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Perimenopause and Cognition

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Introduction: what motivates the study of perimenopause and cognition?

Is the perimenopausal transition detrimental to cognitive function? This is an often-asked question in clinical practice, because self-reported memory problems are common during mid-life[1,2]. The Seattle Midlife Women's Health Study reported that of 230 women aged 33 to 55 years who were interviewed about their perceived cognitive function, 60% noticed an unfavorable memory change "over the past few years"[1]. In this cross-sectional survey, women reported problems with recall of words and numbers, disruptions in everyday behavior (e.g., losing household items), difficulty concentrating, needing to use memory aids and forgetting events (e.g., appointments). Factors that were associated with perceived memory dysfunction were being a worker, job stress and multiple life roles --but not perimenopause transition stage--suggesting that the perceived memory difficulties were predominantly a function of stress and multiple burdens resulting in diminished attention and concentration. The Study of Women's Health Across the Nation (SWAN) also reported a cross-sectional association between self-reported forgetfulness and being perimenopausal[2]. Forgetfulness was common in middle age: in this sample of 12,425 women aged 40–55

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years, unadjusted for sociodemographic factors, 31% of premenopausal, 44% of early or late perimenopausal and 42% of naturally menopausal women endorsed forgetfulness. After adjustment for race/ethnicity, age, education, economic hardship, marital status, parity, body size, health habits and symptoms of anxiety, depression and poor sleep, perimenopausal women were 1.4 times more likely to report forgetfulness than were premenopausal women. Thus, in the SWAN cross-sectional survey, self-reported forgetfulness did appear to be related to perimenopause independently of several relevant characteristics, including stress symptoms.

In addition to the desire to address women's clinical questions, research interest in the relation between perimenopause and cognition is fueled by pre-clinical evidence that estrogens have salutary neurophysiologic effects, leading researchers to postulate that a drop in estrogen (which occurs during perimenopause) would be detrimental to cognition[3,4]. For example, the hippocampus and prefrontal cortex, which serve episodic and working memory, are rich in estrogen receptors[3]. In animal and *in vitro* models, by genomic and non-genomic pathways, estrogens elevate levels of neurotransmitters such as serotonin and acetylcholine, promote neuronal growth and formation of synapses, act as antioxidants and have regulatory effects on calcium homeostasis and second messenger systems[3–7].

Beyond attempting to understand the concurrent effects of perimenopause on cognition, an emerging paradigm is endeavoring to connect biological changes that occur in other systems during the menopause transition with the risk of future cognitive dysfunction. This novel framework proposes that perimenopausal worsening of cardiovascular risk factors may result in cognitive decline and dementia in late life, and therefore conceives of the perimenopause as a potential window of opportunity for targeting modifiable cardiovascular risk factors in an effort to delay or prevent these conditions in the future[8].

In this chapter, we will: detail the theoretical basis underlying why cognitive function may be affected by the perimenopause; review the results of longitudinal studies of measured cognitive performance during the perimenopause; and describe the potential linkages between perimenopausal cardiovascular risk and cognitive function in later life. We will concentrate on data that come directly from the perimenopausal transition stage whenever possible, but in some instances such data are not available. Thus, we will include some preclinical or clinical information based on menopausal animal models or early postmenopausal women when relevant.

Mechanisms underlying the relation between perimenopause and cognition

Changes in sex steroids may have indirect and direct CNS effects

When considering the mechanisms by which the perimenopause might impact cognitive function, it is important to consider both the indirect and direct effects of hormonal changes on the brain. *Indirect effects* are the effects of hormonal changes on brain systems associated with menopausal symptoms such as mood, sleep disturbance, and hot flashes. *Direct effects* are effects on neural systems subserving cognitive functions. Indirect effects will be reviewed first.

The serotonin system, mood, and cognition

SWAN demonstrated that objective changes in cognition across the menopausal transition were not accounted for by self-reported menopausal symptoms (hot flashes, anxiety, depression and sleep disturbance)[9]. However, the anxiety and depressive symptoms themselves were associated with small decrements in psychomotor speed, consistent with emerging evidence from basic science studies, showing that the effects of estrogen on

depression and anxiety are largely mediated by estrogen receptor *beta* effects on serotonin and hypothalamic-pituitary-adrenal (HPA) axis function[9–12].

Interventional research done in early postmenopausal women (mean age 52 years) suggests that estrogen effects on serotonergic function may be a key mechanism relating mood and cognitive symptoms in the menopausal transition[13]. One open-label study randomized 19 early menopausal women to either a tryptophan depletion procedure (a reversible pharmacological challenge that results in low levels of serotonin) or a sham (control) procedure before and after 8 weeks of transdermal estradiol treatment[13]. Verbal memory decreased significantly after the tryptophan depletion challenge, but estradiol treatment buffered this effect. Spatial learning did not decrease significantly as a result of tryptophan depletion and estrogen had no influence on spatial learning. In addition, estradiol enhanced mood on the day after the depletion challenge. This study provides experimental support for the beneficial effect of estrogen on serotonergic function in relation to both memory and mood. Additional support for the thesis that estrogen acts through the serotonergic system to modulate mood and cognitive performance comes from a study examining the effects of estrogen supplementation on serotonin systems and cognitive function in 10 early postmenopausal women (mean age 54 years) who completed cognitive assessments and positron emission tomography (PET) scans before and after 10 weeks of treatment with transdermal estradiol[14]. The PET radioligand (18F) deuteroaltanserin was used to probe the influence of estrogen on 5-HT (2A) receptor binding. With estradiol treatment, 5-HT (2A) receptor binding significantly increased in right frontal cortex. Estradiol treatment also enhanced category fluency (a measure of executive function) and Trails A (a measure of psychomotor speed).

The cortisol pathway, menopause symptoms, and cognition

Women often attribute cognitive problems to hot flashes, the cardinal symptom of the menopausal transition. Several investigations report no relation between performance on cognitive tests and self-reported hot flashes[9,15,16]. However, one small study found that moderate-to-severe objectively measured hot flashes, but not subjectively reported hot flashes, were related to declines in verbal memory[17]. In that investigation, women subjectively reported only 40% of their objective hot flashes. Thus, the possibility that hot flashes contribute to the memory deficits observed in the menopausal transition remains open.

Higher cortisol levels or greater cortisol reactivity may be one mechanism that links hot flashes, depressive or anxiety symptoms to perimenopausal decrements in cognitive performance. Cortisol increases after a hot flash[18], experimental administration of corticosteroids produces verbal memory impairment, and higher endogenous cortisol levels are associated with poorer performance on memory tasks[19–26]. Estrogen may also *buffer* the stress response. Young women show less cortisol responsivity to a laboratory stressor compared to men[27]. Although research on dynamic change in the HPA axis is lacking in perimenopausal women, in premenopausal women, HPA responsiveness varies across the menstrual cycle, with some studies showing greater responsiveness during the luteal versus follicular phase[19,28], but others showing the opposite effect[29]. Seeman and colleagues also found a greater HPA response to a stress challenge in postmenopausal women compared to older men[30]. Indeed, a meta-analysis of results from 34 laboratory stress studies concluded that the effect of aging on cortisol responsivity is three times greater in women than in men[31].

The only published data about changes in the HPA axis during the perimenopause are from the Seattle Midlife Women's Health Study, which examined longitudinal changes in HPA activation[32,33]. An increase in overnight urinary cortisol levels during the late

perimenopause was observed; cortisol levels returned to lower levels when women reached postmenopause.

Perimenopausal changes in sex steroids—direct CNS effects

Estrogen fluctuations and withdrawal have myriad direct effects on the central nervous system (CNS) that have the potential to influence cognitive functions such as psychomotor speed and memory. As noted in the introduction, examples of estrogen-related CNS actions include: increasing levels of neurotransmitters, enhancing neuron growth and formation of synapses, acting as antioxidants and having regulatory effects on calcium homeostasis and second messenger systems[3–7]. A critical determinant of the effects of estrogen on the CNS and other health outcomes, including cardiovascular disease[34,35], appears to be the *timing of estrogen exposure in relation to the menopausal transition and/or age*. In the case of cognitive outcomes, some evidence supports the "critical window hypothesis"--that exposure early in the menopausal transition or postmenopausal period confers cognitive benefit whereas exposure later in the menopausal transition confers neutral or detrimental effects[36,37].

Animal models of menopause--ovariectomy

Our understanding of the CNS mechanisms of estrogen action comes from basic science studies and human studies. Basic science studies in rodents and non-human primates rely on an ovariectomy (OVX) model of surgical menopause, which results in the abrupt withdrawal of estrogen (and other ovarian hormones). OVX models, therefore, do not mimic a natural menopausal transition. Additionally, OVX models do not produce levels of follicle stimulating hormone (FSH), gonadotropin releasing hormone (GNRH), luteinizing hormone (LH) and testosterone that are typical of the natural menopause[38]. Data from the OVX model suggest that estrogen effects on the cholinergic system are a critical factor contributing to memory declines associated with estrogen loss. Cholinergic systems play a central role in age-related changes in attention and memory function[39].

Animal models of menopause—induced ovarian failure

There are ongoing efforts to create and test an animal model of the natural menopause that parallels features of the human perimenopause, including a gradual reduction of estrogen and progesterone, and more typical levels of FSH, GnRH, LH and testosterone. One of these models, accelerated ovarian failure, represents a gradual loss of ovarian steroid hormones over time[40]. This effort centers on a technique developed in mice that relies upon exposure to 4-vinylcycohexene diepoxide (VCD) to selectively destroy primordial and primary follicles. Mice exposed to VCD show hormonal features typical of the human perimenopause, including estrous acyclicity and fluctuating estrogen levels, and ultimately, undetectable estrogen levels. Emerging evidence from the VCD model demonstrates the importance of considering the approach to modeling the perimenopause when evaluating the impact of the perimenopause on cognition and brain function[40].

In the first study to compare the cognitive effects of surgical versus transitional VCD model of the menopause, Acosta colleagues compared middle-aged rats assigned to: 1) sham surgery; 2) OVX surgery; 3) VCD; or 4) VCD then OVX (VCD/OVX). The inclusion of the latter group provided the opportunity to examine the effects of removal of residual ovarian output (e.g., androgen) after VCD and follicular depletion. The value of the VCD model in modeling perimenopausal hormone levels was evident in the finding that the two groups with intact ovaries (sham and VCD) had lower LH and FSH levels, and higher androstenedione levels, compared with the two groups with no ovaries (OVX and VCD-OVX). Only the SHAM group exhibited high progesterone levels relative to all other groups. The behavioral effects of OVX versus VCD were evident on a measure of spatial

working memory and short-term retention. Specifically, the VCD group showed more errors compared with the SHAM and VCD-OVX groups, whereas the OVX group was marginally different from the VCD group and did not differ from sham. Memory tests were carried out before and after pharmacological reduction of acetylcholine (i.e., scopolamine treatment), but the extent to which this manipulation reduced memory performance was similar across groups, suggesting no differential sensitivity to cholinergic loss in the OVX versus VCD model. The predictors of memory performance differed in the OVX versus VCD models. In OVX animals (OVX and VCD-OVX), higher FSH was associated with fewer working memory errors after scopolamine challenge. In VCD animals, higher androstenedione levels were associated with more working memory errors. These data suggest some caution in extrapolating findings concerning the impact of the perimenopause on cognitive function from models of surgical menopause to transitional models of menopause.

This research team next investigated the cognitive effects of estrogen therapy, specifically conjugated equine estrogen (CEE), in OVX and VCD animals[41]. The primary finding was that CEE had a beneficial effect on cognition in the OVX rats but had a negative or neutral impact in the VCD rats in three separate cognitive tests. First, on the delay trial of a spatial and reference memory test, CEE enhanced performance in OVX animals but did not impact performance in VCD animals. Second, CEE enhanced working memory performance across increasing levels of difficulty in OVX animals, whereas CEE decreased the performance in VCD animals. Third, on a measure of long delay (8 hour) spatial memory, CEE enhanced memory retention in OVX rats, but had no benefit in VCD rats. Notably, as in the previous investigation, androstenedione levels predicted poorer cognition in the VCD animals, such that higher levels were associated with worse performance regardless of CEE treatment. These findings suggest a need for caution in extrapolating data concerning estrogen therapy and cognitive function from OVX models to a transitional VCD model.

Critical timing -- OVX effects differ by age

Among OVX studies, those examining the effects of OVX on cognition and brain function in middle-aged rats are especially important in understanding the impact of hormonal changes during the menopausal transition. Two studies by Markowska and Savonenko demonstrated the importance of considering the age of animal when examining the impact of OVX on cognition[42,43]. Their first study examined the impact of OVX and estrogen supplementation on cognitive performance in middle-aged female rats, beginning 1 month after OVX or sham surgery, and monthly thereafter as they aged. The most prominent effect of OVX in middle aged females was accelerated aging in working memory function, but not in reference memory. The cognitive impairment emerged gradually, first occurring 4 months after ovariectomy. Initially, the decrement was observed in tasks that placed more demands on working memory, and then was detected progressively in the easier tasks. Five months after OVX, when the animals reached old age, half of the animals received estrogen and half received vehicle. Estrogen administration improved deficits on one measure of working memory in old rats only when administered in a manner that mimicked estrogen fluctuations across the estrous. Ovariectomy also increased cognitive sensitivity to cholinergic withdrawal (i.e. scopolamine) in aging rats, but estrogen was not effective in reversing those cognitive deficits in those older animals. These findings contrasted with previous demonstrations that estrogen reverses memory deficits induced by scopolamine in younger rats[44,45]. Overall, this study demonstrated that abrupt estrogen withdrawal has differing cognitive effects across a variety of cognitive measures, but does appear to accelerate cognitive aging on some measures. Additionally, the finding suggests that the beneficial effects of estrogen in reversing memory deficits induced by cholinergic withdrawal in younger animals are not evident in older animals. Thus, following abrupt hormonal decline,

estrogen interacts with the cholinergic system to enhance memory in younger rats but not older rats.

A follow-up study by Savonenko and Markowska directly contrasted the cognitive effects of OVX in middle aged and older rats, and the effects of estrogen supplementation and cholinergic withdrawal in the two age groups[43]. The cognitive task was a T-maze active avoidance task, which depends on the integrity of the hippocampus and amygdala, as well as the cholinergic system. Results supported a critical "time window" in middle age during which estrogen supplementation conferred benefits and after which time estrogen supplementation was ineffective. Specifically, when the cholinergic system was compromised by scopolamine, middle aged and older rats showed different sensitivities to estrogen withdrawal by OVX and estrogen supplementation. In middle aged rats, estrogen withdrawal did not increase sensitivity to the memory impairments that follow scopolamine challenge. In older age rats, estrogen withdrawal exacerbated the effect of scopolamine. Similarly, in middle age rats, estrogen supplementation decreased the extent to which scopolamine impaired performance on the T-maze. By contrast, estrogen supplementation was ineffective in protecting against scopolamine-induced memory deficits in older rats. These findings suggest that the effects of estrogen withdrawal and supplementation are evident on this particular task only when the cholinergic system was experimentally compromised by scopolamine.

Human pharmacological challenge studies support critical timing

An age-related "window of opportunity" for estrogen to benefit cognition in women is supported by a cholinergic challenge trial by Dumas and colleagues[46]. A stratified sample of postmenopausal women, aged 50–62 years or aged 70–81 years, were randomly assigned to receive oral estradiol (2 mg/day) or placebo for 3 months. The women then completed a cholinergic challenge, which consisted of three conditions: 1) 2.5 mg/kg scopolamine (anti-muscarinic challenge); 2) 20 mg mecamylamine (anti-nicotonic challenge), and 3) placebo, in randomized order. In both age groups, there was a decrease in memory during the anticholinergic challenge. Estrogen at the 2 mg/day dose reversed the challenge-induced impairment on verbal memory in the younger, but not in the older, group. These findings parallel findings from the basic science literature, suggesting that estrogen ameliorates memory impairments due to cholinergic withdrawal in young, but not older postmenopausal women. Notably, an earlier clinical trial by this same research team demonstrated that treatment with 1 mg oral estradiol reversed scopolamine-induced declines in attention and psychomotor speed, suggesting that estrogen interacts with the cholinergic system to influence psychomotor speed and attention[47].

Human neuroimaging studies —a window to estrogen's CNS effects

The impact of ovarian hormone withdrawal on brain function and the importance of the cholinergic system in the context of ovarian hormone withdrawal are evident in a series of neuroimaging studies by Michael Craig and colleagues[48–50]. In these studies, healthy premenopausal women underwent pharmacological ovarian hormone suppression with leuprolide acetate, and given a verbal memory task. Hormone suppression produced decreased activation in the left prefrontal cortex, anterior cingulate, and medial frontal gyrus[49]. A subsequent study demonstrated that brain function returned to baseline when ovarian hormone levels returned to normal[48]. Like ovarian hormone withdrawal, scopolamine treatment reduced activation in the left inferior frontal gyrus during verbal encoding, and the combination of estrogen suppression and cholinergic suppression led to dramatic decreases in activity in this area[50]. The left inferior frontal gyrus is involved in processing of the meaning of verbal material. Together these data suggest that estrogen withdrawal might negatively affect the extent to which verbal information is meaningfully

processed and estrogen supplementation might enhance the encoding of verbal information into memory by enhancing the depth of semantic processing.

Estrogen also appears to enhance hippocampal function when administered in the perimenopausal period[51]. A recent fMRI study investigated brain function in two groups of women, one that initiated hormone therapy beginning in the perimenopause and continuing to older age, and the other that used no menopausal hormone therapy. At the time of the neuroimaging, women were on average 60 years of age. The neuroimaging task was a delayed word list task (verbal memory) that included an encoding phase, a 15-minute delay, and a retrieval phase to parallel clinical neuropsychological measures of verbal memory. Early continued use of estrogen was associated with enhanced verbal memory and enhanced function in the hippocampus during memory retrieval, concordant with the critical timing hypothesis. Similar findings of a benefit of early estrogen treatment on hippocampal volume have been reported[52].

Relation of critical timing and health cell bias theories

An alternative to the critical timing hypothesis is the “healthy cell bias” of estrogen introduced by Roberta Diaz Brinton[53]. The healthy cell bias posits that as the continuum of neurological health progresses from healthy to unhealthy, the effects of estrogen supplementation progresses from beneficial to neutral or detrimental. In this paradigm, estrogen confers beneficial effects for neurological function and survival if neurons are healthy at the time of estrogen exposure. Conversely, estrogen exposure negatively impacts neurological function and survival if neurological health is compromised. Given that cells are more likely to be healthy earlier in the perimenopausal period than later in the postmenopausal period, the healthy cell bias and the critical window hypothesis overlap. There is mounting evidence that the negative impact of hormone therapy is most evident in women whose cognitive performance is lower than expected at the time of estrogen exposure[54,55]. Also consistent with the healthy cell bias hypothesis is evidence from a randomized clinical trial that even older women can benefit from estrogen provided that they perform at or above expected levels of performance on verbal memory tasks[56].

Human longitudinal studies of perimenopause and cognitive performance

Longitudinal studies of measured cognitive performance during perimenopause

There are four published longitudinal reports on the subject of perimenopause and measured cognitive performance[9,57–59]. Three of these studies focused on the relation between the perimenopause transition and cognition and the fourth addressed the question of whether perimenopausal symptoms contribute to the subtle decrements in cognitive function observed during perimenopause.

The Kinmen Women-Health Investigation (KIWI) studied longitudinal cognitive performance in a sample of 694 Chinese residents of Kinman, Taiwan[57]. At baseline, KIWI participants were premenopausal and averaged 46 years of age. Cognitive tests included assays of verbal memory, verbal fluency, mental flexibility and processing speed. At an 18-month follow up assessment, performance on all cognitive tests improved, an expected learning effect (see below for further explanation of learning effects)[60]. However, women who transitioned to perimenopause during the follow-up period manifested statistically significantly *less improvement* in verbal fluency than did those who did not transition.

The remaining three longitudinal analyses of measured cognitive performance during the menopause transition come from the Study of Women’s Health Across the Nation (SWAN). SWAN is a multi-site, community-based, longitudinal cohort study, ongoing at seven clinical centers in the United States[61]. At baseline, SWAN participants were between 42 and

52 years old, premenopausal or early perimenopausal and self-identified (per protocol requisite) as African-American, Caucasian, Chinese, Japanese or Hispanic.

At SWAN baseline, only the SWAN Chicago site assessed cognitive performance, using a test of processing speed and a test of working memory (the ability to keep information in mind and manipulate it). All seven SWAN sites began measuring cognition at the fourth annual follow-up visit. The SWAN cohort cognitive assessment included the same two tests that had been used by Chicago-SWAN and added a third test of verbal memory[62–65].

The Chicago SWAN site-specific results included information from about 800 women followed for an average of 2 years[58]. Like the KIWI study, Chicago SWAN witnessed small improvements over time in cognitive processing speed and working memory, consistent with expected learning in this age range. But, unlike KIWI, advancement to perimenopause during the observation period did not dampen the learning effect. Subsequently, a four-year longitudinal analysis based on the entire SWAN cohort (N= 2362) found that being perimenopausal transiently reduced measured cognitive performance[59]. A learning effect was also evident in this larger study: cognitive processing speed improved with each annual visit during premenopause, early perimenopause, and postmenopause. But *during late perimenopause women did not demonstrate learning* (improved cognitive processing speed) with repeated testing. Similarly, during premenopause and postmenopause, verbal memory scores got better at each follow-up, but *while participants were early or late perimenopausal their verbal memory tests did not improve*. Compared to the Chicago site-specific report, the SWAN cohort sample size was much larger, the follow-up time doubled and the effects of previous and current hormone use were accounted for in the statistical models; each of these factors likely contributed to the different results.

In both KIWI and SWAN, the cognitive performance difficulties during perimenopause were subtle: they were evidenced by a *lack of improvement with repeated annual testing, not a decline in scores*. This underscores the relevance of the “learning effect” in studies of mid-life cognitive performance. When serial cognitive tests are given to middle aged individuals, increasing scores with repeated administrations are the norm; this is termed “the learning effect”. A lack improvement with successive test administrations during midlife, therefore, may be interpreted as an indicator of abnormal cognitive function[60]. KIWI and SWAN participants ranged in age from 40 to 61 years, and thus would be expected to improve with repeated tests. The lack of learning, isolated to the perimenopausal stage of the transition, argues for a transient detrimental effect of perimenopause on cognitive performance.

Mechanistic hypotheses

What mechanisms might account for a perimenopause-associated alteration in cognitive function? Reviewed above, an estrogen-related pathway is plausible: estrogen benefits hippocampal and prefrontal cortical function, potentially enhancing verbal memory and executive function, cognitive domains that are consistent with the results from KIWI and SWAN[4,6,66,67]. The drop in estrogen that accompanies perimenopause could, therefore, negatively impact cognitive performance[68].

Menopause transition symptoms could also lead to poorer cognitive performance. The most recent SWAN analysis addressed the question of whether vasomotor, depressive, anxiety, or sleep disturbance symptoms, which are associated with perimenopause, are themselves related to poorer cognitive function during the transition[9,69–77]. SWAN reported that higher levels of depressive and anxiety symptoms were directly related to slightly poorer cognitive performance. However, the presence of menopause transition symptoms did not account for the cognitive decrements observed during perimenopause. Specifically, women with more depressive symptoms did worse on the test of cognitive processing speed and those with

higher degrees of anxiety demonstrated less learning in the domain of verbal memory. Neither sleep disturbances nor vasomotor symptoms had a direct effect on concurrent cognitive performance and learning. These results are consistent with evidence that attention and concentration deficits accompany depressive and anxiety disorders[78–81]. But, when all four of these menopause transition symptoms (vasomotor, depressive, anxiety, and sleep disturbance) were added to models of menopause transition stage and cognition, the negative effect of late perimenopause on learning was unaltered, suggesting that the presence of these symptoms did not account for the perimenopause-associated learning decrement.

Perimenopausal cardiovascular risk and cognition

The perimenopause is associated with adverse changes in a number of cardiovascular risk factors (reviewed by Chae and Derby in this volume). A growing body of evidence links cardiovascular risk status, particularly during midlife, with cognitive decline and dementia later in life. Furthermore, women with the highest levels of vascular risk factors during perimenopause remain in the highest risk groups after menopause, resulting in protracted exposure to this potentially damaging cardiovascular risk profile[82]. Thus, the perimenopause may be a critical time in the lifespan when preventive efforts to reduce the risk of subsequent cognitive disability are warranted.

Vascular disease and dementia

Traditionally, Alzheimer's disease and vascular dementia, the leading causes of dementia in the elderly, have been considered distinct clinical entities. However, accumulating evidence suggests an association between vascular disease and cognitive decline and dementia regardless of subtype, with vascular pathology contributing to at least half of all dementia cases[83–86]. Furthermore, data from imaging and clinical-neuropathological correlation studies suggest that the presence of vascular pathology exacerbates the clinical expression of Alzheimer's disease[87–91]. Vascular risk factors are associated with cognitive decline and dementia in older populations[83,85,86,90]. A summary index of vascular risk factor status, the Framingham Stroke risk profile, has been associated longitudinally with deficits in a range of cognitive functions[92]. Finally, white matter hyperintensities, markers of ischemia in the brain, have been linked to deficits in cognitive function, particularly frontal/ executive functions (e.g., planning, strategy use and task switching)[93–97].

Midlife risk factors and cognition

Given that the natural history of both Alzheimer's disease and vascular disease span decades, the impact of vascular risk factors on cognitive decline and dementia may be cumulative over the lifespan[84]. Just as subclinical vascular disease begins decades prior to clinically overt cardiovascular disease, the neurodegenerative changes that underlie dementia begin many years prior to clinical diagnosis. There is accumulating evidence linking risk factor status during middle age with cognitive decline and dementia in older age[8]. A retrospective cohort study of participants in the Kaiser Permanente medical care Plan demonstrated that presence of diabetes, hypertension high cholesterol or smoking measured at approximately 40 each predicted the diagnosis of dementia 20 to 30 years later. The presence of all four of these risk factors during midlife doubled the risk of developing dementia in later life[98].

Cardiovascular risk factors ascertained in mid-life predict risk of cognitive decline and dementia better than those measured in late life. Midlife risk assessment may have greater predictive power because it may capture the cumulative impact of a lifetime of putative exposures. Additionally, some vascular risk factors, such as blood pressure and serum cholesterol, decline during the years immediately preceding the onset of dementia[99,100]. If

the risk factors were measured in the years proximal to dementia onset, this drop in blood pressure and cholesterol would obscure the true relation between life-long hypertension or hypercholesterolemia and late life cognitive function.

Blood pressure and cholesterol

Finnish population-based studies report that elevated blood pressure and serum cholesterol levels measured in midlife (mean age 50 years) predict onset of mild cognitive impairment (thought to be a marker of preclinical dementia)[101], and Alzheimer's disease 20 years later[100,101]. The association of midlife blood pressure with dementia in later life has been confirmed in men in the Honolulu-Asia aging study and among men and women in a Swedish cohort[99,102].

Body mass index (BMI)

BMI measured between 40 to 44 years of age is a strong predictor of subsequent Alzheimer's disease[103]. In the Cardiovascular Health Study, BMI at age 50 was positively associated with dementia risk in later life, while BMI measured after age 65 showed an inverse association with dementia risk[104].

Midlife diabetes onset

Onset of diabetes prior to age 65, but not after it, predicts the development of mild cognitive impairment or dementia[105,106]. Diabetes duration of at least 10 years is also associated with higher incidence of mild cognitive impairment[105]. A case-control twin study found that diabetes onset prior to age 65 more than doubled the risk of dementia, while onset after age 65 was not significantly associated with incident dementia risk[106].

Summary

Perimenopause may have *contemporary* as well as *long term* effects on cognitive function. The contemporaneous impact of perimenopause on cognition appears to be both transient (occurring only during perimenopause) and subtle. In both KIWI and SWAN, the only published longitudinal studies of measured cognitive performance during the menopause transition, an absence of improved test scores with repeated annual measurements, not a decline in test scores, was evident during perimenopause.

The presence of menopause transition symptoms could *indirectly* mediate the effect of perimenopause on cognitive performance. SWAN, the perimenopausal decrement in cognitive performance was not accounted for by vasomotor, depressive, anxiety or disturbed sleep symptoms. While several studies report no relation between performance on cognitive tests and self-reported hot flashes, one small study did find that moderate-to-severe objectively measured hot flashes, but not subjectively reported ones, were related to declines in verbal memory. Thus, the possibility that hot flashes contribute to the memory deficits observed in the menopausal transition remains open.

The increases in anxiety and depressive symptoms that accompany the perimenopausal transition have an independent effect on cognitive performance. This is consistent with basic science findings that the effects of estrogen on depression and anxiety are largely mediated by estrogen receptor *beta* effects on serotonin and hypothalamic-pituitary-adrenal (HPA) axis function. Additionally, higher baseline cortisol levels or greater cortisol reactivity could link hot flashes, depressive or anxiety symptoms with perimenopausal decrements in cognitive performance. While there is mounting evidence for a cortisol-stress-cognition link in older men and women, this pathway has not been directly explored in perimenopausal women.

Long term cognitive consequences of perimenopause may stem *directly* from the decline in estradiol level that accompanies this transition. Animal and human experimental models show that estradiol protects against the detrimental mood and cognitive changes that result from serotonin withdrawal. Similarly, estrogen defends against cognitive changes following cholinergic depletion in midlife women and middle aged female rats. These studies suggest that the loss of estrogen at midlife results in changes in cholinergic and serotonergic function which in turn contribute to mood problems and cognitive deficits.

Age and/or health status may be determinants of the impact of sex hormones on cognitive function. In both animal and human experimental models, estrogen benefits cognitive function early in the menopausal transition but not later in life. In observational studies, early estrogen use is associated with improved memory and hippocampal function later in life.

Worsened cardiovascular risk factors, which accompany the perimenopause, may be a pathway by which the menopausal transition affects cognitive function in older age. Cardiovascular risk factors, particularly those present in mid-life, have been linked to cognitive decline and dementia in later life. Women with the highest levels of vascular risk factors during perimenopause maintain the highest risk levels after menopause, resulting in protracted exposure to a cardiovascular risk profile that may ultimately lead to dementia.

Clinical Implications

Information about the short and long-term effects of perimenopause on contemporary cognitive function and risk of future cognitive decline is scant—but is there anything that can be used to inform clinical practice? Albeit based on limited longitudinal data, it appears that there is a small (but probably perceptible to the woman) decrement in perimenopausal cognitive performance that resolves in postmenopause. This knowledge may be of use in counseling perimenopausal patients who raise concerns about memory dysfunction. Also noteworthy from a clinical perspective is that cognitive complaints during perimenopause may be the result of perimenopausal anxiety or depressive symptoms, thus clinicians should be alert to the potential memory-mood link. The perimenopause is also an opportune time to evaluate and treat modifiable cardiovascular risk factors, not only for primary prevention of cardiovascular disease but also because doing so may lessen the risk of cognitive decline or dementia. Finally, although several lines of evidence suggest that exogenous estrogens may result in beneficial cognitive outcomes when given in the perimenopause or early postmenopause, this notion of critical timing remains experimental.

Research Directions

Longitudinal studies of measured cognitive performance during the menopause transition are scant; more are needed. Insights into the neurobiology of the perimenopause can be gained from future studies examining the effect of the perimenopause on the HPA axis in relation to cognition and mood. Further investigation of the critical timing hypothesis (and the related healthy cell bias hypothesis) is fundamental to our understanding of the care of perimenopausal women. Understanding of the cognitive biology of menopause will also be improved by making use of new animal models of the menopause transition, in which there is a gradual depletion of ovarian follicles, more closely mimic the biology of natural menopause in humans.

Synopsis

The contemporaneous impact of perimenopause on cognition appears to be both transient and subtle, characterized by an absence of improved scores with repeated annual cognitive

testing, rather than a decline in scores. In the Study of Women's Health Across the Nation, the perimenopausal decrement in cognitive performance was not accounted for by self-reported vasomotor, depressive, anxiety or disturbed sleep symptoms, but the increases in anxiety and depressive symptoms that accompanied perimenopause transition had independent, unfavorable effects on cognitive performance. Animal and human experimental models find that estradiol protects against the detrimental mood and cognitive changes that result from serotonin withdrawal and defends against cognitive changes resulting from cholinergic depletion. Animal and human experimental and observational studies also support the critical timing hypothesis--that estrogen benefits cognitive function when instituted early in the menopausal transition but not later in life. Worsened cardiovascular risk factors, which accompany the perimenopause, may also be a pathway by which the menopausal transition affects cognitive function in older age.

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