of estrogen therapy.

During the second half of the 20th century, estrogen was shown to relieve common menopausal symptoms such as hot flashes and night sweats. Subsequent clinical trials showed that estrogen also prevents bone loss. Based on these findings from rigorous scientific studies, menopausal hormone therapy was approved by the Food and Drug Administration (FDA) and became well accepted for treatment of menopausal symptoms and for prevention of osteoporosis. Most of the prescriptions for menopausal hormone therapy were written by gynecologists and family doctors for women experiencing symptoms shortly after the onset of the menopause transition. A smaller number were for older women to prevent osteoporosis.

However, for many years estrogen was also used under circumstances where there was no definitive proof of efficacy. One idea that was promoted and became part of popular lore was that the ebb of estrogen levels after the menopause represented a disease-like condition or "estrogen deficiency" that needed to be treated using "estrogen replacement". Many thought that such replacement would keep a woman "forever young." In the mid-1980s, another potential reason to use menopausal hormone therapy emerged from observational studies: prevention of coronary heart disease. Women taking menopausal hormone therapy appeared to have a lower risk of heart disease, though a higher risk of breast cancer, than women who did not take hormones. Given that heart disease is far more common than breast cancer, many researchers thought that the benefit from menopausal hormone therapy would outweigh the risk.

Based on these observations, along with evidence suggesting that estrogen improves blood cholesterol levels, several professional bodies recommended that menopausal hormone therapy be considered for the prevention of heart disease, especially in high-risk women (e.g., those with existing heart disease or high blood cholesterol levels). Unfortunately, however, observational studies have limitations, one of the most important being that they do not establish causality. In this case, it was impossible to tell whether the women who took hormones had better heart health because of the menopausal hormone therapy -- or whether the women who chose ("self-selected") to take hormones were simply healthier to begin with. Nevertheless, as a result of the new recommendations, hormones were increasingly prescribed to older women for the express purpose of lowering blood cholesterol and preventing heart disease.

Recognizing that practice recommendations related to menopausal hormone therapy were outpacing the scientific evidence, the NIH undertook two clinical trials of hormone therapy as part of the WHI, a long-term effort begun in 1991 to identify strategies for preventing heart disease, breast and colorectal cancers, and osteoporosis in postmenopausal women. Participants were randomly assigned to menopausal hormone therapy or placebo, so self-selection for hormone therapy was not an issue. By design, the trials used the same hormones and the same doses that were associated with the apparent benefit reported in the observational studies mentioned above. They enrolled more than 27,000 women, ranging in age from 50-79 years. Those who had a uterus were assigned to take either a pill containing estrogen and progestin (0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate--Prempro) or a placebo; those who had undergone a hysterectomy were assigned to take either an estrogen pill (0.626 mg of conjugated equine estrogen--Premarin) or a placebo.

When the trials began, many researchers expected that, after the 8 years, menopausal hormone therapy would be shown to:

- reduce heart disease
- have no effect on stroke
- increase blood clots
- increase breast cancer
- decrease hip fractures
- and decrease colorectal cancer.

Although researchers anticipated some adverse effects, they believed that the overall benefits of menopausal hormone therapy would be shown to outweigh the risks. Instead, the trial of estrogen plus progestin was stopped in 2002 after just over 5 years because of increased risks of heart disease, stroke, blood clots, and breast cancer due to menopausal hormone therapy and because these risks exceeded the benefits from reduced risks of hip fractures and colorectal cancer. The trial of estrogen alone was stopped in 2004 after almost 7 years because estrogen increased risk of stroke and did not benefit heart disease. The estrogen alone trial also showed that the hormone increased blood clots and decreased hip fractures, but had no effect on breast or colorectal cancer. Subsequently, investigators conducting an ancillary study found that both hormone preparations increased the risk of memory problems and dementia in women aged 65 and older.

As a result of WHI findings, professional bodies altered their recommendations, and the FDA required a “black box” warning that menopausal hormone therapy should not be used for the prevention of heart disease or dementia. The drugs remain approved for moderate to severe hot flashes or night sweats, vaginal atrophy, and the prevention of osteoporosis, but with cautions to use the lowest doses for the shortest

amount of time needed to achieve the desired effect. The FDA requires all formulations of menopausal hormone therapy to carry the same language.

After 2002, the number of women using postmenopausal hormone therapy fell from about 16 million to about 6 million in 2006, a decline of more than 60%. The main use of menopausal hormone therapy has reverted back to the short-term treatment of moderate to severe hot flashes and night sweats, symptoms that are most prevalent in the years immediately surrounding onset of menopause, although, in a small proportion of women, they persist for much longer. Evidence from national databases indicates that the drop in menopausal hormone therapy use occurred in women below 60 years of age as well as in older women, and anecdotal evidence from gynecologists and from news stories suggest that many younger women with hot flashes and night sweats forego menopausal hormone therapy because they fear its adverse health consequences.

Although the WHI showed that menopausal hormone therapy is not effective for preventing heart disease in women generally, there has been much interest in learning whether certain groups of women (e.g., younger women or women closer to menopause) may experience less harm or even some benefit in terms of disease outcomes. Several WHI publications have touched on the topic, and, in general, have suggested that while the risk of stroke due to menopausal hormone therapy is not affected by age or time since menopause, the risk of heart disease may not be increased in younger women or those close to menopause who take hormones.

In an attempt to provide more definitive information to guide treatment choices, the WHI investigators recently published analyses of the combined trial data that examined various subgroups of women. The results suggest that women who begin menopausal hormone therapy within 10 years of menopause may have less risk of coronary heart disease due to the therapy than women farther from menopause.

Women who began treatment more than 20 years after menopause experienced a significant increase in risk. There was a similar non-significant trend for total mortality. As before, menopausal hormone therapy did not reduce the overall risk of heart disease, and increased stroke risk regardless of years since menopause. Further exploratory analyses also suggested that the increased risk of heart disease in older women due to hormones occurred primarily among those with persistent moderate to severe hot flashes. Women with these symptoms were also more likely to have risk factors for heart disease such as high blood pressure, high blood cholesterol, diabetes, and excess weight.

The more detailed analyses provide some reassurance to women who begin menopausal hormone therapy within 10 years of entering menopause that short-term treatment (up to 4 or 5 years) of hot flashes and night sweats is not accompanied by an increased risk of heart disease. However, even women who begin menopausal hormone therapy soon after menopause need to be screened and treated for cardiovascular risk factors such as high blood pressure and to have regular mammograms. The findings should further discourage menopausal hormone therapy in women who are more distant from menopause. In these women, particularly those with hot flashes and night sweats, the focus should be on identifying and treating cardiovascular risk factors. The overall findings are consistent with current recommendations and may aid in their implementation by encouraging doctors and patients to focus on the appropriateness of menopausal hormone therapy based on an individual's situation and medical history. According to the current recommendations, menopausal hormone therapy should not be used for prevention of heart disease, but can be used for the short-term treatment of menopausal symptoms.

Researchers are still interested in following up on results from animal and laboratory studies supporting the hypothesis that menopausal hormone therapy may

slow the earliest stages of arterial disease. Upcoming trials, including some supported by NIH, will test whether hormones given at a younger age can forestall development of the earliest stages of atherosclerosis. However, even if the results show a benefit or lack of harm among younger women, they should not be taken to mean continuing to use hormones as the women grow older would be safe. As women age, they are increasingly more likely to develop artery disease, and the point at which any potential benefit of menopausal hormone therapy becomes outweighed by the risk of harm is not yet known. Addressing the remaining issues would require a trial of about 30,000 women close to the menopause, randomly assigned to take menopausal hormone therapy or placebo and followed for 20 years. Such a trial would not be feasible due to serious ethical concerns about the risk of stroke, blood clots, and breast cancer among participants, technical issues such as poor long-term adherence to menopausal hormone therapy, and the prohibitive cost. Finally, to the extent that the motivation for pursuing a large trial would be a desire to prevent cardiovascular disease among women, it should be noted that further deployment and improvement of existing prevention strategies, such as the identification and adequate treatment of known risk factors, offers far better potential for safely and effectively reducing cardiovascular disease burden.

Another important question arose after publication of the main WHI findings: Would the results have been different if other types of hormones, such as estradiol or progesterone, had been used instead of conjugated equine estrogens? First, it should be reiterated that the hormones tested by the WHI were chosen because they were the same ones that appeared to be beneficial in early observational studies -- and, even so, the results of the WHI trials and the early observational studies were quite different. Second, it should be noted that trials using oral estradiol have been conducted in women with existing disease, and they have uniformly showed a lack of cardiovascular benefit.

One small trial using oral estradiol found a slight benefit for slowing the thickening of the arteries that supply blood to the brain. However, trials using such surrogate outcomes rather than clinical disease outcomes are not definitive.

A separate but related issue is whether the method used to administer menopausal hormone therapy affected the WHI results. In the human body, estradiol and progesterone are released directly into the bloodstream, whereas when the hormones are given by mouth, they must first pass through the liver, where a large amount of hormone is rendered inactive. Most of the proteins involved in blood clotting, lipid metabolism, and inflammation are manufactured in the liver, and oral estradiol in particular has profound effects on all of these molecules. Therefore, the action of oral hormones in the liver may contribute to adverse cardiovascular effects. On the other hand, estradiol given transdermally is distributed throughout the body, has minimal, if any, effect on molecules involved in blood clotting, lipid metabolism, and inflammation, and may have direct and potentially beneficial effects on the normal arterial lining. Some of the surrogate outcome trials will use non-oral routes of administration, and may provide additional information about whether the route of administration affects the outcome of menopausal hormone therapy.

Thank you for the opportunity to address these issues of great importance to women. I would be pleased to answer any questions the committee may have.