Estrogen and the Brain

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Dr. Kirk's interests include clinical prevention, medical education, and health policy.

Clinical Case

> Ms. B is a 69-year old woman who is in good health. She had a hysterectomy for fibroids at age 51 and has been on estradiol 1 mg. per day since then. On a bone mineral density measurement 4 years ago she had a T-score of minus 1.2 at the lumbar spine, consistent with osteopenia. This has remained stable on a repeat bone mineral density measurement in the past year. She has no identified cardiovascular risk factors, maintains ideal body weight, and exercises regularly. She has recently read newspaper reports about the Women's Health Initiative results and asks your advice on her estrogen therapy, especially whether it might help prevent Alzheimer's disease. Her mother died in her late 80's of Alzheimer's disease and Ms. B is especially concerned about developing Alzheimer's. She states, "I'm afraid my brain will wear out before my body does."

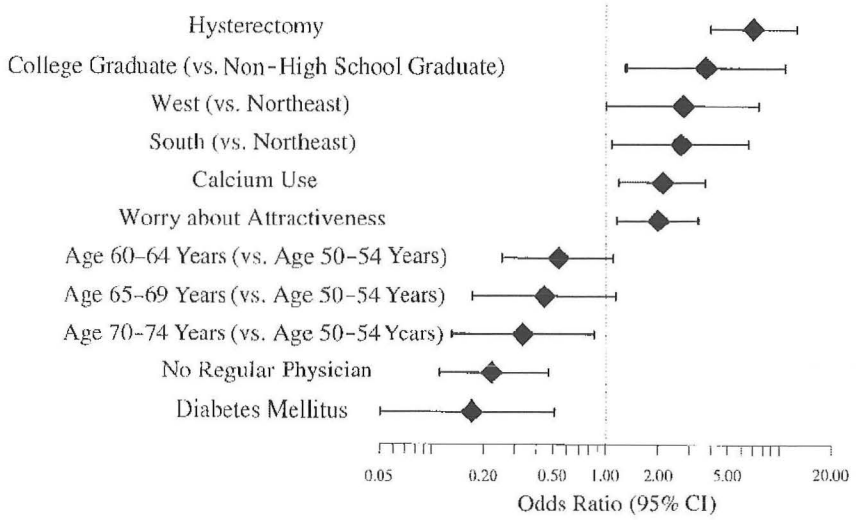
In a landmark 1923 article, Allen and Doisy demonstrated that fluid collected from the folliculi of sows' ovaries (liquor folliculi) when injected into ovarectomized mice and rats induced estrual hyperemia, growth, and hypersecretion in the genital tract and produced vaginal cornification. [1, 2] Doisy and several other investigators continued work to identify the hormone responsible for these changes and independently isolated estrogenic compounds from the urine of pregnant women around 1930. [3] Butenandt identified the structure of estrone in 1930 [4] and MacCorquodale identified that of 17-beta-estradiol in 1935. [5] Estrogen preparations became available soon thereafter and the use of estrogens for therapy of postmenopausal symptoms was reported as early as 1935. [6, 7] Orally active estrogens were synthesized in the late 1930's. [4, 8] and the Food and Drug Administration approved a preparation for therapeutic use in 1942. [9]

Use of Postmenopausal Estrogen

Estrogen therapy has been used for over six decades in the treatment of menopausal symptoms. The frequency of its use has varied based on the evidence available on its risks and benefits. Literature available to the public in the 1960's extolled the benefits of estrogen therapy in preserving youth. In the early 1970's documentation of the risk of endometrial cancer with the use of unopposed estrogens greatly reduced its use in women with a uterus. [10] In the last decades of the 20th century, the reduction of this risk by combining the estrogen with progestin and the suggestion of observational studies of broad health benefits of estrogen therapy led to very wide use beyond the treatment of postmenopausal symptoms. However many questions remain about its long-term use to prevent disease and prolong life. Recent randomized controlled trials of estrogen with or without progesterone have concluded that in some women the risks of hormone replacement outweigh the benefits. [11, 12]

In 1995 Keating sampled a national U.S. population-based cohort of postmenopausal women age 50 to 74 years regarding their use of hormone replacement therapy (HRT). [13] The overall rate of current HRT use was 37.6%, with the highest rates seen in the South (45%) and West (42%). Women who had undergone hysterectomy had higher rates of HRT use (58.7%) compared to women who had not undergone hysterectomy (19.6%). (Figure 1.) The rate of hysterectomy did not account for all of the regional variance. Women were also more likely to use HRT if they were college graduates, used calcium supplements, or were younger. Women with no regular source of health care or with underlying diabetes were less likely to use HRT.

Figure 1. Multivariate correlates of use of postmenopausal hormone replacement therapy.



The rate of use for HRT in this study was higher than most previous studies. [14, 15, 16] This may reflect evidence from largely observational studies at that time (1995) suggesting broad benefits for HRT combined with increasing rates of hysterectomy.

The public's attention to possible adverse effects of HRT was increased significantly when the estrogen/progestin arm of the Women's Health Initiative was discontinued on May 31, 2002. The Women's Health Initiative investigators reported results of a multicenter study of over 16,600 women age 50 to 79 years randomly assigned to HRT or placebo. The results leading to this decision were published in July. [10] A summary of those results is presented in Table 1.

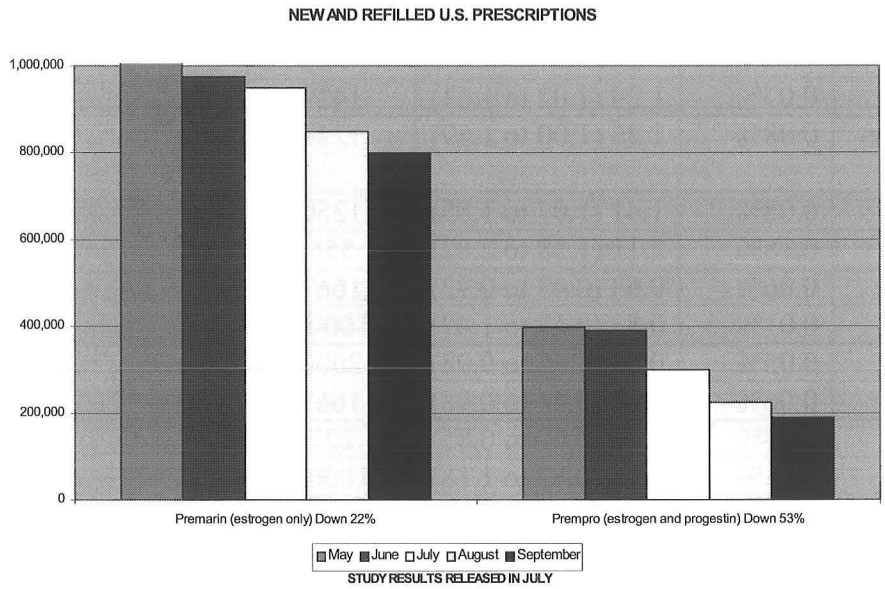
Table 1. Women's Health Initiative Outcomes

Outcome	ARR/*ARI*	RR (95%CI)	NNT/*NNH*
Primary			
CHD	0.07%	1.29 (1.02 to 1.63)	1429
Invasive Breast Cancer	0.08%	1.26 (1.00 to 1.59)	1250
Secondary			
Stroke	0.08%	1.41 (1.07 to 1.85)	1250
Thromboembolism	0.18%	2.11 (1.58 to 2.82)	556
Colorectal Cancer	0.06%	0.63 (0.43 to 0.92)	1667
Endometrial Cancer	0.01%	0.83 (0.47 to 1.47)	10000
Hip Fracture	0.05%	0.66 (0.45 to 0.98)	2000
Vertebral Fracture	0.06%	0.66 (0.44 to 0.98)	1667
Total Fracture	0.44%	0.76 (0.69 to 0.85)	227
Death	0.01%	0.98 (0.82 to 1.18)	10000
Global Index	0.19%	1.15 (1.03 to 1.28)	526

ARR/ARI=Absolute Risk Reduction/Increase, RR=Relative Risk,
NNT/NNH=Number Needed to Treat/Harm

The lay press published numerous articles on the risks and benefits of estrogen therapy. [17] Although only the estrogen/progestin arm of the Women's Health Initiative was suspended, the sales of Prempro®, the preparation used in the suspended arm of the study, and Premarin®, the most widely prescribed estrogen therapy, declined significantly. (Figure 2.) The study results support the fact that these risks are probably a class effect. Until further data are available, when advising patients the Women's Health Initiative results can be extrapolated to all estrogen/progestin combinations.

Figure 2.



This information has caused women taking HRT and their health care providers to reevaluate the risks and benefits of their therapy. Most physicians have been repeatedly queried regarding their opinion about taking hormones after menopause, if not by patients, then by family members, friends, and colleagues. A significant factor in motivating patients' continued interest in hormone replacement therapy is the potential for benefit in delaying or preventing some of the physiologic changes associated with age. In most western nations we have a large population with an increasing life expectancy and great interest and expectations regarding maintaining quality of life and physical and mental function. In my discussions with patients, the issue of whether estrogens prevent dementia frequently arises as it did in the case outlined above.

Estrogen Actions in the Central Nervous System

Both male and female gonadal steroids freely cross the blood-brain barrier. In addition to their permanent effects on the developing brain, they have been shown to have effects on mature neurons. [18, 19] In the early 1960's estrogen receptors were identified that bind to DNA and regulate gene expression. [20, 21] These receptors have been found not only in cells involved in reproduction (uterus, mammary glands, pituitary), but also in multiple regions of the brain not primarily involved in reproduction, including the hippocampus, cerebral cortex, midbrain, and brainstem. Sensitive estrogen receptor labels have further identified potential locations of estrogen action in the pyramidal cells of the ventral hippocampus.

It was originally thought that estrogen acted only through these intracellular hormone receptors, with the hormone-receptor complexes modifying the cell function, usually through the cell's DNA, i.e. genomic effects. However many of estrogen's effects are found to occur very soon after exposure and in areas where estrogen receptors have not been identified. Thus estrogen appears to act by both genomic and nongenomic mechanisms.

These nongenomic effects include rapid action on the excitability of neuronal and pituitary calls, activation of cyclic AMP and mitogen-activated protein kinase pathways, actions modulating G protein coupling and affecting calcium currents and gonadotropin-releasing hormone release, effects on calcium channels and calcium ion entry, and protection of neurons from damage by excitotoxins and free radicals (neuroprotective). [18]

The hippocampus is involved in learning and memory as well as in the control of autonomic and vegetative functions. In animals, estrogen has a positive effect on memories in which the hippocampus plays a role. [22] Estrogen appears to regulate the cyclic formation and breakdown of excitatory synapses in the hippocampus. [23] In animals estrogen regulates synaptic plasticity by stimulating axonal sprouting and dendritic spine formation on CA1 pyramidal neurons. [24] These changes are mediated through the N-methyl-D-aspartate (NMDA) glutamate receptors. [25, 26]

When oophorectomized rats are given estrogen, there is also an increase in choline acetyltransferase and potassium-stimulated acetylcholine release in regions of the brain. [27, 28] Estrogen prolongs survival of cholinergic neurons and colocalizes with nerve growth factor receptors in cholinergic neurons in the basal forebrain, thus estrogen is neurotrophic. [29, 30]

Estrogen has also been shown in vitro to promote the breakdown of the beta-amyloid precursor protein. [31] It reduces plasma levels of apolipoprotein E (ApoE) and may modify inflammatory responses that have been implicated in neuritic plaque formation. [32] Estrogen may also increase cerebral blood flow. [33]

Thus it appears that estrogen has an array of actions in the brain that may influence behavior and physiologic processes. Many of these have the potential to specifically counter changes associated with aging of the brain and Alzheimer's disease. If this is the case, one would expect estrogen to have positive effects in clinical studies of cognitive function. These hypothetical benefits would include improved cognition in women with estrogen deficiency and the potential to delay or prevent the onset of dementia, especially the most common dementing illness, Alzheimer's disease.

Epidemiology of Alzheimer's disease

Before menopause, estradiol, derived primarily from the ovaries, is the predominant estrogen in women. About a quarter of this estradiol is converted to estrone. Estrogen receptors throughout the body are more sensitive to estradiol than to estrone. Estriol, a second metabolite of estradiol has the lowest receptor affinity. [34, 35] Beginning around age 40, the production of estradiol becomes erratic and there is a rapid decline in estrogen levels at the cessation of ovulation at a mean age of 51 years. [36] In men, and in women after menopause, the main source of estrogens is conversion of circulating androgen steroid hormone precursors. Postmenopausal women have much lower levels of circulating estrogens than men.

If estrogen has a protective effect on cognition, one would expect postmenopausal women, with low estrogen levels relative to older men, to manifest a greater decline in cognition leading to a higher incidence of clinically apparent dementia. A large proportion of people with Alzheimer's disease are women. This is because there are a larger number of women alive than men at ages when Alzheimer's disease is common. If postmenopausal women have a greater chance of

developing Alzheimer's disease than men, this would be reflected in the age-related incidence of Alzheimer's disease in women compared to men.

Studies comparing the incidence and prevalence of Alzheimer's disease in men and women have had variable results. [37, 38, 39, 40, 41, 42] Many of these studies had small sample size and lacked tests for statistical significance. Hebert and colleagues looked at the incidence of onset of Alzheimer's disease in a large prospective cohort in East Boston. [37] In a population of 3809 people age 65 and older, 467 were analyzed for prevalence of Alzheimer's disease and 642 for incidence of Alzheimer's disease over an average of 4.3 years. The odds ratio for developing Alzheimer's disease in men compared to women was 0.92 (95 percent confidence interval, 0.51, 1.67). The investigators analyzed prevalence of Alzheimer's disease in men compared to women, controlling for age, and found an odds ratio of 1.29 (95 percent confidence interval, 0.67, 2.48) They concluded that there is no significant difference in the incidence or prevalence of Alzheimer's disease for men and women. A more recent population based study followed 5677 elderly residents of Cache County, Utah over 3 years for the development of dementia. [43] They found the incidence of Alzheimer's disease to be the same in men and women until age 80. The odds ratio among women over 80 in their population compared to men was 2.11, (95 percent confidence interval, 1.22, 3.86).

The lifetime risk of Alzheimer's disease is determined by the rate of development of the disease and the death rates among people with and without the disease. Even if the incidence of Alzheimer's disease is the same in men and women, men die at a faster rate than women. Thus by 90 years of age, 33 percent of women and 23 percent of men will have Alzheimer's disease. This produces a lifetime risk of 32 percent for women and 18 percent for men. The burden of suffering for Alzheimer's disease overall is significantly greater for women and the people who provide their care. If the risk for or severity of Alzheimer's disease could be reduced for these women or their cognitive function improved by an intervention such as estrogen, the benefits for these people and the reduction in the costs of their care would be great.

Estrogen Therapy and Cognition in Postmenopausal Women

Large population studies do not show an abrupt decline of cognitive function in women during the decades they are postmenopausal. [34] Several studies have measured endogenous hormone levels in healthy elderly women not using estrogen replacement and correlated them with cognitive function. [34] They have found no consistent evidence that low levels of endogenous estrogen are associated with decreased cognitive performance. This does not rule out the possibility that higher estrogen levels achieved with replacement might maintain or enhance cognitive function, given estrogen's effects on the brain.

Yaffe and colleagues reviewed several observational studies on the use of estrogen for preventing cognitive decline. [27] They found five observational studies that evaluated the association of estrogen therapy and cognitive performance in postmenopausal women. [44, 45, 46, 47, 48] The results of two of these studies were inconclusive, two reported no improvement in cognition with estrogen therapy, and one found improved cognitive function with estrogen use. (Table 2.)

Table 2. Observational Studies of Estrogen and Cognition in Nondemented Postmenopausal Women

Source, y	Study Design	No. Subjects	Findings
Barrett-Connor and Kritz-Silverstein, 1993	Prospective cohort	800	Test scores were not associated with current or past use of estrogen, duration of use, or dose
Kampen and Sherwin, 1994	Cross-sectional	71	Estrogen use associated with better scores on Paragraph Recall (P<.05), but not with better scores on any other tests
Robinson et al, 1994	Cross-sectional	72	Estrogen use associated with better score on proper name recall (P=.01), but not on word recall
Kimura, 1995	Cross-sectional	54	Specific results not reported, but estrogen users "had better scores than those not on therapy"
Paganini-Hill and Henderson, 1996	Nested case-control	214	No association between estrogen use and test score

As has been demonstrated by the results of randomized controlled trials on HRT and heart disease, observational studies are susceptible to confounding, since the choice of treatment was made by the subjects and their physicians, rather than by randomization in the study. Known effects on cognition such as age, education, and depression, can be, and sometimes are controlled for in these studies. However there may be many unknown factors that affect the decision to prescribe estrogen therapy and also have an impact on cognitive function.

Leblanc and colleagues at the Evidence-based Practice Center at Oregon Health Sciences University reviewed randomized, double blind, placebo-controlled trials and cohort studies to determine the evidence of the use of HRT to prevent cognitive decline in nondemented postmenopausal women for the U.S. Preventive Services Task Force.[49] In the published literature, they found 9 randomized controlled trials [50, 51, 52, 53, 54, 55, 56, 57, 58] and 8 cohort studies.[34, 59, 60, 61, 62, 63, 64, 65] Cohort studies were included because they are likely to follow patients for longer periods of time than more expensive randomized controlled trials. However they suffer some of the potential deficiencies noted for observational studies in that therapy is not assigned randomly as a part of the study.

The designs and measurements used in the randomized controlled trials were diverse and of varying quality. The duration of use of the estrogen or placebo ranged from 21 days to 6 months. The results of the randomized controlled trials are presented in Table 3.

Table 3. Hormone Replacement Therapy (HRT) and Cognition in Randomized Controlled Trials.

Author	No. Subjects	Mean Age	HRT Form	Menopausal Symptoms	Duration Of Use	Main Result
Anowsky and Chavez 2000	13	69	Oral	No	30 d	No improvement on a working memory task
Shaywitz et al 1999	92	50.8	Oral	Not stated	21 d	No improvement on 2 working memory tasks
Polo-Kantola etal 1998	124	56.3	Trans-Dermal	Not stated	3 mo	No improvement on 7 tests of attention or 2 tests of working memory
Phillips and Sherwin 1992	19	48.2	Intra-Muscular	Yes	2 mo	Performance better on 3 out of 4 tests of verbal recall; no difference on working memory or visual recall tasks
Ditkoff et al 1991	36	53	Oral	No	3 mo	No improvement on 2 tests of attention
Sherwin 1988	20	45.4	Intra-muscular	Yes	3 mo	Improvement on all 4 tests of working memory, reasoning, speed of perception, and verbal recall
Fedor-Freybergh 1977	21	56.5	Oral	Yes	3 mo	Improvement on all 4 tests of attention and reaction time
Hackman and Galbraith 1976	18	29-68	Oral	Yes	6 mo	Improvement on a memory battery
Vanhulle and Demol 1976	26	57.8	Oral	Yes	3 mo	Borderline improvement on 2 of 5 tests of attention

In a subsequent review, Hogervorst and colleagues reviewed all double-blind randomized controlled trials of the effect of estrogen replacement therapy or of replacement therapy with estrogen and progesterone on cognitive function in postmenopausal women. [66] They identified 15 trials involving a total of 566 women, including the nine that were reviewed by Leblanc. The mean age of subjects was 55 years with a wide range (29 to 91 years). Treatment lasted from 2 weeks to 9 months, with 3 months being most common. The form and doses of hormone therapy varied widely among studies as did the tests used to assess cognitive function of the study participants.

Only two studies showed a significant effect of HRT. [47, 49] These studies were done by the same group on women undergoing oopherectomy in association with a hysterectomy for benign reasons. They were randomized to receive 10 mg. of estradiol intramuscularly per month or placebo for two to three months immediately after their surgery. These were relatively young women (mean age under 50 years) and the positive results were only achieved on one aspect of a test of verbal memory, on a test of abstract reasoning, and a test of speed and accuracy. Because of timing of the intervention, immediately after oopherectomy, women in the control group had significantly more postmenopausal symptoms than women receiving estrogen.

When the results of these 15 trials and 18 epidemiological studies were analyzed, it was found that 24 of the total of 33 studies found one or more positive effects of HRT on cognition, a pattern that

seems to indicate a favorable effect of HRT on cognitive function. [34] Each of the studies employed multiple measures of cognitive function. If one looks at the total number of tests in the studies, only 45% showed a positive effect of HRT. This may be because HRT only has an effect on selective cognitive functions in which case the tests that improved would be those measuring a particular area of cognition, such as memory. When analyzing the results in this way, Hogervorst and colleagues found no such specificity. [34] Instead they found significant inconsistency in the results of tests of similar cognitive functions.

They assessed the attributes of the studies to determine what might account for these wide inconsistencies. Epidemiological studies were more likely to produce a positive result (17 of 18) than experimental studies (7 of 14). As previously discussed, epidemiological studies have a much greater potential to introduce bias than experimental trials. However the cost and time required for experimental trials generally limit the number of subjects and the length of the intervention. Overall, the evidence for improved cognition in health women treated with hormone replacement after menopause is small and inconsistent.

Several cohort studies have been published subsequent to these reviews. [67, 68, 69, 70] The results continue to be mixed. One of these studies showed no benefit of estrogen therapy. [61] Two studies showed benefit [62, 63], but the benefits did not remain significant when controlled for other variables affecting cognition. One study showed significant benefit with estrogen therapy, but only on some measures of verbal learning and memory and on none of several other measures of cognitive function.[64]

The Women's Health Initiative Investigators will be publishing their results of the effects of estrogen plus progestin on health-related quality of life in the *New England Journal of Medicine* on May 8, 2003. [71] In addition to cognitive functioning, they compared results of instruments measuring quality of life and functional status, depression; sleep disturbances, sexual functioning, and menopausal symptoms between groups of women treated with estrogen and progesterone or placebo. Between baseline and year one, they found small but statistically significant positive effects of estrogen plus progestin on physical functioning, bodily pain, and sleep disturbance. By the end of year three, the differences were no longer significant. They found no differences at any point between the groups of women in their measures of cognitive function.

They did find a significant reduction in vasomotor symptoms in women who characterized these symptoms at baseline as moderate to severe. However a subgroup analysis of these symptomatic women revealed no significant differences in the other quality of life measures. Thus this large prospective randomized placebo-controlled trial concludes that even in women with significant vasomotor symptoms, cognitive function and other measures of quality of life are not improved with hormone replacement therapy.

In sum, there have been a relatively large number of studies looking at the effects of estrogen on cognition in postmenopausal women. The majority of these are cohort studies. Both the cohort studies and randomized controlled trials use a wide variety of cognitive measures and therapeutic interventions. There is no data from these trials to suggest any deleterious effects to cognition from estrogen therapy. There is little data to support its benefit in asymptomatic postmenopausal women. Even in women with postmenopausal symptoms, cognitive function had only consistently improved in a small subset of areas. These new results from the Women's Health

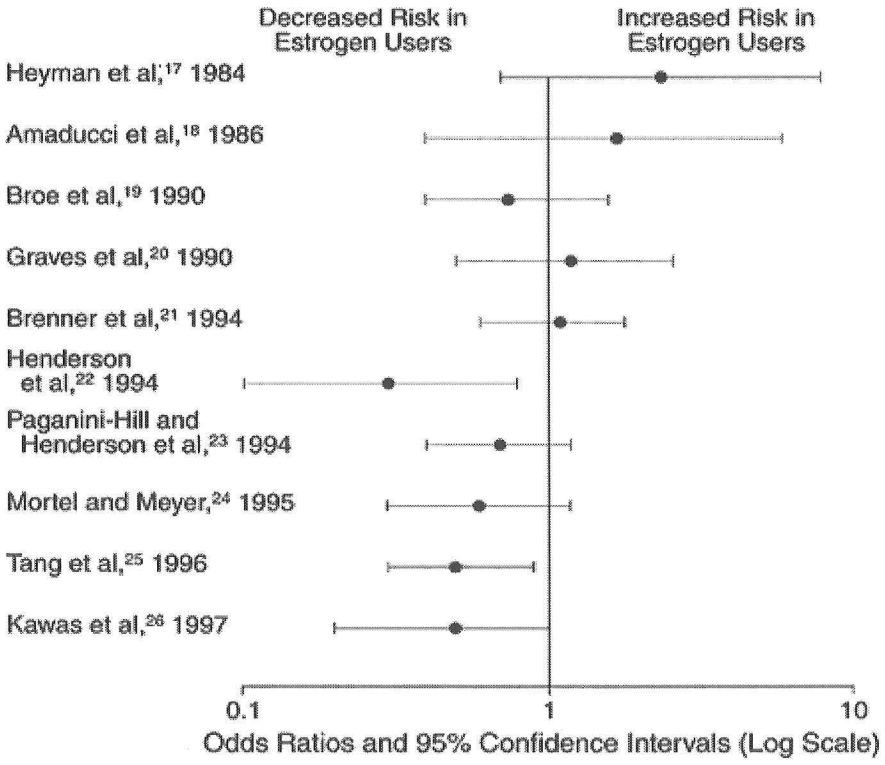
Initiative, which enrolled a large number of women in a randomized controlled trial, create significant doubt that there are sustained benefits even for symptomatic women.

Estrogen Therapy and the Risk of Alzheimer's disease in Postmenopausal Women

The basic effects of estrogen on the brain suggest that estrogen might be protective for the development of dementia, especially Alzheimer's disease. Serum estrogens have been found to be lower in women with Alzheimer's disease than age-matched controls in some studies, but these results are not consistent. [34, 72] Meta-analysis of the results of such studies suggests a correlation between lower levels of estrogen and Alzheimer's disease (weighted mean difference= -8.73, 95 percent confidence interval –9.58 to –7.87). However the heterogeneity was very high which implies that the studies were not comparable. Of the eight studies analyzed, two found higher estrogen levels in Alzheimer's patients, two found higher levels in controls and four found no significant differences.

There have been 8 case-control studies [73, 74, 75, 76, 77, 78, 79, 80] and 2 prospective cohort studies [81, 82] conducted to evaluate the association between Alzheimer's disease and other dementias and estrogen therapy. [27] The results of these studies are summarized in Figure 3.

Figure 3. Risk of developing Alzheimer's disease in women receiving estrogen.



The results of these studies have been variable ranging from a protective effect from estrogen for Alzheimer's disease to increased risk for Alzheimer's disease with estrogen therapy. One of the case-control studies [71] and the two prospective studies [74, 75] demonstrated a statistically lower

risk of developing dementia in postmenopausal women who had taken estrogen compared with those who had not. Of the remaining case-control studies, 2 showed a nonsignificant risk of dementia among estrogen users, two showed no difference in the risk of dementia, and 3 found a nonsignificant decrease in the risk of dementia among estrogen users compared with nonusers.

These observational studies were then combined into a meta-analysis to determine if more significant differences could be found with larger groups of subjects. The results of the meta-analysis are summarized in Table 4. The meta-analysis suggests a 29% decreased risk for developing dementia among estrogen users. However the findings from meta-analyses are only as reliable as the individual studies included. All controlled or adjusted for age, but most were not adjusted for education and none were adjusted for depression, all factors known to be associated with dementia. Being observational, they are susceptible to multiple confounding and compliance biases.

Table 4. Results of Meta-analyses of Estrogen and Dementia Risk*

Study Design	No. of Subjects	Summary OR (95% CI)	P Value for Test of Heterogeneity
All Studies			
Any dementia diagnosis	3977	0.71 (0.53-0.96)	.10
Any AD diagnosis	3587	0.71 (0.52-0.98)	.11
Case-control studies			
Any dementia diagnosis	2381	0.79 (0.56-1.12)	.09
Any AD diagnosis	1991	0.80 (0.56-1.16)	.11
Prospective studies			
AD diagnosis	1596	0.48 (0.29-0.81)	.86

*OR indicates odds ratio; CI, confidence interval; AD, Alzheimer disease

Three studies have been published since this meta-analysis. One was a case-control study of 222 women in a population-based study who developed Alzheimer's Disease compared to 222 matched controls without Alzheimer's from the same population.[83] Women in either group who took estrogen for at least 6 months were considered users. They found that control subjects were more likely to have used estrogen than were Alzheimer's disease women (OR=0.47, 95% confidence interval, 0.18, 0.96). When they controlled for education or age at menopause, their results remained statistically significant, but the confidence intervals included 1.

Balderischi and colleagues carried out a cross-sectional survey of 1582 women in Italy, who were screened for dementia and queried about estrogen use.[84] They found 92 patients with Alzheimer's disease and when compared to the remainder of the women, the demented women were less likely to have ever used HRT. When adjusted for age, education, ages at menarche and menopause, smoking, alcohol use, body weight, and parity, Alzheimer's disease was much less likely in women who had used estrogen compared to those who had not (OR=0.28, 95 percent confidence interval, 0.08, 0.98). In both these studies, estrogen use was ascertained from

surrogates for patients with Alzheimer's disease and from the controls themselves, risking potential bias in under-reporting use in the women with Alzheimer's disease.

The women in the Cache County, Utah cohort were also assessed for estrogen use.[38] They found that women who had used estrogens for more than 10 years had a decreased risk of Alzheimer's disease (OR=0.41, 95 percent confidence interval 0.17, 0.86), regardless of whether they currently used estrogens.

Hogervorst and colleagues repeated a meta-analysis of a total of fifteen studies undertaken to determine if there were protective effects of estrogen for Alzheimer's disease. [34] They found the overall odds ratio to be 0.56 for risk of Alzheimer's disease with estrogen therapy with a 95% confidence interval of 0.46 to 0.68. The studies were however very heterogeneous, suggesting an unidentified bias. Using only studies including more than 150 subjects in the meta-analysis, they still found a protective effect of estrogens with an odds ratio of 0.46 (95 percent confidence interval, 0.36, 0.59) and that the heterogeneity was no longer significant.

Studies done since 1994 were noted to be much more rigorous in their design in that they adjusted for more potential confounds, such as age and education, than earlier studies. When including only the 10 studies published since 1994, the results still favored estrogen use with an odds ration of 0.49 (95% confidence interval, 0.46, 0.68). Thus the statistical analysis supports the fact that estrogen therapy in postmenopausal women reduces the risk of Alzheimer's disease. However there are many other factors that may make the results of these epidemiological studies invalid.

Methods for diagnosing the cause of dementia premorbidly are not optimal. The studies analyzed used a variety of methods and many included women with dementia other than Alzheimer's type. However estrogen's effects on the brain suggest that it's potential benefit is not limited to cognitive decline caused by Alzheimer's disease.

An area of potential bias is the method used to ascertain estrogen use. In cross sectional studies where the population is sampled at one point in time, those in the population with dementia by definition have cognitive deficits which might impair their recall of previous or even current estrogen use. Most commonly surrogates such as caregivers provide this information. While they may be aware of the patient's current medications, they are less likely to accurately know previous medications. Estrogens may be discontinued when a woman develops dementia and thus surrogates' reports would underestimate lifetime estrogen exposure.

If estrogen is protective, one might expect that this protection would be reflected in a dose response. Women who have taken estrogens longer and/or at a higher dose may derive more protection from dementia. The studies to date do not have the detail to allow such analyses, although they suggest that a longer duration is more protective. Epidemiological studies have shown that women who take hormones after menopause often have higher educational levels and socioeconomic status, both of which are associated with a lower rate of Alzheimer's disease. Some of the studies have controlled for education, but they did not find that this negated the protective effect of estrogen. A final potential bias is that these analyses were only done on published studies that may report a more positive outcome than unpublished data, resulting in publication bias.

Data from population studies currently available are encouraging in that they appear to show some protective effects of estrogen in the development of dementia, especially Alzheimer's disease. For a variety of reasons these studies are open to potential bias. Some of these biases are the same as those of epidemiological studies assessing the benefits of estrogen therapy for coronary artery disease. The results of those studies have been called into question with the availability of the results from a large randomized controlled trial, the Women's Health Initiative. [12] There are two large prospective randomized placebo controlled studies under way which are designed to assess the effects of estrogen on dementia and cognitive function in postmenopausal women. The first is an arm of the Women's Health Initiative (WHIMS) looking at memory [85] and the Women's International Study of long Duration Oestrogen after the Menopause (WISDOM). [86] These studies are due to report their findings in 2006 and 2010.

Estrogen Therapy and Cognition in Women with Alzheimer's disease

There is a large variability in the invariable decline of cognitive function with age, ranging from "successful" aging to dementia. The factors contributing to the amount of this decline are many and have not all been delineated. Since estrogens appear to have a positive effect on many aspects of the structure and function of the brain that are altered by Alzheimer's disease, could therapy with estrogens decrease the decline or actually improve cognitive function in women with dementia?

A group from the Cochrane Collaboration recently reviewed all double-blind randomized controlled trials assessing the effect of HRT on cognitive function in postmenopausal women with Alzheimer's disease or other types of dementia. [87] They found the results of seven such trials in the literature, but only five had enough information to be included in the analysis. [88, 89, 90, 91, 92] The five trials included 246 women with dementia at baseline, with from 14 to 120 women participating in each trial. The mean age of the women participating in the trials was 77 years, but ranged from 56 to 91 years. The studies generally did not control for age, education or depression.

The duration of treatment ranged from 8 weeks to 12 months, with an average of 6 months. A variety of treatments were used with the most common being Premarin®, usually with a progestin in women at risk for endometrial hyperplasia. Compliance was generally monitored with pill counts or estrogen levels.

The cognitive tests used to assess function at baseline and during the therapy varied significantly among the studies, as were the components of cognition tested. Although all the studies did not limit their subjects to only those with Alzheimer's disease, the majority of women in the total trials had met the criteria for Alzheimer's rather than other etiologies of dementia.

In the short term, one to two months, there was an overall positive effect on the Folstein Mini-Mental State Exam (MMSE) in women treated with either 0.625 or 1.25 mg. of conjugated equine estrogen. However this effect did not persist at 6 and 12 months and the MMSE only increased by 1 at the early intervals, which is not likely to be clinically significant.

Tests of memory, digit span, language, information processing, concentration, dementia severity, clinical impression of change, and depression scales did not change in women treated with

estrogen. In several individual tests treatment was worse than placebo in its effect on performance. The studies were not large enough to separately assess women with early onset versus late onset dementia, nor were they ably to do subgroup analyses on women with milder cognitive decline, who may be more likely to benefit.

The reviewers concluded that there is currently no evidence to support the use of HRT or ERT for cognitive improvement or maintenance in women with Alzheimer's disease.

A more recent randomized controlled trial evaluated 120 postmenopausal women with Alzheimer's disease who had undergone hysterectomy, so were able to receive unopposed estrogen. They were randomized to receive either conjugated equine estrogen (Premarin®) in doses of either 0.625mg. or 1.25 mg. per day or placebo for 12 months. They measured estradiol levels and did cognitive assessments at baseline and during the study. Estradiol levels correlated with estrogen dose. There were no differences among the groups in cognition at baseline or with therapy. This study confirms the conclusion of the reviewers of the five previous studies.

Conclusion

The early results of the Women's Health Initiative, published in July 2002, demonstrated significant risks of postmenopausal therapy with estrogen and progestin. Subsequently the U.S. Preventive Services Task Force and the Food and Drug Administration have revised their guidelines for the use of postmenopausal estrogen plus progestin to short-term relief of vasomotor or urogenital symptoms or for the prevention of osteoporosis after careful consideration of alternatives. [93, 94] The results of the new Women's Health Initiative report to be published in May seem to support this recommendation for fairly limited use.

Animal and in vitro studies of estrogen's effects on the brain demonstrate that it is biologically plausible that a decline in estrogen levels has a detrimental effect on brain functions that would adversely affect cognition and mood. They also suggest that estrogen could inhibit some of the age-related changes in the brain and those associated with Alzheimer's disease.

If this were true, one would expect clinical studies to show an increased incidence of Alzheimer's disease in women compared to men, improvement in cognitive function in women treated with estrogens, and a decrease in risk or the delay of onset of Alzheimer's disease in postmenopausal women treated with estrogen compared to those who were not.

There are a large number of clinical studies addressing these important research questions. The majority of them are based on epidemiological rather than experimental designs, because of the inherent difficulty of this research. The time is long and the costs are high to conduct randomized controlled trials to study a long-term intervention with estrogen on an outcome, dementia, which usually occurs very late in life. The quality of many of the studies reviewed is uneven and poor and the results are inconsistent.

The incidence of Alzheimer's disease does not seem to be significantly increased in postmenopausal women compared to men. Although there is evidence suggesting that risk increases for women over 80. Even if the incidence is the same for men and women, because the

life expectancy of women is greater than men, there are many more women living with Alzheimer's disease than men.

The results of studies of estrogen's effects on cognition in healthy postmenopausal women are diverse and inconsistent. Most studies show some benefit, but only on selected cognitive tests, an observation that has not consistently been reproduced among studies. Treating women with Alzheimer's disease with estrogens for as long as one year does not appear to provide clinically significant improvement in their function. The most positive apparent clinical effects of estrogen on the brain to date are the results of meta-analyses of studies of the effect of estrogen therapy on the reduction of risk of dementia in women. These studies however are subject to many of the same confounding factors of those reporting cardiac protective effects of estrogens. Further data from randomized controlled trials are required to definitively answer the question of whether estrogens protect postmenopausal women from Alzheimer's disease. These trails are ongoing and results should be available in three to seven years.

In the meantime, we will need to share the currently available information with our patients to assist them in making decisions regarding hormone replacement therapy for themselves. My patient, Ms. B, with osteopenia and a family history of Alzheimer's disease has so far chosen to remain on estrogen replacement therapy. I hope to be able to confirm for her in three to seven years that randomized controlled trials affirm her hope that her estrogen therapy will reduce her risk for Alzheimer's disease.

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