UNIVERSITY of WASHINGTON

GYNECOLOGIST'S APPROACH TO MENOPAUSE AND COGNITION

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Diagnosis of menopause as cause of symptoms

- Hormone levels
  - estradiol levels not reliably correlated with scores on memory tests
  - Determination of menopause is clinical, not based on threshold hormone levels
- Diagnosis of exclusion—optimize other factors
- Correct hormonal imbalance if indicated
  - Perimenopausal people may benefit from oral contraceptives to smooth erratic hormonal variability
- Treat vasomotor symptoms directly
  - Several nonhormonal approaches
  - No clear evidence that improvement in hot flashes improves cognition

Cognitive Changes

- Evidence that verbal learning and memory, and to a lesser extent processing speed, can decline slightly in perimenopause
  - Ability for new learning appears most affected
- Although depression, anxiety, or sleep disturbance are related to cognitive decline, neither mood nor age account for these cognitive changes
- Unclear whether transient issues with cognition resolve after menopause
- Studies show reported hot flashes do not correlate with cognitive performance
  - However, women with hot flashes (measured by skin conductance) have affected memory performance

Maki PM, et al. *Menopause*. 2008;15(5):848-856; Lehert P, et al. *Climacteric.* 2015;18(5):678-689.

Clinical Factors affecting Cognitive Function in Menopause

- Sleep
- Mood (depression, anxiety)
- Family pressures (‘sandwich’ generation)/situational stress
- Age at menopause
- Vasomotor symptoms of menopause (hot flashes, night sweats)

Cognitive Changes

- Observational studies show that some activities and lifestyle choices may help protect against dementia:
  - Maintaining an extensive social network
  - Staying active mentally
  - Engaging in regular physical exercise
  - Increasing dietary intake of omega-3 fatty acids and certain vitamins from natural foods
  - Following a Mediterranean diet
  - Abstaining from tobacco use
  - Consuming alcohol in moderation
- Trials of dietary supplements and vitamins have generally failed to show significant cognitive benefit

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Hormone Therapy and Cognition

- In RCTs, HT has a small or no overall effect on short-term or long-term cognition
- Timing of administration (early or remote from menopause transition) or mode (oral vs transdermal) has not shown significant effect on cognition
- Women who undergo surgical menopause who initiate HT may benefit from improved cognitive skills such as verbal memory, at least in the short term

Epperson CN, et al. *J Clin Endocrinol Metab*. 2013;98(9):3829-3838; Phillips SM, et al. *Psychoneuroendocrinology*. 1992;17(5):485-495.

Clinical Trials

- Kronos Early Estrogen Prevention Study (KEEPS) found no cognitive benefit or harm of oral or transdermal estrogens
- WHI Memory Study of Younger women (WHIMSY) found no sustained cognitive benefit or risk from oral estrogen in women from the WHI aged 5—55 at randomization
- Early versus Late Intervention Trial (ELITE) found no cognitive benefit or risk of oral estradiol when given to women close to or more remote from menopause
- Small clinical trial showed cognitive benefits of estrogen in women with moderate to severe vasomotor symptoms
- WHI Memory Study (WHIMS), in women over 65, risk of dementia was doubled for women using estrogen and progestin, but not those on estrogen alone

Menopause Practice, A Clinician's Guide, 6th Edition, 2020

What about younger women?

Surgical menopause before average age of menopause or primary ovarian insufficiency (before age 40)

- Likely to be associated with increased risk of cognitive decline
- Risks associated with hormone therapy in older women do not apply
- Other risks mitigated by hormone replacement: bone loss, sexual function decline, heart disease

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Current recommended hormone regimens

- Transdermal estradiol considered the safest formulation as not associated with increased stroke risk
- Micronized progesterone most commonly used oral progestogen
- Estrogen used alone if uterus has been removed
- Intrauterine progestin (IUD) is popular but not FDA-approved for this indication
- No data to support any particular regimen for cognitive effects
- Duration of use?? Shared decision-making with annual review of benefits and risks