

## Fortnightly review: Hormone replacement therapy

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# Clinical review

## Fortnightly review

### Hormone replacement therapy

Elizabeth Barrett-Connor

The number of women who will live half their adult lives after the menopause increases every year.<sup>1</sup> A challenging question for doctors is how women should be counselled about postmenopausal oestrogen therapy.

#### Methods

This review is based on observations during 25 years of research into women's health, and on Medline searches on oestrogen or menopause. Only recent publications are cited. Unless otherwise stated, oestrogen therapy refers to treatment of postmenopausal women with pharmacological doses of oral oestrogen taken alone or with an oral progestogen.

#### Menopausal symptoms

About 75% of women in English speaking countries experience no troublesome symptoms during the menopause transition.<sup>2</sup> Population studies have shown that symptoms are less common or different in other countries, and more common and more severe after an induced menopause. Hot flushes and night sweats are the only symptoms universally reported to respond (usually almost immediately) to oestrogen. Without treatment, hot flushes typically disappear within 1-2 years, but in some untreated women they continue for more than 20 years.

After the menopause the vaginal wall becomes thinner and less vascular, changes which may be accompanied by vaginal dryness and dyspareunia. Intravaginal oestrogen prevents and treats these symptoms and also reduces the risk of recurrent urinary tract infection, probably by modifying the vaginal flora.<sup>3</sup> Urinary incontinence, which becomes more common with increasing age, is not usually improved by oestrogen.<sup>4</sup>

#### Coronary heart disease

Nearly every observational study has found a decreased risk of heart disease in women who ever used oestrogen. A recent meta-analysis of 25 published studies found a summary relative risk of 0.70 for coronary heart disease among women who used oestrogen (primarily unopposed oestrogen); in seven studies that separately assessed oestrogen plus a progestogen, the risk estimate was 0.66.<sup>5</sup>

#### Summary points

Five or more years of postmenopausal oestrogen is the standard of care for the prevention or treatment of osteoporosis; benefit requires continued use

Oestrogen increases the risk of endometrial cancer during and after use, unless it is taken with adequate progestogen

It probably increases the risk of breast cancer, but only during current use

It may reduce the risk of coronary heart disease

Routine oestrogen treatment should not be recommended until more risk:benefit data are available from clinical trials

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Most of the biases in these observational studies would spuriously increase the oestrogen benefit (see box). Recently, Hemminki and McPherson reviewed 22 randomised trials of short term oestrogen therapy in which cardiovascular events were recorded as reasons for dropouts or adverse events.<sup>6</sup> The summary risk ratio was higher (1.39) in users than in non-users—an unlikely result if oestrogen really reduces the risk of cardiovascular disease by 30%.

Cardioprotection is plausible: oestrogen is an antioxidant and calcium channel blocker, and favourably alters multiple intermediary variables, including concentrations of high and low density lipoprotein cholesterol, LP(a), plasminogen activator inhibitor-1, fibrinogen, and vascular reactivity. In the postmenopausal oestrogen and progestins intervention trial (PEPI), oestrogen alone or with a progestogen lowered low density lipoprotein, raised triglycerides, and had little or no effect on weight, fat distribution, blood pressure, and fasting glucose or insulin concentrations.<sup>7</sup> The addition of daily or cyclical medroxyprogesterone acetate, but not cyclical micronised progesterone, halved the oestrogen induced increase in high density lipoprotein and raised plasma glucose concentrations.

### Bias in studies of use of oestrogen and heart disease<sup>5</sup>

Source of bias	Effect of risk on heart disease
Bias in who is prescribed oestrogen:	
More educated	Decrease
Higher social class	Decrease
Osteoporosis*	Decrease
No diabetes, heart disease, or hypertension	Decrease
Healthier† before treated	Decrease
Bias in who takes oestrogen:	
Compliant women	Decrease
Bias in diagnosis:	
False positive exercise tolerance tests in women taking oestrogen, leading to angiography	Decrease

\*Thinner women have more osteoporosis and less heart disease.  
†Fewer risk factors and healthier behaviour.

### Stroke

Hormone therapy is not consistently associated with a reduced or increased risk of stroke.<sup>8,9</sup> One study designed to examine haemorrhagic and thromboembolic stroke separately found that oestrogen use was not related to either type of stroke.<sup>10</sup>

### Osteoporosis

Data from many observational studies<sup>8</sup> and one clinical trial<sup>11</sup> show that oestrogen reduces the risk of hip fracture by about 30% and of spine fracture by about 50%. The reduction in fracture risk by oestrogen exceeds that expected based on bone density alone.<sup>12</sup> Oestrogen must be continued indefinitely; 10 years after it had been stopped, bone density and fracture risk were similar in women who had used oestrogen and those who had not.<sup>13</sup>

In clinical trials, oestrogen reduces bone turnover and increases bone density in postmenopausal women of all ages, in part because it improves calcium homeostasis. Calcium supplementation potentiates the effect of oestrogen on bone mass.<sup>14</sup> The addition of androgenic progestogens or testosterone (but not medroxyprogesterone acetate or micronised progestosterone) may further increase bone formation.<sup>15,16</sup>

### Endometrial cancer

More than 30 observational studies have found that unopposed oestrogen (oestrogen without a progestogen) increases the risk of endometrial cancer.<sup>17</sup> The excess risk increases with dose and duration of oestrogen (10 years of unopposed oestrogen increases the risk 10-fold), is apparent within two years of the start of treatment, and persists for many years after oestrogen is stopped. Oestrogen induced uterine cancer is usually but not always of a low stage and grade at diagnosis. It is almost entirely prevented by giving progestogen as well. The rare endometrial cancer observed in women taking combined therapy may reflect poor compliance with progestogen.<sup>18</sup>

Oestrogen greatly increases the risk of atypical endometrial hyperplasia, a premalignant lesion. In a three year trial,<sup>7</sup> one third of women assigned to unopposed oestrogen developed adenomatous or atypical endometrial hyperplasia, whereas hyperplasia occurred in less than 1% of women taking oestrogen plus a progestogen.

### Breast cancer

Most studies have found no increased risk of breast cancer in women who had ever used oestrogen, usually for less than two years. But, as a collaborative reanalysis of data from 51 studies has shown, the risk of breast cancer increases with long term oestrogen use.<sup>19</sup> Among women who used oestrogen for five years or longer (median use 11 years), the summary relative risk for breast cancer was 1.35. Although the increased relative risk was highly significant ( $P < 0.0001$ ), the excess number of women with breast cancer after oestrogen use for 5, 10, or 15 years was small: 1-3, 3-9, and 5-20 cases, respectively, per 1000 women who began oestrogen when aged 50-70. The overall risk was similar when oestrogen plus progestogen was used, but data on long term use of combined therapy were sparse.

Several biases in the observational studies would be expected to spuriously reduce any oestrogen-breast cancer association (see box). Women taking oestrogen tend to have early stage breast cancers,<sup>19</sup> probably reflecting more frequent examinations and mammograms. The increased risk is not entirely explained by better surveillance and detection of more benign cancers, because there is evidence for increased mortality when breast cancer is associated with oestrogen.<sup>20</sup>

The five year delay between starting hormone therapy and increased risk of breast cancer may reflect the common practice (in North America, where most studies were done) of requiring a normal mammogram before oestrogen is prescribed. Five years after stopping oestrogen there is no longer an increased risk of breast cancer<sup>19</sup>; this is compatible with the thesis that oestrogen is a promoter rather than a cause of breast cancer.

### Bias in studies of use of oestrogen and breast cancer<sup>5</sup>

Source of bias	Effect on risk of breast cancer
Bias in who takes oestrogen:	
No family history of breast cancer	Decrease
Negative mammogram before oestrogen started	Decrease
Premature menopause or oophorectomy	Decrease
Osteoporosis*	Decrease
Higher social class	
Thinner*	Decrease
Late first pregnancy	Increase
Bias in diagnosis:	
More mammograms and examinations	Increase

\*Thinner women have more osteoporosis and less heart disease

Breast density on radiography increases in the first year of hormone therapy in about one third of women, making interpretation of mammograms more difficult.<sup>21</sup> Density on mammography is a marker for increased risk: in several studies increased breast density predicted a twofold increased risk of breast cancer.<sup>22</sup>

## Other risks and benefits

**Risks**—Oestrogen doubles the risk of having gall bladder surgery<sup>23</sup> and significantly increases the risk of having a hysterectomy.<sup>7</sup> In observational studies, oestrogen doubles the risk of deep vein thrombosis and pulmonary embolism—but the absolute risk is low, about three cases per 10 000 treated women per year. The oestrogen-thrombosis association has been confirmed in a randomised clinical trial.<sup>24</sup>

**Benefits**—Six of 11 observational studies found that oestrogen reduces the risk of colon cancer.<sup>25</sup> A meta-analysis of 10 observational studies showed significant protection from Alzheimer's dementia, with a summary risk estimate of 0.71, but results of eight small uncontrolled trials of oestrogen in women with dementia are not persuasive.<sup>26</sup>

**Quality of life**—Oestrogen therapy improves well-being in women with hot flushes and may improve quality of life in such women independent of complete resolution of hot flushes.<sup>27</sup> A recent trial found no improvement in quality of life among asymptomatic older women, however.<sup>28</sup>

## Mortality

At least 12 studies have found that oestrogen is associated with longer survival.<sup>29</sup> Lower death rates are not entirely explained by a reduced risk of cardiovascular death; rates are also lower for diseases thought to be unrelated to oestrogen. This non-specific benefit may reflect the multiple biological effects of oestrogen, or the selective use of oestrogen by healthy women.<sup>30</sup>

## Who to treat

Oestrogen is the treatment of choice for menopause symptoms and osteoporosis. Oestrogen is also the drug of choice for the prevention of fractures. Bone densitometry is the best predictor of fracture risk, but less expensive tests to identify women who should receive prophylactic oestrogen are needed. Contraindications to postmenopausal oestrogen are few: liver disease, vaginal bleeding, or a history of deep vein thrombosis, pulmonary embolus, or oestrogen dependent cancer.

## Women at high risk

**Dyslipidaemia**—Oral oestrogen lowers concentrations of low density lipoprotein and raises high density lipoprotein cholesterol, Lp(a), and triglyceride concentrations. Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) lower low density lipoprotein more than oestrogen, and (unlike oestrogen) have been shown to prevent heart disease in clinical trials. Transdermal oestrogen raises high density lipoprotein and triglyceride concentrations less than oral oestrogen; the clinical importance of these differences is not known.

**Heart disease**—It is not clear that oestrogen improves survival in women who have coronary heart disease. A recent study found the same prognosis after myocardial infarction in women who were or were not taking oestrogen.<sup>31</sup> In another study, oestrogen use was associated with less stenosis after atherectomy but not after angioplasty.<sup>32</sup> The heart and oestrogen/progestin replacement study (HERS) was designed to determine whether oestrogen plus continuous medroxyprogesterone acetate is better than placebo in preventing recurrent events in women with heart disease; results are expected shortly.<sup>33</sup>

**Breast cancer**—Studies of women who had breast cancer have not shown that replacement oestrogen increases the risk of new or recurrent breast cancer, but the total number of women studied is too small for informed clinical decisions. Women who have severe symptoms one year after menopause induced by chemotherapy may elect to use oestrogen despite the unknown risk. Randomised trials of oestrogen in women with breast cancer are just beginning.

## All women

Oestrogen as the standard of care depends on the risk: benefit ratio—which varies according to the postulated benefit and the frequency of coronary heart disease. Where heart disease is common, the population benefit would exceed adverse events if hormone therapy really does reduce cardiac deaths by 25%.<sup>8</sup> In England and Wales, heart disease causes more deaths in women than men, but deaths tend to occur later (fig 1). In older women heart disease is a more common cause of death than cancer (fig 2).<sup>34</sup> Nevertheless, the prescription of oestrogen to prevent heart disease in healthy women is premature, because neither the fact nor magnitude of cardioprotection can be known without clinical trials.

Overall, breast cancer is less common than heart disease, but in women aged under 65 breast cancer is more common than heart disease. Women who are making oestrogen decisions in the perimenopause typically have friends in their age group with breast cancer, not with heart disease. This may explain why a lifetime favourable risk:benefit ratio coupled with even a small increased risk of breast cancer is unacceptable

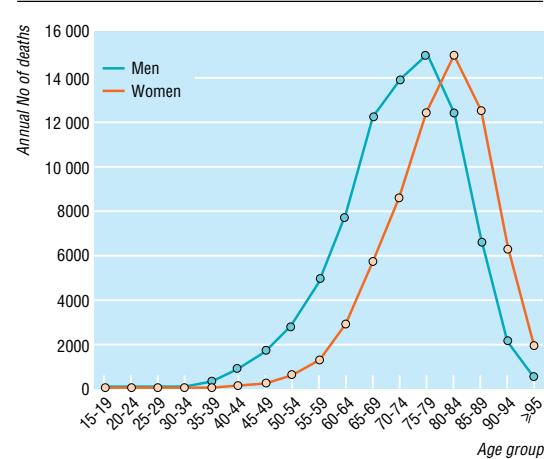


Fig 1 Deaths from coronary heart disease, England and Wales, 1989-93. Reproduced with permission<sup>34</sup>

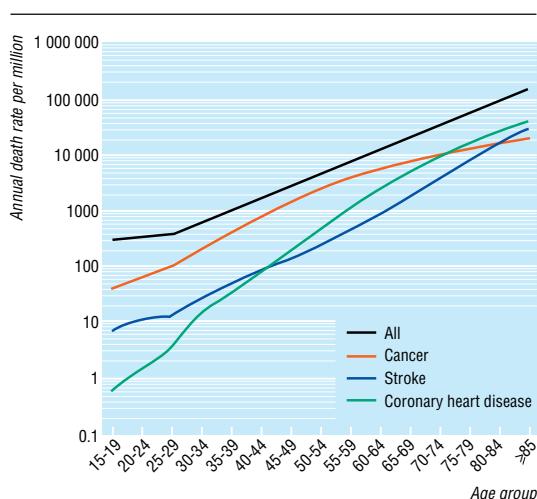


Fig 2 Mortality in women, England and Wales, 1989-93. Reproduced with permission<sup>34</sup>

for many women. Newer treatments such as tibolone, raloxifene, and soy phyto-oestrogens may preserve bone without cancer risk; their effect on cardiovascular disease is unknown.

### How to treat

All too often the prescription of a single hormone regimen for all women, large and small, young and old, causes side effects (mastalgia, bloating, bleeding, "premenstrual tension," and depression). Side effects reduce compliance. They can be minimised or prevented by starting with half the dose, or resolved by halving the dose or changing the hormone or route of delivery. Although head to head comparisons of different hormones are sparse, it is widely believed that transdermal oestrogen causes less mastalgia, nausea, and deep vein thrombosis than oral oestrogen, and that progestogen causes depressed mood in some women.

Oestrogen replacement doses are designed to prevent bone loss; standard doses of progestogens are designed to prevent endometrial cancer (see boxes).<sup>35</sup> The amount of oestrogen recommended to prevent bone loss is not based on large studies that gave a range of doses. Standard doses preserve bone in most postmenopausal women, but some women require more oestrogen or testosterone. New studies suggest that many women need only 0.3 mg conjugated equine oestrogen (or equivalent) plus 1000 mg daily calcium to preserve bone, a regimen that causes little mastalgia, bleeding, or endometrial hyperplasia.<sup>36 37</sup> Response to treatment can be assessed within three months by using bone turnover markers. New options for women who cannot take oestrogen include alendronate, miacalcin, and raloxifene.

Lipoprotein changes are similar with large or small doses of oral oestrogen, but transdermal oestrogen raises high density lipoprotein less than oral oestrogen.<sup>38</sup> All progestogens mask some of oestrogen's favourable effect on high density lipoprotein. The importance of these differences is not known; favourable lipoprotein changes probably do not explain most of oestrogen's apparent cardioprotection.

Prevention of endometrial hyperplasia and cancer induced by oestrogen depends on both dose and duration of progestogen use.<sup>39</sup> Uterine protection requires 12 days of cyclical progestogens or combined continuous regimens. The former causes scheduled bleeding and the latter causes unpredictable spotting or bleeding, which usually resolves within nine months. Studies are under way to determine whether the endometrium can be protected by a vaginally delivered progestogen and whether women taking low dose oestrogen need progestogen.

### When to treat

There are several arguments for starting oestrogen later rather than at the age of menopause: current use of oestrogen is associated with a lower risk of heart disease and fracture than past use; women are not likely to take oestrogen from menopause to grave<sup>12</sup>; most women have heart disease and hip fractures after age 65, so fewer women would need to be treated to prevent these conditions if hormone therapy was begun later<sup>40</sup>; delaying oestrogen reduces the duration of treatment and presumably the risk of breast cancer while still protecting bone<sup>13</sup>; and delaying oestrogen facilitates the identification of the woman at high risk for fracture because bone density at age 60 is a better predictor of future fracture risk than is perimenopausal bone density.

Delaying treatment is not recommended for women who have a premature menopause, symptoms, or osteoporosis. It is an option for asymptomatic recently menopausal women who are at no particular risk for fracture; such women can safely wait 10 years for the results of the primary prevention trials in progress—the women's health initiative in the United States and the women's health initiative menopause study in the United Kingdom and Europe. Even better, women can be encouraged to participate in such trials.

#### Bone conserving doses of oestrogens

These are average doses for a postmenopausal woman in her sixth decade. Younger women may require higher doses; older women may require less.<sup>35</sup>

Conjugated equine oestrogens	0.625 mg daily
Oestrogen sulphate	1.5 mg daily
Oestradiol 17 $\beta$ :	
Oral	1-2 mg daily
Transdermal	0.05 mg daily
Implant	50 mg six monthly

#### Doses of oral progestogens for endometrial protection

These minimum doses are protective when given 12 days per calendar month.<sup>35</sup>

Norgestrel	0.15 mg
Norethisterone	1 mg
Medroxyprogesterone acetate*	10 mg
Dydrogesterone	10 mg
Micronised progesterone	200 mg

\*Equally protective as 2.5 mg daily continually throughout calendar month.

## Conclusions

We cannot, in the absence of randomised controlled clinical trials, be completely confident that long term prophylactic oestrogen is effective. Consistent but circumstantial data point to a decreased risk of heart disease and an increased risk of breast cancer. Individualised counselling should be based on each woman's risk status and concerns.

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### An interesting encounter Did I teach him survival skills and healthcare priorities?

There is a paraplegic—I wonder what the aetiology is—who, seated on the ground with his crutches next to him, asks for donations at the entrance to the supermarket. He is a pleasant man and always has a smile despite his disabilities. As a member of the middle class in an Asian society and a healthcare professional, I sympathise with his plight and realise that society must do more and that we should be part of the pressure group that tries to achieve this. But, caught up in a society that is privatising the basic services, we realise that we have to do enormous amounts in education and other things to see that our children get a decent start in life, and our priorities are elsewhere. My normal response is to give him some money or some food bought from the nearby shop.

The other day when I passed him there was a new group—a mother and her children—on the other side of the entrance, who

were also asking for donations. The children were thin and the hair slightly brown—was it early kwashiorkor or the dust in unwashed hair? I took a long hard look—especially at the children—and gave my token donation to the mother in the hope that it would be for nutrition for the children. He saw what happened but nevertheless gave his usual smile.

The next day when I passed him his own two children were playing by his side and the little son was using one of the crutches as a toy. I gave him double what I normally give, and wished that my students would learn how to identify healthcare priorities as fast.

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