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HEALTH | YOUR HEALTH

The Link Between Menopause and Alzheimer’s

With Alzheimer’s afflicting more women than men, researchers are studying whether the hormonal changes that occur in menopause may affect the development of the disease.

ILLUSTRATION: JAMES STEINBERG
Women make up nearly two-thirds of patients with Alzheimer's disease in the U.S., in part because they live longer than men. Now, researchers are exploring whether hormonal changes related to menopause affect the development of the disease.

“The truth is that Alzheimer’s is not a disease of old age, it’s a disease of middle age,” says Lisa Mosconi, director of the Weill Cornell Women’s Brain Initiative in New York City, a research program aimed at reducing Alzheimer’s risk. “In reality, the brain changes start in mid-life.”

Most people think of how menopause affects fertility. But Dr. Mosconi says its effect on the brain is what results in night sweats, hot flashes and even memory changes. Those symptoms are caused by declining levels of estrogen and other hormones. Estrogen protects the female brain from aging and stimulates neural activity. It may help prevent the buildup of clusters of proteins, or plaques, that are linked to Alzheimer’s disease.

Studies show that when estrogen production declines during menopause, the brain’s metabolism appears to slow down and it becomes less efficient.

For decades many women entering menopause tempered its effects with hormone replacement therapy. But in 2003 a large randomized controlled study called the Women’s Health Initiative was halted after the women taking HRT had an increased risk of heart attacks and breast cancer. Some women also showed a small increased
likelihood of developing dementia. Since then HRT has fallen out of favor though many women continue it. When researchers re-examined the data they noticed that the trials focused on older women—on average age 63 and more than a decade past menopause. When they looked solely at the women in their 50s, they found estrogen therapy reduced the risk of mortality related to heart disease and breast cancer.

“The jury is still out and we’re still trying to sort out all of the current data, whether hormone replacement therapy will help prevent the development of Alzheimer’s disease or even put women at risk,” says Howard Hodis, a professor of preventive medicine at the Keck School of Medicine at the University of Southern California, Los Angeles. “This issue is complicated by a lot of factors—not just timing as to when women start HRT, but also the hormone regimen, what kind of hormone or estrogen that is used and the route of delivery.”

In a study published in December in the journal PLOS One, Dr. Mosconi and co-researchers documented how healthy women’s brains change before and after menopause. The 59 women in the study had higher rates of brain-energy decline and shrinkage in the memory centers, as well as higher rates of Alzheimer’s plaques compared with 18 men of similar age.

“Women’s brains seemed to age faster than men’s brains during the transition to menopause,” Dr. Mosconi says. “This accelerated aging process is likely related to the loss of estrogen in the brain and all the hormonal changes going on inside the brain.”

“It’s not that menopause causes Alzheimer’s disease,” she adds. “It’s more like for the average woman, if you have an Alzheimer’s predisposition, menopause may accelerate the process.”

Such changes don’t affect all women. About 20% of women don’t suffer from the hormonal changes associated with menopause, Dr. Mosconi says, and the other 80% have varying effects, from mild to severe.

In a 2017 study published in the journal Neurology, Dr. Mosconi and co-researchers used PET scans to analyze the brain activity of 42 healthy 40- to 60-year-old women and 18 men of a similar age.
Perimenopausal women had a 15% to 20% reduction in brain metabolism compared with the men, while postmenopausal women had over 30% reduction. Perimenopause, which lasts an average of one to five years, is the transition period that leads to menopause.

Postmenopausal women also showed the emergence of Alzheimer’s plaques in the brain. Alzheimer’s plaques don’t necessarily mean that a person will get the disease but indicate a higher risk for developing it.

Dr. Mosconi said there is some evidence that estrogen therapy initiated within five years of menopause, particularly during perimenopause, may also protect against dementia though more research is needed.

But other experts say it isn’t clear whether hormone therapy can help—or harm—cognitive health and affect the development of Alzheimer’s disease in women.

Dr. Hodis was the lead researcher in a trial that randomly placed more than 600 healthy women into groups who either started taking an oral form of estrogen therapy within six years of menopause or more than 10 years after menopause.

Their findings, published in the New England Journal of Medicine in 2016, found that the women who started taking estrogen earlier had a reduction in the progression of atherosclerosis, or hardening of the arteries, which can lead to strokes and heart attacks. Another 2016 study in the journal Neurology showed that there was no difference between the two groups of women in cognitive decline, a potential precursor to Alzheimer’s disease. An earlier randomized controlled study had similar findings.

Roberta Diaz Brinton, director of the Center for Innovation in Brain Science at the University of Arizona in Tucson, and senior author of the PLOS One study has been studying why the female brain is at risk for Alzheimer’s disease for three decades. She says estrogen therapy may be a useful intervention for women in perimenopause who experience a lot of symptoms such as hot flashes, insomnia and depression. Dr. Brinton is studying whether estrogen therapy can lower a woman’s risk of Alzheimer’s.

She is developing an estrogen-only formulation which targets the estrogen receptors in the brain, but not in the breast or uterus. One small clinical trial to be published this year demonstrated the safety of the formulation. Its efficacy against Alzheimer’s is now being tested. “Estrogen therapy alone is not going to be the panacea,” she says. “Exercise, diet, sleep. These are all important.”

Timing is key. Estrogen therapy is unlikely to be effective in women 60 or older who are
no longer experiencing menopausal symptoms. “The time to intervene is when women are having symptoms very early on in this process potentially at the inception of perimenopause,” Dr. Brinton says.

She noted that the women in Dr. Hodis’s study were all post-menopausal so their brains were no longer responsive to estrogen. Her research is focused on determining the process that leads to a loss of estrogen response in the brain.

Dr. Mosconi currently has funding to look at hormonal and brain changes in both men and women at risk of developing Alzheimer’s disease. For men, she says testosterone levels lower very gradually over time, typically in one’s 70s.

Paula Spencer Scott is participating in a study examining hormonal and brain changes in people at risk of developing Alzheimer’s disease. PHOTO: JAMES SCOTT
The study will follow about 200 men and women between ages 40 and 65 over two years. Among the participants is Paula Spencer Scott, a 58-year-old Fort Collins, Colo., resident, who has written a book on Alzheimer’s. Ms. Scott’s father and maternal grandmother suffered from different types of dementia, as did her father-in-law and both her mothers-in-law. As part of the study she had several different brain scans over the summer. She gave blood for testing and did an extensive lifestyle survey. “It was a low-risk opportunity for me to help unravel these kind of mysteries about what causes Alzheimer’s,” she says.

Ms. Scott has three daughters and says “figuring out hormonal influences on dementia would help them when they approach menopause.”