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### **The menopause transition and hormone use: effects on cognitive performance in midlife women**

A recent publication from the Women's Health Across the Nation (SWAN) study by Greendale and colleagues has followed 2362 participants for 4 years during the menopause transition [1]. Major exposures were time spent in the menopause transition, hormone use prior to the final menstrual period, and postmenopausal current hormone use. Outcomes were longitudinal performance in three domains: processing speed (Symbol Digit Modalities Test (SDMT)), verbal memory (East Boston Memory Test (EBMT)) and working memory (Digit Span Backward).

Premenopausal, early perimenopausal and postmenopausal women exhibited learning capacity by scoring higher with repeated SDMT administration ( $p = 0.0008$ ) but scores of late perimenopausal women did not improve over time ( $p = 0.2$ ). EBMT delayed recall scores climbed during premenopause and postmenopause ( $p = 0.01$ ) but did not increase during early and late perimenopause ( $p = 0.14$ ). Scores on the initial SDMT, EBMT-immediate and EBMT-delayed tests were 4–6% higher among prior hormone users ( $p = 0.001$ ). On the SDMT and EBMT compared to the premenopausal referent, postmenopausal current users demonstrated poorer cognitive performance ( $p = 0.05$ ) but the performance of postmenopausal non-hormone users was indistinguishable from that of premenopausal women.

The authors conclude that, consistent with transitioning women's perception of their memory difficulties at this time, perimenopause was associated with a decrement in cognitive performance characterized by women not being able to learn as well as they had during the premenopause. Improvement in learning rebounded to premenopausal levels post menopause, suggesting that menopause transition-related cognitive difficulties may be time-limited. Hormone initiation prior to the final menstrual period had a beneficial effect, whereas initiation after the final menstrual period had a detrimental effect on cognitive performance.

#### **Comment**

It will be no surprise to anyone consulting with symptomatic women around the menopause that a frequent complaint is increased loss of memory and difficulty in decision-making during the menopause transition. This has been confirmed in the large longitudinal SWAN study, with an interesting additional finding of spontaneous improvement several years after menopause. Whether menopausal symptoms, e.g. vasomotor symptoms, mediate the cognitive dysfunction during the menopause transition has still to be investigated. However, an observation in this non-randomized study was the apparent beneficial effect of hormone therapy when initiated during the perimenopause. This is compatible with a therapeutic window of effect during perimenopause and is in keeping with our Australian REMEMBER study which suggested that early intervention of hormone therapy from around menopause may benefit some cognitive domains, including attention and concentration [2]. However, as in the SWAN study, late initiation of hormone therapy many years after menopause was not beneficial. A recent systematic review by Pauline Maki and Erin Sundermann of randomized, controlled trials concluded that there is some evidence of benefit from estrogen-alone therapy on verbal memory and executive function in younger postmenopausal women [3]. Added medroxyprogesterone acetate, however, may produce detrimental effects. The conclusion to be drawn from these papers is that this is a very important area that requires much more study and funding. The data are continuing to point towards a possible therapeutic window of

opportunity for both neuro- and cardioprotection in some symptomatic women near menopause. The future of hormone therapy may be regimens that minimize or omit systemic progestogens and start soon after the onset of debilitating perimenopausal symptoms.

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