AUSTRALASIAN MENOPAUSE SOCIETY
EMPOWERING MENOPAUSAL WOMEN

Information Sheet

Oestrogen and cognition in the perimenopause and menopause.

KEY POINTS

- Women commonly report memory or cognition changes associated with the menopause transition and menopause. Women may refer to this as 'brain fade' or 'brain fog'.
- However, the contributing roles of menopause related to oestrogen decline, aging, effect of co-morbidities, psycho-social functioning and menopause-related symptoms such as insomnia and hot flushes need clarification.
- Cognitive changes associated with the menopause transition include reduced processing speed and reduced verbal memory. Verbal memory is defined as the ability to encode words and it is influenced by circulating oestradiol.
- MHT has positive or neutral effects of cognitive function in younger peri- or postmenopausal women. The age of the woman, MHT preparation and baseline cognitive function influence this effect.
- Cognitive testing is not indicated unless the symptoms are progressive and interfere with work performance or relationships.

Memory loss in the menopause.

Memory loss associated with menopause comprises poor recollection of recent events (recent recall) or of a while ago (delayed recall). This may manifest as:

- Loss of immediate focus (what was meant to be done)
- Appointments not met
- Distraction
- Misplacement of items
- Time lapses

These are not related to normal cerebral functioning such as learning, deduction and reasoning.

The incidence of memory problems in the menopause transition is reported by up to two thirds of women. It is thought these are transient and do not become chronic postmenopausal issues. There is no evidence that these functional deficits are indicative of dementia or precede neurodegenerative disease[1].

Memory problems associated with menopause are multifactorial. The process of menopause transition takes 5-8 years with symptoms described consistently in

observation studies (Study of Woman Across the Nation (SWAN) [2]. 50-80 % of women experience vasomotor symptoms (hot flushes, night sweats). Hot flushes are associated with hyperintensities on brain imaging and changes in brain function on fMRI. Cognitive symptoms are associated with depression which may also be increased during the perimenopause. Observational studies indicate an increased risk of memory deficits and Alzheimer's disease associated with premature surgical oophorectomy.

Effects of oestrogen on the brain

There are three common physiological oestrogens (oestradiol, oestrone and oestriol) of which oestradiol (E2) is seen to decline rapidly over the menopausal transition. This decline in E2 has been associated with a number of changes in the brain including cognitive changes, effects on sleep and effects on mood (see AMS Information Sheet: Sleep disturbance and the menopause). The role of oestrogen in cognition is indicated by:

- E2 interacts with the cholinergic, dopaminergic and mitochondrial functions[3].
- Oestrogen effects on brain volumes and neuronal connectivity
- Sex differences observed in the risk, onset and severity of neurodegenerative disease such as Alzheimer's, Parkinson's and stroke occur[4].
- Evidence of E2 interactions in a number of neuropsychiatric disorders including Alzheimer's disease, schizophrenia, and depression.
- Oestrogen action in the regulation of neuronal survival and neurotrophism[5].
- Positive correlation between endogenous oestrogen exposure and cognitive status later in life[6].

Effect of oestrogen therapy

Studies indicate mixed effects regarding oestrogen therapy and cognitive function with the hypothesis of a "window of opportunity" postulating that younger age or fewer years since menopause may be associated with positive effects of oestrogen whereas commencement of oestrogen therapy in later years is associated with an increased risk of dementia. The evidence suggests increased harm when oestrogen is given to women with poor baseline cognitive function. The evidence is summarised below:

- Observational data suggest that MHT initiated in mid-life may provide protection against the development of dementia[7].
- The Women's Health Initiative (WHI) Memory Study (WHIMS) found that women aged over 65 years who commenced combined menopausal hormone therapy (MHT) with conjugated equine estrogens (CEE) and medroxyprogesterone acetate experienced a twofold increased risk of probable dementia[8]. The WHIMS -MRI study demonstrated greater brain atrophy in frontal cortical and hippocampal regions in women receiving CEE versus women taking placebo[9].

CEE alone had a neutral effect on cognition and brain function in the WHIMS study[10]. Follow-up after 18 years of women who participated in the WHI CEE alone randomised controlled trial showed a 26% reduction in death due to Alzheimer's disease[11].

- The postmenopausal brain shows a decrease in hippocampal activation which is related to worse memory performance. The left hippocampus is more active in encoding verbal memory. It recruits the contralateral hemisphere with age, which requires oestradiol connectivity between the left and right hippocampus [12,13]. Women who start MHT early show better memory and hippocampal function – more youthful function on memory performance[11]. MRI studies indicate that E2 treatment dose-dependently enhances hippocampal volume in postmenopausal women[14] with a volume reduction in postmenopausal women not on MHT[15]. In addition, it benefits pre-frontal cortex function. The WHI Study of Cognitive Aging (WHISCA) showed that CEE/MPA worsened verbal memory, whereas CEE alone had no influence on cognition[16].
- Assessment of functional MRI changes suggest that there is improved efficiency of brain function during a sustained attention task in postmenopausal females receiving E2 and that during a working memory task, postmenopausal women had increased frontal lobe activation as task difficulty increased following treatment with E2 [17,18,19].
- Four randomized controlled trials of MHT (WHIMSY[20], KEEPS[21], ELITE-COG[22] and COGENT[23]) have shown a neutral effect on cognitive function in the early post-menopause. Whereas results from WHISCA, a sub-study of the WHI investigating cognition, indicated that combined MHT had a negative impact on verbal memory but no effect on other cognitive domains in woman older than 65 years[16].
- Surgical premature or early menopause increases the risk of Alzheimers by 70%[24]. If MHT commences before the age of 50, that risk is removed.
- MHT may correct the memory deficit directly, but the improved cognition may be due to improvement in other symptoms that are synergistic in exacerbating the memory loss such as sleep deprivation and hot flushes[25,26]. Reassurance can be given that such lapses are common and transitory[27].

Effect of other therapeutics

- A meta-analysis concluded that adjuvant anti-oestrogen therapy (tamoxifen or aromatase inhibitors) used in breast cancer is associated with impairment in verbal learning/ memory compared with control women either without breast cancer or with breast cancer but not treated with anti-oestrogen therapy. Addition of chemotherapy resulted in greater, although transient, cognitive impairment compared with adjuvant anti-oestrogen therapy alone. Wagner et al[28] Observational studies suggest that the risk of dementia is either not increased or is reduced with these agents[29].

- Limited evidence suggests that raloxifene, a SERM used to treat osteoporosis, is associated with improvement in verbal memory[12].

Advice to women

- At present, it is premature to recommend MHT for cognitive function until more substantiated clinical correlates are available.
- Lessening vasomotor symptoms with MHT or non-hormonal treatments may improve cognitive function.
- Improving sleep, using mnemonic devices or engaging in physical activity may also lessen menopause transition cognitive deficits[30].
- Cognitive testing is not indicated unless the symptoms are progressive and interfere with work performance or relationships.

Further Information

http:www.alz.org

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