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Perspective Article

Hylonome

The risks and benefits of HRT

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Abstract

For many years hormone replacement therapy (HRT) was regarded as the gold standard for treatment of osteoporosis. In recent years this status has been challenged, because of the lack of a robust evidence base for anti-fracture efficacy, emerging evidence of adverse extraskeletal effects and the demonstrated efficacy of a number of alternative options in the prevention of osteoporotic fractures. The current consensus is that HRT is no longer regarded as a front-line option for prevention of osteoporotic fractures and that its use for this purpose should be restricted to women with osteoporosis who have menopausal symptoms and to older women who are intolerant of other therapies and /or express a strong preference for HRT despite being informed about potential adverse effects. Nevertheless, the mechanisms by which estrogen exerts its beneficial skeletal effects remain a major area of research that has important implications for the development of novel therapies.

Keywords: HRT, Estrogen, Osteoporosis, Cardiovascular Disease, Breast Cancer

Introduction

The observation by Fuller Albright in 1941 of the association between estrogen deficiency and osteoporosis[1] was followed, some years later, by the demonstration that estrogen prevented bone loss during and after the menopause[2-4]. These studies were supplemented by a number of observational studies indicating that estrogen also reduced fracture risk[5-8]; subsequently estrogen, either unopposed or used in combination with a progestagen, became widely used in the prevention of osteoporosis. The advent of a more rigorous evidence-based approach to clinical practice, together with new evidence on the risks and benefits of HRT, has forced re-evaluation of its role in the management of osteoporosis. This paper focuses on recent developments both with respect to anti-fracture efficacy and extraskeletal effects and their influence on the positioning of HRT in the prevention of osteoporotic fractures in postmenopausal women.

Benefits of HRT

Effects on fracture. Until recently the majority of evidence for anti-fracture efficacy of HRT was derived from observational and case cohort studies, These demonstrated a reduction of around 50% in hip and other non-vertebral fractures in women taking HRT[6-8] and small prospective studies also indicated a reduction in clinical vertebral fractures[9,10]. Meta-analyses of randomized controlled trials have produced conflicting results; thus Torgeson and Bell-Syer[11,12] reported that the pooled mean estimate of relative risk was significantly reduced, both for vertebral and non-vertebral fractures whereas Cranney et al.[13] concluded that there was no significant reduction in either fracture type.

The uncertainty surrounding anti-fracture efficacy of HRT has mainly arisen as a result of two factors. Firstly, randomized controlled trials of HRT with fracture as the primary endpoint have generally been small and imperfect in their design. Secondly, the results of observational and case-control studies are likely to be confounded by inherent differences between HRT users and non-users, the former being more healthy than the latter in a number of respects[14]. In such studies, therefore, any benefits of HRT are likely to be overestimated. Some clarification has been provided by the recent Women's Health Initiative (WHI) study[15], a randomized controlled trial of continuous combined HRT (conjugated equine estrogen 0.625 mg daily and medroxyprogesterone acetate 2.5 mg daily) in 16,608 healthy postmenopausal women, which demonstrated significant reductions in clinical fractures, including hip fractures, after a mean duration of treatment of 5.2 years. Morphometric (asymptomatic) vertebral fractures were not assessed. It should be emphasised that women in this study were not selected on the basis of high fracture risk and that fracture reduction was a secondary endpoint; nevertheless, the data

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provide definitive evidence for anti-fracture efficacy in this population. The effects of unopposed estrogens, which were also investigated in this study, are awaited.

Menopausal symptoms

The relief by HRT of menopausal vasomotor and urogenital symptoms is well documented and HRT remains the first option for women who are sufficiently symptomatic to require treatment. In many cases, treatment is only required for a relatively short time period, i.e., between one and two years.

Colorectal cancer

Another benefit suggested by observational studies[16] and subsequently confirmed in large randomized controlled trials[15] is protection against colorectal cancer. This is a significant health benefit since this form of cancer is common and increasing and is associated with a significant mortality. The mechanism by which protection occurs is unknown.

Risks of HRT

Breast cancer. The increase in risk of breast cancer in postmenopausal women taking estrogens has been known for many years and there are biologically plausible mechanisms to support this finding[17]. Overall, the reported increase in relative risk has been around 30% after five years' use and several studies have indicated that risk increases with increasing duration of use; however, following cessation of therapy the risk declines to levels seen in non-users. In the WHI study, in which invasive breast cancer was the main primary outcome measure, this increase in risk was confirmed and it was also found that breast tumours diagnosed in women treated with HRT were more advanced than in those receiving placebo.

More recently, the Million Women Study, an observational study in nearly one million postmenopausal women in the UK[18], showed a higher level of risk increase in women taking combined HRT, with a 100% increase in relative risk, whereas unopposed estrogens were associated with a 30% increase in relative risk; the relative risk in women taking tibolone was intermediate (1.45). In this study, the increase in risk was seen after only 1-2 years of HRT.

Other cancers

It is well established that unopposed estrogen therapy is associated with an increased risk of endometrial cancer and that this excess risk is reduced or eliminated with combined therapy, the protective effect appearing to increase with the number of days that progestogen is administered in the 28 cycle. Results from the WHI study indicate that combined HRT may be associated with a small increase in risk of ovarian cancer.

Cardiovascular disease

Although observational studies indicated that HRT was cardioprotective[19,20], a number of randomized controlled trials have subsequently shown either an increased risk or no effect of HRT in postmenopausal women at normal or increased risk prior to therapy. In the WHI trial a 30% increase in relative risk was demonstrated in women taking combined HRT and there was also a 41% increase in the relative risk of stroke. Similarly, in the HERS study[21] a significant increase in relative risk of coronary heart disease and associated mortality was documented in women with pre-existing heart disease; in both of these studies the increase in risk was most evident in the first year of HRT use. Since coronary heart disease is the most common cause of death in postmenopausal women, these findings have a highly significant effect on the risk:benefit ratio of HRT.

In addition to this increased risk of heart disease and stroke, an increase in risk of venous thromboembolism has been consistently demonstrated[22,23]. This includes deep vein thrombosis, pulmonary embolism and retinal vein thrombosis.

Cognitive function

Although some observational studies indicated beneficial effects of estrogen on cognitive function and risk of dementia[24], in a sub-study of the WHI study (WHIMS), no evidence of improvement of cognitive function was demonstrated in women taking combined HRT. Indeed, in treated women older than 65 years, there was an increased risk of probable dementia.

Other side-effects

Other unwanted side-effects of HRT include vaginal bleeding, breast tenderness, headache and upper gastrointestinal symptoms.

What is the risk/benefit ratio for HRT?

Communication of the risks and benefits of HRT in clinical practice requires that relative risks are translated into absolute risks. The latter are critically dependent on the underlying prevalence of the disease in question and this in turn is strongly influenced by age[25] as well as by the risk factors present in the individual. Thus the risk/benefit ratio of HRT for a 50-year-old woman is generally different from that in a 65-year-old woman but will also vary between women of the same age. In addition, there is emerging evidence for differences in the risk/benefit ratio for combined versus unopposed HRT (Table 1).

In terms of the use of HRT in osteoporosis, long-term preventative strategies starting at or soon after the menopause are unlikely to be cost-effective and current practice is to target those with a high fracture probability for

	Women aged 50-69 yrs	Women aged 60-69 yrs
Excess incidence per 1000 HRT users over 5 yrs		
Breast cancer	3.2	4.0
Stroke	1.2	4.0
Pulmonary embolism	1.6	4.0
Total excess	6/1000	12/1000
	1 in 170 users	1 in 80 users
Reduction in incidence per 1000 HRT users over 5 yrs		
Colorectal cancer	1.2	3.0
Hip fracture	0.5	2.5
Total deficit	1.7/1000	5.5/1000
	1 in 600 users	1 in 180 users
Overall balance	**Net excess**	**Net excess**
	4.3/1000	**6.5/1000**
	1 in 230 users	**1 in 150 users**

Table 1. Estimated change in incidence of risks and benefits for 5-year use of HRT[25].

intervention. The majority of such women are 65 years or older and are at a higher risk of coronary heart disease and breast cancer than women aged around 50 years. The beneficial effects of HRT on menopausal symptoms will not be relevant for the majority of these older women whereas side-effects such as vaginal bleeding and breast tenderness will be particularly unwelcome. In view of these considerations and the proven efficacy of other, non-hormonal interventions, HRT is now regarded as a second-line option for the prevention of fractures in postmenopausal women.

The above views, which have been recognised by the majority of metabolic bone disease clinicians for some years, have recently been endorsed by the European Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA). They concluded the following:

- The risk:benefit ratio of HRT is favourable for younger postmenopausal women with climacteric symptoms, although the minimum effective dose should be used for the shortest possible duration.

- For prevention of osteoporosis or osteoporotic fractures in postmenopausal women, the risk:benefit ratio of HRT is unfavourable and HRT should therefore not be regarded as a front-line option

- In healthy postmenopausal women without climacteric symptoms, the risk:benefit ratio of HRT is generally unfavourable

Conclusions

From being perceived as a panacea for postmenopausal women's health, HRT is now primarily regarded as being a front-line option only in women with severe climacteric symptoms. In terms of absolute risk, the risks and benefits of HRT are quite small and its demise as a treatment for osteoporosis has been influenced more by the availability of other options than by its adverse effects. Nevertheless, it remains an option for a minority of postmenopausal women at risk of osteoporotic fracture.

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