Medical Xpress

# Hormone therapy for postmenopausal brain performance has no effect, whether started early or late

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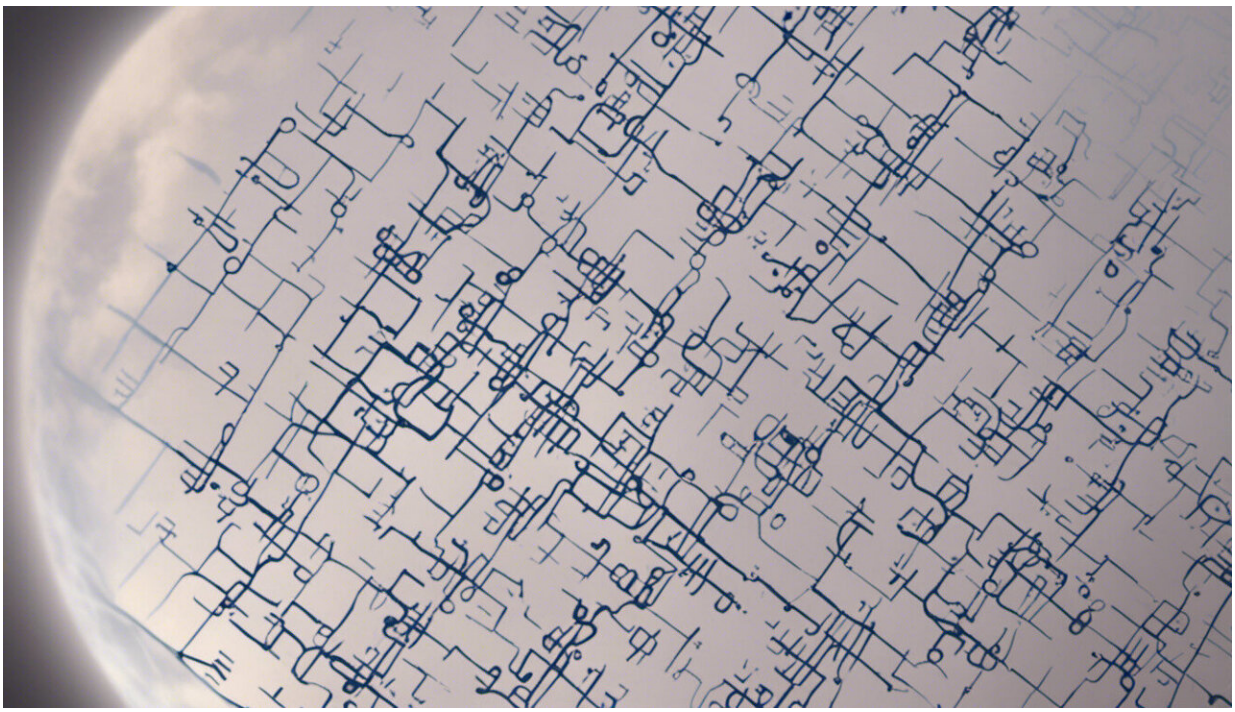

Credit: AI-generated image (disclaimer)

A study led by a scientist at the Stanford University School of Medicine shows that hormone therapy has a negligible effect on verbal memory and other mental skills regardless of how soon after menopause a woman begins therapy.

The study is the first large, long-term clinical trial to compare the effects of estradiol, a type of estrogen, on the mental capabilities of women who commence treatment soon after menopause versus those who begin after a long delay.

"Our results suggest that healthy women at all stages after menopause should not take estrogen to improve memory," said the study's senior and lead author, Victor Henderson, MD, professor of health research and policy and of neurology and neurological sciences. "At the same time, they don't need to be overly concerned about negative effects of estrogen on memory."

The study, published online July 18 in *Neurology*, addresses one specific aspect of a longstanding controversy concerning the benefits and harms of hormone therapy for postmenopausal women, whose bodies no longer produce estrogens and progesterone as they did during childbearing years.

## Doubts about benefits

Hormone therapy was extremely popular in the United States in the latter part of the last century, but its use—while still widespread, with users numbering in the millions—has dropped off considerably since 2002, when findings from the Women's Health Initiative, a large-scale longitudinal study, raised deep doubts about many of what had been believed to be the treatment's broad benefits.

The evidence since then has been mixed on many counts, with a number of small studies, typically relatively short in duration, continuing to suggest potential benefits from hormone therapy. One question is whether the retention of mental abilities—such as memory, reasoning, planning and selective attention—is improved by starting hormone therapy soon after menopause rather than many years later.

The new study is part of a recently completed trial, the Early versus Late Intervention Trial with Estradiol, which enrolled large numbers of postmenopausal women to examine hormone therapy's potential for countering atherosclerosis. One thing ELITE sought to determine was whether outcomes for women taking estradiol, the dominant natural sex steroid in premenopausal women, and progesterone, another steroid involved in the menstrual cycle, would be different than that of women who took Prempro, which was used as part of the Women's Health Initiative in the early 2000s. Prempro is a mixture of modified estrogens derived from mares' urine combined with medroxy-progesterone acetate, a substance whose effects approximate but do not duplicate those of progesterone.

The trial also sought to determine when women should begin hormone therapy to ensure maximal benefits. Depending on the hoped-for clinical outcome, some evidence, mostly from animal studies, suggests that for a woman to benefit from hormone replacement, it may be essential to start soon after menopause, before the rapid postmenopausal decline in estrogen and progesterone availability irreversibly damages hormone-starved cells and tissues.

## Estradiol or placebo

For the ELITE trial, which took place at the University of Southern California where Henderson's collaborators are based, healthy postmenopausal women were divided into two groups: an "early group," composed of women whose last menstrual period had occurred no more than six years prior to the start of the study, and a "late group," composed of women whose last period had occurred at least 10 years before the start of the study. Women in the two groups were then randomly assigned to daily oral regimens of either estradiol or a placebo. Estradiol-receiving women who hadn't undergone hysterectomies were also given progesterone, which can help protect against estrogens' uterine-

cancer-promoting effect. Women receiving placebo instead of estradiol got a progesterone placebo instead of progesterone.

Henderson and his collaborators received funding to study hormone therapy's effects, over a five-year duration, on these women's cognitive abilities. This adjunct trial, called ELITE-cog, analyzed tests of mental abilities of 567 women between the ages of 41 and 84, representing both the "early" and "late" groups of women. The women's verbal memory; their executive functions, such as judgment, planning, reasoning and focusing attention; and their overall neuropsychological condition were assessed at the beginning of the trial and at 2.5 years and five years later.

The difference between the two groups of women on any of these measures was negligible, Henderson and his colleagues found. In fact, there was no appreciable difference in test performance between women receiving estradiol and those given a placebo, regardless of how soon after menopause the women began treatment, the study indicated.

Even when the scientists, in a separate analysis, excluded data from all women in the "early group" who'd begun hormone therapy any later than three years after menopause, they observed neither positive nor negative effects on these women's mental ability compared to that of women initiating treatment more than 10 years after menopause.

Henderson, who is also the director of the Stanford Alzheimer's Disease Research Center, cautions that because women with cognitive deficits or outright dementia were excluded in this analysis, the study's results apply only to women with good mental skills at the time they begin treatment. Also, the findings cannot be extrapolated to cardiovascular or other health outcomes of hormone therapy, which must be assessed individually, he said. Indeed, Henderson noted that there's now some evidence that hormone therapy, initiated early, may have beneficial cardiovascular effects, while it is clear that late hormone therapy can

contribute to heart disease.

Hormone therapy during the first five years after the onset of menopause is still approved for relief of moderate-to-severe hot flashes and night sweats, and also has beneficial effects on bone density. "If you're considering hormone therapy for those reasons, this study indicates that there's no particular reason to fear harmful effects on cognition over a five-year period of use," said Henderson. "But there's no reason to expect that this treatment, by itself, will result in meaningful improvement of mental abilities, either."

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

**More information:** Victor W. Henderson et al. Cognitive effects of estradiol after menopause, *Neurology* (2016). DOI: 10.1212/WNL.0000000000002980

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