Combination hormone replacement therapy and dementia

Reason for posting: Observational studies have suggested that hormone replacement therapy (HRT) may reduce the risk of cognitive decline in postmenopausal women.[1] However, results from the Women's Health Initiative Memory Study (WHIMS)[2,3] recently prompted a letter to Canadian health care professionals from Wyeth Canada warning that combination HRT may increase a woman's risk of dementia.[4]

The trial: The WHIMS trial[2] prospectively followed 4381 postmenopausal women over the age of 65 who did not have dementia at study entry. The women were randomly assigned to receive either 1 daily tablet of 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate (n = 2229) or a matching placebo (n = 2303). The women were followed for 4.2 years on average, and the incidence of dementia and mild cognitive impairment was determined in both groups with the use of structured cognitive assessments. The absolute risk of dementia was low in both groups (1 in 222 of women in the HRT group and 1 in 455 of those taking placebo), but the relative risk of dementia was doubled for those taking HRT (hazards ratio [HR] 2.05, 95% confidence interval [CI] 1.21–3.48). Alzheimer's disease was the principal form of dementia. The increased risk began in the second year of use, was observed in all age groups (but highest among those over 75) and persisted throughout the study. In addition, the combination HRT did not appear to prevent mild cognitive impairment, which occurred at the same rate in both groups (HR 1.07, 95% CI 0.74–1.55).

In a separate WHIMS study[3] with identical study groups (combination HRT v. placebo), participants were followed up with annual Mini-Mental State Examinations (MMSE), but there were no differences between the groups in overall cognitive function. However, more women in the HRT group than in the placebo group had clinically significant declines in MMSE scores (6.7% v. 4.8%, p = 0.008).

What to do: Age-standardized rates of dementia are higher among women than among men,[5] a difference hypothesized to be due to postmenopausal estrogen decline.[2] However, combination HRT not only fails to prevent dementia, but it may increase the risk of it. Using the absolute risks generated from the WHIMS trial, we can estimate that treating 434 women over the age of 65 with combination HRT for 1 year would cause 1 new case of dementia. This risk should be appropriately figured into one's informed consent discussion about combination HRT use. Because the average age of women in the WHIMS trial was 71, the applicability of these risks to women under the age of 65 is unknown. It is also unclear whether other routes of delivery (e.g., transdermal) or different doses would confer the same risks of dementia. The failure of combined HRT regimens to prevent cardiovascular events[6,7] has led to speculation that the progestins in combination regimens may attenuate any potential benefit conferred by estrogen alone. Results from an arm of the WHIMS trial currently underway that involves women with a hysterectomy who are taking either estrogen alone or a placebo may help to end this controversy.[2] In the meanwhile, when HRT is indicated, it appears wise to use the lowest effective dose of combination HRT, for limited rather than prolonged periods.

Eric Wooltorton
CMAJ

References

1. Humphries KH, Gill S. Risks and benefits of hormone replacement therapy: The evidence speaks. *CMAJ* 2003;168(8):1001-10.
2. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003;289:2651-62.
3. Rapp SR, Espeland MA, Shumaker SA, Henderson VW, Brunner RL, Manson JE, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women. The Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003;289:2663-72.
4. Important safety information on estrogen plus progesterone [Dear Health Care Professional Letter]. Markham (ON): Wyeth Canada; 2003 May 28. Available: www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/premplus_e.html (accessed 2003 June 24).
5. Canadian Study of Health and Aging Working Group. Canadian Study of Health and Aging: study methods and prevalence of dementia. *CMAJ* 1994;150(6):899-913.
6. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33.
7. Yusuf S, Anand S. Hormone replacement therapy: a time for pause [editorial]. *CMAJ* 2002;167(4):357-9.