

Hormone therapy and cognition: What is best for the midlife brain?

Memory issues are a common source of concern for midlife women. ObGyns are in a unique position to advise women about the roles of menopause and vasomotor symptoms in cognitive function, help normalize the midlife cognitive experience, and help women maintain brain health into late life.

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CASE HT for vasomotor symptoms in peri-menopausal woman with cognitive concerns

Jackie is a 49-year-old woman. Her body mass index is 33 kg/m², and she has mild hypertension that is effectively controlled with antihypertensive medications. Otherwise, she is in good health.

During her annual gynecologic exam, she reports that for the past 9 months her menstrual cycles have not been as regular as they used to be and that 3 months ago she skipped a cycle. She is having bothersome vasomotor symptoms (VMS) and is concerned about her memory. She says she is forgetful at work and in social situations. During a recent presentation, she could not remember the name of one of her former clients. At a work happy hour, she forgot the name of her coworker's husband, although she did remember it later after returning home.

Her mother has Alzheimer disease (AD), and Jackie worries about whether she, too,

might be developing dementia and whether her memory will fail her in social situations.

She is concerned about using hormone therapy (HT) for her vasomotor symptoms because she has heard that it can lead to breast cancer and/or AD.

How would you advise her?

HT remains the most effective treatment for bothersome VMS, but concerns about its cognitive safety persist. Such concerns, and indeed a black-box warning about the risk of dementia with HT use, initially arose following the 2003 publication of the Women's Health Initiative Memory Study (WHIMS), a randomized, placebo-controlled trial of HT for the primary prevention of dementia in women aged 65 years and older at baseline.¹ The study found that combination estrogen/progestin therapy was associated with a 2-fold increase in dementia when compared with placebo.

One of the critical questions arising even before WHIMS was whether the cognitive risks associated with HT that were seen in WHIMS apply to younger women. Attempting to answer the question and adding fuel to the fire are the results of a recent case-control study from Finland.² This study compared HT use in Finnish women with and



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without AD and found that HT use was higher among Finnish women with AD compared with those without AD, regardless of age. The authors concluded, “Our data must be implemented into information for the present and future users of HT, even though the absolute risk increase is small.”

However, given the limitations inherent to observational and registry studies, and the contrasting findings of 3 high-quality, randomized controlled trials (RCTs; more details below), providers actually can reassure younger peri- and postmenopausal women about the cognitive safety of HT.³ They also can explain to patients that cognitive symptoms like the ones described in the case example are normal and provide general guidance to midlife women on how to optimize brain health.

Closer look at WHI and RCT research pinpoints cognitively neutral HT

In WHIMS, the combination of conjugated equine estrogen (CEE; 0.625 mg/d) plus medroxyprogesterone acetate (MPA;

2.5 mg/d) led to a doubling of the risk of all-cause dementia compared with placebo in a sample of 4,532 women aged 65 years and older at baseline.¹ CEE alone (0.625 mg) did not lead to an increased risk of all-cause dementia.⁴

Whether those formulations led to cognitive impairment in younger postmenopausal women was the focus of WHIMS-Younger (WHIMS-Y), which involved WHI participants aged 50 to 55 years at baseline.⁵ Results revealed neutral cognitive effects (ie, no differences in cognitive performance in women randomly assigned to HT or placebo) in women tested 7.2 years after the end of the WHI trial. WHIMS-Y findings indicated that there were no sustained cognitive risks of CEE or CEE/MPA therapy. Two randomized, placebo-controlled trials involving younger postmenopausal women yielded similar findings.^{6,7} HT shown to produce cognitively neutral effects during active treatment included transdermal estradiol plus micronized progesterone,⁶ CEE plus progesterone,⁶ and oral estradiol plus vaginal progesterone gel.⁷ The findings of these randomized trials are critical for guiding decisions regarding

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Although a recent case-control study found that HT use was higher among women with AD, RCT data reassure younger peri- and postmenopausal women about the cognitive safety of HT

TABLE 1 Hormone therapy formulations shown to produce cognitively neutral effects in early postmenopausal women

- Transdermal estradiol (50 µg/wk) plus micronized progesterone (200 mg, 12 d/month)
- Oral conjugated equine estrogen (0.45 mg) plus micronized progesterone (200 mg, 12 d/month)
- Oral estradiol (1 mg/d) plus vaginal progesterone gel (10 d/month)

the cognitive risks of HT in early postmenopausal women (TABLE 1).

What about women with VMS?

A key gap in knowledge about the cognitive effects of HT is whether HT confers cognitive advantages to women with bothersome VMS. This is a striking absence given that the key indication for HT is the treatment of VMS. While some symptomatic women were included in the trials of HT in younger postmenopausal women described above, no large trial to date has selectively enrolled women with moderate-to-severe VMS to determine if HT is cognitively neutral, beneficial, or detrimental in that group. Some studies involving midlife women have found associations between VMS (as measured with ambulatory skin conductance monitors) and multiple measures of brain health, including memory performance,⁸ small ischemic lesions on structural brain scans,⁹ and altered brain function.¹⁰ In a small trial of a nonhormonal intervention for VMS, improvement in VMS following the intervention was directly related to improvement in memory performance.¹¹ The reliability of these findings continues to be evaluated but raises the hypothesis that VMS treatments might improve memory in midlife women.

Memory complaints common among midlife women

About 60% of women report an undesirable change in memory performance at midlife as compared with earlier in their lives.^{12,13} Complaints of forgetfulness are higher in

perimenopausal and postmenopausal women compared with premenopausal women, even when those women are similar in age.¹⁴ Two large prospective studies found that memory performance decreases during the perimenopause and then rebounds, suggesting a transient decrease in memory.^{15,16} Although cognitive complaints are common among women in their 40s and 50s, AD is rare in that age group. The risk is largely limited to those women with a parent who developed dementia before age 65, as such cases suggest a familial form of AD.

What causes cognitive difficulties during midlife?

First, some cognitive decline is expected at midlife based on increasing age. Second, above and beyond the role of chronologic aging (ie, getting one year older each year), ovarian aging plays a role. A role of estrogen was verified in clinical trials showing that memory decreased following oophorectomy in premenopausal women in their 40s but returned to presurgical levels following treatment with estrogen therapy (ET).¹⁷ Cohort studies indicate that women who undergo oophorectomy before the typical age of menopause are at increased risk for cognitive impairment or dementia, but those who take ET after oophorectomy until the typical age of menopause do not show that risk.¹⁸

Third, cognitive problems are linked not only to VMS but also to sleep disturbance, depressed mood, and increased anxiety—all of which are common in midlife women.^{15,19} Lastly, health factors play a role. Hypertension, obesity, insulin resistance, diabetes, and smoking are associated with adverse brain changes at midlife.²⁰

Giving advice to your patients

First, normalize the cognitive complaints, noting that some cognitive changes are an expected part of aging for all people regardless of whether they are male or female. Advise that while the best studies indicate that these cognitive lapses are especially common in perimenopausal women, they

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The hypothesis that treatment of VMS might improve memory in midlife women cannot be reliably proven with currently published data

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TABLE 2 Patient Health Questionnaire (PHQ)-2

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3

- A score ≥ 3 indicates probable major depressive disorder.
- Patients who screen positive should be further evaluated with the PHQ-9 or other screening instruments to determine whether they meet criteria for a depressive disorder.
- Welcome to the Patient Health Questionnaire (PHQ) Screeners. Screener overview. <http://www.phqscreeners.com/select-screener/36>. Accessed June 28, 2019.

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Patients can keep their brains healthy by treating hypertension, reducing BMI, engaging in regular aerobic exercise, eating a Mediterranean diet, maintaining an active social life, and engaging in novel challenging activities

appear to be temporary; women are likely to resume normal cognitive function once the hormonal changes associated with menopause subside.^{15,16} Note that the one unknown is the role that VMS play in memory problems and that some studies indicate a link between VMS and cognitive problems. Women may experience some cognitive improvement if VMS are effectively treated.

Advise patients that the Endocrine Society, the North American Menopause Society (NAMS), and the International Menopause Society all have published guidelines saying that the benefits of HT outweigh the risks for most women aged 50 to 60 years.²¹ For concerns about the cognitive adverse effects of HT, discuss the best quality evidence—that which comes from randomized trials—which shows no harmful effects of HT in midlife women.⁵⁻⁷ Especially reassuring is that one of these high-quality studies was conducted by the same researchers who found that HT can be risky in older women (ie, the WHI Investigators).⁵

Going one step further: Protecting brain health

As primary care providers to midlife women, ObGyns can go one step further and advise patients on how to proactively nurture their brain health. Great evidence-based resources for information on maintaining brain health include the Alzheimer’s Association (<https://www.alz.org>) and the Women’s Brain Health Initiative (<https://womensbrainhealth.org>). Primary prevention of AD begins decades

before the typical age of an AD diagnosis, and many risk factors for AD are modifiable.²² Patients can keep their brains healthy through myriad approaches including treating hypertension, reducing body mass index, engaging in regular aerobic exercise (brisk walking is fine), eating a Mediterranean diet, maintaining an active social life, and engaging in novel challenging activities like learning a new language or a new skill like dancing.²⁰

Also important is the overlap between cognitive issues, mood, and alcohol use. In the opening case, Jackie mentions alcohol use and social withdrawal. According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), low-risk drinking for women is defined as no more than 3 drinks on any single day and no more than 7 drinks per week.²³ Heavy alcohol use not only affects brain function but also mood, and depressed mood can lead women to drink excessively.²⁴

In addition, Jackie’s mother has AD, and that stressor can contribute to depressed feelings, especially if Jackie is involved in caregiving. A quick screen for depression with an instrument like the Patient Health Questionnaire-2 (PHQ-2; **TABLE 2**)²⁵ can rule out a more serious mood disorder—an approach that is particularly important for patients with a history of major depression, as 58% of those patients experience a major depressive episode during the menopausal transition.²⁶ For this reason, it is important to ask patients like Jackie if they have a history of depression; if they do and were treated

medically, consider prescribing the antidepressant that worked in the past. For information on menopause and mood-related issues, providers can access new guidelines from NAMS and the National Network of Depression Centers (NNDC).²⁷ There is also a handy patient information sheet to accompany those guidelines on the NAMS website (<https://www.menopause.org/docs/default-document-library/menonote-menopause-and-depression.pdf>).

CASE Resolved

When approaching Jackie, most importantly, I would normalize her experience and tell her that memory problems are common in the menopausal transition, especially for women with bothersome VMS. Research suggests that the memory problems she is experiencing are related to hormonal changes and not to AD, and that her memory will likely improve once she has transitioned through the menopause. I would tell her that AD is rare at midlife unless there is a family history of early onset of AD (before age 65), and I would verify the age at which her mother was diagnosed to confirm that it was late-onset AD.

For now, I would recommend that she be prescribed HT for her bothersome hot flashes

using one of the “safe” formulations in the Table on page 24. I also would tell her that there is much she can do to lower her risk of AD and that it is best to start now as she enters her 50s because that is when AD changes typically start in the brain, and she can start to prevent those changes now.

I would tell her that experts in the field of AD agree that these lifestyle interventions are currently the best way to prevent AD and that the more of them she engages in, the more her brain will benefit. I would advise her to continue to manage her hypertension and to consider ways of lowering her BMI to enhance her brain health. Engaging in regular brisk walking or other aerobic exercise, as well as incorporating more of the Mediterranean diet into her daily food intake would also benefit her brain. As a working woman, she is exercising her brain, and she should consider other cognitively challenging activities to keep her brain in good shape.

I would follow up with her in a few months to see if her memory functioning is better. If it is not, and if her VMS continue to be bothersome, I would increase her dose of HT. Only if her VMS are treated but her memory problems are getting worse would I screen her with a Mini-Mental State Exam and refer her to a neurologist for an evaluation. ●

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