Critical Appraisal

Hormone replacement therapy and memory

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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(20): 2651-62.**

Research question

What effect does estrogen plus progestin (E+P) have on incidence of dementia and mild cognitive impairment (MCI) in postmenopausal women?

Type of article and design

Randomized, double-blind, placebo-controlled, multicentre trial.

Relevance to family physicians

Previous observational studies suggested that estrogen replacement therapy improves cognition and can prevent development of dementia in postmenopausal women.[1-3] Recent meta-analyses, however, have concerns about these studies' design and methods and have reached conflicting conclusions.[3-5]

A recent Canadian study suggests there are 60 150 new cases of dementia each year in Canada.[6] According to Health Canada,[7] women's life expectancy is 26% longer than men's, but women's likelihood of living with dementia and in institutions is more than twice that of men. We have awaited results of large randomized controlled trials to better define the relationship between hormone replacement therapy (HRT) and dementia in postmenopausal women.

Overview of study and outcomes

All participants in the Women's Health Initiative (WHI) Memory Study had first met enrolment criteria for the WHI[8] HRT trials. The WHI Memory Study enrolled women 65 and older free of probable dementia. Participants were asked to name a "designated informant" to describe their cognition and behaviour.

From the 4894 eligible participants in the WHI HRT trial, 4532 postmenopausal women were recruited. Participants received one tablet daily of 0.625 mg conjugated equine estrogen and 2.5 mg medroxyprogesterone acetate (n = 2229) or placebo (n = 2303). Mean time between randomization and previous Modified Mini-Mental State Examination (3MSE) for all subjects was 4.05 years.

The study had four phases. All participants had to undergo phase 1, a 3MSE at baseline and annually thereafter. Subjects were flagged to undergo phases 2 (an expanded neuropsychologic battery) and 3 (clinical examination by a local expert) if their 3MSE scores were below a designated cut-off adjusted for level of education. At the end of phases 2 and 3, local experts (geriatrician, geriatric psychiatrist, or neurologist) classified participants as having no dementia, MCI, or probable dementia, according to *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, criteria. All those

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Critical Appraisal

with probable dementia went on to phase 4 (computed tomography scans and laboratory tests to rule out reversible causes of dementia).

The primary outcome was incidence of probable dementia; incidence of MCI was the secondary outcome. The study was blinded to investigators; monitoring was conducted semiannually by an independent data and safety monitoring board. Adherence was recorded annually for the HRT group. The trial was designed to have >80% statistical power to detect an observed 40% relative reduction in incidence of dementia in the HRT group.

Results

The WHI Memory Study ended when the E+P component of the WHI HRT trial was terminated early.

Primary outcome. Overall, 61 cases of dementia were identified: 40 (66%) in the E+P group and 21 (34%) in the placebo group. Women in the E+P group had twice the risk of probable dementia compared with women in the placebo group (hazard ratio [HR] 2.05; 95% confidence interval, 1.21 to 3.48; 45 vs 22 per 10 000 person-years; $P = .01$). Cumulative HRs indicate that groups diverged 1 year after randomization and continued to diverge through 5 years' follow up. Even after excluding the 265 participants at increased risk of developing dementia at baseline, the HR for probable dementia was 2.64 in the E+P arm versus placebo.

Secondary outcome. Risk of being diagnosed with MCI was statistically similar between groups (HR 1.07; 95% confidence interval 0.74 to 1.55; 63 vs 59 cases per 10 000 person-years; $P = .72$).

Other. Alzheimer's dementia was most common in both treatment (20 [50.0%]) and placebo (12 [57.1%]) groups. Age and baseline 3MSE score had a statistically significant effect ($P < .001$ for both) on risk of developing probable dementia.

Analysis of methodology

This very large, well designed and executed randomized controlled trial had good follow up. Risk of probable dementia in the E+P group was twice that in the placebo group, and evidence of increased risk appeared as early as 1 year.

Some contentious points remain. Most well recognized is the treatment hormones used: oral conjugated equine estrogen and medroxyprogesterone acetate. Can these findings be generalized to all HRT preparations?

Also important is how quickly differences appeared. Some cases of probable dementia showed up during the first year, suggesting some participants already had preclinical dementia. Results remained robust, however, even when low baseline 3MSE scores were removed from the analysis; the relationship between probable dementia and hormone use persisted (HR 2.64).

Certain possibly confounding risk factors for dementia, including family history and apolipoprotein E4 levels, were not considered. Baseline characteristics were similar in groups, except for a slightly lower prevalence of stroke ($P = .01$) and a slightly higher use of statins ($P = .02$) in the E+P group. Controlling for prior statin use, however, did not alter findings.

Adherence rates decreased each year in the treatment group ($P < .001$); controlling for adherence did not change results.

Application to clinical practice

This large, randomized, rigorously controlled trial on the effects of HRT on MCI and dementia provides detailed and extensive data about participants. Drug administration ceased in July 2002; average exposure to HRT was 5.6 years. Both the

WHI HRT and WHI Memory Study trials continue to monitor outcomes. This study provides convincing, good-quality evidence that HRT does not improve cognition or prevent dementia in postmenopausal women.

Bottom line

- Use of E+P increases women's risk of probable dementia twofold compared with placebo (HR 2.05).
- Use of E+P does not prevent MCI (HR 1.07) and should not be prescribed to improve cognition or prevent dementia in postmenopausal women.
- This study provides convincing evidence that the risks of E+P outweigh the potential benefits.

Points saillants

- Le recours à l'œstrogène + progestatif (Œ+P) augmente du double le risque de démence probable chez les femmes par rapport au placebo (taux de risque 2,05).
- Le recours à l'Œ+P ne prévient pas la déficience cognitive légère (taux de risque 1,07) et il ne faut pas en prescrire pour améliorer la fonction cognitive ou prévenir la démence chez les femmes postménopausées.
- Cette étude dégage des données scientifiques convaincantes en faveur du fait que les risques de l'Œ+P excèdent ses bienfaits potentiels.

References

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