

REVIEW ARTICLE

Hormone replacement therapy (HRT)—risks and benefits

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Despite 50 years of use, the first large randomized placebo-controlled clinical trials of postmenopausal hormone treatment and disease have only been reported in the last few years. These trials provided some surprising results, and raise questions about the short-term risk and long-term benefit of estrogen. Because clinical trials are the cornerstone of evidence-based medicine, this paper emphasizes clinical trial results whenever such are available.

Clinical trials have shown that estrogen therapy is very effective treatment for vasomotor symptoms (hot flushes and night sweats),¹ which can begin several years before the last menstrual period when hormone levels are fluctuating.² Clinical trials have also shown that estrogen can reduce vaginal dryness and urethritis, and that topical estrogen is at least as effective as systemic estrogen.³ The big questions about hormone therapy are not about short-term use for vasomotor symptoms or topical use for urogenital symptoms, but about long-term systemic use with its possible benefits, such as prevention of fractures, heart disease, colon cancer, or dementia, and risks, most notably breast and uterine cancer.⁴

Osteoporosis

It has been recognized for more than 50 years that bone loss in women is unequivocally accelerated by estrogen deficiency. Estrogen halts or slows bone loss—probably for as long as it is continued in the majority of women. The largest three-year Postmenopausal Estrogen/progestin Interventions (PEPI) trial⁵ showed sustained increases in bone mineral density when conjugated equine estrogen (CEE) was used alone, with medroxyprogesterone acetate (MPA), or with micronized progesterone (MP). Bone density may be further increased when a more androgenic progestogen is used, but no large trial with head-to-head comparisons has been published.

Although observational data from epidemiological studies suggest that estrogen reduces the risk of vertebral and hip fractures,⁴ only a few clinical trials with fracture outcomes have been published.^{6–10} The studies that claim benefit are flawed by small size, poor compliance, or an analysis based on number of fractures, not number of women with fractures.^{6–9} In the largest published study, the Heart and Estrogen/progestin Replacement Study (HERS), nearly 3000 women (average age 67 years) were randomly assigned to daily CEE and MPA or

placebo; although there were 260 clinical fractures during the 4-year trial, there was no significant difference in the fracture rate at any site by treatment assignment.¹⁰ Unfortunately, no vertebral x-rays were obtained, but there was no difference in height loss, a marker for subclinical vertebral fractures. Bone density, measured in a subset, showed that HERS women had relatively good bone mineral density and few would have met current criteria for osteoporosis; the expected differences in the rate of bone loss between HRT and placebo-treated women was observed, but the placebo group lost relatively little bone per year.¹¹

These data do not tell us anything about the potential protective effect of estrogen for women with osteoporosis, because HERS was designed to study women with heart disease, not women selected because they had low bone mineral density. The data do suggest that it would be necessary to treat a large number of postmenopausal women unselected for osteoporosis in order to prevent one clinical fracture.

Three other observations need to be considered when deciding whether and how to use estrogen for the prevention of osteoporosis. First, all available data suggest that estrogen must be continued indefinitely; women who have stopped estrogen for more than 10 years appear to have almost the same bone density and fracture risk as women who never used it.¹² Second, estrogen started in old age preserves bone, so women who have not used it soon after the menopause may still benefit; although estrogen will not restore bone to youthful levels, it will stabilize bone resorption, which may itself protect against fracture.¹³ And third, pooled data from 31 studies suggest the use of estrogen plus calcium supplementation is twice as effective as estrogen alone in preserving bone mineral density.¹⁴

Coronary heart disease

More than 30 observational studies have suggested that estrogen prevents heart disease in postmenopausal women,⁴ and multiple beneficial effects of estrogen on intermediate variables such as lipids and vascular reactivity have been documented in clinical trials or the laboratory.¹⁵ In PEPI, the largest published clinical trial of heart disease risk factors, women assigned to estrogen with or without MPA or MP had significantly more favourable levels of LDL and HDL cholesterol than women assigned to placebo.¹⁶

It was therefore surprising when HERS, the first large placebo-controlled clinical trial in women assigned to CEE and MPA¹⁰ with coronary heart disease as the primary outcome, showed no reduction in the risk of fatal and non-fatal coronary

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disease, or in any other cardiovascular endpoint. In the first year of the trial there was actually a 50% increased risk in women on active treatment, with a suggestion that this was reversed later in the 4-year study. The late benefit may have been overstated in the publication; there was no significant trend toward less heart disease in the last 2 years when account is made for the increased risk in the first year. To better evaluate delayed benefit, a 3-year extended follow-up study is underway.

The HERS results were unexpected and unpopular, and the trial has been criticized for many reasons. One common critique is that it is only one trial—with no other trial evidence of early harm. In fact, a review of 22 small published trials in 4124 women found a 1.4-fold increased risk of cardiovascular disease after short-term (usually less than 2 years) therapy.¹⁷ A second paper that added data from six unpublished short trials in 645 women yielded a cumulative 1.8-fold increased risk of cardiovascular disease in women treated with (mainly unopposed) estrogen.¹⁸

In 2000, the Women's Health Initiative (WHI) investigators and participants were advised that a small increased risk of cardiovascular disease (both myocardial infarction and stroke) was observed in the first year of this very large (27 348 women) trial as well.¹⁹ According to the press release, the excess risk was seen in WHI women with and without heart disease and in women using CEE alone or with MPA. These results appear to disprove two other common comments about HERS: that harm, if real, would be seen only in women on combined therapy or only in women with heart disease.

Recently the results of the Estrogen Replacement and Atherosclerosis (ERA) study were published.²⁰ This study of 300 women randomly assigned to placebo, opposed, or unopposed estrogen found no change in coronary artery atherosclerosis after three years. (Coronary atherosclerosis was ascertained by angiography, which may be insensitive to changes that could be seen using coronary artery intravascular ultrasound.)

It is therefore premature to conclude there is any immediate or delayed cardiovascular benefit from HRT, at least in its present most commonly prescribed regimens. Unfortunately, HERS, WHI, and ERA all used the same oral estrogen and dose, so nothing can be concluded about the possible benefit of other estrogens, other doses, other progestogens, or non-oral drug delivery. It should be noted, however, that a large majority of the observational studies initially suggesting benefit were conducted in the US where more than 80% of estrogen and progestogen used were the same products used in these trials.

Breast cancer

For many years any association of HRT with breast cancer risk was vigorously denied, citing negative or contradictory observational studies. Several early studies did, however, suggest that such harm might be apparent in women with long-term HRT use.²¹ The comparison of ever versus never use women in observational studies greatly dilutes the number of long-term users, because the majority of ever users use hormones for less than 2 years.²²

In 1997 the Collaborative Group from Oxford reanalysed 51 observational studies of HRT and breast cancer, which included 52 705 women with breast cancer.²³ There was an increased risk of breast cancer only in women who had used HRT for five

or more years; the risk for each year of added use was the same as the risk for each year of delayed menopause—providing internal consistency for an estrogen-breast cancer association. The absolute risk, however, was relatively small, an additional 3–9 cases/1000 women for 10 years of use and an additional 5–20 cases/1000 women for 15 years of use. Further, many studies have noted that breast cancer occurring in women taking estrogen is more likely to be *in situ*, node negative, and estrogen-receptor positive, and to have a better prognosis than non-HRT associated breast cancer.²⁴

Since then, at least four large epidemiological studies (each with >1000 breast cancer cases) have also reported an increased risk of breast cancer in women who used HRT for at least 4 or 5 years.^{25–28} In some of these studies, the risk was greater in women who used estrogen plus a progestogen than in women who used unopposed estrogen. Because only 12% of the women in the Collaborative Group analysis²³ were taking a progestogen, it is possible that the absolute risks shown above underestimate the risk for women taking combined therapy.

An increased risk when estrogen is taken with a progestogen is concordant with PEPI clinical trial results, in which women taking estrogen plus a progestogen had at least twice the rate of increased breast density as women taking unopposed estrogen.²⁹ Nearly all women who developed increased breast density on either regimen did so in the first year of PEPI. These observations from a clinical trial are important because increased breast density is a risk factor for breast cancer in postmenopausal women.³⁰

Other evidence that estrogen increases breast cancer risk comes from studies of selective anti-estrogens such as tamoxifen and raloxifene. Both agents have been shown to reduce the risk of breast cancer in clinical trials.^{31,32} In an interesting sidelight to the Italian Tamoxifen Trial, overall breast cancer rates were very low, except in women taking HRT. However, 8 of 390 women taking HRT plus placebo developed breast cancer versus 1 of 362 women taking HRT and tamoxifen.³³

Much has been made of other recent trials that found no increased risk of breast cancer associated with HRT; these papers are often cited as showing that the evidence for an estrogen-breast cancer association is inconsistent. In fact, in nearly every instance, the study was too small and/or the number of long-term users too few to make any conclusions. For example, the National Health and Nutrition Examination Survey (NHANES) follow-up study of a representative sample of US women reported no excess risk of breast cancer in women using HRT, but there were only 219 incident breast cancer cases and only 36 women who had used estrogen for more than 3 years.³⁴

It is increasingly difficult to deny that HRT for 5 or more years increases the risk of breast cancer. Since long-term HRT is required for the optimal prevention of bone loss, as noted above, this poses a real conundrum for the patient and her physician.

Endometrial cancer

As shown in the PEPI trial, unopposed estrogen increased endometrial hyperplasia at a rate of 10% per year, and also caused atypical potentially precancerous histology in some women.¹⁶ No such changes were observed in women taking estrogen plus continuous or cyclic MPA or cyclic MP. In observational studies the endometrial cancer risk for 5 years of unopposed estrogen

use is increased 4–5 fold, and the risk for 10 years use, 10-fold.³⁵ When the cancer causes bleeding an early diagnosis and good prognosis are expected, but the relative risk for invasive cancer is also increased. Women who take 10–12 days of a progestogen with their estrogen appear to be protected from endometrial cancer; the few reported cancers may be caused by non-compliance with the progestogen.³⁶

Colon cancer

More than 10 observational studies have shown a reduced risk of colon cancer in women taking HRT.³⁷ There are no published clinical trial data about HRT and colon cancer or polyps.

Memory loss and dementia

More than half of the observational studies suggest that women who take estrogen preserve or improve cognitive function better than women who do not.³⁸ These results have not been confirmed by the only two published large randomized clinical trials, one a prevention trial in cognitively intact women³⁹ and one a treatment trial in women with early Alzheimer's disease⁴⁰ In HERS, approximately 1000 cognitively intact women with heart disease completed six cognitive function tests before and 4 years after randomization to HRT or placebo; women assigned to HRT did not perform better on any test than women assigned to placebo.³⁹ In the Alzheimer's treatment trial, 120 women were randomly assigned to placebo, or unopposed CEE in the standard (0.625mg) or high (1.25 mg) dose; women did not differ by treatment on global assessment of change, the primary outcome, but scores on the clinical dementia rating scale were worse in women assigned to estrogen.⁴⁰ Thus, at present, there is no evidence that estrogen taken for at least one year prevents memory loss or slows the progression of dementia.

Venous thromboembolic disease

Recent observational studies have suggested a 2–4 fold increase in venous thromboembolic events (VTE) in women taking postmenopausal HRT. This was confirmed in the HERS trial, where the risk of VTE was increased 2.7-fold with an excess risk of 3.9 per 1000 women-years.⁴¹ Put another way, approximately 1 in 250 women treated with HRT for one year would develop a VTE, whereas the annual rate for older women not taking HRT is approximately 1 in 750. The risk for VTE was increased among women with a lower-extremity fracture, cancer, and for 90 days after inpatient surgery or non-surgical hospitalization, and was reduced by half in women using aspirin or statin therapy. While the risk of pulmonary embolism decreased with time, there was no significant trend over 4.1 years for decreasing risk of deep vein thrombosis.

Conclusions

Despite the ubiquity of estrogen receptors in diverse human tissues and its multiple genomic and non-genomic effects, randomized clinical trial evidence of benefit or harm is very small, and is presently limited to only a few important outcomes: reduced vasomotor and urogenital symptoms, and an increased risk of VTE that does not wane over time. Intermediate outcomes

suggest cardiovascular benefit and prevention of bone loss, but clinical trial evidence showing prevention of cardiovascular disease or hip fracture is lacking. Fortunately, other medications have been shown to be effective in reducing women's risk of coronary heart disease and stroke (e.g. statins)⁴² and vertebral fractures (e.g. calcium and vitamin D, alendronate, risedronate and raloxifene).⁴³ Intermediate endpoints such as an increased risk of endometrial hyperplasia with unopposed estrogen, or of breast density with opposed or unopposed estrogen may prove useful markers for determining whether to continue a woman on HRT.

Within the next 5–10 years, outcomes from the Women's Health Initiative (WHI) in the US⁴⁴ and the Women's Intervention Study of Long Duration Oestrogen after Menopause (WISDOM) trial in the UK⁴⁵ are expected to further define the risks and benefits of long-term HRT. Until then, it seems prudent to confine the use of HRT to 1) symptomatic women; 2) oophorectomized women up to age 50–55, the usual age of menopause, and 3) for prevention or treatment of osteoporosis for the first 5 years after the menopause. The five-year duration appears to carry no increased risk of breast cancer. Alternative proven therapies should be chosen for long-term prevention.

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