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COGNITIVE CHANGES WITH REPRODUCTIVE AGING, PERIMENOPAUSE AND MENOPAUSE

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INTRODUCTION

Cognitive decline and dementia are a growing public health problem, with the worldwide prevalence of dementia expected to triple by the year 2050¹. Evidence suggests that midlife may be a critical period in the natural course of dementia². For women, understanding the effects of in reproductive aging on cognition in midlife and beyond remains a topic of great interest, particularly given that estrogens are involved in a number of cellular pathways that underlie brain function³. Of particular interest is whether the perimenopause is a therapeutic window in which hormone therapy may prevent cognitive decline. To contextualize this emerging evidence, the following chapter summarizes mechanisms that may link hormones to cognitive function, briefly discusses evidence from observational studies of the longitudinal changes in cognition occurring over the menopause transition, and concludes with discussions of the emerging evidence from clinical trials of estrogen therapy administered around menopause and remaining gaps in our understanding of the cognitive effects of menopausal hormone therapy.

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1. MECHANISMS LINKING ESTROGEN TO NEURAL AND COGNITIVE PROCESSES

Estrogen receptors are plentiful in areas of the brain controlling memory and executive cognitive function⁴. Estrogen receptor isoforms are differentially expressed within the brain^{5,6}, respond to estradiol in unique ways^{7,8}, and initiate numerous intra- and extracellular actions in both neural and peripheral substrates⁹. For instance, estrogen receptor isoform, ER β , is expressed primarily in the cerebral cortex and hippocampus, while ER α signaling occurs largely in magnocellular cholinergic neurons of the basal forebrain^{5,10}. In aging, memory function is affected by shifts in the ratio between ER α and ER β and subsequent modifications in estrogen-regulated gene transcription^{11,12}.

The means through which estrogens elicit brain effects are varied, and include alterations in neurotransmission as well as neurotrophic and neuroprotective actions. Estradiol has been shown to enhance cell growth and differentiation through regulation of genomic processing and growth factor subtypes^{13,14}. Particularly relevant to memory formation, estradiol promotes cell growth and survival through trophic mechanisms of basal forebrain and hippocampal neurons, regions involved in memory and executive cognitive function. Estrogens have been found to elevate dendritic spine density and synaptogenesis in the Cornu Ammonis 1 (CA1) field of the hippocampus^{15,16} and prefrontal cortex^{17,18}. Estradiol is also associated with an increase in neurogenesis of the dentate gyrus¹⁹. Although both progesterone and estradiol have been shown to increase excitatory synapses and dendritic spine density²⁰, only estrogens enhance CA1 long-term potentiation, a critical factor in episodic memory formation²¹.

Further, estradiol has been shown to attenuate neurodegenerative processes associated with Alzheimer's disease (AD), the most common type of dementia²². In particular, estradiol has been shown to attenuate tau hyperphosphorylation²³ and deposition of amyloid β ²⁴, and has also been shown to reduce the inflammatory sequelae of amyloid β ²⁵.

Estrogen and Brain Metabolism

Estradiol may also effect cognitive processes by maintaining glycolytic metabolism²⁶, an important indicator of healthy aging. Estrogenic signaling promotes glycolytic over ketogenic metabolism by acting as a critical regulator of the glycolytic pathway. Moreover, estrogens maintain healthy mitochondrial bioenergetics²⁷ through regulation of Ca²⁺ homeostasis, protection against free radical proliferation, trafficking of cholesterol, and clearance of amyloid β ²⁷. Cellular accumulation of amyloid β is often hastened by reduced mitochondrial bioenergetics followed by subsequent hypometabolism²⁷. Importantly, reinstating estrogenic systems does not necessarily reverse glycolytic dysfunction. Multiple studies now point to the presence of a critical period for the introduction of exogenous estrogens and a healthy cell bias. Specifically, exogenous estrogen may support glycolytic metabolism in healthy neuronal cells or exacerbate pathological burden in the setting of neurodegeneration^{28,29,3}.

In addition to the effects of exogenous estrogen, menopause-associated shifts in endogenous estrogens may cause glycolytic dysregulation. For example, a drastic reduction in estrogen acutely disables the cell's recruitment and utilization of glucose for aerobic glycolysis; thus, shifting metabolism to a ketogenic phenotype. The ketogenic metabolic process is far less efficient and requires recruitment of ketone bodies from peripheral organs while concurrently initiating the fatty acid oxidation (FAO) pathway. The FAO pathway breaks down local myelin sheath and is increasingly activated with the depletion of ketone body reserves²⁹. The shift to ketogenesis triggers increased accumulation of mitochondrial amyloid β and oxidative stress³⁰, as well as progressive hypometabolism and white matter changes in areas implicated in AD pathogenesis^{31,32}. Further, the impact of estrogen on insulin-regulating mechanisms, such as glucose transporter isoforms³³, Insulin Growth Factor-1 (IGF-1), and insulin-degrading enzyme (IDE), is likely critical in maintaining insulin and glucose homeostasis and promoting healthy metabolism in neural substrates, particularly in regions that are vulnerable to AD pathology, such as the hippocampus³⁴.

Estrogenic neuroprotection

Estradiol exhibits neuroprotection in models of oxidative stress, excitatory neurotoxicity, ischemia, and apoptosis^{35,36,37}. As previously noted, estradiol is critical to Ca^{2+} homeostasis and initiates downstream signaling that promotes neuroprotection through long-term and acute reactions.

Estradiol has also been shown to reduce oxidative stress, where disruption of the electron transporter chain can trigger impaired ATP synthesis and an elevation of reactive oxygen species. The culmination of such dysregulation could, thus, cause cell damage as well as neurodegenerative processes^{38,39}. Relevant to AD and related dementias, estradiol appears to reduce amyloid burden by increasing antioxidants, such as glutaredoxin, peroxiredoxin-V, and MnSOD^{40,26}.

In summary, estrogens are influential in various neural cellular systems, suggesting mechanisms through which the menopausal decline in estrogen could interfere with cognitive functioning. To examine this hypothesized effect, the following section reviews findings from longitudinal observational studies of cognition across the menopause transition.

2. LONGITUDINAL DATA REGARDING THE EFFECT OF MENOPAUSAL HORMONE CHANGES ON COGNITIVE FUNCTION:

Although memory complaints are common during menopause⁴¹, longitudinal data regarding the impact of menopausal hormone changes on cognitive function are limited. Most longitudinal studies of cognitive aging have focused on individuals over the age of 65; few have examined both hormone trajectories and cognitive performance across the menopausal transition and thus there is little data regarding the relative contributions of chronologic and reproductive aging to cognitive function. Only two longitudinal cohort studies have reported longitudinal cognitive data for women transitioning through menopause, the Kinmen Women-Health Investigation (KIWI)⁴² and the Study of Women's Health Across the Nation

(SWAN)⁴³. As reviewed by Greendale et al (2011)⁴⁴, both studies observed decrements in cognitive function specifically in perimenopause. The effects were subtle, evidenced by reduced “learning effects” over repeated cognitive assessments rather than by a decline in cognitive performance. KIWI was limited to only 18 months of follow-up of initially premenopausal women⁴². In SWAN, pre- and postmenopausal women showed improvements over four annual assessments, while women who were late-perimenopausal did not⁴³.

Whether trajectories of menopausal hormones predict later cognitive decline remains an unanswered question. This question is currently under investigation in the ongoing SWAN study, which is the only large cohort to have characterized hormone changes and cognition over the entire menopause transition. The multi-site study began in 1996, enrolling 3,302 women at seven clinical centers across the United States⁴⁵. Women were initially 42–52 years of age, and were pre- or early perimenopausal. To date, over 20 years of follow up have documented hormone trajectories across the menopausal transition and have identified heterogeneity in the rates and patterns of change across women⁴⁶. Cognitive assessments began at the fourth annual SWAN visit and are ongoing. These data will provide new information regarding both short- and long-term cognitive effects of the endogenous hormone changes occurring during the menopause.

In the following sections, we examine efforts to mitigate the cognitive and physiologic changes in menopause, reviewing data from intervention trials and attempts to address gaps in our understanding of the cognitive effects of menopausal hormone therapy.

3. HORMONE THERAPY TRIALS AND EMERGING SUPPORT FOR THE CRITICAL WINDOW HYPOTHESIS

While early observational and basic science studies revealed promising cognitive and neuroprotective outcomes from hormone therapy, large clinical trials such as the Women’s Health Initiative (WHI) and Women’s Health Initiative Memory Study (WHIMS), exposed significant risks, including cognitive risks, associated with treatment^{47,48}. Over time, findings revealed that age of initiation of hormone therapy may be primary contributing factor to discrepancies between studies reflecting treatment benefits in cognition from those that suggested harm. That is, a critical window of treatment initiation is a key determinant in positive versus deleterious outcomes.

WHI Hormone and Cognition Therapy Trials:

Given the positive effects seen in both basic science and observational epidemiologic studies, the WHI/WHIMS findings of elevated risk for cognitive impairment and dementia were stunning. In the massive WHI trial, 161,809 women aged 50–79 years participated in various clinical trials between 1993 and 1998. In the hormone treatment trial, over 27,000 women were administered a combination of oral estrogen (conjugated equine estrogen, CEE) and progesterone (medroxyprogesterone acetate, MPA), CEE alone (if hysterectomized), or placebo over a period of 5.2 years, at which time the study was discontinued due to adverse outcomes, particularly increased incidence of invasive breast

cancer in CEE + MPA group, and elevated risk of stroke and blood clots in the CEE + MPA and CEE-alone trials⁴⁷.

The WHIMS included 4,532 postmenopausal women in the WHI hormone therapy trial who were age 65 at study baseline and free of clinical dementia. WHIMS women completed cognitive assessments at annual in-clinic assessments and via semiannual mailed questionnaires. Findings from this sub-study revealed that CEE + MPA treatment offered minimal protection against cognitive decrements, and actually increased the likelihood of dementia⁴⁸. A similar but statistically insignificant finding was evident in the CEE-alone group. Critically, all participants were several years beyond the menopausal transition at WHIMS baseline⁴⁹.

The cognitive effects noted in the seminal WHI and WHIMS studies were supported by imaging findings. In the WHIMS-MRI study, former hormone therapy users exhibited decreased hippocampal, frontal, and total brain volumes, although there was no evidence to suggest between-group differences in ischemic burden⁵⁰. Importantly, at study baseline, lower global cognition⁵¹ and increased white matter lesion burden⁵² were found to be significant moderators of structural change, suggesting that individuals with poorer neurologic health at treatment outset were likely to experience deleterious outcomes⁵³.

The WHI ancillary Study of Cognitive Aging (WHISCA) assessed long-term cognitive effects following hormone therapy. The study included a sample of 2,305 postmenopausal WHIMS participants who completed a comprehensive cognitive battery following the cessation of study treatment with hormone therapy or placebo. Those who received CEE-alone showed neither beneficial nor deleterious cognitive effects⁵⁴, and those who received CEE + MPA demonstrated decreased verbal learning and memory during a 4–5 year span⁵⁵. Neither group experienced significant effects on affective symptoms^{54,55}.

Emerging Support for the Critical Window Hypothesis:

In contrast, multiple previous studies revealed benefits of hormone therapy use when treatment commenced proximal to the menopause transition. For example, 727 women who initiated hormone therapy around menopause ($n = 81$) performed better than untreated women on verbal fluency and memory tasks⁵⁶. Treated women exhibited improved verbal memory years later versus untreated women, who generally demonstrated declines in performance at follow-up⁵⁶. These results were consistent with those of women receiving hormone therapy shortly following oophorectomy⁵⁷. Moreover, Bagger et al. (2005)⁵⁸ indicated that women receiving hormone therapy in a randomized trial over 2–3 years around the menopause transition showed decreased incidence of impaired cognition by 64% in follow-up testing occurring between 5 and 15 years later.

Similarly, 428 women who received hormone therapy before age 56 outperformed those who were treated after age 56 on verbal fluency, psychomotor speed, and global cognition measures (i.e., Mini-Mental Status Examination)⁵⁹ in a cross-sectional study. By contrast, the group of women in this study who received hormone therapy after 56 years of age exhibited worse global cognition than the group who never received treatment⁵⁹. Consistent with these findings, a study of women with a mean of 48.8 at treatment outset and duration

of 5.2 years outperformed women who never received treatment on mental flexibility and global cognition tasks, as well as those women whose treatment duration was 14.30 years on average⁶⁰. An observational study (the Cache County cohort) revealed a similar pattern of findings, where former voluntary hormone therapy users, who initiated treatment shortly following menopause demonstrated lower risk of developing AD than current users who were older⁶¹.

Supporting this hypothesized timing-dependent pattern, a secondary analysis of the WHIMS data (the Women's Health Initiative Memory Study-Young; WHIMS-Y) surveyed data from 1,326 participants ages 50 to 55 from the WHI CEE-alone trials, in which treatment commenced shortly following menopause. Results from Espeland et al. (2013)⁶² indicated that women who received hormone therapy exhibited no declines or improvements in cognition in the years after treatment discontinuation. In contrast, women aged 65–79 and receiving treatment showed persisting declines in working memory, executive functioning, and global cognition regardless of hysterectomy status or drug formulation.

In total, these studies supported the idea that hormone therapy treatment can promote both deleterious or beneficial effects on cognitive health⁹, depending on the timing of administration. Specifically, administration of exogenous hormones must occur in a narrow window of time around the menopausal transition in order to be useful in treating symptoms of estrogen depletion^{63,28,64,65}. The importance of timing is secondary to the health of underlying cells and substrates (i.e., the healthy cell bias and intact mitochondrial bioenergetics), and as noted, women in the WHIMS trials were 65+ years of age. Imaging data reinforce this timing hypothesis^{66,67}.

In addition to the evidence elevating the importance of timing of estrogen administration, a number of other factors appear to contribute to disparate results in hormone therapy research, including heterogeneous effects of varied routes of administration, hormone formulations, and treatment schedules (i.e., continuous versus pulsed administration). These factors have been shown to influence treatment outcomes regardless of treatment timing^{68,69}. The WHIMS trial, for instance, used a combination of synthetic progestin (MPA) and estrogen. Nilsen & Brinton (2003)⁷⁰ argued that MPA might oppose the neuroprotective effects of estradiol *in vitro* in hippocampal neurons, specifically highlighting findings of adverse effects of CEE + MPA on verbal memory performance. Women having been treated with MPA formulations exhibited declines in verbal memory performance even when therapy was started soon after the menopause (mean age = 52)⁶⁹.

Additional variables likely contributing to disparate outcomes in hormone therapy research include, but are not limited to, factors in reproductive history, such as age at menarche, advanced age of last pregnancy, increased duration of reproductive period, and historical oral contraceptive use, each being positively correlated with cognition in advancing age (ELITE and WISH trials)⁷¹.

Observation of the healthy user bias and critical window hypothesis have driven efforts to inform who might benefit from hormone therapy, and for whom treatment would be contraindicated, thus spurring further concentration on bioenergetic functioning. For

example in 2015, Espeland et al.⁷² re-evaluated WHIMS data and noted outcomes varied depending on the presence or absence of diabetes. Women who had type II diabetes randomized to the CEE group were at higher risk of developing cognitive impairment and probable dementia versus age-matched peers without diabetes, and those with diabetes who were randomized to placebo. Women with diabetes in the CEE-alone group were at further elevated risk for cognitive impairment and probable dementia. These findings were not associated to prior cognitive functioning, history of cardiovascular disease, obesity status, pre-diabetes, or hypertension, and results were sustained 10 years following termination. Espeland et al. (2015)⁷² argued that individuals metabolically reliant on ketogenesis would experience exacerbated metabolic dysregulation with the re-introduction of estrogens. That is, exogenous administration would likely suppress existing ketogenic processes before glycolytic metabolism could be restored, and therefore escalate bioenergetic dysregulation. Women treated with CEE + MPA presumably did not experience compounded cognitive deficits, as the MPA opposed estrogen's actions on ketogenic metabolism.

4. ADDRESSING GAPS IN UNDERSTANDING FOLLOWING WHI TRIALS

Several recent studies have aimed to explain discrepant findings around the cognitive risks and benefits of hormone therapy. The following such studies were designed not only to address conflicting outcomes, but to resolve remaining controversies in the literature. The Kronos Early Estrogen Prevention Study-Cognitive and Affective Study (KEEPS-Cog) study, an ancillary study of the large, randomized controlled KEEPS trial (primarily focused on cardiovascular outcomes of hormone therapy), was designed to investigate alterations in cognition and mood following hormone treatment in early menopause⁷³. The KEEPS-Cog study revealed findings that were consistent with those of the WHIMS-Y trial⁷⁴. A total of 662 early menopausal women treated with transdermal estradiol + micronized progesterone [mP], low-dose CEE + mP, or placebo exhibited neither significant increases nor decreases in performance on measures of attention or memory compared to placebo. However, participants who received oral CEE showed reduced depression and anxiety symptoms over the course of four years. All women were within three years of their final menstrual period and were neither hysterectomized nor oophorectomized. Further, KEEPS-Cog researchers utilized a transdermal estradiol formulation as well as a lower CEE dose than that of the WHIMS. Finally, estrogen was opposed with a micronized progestin in a pulsed fashion to better approximate cyclic exposure and naturally occurring progesterone, while the WHIMS trial used a continuous MPA administration⁷⁴. These key differences in study design and enrollment likely contributed to the discrepant findings between the KEEPS-Cog and the WHIMS. The KEEPS participants will be re-evaluated approximately a decade after randomization in the KEEPS-Continuation Study, which will investigate long-term cognitive and mood outcomes of menopausal HT, as well as neuroimaging correlates of brain health and AD related biomarkers.

Last, the Early versus Late Intervention Trial with Estradiol (ELITE), another large randomized control trial, included both women who were within six years of menopause and those who were ten or more years outside of menopause, with the intent to further examine the window of opportunity hypothesis⁷⁵. In this trial, women with recent or remote (>10 years after FMP) menopausal transition status received oral estradiol for up to 5 years. Like

KEEPS-Cog and the WHIMS-Y studies, ELITE findings revealed no cognitive harm or benefit for younger women. In contrast to WHIMS, the ELITE data suggested no harm or benefit on cognition for the women randomized to HT 10 years after menopause.

5. CONCLUSIONS: IMPLICATIONS FOR CLINICAL PRACTICE

Overall, cognitive complaints are common among middle aged women, and analyses suggest that women experience subtle cognitive changes during the menopausal transition that are not explained by confounding variables, such as vasomotor symptoms, mood, sleep disturbance, etc⁷⁶. Current data suggest that these changes may be transient, and whether they predict continued cognitive decline at older ages is currently being explored. Whether the patterns and rates of change in hormones over the menopause transition predict changes in cognitive function remains a critical question.

The conclusion that menopausal hormone therapy will not induce cognitive harm is supported by the accumulation of recent and large controlled trials, specifically when treatment is initiated at or near the menopausal transition and women are characterized as metabolically healthy. However, further characterization is needed to discern those who will benefit from those who will not, and those women for whom treatment is contraindicated entirely. Ideally, a woman seeking to manage symptoms occurring during the menopausal transition would have specific and personalized guidance, such that she need not carry undue concerns, or be unaware of real risks.

Supporting the need for personalizing medical consultation, a recent KEEPS publication specifically examined the pharmacogenomic interactions of hormone therapy (i.e., transdermal 17 β -estradiol [50 μ g/day], oral CEE [0.45mg/day], each combined with progesterone [200mg/day], or placebo and 764 candidate single nucleotide polymorphisms [SNP]). Outcomes included carotid artery intima-medial thickness (CIMT) and coronary artery calcification (CAC) in 403 women 4 years after randomization in the KEEPS. Miller et al. (2016)⁷⁷ described a pharmacogenomic interaction in the CIMT innate immunity pathway such that genetic variants appeared to interact with hormone therapy status to affect cardiovascular phenotypes. Other suggested genetic variations that may interact with hormone therapy include non-innate immunity pathway factors such as SNPs involved in the coagulation cascade, changes in beta adrenergic receptors following menopause, and triglyceride, fasting blood glucose, and diastolic blood pressure status. Certainly, the interaction of hormones and conventional cardiovascular risk factors such as hypercholesterolemia, hypertension, and type II diabetes would be important to consider, as these can exacerbate calcium accumulation in coronary arteries. In total, further research is necessary to elucidate how estrogen receptor polymorphisms contribute to cardiovascular disease and the implications of pharmacogenomic interaction with hormone therapy⁷⁷.

Aside from pharmacogenomics interactions, many more general questions remain unanswered regarding hormone therapy use at menopause. For example, what time period of use is optimal for cognitive health while minimizing risks of cancers and cardiovascular morbidities? Findings to date support the use of brief, low-dose hormone therapy treatment^{78,79,80,81}; however, the precise definition of *brief* remains uncertain.

The KEEPS represented one of the first attempts to partially approximate the premenopausal status with menopausal HT. The trial used 4 years of a native estrogen, 17 β -estradiol, comparing this form of HT to the commonly prescribed oral CEE (0.45mg/day) and placebo. The KEEPS used a pulsed-dose of a natural hormonal progesterone analogue [micronized progesterin] in contrast to continuous, synthetic progesterone (MPA). To our knowledge, no studies have attempted to fully mimic the premenopausal hormone cycles with menopausal HT, effectively delaying the transition or attenuating the abruptness of change. Data from such a trial would clarify why women's risk for cardiovascular disease shifts upward with menopause⁸², and why women evidence differential risk for AD dementia compared to men^{83,84}.

Altogether, data are still needed guide the healthcare of women entering the menopausal transition. Specifically, data to assist women in making personalized informed decisions regarding management of their menopausal symptoms and the prevention of future adverse health outcomes.

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Key Points

- Estrogens influence neuroprotective and neurotrophic mechanisms underlying various cognitive processes in addition to regulating sexual and reproductive characteristics.
- Longitudinal studies of cognition in the menopausal transition suggest transient, reduced practice effects or encoding over repeated assessment in perimenopause as opposed to declines in performance.
- Although the WHI/WHIMS trials reflected cognitive harm following use of exogenous hormone treatment, a number of confounds in study design have since been identified.
- Large clinical trials, such as KEEPS-Cog and ELITE, have shown neither deleterious nor beneficial cognitive outcomes with hormone therapy when women are metabolically healthy and treatment commences at or shortly after the menopausal transition.
- A number of questions regarding hormone therapy remain, particularly the optimal duration of hormone therapy administration and pharmacogenomic interactions related to treatment.

Synopsis

This chapter reviews the role of endogenous estrogen in neural and cognitive processing, followed by an examination of longitudinal cognitive data captured in various stages of the menopausal transition. The remaining text reviews the contradictory results from major hormone therapy trials to date, evidence for the “timing hypothesis,” and closes with recommendations for future research and for practicing clinicians.

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