Oestrogen replacement therapy did not improve cognitive decline in Alzheimer's disease after hysterectomy

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QUESTION: In women with mild to moderate Alzheimer's disease (AD) who have had hysterectomies, what is the effect of oestrogen replacement therapy on outcomes?

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Design

15 month randomised (allocation concealed*), blinded (clinicians and patients)*, placebo controlled trial.

Setting

32 AD centres in the US.

Patients

120 hysterectomised women who were >60 years of age (mean age 75 y) with a diagnosis of mild to moderate AD, no depressive disorder, and normal gynaecological examination results were enrolled in the study. Exclusion criteria were myocardial infarction in the previous year, history of thromboembolic disease or hypercoagulable state, hyperlipidaemia, or use of excluded medications. 97 patients (81%) completed the study.

Intervention

Patients were allocated to conjugated equine oestrogens (Premarin) at doses of 0.625 mg (n=42) or 1.25 mg (n=39), or to placebo (n=39).

Main outcome measures

Change in score on the Alzheimer's Disease Cooperative Study version of the Clinical Global Impression of Change scale. Secondary outcomes included change in score on the Mini-Mental State Examination, the Alzheimer's Disease Assessment Scale-Cognitive, and the Clinical Dementia Rating Scale (CDRS).

Main results

The study had 81% power to detect a 29% difference between oestrogen and placebo groups in the proportion of patients who worsened. To assess the overall efficacy of oestrogen, the 2 oestrogen groups were combined. The oestrogen and placebo groups did not differ for any outcome except that of a change in the CDRS which favoured the placebo group (p=0.01) (table).

Conclusion

In women with mild to moderate Alzheimer's disease who have had hysterectomies, oestrogen replacement therapy did not improve global, cognitive, and functional decline.

*See glossary.

Conjugated equine oestrogens v placebo for Alzheimer's disease at 12 months†

Outcomes	Oestrogen	Placebo	RRI (95% CI)	NNH
Patients worsened on the ADCS-CGIC	80%	74%	10% (-10 to 43)	Not significant
Difference in mean change (CI)				
Change in ADCS-CGIC	5.1	5.0	0.1 (-0.27 to 0.47)	
Change in MMSE	-2.7	-3.1	0.4 (-1.08 to 1.88)	
Change in ADAS-Cog	5.6	3.6	2.0 (-0.54 to 4.54)	
Change in CDRS	0.5	0.2	0.3 (0.09 to 0.5)	

†ADCS-CGIC=Alzheimer's Disease Cooperative Study version of the Clinical Global Impression of Change; MMSE=Mini-Mental State Examination; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive; CDRS=Clinical Dementia Rating Scale. Other abbreviations defined in glossary; RRI, NNH, and CI calculated from data in article.

COMMENTARY

This definitive study by Mulnard *et al* is the first on which treatment decisions about the use of Premarin in established AD can be based. It clearly shows that Premarin has no useful effect on symptoms or disease progression in AD. Although only powered to detect a relatively large effect size, the negative results give no grounds for thinking that larger or longer studies of Premarin would reveal a smaller effect. The rigorous, 1 year, parallel arm design contrasts with the weaknesses of the many positive but smaller and shorter crossover studies which have fuelled interest in the hypothesis.

Several questions remain. Firstly, could oestrogen delay onset of AD? Effects on disease initiation may be independent of effects on rate of progression. For example, apolipoprotein E $\epsilon 4$ allele hastens onset but not progression. Epidemiological studies show reduced risk of dementia in patients taking hormone replacement therapy (HRT).¹ Those taking HRT, however, tend to be from higher socioeconomic groups, better educated, and healthier, all of which make them less likely to develop AD. The results of 2 ongoing prospective trials will provide more reliable evidence, but they are not due to report for 6-10 years.^{2 3}

Secondly, might other oestrogen preparations be more effective than Premarin? Premarin, unlike oestradiol, has not been shown to have objective effects on cognitive function in healthy, elderly women.⁴

Finally, is there any possibility of prolonging the positive effect of Premarin seen on some measures at 2 months? Unfortunately, *in vitro* work has not clearly shown a way of averting the loss of neurotrophic activity that arises with continuing exposure to oestrogens.⁵ This effect may explain why so many short studies have been positive.

Although the death knell is sounding for the idea that HRT offers clinically useful neuroprotection, talk of its demise is premature. Trials with other oestrogen preparations may be positive.

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