

REPRODUCTIVE ENDOCRINOLOGY

Regional brain atrophy after postmenopausal hormone therapy

Postmenopausal estrogen therapy accelerates regional brain atrophy in women aged ≥ 65 years, especially if their cognitive abilities have started to decline before initiation of therapy. “This suggests that estrogen may adversely affect thinking skills among women whose brains may already be beginning a neurodegenerative disease process,” says Susan Resnick (National Institute on Aging in Baltimore, MD), the lead author of the study.

“...these findings might provide an explanation for ... hormone-therapy-related cognitive decline...”

Previously, the Women’s Health Initiative Memory Study (WHIMS) showed that conjugated equine estrogen (0.625 mg daily) with or without medroxyprogesterone acetate (2.5 mg daily) increases the risk of dementia in women aged ≥ 65 years compared with placebo. Resnick and colleagues performed a follow-up study in WHIMS

participants to explore potential mechanisms that could explain this adverse effect.

The investigators conducted MRI scans on 1,403 women (aged 71–89 years) to measure total and regional brain volumes. They found that two brain regions (the frontal lobe and the hippocampus) were smaller in volume in women who had received conjugated equine estrogen or conjugated equine estrogen plus medroxyprogesterone acetate therapy (mean decrease $2.35 \pm 0.81 \text{ cm}^3$ and $0.10 \pm 0.05 \text{ cm}^3$, respectively) than in those in the placebo group. The greatest hippocampal differences were observed in women who had the poorest cognitive abilities at enrolment, as measured by the Modified Mini-Mental State Examination. As shrinkage of the hippocampus is a known risk factor for dementia, these findings might provide an explanation for the hormone-therapy-related cognitive decline in postmenopausal women that was reported in the WHIMS. Nevertheless, the mechanisms by which exogenous estrogen exerts its adverse effects on the brain are not known.



Limitations of the study include its cross-sectional design, the lack of data in women younger than 65 years and the lack of data on brain volumes before treatment. Despite these limitations, this study strongly suggests that women who are older than 65 years and/or experience cognitive decline should not start hormone replacement therapy.

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Original article Resnick, S. M. *et al.* Postmenopausal hormone therapy and regional brain volumes: the WHIMS-MRI Study. *Neurology* 72, 135–142 (2009).