Hormone replacement therapy and Alzheimer’s disease

What is hormone replacement therapy?
Hormone replacement therapy substitutes estrogen from a pharmaceutical source for a woman’s natural supply. Production of estrogen by the ovaries declines as women age and then virtually stops around menopause.

How has hormone therapy been used?
In some women, declining estrogen may cause such troubling symptoms as hot flashes, night sweats and vaginal dryness. Short-term hormone replacement therapy has been approved by the U.S. Food and Drug Administration (FDA) to relieve these symptoms if they occur.

The FDA first approved use of estrogen in the 1940s. In the 1970s and 1980s combination estrogen and progestin therapy became the standard treatment for women with a uterus as mounting evidence showed that taking estrogen by itself is associated with a significantly increased risk of cancer of the uterus. Women who have had a hysterectomy may take estrogen without added progestin.

As growing numbers of women began to use hormones to relieve menopausal symptoms, the therapy attracted attention as a possible treatment or preventive strategy for certain disorders associated with aging, including osteoporosis, heart disease and Alzheimer’s disease.

Interest in these benefits arose from “observational studies” in which women taking hormones for menopausal symptoms appeared to experience a reduced risk of developing these other conditions. An observational study can suggest a relationship between a treatment and an outcome, but cannot provide rigorous evidence for cause and effect.

The “gold standard” for evidence of effectiveness is a double-blind, placebo-controlled clinical trial in which one group of participants is randomly assigned to receive the investigational treatment and a similar group receives a placebo. Neither participants nor researchers know who is getting either treatment.

The Women’s Health Initiative: Documenting the effects of hormone replacement therapy
In 1991, the National Institutes of Health (NIH) launched the Women’s Health Initiative (WHI), a large-scale placebo-controlled, double-blind clinical trial enrolling more than 161,000 women ages 50 to 79, to clarify the risks and potential benefits of hormone replacement. A substudy of the WHI called the Women’s Health Initiative Memory Study (WHIMS) was specifically designed to test whether hormone replacement therapy might help prevent or delay cognitive decline or Alzheimer’s disease. WHIMS enrolled nearly 7,500 women ages 65 to 79.

Both WHIMS and its parent study WHI included treatment tracks in which women were taking estrogen combined with progestin and estrogen alone.

Both treatment regimens were stopped ahead of schedule due to risks documented by the study, including increased risk of dementia. In May 2003, researchers reported that women who had been taking estrogen combined with progestin experienced twice the risk of developing dementia as women taking a placebo. In June 2004, additional WHIMS data showed that women on estrogen-only therapy also had a slightly greater dementia risk.

In terms of actual numbers, WHIMS results suggest that combination therapy could cause an additional 23 cases of dementia per 10,000 women per year, while estrogen-only therapy could trigger an additional 12. The estrogen-only increase was not considered statistically significant.

These increases in risk surprised researchers. In addition to the observational data suggesting a benefit for mental function, laboratory studies involving nerve cell cultures...
and animal studies had indicated that hormone replacement therapy might reduce dementia risk.

Although the increase in risk was seen in both treatment groups, the risk for any individual woman was small and the actual numbers of women who developed dementia were small. But in considering impact on public health, even a small increase in risk is not acceptable in a treatment under evaluation for its ability to prevent disease in healthy women.

Increasing age remains the single greatest risk factor for dementia for either women or men, with the risk of developing dementia approximately doubling every five years after age 65. To put the increased risk observed in the WHIMS study into perspective, a 65-year-old woman on estrogen plus progestin therapy would have the increased risk profile of a 70-year-old woman who was not taking hormone therapy.

Because the women in WHIMS were age 65 or older, results do not shed light on the effect of menopausal hormone therapy on cognition in younger women. Some experts continue to believe that beginning hormone therapy earlier in life, closer to the time of menopause, might help protect the brain.

Recommendations

- Based on the results of WHIMS, experts concur that menopausal hormone therapy should not be prescribed for older women to maintain or improve cognitive function. The Alzheimer’s Association agrees with this recommendation. An editorial accompanying WHIMS results in the May 28 issue of JAMA expresses the opinion that combined hormone therapy “should not be recommended for prevention of any outcome, including Alzheimer’s disease.”

- According to the National Institute on Aging (NIA), results from the Women’s Health Initiative do not directly address decisions about short-term use of hormone therapy by younger women to relieve symptoms of menopause. Risks and benefits for any individual woman seeking menopausal symptom relief are complex. The U.S. Food and Drug Administration (FDA) advises women to talk with their health care providers and, if they agree that hormone therapy is appropriate, use the lowest effective dose for the shortest duration that achieves treatment goals.

- The FDA has mandated that labels of all products containing estrogen or a combination of estrogen and progestin must carry a boxed warning stating that the drugs may slightly increase the risk of heart attacks, stroke, blood clots and breast cancer. The label must also state that results of WHIMS showed that combined estrogen/progestin therapy failed to prevent memory loss and slightly increased a woman’s risk of developing dementia.

Where can I get more information?

The National Institute on Aging (NIA) offers materials on menopausal hormone therapy, including results from WHI and WHIMS, at http://www.nih.gov/PHTindex.htm. Print copies are also available from NIA’s Alzheimer’s Disease Education and Referral Center (ADEAR) at 1.800.438.4380.

The Alzheimer’s Association, the world leader in Alzheimer research, care and support, is dedicated to finding prevention methods, treatments and an eventual cure for Alzheimer’s.

24/7 Helpline  1.800.272.3900
TDD Access  312.335.8882
Web site www.alz.org
e-mail info@alz.org
Fact sheet updated June 22, 2004