CLINICAL PRACTICE

Menopause and HRT — keeping perspective

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Publication during the past 4 years, particularly in 2002, of the results of randomised controlled trials (RCTs) on hormone replacement therapy (HRT) has led to a re-evaluation of HRT and management of the menopause. The long-term benefits of HRT, particularly the prevention of coronary heart disease (CHD) claimed on the basis of observational studies, have been challenged. Many women have discontinued HRT and many clinicians have had second thoughts, and it is important to keep perspective.

HRT has been the subject of research for the last 50 years, but the following are the first RCTs on the long-term benefits and risks to be published. The main conclusions were:

1. HERS[1] and HERS II[2] (Heart and Estrogen/Progestin Replacement Study): 'Postmenopausal hormone therapy should not be used to reduce the risk for CHD events in women with CHD.'

2. EVTET (Estrogen Venous ThromboEmbolism Trial)[3]: 'Our study provides evidence which strongly supports that initiating HRT in women with previous VTE most probably increases the risk of recurrent VTE.'

3. WEST (Women's Estrogen for Stroke Trial)[4]: 'Estradiol does not reduce the mortality or the recurrence of stroke in postmenopausal women with cerebrovascular disease. This therapy should not be prescribed for the secondary prevention of cerebrovascular disease.'

4. WHI (Women's Health Initiative) Trial[5]: 'The combined postmenopausal hormones 0.625 mg/d plus MPA 2.5 mg/d should not be initiated or continued for the primary prevention of CHD . . . The substantial risks for cardiovascular disease and breast cancer must be weighed against the benefit for fracture in selecting available agents to prevent osteoporosis . . . These results do not necessarily apply to lower dosages of these drugs, to other formulations of oral estrogens and progestins, or to estrogens and progestins administered through the transdermal route.'

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5. In September 2002 Beral *et al*.[6] analysed and reviewed these four trials and concluded that 'the results from many observational studies, suggesting that both combined oestrogen/progestagen and oestrogen-alone HRT substantially reduced the risk of coronary heart disease, must now be regarded as severely biased'.

In October 2002, to the dismay of many investigators, the Medical Research Council in the UK, stopped the WISDOM study (Women's International Study of Long Duration Oestrogen after Menopause) because 'in the light of the new evidence and the slow recruitment to date, WISDOM was considered unlikely to provide substantial evidence to influence clinical practice in the next ten years'.[7]

The findings of these RCTs are contrary to those of many previous observational studies and it is thought that the discrepancy is primarily due to a 'healthy user bias', namely that in the observational studies women who chose to take, or who were prescribed HRT, were healthier and lived healthier lives that those who did not. The WHI trial[5] found that after an average of 5.2 years of conjugated equine oestrogens 0.625 mg/d (CEE) plus medroxyprogesterone acetate 2.5 mg/d (MPA) the risks of CHD, stroke and breast cancer were significantly increased but the risks of colorectal cancer and hip fracture were significantly decreased, with the risks outweighing the benefits. These conclusions have been taken to include all forms of HRT, both in the short and long term, and to apply to all postmenopausal women. There are, however, a number of important considerations regarding the RCTs published so far.

Secondary versus primary prevention of CHD

All the studies, with the exception of the WHI,[5] have been secondary prevention trials involving women with a history of cardiovascular disease, including CHD, stroke and venous thromboembolism (VTE), and the results therefore may not apply to healthy women. The WHI trial,[5] intended as a primary prevention trial, has been criticised because 7.7% of the women had cardiovascular disease on entry and the average age of the women was 63.3 years (45% were aged 60 - 70 years and 21% were 70 years or older). It has been suggested that a significant proportion of the older women had undiagnosed atherosclerosis and that the results in the WHI trial do not reflect the situation in younger healthy postmenopausal

women. In ovariectomised cynomolgus monkeys on an atherogenic diet, oestrogens prevent atherosclerosis in those with initially healthy coronary arteries but are of no benefit in those with existing disease.[8] In younger postmenopausal women with healthy coronary arteries oestrogen may help to prevent atherosclerosis, but in older women with damaged arteries oestrogen may initiate thrombosis or an inflammatory reaction in unstable atherosclerotic plaques. HRT is contraindicated in women with established CHD or those who have had a stroke, and the prevention of CHD can no longer be regarded as one of the major benefits of HRT. However, the question of the effect of HRT on the cardiovascular system, and possible primary preventive benefit, in younger healthy postmenopausal women has not been fully resolved.

Combined oestrogen-progestin versus oestrogen-only HRT

A second consideration is that the HERS,[1] HERS II[2] and WHI[5] trials all involved continuous combined CEE plus MPA. The arm of the WHI trial involving CEE alone in hysterectomised women has however not been stopped and is ongoing as, according to the WHI authors, 'the balance of overall risks and benefits remains uncertain'.[5] Progestins are essential to prevent endometrial cancer in women with uteri, but oestrogen-only HRT in hysterectomised women may have significant benefit/risk advantages over oestrogen-progestin HRT. Observational studies[9] have found that the addition of progestins reduces the beneficial effects of oestrogens on plasma lipids[10] and on the incidence of cardiovascular disease. The main criterion for stopping the WHI trial of CEE plus MPA was the significant increase in the incidence of breast cancer. The incidence of breast cancer in postmenopausal women who have received combined progestins and oestrogens may be significantly greater than with oestrogens alone[11,12] and this may affect the balance of risks and benefits in clinical trials.[13] The findings of the WHI trial of CEE plus MPA may therefore not be applicable to hysterectomised women who receive oestrogen-only HRT. Although the incidence of breast cancer is increased with HRT,[14] mortality does not appear to be increased and may in fact be decreased.[15-18] Furthermore, colorectal cancer, the incidence of which decreases with HRT, has a high mortality rate (5-year survival after surgery is only between 40% and 50%[19]), and the reduction in morbidity and mortality from colorectal cancer when using HRT may exceed any increase associated with breast cancer. The evaluation of the overall morbidity and mortality of all cancers is an important consideration in evaluating the long-term risks and benefits of HRT.

Relief of menopausal symptoms

The third consideration regarding benefits is the relief of menopausal symptoms, in particular hot flushes and night sweats, which can be very distressing and incapacitating. Vasomotor symptoms occur most frequently and severely immediately after the menopause but may persist for many years. HRT is often the only completely effective treatment for hot flushes. In the WHI trial[5] women with menopausal symptoms were excluded and relief of symptoms was not included in the balance of benefits and risks. Relief of symptoms, however, is the prime overwhelming need for many, if not most postmenopausal women and frequently far outweighs all other considerations. Relief of symptoms must be given due weight in any assessment of the benefits and risks of HRT, both in the shorter and longer term.

Conclusion

The US Preventive Services Task Force (USPSTF)[20] recently reviewed all the evidence on HRT for the primary prevention of chronic conditions and recommended 'against the routine use of estrogen and progestin for the prevention of chronic disease in postmenopausal women', concluding that 'the evidence is insufficient to recommend for or against the use of unopposed estrogens for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy'.

The USPSTF further concluded that 'although the harms are likely to outweigh the chronic disease prevention benefits for most women, the absolute increase in risk from HRT is modest. Some women, depending on their risk characteristics and personal preferences, might decide that the benefits outweigh the potential harm . . . The balance of benefits and harms for an individual woman will be influenced by her personal preferences, individual risks for specific chronic diseases and the presence of menopausal symptoms.'

In the WHI trial of CEE plus MPA involving mainly older postmenopausal women the absolute risks were small and the attributable risks even smaller. In younger postmenopausal women the risks of chronic disease are considerably lower and the acute benefits of HRT, in particular the relief of menopausal symptoms, are much greater, and for many women far outweigh any possible risks. The balance of benefits and risks in individual women varies greatly. HRT must be individualised and each woman has to come to a personal decision with the advice and help of her clinician.

In general, HRT appears to be of little benefit, and is contraindicated, in established diseases including CHD, stroke and Alzheimer's disease. However, HRT may be of significant benefit in preventing the development of pathological changes in the cardiovascular and central nervous systems and in bone and other tissues. The prevention of osteoporosis has been one of the main benefits of HRT,[21] although other agents for treatment, including selective oestrogen receptor modulators (SERMs) and bisphosphonates, are now available but expensive. In spite of recent research it is possible that the use of HRT in younger healthy postmenopausal women provides a

'window of opportunity' in the primary prevention of osteoporosis, cardiovascular disease and Alzheimer's disease.[22] Recent RCTs have necessitated a critical reappraisal of HRT, but it is important to keep perspective when considering the needs, benefits and risks in each postmenopausal woman. Ongoing trials should resolve many of the outstanding questions. Meanwhile HRT still has an important and major role to play in the care of menopausal women.

Addendum

Since this article was written the 'Million Women Study' of 1 089 110 UK women aged 50 - 64 years recruited for mammography has been published.[23] The subjects' use of HRT and personal details were analysed in detail. Current oestrogen-progestogen users had a *substantially greater* risk of breast cancer than oestrogen-only users (RR 2.00 (1.88 - 2.12) v. 1.30 (1.21 - 1.40), $p < 0.0001$). The RRs for CEE 0.625 mg + MPA 2.5 mg as used in the WHI trial were 1.62 (1.34 - 1.90) and 2.42 (2.08 - 2.81) ($p < 0.0001$) for < 5 and ≥ 5 years, respectively. The use of HRT by women aged 50 - 64 in the UK over the past decade was estimated to have resulted in 20 000 extra cases of breast cancer, 15 000 associated with combined oestrogen and progestogen. It now seems established that the use of combined oestrogen-progestogen preparations of whatever type is associated with a significantly greater increase in the risk of breast cancer than oestrogen-only preparations of whatever type. This will require a re-evaluation of the use of combined oestrogen-progestogen preparations compared with oestrogen-only preparations in the care of postmenopausal women.

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