Impact of Hormonal Changes on Cognition

By Kate Wells, MBA

The steady increase in reported incidence of subjective cognitive impairment is a demographic trend needing systemic solutions. Data consistently identifies women having significantly higher risk for Mild Cognitive Impairment (MCI) and Alzheimer Disease (AD). In a July 2018 report from the Alzheimer's Association, Maria Carrillo, PHD Chief Science Officer stated "more women than men have Alzheimer's disease or other dementias; almost two-thirds of Americans with Alzheimer's are women".[1] Although women appear to sustain cognitive performance longer than men, once MCI progresses to dementia, the gap closes quickly. Memory challenges are a frequent complaint associated with midlife. Over 40% of perimenopausal and postmenopausal women reported forgetfulness compared to 31% of premenopausal women[2], and approximately 63% of midlife women reported undesirable memory changes in the Seattle Midlife Women's' Study.[3] Just as cardiovascular disease and diabetes can be identified at the asymptomatic stage and preventive measures taken, so can MCI. Risk factors are increased lipids, obesity, elevated inflammatory markers, sedentary lifestyle, insufficient neuroprotection from hormones, and insulin resistance. This article will focus on the potential of hormone intervention strategies for reducing the pace of MCI.

Cognitive function does not rely on a specific brain region but is determined by neuronal network interactions. Numerous studies have investigated the relationships between hormonal effects and cognitive function. Estrogen receptors are found, for example, in the hippocampal areas, amygdala, basal forebrain, pituitary, hypothalamus – the first three of which are strongly associated with memory and mood. Estrogen is known to increase the density of pyramidal hippocampal neurons and increase synaptic plasticity in the hippocampus via activation of estrogen receptors.[4] Estrogen has also been shown to protect against oxidative damage[5], beta amyloid toxicity[6], and to influence acetylcholine, serotonin, dopamine and norepinephrine, all neurotransmitters involved in learning and cognition[7]. Estrogen influences dilation of the cerebral vascular system, enhancing dilation of vessels and increasing mitochondrial energy production.[8,9] When a woman's estrogen levels drop during and after menopause, neurons and synapses begin to lose function. This loss of function can quickly lead to functional changes in the brain associated with AD, specifically in the hippocampus, hypothalamus, posterior cingulate gyrus, and the prefrontal cortex.[1]

Hot flashes are one the most obvious and useful symptoms for the clinician to work with. Research by Maki et al[10] identified that the total number of hot flashes plus sleep deprivation and verbal knowledge were significant predictors of delayed verbal memory. Further, verbal fluency correlated positively with the number of daytime hot flashes, and there is a significant relationship between the number of hot flashes during sleep and

immediate paragraph recall. Hot flashes appear to be most strongly associated with declines in logical thinking rather than strategic or organizational thinking.

Both estrogen *and* progesterone are associated with changes in brain activation patterns. Progesterone is associated with changes in regional brain activation during a visual memory task, with activation in the left prefrontal cortex and right hippocampus specifically impacting verbal memory[11]. Progesterone has multiple non-reproductive functions in the central nervous system that regulate cognition, mood, inflammation, mitochondrial function, neurogenesis and regeneration, myelination, and recovery from traumatic brain injury[12]. A 2010 article reviewing the use of progesterone to treat traumatic brain injury established that progesterone has been shown to reduce cerebral edema, reestablish a compromised blood brain barrier, improve vascular tone, down-regulate the expression of inflammatory factors, and reduce excitotoxic damage.[13] Vitamin D deficiency can, however, diminish progesterone's neuroprotective effect. Ensuring optimal levels of vitamin D improves outcomes.

The average age of menopause in the United States is around 51 years old, but onset can vary significantly. Perimenopause can begin as early as age 40 with about 5% of women entering perimenopause between ages 40 and 45.[14] Premature menopause refers to menopause onset before age 40 and currently this applies to about 1% of women in the United States.[15] There are a variety of factors contributing to premature menopause: genetic defects, spontaneous ovarian failure, radiation or chemotherapy treatment for cancer and surgery – in particular oophorectomy. The sudden drop in key sex hormones estrogen, progesterone, and testosterone frequently associated with premature menopause results in very similar symptoms to regular menopause, in particular hot flashes, night sweats, vaginal dryness, and mood changes.[16] A 2014 study[17] concluded that in comparison with women who underwent menopause at age 50 or over, women who underwent premature menopause had a more than 40% increased risk for poor performance on verbal fluency and visual memory tasks. The study also identified a 35% increased risk of decline in psychomotor speed but was not significantly associated with increased risk of dementia. The collective drop in progesterone, estrogen and testosterone at premature menopause results in disruption of the hypothalamic-pituitary-gonadal axis[18] with corresponding influences on sleep. Changes in sleep patterns further compound impacts on cognition and memory.

While there has been much research on how and when to treat early onset menopause, it would seem that there is little research that differentiates actual age of early onset menopause. However, a study by Kurita et al[19] compared induced and spontaneous menopause and found no significant cognitive difference when induced menopause was analyzed as a pooled sample but revealed worse verbal and special memory in women with earlier induced menopause after splitting the study group into age at oophorectomy. The age at which estrogen replacement begins appears to have significant impact, particularly if bioidentical replacement is used. Women experiencing premature and early onset menopause can be considered good candidates for hormone replacement with the goal of approximating the normal premenopausal levels and

patterning. Estrogen replacement should always be balanced with progesterone. Hormone replacement is best begun when there are healthy receptors, rather than later when receptor function has declined.

Recent research into the correlations between reproductive history and dementia identified that increased number of months pregnant can reduce AD risk by as much as 20%.[20] Theories as to why include the beneficial impacts of pregnancy on the immune system, but with what is known about the protective effects of progesterone – the increased progesterone levels experienced during pregnancy could also play a significant role.

The debate continues about use of synthetic or bioidentical hormone replacement as a tool to optimize the HPA axis. A 2009 review of studies related to use of conjugated equine estrogens (CEE) vs bioidentical estradiol replacement found 15 out of 20 estradiol studies demonstrated cognitive benefit with estradiol use, 5 out of 20 showed no benefit, with no studies demonstrating harm. In comparison, only 6 of 14 studies with CEE showed benefit, 8 of 14 showed no benefit and of the 8, 2 indicated harm.[21]. A very recent study lead by Dr. Zeydan, Associate Professor of Radiology at the Mayo Clinic[22], reported on a 7-year study the results of which illustrated that transdermal estrogen preserves measures of cognitive function and brain architecture in postmenopausal women. Results identified less cortical atrophy, less development of amyloid on brain imaging, and better performance on memory tests for those on topical estrogen.

It is important to understand that a high proportion of studies on the impact of HRT on cognition focus on conjugated equine estrogens, not on bioidentical estrogen. The Mayo study identified that women on CEE's had more white matter hyperintensities, greater ventricle enlargement and more cortical thinning. Women on transdermal estradiol (with oral micronized progesterone for 12 days of the month), showed higher attention and executive function scores, better sleep scores and demonstrated a correlation with preserved cortical volume of the dorsolateral prefrontal region, the area of the brain involved in executive functions including working memory and cognitive flexibility. Regarding dosing considerations, a study published in the Neurobiology of Aging identified that a 2mg oral beta-estradiol over three months increased bilateral posterior hippocampal voxel-based gray-matter volume, whereas placebo of 1 mg oral-beta estradiol dose showed no significant effects. [23]

These are exciting times for practitioners in the functional medicine arena. With growing understanding of the complex etiology of cognitive impairment in its various forms, a knowledge of ways to work with biochemistry for positive, protective effects is crucial. Bioidentical hormone replacement is not the sole answer but starting replacement to ensure optimal functioning when levels change can play a significant part in protecting brain functions. It isn't necessary to wait until the typical age of menopause to see if hormone replacement should be considered. Explore the following with all women patients: history of early menopause, distracted sleep patterns, hot flashes both during the day and at night. Each patient is an individual, test to establish free circulating free

hormone levels, evaluate symptoms (be aware that hot flashes, a leading indicator of insufficient estrogen, are frequently under reported) and treat not only with relief of symptoms in mind, but with neuroprotection as a clinical goal.

References

1. https://www.alz.org/aaic/releases_2018/AAIC18-Mon-women-dementia-risk.asp
2. Gold EB, Sternfeld B, Kelsey JL, et al. Relation of demographic and lifestyle factors to symptoms in a m population of women 40-55 years of age. Am J Epidemiol.2000;152:463-473.
3. Woods NF, Mitchell ES, Adams C. Memory functioning among midlife women: observations from the Se Women's Health Study. Menopause. 2000;7:257-265.
4. Joanna L. Spencer, Elizabeth M. Waters, Russell D. Romeo, Gwendolyn E. Wood, Teresa A. Milner, an McEwen, Uncovering the Mechanisms of Estrogen Effects on Hippocampal Function. Front Neuroendoc 29(2): 219–237.
5. Alex F. Bokov, Daijin Ko, Arlan Richardson. The effect of gonadectomy and estradiol on sensitivity to ox Endocr Res. 2009; 34(1-2): 43–58.
6. Jon Nilsen, Shuhua Chen, Ronald W Irwin, Sean Iwamoto, and Roberta Diaz Brinton, Estrogen protects from amyloid beta-induced apoptosis via regulation of mitochondrial proteins and function. BMC Neuros
7. E Jacobs, M D'Esposito Estrogen shapes dopamine-dependent cognitive processes: implications for wo Journal of Neuroscience, 2011
8. E.B. Engler-Chiurazzi, C.M. Brown, J.M. Povroznik, and J.W. Simpkinsa, Estrogens as neuroprotectants actions in the context of cognitive aging and brain injury. Prog Neurobiol. 2017 Oct; 157: 188–211.
9. Virginia M. Miller, PhD and Sue P. Duckles, PhD. Vascular actions of estrogens: functional implications. 2008 Jun; 60(2): 210–241.
10. Maki PM1, Drogos LL, Rubin LH, Banuvar S, Shulman LP, Geller SE. Objective hot flashes are negative verbal memory performance in midlife women. Menopause. 2008 Sep-Oct;15(5):848-56
11. Berent-Spillson A, Briceno E, Pinsky A, Simmen A, Persad CC, Zubieta JK, Smith YR. Distinct cognitive estrogen and progesterone in menopausal women. Psychoneuroendocrinology. 2015 Sep;59:25-36.
12. Drinton RD, Thompson RF et al. Progesterone receptors: Form and function in brain. Frontiers in Neuro Volume 29, Issue 2, May 2008, Pages 313-339
13. Cekic, M Stein DG. Progesterone Treatment for Brain Injury: An Update. Future Neurology. 2010;5(1):3
14. Miro F, Parker SW, Aspinall LJ, Coley J, Perry PW, Ellis JE. Sequential classification of endocrine stage reproductive aging in women: the FREEDOM study. Menopause. 2005;12:281–290.
15. Luborsky JL, Meyer P, Sowers MF, Gold EB, Santoro N. Premature menopause in a multi-ethnic popular menopause transition. Hum Reprod. 2003;18:199–206
16. Rocca WA, Bower JH, Maraganore DM, et al. Increased risk of cognitive impairment or dementia in wom underwent oophorectomy before menopause. Neurology. 2007;69:1074–1083
17. Ryan J, Scali J, Carriere I, Amieva H, Rouaud O, Berr C, Ritchiea K, Ancelin M-L. Impact of a premature cognitive function in later life. BJOG 2014; DOI:10.1111/1471-0528.12828121:1729–1739.
18. Morrison JH, Brinton RD, Schmidt PJ, Gore AC. Estrogen, menopause, and the aging brain: how basic inform hormone therapy in women. J Neurosci. 2006;26:10332–10348.
19. Kurita K, Henderson VW, Gatz M, St. John, J, Hodis HN, Karim R, Mack WJ. Association of bilateral oop cognitive function in healthy, postmenopausal women. Fertil Steril. 2016 Sep 1; 106(3): 749–756.e2.
20. Molly Fox, PhD Carlo Berzuini, PhD, Leslie A. Knapp, PhD, and Laura M. Glynn, PhD. Women's Pregna and Alzheimer's Risk: Can Immunoregulation Explain the Link? Am J Alzheimers Dis Other Demen. 201 516–526.
21. Whitney Wharton, Carey E. Gleason, et al. Potential role of estrogen in the pathobiology and prevention disease. Am J Transl Res. 2009; 1(2): 131–147.

22. https://www.mdedge.com/clinicalneurologynews/article/204936/alzheimers-cognition/transdermal-estrad
23. Kimberly Albert, Jessica Hiscox, Brian Boyd ,Julie Dumas, Warren Taylor, Paul Newhouse. Estrogen en hippocampal gray-matter volume in young and older postmenopausal women: a prospective dose-respo Neurobiol Aging, Volume 56, August 2017, Pages 1-6