Review: oestrogen therapy after menopause may improve cognitive performance and may reduce the risk of developing dementia

Yaffe K, Sawaya G, Lieberburg I, et al. *Estrogen therapy in postmenopausal women. Effects on cognitive function and dementia.* JAMA 1998 Mar 4;279:688-95.

Question

In postmenopausal women, does oestrogen therapy improve cognition, prevent development of dementia, and reduce dementia severity?

Data sources

Studies were identified by searching Medline (January 1966 through June 1997) using the key words hormone replacement therapy, estrogen, estrogen replacement therapy, menopause, cognition, dementia, Alzheimer's disease, and memory; scanning the bibliographies of identified articles; and consulting experts.

Study selection

Studies were selected if they investigated the possible biological mechanisms of the effect of oestrogen on the central nervous system or if they contained primary data on the effect of oestrogen on cognitive function or dementia in women. Case reports and studies in premenopausal women were excluded.

Data extraction

Studies were reviewed for methods and sources of bias. Data were extracted on study design, patient characteristics, intervention, and cognitive outcomes.

Main results

7 randomised and 1 non-randomised controlled trials were identified that evaluated the effect of oestrogen therapy on

cognitive function. No meta-analysis was attempted because of methodological problems in the trials; however, 6 trials concluded that oestrogen therapy improved cognitive function.

10 observational studies were identified which measured the effect of postmenopausal oestrogen use on risk of developing dementia. A meta-analysis of these 10 studies showed a reduction in odds (odds ratio [OR] 0.71, 95% CI 0.53 to 0.96) of developing any type of dementia in women taking postmenopausal oestrogen. For Alzheimer's disease (using National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria) there was heterogeneity between studies' results that may have been due to study design: the summary OR for Alzheimer's disease from prospective cohort studies was 0.48 (CI 0.29 to 0.81) and for case control studies was 0.79 (CI 0.56 to 1.12).

1 randomised controlled trial and 1 non-randomised controlled trial of oestrogen in Alzheimer's disease were identified, both of which were small and inconclusive.

Conclusion

Oestrogen therapy may improve cognitive performance in women with postmenopausal symptoms and may reduce the risk of developing dementia.

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For correspondence: Dr K Yaffe, UCSF/VA Medical Center (111G), 4150 Clement Street, San Francisco, CA 94121, USA. Fax +1 415 750 6641.

Commentary

Early this century, theorists of aging argued about the secretions of sex glands and their role in the restoration of mental and physical strengths in senescence. Contemporary women are advised that oestrogen will enhance their wellbeing and reduce the risks of heart disease and osteoporosis. Some recent evidence suggests that the prevention of cognitive decline in late life should be added to these potential benefits of postmenopausal oestrogen replacement therapy.

Yaffe *et al* provide a useful and timely examination of 3 questions that should be read by physicians asked to advise on this issue. Firstly, are there plausible neurobiological explanations for the claimed benefits of oestrogen on postmenopausal cognitive function? Secondly, does oestrogen benefit cognitive function (or dementia) in postmenopausal women? Thirdly, does oestrogen reduce the risk of dementia in postmenopausal women? Their answers add up to a cautious maybe, which is the single, but important, nugget of wisdom to

be gleaned from their careful and comprehensive review. Appropriately, they cite likely sources of error: differences between women in educational attainments, the presence of concurrent depressive symptoms, and the use of multiple cognitive tests. Inspection of separate studies and a satisfactory combination of results in an overall meta-analysis did not allow any more specific conclusion than the general wish to see more and better research.

Weaknesses are minor. The authors efficiently summarise biological explanations of oestrogen's possible benefits but do not suggest which of the many they summarise is the most plausible candidate. Given that none of the studies evaluated the effects of oestrogen therapy on cognitive performance after taking account of confounding by age, educational attainment, and current depressive symptoms, the authors are correct to conclude that oestrogen may reduce the risk of Alzheimer's disease through various mechanisms. However, research design in the field of cognitive

aging in women is complex and has to take account of a number of factors. Low educational attainment is a controversial risk factor for dementia but is an established source of spurious low scores on mental ability tests in old age. Low self esteem is an important source of poor motivation to succeed on mental ability tests, and measures of depression may not provide accurate estimates of its effect. Perhaps most important of all is the physical health of older women, with those in poor health doing less well on mental ability tests. Until studies which take account of these factors provide support for the maintenance or restoration of cognitive function by oestrogen in older women, the claimed cognitive benefits may be attributable mainly to the sustained physical wellbeing of many women who maintain postmenopausal oestrogen therapy.

Lawrence J Whalley, MD, FRCPsych
University of Aberdeen
Aberdeen, UK