Hormone Therapy and Cognition: Ten Years After the Women’s Health Initiative

Until a decade ago, hormone therapy with estrogen was generally thought to benefit women’s cognitive functions, as the risk for older women developing dementia was attributed to lower naturally occurring estrogen levels after menopause. However, hormone therapy gained a poor reputation when the Women’s Health Initiative (WHI) study of a specific combined estrogen-plus-progestin therapy was halted 10 years ago.

This clinical trial, part of a series of WHI studies sponsored by the National Institutes of Health, was designed to test whether post-menopausal combination hormone therapy prevents cardiovascular disease without increasing the risk of breast cancer. Scientists conducting this study on hormones and cardiovascular disease became concerned about data pointing to a slightly elevated risk of cardiovascular disease, stroke and breast cancer among the post-menopausal women receiving the specific treatment - Prempro.

As a result, the scientists terminated this study, earlier than planned, in July 2002, and halted an estrogen-only WHI clinical trial in 2004 based on an increased risk of stroke and no overall apparent benefit in reducing cardiovascular disease.

Ever since, millions of women have been wary of hormone therapy, or have received hormone therapy for menopausal symptoms such as hot flashes – while still wondering about the potential risks, and perhaps hoping the treatment will also help maintain cognitive functions.

A decade after the WHI trials ended, hormone therapy remains an important area of women’s health research. Further evaluations of the WHI data showed that the reported cardiovascular risks found in the original study pertained mainly to women who started hormone therapy long after menopause. In addition, in 2007, follow-up analyses of the results of the WHI estrogen-alone trial and findings from an ancillary WHI estrogen-alone study suggested that women who used these treatments in the first years after menopause may not be at risk. In fact, it was women who were older than 60 and several years since the onset of menopause when they initiated therapy who had an increased risk for cardiovascular disease.

Moreover, new research suggests that hormone therapy with estrogen may still hold promise for maintaining health, perhaps even in relation to cognitive functions including memory.

What’s a woman to think about this seemingly contradictory evidence?

Dr. Pauline Maki, Professor of Psychiatry and Psychology at the University of Illinois at Chicago, has spent much of her career studying the effects of estrogen on women’s health, particularly in the areas of memory and cognition. Even she acknowledges the topic is extremely complicated.

Although she cautions that there is no definitive answer yet, Maki said she believes that, ultimately hormone therapy with estrogen may be shown to reduce risk for dementia/Alzheimer’s disease and memory loss – but only if a woman is healthy enough and, perhaps, young enough to benefit.

Alzheimer’s disease is a particularly acute concern for women. Compared with men, women have a higher risk and incidence of this neurodegenerative disorder because of a variety of gender-related risk factors which include genetics, higher rates of depression, lower exercise rates, and...
factors related to menopause and hormones, Maki said.

As Director of the Women’s Behavioral Health Research Division in Yale’s Department of Psychiatry, our center’s Director, Dr. Mazure, invited Maki to be the annual Grand Rounds visiting lecturer in May. Maki spoke about the evolving research on hormone therapy with estrogen and cognitive function in the ten years since the WHI trials ended.

According to Maki, by the time the women who participated in the WHI trials started their hormone therapy (the average age was 63), the chances of treatment benefiting these women had been minimized.

There are two hypotheses for why this may be so. The first hypothesis is that there is a critical window of opportunity – during the first six years to 10 years after menopause – for healthy women to benefit from hormone therapy with estrogen.

The second hypothesis is that women with healthy nerve cells in the brain will benefit from hormone therapy with estrogen, while women with unhealthy cells will not. This is known as the healthy cell bias hypothesis, put forth in 2005 by Dr. Roberta Diaz Brinton of the University of Southern California.

Put simply, if initiated when a woman is transitioning to menopause, estrogen therapy will have a beneficial effect only if neurological decline has not occurred. Once nerve cells are unhealthy, as in neurodegenerative disorders such as dementia/Alzheimer’s disease, these cells will not benefit from estrogen exposure. Estrogen may actually worsen neural deterioration.

“This may explain why women who are earlier in the transition may benefit from hormone therapy,” Maki said. These women tend to be younger and are more likely to be healthy. Moreover, “cognitively intact women early in the transition may be the ones who could benefit the most,” she said.

There were clues to support the healthy cell bias hypothesis even in the results of the WHI trials that were terminated, Maki said. As noted earlier, the WHI studies on hormone therapy and cardiovascular disease included two clinical trials: a conjugated estrogen-plus-progestin (Prempro) study of more than 16,000 women with a uterus, and a conjugated estrogen-alone (Premarin) study of more than 10,000 women who previously had a hysterectomy. In each trial, women were randomly assigned to either the hormone therapy or to placebo.

As part of the overall WHI studies, researchers also enrolled subgroups of the women in the hormone therapy trials in an ancillary study of hormone therapy’s effects on dementia risk and cognitive impairment. All of the women in this WHI Memory Study (WHIMS) were 65 or older when the trials began; more than half were at least 70.

The women in the WHI Memory Study treated with combination hormone therapy showed a substantial increase in dementia/Alzheimer’s disease. The women treated with estrogen-only therapy, however, did not show a substantial increase in dementia/Alzheimer’s disease, according to Maki. “One finding that has emerged since the WHI is that when certain forms of synthetic progesterone are given in combination with estrogen, the effect on cognition is negative regardless of the woman’s age or health,” she said.

The two arms of the WHI Memory Study were also terminated in 2002 and 2004. A close look at the results, Maki said, shows that the women who accounted for the increase in dementia fared poorly on cognitive ability scores at the start of the study. “What the WHI data clearly showed us,” Maki said, “is that these are the women we should avoid giving estrogen.”

Maki said the healthy cell bias hypothesis is now increasingly supported by emerging evidence.

The key support, according to Maki, is a 2009 study, by Dr. Mary C. Tierney at the University of Toronto, of the effects of hormone therapy with estrogen on delayed verbal recall – a key measure of working memory. (The ability to acquire and recall...
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new verbal information, according to Maki, may be among the best predictors of risk for Alzheimer’s disease.

Dr. Tierney enrolled 142 women volunteers, aged 61 to 87, in a randomized two-year trial in which half the women received estradiol and norethindrone (a progesterone), or placebo. Overall, she found the hormone therapy had no negative effect on delayed verbal recall. However, the women who had good verbal memory and cognition at the start of the study showed significant improvement in these areas after hormone therapy.

“These findings,” according to the study published in the journal Psychoneuroendocrinology, “support the hypothesis that estrogen exposure will have a more beneficial effect in women with healthy neurons, as it is unlikely that a woman would have significant neurodegenerative changes with a normal score or better.”

More recently, a study published this July in the journal Neurobiology of Aging suggests that the beneficial effects of estrogen therapy on cognitive functions may be blunted by stress. This study, by Dr. Laura D. Baker at the University of Washington, was also a randomized trial, in which 39 healthy postmenopausal women received estradiol, by skin patch, or placebo over eight weeks. In the last four days of the trial, the volunteers also received placebo, or oral hydrocortisone to induce high levels of the stress hormone cortisol.

Women who received the hormone therapy showed improvement in memory and attention, but the improvement was blocked by the administration of the cortisol. Although the sample size was small and the study duration was short, these findings suggest that beneficial effects of estrogen can be modified by stress.

In Maki’s view, the key point from these two recent studies is that memory improved with the administration of estrogen in healthy postmenopausal women. “What did those women who benefited have in common? They had good verbal memory, good cognitive ability, at the start of the studies,” she said.

There remains an urgent need for answers on the safety and efficacy of hormone therapy with estrogen in relation to cognition, Maki said, as women facing menopause seek information and society looks for ways to address a looming dementia/Alzheimer’s disease epidemic. The prevalence of Alzheimer’s is expected to triple by 2050, and the cumulative cost is expected to top $20 trillion, according to estimates Maki cited in her presentation.

“I argue that one of the biggest questions left to be answered is what can a woman with menopausal symptoms take for her hot flashes – with either neutral or beneficial effects for cognition and memory?” Maki said in a recent interview. “Probably there is not one answer for all women.”

The Women’s Health Initiative also included clinical trials with postmenopausal women to test:

- whether calcium and vitamin D supplements reduce the risk for colorectal cancer and the frequency of hip and other bone fractures.

- The effects of a low-fat diet on the prevention of breast and colorectal cancer, and heart disease.

For more information, visit www.nhlbi.nih.gov/whi/background.htm