Cognitive Consequences of Perimenopause

A possible contribution of perimenopause should be considered when evaluating women with cognitive complaints.

By Ronald Devere, MD, FAAN

Although cognitive impairment has been shown to occur during perimenopause,[1] this is not routinely incorporated into assessments of memory and other cognitive impairments of women in this stage of life. Indeed, as a cognitive neurologist, I have heard and read little on the topic and its role in evaluating cognitively impaired individuals. What we all have heard for many years is that starting estrogen after menopause can worsen cognitive decline and increase risk for cerebral and cardiovascular disease.

Perimenopause and Cognition

Physiologic Connections

There are several potential mechanisms by which perimenopause might lead to cognitive decline.[2-4] Estrogen influences functions in many brain regions involved in learning, registering, and retrieving information for language and judgement, including the hippocampus, striatum, and prefrontal cortex. Estrogen loss is accompanied by reduced dendritic spine density and synapse formation in the hippocampus and basal forebrain, leading to decreased cholinergic and serotonergic with direct effects on both cognition and mood. Indirectly, mood disturbances further worsen cognitive dysfunction. The vasovagal effects of perimenopause that result in hot flashes increase cortisol levels and this may also worsen memory. With estrogen loss, there may also be reduced cardiovascular and cerebrovascular health to create an indirect negative effect on brain health.

Clinical Connections

There are many published reports and studies regarding the clinical effects of perimenopause on cognitive and physical health. In an open-label study 19 women in early menopause were randomly assigned to a tryptophan-depletion procedure (reversible and causes low levels of serotonin) or a control procedure before and after 8 weeks of transdermal treatment with estradiol. In the women given the tryptophan-depletion procedure, verbal memory and mood decreased significantly and both improved with estradiol treatment. This study provided support for the beneficial effects of estrogen on serotonin function in relation to memory and mood.[5] In a similar study, estradiol treatment enhanced category fluency (a measure of executive function) and Trails A (measure of psychomotor speed), both important tests in neuropsychological evaluations.[6]

Longitudinal studies of perimenopause and cognitive performance have focused on either the relationship between perimenopause and cognition or whether perimenopausal physical symptoms (eg, flushing or night sweats) contribute to subtle deficits in cognitive function.

In the Kinman Women Health Investigation (KIWI) cognitive performance in 694 Chinese women who were age 46, living in Taiwan, and premenopausal were followed longitudinally. Verbal memory, verbal fluency, mental flexibility and processing speed were measured at baseline and 18 months later. All cognitive tests improved, which was expected because of the learning effect of repeat neuropsychologic testing. Women who transitioned to perimenopause, however, showed less improvement in verbal memory than did those who did not. Similar studies in the US followed 800 women of all ethnic groups, age 42 to 52 for 2 years. Small improvements in processing speed and working memory were seen with repeated testing as in the KIWI study in those who remained premenopausal group. In those who had transitioned to perimenopause, there were no such improvements. It should be noted that during midlife, lack of improvement with repeated tests may be interpreted as an indicator of cognitive dysfunction.[7]

Overlap and Misdiagnosis

Across cultures, in studies of perimenopausal women, 35% to 62% reported memory changes. These symptoms correlated with poorer performance on objective neurocognitive testing with decreases in verbal memory, verbal fluency, and executive function that were independent of perimeno-

pausal symptoms (eg, hot flashes, sleep disturbances, depression, and anxiety) suggesting that cognitive changes were not caused by these symptoms.[4,8-10] Although the cognitive deficits recorded appear to mimic deficits seen in mild cognitive impairment (MCI) and some early cases of dementia, it has been suggested that it be distinguished from MCI with the term menopause-related cognitive impairment because the high incidence (50%) of conversion to dementia seen in MCI is not present. It has been noted that laboratory indications of impending menopause and common symptoms of hot flashes may not occur early, and this can lead patients and physicians to think another cognitive disorder is present, leading to a misdiagnosis.[11] Similarly, if symptoms of a menopause-related cognitive impairment persist past the transition or significantly interfere with function, another etiology should be considered.

Menopause-Related Cognitive Impairment

In a case presentation, a woman, age 55, with 1 year of progressive memory loss and behavioral changes (losing objects, neglecting personal grooming), a 4-year history of depression and menopause at age 54 had overall cognitive ability at the 98th percentile but working memory in the 12th percentile and verbal fluency in the 20th percentile. She was diagnosed with menopause-related cognitive disorder and treated with hormone therapy. After 15 months, repeat cognitive showed stabilization of cognitive skills, with working memory rising to the 88th percentile, and resolution of behavior symptoms. She completed a graduate program and 4 years after presentation was in a leadership position in education.[11] The author of this case report defined menopause-related cognitive impairment as shown in the Box.

Box Menopause-Related Cognitive Impairment as Defined by Devi[11]

1. Subjective change in cognition in the context of persistence change in frequency and quality of menses for at least 12 months not related to other factors, such as pregnancy or cancer.
2. Laboratory evidence of perimenopause and menopause such as elevated follicle stimulating hormone (FSH) is helpful but not necessary for diagnosis.
3. Objective evidence for cognitive change in one or more cognitive domains, greater than expected for patient's age, education, and background.
4. No evidence for other medical conditions that could cause cognitive decline.
5. No evidence for dementia.

Hormone Treatment and Cognition

In a prospective, double-blind study on the cognitive effects of estradiol initiated within 6 years of menopause was compared to initiation of estradiol 10 or more years after menopause. Cognitive testing occurred at baseline, 2.5 years, and 5 years. There were no differences in verbal memory, executive function, or global cognition in women who took estradiol within 6 years of menopause vs those who took it 10 or more years after menopause. In this study, postmenopause was defined as absence of vaginal bleeding for at least 6 months (natural menopause) or bilateral oophorectomy (surgical menopause) and serum total estradiol of < 25 pg per mL.[12]

Estradiol neither benefitted nor harmed cognitive abilities regardless of the time since menopause. The authors addressed that other studies[13-15] showed cognitive improvements, especially in verbal and episodic memory, in women treated with estrogen postmenopausally, noting that these studies had small sample sizes, smaller age range, and shorter treatment duration. A limitation of this large trial was that serum levels of estradiol were above those associated with meaningful outcomes in other studies such as vasomotor symptom reduction and fracture prevention, and the study lacked power to exclude small treatment effects in subgroups. Overall, the results indicate that neither postmenopausal women near the time of menopause nor women further from the time of menopause need be overly concerned that hormone treatment adversely affects cognitive abilities over a 5-year period.

The North American Menopause Society recommends hormone therapy for treatment of cognitive symptoms following surgical menopause but not after early natural menopause because of the neutral benefits seen in some studies. Hormone therapy is not recommended at any age to prevent or treat cognitive decline or dementia but is recommended for indirect treatment vasomotor symptoms and sleep disturbances. Symptomatic relief may indirectly effect memory and concentration positively.

Conclusion

Studies show that estrogen plays a role in normal cognitive function. Estrogen decrease during perimenopause can lead to flushing, mood changes, and in some studies, mild cognitive changes (eg, mild memory loss, verbal fluency impairment, and slowed psychomotor speed). This menopause-related cognitive decline is very mild and may mimic MCI, but not dementia. Although there is controversy in the literature about the presence of cognitive decline in perimenopause, there is not enough evidence to state that it does not ever occur, making it important not to ignore the concept of low estrogen and mild cognitive decline.

Neurologists must consider perimenopause when evaluating women with memory decline. A detailed neuropsychologic

battery of tests are indicated as in any individual with memory impairment, along with a brain MRI and standard laboratory testing as for any other cognitively impaired individual.

Small cognitive decrements that may occur during perimenopause usually resolve by menopause. This information can help counsel perimenopausal women with concerns about memory problems. It is also important when addressing concomitant symptoms of anxiety or depression that can also affect cognition. Perimenopause time is an excellent time also to evaluate and treat modifiable cardiovascular risk factors that will improve cardiovascular health and lessen risk of vascular-related cognitive decline and dementia. If the patient meets the suggested criteria for menopause-related cognitive impairment, a short-term trial of estrogen (6-12 months) should be considered with consultation as needed with a gynecologist and careful follow up during the trial period.

Women with high risk of stroke or clinically evident cardiovascular disease, especially MRI evidence of multiple small white matter strokes and mild cognitive decline frequently worsen clinically and are not good candidates for estrogen therapy.

More studies are needed to examine the effect of perimenopause on the hypothalamic pituitary axis in relation to cognition and mood. ■

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