

Virtual Mentor

Ethics Journal of the American Medical Association

November 2005, Volume 7, Number 11

Clinical Pearl

Post Women's Health Initiative—Menopausal Women and Hormone Therapy

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In July 2002, the first results from the Women's Health Initiative (WHI) trial found an increased risk of heart disease, breast cancer, deep vein thrombosis, stroke and gall bladder disease for post-menopausal women who received hormone therapy [\[1\]](#). Although this study primarily targeted older women—the average age was 63—it raised the question: “Who are appropriate candidates for hormone therapy (HT)?” The study results suggested a narrower use of HT than expected: women who may be appropriate candidates for hormone therapy include those under 40 with premature menopause as a result of surgery or endocrine-system deficiencies; women with symptoms of menopause who don't respond to lifestyle adaptations; and older menopausal women who experience persistent severe symptoms and bone loss.

The Women's Health Initiative

The Women's Health Initiative was a prospective, randomized, double-blind, placebo-controlled study of more than 16 000 healthy, postmenopausal women between the ages of 50 and 79, who received either estrogen plus progestin [EPT] (0.625 mg CEE/2.5 mg MPA), estrogen alone [ET] (CEE 0.625 mg), or a placebo. The primary outcome studied was the effect of the 2 treatment types on prevention of cardiovascular disease (coronary artery disease and stroke), breast and colorectal cancer, and bone fractures. A separate study of women over 65 enrolled in the WHI assessed the effects on dementia and Alzheimer's disease (see table). Neither study was designed to assess the effect of the specific hormone treatment on hot flashes or vaginal dryness. Four percent of WHI participants had moderate to severe vasomotor symptoms (ie, hot flashes).

Event-Attributable Risk or Benefit Per 10 000 Women/Year*

	EPT Arm⁷	E Arm
CHD	Risk (6)	Benefit (5)
Breast Cancer	Risk (8)	Benefit (7)
Dementia	Risk (23)	Risk (12)
Stroke	Risk (7)	Risk (12)
Venous Thromboembolism	Risk (18)	Risk (7)
Pulmonary Embolism	Risk (8)	Risk (3)
Colorectal Cancer	Benefit (6)	Risk (1)
Hip Fractures	Benefit (5)	Benefit (6)
Total Fractures	Benefit (47)	Benefit (56)

*Numerals in parentheses indicate absolute increases in risk or benefit attributable to either EPT or ET. That is, a risk (or benefit) of 6 means that 6 additional cases of a given outcome were experienced (or avoided) among subjects who received HT than among subjects on placebo [1-8]. Source: WHI

The WHI findings suggest that older women should *not* take hormone therapy to prevent heart disease or Alzheimer's disease. In the absence of clinical trial data for various estrogen and progestin compounds, the clinical trial results should probably be generalized to all agents within the same family, especially with regard to adverse effects. In particular, many women are requesting “bio-identical” hormones, which are either FDA-approved hormones or hormones compounded by pharmacies prepared in unique individualized dosage forms. The scientific evidence regarding both safety and efficacy for compounded therapies is currently lacking, and thus the same generalized risk and benefit data should apply.

Menopausal Women

Women often start hormone therapy at menopause to control vasomotor instability or urogenital atrophy or to prevent bone loss. Seventy-five percent of HT users initiate therapy within 5 years of menopause. In a 1999 national survey, 24 percent had used HT—3 percent EPT for =5 years, and 10 percent used ET for =5 years. In addition to over 90 percent relief of vasomotor symptoms, estrogen therapy has been found to improve (particularly REM) sleep, thus mitigating the fatigue associated with sleep disturbances [9].

Women often stop hormone therapy because of fear of breast cancer; hormone therapy-related bleeding; side effects such as breast tenderness, bloating, headaches, or mood changes; resolution of symptoms over time; fear of long-term use, or because they prefer natural methods.

Current Position Statements

The FDA has approved hormone therapy for the treatment of moderate-to-severe vasomotor symptoms associated with menopause, the treatment of vulvar and vaginal atrophy, and the prevention of postmenopausal osteoporosis [10].

The 2004 American College of Obstetricians-Gynecologists executive summary on hormone therapy states that, for selected women, HT remains an effective treatment for controlling vasomotor symptoms or vaginal atrophy and for retarding osteoporosis [11]. An individualized risk/benefit analysis by the physician and patient is recommended along with informed discussion before initiation of HT and periodic re-assessments after it is prescribed. In older postmenopausal women, the risks of HT are often felt to exceed the benefits for the prevention of chronic diseases. Future research is needed to clarify optimal timing and duration of hormone therapy because many believe that recent data does not address the effect of HT during or soon after the menopausal transition, its subsequent impact on disease processes, or the benefits and risks in women with premature menopause.

The 2004 North American Menopause Society Position Statement 12 on HT states similarly that the primary indication for systemic HT is the treatment of moderate-to-severe menopausal symptoms. Local estrogen is recommended for moderate-to-severe vulvar and vaginal atrophy. The primary indication for progestin is endometrial protection. HT should not be used for first or second degree prevention of coronary heart disease (CHD) or stroke. The lowest effective dose of HT for the shortest duration needed is recommended. Candidates for extended use of HT include women who decide, after thoughtful discussion with a physician and in the context of ongoing medical supervision, that the benefits of symptom relief outweigh risks. Such decisions usually follow a failed attempt to withdraw from HT. Other possible candidates are women with moderate-to-severe menopausal symptoms who are at high risk for osteoporotic fractures and women at high risk for osteoporosis for whom alternate therapies are not appropriate.

Lower Doses of Hormone Therapy

Research findings show that lower doses of EPT and ET relieve vasomotor symptoms, prevent vaginal atrophy, are associated with a reduced incidence of endometrial bleeding—especially in the early months of therapy—provide effective endometrial protection, and prevent early postmenopausal bone loss [13-16]. These lower-dose options provide clinicians and patients with expanded options for individualizing ET/EPT.

Counseling Women about HT

When counseling women, it is important to document each individual woman's reasons for considering ET/EPT (eg, quality-of-life, severity of symptoms), consider the individual risks and benefits of short-term ET/EPT use, and review indications for ET/EPT annually. The WHI data are not relevant for women with premature menopause or for symptomatic menopausal women. For women younger than 50 or those at low risk for CHD, stroke, osteoporosis, and breast or colon cancer, the absolute risk or benefit from ET or EPT is likely to be even smaller than for the women in the WHI, although the relative increase in risk may be similar [17-18].

Non-HT Alternatives for Menopausal Symptoms

Lifestyle modifications may provide limited relief for women with mild symptoms or those for whom hormone therapy is not desired, not recommended, or

contraindicated. Possible lifestyle changes include exercise, cooling body core temperature with fans or layered clothing, avoiding hot and spicy foods that may trigger hot flashes, paced respirations, or other relaxing activities.

Alternative nonprescription therapies being studied include phytoestrogens/isoflavones, soy-derived dietary supplements, red clover, and black cohosh. Studies have shown no significant effect over placebo on hot flashes with Vitamin E, dong quai, ginseng, and evening primrose oil [19, 20]. For many alternative or complementary products, side effects and drug interactions occur but are not well known. Long-term safety and efficacy data are lacking. Small pilot studies suggest efficacy on hot flash reduction with low dose antidepressants and gabapentin [21, 22]. Long-term, adequately powered, randomized, placebo-controlled clinical trials with defined entry criteria are needed.

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