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# Women, Estrogen, Cognition and Alzheimer's Disease

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Converging evidence over almost 2 decades has built a strong case for 17 beta estradiol (estradiol, E2) as protective of the post menopausal female brain. Multiple investigations and meta analysis, including basic science, observational and clinical studies, strongly suggest significant benefits to cognitive function and decreased risk of dementia for women on estradiol, especially with transdermal delivery. Conjugated equine estrogens (CEE), on the other hand, may negatively impact cognitive function, or confer no benefit, and may increase the risk of dementia in women over 65. It is imperative that clinicians be aware of this substantial data so that we can educate our patients, and the general public, about the significant protective benefit of estradiol and offer our patients the best possible options for maintenance of cognitive health.

Women do not arrive at the menopausal transition with equal health status or equal risk of Alzheimer's disease or any other age related disorder. As is always the case, each woman must be considered as unique, and an in depth history, physical exam and laboratory analysis will need to be completed in order to make optimal health recommendations.

## CEE

Conjugated equine estrogen (CEE) derived from the urine of pregnant mares (Premarin® and Prempro®), was approved by the FDA in 1942 and is the primary form of postmenopausal estrogen replacement used in the United States. CEE consists of 50 to 70% estrone and 22 to 32% equilin and 7 or more other poorly characterized estrogens, not found in the human female [1]. Prior to menopause the major estrogen is ovarian produced estradiol, a very potent estrogen, with a high density of receptors in the brain. More recently some clinicians and their patients are shifting to the use of topical estradiol, and many products are now available including estradiol patches, gels and creams. The advantages of this form of estrogen compared to oral equine estrogens are well demonstrated but seldom discussed clearly in the public forum. This will be addressed after a brief review of the epidemiology of Alzheimer's disease.

## Alzheimer's Disease

A large upsurge in Alzheimer's disease (AD) is expected with the continuing demographic shift to a much more elderly population. Incidence rates for AD are predicted to increase from 4.5 million in 2000 to 13.2 million in 2050 as baby boomers age[2]. Female gender is significantly related to increased incidence of AD and women are at greater risk of

developing Alzheimer's with an estimated odds ratio of 1.56 [3]. Women currently make up 68% of those with Alzheimer's disease and that group is estimated to be between 5 to 10 % of the total current population of the United States [4].

Epidemiologic studies estimate that if it were possible to increase cognitive reserve by 5%, that effect would decrease Alzheimer's Disease by one third [5]. Interventions that diminish AD incidence in women in a substantial way would clearly result in significant quality of life enhancement and have enormously beneficial social and economic impact.

There is increasing evidence that the pathology of Alzheimer's starts decades before the onset of the clinical symptoms. Once the symptoms of dementia appear, significant neuronal loss has already occurred and disease progression is inevitable. The time for early detection and intervention is the beginning of the asymptomatic period of neurologic damage, rather than years later at the onset of symptomatic dementia. Though research has not identified exactly when brain deterioration begins, there is compelling evidence that the steep drop in estrogen levels during the menopausal transition is closely linked to an increased risk of cognitive decline and subsequent dementia in women [6,7]. Thus beginning estradiol during the menopausal transition is likely to delay the onset of dementia, and may prevent Alzheimer's Disease in many women.

### **Basic science weighs in**

In basic science research, animal and in vitro studies demonstrate multiple mechanisms for beneficial estrogen action in the brain. Estrogens have been found to be associated with the maintenance and protection of brain structures, hence it is biologically plausible that maintaining high levels of estrogens in postmenopausal women could be protective against cognitive decline. Research, as detailed below, supports the rationale for these positive effects and provides insight into the mechanisms of estradiol in the brain.

Estrogen receptors (ER) are found in selective areas of the brain, including the hippocampal areas, amygdala, basal forebrain, pituitary, and hypothalamus. The hippocampal and amygdala areas, along with the basal forebrain, which are strongly associated with memory and mood are also areas selectively impacted by neurodegeneration in AD [8-12]. Estrogen increases the density of pyramidal hippocampal neurons, and increases synaptic plasticity in the hippocampus via activation of estrogen receptors [13-15].

Cumulative evidence supports a facilitative role for estrogen on the major neurotransmitter systems in the brain [16,17]. Neurotransmitters influenced by estrogen include acetylcholine, serotonin, dopamine and norepinephrine, and all of these are involved in the cognitive functions impacted in AD [18]. The cholinergic system is involved in attention, learning and memory. The primary site for the cholinergic system is the basal forebrain, an area with early pathologic changes in AD. Basic science demonstrates that estrogen enhances the action of the cholinergic system [19-25]. Therefore, the sharp fall in estrogen at the time of menopause could contribute to a decline in the cholinergic system and result in cognitive loss and predispose to AD. Estrogen has favorably impacted brain dopamine, norepinephrine, and serotonin activity in multiple studies [26-30].

In other research estradiol protected the brain from injury, including stroke, [31,32] lipid peroxidation and oxidative damage [33] and beta amyloid toxicity [34,35]. Beta amyloid (AB) plaque deposition is one of the hallmarks of AD. Many animal model studies suggest that estrogen reduces AB levels and estrogen deficiency accelerates beta amyloid plaque formation [36]. Studies also show that estrogen increases clearance of insoluble AB from CSF.[34,37]. Estrogen has been shown to reduce inflammatory response to AB [37] and to protect against AB mediated toxicity [34,35,38]. Given this widely acknowledged relationship between estrogen, AB and AD the likelihood is high that the sharp drop in estrogen at menopause contributes to detrimental cognitive effects and increases the risk of AD.

Estrogen demonstrates beneficial impact on cerebral blood flow. Estrogen receptors are found in both cerebrovascular smooth muscle and endothelial layer cerebral cells. Increased dilation of vessels and improved cerebral flow appears to be mediated by estradiol's effect on vasoregulators such as nitric oxide and prostanoids [37,38]. Significantly, estrogen effects on nitric oxide production occur in the hippocampus and forebrain [39,40], areas of degeneration in AD. Cerebral blood flow is favorably impacted by estrogens ability to increase mitochondrial energy production [41-44], Reactive oxygen species and peroxides, the harmful byproducts of mitochondrial energy production are less damaging in the presence of estrogen.[42]. The neuroprotective actions of E2 appear to be mediated through both the classic genomic [45,46], and more rapid cell membrane receptor mechanisms [47,48,49] and are expressed via both estrogen receptor alpha (ER $\alpha$ ) and estrogen receptor beta (ER $\beta$ ) subtypes [50]. This evidence further strengthens the plausibility of the beneficial and protective impact of estrogen on cognition and AD.

## **CEE versus Estradiol**

Although the basic science studies make a very strong case for the advantages of estrogen replacement at menopause the results of observational and clinical studies of estrogen and progestin therapy in postmenopausal women are more mixed. Basic science extensively characterized the neurological effects of estradiol and almost no studies of the effects of estrone or CEE have been performed. The differing neurobiology of estradiol versus CEE may be a major factor in these conflicting results. Sixteen observational studies have been published over the last 20 years to evaluate the effect of post menopausal hormone therapy on the risk of dementia. The majority of these studies evaluated the impact of conjugated equine estrogens (Premarin® and Prempro®), the hormone replacement most used in the United States, however some estradiol studies were included. Four meta-analyses from the above observational studies concluded that there was a significant reduction in the risk of developing dementia in the group of women who currently used or had used hormone therapy [51-54]. Importantly, the above meta studies concluded that the neuroprotective effect from estradiol treatment was more substantial than that with CEE, and that the addition of medroxyprogesterone (Provera) as the progestin was detrimental [51-54].

In the excellent 2009 review article, the University of Wisconsin group, summarize the clinical studies of the last 17 years, comparing the cognitive impact of estradiol versus CEE in menopausal women [55]. 15 of 20 estradiol studies show cognitive benefit, 5 of 20 show no benefit. None show harm. Only 6 of 14 CEE studies show cognitive benefit, 8 of 14 show no benefit. However 2 of the 8 “no benefit” CEE studies show harmful cognitive effects. Both harmful results were from the Women’s Health Initiative Memory Study (WHIMS) [56,57], a sub-study of the WHI, and we will review the important differences in these studies below. It is important to point out that the majority, but not all, of the Estradiol studies used transdermal estradiol and topical application of estradiol may improve clinical outcomes whereas the CEE was always administered orally. Hence age, route of delivery, together with type of estrogen, progestin use and progestin type, are probably all critical pieces of the puzzle. The overwhelming weight of evidence in the clinical trials supports improved cognition and lower AD risk with estradiol use, but is inconclusive regarding CEE use.

## **MPA**

The WHIMS, a sub-study group, of the very influential 2002 Women’s Health Initiative Study (WHI), found an increased risk for mild cognitive impairment and dementia in postmenopausal women 65 years and older, treated with equine estrogens and the synthetic progestin, medroxyprogesterone [58-61]. An updated report in 2009 by Resnick et al., of the WHIMS CEE alone (no medroxyprogesterone, MPA) arm of the study showed no harmful effect of verbal memory over time and no increased risk of AD. This implicates the addition of MPA as a causal factor in the deleterious results [62,63]. A possible mechanism for this effect is elucidated in a 2011 study showing medroxyprogesterone acetate antagonizes estrogen up-regulation of brain mitochondrial function [64]. Space does not allow a full discussion of progesterone and progestin impact on neurocognition.

A new study from Stanford highlights important differences between estradiol and CEE on cognitive effects [65]. 68 women, aged 49 to 68 with at least one risk factor for AD, on either estradiol or CEE were included in the study. Each woman underwent a very extensive battery of neuropsychological testing, to differentiate as precisely as possible their cognitive abilities. Women receiving estradiol showed significantly better verbal memory performance compared with women on CEE regardless of age, years of education, IQ scores, risk factors for AD, including APOE4, duration of endogenous and exogenous estrogen exposure, or concurrent progesterone use. After controlling for menopause -related variables such as length of endogenous and exogenous estrogen exposure, results also showed significantly better attention, working memory, processing speed and executive function performance among women receiving estradiol. Declines in verbal memory are thought to be one of the early signs of Alzheimer’s Disease [66,67], particularly when delayed word list and story recall measures are combined as in this important study.

What accounts for the difference between estradiol studies and CEE in clinical studies? CEE contains primarily estrone. As previously noted human brain tissue is rich in estradiol receptors, and the most abundant premenopausal estrogen is estradiol. At menopause, however, levels of estradiol decrease precipitously to approximately 1/10th of those found in menstruating women,

whereas levels of estrone decline to a lesser extent [68]. In order to enhance the estradiol cognitive receptor actions in brain tissue, and to more closely mimic the premenopausal brain state, estradiol appears the better choice.

### **Transdermal Estradiol**

Research suggests transdermal estradiol offers advantages over oral estradiol or CEE. The transdermal delivery avoids the deleterious impact of hepatic 1<sup>st</sup> pass, including increased estrone to estradiol level, lower estradiol level, and increased inflammatory and procoagulation markers. Women on oral estrogen, either CEE or estradiol, increase their CRP levels while women on topical estradiol do not [69-71]. Elevated CRP is also associated with increased risk of Alzheimer's disease and cerebrovascular dementia, which often co-occur [72,73]. Topical estradiol lowers fibrinogen, a coagulation marker and oral estradiol does not [70]. Oral Estradiol raises procoagulation effects by increasing prothrombin activation peptide, increasing F1 and F2, decreasing activity of antithrombin and lowering plasminogen, while transdermal estradiol has no procoagulation effects [74]. In a UK observational study with over 15,700 cases and 59,900 controls, there was no increased stroke risk with transdermal E2 treatment at a dose of 50 micrograms per day or less as there was with oral estrogen [75]. Higher plasma levels of estradiol are associated with transdermal estradiol use [76], and higher levels of estradiol correlate with better neurological health in postmenopausal women [77]. Gleason found better verbal memory in middle aged women with a parental history of AD (carriers of APOE4 were limited) who were using opposed topical estradiol compared to those using opposed CEE use or who had never used hormone therapy. The no hormone group also outperformed the CEE group [78]. Joffe demonstrated a significant positive brain effect in their fMRI study of 35 recently post menopausal women after topical E2 compared with 35 controls using topical placebo. Measures of fMRI activation showed increases in the frontal cortex during tests of verbal and spatial memory after topical estradiol use but not after placebo. Joffe concluded that working memory and executive function, residing in frontal cortex, were improved with transdermal estradiol [79].

### **Healthy cell bias**

Some researchers critical of WHIMS have argued that it was not a prevention study because the participants, all 65 years or older, were beyond the age of primary prevention [80]. Critics argue that a study with women at the onset of menopause may have yielded more positive results; and from this has evolved the "healthy neuron bias" theory. Because of the unexpected negative effects of combined premarin® and provera® on cognition and AD risk in women over 65 many researchers have taken a critical look at the study. Healthy neuron proponents suggest that early menopausal women have healthy neurons, and when exposed to estrogen, maintenance and protection of the brain cells results. In older women, further from menopause, neuronal architecture has undergone degenerative changes, and when exposed to estrogen at this time, a further degenerative effect ensues [80,81]. Several studies show increased hippocampal volume in postmenopausal women only if they began estrogen within a limited window of time, close to cessation of menses [82,83]. Short term treatment with higher levels of estradiol (1 mg per day, then 2 mg per day) compared to placebo partially blocked an anticholinergic drug-induced challenge to verbal memory in younger women, aged 50–62, but further impaired verbal memory with this drug in older women, aged 70–81 [84]. Basic science suggest mechanisms by which the response to estrogen is less favorable if treatment is initiated following long term ovarian hormone deprivation [85].

### **Topical estradiol for AD?**

While the critical timing theory of early initiation of estrogen has strong support in the literature, and basic science tells us early estrogen replacement has more neurocognitive benefit, some studies suggest that estradiol may continue to have benefit even in older women diagnosed with AD. In 2 randomized trials Asthana et al. find improvement in cognition in women with dementia with a 0.1 transdermal estradiol patch [86]. A second placebo controlled, double blind study shows positive cognitive response to transdermal estradiol in women with Alzheimer's disease [87]. The type of estrogen, estradiol, and the topical route of administration, as opposed to the oral route, may be critical factors in the beneficial dementia results above.

### **Symptomatic or Not**

In their 2001 meta analysis Le Blanc [53] made note of differences in results in women who were symptomatic compared with those who were not. Women with vasomotor symptoms, that is, hot flashes and/or night sweats, treated with estrogen had

significant improvement in verbal memory, vigilance, reasoning and motor speed. Women who were asymptomatic had no benefit. Possibly postmenopausal women without these or other low estrogen symptoms, have higher estradiol levels therefore they accrue no additional benefit from replacement of estrogen. A 2012 study finds better semantic memory in midlife postmenopausal women with higher total and free endogenous estradiol levels [88]. No association was found with estrone levels [88]. In the KEEPS study, (Kronos Early Estrogen Prevention Study) [89], currently in progress, the initial evaluation found a significant association between higher estradiol levels and improved performance on the mini-mental status exam. This supports the importance of a careful evaluation by the clinician to assess the need for estrogen replacement including estradiol levels.

### **What now?**

More studies will undoubtedly be needed in this area as the population of aging women continues to increase. More and more women are living longer and unfortunately the number with Alzheimer's increases with each year of age [90,91]. The KEEPS and KEEPS C/A (KEEPS cognitive and affective study) are large scale longitudinal studies with transdermal estradiol as one of the major hormone variables. KEEPS is due to report out in 2013. Potentially, these results will help answer many pressing questions on the risks and benefits of hormone replacement.

There is no formulaic protocol for assessing the need for estradiol replacement. In my 17 years of helping women make this decision the most frequent concerns at the time of menopause are vasomotor symptoms, especially if they result in loss of sleep, mood issues and cognitive loss including word finding, learning and memory. In my experience, if a woman's serum estradiol level is below 25pg/ml, and they are often below 10pg/ml, the above symptoms will improve with topical estradiol, however dosage must be individualized.

### **Conclusion**

Because many women will live half of their life after menopause, it is crucial that decisions made at the time of menopause, with cognitive and other long term health consequences, are carefully considered. A menopausal woman, with the guidance of her health care provider, has a complex decision to make regarding hormone replacement. The risk of osteoporosis, cardiovascular disease, breast, uterine and ovarian cancer, along with dementia risk must be weighed. Here only the cognitive and dementia related issues are addressed due to limited space. For clinicians, consideration of all variables is a time consuming process and each woman needs an in depth consultation taking into account her family history, personal medical history, risk factors, symptoms and concerns. A laboratory analysis will help guide this decision. A diet high in vegetables, adequate in high quality protein and fat, and low in sugar, trans-fats, alcohol and processed foods is advantageous. Evidence suggests that life style factors such as physical activity, lower exposure to stress, and toxin avoidance improve outcomes.

Even with the ideal consultation with a well informed practitioner, there are not always clear cut answers because the data is inconclusive. However, the preponderance of evidence supports the beneficial effects of transdermal estradiol on cognition and the protective effects regarding Alzheimer's disease. We await the KEEPS, KEEPS C/A, and other studies to help us understand how to optimize cognitive and other health factors for women both at the time of the menopausal transition and throughout the many years that follow.