



Canadian consensus on hormone replacement therapy

Estrogen and progestin use in postmenopausal women

Summarized from a statement of the Society of Obstetricians and Gynaecologists of Canada

The Society of Obstetricians and Gynaecologists of Canada (SOGC) brought together an advisory committee made up of national experts on menopause to assist them in reviewing the findings of the Women's Health Initiative (WHI) study.¹ The WHI, a landmark study providing critical information on a variety of end points relating to risks and benefits of hormone replacement therapy (HRT) for postmenopausal women, is the largest randomized placebo-controlled clinical trial on HRT.

One arm of the study was halted in June 2002.² This arm was designed to define the risks and benefits of continuous administration of the estrogen-progestin combination, conjugated equine estrogen (0.625 mg/d) and medroxyprogesterone acetate (2.5 mg/d), to healthy postmenopausal women with a uterus. Primary outcomes were heart disease and breast cancer. Secondary outcomes were stroke, thromboembolism, osteoporotic fractures, and colorectal cancer.

The study excluded women with severe menopausal symptoms and enrolled women up to age 79 as long as they were healthy. Average age at entry to the study was 63.2 years: 33% were 50 to 59, 45% were 60 to 69, and 21% were 70 to 79. The WHI's safety monitoring board² recommended premature cessation of the combination Premarin/Provera arm on June 9, 2002, because risks of breast cancer and cardiovascular disease, although small, outweighed potential benefits (fewer osteoporotic

fractures and possibly reduced incidence of colorectal cancer) in these asymptomatic subjects. The authors concluded that continuous combined HRT was ineffective for primary prevention of heart disease (**Table 1**).

Extensive media coverage of the WHI findings²⁻⁶ has resulted in confusion and uncertainty about the appropriate use of, and appropriate counseling about, combined continuous HRT. The SOGC has prepared the following statement to assist health care professionals in counseling menopausal women about health promotion and disease prevention in the postmenopausal years. This statement is restricted to comments on the recent WHI publication¹ regarding cessation of the estrogen-progestin arm of the WHI study. The estrogen-only arm of the WHI for women who have undergone a hysterectomy is continuing, and information on risks and benefits in this population has not yet been released. Important lifestyle approaches to health promotion as well as alternative therapies have been reviewed recently by the SOGC and other professional bodies and are discussed in a consensus document at www.sogc.org.

Overview of WHI study results

- Continuous combined HRT was ineffective in preventing cardiovascular disease, and slightly increased the risk of coronary artery disease (CAD), by seven excess CAD cases per 10 000 women yearly.

Table 1. Attributable risks from daily combined continuous HRT reported in the WHI trial

RISK FACTORS	COMBINED CONTINUOUS HRT (N = 8506)	PLACEBO (N = 8102)	CASES PER 10 000 WOMEN YEARLY ATTRIBUTABLE TO HRT
Coronary artery disease	164	122	7
Stroke	127	85	8
Venous thromboembolism	151	67	180
Osteoporotic fractures	650	788	-5
Cancers			
• Invasive breast	166	124	8
• Colorectal	45	67	-6
• Endometrial	22	25	0

- Women who took continuous combined HRT had an increased incidence of stroke (eight excess cases per 10 000 women yearly).
- Incidence of venous thromboembolism and pulmonary embolism increased from 0.12% to 0.2% (18 excess cases per 10 000 women yearly).
- Risk of breast cancer increased in women who used continuous combined HRT for 5 years or more (eight excess cases per 10 000 women yearly or less than 0.1% increase per year of use).
- Continuous combined HRT reduced the risk of hip (five fewer cases per 10 000 women yearly), vertebral, and other osteoporotic fractures.
- Continuous combined HRT was associated with a nonsignificant reduction in risk of colorectal cancer (six fewer cases per 10 000 women yearly).

Analysis of study results

Every study has its limitations, and the WHI study is no exception. The study did not attempt to quantify quality-of-life variables related to use of HRT to control menopausal symptoms, but rather to examine whether HRT should be given to most menopausal women to prevent cardiovascular disease and osteoporosis. When interpreted in this context, the WHI study report provides meaningful information about HRT for individual women, their health care providers, and public health officials.

Coronary artery disease. The WHI has shown that combined continuous HRT should not be used for primary prevention of CAD in healthy, largely asymptomatic women in the three decades after menopause. In fact, use of continuous combined HRT in this population was associated with a small but significant risk of adverse cardiovascular events. Deaths due to cardiac disease were not significantly increased (15 and 13 per 10 000 woman-years in estrogen-progestin and placebo groups, respectively). At present, with no evidence of cardiovascular protection from combined continuous HRT, primary prevention of CAD depends on healthy lifestyle choices (smoking cessation,

exercise, weight control) and pharmaceutical agents with established value for preventing or treating cardiovascular disease, such as lipid-lowering agents and antihypertensive agents.

The WHI investigators deliberately chose not to enrol women with acute symptoms; as a result, only one third of subjects entered the trial before age 59. To date, data published on the 2839 combined continuous HRT users between age 50 and 59 do not allow definitive conclusions about cardiovascular risks and benefits of combined continuous HRT if started immediately at menopause. Whether the absolute risks reported by the WHI for women from age 50 to 79 apply to symptomatic women in their late 40s or early 50s is doubtful; however, these findings based on a large prospective trial can assist with counseling about risks for symptomatic women who elect to use HRT. Risks of non-fatal heart attack and stroke reported by the WHI amount to less than 0.1% per year of use. Rates of deep vein thrombosis and pulmonary embolism, which increase with age, doubled from approximately 0.1% per year to 0.2% per year.

New information about stroke. Previous evidence about combined continuous HRT use and stroke was based on numerous epidemiologic studies with inconsistent stroke end points and various definitions of combined continuous HRT use. In considering results of the WHI, it is important to remember that two thirds of the study population was older than 60 years. Although the WHI reported that combined continuous HRT appeared to increase the incidence of non-fatal stroke, the absolute risk was very small and was not statistically significant after adjusting for multiple testing. The characteristics of patients at greatest risk of stroke could become clear as investigators continue their evaluation with more explanatory analyses.

Breast cancer. Continuous combined HRT was associated with an increase in incidence of invasive breast cancer. This risk for individual women was very small—less than

0.1% per year of use (eight more cases per 10 000 women yearly)—and was similar to risks estimated in previous epidemiologic studies.

A meaningful finding of the WHI study is that breast cancer risk was not significantly increased during use of combined continuous HRT for up to 4 years. Only women who had used combined continuous HRT before enrolment in the WHI study showed this increased incidence of breast cancer, so risk of breast cancer increased only after 4 years' use. Frequency of surveillance by mammography was equivalent in both groups.

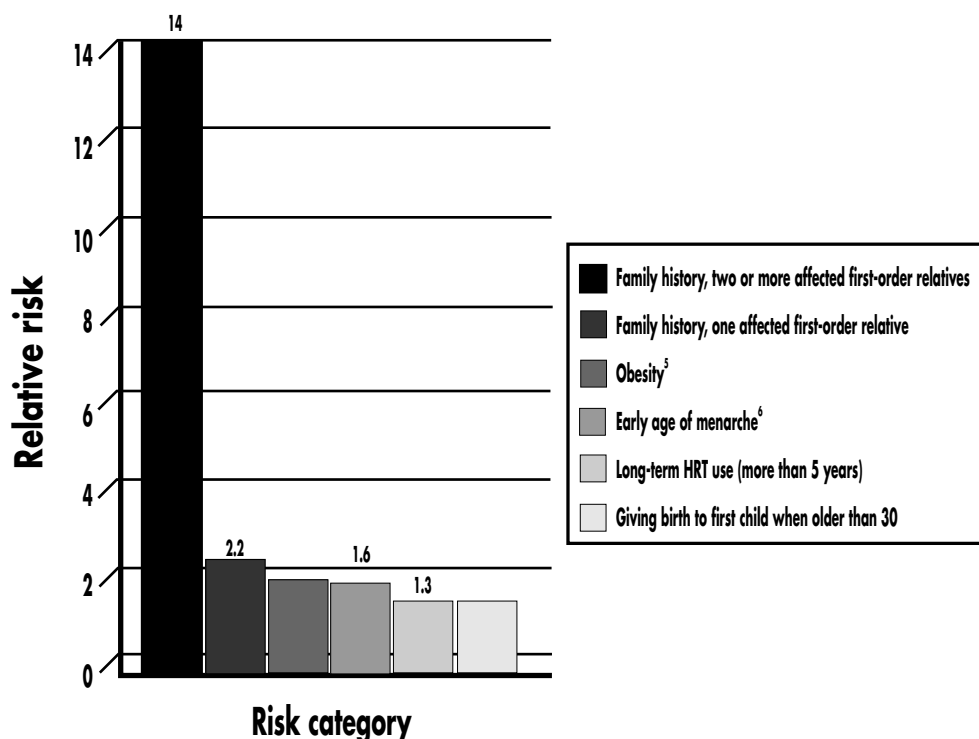
Because there was no significant increase in in situ cancers, it is uncertain whether the reported risk of invasive breast cancer among combined continuous HRT users was due to formation of new cancers. Combined continuous HRT could help with early diagnosis of pre-existing cancers or hasten preclinical to clinical conversion. In an older population, such as that in the WHI study, more pre-existing breast cancer might reasonably be expected. Subgroup analysis by age is critical to understand the attributable risks.

The effect from duration of use was virtually the same as that reported in the collaborative analysis published in 1997.⁵ Breast cancer risk was the same in estrogen-progestin and placebo groups for 4 years in the WHI study; in the collaborative study, breast cancer incidence was not significantly elevated until after 5 years of use (**Figure 1**^{5,6}).

New information about osteoporotic fractures. This was the first large clinical trial to confirm reduction in osteoporotic fracture incidence for women who choose combined continuous HRT.

How should results be applied to individual patients? Further analysis of the WHI results will help determine specific risk factors that could be useful for individualizing application of results. Although more than two thirds of the women were older than 60, there were 5522 women aged 50 to 60, more than in any previous study and more than the sum of patients in nearly all previous randomized controlled trials.

Figure 1. Relative risks of breast cancer placed in perspective: *The greatest single risk factor, after sex and advancing age, is the presence of two or more affected first-order relatives. Several commonly experienced risks include being 20% overweight, delaying childbirth until 30 or older, consuming three glasses of alcohol daily, and lack of regular exercise. Long-term use of combined continuous HRT is of comparable magnitude to this group of risk factors. Risks do not appear to be additive. In the WHI, the Gael model for computing and predicting risk of breast cancer did not identify women who were at higher risk for a diagnosis of invasive breast cancer.*



More in-depth analysis of the WHI study will likely provide useful information about baseline risk of cardiovascular disease and cancer in women aged 50 to 59. There are lower baseline risks for thromboembolism, stroke, myocardial infarction, and breast cancer in a younger population because each of these risks increases with age.

Are results applicable to other regimens? Results of the WHI study do not indicate the effects of other hormone doses, routes of administration, and formulations or of the use of progestins alone. There are theoretical reasons why different formulations might have different biological effects or greater safety, but no data from large clinical trials support recommendations at this time. Lower dosage and alternative delivery methods are promising options, but adverse event profiles for these approaches have not been determined in studies involving large numbers of women.

How long to continue combination therapy? Women taking combined continuous HRT for relief of menopausal symptoms generally find vasomotor symptoms spontaneously ease within 2 or 3 years. Women using combined continuous HRT for ongoing symptom relief should re-assess their medication and route and dosage regularly with their physicians, considering potential risks and benefits as well as effective alternatives.

Women taking estrogen only. The estrogen-only arm of the WHI study of women who had previously undergone hysterectomy is continuing. The risk-benefit profile has not been determined for these women. Women who plan to take estrogen-only therapy should undergo standard breast health monitoring. In the absence of data, using the lowest effective dose and shortest duration of estrogen for treatment objectives is prudent. Unopposed estrogen is not recommended for women with a uterus because of the risk of endometrial hyperplasia or cancer; if unopposed estrogen is prescribed, it must be accompanied by rigorous endometrial surveillance.

Are results applicable to women with premature menopause? These results offer no basis for modifying treatment recommendations for prematurely menopausal women.

How to stop combined continuous HRT. There is no scientific basis for counseling women on how to stop combined continuous HRT. Practically, women can decrease the dose slowly or use combined continuous HRT on alternate days for several weeks. Women reducing or stopping combined continuous HRT should be advised to anticipate withdrawal bleeding. Physicians may discuss alternative therapies, routes of administration, and combinations for continuous HRT.

Informed choice

The SOGC recommends that women discuss these issues with their health professionals so they can make an informed choice about combined continuous HRT for menopausal symptoms.

Conclusion

The best treatment for distressing menopausal symptoms remains HRT. Alternative (nonhormonal) therapies are limited in their effectiveness, and safety has not been tested in large-scale trials like the WHI study. Combined continuous HRT should not be recommended routinely for all postmenopausal women because it does not appear to offer cardiovascular protection and because the slightly increased risk of cardiovascular disease and breast cancer outweigh the benefits in asymptomatic women. Short-term use remains an option for osteoporosis prevention, and may be considered in conjunction with benefits, risks, tolerance, and the cost of alternatives.

The SOGC has revised its 2000-2001 *Consensus on Menopause and Osteoporosis*. The full-text version of this statement and patient resources are available at www.sogc.org. ♦

La SOGC a révisé son Consensus sur la ménopause et l'ostéoporose 2000-2001. Il est disponible à www.sogc.org.

References

1. 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.
2. Speroff L, Berga S. WHI trial arm with E/P finds an increase in breast cancer [Special Report]. Comments by Dr Leon Speroff and Dr Sarah Berga, *OB/GYN Clinical Alert* 2002;19(4):25-32.
3. American College of Obstetrician and Gynecologists. *Questions and answers on hormone therapy. In Response to the Women's Health Initiative Study Results on estrogen and progestin hormone therapy*. Washington, DC: American College of Obstetrician and Gynecologists; 2002. Available from: ACOG.NET via the Internet. Accessed 2002 Dec 19.
4. Stevenson JC, Whitehead MI. Hormone replacement therapy; findings of women's health initiative trial need not alarm users. *BMJ* 2002;325:113-4.
5. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. *Lancet* 1997;350:1047-59.
6. Huang Z, Hankinson SE, Colditz GA, Stampfer MJ, Hunter DJ, Manson JE, et al. Dual effects of weight and weight gain on breast cancer risk. *JAMA* 1997;278(17):1407-11.

...