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A scientific update on the critical window of hormone therapy and cognition: who, what, when?

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This presentation will provide a review of the clinical studies to date examining the critical window hypothesis of hormone therapy (HT) and cognitive function. The rationale for examining HT as an intervention to prevent or delay the onset of Alzheimer's disease (AD) came from observational studies showing a 29% reduced risk of AD among women with a history of HT use. The critical window hypothesis was initially put forth to explain the discrepancies between those observational studies and the results from randomized trials showing no cognitive benefit of HT in women with an AD diagnosis. Later the hypothesis was also used to explain the discrepancy between the observational studies and the Women's Health Initiative Memory Study (WHIMS) which showed a doubling of AD incidence in women aged 65 years and older who were randomized to receive combination HT. It is under-recognized that conjugated equine estrogen (CEE) alone had no significant effect on AD risk in WHI. Indeed large RCTs of CEE showed neutral cognitive effects of estrogen therapy on cognition, even in older women. New long-term follow-up data from the WHI lend some insights into the critical window hypothesis for AD prevention but raise questions about the consistency of AD findings in the WHI generally. A 2017 publication in JAMA examined mortality in WHI participants over an 18-year follow-up and showed that women randomized to CEE were less likely to die of AD than women randomized to placebo. This effect was independent of timing of initiation. Notably, CEE plus medroxyprogesterone acetate (MPA) had no effect on AD mortality. Overall, the findings on the critical window hypothesis are inconsistent but new data from WHI showing a reduced risk of AD in women randomized to CEE is consistent with the initial observational studies that showed a reduction in AD with estrogen therapy.

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