The Women's Health Initiative (WHI) is a large, prospective, placebo-controlled trial sponsored by the National Institutes of Health (NIH). Its aim is to explore interventions that may yield preventive health benefits for post-menopausal women.1

The combined hormone replacement therapy (HRT) arm of the WHI was prematurely discontinued by the study's safety monitoring panel in July 2002.1 This arm involved 16,608 women who were taking either combined HRT (Premarin™ 0.625 mg/medroxyprogesterone 2.5 mg daily) or a placebo.

The investigators concluded that the risks associated with combined HRT, after four years of use, outweighed its benefits as a preventive agent. Not only did the daily combination of estrogen and progestin fail to prevent coronary heart disease, it increased the risk of coronary events, strokes, and venous thrombosis. Furthermore, after four years, the increasing rates of breast cancer made the overall risk/benefit ratio unacceptable for a therapy that was supposed to prevent serious disease (Figure 1). The authors recommended that, although the risk of osteoporotic fracture was reduced by combined HRT, the choice of this regimen for fracture prevention would have to be weighed against its tendency to increase the risk of coronary heart disease and breast cancer.1

The publication of the WHI results sparked widespread media attention. Many of our patients, and their families, expressed justifiable concern over the recommendations we had made regarding HRT before the results of the study.
were published. Many of us are still fielding tough questions about the applicability of these results to individual women in our practices.

The following questions represent those we may encounter in the wake of this important study. Suggested answers are derived from the WHI itself, as well as from recommendations by the Society of Obstetricians and Gynaecologists of Canada and the American College of Obstetricians and Gynecologists.

1. Is HRT dangerous?

No. It is not dangerous to use HRT. However, there are certain risks associated with its use. The WHI was stopped earlier than planned because the health risks associated with taking combination HRT outweighed the benefits, after four years of use. The investigators were mainly interested in studying how frequently coronary heart disease and breast cancer occurred in users of HRT as opposed to a similar group of women using a placebo. They discovered that the estrogen/progestin HRT users had more breast cancers, more coronary artery events, more strokes, and more venous thrombosis (Table 1). There was no difference in death rate between the two groups.
2. Are there any benefits to HRT?

Yes. The WHI study showed that women using combination HRT had fewer osteoporotic fractures and less colon cancers. Other well-designed studies have demonstrated that estrogen replacement helps relieve the menopausal symptoms of hot flashes and night sweats. Post-menopausal women who have symptoms of depression as well as hot flashes are more likely to show an improvement in mood when they use HRT.4

<table>
<thead>
<tr>
<th>Table 1</th>
<th>WHI study results</th>
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<tbody>
<tr>
<td></td>
<td>Excess events per 10,000 women/year with combined HRT use</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>7</td>
</tr>
<tr>
<td>Stroke</td>
<td>8</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>8</td>
</tr>
<tr>
<td>Venous Thrombosis</td>
<td>18</td>
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<tr>
<td>Colon Cancer</td>
<td>-6</td>
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<tr>
<td>Hip Fracture</td>
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3. Who should take HRT?

The most common reason for taking HRT is for the relief of menopausal symptoms, such as hot flashes and night sweats. Estrogen continues to be the most effective way to control these symptoms.5 As with any medication, it makes sense to use HRT at the lowest possible dose that gives the desired effect. Many women will feel better at a dose equivalent to 0.3 mg of Premarin™ per day, while others may need a higher dose. The results of the WHI and other studies suggest that the risk of breast cancer increases with the length of HRT use.6,7 Therefore, HRT should be used for the shortest time possible. It would be reasonable to temporarily stop taking the medication every few months, to see if the symptoms still exist.

HRT is also used for the relief of vaginal dryness. This symptom can often be alleviated by applying vaginal estrogen cream,
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Many women use HRT for osteoporosis prevention and treatment. HRT is still a good choice for these women if they are experiencing menopausal symptoms. It is the only agent that builds bone and controls hot flashes. On the other hand, if osteoporosis is the only reason for considering HRT, it might make more sense to choose another medication such as a bisphosphonate or raloxifene. These other agents prevent osteoporotic fractures, but do not appear to increase the risk of breast cancer or heart attack.

Several years ago, doctors were recommending HRT to prevent coronary heart disease. This recommendation was based on the results of population studies that suggested a cardiac benefit for women using HRT. Newer, more sophisticated studies, such as the WHI, have made us change our way of thinking to reflect the latest scientific evidence. Women should not take HRT in an attempt to prevent a heart attack. In fact, women with a history of coronary heart disease should likely avoid HRT if possible.
4. What are the risks with HRT?

The WHI study is very important in that it helps us to quantify the risks and benefits of HRT for healthy women. The magnitude of the risk is best described in terms of the number of extra “events” that can be expected in 10,000 women using HRT for one year. The study found that there were an extra seven heart attacks, eight strokes, 16 venous blood clots, and eight cases of breast cancer per 10,000 women using combined HRT (Table 1). In terms of benefits, there were six fewer colon cancers and five fewer hip fractures per 10,000 women using combined HRT. The magnitude of risk is small, as is the magnitude of benefit. An awareness of these numbers will help women make informed choices about their use of HRT.

Each woman needs to make her own decision about the amount of risk she is willing to take in order to gain the possible benefit of HRT. The use of any treatment, including non-hormonal therapies and herbal remedies, carries some risk. In many cases, all the risks are not known. It would be unrealistic to try to live life without any risk at all. For example, most of us have chosen to engage in the fairly risky behaviour of driving a car. We know that there is a small possibility of being hurt or killed while driving, but we have decided to take the risk in order to achieve the advantage of mobility. Similarly, a woman may choose to use HRT because it allows her to function more effectively during the day, and sleep better at night, even though she knows that her chances of having a heart attack or breast cancer are slightly increased.

5. Are plant-based forms of estrogen better?

The results published from the WHI give us information about only one type of HRT regimen (Premarin™ 0.625mg and medroxyprogesterone...
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2.5 mg, taken daily). Another branch of the WHI is studying hysterectomized women taking Premarin™ alone. This study has been allowed to continue. These women are being monitored with the same safety standards applied in the study that was prematurely stopped. We can conclude that, although we do not know yet the details, Premarin™ alone does not carry as much risk as the combined type of HRT. Unfortunately, a woman with an intact uterus cannot use Premarin™ alone without substantially increasing her risk of uterine cancer.

There are several different forms of HRT available in Canada that are different from the Premarin™ and medroxyprogesterone studied in the WHI. Some forms are derived from plant sources, and others are synthetic. A recently published study suggests that, in contrast to continuous combined HRT, transdermal estrogen therapy (delivered by patch or gel) and HRT using intermittent progestin may not be associated with an increased risk of breast cancer. Unfortunately, there are simply no large, well-designed studies, like the WHI, which have involved these other forms of HRT. We need more research to be able to tell whether or not there are important differences in the risk/benefit ratio among these various choices.

Some of the over-the-counter products that can be purchased without a doctor’s prescription have actions that resemble estrogen. Traditional medicines have frequently been recommended for the relief of menopausal symptoms. A large number of Canadians have tried these remedies. Women may get relief of menopausal symptoms when they take black cohosh 40 mg per day, soy isoflavone 50 mg to 60 mg per day, red clover 40 mg per day, or flaxseed 40 mg per day. Mildly depressed mood may be improved with St. John’s Wort. These products have been studied in small, short-term, randomised trials and appear to have some scientific evidence to support their use. On the other hand, there is no scientific support for some other popular products such as wild Mexican yam, oil of evening primrose, and chasteberry. Similarly, the combination of several herbs together in “menopause formulations” is not supported by any reputable studies. Herbal remedies may be unhelpful, expensive and even potentially dangerous. All these products are largely uncontrolled and unregulated by the government. Long-term effects of non-prescription therapies are essentially unknown.

6. Are there any non-hormonal medications to replace HRT?

Yes. While there is no perfect substitute for HRT as of yet, various alternatives are available. Menopausal symptoms may be triggered by stress, excess caffeine intake, alcohol consumption, or spicy foods. An effort should be made to avoid situations that trigger hot flashes and night sweats. Flashes may be reduced by low doses of the anti-hypertensive, clonidine. There is also some evidence for anti-depressants such as venlafaxine. A bedtime sedative may be prescribed in order to help insomnia and night sweats. Vaginal lubricants are helpful for dryness and Replens™ can help restore the vaginal lining (Table 2).
Mood swings are best helped by anti-depressant or anti-anxiety therapy. Stress management, a balanced diet, and regular exercise can be beneficial.

A poor calcium intake and/or Vitamin D deficiency are important risk factors for osteoporosis. Women over age 45 should attempt to take 1200 mg to 1500 mg of calcium daily, as well as 800 IU per day of Vitamin D. Weight-bearing exercise, such as walking, helps preserve bone mass. Women with established osteoporosis, or with multiple risk factors (family history, premature menopause, thin body build, smoking, excessive alcohol intake, etc.) should consider using raloxifene, calcitonin, or a bisphosphonate (etidronate, alendronate or risedronate).14

7. Would you take HRT or would you recommend it to your partner?

I think this is a fair question. For my part, the answer is “yes.” But, I would use it for the shortest time possible and in the lowest effective dose. HRT has proven benefits in terms of symptomatic relief. Therefore, if hot flashes distract me from my job or interfere with my sleep, I would start HRT. I feel I owe my family, my patients, and myself a “duty of care” that would be compromised if I were unable to perform to the best of my abilities. I recognize that there are risks associated with the use of HRT, but I regard them as relatively small, particularly for less than five years of use. I am most comfortable with a treatment that has been subjected to scientific scrutiny. At least it is the “devil I know” as opposed to alternative therapies whose potential side-effects and long-term risks are a mystery. Finally, I like getting value for my hard-earned money. Compared to the alternatives, particularly the herbal remedies, HRT is the best buy in town.
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References

Take-home message

• Combination HRT is no longer recommended for the prevention of coronary artery disease. The use of combination HRT for more than four years is associated with an unfavourable risk/benefit ratio, with regard to its ability to prevent serious medical conditions.

• Each individual, with the help of her physician, should assess her reasons for HRT use and its possible benefits. These must be weighed against her risk of cancer, coronary events, and thrombosis.

• A woman’s own comfort level with the specific risks of treatment and non-treatment need to be validated. Alternatives should be considered where applicable.