# HRT and Alternatives: A "Natural" Choice?

**Lucy Gilbert, MD, MSc, FRCOG**
Presented at the 10th McGill International Symposium on Reproductive Endocrinology and Infertility and Women's Health, October 2005



Eighty per cent of women experience menopausal symptoms. In one-third of women, the symptoms are severe enough to interfere with quality of life. Concerns about the risks of hormone replacement therapy (HRT) have increased an interest in natural and bio-identical alternatives.

Using two illustrative cases, I have summarized the current evidence on the risks and benefits of HRT to serve as a prescribing guide.

## Eliza's Estrogen

- Eliza, 45, had her uterus and both ovaries removed when she was 38 and has been on estrogen ever since.
- After seven years of estrogen replacement therapy (ERT), she asks if she should stop.

### *Counseling points*

Eliza's risk of breast cancer is significantly lower than that of the general population for two reasons—the estrogen levels achieved with ERT are usually only about 70% of those of endogenous estrogens and she is not exposed to progesterone. The risk to the breast with ERT alone is very low compared to combined HRT.[1-4]

Her risk of thrombosis is equal to or less than the average 45-year-old who has estrogen from her own ovaries. Stopping her estrogen now could increase her risk of heart disease above the background population.

If Eliza comes to you 10 years from now, when she is 55 years old, the accumulated risk to her breast is higher (the countdown for years of exposure is not from 38 when she started her ERT, but from about 50, the age of natural menopause). Her risk of breast cancer is now slightly higher than that of the general population and so is her risk of thrombosis. This is a good time to discuss stopping HRT. If she does decide to stop, gradual reduction is better tolerated and preferable.

*Go to page 88 for another case!*

## Francine's Flushes

- Francine is a 50-year-old teacher who wants relief from severe hot flushes and night sweats that interfere with her sleep and affect her work.
- In the last year, her periods have become infrequent.
- She is a non-smoker and has no significant personal or family history.
- Her body mass index is 24.
- Francine explains that one of her colleagues had a saliva test to detect hormonal imbalance and has been prescribed bio-identical hormones made up by a compounding pharmacist; she, too, would like to be tested and be prescribed bio-identical hormones or a natural product.

### *Are lab tests indicated to determine management?*

Assays of reproductive hormones in saliva by batch testing have not been validated. Serum assays for estradiol and gonadotropins are validated, but have little role in clinical decision-making in a symptomatic peri- or post-menopausal woman, as they have a wide range of normality and vary at different points in time. Francine's decision to use HRT should be based on the impact of her symptoms on her quality of life and on her willingness to accept the risks.

### *What are the roles of natural products and bio-identical products?*

A systematic review of herbal medicinal products for the treatment of menopausal symptoms showed no convincing evidence for any herbal medicinal product in the treatment of menopausal symptoms.[3] The active ingredient in transdermal estradiol patches, estrogel, vagifem vaginal pessaries and many of the licenced HRT products is bio-identical estradiol. The advantage of using a licensed product is that it has been through clinical trials and the dose and quality of the product is regulated. Natural products are not necessarily safe because they have not been through quality controls for monitoring contaminants (insecticides and other environmental poisons) and are not controlled by the dosage regulations that licensed medications are required to meet.

### *What are the risks and benefits of HRT for Francine?*

ERT is pro-thrombotic and increases the risk of arterial and venous thromboembolic events two- to threefold. However, Francine's baseline risk is low (about 1/5,000), so her absolute risk of thrombosis, even if doubled or tripled with HRT, remains low. In the Women's Health Initiative (WHI) trial of estrogen and progestin replacement therapy (E+PRT), the average patient was much older (median age of 62) and overweight (median body mass index of 27); one-third of these women was morbidly obese.[4]

Because the baseline risk of thrombosis is much higher in such women, a further two- to threefold increase of this already elevated risk does have significant adverse cardiovascular and cerebrovascular consequences. Apart from the pro-thrombotic risks, the other cardiovascular effects of estrogen are


**Dr. Gilbert** is an Associate Professor, Department of Obstetrics and Gynecology, McGill University. She is also the Chief, Division of Gynecological Oncology, McGill University Health Centre, Director, Women's Health and Menopause Clinic, and Director, Gynecology Oncology Fellowship Program, McGill University, Montreal, Quebec.

beneficial and include improved lipid profile, vascular endothelial protection, vasodilatory effect and reduced insulin resistance. However, these benefits are realized only if HRT is started early in the post-menopausal period, before irreversible changes set in.

The WHI trial of ERT[5] showed that in women between the ages of 50 and 59, cardiovascular adverse events were lower in the ERT arm than in the placebo arm.

Estrogen and progestin increase the risk of breast cancer. The increase in risk is time- and dose-dependant. After about five years of use, the risk increases by 26%.[4] To put matters in perspective, had Francine's natural menopause been delayed until age 55, her risk of breast cancer would be increased to the same extent.[2] The benefit of HRT is effective relief of symptoms.

### *What should you recommend to Francine?*

Francine could be reassured that, should she choose to go on HRT for two to three years for symptom control, the risks would be negligible. Oral progesterone and transdermal estradiol in the form of a patch or gel (which delivers bio-identical estrogen) have the most favourable cardiac effects on lipid profile and vascular endothelium. As Francine is still peri-menopausal, she may have poor cycle control on continuous combined HRT. A long cycle regime of continuous estrogen with progestin for two weeks, every three months, to give four withdrawal bleeds a year, or the standard cyclical regime with continuous estrogens with progestins every two weeks, are reasonable options. Oral premarin and provera are not bio-identical, but have the advantage of being less expensive.

*cme*

References
1. Beral V: Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003; 362(9382):419-27.
2. 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(9084):1047-59.
3. 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(3):321-33.
4. Anderson GL, Limacher M, Assaf AR, et al: Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. JAMA 2004; 291(14):1701-12.
5. Huntley AL, Ernst E: A systematic review of herbal medicinal products for treatment of menopausal symptoms. Menopause 2003; 10(5):465.