Assessing Benefits and Harms of Hormone Replacement Therapy

Clinical Applications

Heidi D. Nelson, MD, MPH

CLINICAL CONTEXT

Initiating Therapy in a Low-Risk Symptomatic Woman

A 51-year-old woman seeks your advice on initiating hormone replacement therapy (HRT). She has been having irregular menstrual periods throughout the past 6 months and has had increasingly frequent episodes of hot flashes that sometimes disturb her sleep. She has been using a soy product that initially controlled her symptoms; however, its effect has diminished. She has no other major health problems, is a nonsmoker, and has no strong family history of cancer or cardiovascular disease, although some relatives have osteoporosis.

She needs advice for 2 issues: appropriate use of HRT for the short-term relief of menopausal symptoms and the role of HRT in preventing chronic conditions. It is important to separate these issues because short-term (<5 years) and long-term (≥5 years) benefits and harms differ.1

Hormone replacement therapy effectively relieves menopausal symptoms and can be used only as long as symptom control is necessary. Estrogen is combined with a progestin for a woman with a uterus to prevent endometrial hyperplasia and endometrial cancer, although unexpected vaginal bleeding requires evaluation. The daily combined regimen is common in the United States, although other regimens are also used. Several formulations, doses, and regimens are effective and should be individualized.

Potential short-term benefits include improvement of hot flashes, sleep disturbances, urogenital atrophy, and possibly mood2 and aspects of cognition,3 although these effects may be a consequence of improved sleep. Hormone replacement therapy can improve or maintain bone density,4 although short-term use does not prevent fractures in the future.5

Short-term harms include a 1.8-fold increased risk for cholecystitis,6 a 3.5-fold increased risk of a thromboembolic event in the first year,7 and possibly increased risk of stroke and myocardial infarction (MI). Data from the Women’s Health Initiative (WHI),8 a randomized controlled trial of HRT and primary prevention in postmenopausal women, indicate increased rates of stroke, coronary heart disease (CHD), and thrombosis among women randomized to HRT compared with those taking placebo. It is unknown how much HRT increases the risk for cardiovascular outcomes for women who smoke, are obese, or have hypertension or for other cardiovascular risk factors. Women in the Heart and Estrogen/progestin Replacement Study

See also p 872 and Patient Page.
(HERS), a secondary prevention trial of HRT and cardiac events in women with preexisting CHD, experienced worsening urinary incontinence throughout a 4-year period of HRT use.9 Observational studies suggest a potential increase in breast cancer risk with short-term use, although these are not definitive.1 The WHI reported significantly increased breast cancer risk after 5 years of use.8 Women with undesirable menopausal symptoms might consider the risk-benefit ratio acceptable for short-term use.

The second issue for this patient concerns long-term benefits and harms. Some women find that even though hot flashes are no longer present, HRT provides other positive effects for them, such as improved mood, relief of symptoms of urogenital atrophy, and sense of well-being, although these outcomes vary among individuals. Long-term HRT users continue to have higher bone density than past or never users, and observational studies of long-term use indicate that optimal benefit is obtained when use is begun early in menopause and continued indefinitely.10 The WHI is the first randomized controlled trial to demonstrate protection for hip, vertebral, and other fractures with HRT use. The WHI also indicated reduced risks for colon cancer with HRT use.8 Prevention of dementia with long-term use is suggested by some studies; however, most of these have important methodologic limitations.3

These benefits must be weighed against increasing evidence of important harms. Contrary to previous beliefs that HRT could prevent cardiovascular disease, results of the WHI indicate increased risk for MI and stroke after 5 years of use.8 Observational studies of HRT and breast cancer suggest a 1.2- to 1.4-fold increased risk in breast cancer incidence in long-term users but no increased risk of dying of breast cancer.1 The WHI confirmed these findings, reporting a relative risk for breast cancer of 1.26 (95% confidence interval, 1.00-1.59) after 5 years of use.8 Risk of thromboembolism is higher in the first year of use and diminishes thereafter to approximately a 2-fold increased risk.7,8,11 Long-term harms also include a 2.5-fold increased risk for cholecystitis.6 Use of unopposed estrogen has been associated with ovarian cancer in recent studies.12,13 This patient’s risk-benefit ratio may no longer justify HRT use.

**Discontinuing Therapy in a Long-term User**

A 72-year-old woman has been taking estrogen daily for more than 20 years and is seeking advice about whether to continue.

It was initially begun to control hot flashes after her hysterectomy and oophorectomy, but she has continued to use it because she heard it was good for her heart and bones. She has no known heart disease but has elevated cholesterol levels and diabetes mellitus controlled by oral agents. She has no other major medical problems but complains of chronic back pain and smokes 1 pack of cigarettes daily.

Until the recent publication of the WHI indicating increased risk for CHD,8 there were no primary prevention trials of HRT and cardiac disease in the general population, and results of observational studies were limited by important biases.14 There is now no justification for using HRT for prevention of cardiac disease, and the American Heart Association recommends basing HRT decisions on noncoronary benefits and harms (Box 1).15 Optimizing this patient's diabetes management, treating her hypercholesterolemia, and helping her to stop smoking would better address her cardiac risk factors.

A woman this age with back pain could have a vertebral fracture. Although HRT may have helped maintain her bone density throughout the years, she may now have osteoporosis. Results of a spine radiograph and bone densitometry would be diagnostic. If a nontraumatic vertebral fracture is identified, or if her T score is low (eg, ≤2.5), she has osteoporosis, and another treatment, such as a bisphosphonate, may be indicated. Hormone replacement therapy is approved for prevention but not treatment of osteoporosis. If she has normal or slightly reduced bone density and no fractures, continuing HRT would likely continue to provide osteoporosis prevention but also increase her risks for cardiovascular disease and breast cancer. Although the findings of the WHI were for women receiving estrogen combined with progestin therapy and this woman is receiving estrogen alone, a careful approach would assume comparable risks and discontinue estrogen until new data prove otherwise. The evidence on other benefits, such as prevention of dementia or colon cancer,16 is suggestive but not strong.
benefits and harms of hormone replacement therapy

Box 2. Breast Cancer Risk Assessment Tool

What is the age of your patient? What was the patient’s age at her first menstruation? What was the patient’s age when she first gave live birth to a child? How many of the patient’s first-degree relatives—mother or sisters—have had breast cancer? Has the patient ever had a breast biopsy? How many positive or negative breast biopsies has the patient had? Has the patient had at least one biopsy with atypical hyperplasia? Please indicate the race and ethnicity of the patient, if known.

*The assessment tool was reproduced from the National Cancer Institute and the National Surgical Adjuvant Breast and Bowel Project Biostatistics Center. 19

The patient’s annual mammogram results have all been normal.

She has a strong family history of breast cancer—an important breast cancer risk factor. The contribution of HRT use as an additional risk factor in women with strong family histories is unclear. The Iowa Women’s Health Study found no increase in risk for women using HRT whether they had a family history of breast cancer or not, although several other studies indicate that risks for average-risk long-term users could be elevated. 18 This patient’s risk for invasive breast cancer is estimated to be 2.2% throughout the next 5 years compared with 1.4% for a woman who is the same age and has average risk factors estimated with the Gail model (Box 2). 19 If she decides to discontinue estrogen, she should taper off use throughout several weeks to avoid provoking hot flashes.

A 66-year-old woman who has been receiving HRT since menopause just had her first MI. Her evaluation indicated 2-vessel disease and she was treated medically. All of her medications are reviewed after her discharge from the hospital, and she is still taking HRT.

Results from HERS indicated that women with known CHD who were randomized to conjugated equine estrogen and medroxyprogesterone acetate had a 52% increased risk of MI during the first year of use and increased CHD deaths during the first 3 years of use. 20 After 6.8 years of follow-up in HERS, there were no differences in rates of primary or secondary CHD. 21 How these results apply to the patient who has been receiving HRT for several years before her event is not entirely clear. However, HRT may play a role in promoting recurrent thrombotic events. Recommendations of the American Heart Association support discontinuing HRT after an acute event (Box 1). 15

REFERENCES