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SYMPOSIUM

An Update on Hormone Replacement Therapy

Health and Medicine for Women: A Multidisciplinary, Evidence-Based Review of Mid-Life Health Concerns

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The Department of Obstetrics, Gynecology, and Reproductive Sciences at the Yale School of Medicine hosted a daylong continuing medical education (CME†) symposium titled "Health and Medicine for Women: A Multidisciplinary, Evidence-Based Review of Mid-Life Health Concerns" in September 2010. A number of speakers discussed current research on hormone replacement therapy (HRT) and re-evaluated the results of the Women's Health Initiative (WHI), a landmark, randomized, placebo-controlled trial that still sparks debate almost a decade after its conclusion. This article summarizes this discussion and highlights directions for future study.

Since its approval by the Food and Drug Administration (FDA) in 1942, estrogen has been used to alleviate the symptoms of menopause, a period when endogenous estrogen production declines. For many years, it was widely believed that estrogen replacement also could prevent disease and extend life. In 1991, the Women's Health Initiative (WHI), a landmark, randomized, placebo-controlled trial, was initiated to test the ability of hormone replacement therapy (HRT) — an umbrella term for both estrogen-only and estrogen-progestin treatments — to prevent heart disease and breast cancer in postmenopausal women.

Despite years of promotion and popularity, HRT usage fell dramatically after the conclusion of the WHI.

In 2002, the WHI was terminated early due to trends in the data showing that HRT was actually associated with *increasing* rates of cardiovascular disease [1] and breast cancer [2] in postmenopausal women. However, HRT remains the most effective treatment available today for the disruptive symptoms of menopause. Given the size of the aging population and the increasing number of

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†Abbreviations: CME, continuing medical education; HRT, hormone replacement therapy; WHI, Women's Health Initiative; KEEPS, Kronos Early Estrogen Prevention Study; FDA, Food and Drug Administration; HERS, Heart and Estrogen Replacement Study; CHD, coronary heart disease; TSECs, tissue selective estrogen complexes; SERM, selective estrogen receptor modulator; ACOG, American Congress of Obstetricians and Gynecologists.

postmenopausal women in the United States, interest in the therapeutic potential of estrogen has continued to spark new efforts to understand the long-term health consequences of this powerful drug. In the continuing medical education (CME) symposium in September 2010 at Yale School of Medicine titled "Health and Medicine for Women: A Multidisciplinary, Evidence-Based Review of Mid-Life Health Concerns," a number of speakers revisited the results of the WHI in light of recent evidence.

In his presentation, "Heart Disease in Women: Is it Different than in Men?" Dr. Jeffrey R. Bender, Robert I. Levy Professor of Preventive Cardiology at Yale School of Medicine, discussed the effects of HRT on cardiovascular health. He suggested the possibility that the conclusions of the WHI may have been exaggerated. The WHI enrolled women who were on average 12 years past menopause, with a mean age of 63. He argued that significant vascular disease may have already been present in the study population at the time of therapy initiation and that estrogen may not reverse established pathological changes. In support of this idea, an animal study showed that primates given estrogen replacement immediately after ovariectomy showed a 70 percent reduction in coronary artery atherosclerosis compared to placebo, while those given estrogen after a delay period found no benefit [3]. Furthermore, a subset analysis of women aged 50 to 59 and enrolled in the WHI found a significant reduction in cardiovascular disease [4]. This evidence suggests that if given in low doses early in the menopausal transition, estrogen may be cardioprotective as was once believed. The ongoing Kronos Early Estrogen Prevention Study (KEEPS) investigates estrogen and intermittent progestin on atherosclerosis in the younger population. Its pending results may provide insight into this issue.

In his presentation, "Update on Menopausal Hormone Therapy," Dr. Hugh Taylor, Section Chief of Obstetrics and Gynecology, echoed Dr. Bender. He presented evidence from the Heart and Estrogen Replacement Study (HERS). While HRT appeared to increase the risk of primary CHD events in the first year of treatment in women with established vascular disease, it actually *decreased* risk in subsequent years [5]. He emphasized that the women who received estrogen therapy without progestin showed a reduced incidence of CHD events, a conclusion corroborated by experiments in nonhuman primates [6].

Dr. Taylor also suggested that limitations of the WHI should be carefully considered when interpreting the data on breast cancer.[1] WHI results did not evaluate mortality or the causal link between HRT and breast cancer. Using data on the detection rates of different stages and types of breast cancer, he suggested an alternative hypothesis. Combination therapy may stimulate the growth of previously existing, subclinical cancers, thereby increasing the incidence of *detectable* cancer compared to placebo. Meanwhile, the estrogen-only arm of the WHI trial showed lower incidence of breast cancer than placebo, with the lowest incidence in the subset of women who were highly compliant with the therapy [7]. Estrogen-only HRT may not have the same risk profile as combination therapy, a conclusion supported by a recent cohort study [8]. Estrogen-only HRT could, therefore, be a safe option for symptom management in a younger woman with prior hysterectomy (estrogen without progestin has a stimulatory effect on the uterine lining, which can lead to endometrial cancer), especially if her overall risk for breast cancer is low.

During the review of this article, an 11-year follow-up study of the WHI was published [9]. It demonstrated a two-fold relative increase in mortality due to breast cancer in women who had taken combination therapy compared to placebo. The difference in absolute number of deaths was real but small (2.6 vs. 1.3 deaths per 10,000 women per year). Therefore, combination

[1]Note that recent findings from the WHI [9] were not known to the speaker at the time of this symposium. See discussion on the new study later in this article.

HRT is associated with an increased risk of both breast cancer detection *and* mortality. In an interview with the Washington Post, Dr. Taylor stated that these results necessitate a "paradigm shift" in how we think about HRT and breast cancer [10].

Finally, in her presentation, "Depression, Anxiety, and Cognition in Mid-Life," Dr. Ariadna Forray in the Department of Psychiatry at Yale School of Medicine discussed ways in which estrogen therapy may have psychological benefits in women entering menopause. Estrogen affects multiple systems involved in mood, learning, and memory. When given transdermally, 17β-estradiol has been shown to treat depression in perimenopausal women [11] and accelerate the response to other antidepressants [12]. However, benefits of HRT on cognition and memory seem to apply only to women early in the menopausal transition [13]. This stands in contrast to the WHI, which showed an increased risk of dementia in its study population of mostly postmenopausal women [14]. Dr. Forray emphasized that hormone-based treatment of the cognitive and mood disturbances of menopause may be beneficial only in younger women. The risks and benefits of HRT on the brain remain a focus of investigation.

In light of the WHI results, the American Congress of Obstetricians and Gynecologists (ACOG) recommends using the lowest effective dose of HRT for the shortest possible time to treat menopausal symptoms. However, questions about the long-term health consequences of HRT remain. The women in the WHI were older and taking higher doses of estrogen than women using HRT today. In addition, a number of other hormonal options are available, yet their comparative risks and benefits are unknown. These include different types of hormones — conjugated and synthetic estrogens, phytoestrogens, synthetic progestin, and natural progesterone — and modes of delivery — oral tablets, transdermal patches, local creams, and intrauterine devices. Without further study, deciding on the best treatment plan will continue to involve an amount of guesswork.

Development of new compounds will also help advance HRT. Efforts to develop tissue-selective estrogen complexes (TSECs), which combine estrogen with a selective estrogen receptor modulator (SERM) like tamoxifen, are currently under way. TSECs are designed to deliver estrogen while blocking its dangerous growth-promoting effects on tissues such as the breast or endometrium. HRT will remain the subject of debate and research as long as estrogen remains the most effective agent for treating menopausal symptoms.

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