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Hormone Replacement Therapy Guidelines

Background

This article reviews new evidence-based recommendations from the Society of Obstetricians and Gynaecologists of Canada (SOGC) that clarify the role of hormone therapy (HT) in menopausal women. Results of the large Women's Health Initiative (WHI) study suggesting increased risk of breast cancer and cardiovascular events led many physicians to curb their prescribing of postmenopausal HT.[1] Half of North American HT users stopped using HT as a result.[2] But estrogen is the most effective therapy for hot flashes, which can significantly affect quality of life.[1] In fact, up to 25% of women who stopped HT as result of WHI asked to restart it.[2]

Hormone Replacement Safety Clarified

Participants in WHI were on average 13 years postmenopause, and almost 70% were over the age of 60 at enrollment. Therefore, many of the participants may have had undiagnosed cardiovascular disease.[1] Most were considered at intermediate risk of stroke.[2] In WHI, conjugated estrogens/medroxyprogesterone acetate (*Premarin*) users had a higher rate of cardiovascular events compared to placebo, but only in the first year of use. A similar effect was seen in HERS (Heart and Estrogen/progestin Replacement Study), a secondary prevention study. WHI found an increased risk of ischemic stroke in both the estrogen/progestin and estrogen-only groups. The additional risk of stroke conferred by estrogen/progestin was eight cases per 10,000 women-years, and by estrogen alone, 12 cases per 10,000 women-years. But the WISDOM study found no increased incidence of stroke with estrogen/progestin therapy after an average follow-up of one year. It has been theorized that in older women with atherosclerosis, HT has a prothrombotic effect. In younger women, studies suggest HT does not increase cardiovascular risk, at least in the short-term. During the first ten years postmenopause, the cardiovascular risks of HT are very small. Women with premature menopause taking HT up to the usual age of menopause are at even lower risk.[1]

The SOGC guidelines suggest that HT use (estrogen/progestin) for five years or less does not increase breast cancer risk. They further suggest that when HT (estrogen/progestin) is used for more than five years, breast cancer risk is similar to the risks conferred by daily alcohol use, sedentary lifestyle, or obesity (HR about 1.3).[1] However, a new analysis of the WHI study found that although two years of HT (estrogen/progestin) use did not increase breast cancer risk relative to placebo, thereafter, risk began to increase. Risk had approximately doubled for the HT group by the end of the 5.6-year study. But risk decreased two to three years after HT discontinuation to that of placebo.[3] Another recent study suggests the "safe" period for HT (estrogen/progestin) use in regard to breast cancer risk is two to three years of use.[5] Breast cancer risk conferred by estrogen alone seems to be lower than that conferred by estrogen/progestin.[1]

SOGC Recommendations

For mild vasomotor symptoms, nonpharmacologic therapies might be sufficient. These include exercise; weight loss; avoiding hot drinks, alcohol, and smoking; and keeping cool. HT (estrogen alone or estrogen/progestin for women with a uterus) is the most effective treatment for menopausal symptoms, and should be offered as such to women experiencing vasomotor symptoms [Evidence level A; quantitative systematic review].[1,4] HT has the additional benefit of preventing bone loss and fractures.[1]

Perimenopausal women can be offered a low-dose oral contraceptive or progestin only for vasomotor symptoms. There is fair evidence to

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recommend products with a low dose of estrogen (e.g., 0.3 mg conjugated estrogens or 0.5 mg micronized estradiol or less) for older women. However, women should be apprised that it is not known whether such products reduce fracture risk.[1]

Modifiable cardiovascular risks (e.g., smoking, high blood pressure, overweight) should be addressed in all patients. HT should not be started in patients with high thromboembolic risk. Women at higher risk of breast cancer should be apprised of the risk and be screened appropriately. Benefits vs. risk of breast cancer conferred by longer duration of use should be assessed regularly.[1]

If HT is not desired or appropriate, alternatives include antidepressants (e.g., venlafaxine [e.g., *Effexor XR*]), gabapentin (e.g., *Neurontin*), clonidine, and *Bellergal* (belladonna, ergotamine, phenobarbital).[1]

Vaginal symptoms can be treated with estrogen cream or tablets (e.g., *Premarin, Vagifem*), the estrogen ring (*Estring*), or polycarbophil gel (*Replens*).[1]

Commentary

Women have many questions about the risks and benefits of HT. Safety concerns have caused some women to forgo HT or turn to unproven natural health products. For most newly menopausal women with distressing vasomotor symptoms, the benefits outweigh the risks. Some evidence even suggests HT may reduce the risk of cardiovascular disease in young women. It might also reduce the risk of dementia later in life when initiated early. Caution is warranted when initiating HT in women ten or more years postmenopause due to cardiovascular risk.[1] HT benefits vs. breast cancer risk should be continually evaluated, since risk conferred by HT (estrogen/progestin or estrogen alone) increases with duration of use [Evidence level A; high-quality RCTs].[1,3,5] Attention to modifiable cardiovascular risks and appropriate screenings can improve the benefit/risk ratio for all patients.[1]

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Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the **LEVEL OF EVIDENCE** for the statements we publish.

Level	Definition
A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.

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