Hormone Therapy May Help Cognition, Memory

Three new studies suggest it may have possible benefits, in contrast to results of past trials.

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CHICAGO — Hormone therapy might preserve cognition and memory in postmenopausal women, and even attenuate some of the cognitive deficits that occur in Alzheimer's disease, new research suggests.

Controversy exists over the possible cognitive benefits of hormone therapy in older women, Mary Tierney, Ph.D., said at the International Conference on Alzheimer's Disease. "While preclinical and observational studies have shown a positive effect of estradiol on the brain and cognitive function, randomized controlled trials using conjugated equine estrogens have shown no treatment effects in women at risk for Alzheimer's disease, or in women who have the illness."

In fact, the most widely quoted study, the Women's Health Initiative Memory Study (WHIMS), suggested that hormone therapy (HT) might even hurt, rather than help, said Dr. Tierney of the Sunnybrook Health Sciences Centre, Toronto. The 4-year substudy of the Women's Health Initiative examined the effect of hormone therapy on mild cognitive impairment and dementia in more than 7,000 women aged 65-79 years.

"Forty women in the estrogen plus progesterone group developed dementia of any type, but only 21 in the placebo group did," Dr. Tierney said. "However, there were no significant differences in the estrogen-only arm compared to placebo."

Additionally, she noted, a breakdown of the dementias by etiology showed that many of them were vascular in nature—which contributed to the criticism of the Women's Health Initiative for including women who had experienced a stroke.

These concerns, plus her own hypothesis that the "minidoses" of hormones used in many randomized trials might be too low to offer protective benefit, prompted Dr. Tierney and her colleagues to undertake a new study. The 2-year trial randomized 142 women aged 61-87 years to either placebo or to 1 mg estradiol daily plus 0.35 mg progestin 3 days per week.

The primary outcome was the annual change in scores on the short-delay verbal recall portion of the California Verbal Learning Test (CVLT); the test's other memory components were used as secondary outcomes.

None of the women selected for the trial had dementia, but all had normal or below normal baseline memory scores, Dr. Tierney noted. The subjects' mean age was 74 years; their mean age at menopause was 49 years. The multivariate analysis controlled for age, years of education, apo E4 status, and prior hormone therapy use.

There was no significant difference between groups on the primary end point of delayed recall, Dr. Tierney said. But when she split the group according to baseline CVLT scores, significant differences did emerge. Compared with women who scored below the 50th percentile on their baseline test, those on HT who scored above the 50th percentile showed significantly less decline in delayed verbal recall than did those in the placebo group. Similar, but nonsignificant, differences occurred on immediate recall, interference recall, cued recall, and recognition memory.

The findings suggest that hormone therapy might exert a protective influence on memory among women who have not begun to experience significant cognitive decline, Dr. Tierney said. "Our findings suggest that the critical period for estrogen exposure to benefit cognition may not be limited to the menopause transition, since these women were more than 20 years postmenopausal," but might also be related to the state of brain function when therapy is initiated.

Two studies by another group of researchers suggest that hormone therapy positively influences postmenopausal memory and hippocampal activity, and might offer some protective effect against the cognitive decline seen in Alzheimer's.

Kara Bottiggi Dassel, Ph.D., of the Barrow Neurological Institute, Phoenix, examined the effect of past hormone use on the cognitive deficits of Alzheimer's patients. Dr. Dassel extracted her data from the Arizona Alzheimer's Disease Consortium.

The study included 49 women (average age 75 years) who were categorized as current hormone therapy users (20), past users (18), or never-users (11). All of these women had a diagnosis of Alzheimer's disease; there were no differences in functional levels or Clinical Dementia Rating scores, suggesting that they were of a similar disease stage. The women were evaluated for global cognition, memory, and executive functioning.

While there were no significant differences on measures of memory, past users scored significantly better than never-users on the dementia rating scale, with a mean score difference of 31 points—considered clinically meaningful.

Past users also scored significantly better than never-users on the Controlled Oral Word Association Test and the clock drawing test, both measures of executive function. On the word association test, the mean score difference was 18 words; on the clock drawing test, the mean difference was 3.4. Again, Dr. Dassel said, both differences were considered clinically meaningful.

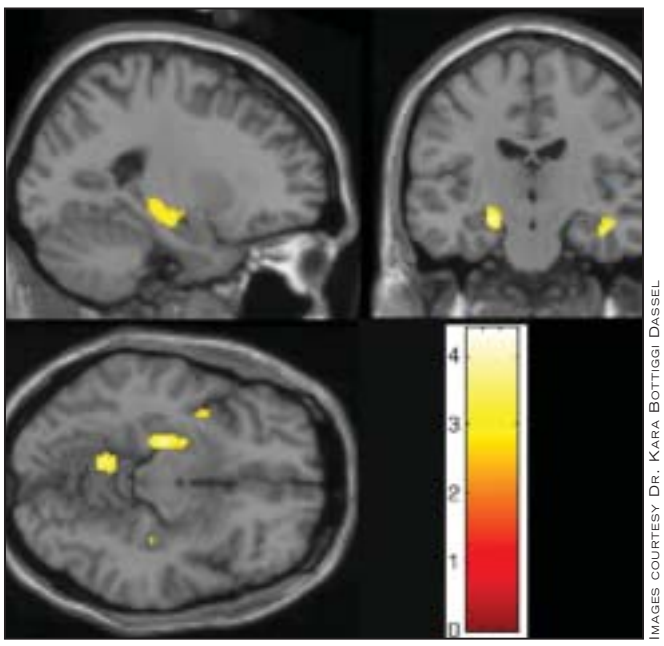
She then examined hormone use by baseline dementia ratings. Women were split into "higher functioning" (mean dementia rating score 68) or "lower functioning" (mean dementia rating score 120).

Among the higher-functioning group, 45% were past hormone therapy users, 45% were current users, and 10% were never-users. Among the lower-functioning group, 25% were past users, 35% were current users, and 40% were never-users.

"The length of illness was similar among women in the higher group, suggesting that there is less of a decline in cognitive functioning in the hormone therapy users."

Dr. Dassel's colleague, Leslie Baxter, Ph.D., presented a study suggesting that hormone therapy also boosts hippocampal activity and might contribute to the persistent differences in memory between men and women as they age.

Dr. Baxter's study comprised 66 postmenopausal women and 37 men aged 50-87 years, all of whom underwent memory testing and functional magnetic resonance imaging of the brain. Again, the women were divided into groups according to their hormone therapy use: never-users (16), discontinuous users (34), and continuous users (16).



Images courtesy Dr. Kara Bottiggi Dassel

A graphic representation shows increased hippocampal activity in discontinuous HT users during a memory task.

There were no between-group differences in age or education. All of these subjects underwent memory testing with the Rey Auditory Verbal Learning Test's total learning and delayed recall tests, and functional magnetic resonance imaging of the brain.

Discontinuous hormone therapy users scored significantly better than men did on all the memory tests. A nonsignificant performance trend also emerged, with discontinuous hormone therapy users performing better than continuous users, continuous users performing better than nonusers, and nonusers performing better than men.

Functional MRI showed that during a memory test (a novelty vs. familiar paradigm), the discontinuous hormone therapy users and men had significantly greater hippocampal activity than the never-users. Continuous users also had higher hippocampal activity than never-users, although not significantly so.

The researchers couldn't draw any conclusions about a definitive time frame during which hormone therapy use was associated with better memory, either in terms of duration of use or in the time of initiation. But, they said, "Both cognitive and … hippocampal integrity measures suggest that women benefited from hormone therapy at any point during menopause—not necessarily continuously—and that it helped preserve the sex difference in memory."

None of the researchers identified any potential conflicts of interest. ■

Maternal Thyroid Disease Linked To Congenital Heart Abnormality

MONTEREY, CALIF. — Women with thyroid disease are 50% more likely to have a child with left ventricular outflow tract obstruction than women without thyroid disease, according to a study that compared about 6,000 women in each of the two groups.

In particular, the risk of aortic valve stenosis and/or coarctation of the aorta appeared to be elevated, Marilyn L. Browne of the New York State Department of Health and her colleagues wrote in a poster presentation at the annual meeting of the Teratology Society. There were no other statistically significant associations between maternal thyroid disease and congenital cardiovascular malformations.

The multicenter case control study was part of the National Birth Defects Prevention Study (NBDPS), which collects data from 10 regions in the United States. The investigators identified 6,068 women with a thyroid disease whose babies were born between October 1997 and December 2004 and compared them with 5,875 controls. There were no significant demographic differences between the case and control groups.

The odds ratios were adjusted for potential confounders, including maternal age, race/ethnicity, education, prepregnancy BMI, gestational diabetes, smoking, alcohol use, and the state of residence at time of delivery.

The investigators acknowledged that their study did not identify the women's underlying thyroid conditions. They recommended that additional studies should evaluate the risks of antithyroid medication and should examine risk by type of thyroid disorder.

Ms. Browne disclosed no conflicts of interest related to her presentation.

—**Robert Finn**