

Risks and benefits of postmenopausal combined hormone replacement therapy

Women and their doctors should not panic

IN 1997, South Australian women around the age of menopause had one of the highest reported rates of hormone replacement therapy (HRT) use in the world.¹ Among women aged 55–64 years, 60% had used HRT and nearly 40% were current users, with a mean length of HRT use of 70 months.

HRT is effective at relieving menopausal symptoms, and many women can stop taking HRT within a few years without recurrence of these symptoms. For the women who do experience return of menopausal symptoms after ceasing HRT, there has been the comfort of observational studies that showed that long-term HRT use, although increasing the risk of breast cancer and thromboembolic disease, reduced osteoporosis, bowel cancer, cardiovascular events, Alzheimer's dementia, and possibly stroke.² Critics of long-term HRT use have argued that selection of relatively healthy women to receive HRT may have influenced its reported long-term effects in unrandomised observational studies.³

Two large randomised trials of postmenopausal long-term HRT use were commenced in the 1990s to determine the benefits and risks. The Women's Health Initiative (WHI) in the United States (see website <<http://www.whi.org>>) focuses on defining the value of different strategies (eg, low-

fat diet, calcium and vitamin D supplementation) that could potentially reduce the incidence of heart disease, breast and colorectal cancer and low-impact fractures in postmenopausal women aged 50–79 years. The Women's International Study of long Duration Oestrogen after the Menopause (WISDOM) (see website <http://www.generalpractice.adelaideuni.org/research_index.htm>) is a UK-initiated, placebo-controlled study of women aged 50–69 years taking oestrogen, or oestrogen and progestogen, for 10 years. Endpoints of the study include fracture, cardiac events, cancer, dementia, thromboembolism, quality of life, and death. Some Australian women have been recruited to the WISDOM study.

Late in the evening (Australian time) of 9 July 2002, the American Medical Association posted a report of a WHI trial and an accompanying editorial on its *JAMA* website.^{4,5} The report revealed that this randomised, placebo-controlled, double-blind trial to evaluate combined oestrogen and progestogen therapy in postmenopausal women had been stopped early because there was compelling evidence that health risks exceeded health benefits.

Graham Colditz (Professor of Medicine at Harvard School of Public Health and one of the authors of the *JAMA*

editorial), who was visiting Australia at the time, and the Cancer Council, New South Wales, were ready to issue press releases (embargoed until 11.30 pm that evening) highlighting the 26% increased risk of breast cancer in women taking HRT. One of these releases was headed "Women advised to stop combined hormone replacement therapy". By the next morning (10 July), the Australian media were awash with headlines and reports that fuelled considerable alarm among women taking HRT. On the same day, the Australian Therapeutic Goods Administration (TGA) requested that the Australian Drug Evaluation Committee (ADEC) establish an Expert Committee to examine the *JAMA* article and provide advice on the significance of the study outcomes in the Australian context, the necessary and appropriate action required of the TGA, and the information that should be provided to Australian health professionals and consumers.

The rapidly convened ADEC Committee reviewed the *JAMA* article and editorial and gave the TGA its report, which was released on the TGA website in the late afternoon of 11 July. The report noted that the WHI trial was designed to investigate the efficacy and safety of long-term combined HRT in preventing diseases such as coronary heart disease and hip fracture in postmenopausal women. It was *not* designed to study the effects of HRT being used to treat menopausal symptoms or established osteoporosis. The mean age of women in the study was 63 years, with two-thirds being over 60. This, and the apparently high frequency of cardiac risk factors in the population (one-third being overweight and one-third obese, 50% being previous or current cigarette smokers, one-third having received treatment for high blood pressure, and over 10% having raised cholesterol requiring medication), may have led to a higher risk of cardiovascular events. However, this must be set against a likely underestimate of the excess risk as a result of treatment dropout and crossover.

There was no difference in overall mortality between the HRT and control groups for the duration of the study (mean, 5.2 years). The absolute increase in disease risk for an individual woman shown in the study was small: among 10 000 women in the age group studied and with their characteristics taking combination HRT for a year, there would be seven more cases of coronary heart disease (37 v 30), eight more cases of invasive breast cancer (38 v 30), eight more cases of stroke (29 v 21), and eight more cases of pulmonary embolism (15 v 7), but six fewer bowel cancers (10 v 16) and five fewer hip fractures (10 v 15), than among women not using HRT. Over the five years of the trial, there would be one extra case of an adverse event per 100 women taking the combined HRT continuously. The Expert Committee noted the increase in harm reported was smaller in the first two to three years after starting HRT than it was after three or more years of combined HRT use.

The conclusions of the Expert Committee are presented in the Box. The Committee recommended that the TGA ensure updating of product and consumer information for all products used in combination HRT, undertake a full review of the use of combination HRT in long-term treatment and prevention of osteoporosis, and review all ongoing trials using combination HRT for chronic diseases.

Conclusions of the Expert Committee of the Australian Drug Evaluation Committee

- Combination hormone replacement therapy (HRT) in any form should not be used for long-term disease prevention in postmenopausal women, because the benefits are not sufficient to justify the risks. This conclusion is not necessarily restricted to the particular products used in the trial, but could potentially apply to all oestrogen/progestin combination hormone products.
- Women can be assured that short-term use of combination HRT and other products to manage symptoms of menopause remains an appropriate treatment option, but women should discuss their particular medical circumstances with their doctors, as individual factors may affect the risks and benefits for them. This is even more so for younger women with a premature menopause, in whom the benefits of HRT would be expected to be greater, and the risks are probably smaller.
- The continued use of combined HRT for women with established osteoporosis is also an acceptable option for many, but women should discuss the benefits and risks with the treating doctor.
- In another arm of the Women's Health Initiative study, which has not been discontinued, the use of oestrogen alone for the prevention of disease in postmenopausal women who have had a hysterectomy continues under investigation. It is unsafe for women who have a uterus to use oestrogen without progestin, as use of oestrogen alone increases the risk of uterine cancer.

The WHI trial report and the abrupt cessation of the combined oestrogen plus progestogen trial have raised concerns among health practitioners, prescribers and consumers of combined HRT products. The previously anticipated health benefits from prolonged combined HRT use — reduced heart disease and strokes — were not borne out in the WHI study. However, the absolute risks associated with HRT are small. Women who are currently taking combined HRT, and their doctors, should not panic, but consider these new findings carefully in the light of their reasons for starting and continuing HRT before deciding whether to continue or stop. In women with osteoporosis, the benefit of a reduced fracture rate with long-term combined HRT must now be balanced against the increased risks of breast cancer, stroke, heart disease and thromboembolism. The relative efficacy and safety of HRT must be considered against that of other interventions, including ensuring adequate calcium intake and vitamin D status, exercise, or taking bisphosphonates or selective oestrogen-receptor modulators.

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1. MacLennan AH, Wilson DH, Taylor AW. Hormone replacement therapy in women at risk of cardiovascular disease and osteoporosis in South Australia in 1997. *Med J Aust* 1999; 170: 524-527.
2. MacLennan AH. Long-term hormone replacement therapy. *Aust Prescriber* 2000; 23: 90-92.
3. Posthuma WFM, Westendorp RGJ, Vandenbroucke JP. Cardioprotective effect of hormone replacement therapy in postmenopausal women: is the evidence biased? *BMJ* 1994; 308: 1268-1269.
4. 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: 321-333.
5. Fletcher SW, Colditz GA. Failure of estrogen plus progestin therapy for prevention. *JAMA* 2002; 288: 366-368. □