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Endogenous and Exogenous Estrogen, Cognitive Function and Dementia in Postmenopausal Women: Evidence from Epidemiologic Studies and Clinical Trials

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Abstract

There are more than 200 published scientific papers showing that estrogen has favorable effects on brain tissue and physiology in cell culture and animal models including nonhuman primates. The biological plausibility for a neuroprotective estrogen effect is overwhelming. However, most studies of endogenous estrogen and cognitive decline or dementia fail to show protection, and some suggest harm. Failure to find any consistent association might reflect the limitations of a single time of estrogen assay or poor assay sensitivity. More than half of the observational studies of hormone therapy suggest benefit. Nearly all long term clinical trials fail to show benefit and the longer trials tend to show harm. Failure to adequately adjust for self-selection of healthier and wealthier women and publication bias could account for some, or all, of the protective effect attributed to estrogen in observational studies. Overall, the evidence does not convincingly support the prescription of early or late postmenopausal estrogen therapy to preserve cognitive function or prevent dementia.

Keywords

estrogen; cognitive function; dementia

Introduction

There are more than 200 published scientific papers showing that estrogen has favorable effects on brain tissue and physiology in cell culture and animal models including nonhuman primates. The biological plausibility for a neuroprotective estrogen effect is overwhelming.[1, 2]

In this paper we review the remarkably less consistent and less convincing evidence for a favorable estrogen effect on preservation of cognitive function and prevention or delay of dementia in postmenopausal women.

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Sex differences in cognitive decline and dementia

Women passing through the menopause transition lose about 90% of their premenopausal estrogen level, and typically have blood estrogen levels about one-fourth the usual levels observed in healthy men of the same age. If estrogen is neuroprotective, it might be expected that postmenopausal women would lose cognitive function more rapidly than men, and would have a higher prevalence of dementia than men of similar age.

Evidence for sex differences in cognitive function change and dementia is mixed. This is in part because population-based data comparing the cognitive function decline in men and women are mainly cross-sectional. For example, the Rancho Bernardo Study compared 12 tests of cognitive function in 551 men and 800 postmenopausal women, with women stratified by never, past and current hormone use. In this early study, there was the expected sex difference in cognitive performance, most notably for better verbal test performance (Buschke recall) for women and better visuo-spatial test performance (Trails B) for men. The slope of decline, however, did not differ for men and women, and, among women did not differ by hormone use status.[3]

Results are similar in prospective studies. In a 10 year population-based Norwegian study of 625 adults, sex differences in eleven cognitive function tests did not change over a 10 year follow-up interval.[4] In a 6 year follow-up Dutch study of 155 older adults, there was no sex difference in the decline of cognitive function tests.[5]

The prevalence of dementia is said to be higher in older women than in older men, but it is not clear whether this is a true sex difference, or differential survival with fewer men surviving to the ages when dementia is most common, or longer survival of women than men after they develop dementia. As reviewed elsewhere[6], only 8 of 19 population-based studies of sex differences in dementia published before 2000 tested for statistical significance: four reported a higher prevalence in women and four reported no difference. Of 12 incidence studies, nine included fewer than 20 male cases, and only one study reported a significantly higher incidence among women.

In a study of community-dwelling older adults (aged 65+) from East Boston, who had a detailed clinical neurological examination for dementia, there was no sex difference in the age-adjusted prevalence of dementia (men vs. women odds ratio (OR) = 1.29; 95% confidence interval CI 0.67-2.48), incidence of dementia (OR = 0.92; 95% CI 0.51-1.67), or in the two-fold increased risk of death in participants with prevalent dementia who were followed for 11 years.[6] The last result is the strongest available evidence that differences in dementia prevalence do not reflect longer survival in women than in men with dementia.

These results contrast with results from a pooled analysis of four European population-based prospective cohort studies of persons aged 65 and older, with 528 incident cases (with excellent clinical diagnosis of dementia type) and 28,765 person years of follow-up.[7] In this study there was a statistically significant excess of Alzheimer's dementia in women compared to men (adjusted relative risk 1.54; 95% CI 1.21-1.96) but not for vascular dementia (0.72; 95% CI 0.47-1.09). The authors note that more men than women aged 80 and older were lost to follow-up (32.2% vs. 26.4%), and that there was an almost doubling of the incidence of Alzheimer's in women between ages 80 and 90, not seen in men. It is therefore possible that the observed sex differences reflect sex differences in survival and loss to follow-up.

Endogenous estrogen

Results from observational studies of endogenous estrogen and cognitive function are inconclusive. Some report harmful associations, some protective, and many fail to identify any clinically meaningful association between serum estrogen levels and cognitive ability.

This may be due, in part, to the difficulty of measuring circulating estradiol in older women. Even the best assay methods (those that extract and separate the estrogens prior to assay) lack sufficient sensitivity to measure estradiol in up to 25% of postmenopausal women. (Measurement of estrone, the primary circulating estrogen after menopause, is less problematic, with 2-4 times higher blood levels than estradiol.) Another source of concern is that most studies are based on single blood samples, not always drawn fasting or in the early morning. While single measurements of most hormones have been shown to reliably characterize average levels over a 2 to 3 year period; estradiol levels are less reproducible.[8] Finally, about 37% of estradiol in older women circulates bound to SHBG and only the non-SHBG bound fraction (commonly termed bioavailable estradiol) or the free fraction is thought to cross the blood brain barrier.[9] Given these caveats, the inconsistency of the literature should not be surprising.

In this review, studies of populations (not patients) that include at least 100 women are preferentially reviewed. In the first large population-based study (532 women 65 years or older from the Study of Osteoporotic Fractures women with the highest estrone levels had significantly poorer performance on one (Digit Symbol) of three cognitive function tests at baseline and a greater reduction in scores on another (Trails B) over 5 years compared with women with lower estrone levels.[10] Total estradiol levels were not related to cognitive performance, and neither estrogen predicted performance on the modified Mini-Mental Status Exam (mMMSE), a measure of global cognitive function. These early results did not support the hypothesis that estrogen preserves brain function, however a later report from the Study of Osteoporotic Fractures showed that women with high concentrations of (measured) free and bioavailable estradiol were less likely to develop cognitive impairment (decrease of 3+ points on the mMMSE after 6 years) than women with low concentrations.[11] Free and bioavailable estradiol levels were not related to baseline cognitive function test scores in this study.

The Rancho Bernardo Study also failed to identify any consistent cross-sectional association of estrone or total and bioavailable estradiol with performance on 12 cognitive function tests in postmenopausal women.[12] By contrast, a cross-sectional analysis of data from the Rotterdam Scan Study found that women with higher (calculated) bioavailable estradiol levels had significantly poorer memory performance (delayed recall).[13] Another large cross-sectional Dutch study found the opposite: women in the highest quintile of either estradiol or estrone were 40% *less* likely to be cognitively impaired (MMSE<27) compared to women in the lowest quintile.[14] There is no obvious reason for these divergent findings of null, harmful, and protective associations. Differences in populations studied, estrogen assays, or cognitive assessment tools are possible explanations, but none seem universal or satisfactory.

Results from case-control studies comparing estrogen levels in women with and without Alzheimer's disease also have been inconsistent; differences were attributed by the authors of a review of 10 such studies to assay sensitivity.[15] Lower levels could reflect lower estrogen levels secondary to the weight loss that often precedes clinical dementia. The Rotterdam study is the only large single-population based study to report whether endogenous estrogens predict future dementia in older non-demented women. Higher levels of total estradiol were associated with an increased 6 year risk of dementia (age-adjusted hazard ratio per standard deviation increase 1.38; 95% CI 1.04-1.84); results were similar for (calculated) bioavailable estradiol.

The association seemed to be mainly for vascular dementia.[16] This single study provides no evidence that endogenous estrogen protects against dementia, and raises the possibility of harm.

Surrogates of endogenous estrogen

Surrogates of endogenous estrogen offer an alternative to measured estrogen, without the limitations of single assays or assay sensitivity. These studies include investigations of cognitive function and bone mineral density, reproductive stage (pre- versus peri- and post-menopause), and duration of estrogen exposure based on lifelong reproductive period (age at menopause minus age at menarche, with or without an adjustment for pregnancy).

Three large studies have looked at lifetime estrogen exposure based on reproductive period and various measures of cognition. The Australian PATH Project [17] and the Melbourne Women's Midlife Health Study[18] found no association of reproductive period or a multifactorial index of estrogen exposure with cognitive performance in older women. In the Rotterdam Study of 3600 postmenopausal women, a greater number of reproductive years (longer exposure to endogenous estrogen) increased the risk of incident dementia, but only in women with at least one *ApoE* ε4 allele.[19] None of these studies support the hypothesis that estrogen delays cognitive decline or lowers dementia risk.

A study of bone does. In the Study of Osteoporotic Fractures, women with osteoporosis based on baseline bone mineral density, bone loss, or vertebral fractures, had poorer cognitive function and a greater risk of cognitive deterioration.[20, 21] Bone mineral density and fracture risk are thought to be markers of cumulative estrogen exposure.

If endogenous estrogens influence cognitive function, this effect might be more apparent during the menopausal transition when estrogen levels are decreasing dramatically and 60% of women report memory problems.[22] The Study of Women's Health Across the Nation (SWAN) found no association between phase of the menopausal transition (or estradiol levels) and several tests of cognitive performance [23] in agreement with a smaller Swedish study.[24] In two other cross-sectional studies among pre, peri, and post menopausal women, premenopausal women outperformed postmenopausal women on some, but not all, cognitive tests.[25, 26] Similarly, women in early versus late postmenopause had better executive function independent of age, but no difference in attention, verbal fluency or memory.[27] Again the data are too inconsistent to draw definitive conclusions.

Epidemiologic Studies of postmenopausal estrogen therapy and cognitive function or dementia

There are many observational studies, and several meta-analyses of these epidemiologic studies of postmenopausal estrogen use and cognitive performance. Favorable results from these studies, reviewed below, drove the wide-spread enthusiasm for postmenopausal estrogen therapy to protect the brain, and the subsequent clinical trials.

Observational studies of elective medications may be misleading if the characteristics of women who are prescribed and take the medications differ from characteristics of women who do not. It was recognized early on that hormone replacement was more often used by women with more education and/or higher socioeconomic status, who had more favorable heart disease risk factors even before the menopause.[28] These differences would also be expected to be associated with better cognitive function. Interpretation of results from the following papers should be considered with this healthy-user self selection bias in mind.

One of the first reviews of studies of postmenopausal estrogen and brain function was published by Haskell in 1997, who reviewed papers published between 1970 and 1996. Among these

studies, 5 of 8 observational studies suggested benefit, 8 of 10 controlled trials showed improvement in at least one cognitive function test, and 3 of the 5 studies that included tests of memory showed “either large improvement or small deterioration”. This review foretold the confusing results and interpretation of subsequent studies.

The first meta-analysis to review epidemiologic studies of postmenopausal estrogen use and dementia included 14 cohort or case-cohort studies; although few individual study associations were statistically significant, the pooled analysis suggested a 34% benefit.[29] Another meta-analysis of 12 studies published between 1966 and August, 2000 also showed mixed results, with a 29% reduced risk of dementia in the pooled analysis.[30]

The Nurses Health Study is one of the largest prospective studies of estrogen therapy and cognitive decline, including 13,087 women aged 70-81 with hormone use data for more than 27 years.[31] Cognitive function tests (obtained by telephone interview two years apart) included global cognition, verbal memory, category fluency and attention. Non-estrogen users showed the least decline in any test performance. Decline was significantly greater in women who started estrogen years after the menopause, raising the possibility that women with memory problems may have begun estrogen to treat perceived memory loss.

The Study of Osteoporotic Fractures included 9655 postmenopausal women, mean age 71, from four U.S. sites.[32] Women completed three cognitive function tests (mMMSE, Digit Symbol Test, Trails B) at baseline, and 67% repeated these tests 4-6 years later. Past but not current hormone users had smaller declines in mMMSE and Trails B at the second testing compared to never users. Only formal education was protective in the cohort overall.

The Kame Project, a prospective study of the 2 year rate of cognitive change in 837 older Japanese women (age 65+) living in Seattle, found that women using unopposed estrogen had improved global cognitive function (Cognitive Abilities Screening Instrument), while women taking estrogen plus a progestin had poorer function, compared to nonusers.[33]

Some longitudinal studies of postmenopausal estrogen use and dementia were based on death certificate diagnosis. In a 3 year follow-up of 800 women aged 65 – 95 from the Rancho Bernardo Study, the relative risk of dementia (listed anywhere on the death certificate) among baseline estrogen users was Increased (OR 1.90; 95% CI 1.10-4.39) compared to nonusers.[34] In contrast, another larger California community-based study with Alzheimer's diagnosis (also based only on the death certificate) reported the risk of dementia was significantly reduced in estrogen users (OR 0.65; 95% CI 0.49-0.88). These authors also reported better protection with higher doses or longer duration of hormone use.[35]

The Cache County Study followed 1889 older postmenopausal women (mean age 75) for three years, and identified 88 new cases of probable Alzheimer's dementia (confirmed by clinical evaluation in 84%). Prior estrogen use reported at baseline, but not current estrogen use at baseline, was associated with a reduced risk of dementia.[36] Data from the UK General Practice Research Database (300 practices with patients followed for as long as 11 years) were used for a matched nested case-control study of older women, comparing the records of prior prescriptions in women with (n= 59) and without (n = 221) a clinical diagnosis of Alzheimer's Disease.[37] In this study, use of postmenopausal estrogen was not associated with incident Alzheimer's dementia.

It is impossible to synthesize these divergent results for a meaningful conclusion.

Clinical trials

Published randomized controlled clinical trials tend to be either small and short or large and long; obviously only the latter have dementia outcomes.

Results from many small short trials in younger women are inconsistent; because the results are not clearly relevant to cognitive function loss or risk of dementia in older women, they are reviewed only briefly here. These studies have been reviewed recently by Sherwin, who performed most of the original controlled clinical trials on recently oophorectomized women; Sherwin concluded that most estrogen trials showed cognitive benefit.[38] Because most of the controlled clinical trials in younger women were conducted in women who had a surgical menopause or severe menopause symptoms, it is unclear whether the observed benefit is relevant to mechanisms for protection of older women against memory loss or dementia,

Results from small clinical trials in older women are contradictory. For example, 3 trials in older women without dementia variously showed worse performance on 2 of 10 tests (70 women, 3 month trial of transdermal estrogen), no significant effect on 5 tests (46 women, 3 week trial of oral estrogen), or better performance on memory and visuospatial tests (37 women, 3 week trial of transdermal estrogen).[39-41] The reasons for these differences are not obvious.

Results from larger longer trials generally suggest harm. The Ultra Low Dose Transdermal estRogen Assessment (ULTRA) trial randomly assigned 417 postmenopausal women aged 60-80 to transdermal very low dose estradiol (0.014 once weekly) or placebo.[42] After two years there was no significant difference in performance on any of seven cognitive function tests. Women in the lowest tertile of endogenous estrogen at baseline, who might have been expected to benefit most, performed significantly more poorly on the MMSE if they were treated with estrogen.

The Heart and Estrogen/Progestin Replacement Study (HERS) clinical trail included 1063 older women who had known heart disease; women were randomly assigned to 0.625 daily conjugated equine estrogen and 2.5 mg of medroxprogesterone acetate. Cognitive function tests were not obtained at baseline, but were performed (after 4.2 years) at the end of the trial. Only one of the five test results differed by treatment assignment: verbal fluency performance was significantly worse in the estrogen-treated women ($p = 0.02$).[43]

The Women's Health Initiative Memory Study (WHIMS) is the largest postmenopausal estrogen trial of dementia ever likely to be conducted, including a subset of 2947 women aged 65 or older who were participants in one of the two Women's Health Initiative (WHI) trials. This study was planned to combine the data from the estrogen alone or estrogen plus medroxyprogesterone acetate arms. All women completed the 3MSE cognitive function test. During a mean follow-up of 5.4 years, women assigned to active therapy performed more poorly than women assigned to placebo on this test of global cognitive function. They were also more likely to develop categorically defined mild cognitive impairment or dementia. The adverse effect on cognition was greater in women who had poorer global cognitive function at baseline.[44]

Three years after WHI enrollment began a subset of 1416 (of 2089 invited) women in the estrogen plus medroxyprogesterone acetate (participants from 14 of the 39 WHIMS sites) began a more extensive study of 16 cognitive function tests which were to have been repeated annually. After an average of only 1.3 years when the WHI trial was concluded prematurely, hormone users had poorer performance on verbal memory ($p < 0.01$ and better performance on figural memory ($p = 0.012$) compared to the placebo group. Results for the other fourteen tests did not differ by treatment assignment.[45]

In 2008 The Cochrane Collaboration reported a detailed meta-analysis of postmenopausal hormone treatment trials and cognitive function.[46] They reviewed all published randomized double-blind controlled clinical trials of estrogen alone or with a progestin and cognitive function which had a treatment period of at least 2 weeks; 16 of 24 trials with usable data published up to the end of 2007 were included. The total number of women in these trials was 10,114. The average duration of the trials was between 4 and 5 years. In the unopposed estrogen and the estrogen plus progestin trials, the cognitive function test results were poorer in the hormone treatment group, but the differences were not statistically significant. The odds of cognitive impairment with unopposed estrogen was 1.34 (0.95-1.90), and with estrogen plus progestogen therapy was 1.05 (0.72-1.54).

The Cochrane report included separate analyses related to differences in hormone regimens and differences in populations. The authors concluded that there was insufficient evidence to show whether benefit or risk differed by specific types of treatment, e.g. transdermal versus oral delivery, standard versus other doses, or estrogen alone versus estrogen with a progestogen. They also concluded that there was insufficient evidence to show whether risk differed by the type of participants, e. g. age 60 vs. older, within 10 years of menopause versus not, surgical versus natural menopause, and presence versus absence of postmenopausal symptoms.

Hormone trials in patients who have dementia are few. The largest trial was conducted in 120 women with mild to moderate senile dementia of Alzheimer's type. Women were randomized for one year to conjugated equine estrogen either 0.625 or 1.25 mg/day or placebo for one year. The primary outcome, global assessment of change with a 7 point scale, showed absolutely no change by treatment assignment, but, the clinical dementia rating scale, a secondary outcome, showed a significant difference (0.5 vs. 0.2, p =0.01) favoring placebo.

The timing hypothesis

Among the many controversies surrounding the generally negative or at best null clinical trial results, the most prominent is related to the notion that women in the trials were too old to benefit. If women already have predementia due to Alzheimers, small strokes, or both (a common combination), then estrogen started in older postmenopausal women might be too late – even harmful given the known excess risk of clotting and stroke associated with estrogen. On the other hand, estrogen begun soon after menopause might not show benefit, because women are still cognitively intact, and there is no reason to expect that estrogen will improve normal cognitive function.

The latter situation may explain the entirely null results in the observational study reported from the Melbourne Women's Midlife Health Project. In this cross-sectional study, 326 women ages 52 to 63 were tested using a 10 word delayed recall three times at one visit. Memory was similar regardless of menopausal status, number of years postmenopause, current or prior use of estrogen, or duration of hormone treatment, and was also unrelated to blood estradiol levels.[18]

A Swedish study examined the association of menopause status on performance on 15 cognitive function tests in 129 premenopausal, 58 perimenopausal, and 55 postmenopausal women. There was no association between any cognitive function test and menopause status or endogenous estradiol (measured using an assay with sensitivity to detect 10.6 pmol/L). Age and education were associated with cognitive function test performance.[24]

In contrast, a follow-up study of recently postmenopausal women who had been randomly assigned to estrogen or placebo in one of four 2-3 year estrogen therapy trials found that women assigned to estrogen in early postmenopause who completed the trial, then discontinued hormone therapy, and returned for cognitive function evaluation 5, l0 or 15 years late, showed

a decreased risk of cognitive impairment (OR 0.36; 95% CI 0.15-0.90) compared to the placebo group.[47] Although these results are compatible with the thesis that short term estrogen therapy in the early phase of menopause provides long term cognitive protection, the results are difficult to interpret because the main analysis was not based on an intention to treat analysis, and women who did not complete the trial and return for follow-up were excluded from these analyses.

A large epidemiologic study directly relevant to the timing hypothesis was reported by Petitti et al in 2008.[48] In this study, 2906 postmenopausal women aged 75 or older (who were members of a health plan) provided an estrogen use history, performed cognitive function tests by telephone, and were followed for dementia for four years. The number of incident dementia cases in this study (n=283) was much larger than prior prospective cohort studies[36, 49] allowing a more comprehensive assessment of the effect of timing. Dementia rates were similar in past or current hormone users whether they began estrogen within 10 years of menopause or later, and whether they used estrogen alone or with a progestin.

Long term benefit for women who initiate hormones at menopause and continue them to age 80, when cognitive impairment is common, is unlikely to be addressed with clinical trials. Only long-term prospective epidemiologic studies are available, and these results are mainly negative

Summary

Most studies of endogenous estrogen and cognitive decline or dementia fail to show protection, and some suggest harm. Failure to find any consistent association might reflect the limitations of a single assay or poor assay sensitivity. More than half of the observational studies of hormone therapy suggest benefit. Failure to adequately adjust for self-selection of healthier and wealthier women and publication bias could account for some, or all, of the protective effect attributed to estrogen. Nearly all long term clinical trials fail to show benefit and the longer trials tend to show harm. Overall, the evidence does not convincingly support early or late postmenopausal estrogen therapy to preserve cognitive function or prevent dementia.

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Abbreviations

SHBG
sex hormone binding globulin

OR
odds ratio

CI
confidence interval

mMMSE
modified Mini-Mental Status Exam

SWAN
Study of Women's Health Across the Nation

WHIMS
Women's Health Initiative Memory Study

WHI
Women's Health Initiative

ULTRA
Ultra Low Dose Transdermal estRogen Assessment

HERS
Heart and Estrogen/progestin Replacement Study