GENDER, HORMONES, AND ALZHEIMER’S DISEASE
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Alzheimer’s disease (AD) is the most common cause of dementia among older adults, affecting about twice as many women as men. In large part, this sex difference occurs because women enjoy a longer life expectancy than men. However, some studies also suggest that AD incidence is increased for women relative to men, particularly among the very old. Exposures to endogenous and exogenous sex steroids of course differ between men and women, and hormones are thus considered as a relevant consideration for any incidence difference. In the laboratory, ovariectomy increases β-amyloid deposition in the brain, an effect attenuated by estradiol administration; other neuroprotective and neurotrophic effects of estrogen might also be expected to benefit AD symptoms or protect against the development of AD. Symptomatic treatment of Alzheimer’s disease. Estrogen has been investigated as therapy for women with mild-to-moderate dementia due to AD. Clinical trials have been relatively small, and most studies — but not all — suggest no benefit of estrogen on cognitive, functional, or global outcomes. The two largest trials were an American study of 120 women without a uterus, where active treatment used unopposed oral conjugated estrogens, and a French study of 117 women, where active treatment was low-dose transdermal estradiol plus oral micronized progesterone. In the US trial, there were no differences after 12 months on most outcomes; and in the French trial, where all participants also received standard therapy with a cholinesterase inhibitor, there were no differences after 28 weeks on cognitive and other outcomes.

Primary prevention: episodic memory and Alzheimer’s disease. Primary prevention of AD is of greater public health import than symptomatic amelioration of dementia. Impairments in episodic memory are associated with increased risk of developing AD up to a decade later. The amnestic variety of mild cognitive impairment, defined largely on the basis of episodic memory deficits in the absence of dementia, is viewed by many as an early, prodromal stage of AD. Episodic memory refers to the conscious recall of information from an earlier event or episode. Clinicians typically assess this form of memory with delayed recall of items from a word list, details from a short story, or figures from a set of drawings. Encoding of episodic memory is highly dependent on hippocampus and other medial temporal lobe structures. In the laboratory, estradiol enhances hippocampal long term potentiation, a process implicated in memory formation. Estradiol can augment learning mediated by the cholinergic system. Estradiol protects cholinergic neurons, which express receptors for estrogen. Estradiol can also enhance memory performance in older ovariectomized primates, and hippocampal blood flow tends to be increased in postmenopausal hormone users compared to nonusers.

Despite promising laboratory findings, there is no compelling evidence that the natural menopausal transition is associated with declines in episodic memory, at least during midlife. Observational evidence on hormone therapy and cognition — for example, from the Cache County cohort and the Nurses’ Health Study — is inconsistent. Importantly, there is now strong clinical trial evidence that starting estrogen-containing hormone therapy in the late postmenopause does not substantially affect episodic memory. For women in the menopausal transition and early postmenopause, clinical trial evidence is more limited. Whereas most studies in this age group do not demonstrate an effect of hormones, there is evidence for short-term improvement in verbal episodic memory for estrogen initiated immediately after surgical menopause. Results from the Women’s Health Initiative clinical trial indicate that hormone therapy begun after age 64 years may actually increase dementia risk. This experimental finding contrasts with a number of observational studies, where hormone use is associated with reduced risk of developing AD. Observational studies may have been systematically biased, since hormone users tend to be healthier and better educated than nonusers or, alternatively, findings from the Women’s Health Initiative may not generalize to younger women who were ineligible for inclusion in this trial. Because most hormone exposure in observational studies represents relatively short-term use by younger women close to the age of menopause, it is speculated that hormone use during an early “critical window” might reduce later risk of AD. Consistent with this formulation, long-term follow-up of midlife participants in clinical trials of hormone therapy indicated that significantly more women in the original placebo groups scored below a cutoff score for cognitive impairment than women in the original hormone groups.
Other considerations. Women's Health Initiative authors speculated that deleterious effects of hormone therapy on dementia incidence may have been due to adverse effects on the cerebral vasculature. Raloxifene, a selective estrogen receptor modulator, appears to present a more neutral cardiovascular profile. Planned analyses in a large clinical trial suggested that a relatively high dose of raloxifene reduced the incidence of cognitive impairment in older postmenopausal women, where cognitive impairment was defined to include both dementia and mild cognitive impairment.20 Little is known about long-term cognitive effects of the phytoestrogens, although one controversial observational study found that tofu consumption in midlife was associated with greater cognitive impairment in old age.21 For androgens and for neurosteroids, cognitive effects in midlife and old age are less well studied than those of estrogen.

Summary and key points. (1) Estrogen therapy does not improve AD symptoms (limited clinical trial evidence). (2) The natural menopause transition is not associated with declines in episodic memory (observational evidence). (3) Initiating hormone therapy after about age 65 does not substantially affect memory (clinical trial evidence). (4) For younger women, hormone therapy after natural menopause does not substantially affect memory; estrogen use after surgical menopause may benefit verbal memory (limited clinical trial evidence). (5) Hormone therapy begun after about age 65 increases dementia risk (clinical trial evidence). (6) For hormones begun during an early critical window, such as the perimenopause and early postmenopause, long-term effects on cognition or AD risk require further research.

References

