

Estradiol preserves key brain regions in postmenopausal women at risk for dementia

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When initiated soon after menopause, hormone therapy with estradiol prevented degeneration in key brain regions of women who were at heightened dementia risk, according to a new study led by Stanford University School of Medicine researchers.

The investigators also found that another type of [hormone therapy](#), marketed under the brand name Premarin, was far less protective. Premarin is a mixture of 30-plus substances derived from the urine of pregnant mares. Estradiol—the dominant sex-steroid hormone in woman—accounts for about 17 percent of Premarin's total content. Other Premarin components exert various endocrinological effects on different tissues.

The randomized study sought to understand the effects of continuing versus stopping hormone therapy on cerebral metabolism. It will be published March 12 in *PLOS ONE*. The findings indicate that hormone therapy's neurological effect on [women](#) at risk for dementia depends critically on when they begin therapy and on whether they use estradiol or Premarin, said lead author Natalie Rasgon, MD, PhD, professor of psychiatry and behavioral sciences and director of the Stanford Center for Neuroscience in Women's Health.

The researchers observed brain regions in and around the hippocampus that are associated with memory and executive function. These regions are among the earliest to show deterioration in [metabolic activity](#) in many forms of dementia, ranging from mild cognitive impairment to

Alzheimer's disease.

When women who had started an estradiol regimen within a year of menopause stayed on the regimen, metabolic activity in a number of these brain regions was preserved. But it declined significantly among those who stopped using the hormone.

Staying on Premarin, however, actually appeared to accelerate some of these brain regions' metabolic decline. If another hormone, progestin (essentially, synthetic progesterone), was taken along with either estradiol or Premarin, it obliterated estradiol's neurological benefit and steepened the decline seen with Premarin.

The study, while too small to give meaningful results for direct tests of cognition, was large enough to achieve a high level of statistical significance for its imaging results.

"Metabolic changes in these brain regions presage overt symptoms of cognitive decline, sometimes by decades," Rasgon said. "We're finding significant changes in women who are still cognitively intact." An implication is that if signs of impending dementia in a woman can be flagged early on, intervention with estradiol could perhaps stave it off.

"This is an important study that addresses several elements of, if not controversy, at least uncertainty regarding hormone therapy for [postmenopausal women](#)," said David Rubinow, MD, PhD, former head of the division of behavioral endocrinology at the National Institute of Mental Health. Rubinow, now professor and chair of psychiatry at the University of North Carolina-Chapel Hill, was not an author of the study but is familiar with it. He said the findings are "absolutely consistent with a large volume of evidence from basic studies in laboratory dishes and in animals" concerning estradiol's protective role in many tissues.

More than 20 million women in the United States are between 45 and 55 years old—an age range at which many once were considered candidates for Premarin or other forms of hormone therapy. Although some women today choose to go on hormone therapy to relieve menopausal symptoms, it used to be widely heralded as protecting postmenopausal women from heart disease, osteoporosis and even cognitive decline. From 1992 through 2001, Premarin was the most widely prescribed drug in the United States. But after negative reports a decade ago from some large multicenter trials, its use has plummeted.

In 2003, one of those trials concluded that dementia incidence among women ages 65-79 who were randomly assigned to PremPro (Preamarin plus progestin) was double that of women on placebo. But there are significant differences between the participants in that study and those in the new one: Women in the earlier study started hormone therapy long after their bodies had stopped producing substantial quantities of estrogen. Another important distinction: Women in the active arm of that earlier trial were put on PremPro, whose progestin component, the new study shows, actually speeds metabolic deterioration in at least dementia-prone women's brains.

For the new study, Stanford scientists recruited several dozen San Francisco Bay Area women who were well-educated, mostly under 60 and in robust health. All of them had initiated hormone therapy within a year of their last menstrual cycle. And all were at heightened risk for dementia because they either had a personal history of major depression; had a first-degree relative—father, mother or sibling—who had suffered from Alzheimer's disease; or had a genotype positive for the infamous Apo4 allele, a gene variant known to greatly increase women's risk for Alzheimer's.

After initial brain imaging by positron emission tomography, study participants were randomly assigned to either remain on their current

hormone therapy regimen or discard it.

Two years later, 45 of the women—28 who had remained on hormone therapy and 17 who had stopped it—had their brains imaged again. Comparisons of PET scans at the outset versus the two-year mark revealed that metabolic activity in the medial prefrontal cortex—essential to decision-making—was better preserved among participants who remained on hormone therapy.

But in several other dementia-forecasting [brain regions](#), changes in metabolic activity varied depending on the hormone formulation. Notably, in a particular spot known as the precuneus/posterior cingular region—where metabolic decline has been strongly documented as predicting, sometimes by a decade or more, outwardly visible dementia among those at risk for it—metabolic activity was quite adversely affected by discontinuation of estradiol, but extremely well-preserved among women who stayed on that regimen. However, the women who stayed on Premarin experienced no slowing of deterioration in metabolic activity in this region. Coupling progesterone to either regimen made things worse.

"We hadn't expected the type of estrogen therapy to have such a distinct effect on the brain," Rasgon said. "Still, estradiol's effects on the body aren't entirely benign. For example, exposure to the hormone raises the risk of breast and uterine cancer. Perimenopausal women with risk factors for dementia should talk to their doctors about whether estradiol-based hormone therapy makes sense."

If these results wind up being replicated in a large sample of postmenopausal women not at risk for dementia, estradiol-based hormone therapy could become more broadly a treatment of choice to preserve optimal brain aging, she said.

Provided by Stanford University Medical Center

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