Menopausal hormone replacement therapy

This week's Update investigates the risks and benefits of hormone replacement therapy in menopause.

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Introduction

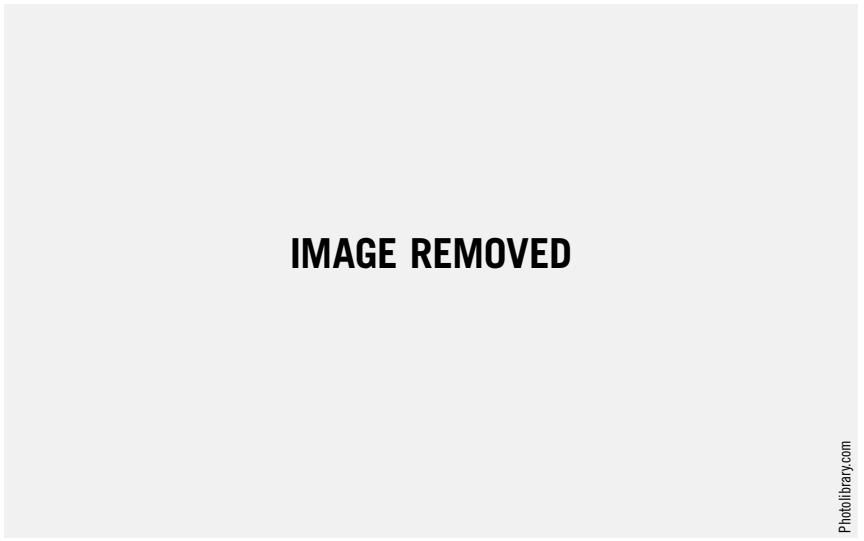
HORMONE replacement therapy (HRT) is the most effective treatment for relief of menopausal vasomotor symptoms.[1]

Before 2002, level 2 observational studies[2,3] of symptomatic women going through menopause suggested that long-term hormone replacement therapy provided not only relief of menopausal symptoms, but also cardiovascular benefits, and a reduced risk of osteoporosis and fractures. These studies also found an increased risk of breast cancer and thromboembolic disease, but overall benefits were thought to strongly outweigh any risks.

To test this hypothesis, a large multicentre randomised clinical trial, the Women's Health Initiative (WHI), was conducted on 27,000 postmenopausal, predominantly white, American women.

Initial results from the WHI[4] were published in 2002. They showed that after five years of combined oestrogen and progestin therapy there was an expected increase in breast cancer and thromboembolic disease, and a reduction in fractures. However, there was also an unexpected increase in cardiovascular disease and thus, using a 'global index' devised especially for this trial, a trend towards net harm rather than benefit for HRT users.

The at-times alarmist reporting of this data in the media led to most HRT users



stopping therapy, often without medical consultation. Various advisory bodies issued strongly worded guidance suggesting HRT should be used at the lowest dose for the shortest possible time, and only in severely symptomatic women.

The publication of the second paper from WHI in 2004,[5] analysing results for oestrogen-only users, showed a reduction in fractures, no increase in cardiovascular disease, no increase in breast cancer, and the expected increase in venous thromboembolic disease.

The discrepancy between the results from earlier observational studies and the major randomised trials led to vigorous debate in the scientific community.

The major difference between the two groups was the age of participants. Women in the observational studies had a mean age of about 50, while the mean age of women in the randomised trials was mid-60s.

The significance of this was initially denied by WHI investigators; however, in recent years, several papers (by WHI investigators and others) have been published showing that for women initiating HRT at the time of their menopause, the risks are few. Outcomes are similar to those seen in observational studies, and there is indeed a 'window of opportunity' for the safe use of hormone therapy to relieve menopausal symptoms in most women.

Epidemiology of the menopause

The menopause is a normal, physiological event marking the last menstrual period and the end of cyclical ovarian follicular activity. The average age of the menopause in Western countries is 50-52 years, and several years younger in poorer, less-developed countries.[6,7] Menopause is defined as premature if it occurs before age 40[10] (see Premature Menopause).

The menopause is associated with a variety of symptoms, the most pathognomonic of which are the vasomotor symptoms of hot flushes,[8] night sweats and insomnia, which affect about 75% of Australian women[9] and of whom 30%-40% will seek help in their alleviation. Other common symptoms include muscle and joint aches and pains; changes in mood, memory and concentration; and urogenital symptoms.

Before considering HRT, many women will try to alleviate their vasomotor symptoms with complementary therapies, for which there is little good evidence of efficacy.[11]

Any decision by the clinician regarding the use of HRT should be part of an overall preventive health strategy for menopausal women, including assessment of metabolic health and advice on lifestyle, diet, regular exercise, cessation of smoking and modest alcohol intake.

Cardiovascular disease is responsible

Declaration of interest: Professor Baber has conducted research for all major pharmaceutical companies involved in menopausal medicine and for Novogen, a manufacturer of over-the-counter phytoestrogen products. Funding for all research has been paid into externally administered trust funds at Royal North Shore Hospital. Professor Baber has received honoraria to cover expenses for presentations made at meetings sponsored by a number of pharmaceutical companies.

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for about 40% of female deaths after the age of 50.[11] Appropriate clinical assessment at this time of a woman's life should include blood pressure, lipids and blood sugars, as well as the above.

The menopause also heralds an increasing risk of osteoporosis, so assessment of bone density should be considered.

For women with moderate to severe menopausal symptoms, HRT is the gold-standard treatment and may be recommended as a first option in the absence of contraindications. Topical, locally acting, low-dose vaginal products are the treatments of choice for women who experience urogenital symptoms in isolation.

Premature menopause

Premature menopause occurs spontaneously in 1% of women before the age of 40, and in 5%-8% of women as a consequence of surgical or medical interventions for the treatment of malignant disease earlier in life.[10]

The diagnosis is often missed and should be considered in any woman younger than 40 with oligomenorrhoea or secondary amenorrhoea.

An early menopause is associated with an accelerated risk of osteoporosis and, probably, heart disease. Women who have undergone premature menopause should normally be offered HRT at least until the average age of the menopause (51 years). There is currently no consensus on the best form of HRT for these women; however, doses used are commonly higher than those used in older women and may need to be adjusted over time. About 50% of women with spontaneous premature ovarian failure will experience some return of ovarian activity, and 5%-10% may become pregnant; therefore, it is prudent to give these women appropriate contraceptive advice.

Vasomotor symptoms

Oestrogen is the most effective therapy for vasomotor symptoms.[1] The standard dose of oestrogen used historically and the one studied in WHI was 0.625 mg conjugated equine oestrogens (CEE), which is equivalent to 1 mg oestradiol orally or 50 µg oestradiol transdermally. Level 1 evidence shows these doses alleviate symptoms by about 80% relative to placebo.

The lowest dose of oestrogen which relieves menopausal symptoms should always be used.

In Australia, standard doses of hormone therapy are 1-2 mg oestradiol orally, 25-100 µg transdermally, or 0.3-0.625 mg CEE orally.

For comparison, a combined oral contraceptive pill containing 20 µg ethinyloestradiol is about dose equivalent to 2.5mg CEE.

Side-effects and risks

Early, dose-related side-effects of HRT may include breast tenderness, fluid retention and breakthrough bleeding. These usually settle quickly with adjustment of dose and regimen. A review within 2-3 months of initiating therapy will help to finetune the treatment regimen and aid with compliance.

In women with an intact uterus and within one year of their last menstrual period, HRT should usually be given in a sequential manner with 10-14 days of progestin per month. Women using sequential oestrogen and progestin will usually experience cyclical vaginal bleeding, while those using continuous combined oestrogen and progestin (the more common regimen for women more than 12 months past their last menstrual period) will commonly experience breakthrough bleeding in the first few months of therapy. The incidence of this bleeding declines within 12 months, by which time about 90% will be amenorrhoeic.

LENGTH OF HRT

Duration of therapy with HRT for most women will be short; symptoms persist in 70% of women for two years or less, and 80% will be free of symptoms within five years. Many women will choose to stop therapy independently.

Observational studies have reported that 40%-50% of women cease hormone therapy within a year and 65%-75% within two years.[5] For longer-term users, it is helpful to suggest they try to come off therapy annually, at a suitable time, to determine whether troublesome symptoms of the menopause persist.

Although tapering hormone therapy is often recommended, the advantage of this approach remains unproven. The decision as to how and when to cease hormone therapy should be made after individual consultation with the patient. Some women will require hormone therapy for a prolonged period of time, and these women should be regularly appraised of the latest evidence and undergo at least annual risk/benefit assessments.[13]

Current opinion on HRT

- The primary indication for HRT is to alleviate symptoms
- HRT increases bone density and reduces fracture risk
- HRT is not appropriate for cardioprotection but does not worsen heart disease in younger women
- Oral HRT increases the risk of thromboembolism. This risk varies with dose, age and delivery system
- HRT use for up to seven years will not increase breast cancer risk. ET appears safer than EPT
- Management should be individualised and HRT should not be initiated in women over 10 years post-menopause.

POSTMENOPAUSAL OSTEOPOROSIS

Bone mineral density peaks in the mid-30s and declines slowly thereafter. There is accelerated loss of bone density after the menopause.

Necessary measures for the prevention and treatment of postmenopausal osteoporosis include regular weight-bearing and strength-training exercise, cessation of smoking, adequate calcium intake and adequate levels of vitamin D.

Despite the fact that HRT does not have a primary indication for prevention and treatment of osteoporosis in Australia, evidence is strong that it has a positive effect,[14] and there is a role for HRT in symptomatic women and in those for whom the use of alternative therapy (such as bisphosphonates and strontium ranelate) is not appropriate.

Low-dose and ultra-low doses of HRT have been shown to prevent bone loss, but there is no data on fracture prevention with this therapy.[15] Initiation of HRT over the age of 60 for the sole purpose of preventing osteoporosis-related fractures is not recommended as a first-line option due to the increased risk of cardiovascular complications seen in this age group.[16]

Similarly, if HRT has been initiated at the time of the menopause for relief of menopausal symptoms which have abated, then the continuation of HRT over the age of 60 for the purpose of fracture prevention should take into account patient preference and risk factors before continuing.

CARDIOVASCULAR HEALTH

There is now strong data to support the hypothesis that oestrogen is cardioprotective when initiated around the time of the menopause.[17,18] A meta-analysis of randomised clinical trials showed a statistically and clinically significant 39% reduction in cardiac events compared to placebo groups when HRT was initiated under the age of 60 years.[19] However, this effect is not seen in older women, and when HRT is initiated in older women, there is an increased risk of cardiac events during the first year of therapy.[20]

It is postulated that this differential effect is related to the presence of vascular oestrogen receptors responsive to exogenous HRT around the time of the menopause, allowing for a beneficial effect on coronary vessels. However, when HRT is administered later in life, these receptors are not present or are present in reduced numbers in vessels already more likely to be damaged by atherosclerotic plaque, which may be disrupted by initial HRT. This explanation has gained support from recent evidence published from WHI investigators[21] showing a reduction in progressive plaque in women initiating oestrogen therapy in their 50s compared to placebo controls.

Notwithstanding this reassuring information on HRT in younger women, it is not recommended that HRT be used as a primary or secondary therapy for cardiovascular disease.

BREAST CANCER

Before the WHI, observational studies suggested a small increase in relative risk of breast cancer with long-term use of HRT.[22] The increase after more than five years of therapy was estimated at 1.35.

The WHI[4] reported a slightly lower relative risk of 1.26 after 5.6 years of oestrogen and progestin therapy. In absolute terms, this was eight extra cases per 10,000 women years.

It is important to put this risk into perspective. The relative risk seen in the WHI, other randomised trials and observational studies is similar to the risk seen for a late menopause, nulliparity or more than three alcoholic drinks per day.[23]

In the oestrogen-only arm of the WHI,[24] breast cancer risk was not increased after 7.1 years (in fact, there was a non-significant reduction in risk RR 0.80 [0.62-1.04] p = .09). This was confirmed in observational studies, which showed no increase in breast cancer for at least 15-20 years.[25]

Further research is required to find the HRT regimen that is safest for the breast. It appears that oestrogen alone is safer than oestrogen and progestin; however, not all progestins may carry the same risk profile.

Data from the E3N study[26] has found that the risk of breast cancer associated with combined HRT may vary depending on the progestin used. Tibolone (see page 29) has different effects on the breast to oestrogen and progestin therapy, and combinations of oestrogen plus selective oestrogen-receptor modulators may also offer breast advantages.

In summary, randomised controlled trial evidence is consistent with that from observational studies and shows no increase in breast cancer for users of oestrogen and progestin HRT for at least five years and for users of oestrogen-only HRT for at least seven years.[27]

OVARIAN CANCER

Data from observational studies and the WHI study show a non-significant increase in ovarian cancer after five years of oestrogen and progestin HRT, but a significant increase after five years of unopposed oestrogen therapy.[28,29] The magnitude of this is about one extra

case in 2500 women and is seen mostly in women who have had a hysterectomy with ovarian conservation. Therefore, the 'at-risk' group is small, and the absolute risk would be classified as rare and does not appear to apply for short-term use.

THROMBOEMBOLIC DISEASE

Thromboembolic disease remains the main short-term serious risk of HRT.[30,31,32] It appears to be greatest in the first year or two, and increases with age, obesity and thrombophilias. The risk for women going through the menopause at the age of 50 is about one extra case per 10,000 women per year. The risk in the WHI appeared to be slightly higher for combined HRT than for oestrogen-only HRT.

Several observational studies and a meta-analysis have suggested that non-oral HRT is not associated with an increased risk of venous thromboembolic disease.

STROKE

The annual rate of stroke in women aged 50-59 is about six per 10,000 per year, rising to 20 per 10,000 per year over the age of 60, and 40 per 10,000 between 65 and 75.

In the WHI clinical trials,[33] both the combined HRT and oestrogen-only arms reported an increased risk of stroke in the entire population. However, the risk was not increased in the 50-59 age group, although the numbers were small.

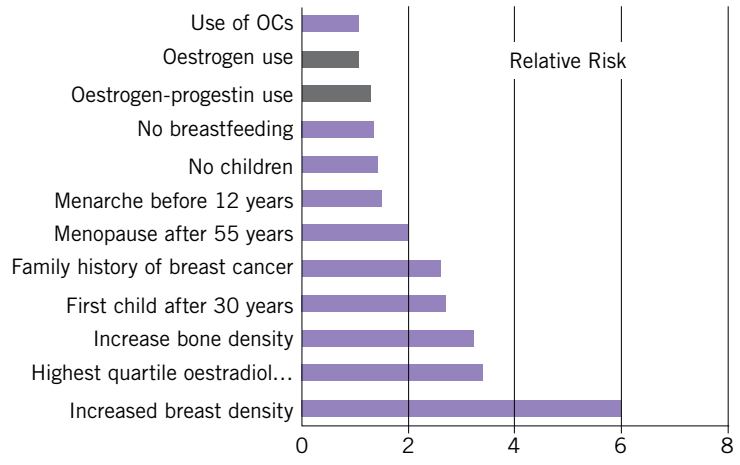
The absolute risk for the entire population in WHI was eight per 10,000 and 12 per 10,000 women years, both falling into the rare category.

Recent observational studies,[34] including the WHI observation study, have all reported no increase in stroke risk in younger women, although there was an increased risk of transient ischaemic attacks in this younger age group.

COGNITIVE FUNCTION

The effect of HRT on cognitive function is likely to remain controversial. Observational studies continue to support the possibility that HRT use around the time of the menopause may provide more benefit than harm,[35] although in the WHI studies of women older than 65, an increased incidence of possible dementia was reported.[36]

HORMONE-RELATED INDICATORS OF THE RISK OF BREAST CANCER



Source: Adapted from ASRM Practice Committee. HT in Postmenopausal Women. Fertil Steril 2008.

KEY POINTS

- **The primary indication for hormone replacement therapy (HRT) is to alleviate vasomotor symptoms in symptomatic women.**
- **For women with moderate to severe menopausal symptoms, HRT is the gold-standard treatment and should be recommended as a first option in the absence of contraindications.**
- **Topical, locally acting, low-dose vaginal products are the treatment of choice for women who experience urogenital symptoms in isolation.**
- **Duration of therapy with HRT for most women will be short; the decision as to how best to cease hormone therapy and when should be made after individual consultation with the patient.**
- **There is no evidence that custom compounded bioidentical hormones have any advantage over conventional HRT, and concerns remain about dose consistency, purity, safety and efficacy of these products.**

Tibolone

Tibolone is a selective tissue estrogenic activity regulator (STEAR). Following oral ingestion, tibolone is converted into oestrogenic and androgenic metabolites which relieve hot flushes and improve energy and sexual wellbeing. The progestogenic delta 4 isomer prevents endometrial stimulation, while breast stimulation is minimised due to tibolone's effect on local breast enzyme activity.

More than 13,000 women have now participated in a range of randomised clinical trials investigating the effects of tibolone in postmenopausal women.[37,38]

Tibolone alleviates menopausal symptoms and reduces fracture risk similarly to other forms of HRT and is another option for use in postmenopausal women.

Tibolone dose not increase mammographic density compared to placebo and mastalgia is an uncommon side-effect.

Women who might specifically benefit from tibolone include those who experience breast pain de novo or while on HRT despite careful dose adjustment; those in whom increased breast density has been noted on mammogram; those with low libido and/or depressed mood; and perhaps those with persistent bleeding problems on other forms of HRT (providing appropriate investigations have been performed).

Although an increase in breast cancer has not been detected in other clinical trials, the LIBERATE trial noted an increased risk of breast cancer recurrence with tibolone use in women with a personal history of breast cancer. Therefore, tibolone cannot be recommended for this group of women.

Management of early side-effects

Many early side-effects have been attributed to HRT, including bloating, weight gain, headaches, breast tenderness and bleeding. Of these, only breast tenderness and irregular bleeding were found to be significantly increased in a Cochrane review[1] of level 1 studies of HRT for vasomotor symptoms.

Breast tenderness is usually transient and responsive to dose adjustment, while breakthrough bleeding also diminishes with time, lower-dosage regimens and time since the last menstrual period.

The key to successful HRT use is to tailor therapy to meet each patient's needs, to adjust the dose and to consider non-oral routes where appropriate.[39,40] Doses should be the lowest that are effective. Continuous combined hormone therapy or tibolone are best avoided until at least 12 months from the last menstrual period. An early follow-up visit 2-3 months after initiating therapy will help to overcome side-effects and improve compliance.

Bioidentical hormones

Some postmenopausal women turn to 'natural' or bioidentical hormone therapy due to safety concerns about conventional hormones. Available data suggests that while some of these products may decrease hot flushes, there is no evidence that they have any advantage over conventional hormone therapy.[41]

Bioidentical conventional hormone therapy products remain available and should be used as first choice. Custom compounded bioidenticals do not have the same level of regulation as pharmaceutical products and concerns remain about dose consistency, purity, safety and efficacy of these products.

In the US, the Food and Drug Administration has begun enforcement action against several compounding pharmacies, stating that the claims made by these pharmacies about the safety and efficacy of compounded hormones are false and misleading, with no credible scientific evidence to support them.[42]

Conclusion

While there is little doubt that the risks of HRT have been sensationalised by some in the medical profession and the media, it remains the most effective treatment for menopausal symptoms, which is the primary indication for its use. Potential side-effects and risks from HRT may be reduced by individualisation of treatment. Emerging data suggests fewer side-effects with lower dose, with judicious choice of progestins and perhaps with the use of non-oral routes in some women.

HRT can and should be offered to informed women for as long as they have debilitating menopausal symptoms. The data do not support the use of HRT for chronic disease prevention.

Recent publications since the initial release of the WHI data in 2002 suggest that when HRT is initiated near the menopause for symptom control and subsequent improved quality of life, there are likely to be additional bone and heart benefits. These outweigh the risks that are not significantly raised under the age of 60.

Women who initiate hormone therapy should be encouraged to try discontinuing therapy from time to time as their duration of therapy increases.

References and the associated patient handout, 'Hormone replacement therapy', available at **medicalobserver.com.au**