The Menopausal Brain

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At the age of 52, I have great appreciation of the clinical significance of the line of research I have been pursuing since age 25–menopause, hormones, and cognitive function. In that 27 years, research on this topic has swung like a pendulum from great promise to great pessimism and back to promise. In the 1990s, there was considerable interest in estrogen and cognition, stemming largely from meta-analyses showing a 29% decreased risk of Alzheimer disease in women who had used hormone therapy (HT).[1] We still do not have a clear indication of how HT affects Alzheimer disease–18-year follow-up data from the Women's Health Initiative show a lower risk of death from Alzheimer disease among women randomized to estrogen-alone therapy,[2] a finding that is opposite earlier Women's Health Initiative findings.[3] Then, and now, there is no treatment for Alzheimer disease, so primary prevention is the key to lowering the incidence of a disease that, by the year 2050, is expected to affect more than 13.8 million patients in the United States, with annual costs of $1.1 trillion (in 2018 dollars). Women are right to fear Alzheimer disease–two thirds of Alzheimer disease patients are women. Thus, understanding the factors that contribute to women's cognitive health and risk of Alzheimer disease is key not only to the well-being of those women but also to the health care system.

It is now widely recognized in the field of Alzheimer disease research that cardiovascular risk factors, physical activity, and diet are linked to risk of Alzheimer disease later in life and that modification of these factors is key in lowering the incidence of dementia. Largely absent from this recognition is the role of the menopausal transition, an event experienced by all women who survive into late life. Not only do women more frequently report cognitive difficulties as they transition from premenopause to perimenopause to postmenopause, but they also perform more poorly on standardized neuropsychological tests, particularly tests of verbal memory, aspects of executive function, and processing speed.[4,5] It is these changes and their neurobiological underpinnings that likely contribute to women's description of "brain fog."

Let me indulge in a bit of informed introspection to illustrate how these cognitive changes affect my daily life at 52. At midlife, I find myself more frequently forgetting where I parked in the hospital parking garage. As in the case described by Dr. Devi[6] in this issue of *Obstetrics & Gynecology* (see page 1325), I, too, can feel lost in this familiar environment. Despite my fund of knowledge in women's brain health, these episodes disturb me. Brain functioning is key to my academic success, my financial well-being, my social and family life, and my path to healthy aging. I am quite sure that if I did not have an understanding of menopause and women's brain health, I would wonder if this was an early sign of Alzheimer disease, a disease which affected my paternal grandmother.

If I think critically about these parking lot lapses, however, I realize that I never encoded the location of my car because I was on my mobile phone checking my calendar, responding to an email, or participating in

See related article on page 1325.

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a teleconference. The brain fog that I experienced was linked to the impossible feat of multitasking. One cannot simultaneously encode a location and contribute meaningfully to a conversation about a grant application. When I was younger, my keen executive functioning and my high-functioning prefrontal cortex allowed me to more easily switch between tasks. Neuroimaging studies of midlife women show that their prefrontal cortex is more active during cognitive tasks than in premenopausal women–it needs to work harder to accomplish the same task.[7] To encode where I parked, I have to encode a spatial location, an ability subserved by the hippocampus. The hippocampus, like the prefrontal cortex, is rich in estrogen receptors. Estrogen helps to maintain hippocampal and prefrontal function as we age.[8] Behavioral and neuroimaging studies show that early postmenopausal women recruit the hippocampus of both hemispheres to accomplish memory tasks and that, the lower the estradiol levels, the more the two hippocampi are functionally connected.[9] I take heart in findings that memory function appears to take the biggest hit in perimenopause but then rebounds.[10]

I attribute my cognitive lapses primarily to menopause-related changes in estradiol, but I also recognize that I do not sleep as well as I used to. Indeed, sleeping was my greatest talent. I am fortunate to not be woken up during sleep by night sweats. My own work with ambulatory hot flush monitors shows that night sweats as well as daytime hot flushes are linearly associated with memory errors.[11] Emerging evidence indicates that treating the hot flushes leads to a rebounding of memory performance.[11] Thus, while HT is not U.S. Food and Drug Administration–approved for the treatment or prevention of cognitive impairment, HT remains the gold standard treatment for vasomotor symptoms and is likely to improve memory in women whose sleep is disrupted by night sweats.

One of the greatest gifts we can give ourselves and patients who express concerns about cognitive lapses is to normalize cognitive lapses, noting that the changes appear to be time-limited and that hormonal changes and menopausal symptoms contribute to those problems. These memory concerns can be used to motivate patients to optimize their long-term brain health by lowering cardiovascular risk factors, engaging in regular walking or other aerobic exercise, and following the Mediterranean diet. Midlife women can be advised to maintain good sleep hygiene, treat depression and anxiety, and consider HT for vasomotor symptoms. Improved understanding of these issues can help to avoid the negative consequences of misattributing menopause-related cognitive difficulties to Alzheimer disease and other dementias, as illustrated in the two cases described by Dr. Devi.

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