Hormone replacement therapy: to use or not to use?

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ABSTRACT

- The main indication for hormone replacement therapy (HRT) is to control menopausal symptoms and improve quality of life.
- Ideally, withdrawal of HRT should be attempted after 4–5 years of therapy.
- HRT reduces fracture risk and remains appropriate therapy for osteoporosis, particularly in women with symptoms.
- HRT is not appropriate for primary or secondary cardioprotection.
- HRT leads to a small increase in breast cancer incidence, which increases with duration of therapy and age.
- HRT increases the risk of thromboembolism.
- Patient management and therapy should be reviewed annually with risk–benefit counselling.

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IN JULY 2002, THE FINDINGS of the oestrogen plus progestin randomised controlled trial of the Women's Health Initiative (WHI) were released to the media a week before they were published in the *Journal of the American Medical Association*.[1] Much has been made about the manner in which these findings were released and, in particular, how the information might have been conveyed in more practical terms to doctors and patients alike.[2]

The WHI trial was stopped prematurely because the test statistic for invasive breast cancer exceeded the pre-determined stopping boundary and also because the trial-specific global index showed that risks exceeded benefits for users of hormone replacement therapy (HRT). It was found, using nominal confidence intervals, that relative risks were significantly increased for the endpoints of cardiovascular disease, thromboembolic disease and stroke, and significantly decreased for colorectal cancer and various fractures. However, a trial such as this, with multiple endpoints, should use adjusted rather than nominal confidence intervals to test individual endpoints for statistical significance (using a Bonferroni correction to compensate for the increased chance of type I error because of multiple testing). When the WHI data were analysed using adjusted confidence intervals, only the changes in incidence of thromboembolic disease and total and other osteoporotic fracture were significant (Box). The increase in breast cancer incidence did not reach statistical significance with either nominal or adjusted confidence intervals.

The WHI trial's press release chose to highlight the relative risks and results that were significant using nominal CIs, leading many women to cease HRT immediately, often with a return of menopausal symptoms. Doctors, yet to read the unpublished paper, were besieged by patients seeking advice, and prescriptions written for HRT fell by 50%.[3] The subsequent cancellation of the Women's International Study of Long Duration Oestrogen after the Menopause (WISDOM),[4] a trial intended to evaluate issues including quality of life and symptom relief in younger women, leaves many important questions unanswered. It is thus pertinent to review the use of HRT in postmenopausal women.

Symptom relief and quality of life

About 600 000 Australian women use HRT, three-quarters of whom began HRT principally to alleviate symptoms and to improve their quality of life.[5] Menopausal symptoms may not be life-threatening, but half of those afflicted find them significant enough to seek help.

HRT remains the most effective proven therapy. The evidence for the efficacy of either HRT or oestrogen replacement therapy (ERT) has been clearly established in Cochrane reviews of published randomised controlled trials: HRT reduced vasomotor symptoms compared with placebo (relative risk [RR], 0.10; 95% CI, 0.6–0.19), and ERT slightly less (RR, 0.35; 95% CI, 0.22–0.56).[6]

Often patients can be weaned from HRT after 3–5 years, but long-term HRT may be appropriate if symptoms persist. Ten per cent of postmenopausal women experience troublesome long-term symptoms. Appropriate counselling on the risks and benefits of long-term HRT should be provided, after which therapy with the lowest effective dose may be resumed for as long as is required, with annual review.

Many other remedies have been proposed for relieving menopausal symptoms, including alternative therapies and antidepressants. Discussion of these is beyond the scope of this article. The synthetic steroid tibolone is discussed elsewhere in this issue of the Journal (*page 635*).[7]

Recent randomised controlled trials of HRT did not evaluate quality of life, menopausal symptoms, cognitive function, dementia, urogenital symptoms, skin or dentition, and cannot properly evaluate risk–benefit ratios of long-term (> 5 years) use.

Summary:

- HRT should not be prescribed without an indication, the most common being relief of menopausal symptoms.

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■ After 5 years of therapy, gradual withdrawal of treatment should be attempted.
■ Long-term HRT for symptom relief may continue after appropriate counselling.

Cardiovascular disease

Observational studies suggest that ERT for postmenopausal women is associated with a lower incidence of ischaemic heart disease.[8,9] The most comprehensive of these studies, the Nurses' Health Study, began in 1985 and was updated in 2000.[10] Current use of HRT was associated with a relative risk for a major coronary event of 0.61 (95% CI, 0.52–0.71), with benefits reducing with long-term use. Findings such as this, consistent across a number of observational studies, have not been supported by recent randomised controlled trials of oral continuous combined HRT. This discrepancy may be explained by a disparity in risk profiles, with women in the observational studies being younger, slimmer and including fewer smokers than those in the WHI study.[11] It might also be related to a change in hormone regimens from unopposed oestrogens and sequential regimens to continuous oestrogen–progestin therapy.[12]

Two secondary prevention trials of HRT and heart disease (in patients with evidence of already established atherosclerosis), the HERS (Heart and Estrogen/Progestin Replacement Study)[13] and ERA (Estrogen Replacement and Atherosclerosis) study,[14] showed no reduction in heart disease or regression of atherosclerotic plaque in users of HRT or ERT. The findings of these and other recent trials accord with the WHI data.[15]

It has been suggested that, because of the older age and risk factors of the women taking part, the WHI trial might also be regarded as a secondary prevention trial. At enrolment, these women had a mean age of 63 years and many were overweight or obese (mean body mass index, 28.5 kg/m^2), while 36% had hypertension, 13% had raised cholesterol levels requiring medication, and 50% were or had been smokers.[1] There is evidence, particularly in macaque monkeys, that oestrogen is effective in preventing cardiovascular disease only when started in individuals without signs of progressive atherosclerosis, and that HRT begun at the time of menopause may have different effects on arterial disease prevalence to HRT begun a decade later.[16]

The mechanisms by which oestrogen may protect against heart disease include endothelial-mediated vascular effects, non-endothelial vascular effects, favourable lipoprotein effects, possible favourable effects on glucose and insulin homeostasis, changes in extracellular matrix and plaque stabilisation, and facilitation of collateral vessel formation.[17]

Summary:

■ HRT and ERT improve surrogate markers of arterial disease.
■ HRT and ERT do not ameliorate established coronary artery disease.

Relative and absolute risk or benefit seen in the oestrogen plus progestin arm of the WHI study* (*n* = 16 608)

Health event	Relative risk† (adjusted 95% CI)	Change in absolute incidence (cases per 10 000 women/year)
Heart attacks	1.29 (0.85–1.97)	+ 7
Strokes	1.41 (0.86–2.31)	+ 8
Breast cancer	1.26 (0.83–1.92)	+ 8
Thromboembolic events	2.11 (1.26–3.55)‡	+ 18
Colorectal cancer	0.63 (0.32–1.24)	− 6
Hip fractures	0.66 (0.33–1.33)	− 5
Total fractures	0.76 (0.63–0.92)‡	− 44
Death	0.98 (0.70–1.37)	
Global index	1.15 (0.95–1.39)	

* Adapted from Rossouw et al.[1]
† Relative risk in oestrogen plus progestin group versus placebo group at 5.2 years.
‡ Statistically significant.

■ Evidence for primary protection against coronary artery disease differs between observational studies and the WHI study.
■ Currently, HRT cannot be advocated for treatment or prevention of coronary artery disease.

Cancer

The WHI press release highlighted the increased risk of breast cancer, consistent with the expectation that invasive breast cancer would be the primary adverse outcome based on previous observational data (RR for combined HRT, 1.53).[18]

The relative risk of 1.26 for invasive breast cancer in the WHI study did not reach statistical significance (95% CI, 1.00–1.59), but its inclusion in the weighted test statistic was significant for an overall adverse effect of HRT. The absolute increase in risk was 8 cases per 10 000 women per year (incidence, 0.38% versus 0.30% per year). Incidence curves first started to separate after 3 years, and separation increased with time. There was no difference in total cancer incidence, as HRT users had decreased incidence of colorectal cancer (consistent with observational data[19,20] and with meta-analysis of randomised trials[15]). Prior HRT users had higher risk of invasive breast cancer than those who had not previously used HRT, suggesting a cumulative effect. Women who had never used HRT before the trial had no increase in risk compared with controls. The groups were comparable with respect to other known risk factors for breast cancer.[1]

The level of risk of breast cancer in the WHI study is consistent with a recent meta-analysis of four randomised trials (overall RR for combined HRT, 1.27; 95% CI, 1.03–1.56).[15] This meta-analysis quantified the absolute risk as an extra 3.2 cases of breast cancer per 1000 users over 5 years for women aged 50–59 years, and an extra 4 cases for women aged 60–69 years.[15] There is no evidence for an increase in breast cancer risk in women under the age of 50 using HRT.

The evidence demonstrates no effect on mortality, perhaps because breast cancers in HRT users have a favourable prognosis. Tumours are smaller, less advanced, and histologically favourable, with a lower incidence of nodal involvement,[15] and are potentially detected earlier because of the patients' close follow-up, therefore providing a survival advantage.

The effects of HRT on breast cancer risk are most consistent with a promoter effect, rather than primary initiation of gene damage, although animal studies suggest oestrogen metabolites may have weak mitogenic activity.[21] It appears that the combination of oestrogen and progestin may have a greater effect than oestrogen alone, but the data from this arm of the WHI study have not been reported to date. In the PEPI (Postmenopausal Estrogen and Progestin Interventions) trial, the combination therapy groups had a greater increase in mammographic density (a marker of breast cancer risk) than women in the control group or those using oestrogen alone.[22]

The WHI data are thus consistent with results of observational studies, demonstrating a modest but smaller absolute increase in breast cancer risk with long-term use of combined HRT compared with the control group. Whether women with a personal history of breast cancer should use HRT is unresolved, as the major international randomised trial (HABITS; Hormonal replacement therapy after breast cancer — is it safe?) is accruing patients slowly (personal communication, Professor John Forbes, Group Coordinator, ANZ Breast Cancer Trials Group), and case–control studies are potentially subject to selection bias.

Observational studies of ovarian cancer incidence remain inconclusive.[23]

Summary:

- Long-term HRT leads to a small increase in breast cancer incidence:
  - Age 50–59 years, 3.2 extra cases per 1000 users over 5 years; and
  - Age 60–69 years, 4 extra cases per 1000 users over 5 years.
- Long-term HRT leads to a reduction in colorectal cancer incidence:
  - Age 50–59 years, 1.2 fewer cases per 1000 users over 5 years; and
  - Age 60–69 years, 3 fewer cases per 1000 users over 5 years.
- Long-term HRT does not appear to affect mortality.

Stroke and venous thromboembolism

The WHI trial reported an increased risk of stroke (RR, 1.41), which was not significant using adjusted confidence intervals (95% CI, 0.82–2.31). Two earlier trials (HERS and WEST [Women's Estrogen for Stroke Trial]) showed that HRT was not significantly related to transient ischaemic attacks or strokes (fatal or non-fatal).[13,24] A systematic review of 18 observational studies dating from 1980 concluded that HRT has a neutral effect on stroke.[25]

The relative risk for venous thromboembolic disease in the WHI study was significantly increased (RR, 2.11; 95% CI, 1.26–3.55). This is consistent with data from a meta-analysis of 12 studies, which associated current oestrogen use with an increased relative risk of 2.14 (95% CI, 1.64–2.81), with the risk greatest in the first year (RR, 3.49; 95% CI, 2.33–5.59).[26] Absolute risk over a 5-year period is thus 1.2 and 4.0 more strokes and 1.6 and 4.0 more pulmonary emboli per 1000 HRT users in the 50–59 and 60–69 years age groups, respectively.[15]

Summary:

- The relationship between HRT and stroke remains uncertain.
- Oral HRT causes a small but significant increase in venous thrombosis and pulmonary embolism.

Skeletal effects

The WHI study found a non-significant reduction in hip and vertebral fracture rates and a significant reduction in rates of total fractures and other osteoporotic fractures (RR, 0.76; 95% CI, 0.69–0.85).[1] These data accord with results of observational studies and demonstrate clear evidence of osteoporotic fracture risk reduction with HRT use. Absolute reductions in hip fracture are 0.5 per 1000 women aged 50–59 years and 2.5 per 1000 women aged 60–69 over 5 years.

Summary:

- HRT still remains the first option for preventing fractures in symptomatic postmenopausal women.
- In women at risk of osteoporotic fracture, therapy should be individualised to include lifestyle advice and evidence-based treatments, including HRT, selective oestrogen receptor modulators and bisphosphonates.
- Long-term use of HRT to prevent osteoporosis may be appropriate in symptomatic women, but individual benefits should be weighed against the potential increase in breast cancer with long-term (> 5 year) use.

In closing, it must be emphasised that the WHI trial examined only oral HRT with conjugated oestrogens and medroxyprogesterone acetate. Thus, it is not yet known whether unopposed oestrogen, other oestrogens and progestins, tibolone, or HRT delivered by non-oral routes have different effects.

Competing interests

None identified.

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