



HRT: Risks and rumours

By David Sturdee

You May be unsure about taking HRT following its recent bad press. What is the situation with HRT and what is its role for women today? By David Sturdee

The negative publicity surrounding hormone replacement therapy (HRT) in recent years has resulted in widespread uncertainty about its merits and even whether it is worth taking at all.

Some doctors are now refusing to prescribe HRT, and many women who have stopped taking it because of the recent scares are now experiencing a return of menopausal symptoms and a marked deterioration in their quality of life.

The human female is the only animal to experience a physical menopause. While other animals remain potentially fertile until death, women today will spend about a third of their lives without the benefits of the female sex hormone oestrogen. By contrast, men slide from one stage of life to the next without abrupt change, maintaining the ability to father children into old age. It is only relatively recently that the menopause has attracted attention; at the beginning of the last century a woman could expect to live to about 48, but now life expectancy is at least 80 years and rising.

Why do women outlive their ovaries and stop producing eggs and oestrogen so early? The reasons are not understood fully, but it is fortunate that no other organ in the body packs up in the middle of life! For many reasons, not being fertile in old age can be considered beneficial. In particular, the human child is the most dependent on its mother of any animal, and needs love, protection and support for many years. This makes sense of a female menopause at

about 50 years, but the associated loss of the sex hormone, oestrogen, can cause devastating symptoms and reduced quality of life, as well as increasing the risk of osteoporotic bone fractures and heart disease.

The transition through the menopause can be very distressing for some women, and the effects of oestrogen deficiency can have a major impact on their quality of life. However, replacement of the natural oestrogen by HRT can prevent menopausal symptoms and osteoporosis, and possibly reduce the onset of heart disease. Despite recent controversies and anxieties, there is still much to be gained from taking HRT selectively.

Menopausal symptoms

In the UK about 80% of women experience some symptoms caused by oestrogen deficiency during the menopause. It is now undisputed that oestrogen therapy is the most effective and suitable treatment for relieving hot flushes and night sweats, and the resulting improvement in the quality of sleep also resolves associated lethargy, irritability, impaired memory and other psychological symptoms. For those severely affected, the improvement in quality of life can be dramatic.

Regrettably, following the anxiety generated by some recent publications, many women have abandoned hormone therapy for various unproven therapies, which are often considered to be 'natural', and therefore risk-free. These include progesterone cream, oil of evening primrose, phytoestrogens, soya-containing foods, black cohosh, ginseng, dietary supplements and acupuncture.

A few small studies have suggested a slight benefit of some phytoestrogens over placebo (an inactive dummy tablet) for hot flushes, but otherwise there is no evidence that any of these treatments is better than a placebo. Indeed some can be dangerous or cause harmful interactions with other medication. For example, black cohosh has been associated with liver damage occasionally necessitating a liver transplant.

Cardiovascular disease

Coronary heart disease (CHD) is the largest single cause of death in women, and reducing the incidence of heart disease would have a major impact on both quality of life and mortality. Various studies have demonstrated an apparent benefit of HRT in reducing CHD by half in post-menopausal women. However, some concerns were raised about the validity of such studies, and it was suggested that women who used HRT tended to have a healthier lifestyle anyway, and were thinner, took more exercise and drank alcohol in moderation.

To try and clarify the possible benefits of HRT in such women, the Women's Health Initiative (WHI) study was performed in the USA. This was an enormous randomised controlled trial of 16,608 post-menopausal women who did not have any clinical evidence of CHD. The first reports from the study, on women aged on average 63 years, who did not have menopausal symptoms and who had taken combined oestrogen and progestogen therapy for about 5 years, were published in 2002. Initially, the report appeared to suggest a dramatic increased risk of breast cancer, heart attack, stroke, and deep vein thrombosis (DVT), in addition to a significant reduction in hip fractures and colon cancer. This was reported in the media in such a way that women taking HRT and those concerned with their management could not fail to be alarmed.

However, figures indicating the increased relative risk were highlighted, a concept not well understood by many, including the medical profession. This gave a distorted view of the real risk, as estimated numbers of extra cases per 10,000 women per year are quite low.

But, even more important was the fact that this study related to women who were considerably older than the vast majority of women who seek HRT, so the relevance is dubious. Furthermore, in 2004 another report from the WHI study, involving women who had had a hysterectomy and had received oestrogen alone for 7 years, showed some rather different effects. The study was stopped at this point because of a slightly increased risk of stroke, but notably there was no evidence of increase in heart disease, and some

reduction in breast cancer risk. Further analyses reported in 2006 and 2007 have shown a significant reduction in some aspects of CHD and the importance of starting therapy around the time of the menopause, when there is likely to be a 'window of opportunity' for protection of the heart, which is not evident if started 10 or more years after the menopause. As always, more studies in humans are required, but evidence also from several studies on animals is strongly supportive of this view.

In older women the use of HRT and tibolone is associated with a small increased risk of stroke, so this needs to be considered particularly in women who may have other risk factors for stroke.

Dementia

The WHI study also assessed the effect of HRT on older women with dementia. Previous studies had suggested that the incidence of Alzheimer's disease was reduced by hormone therapy, but the WHI study did not show this and even suggested an increased risk in older women. Again, the evidence suggests that once the disease process has started, hormone therapy will not be beneficial, but that early initiation of HRT may be protective.

The million women study

The Million Women Study (MWS) was a very large project, observing women aged 50-64 attending the national UK breast-screening programme. About a quarter of all women in this age group took part. The researchers reported that all forms of HRT were associated with an increased risk of breast cancer, and in particular that treatments combining oestrogen and progestogen had a higher risk than those only containing oestrogen or the drug tibolone.

This study was also widely reported by the media, but the medical profession has considerable reservations about the validity of the findings and whether the risk has been overestimated. Certainly there is disagreement between MWS and WHI about the degree of risk, and also the risk of using oestrogen alone.

More recently, MWS has reported on the risk of endometrial cancer (cancer of the womb). It has confirmed that combined oestrogen and progestogen therapy reduces the risk, but has suggested that tibolone may cause an increased risk. However, a more valid, randomised controlled trial of tibolone has now been reported (THEBES) and demonstrated that tibolone has a similar effect on the womb as combined oestrogen and progestogen, which is not only reassuring but provides further evidence against the validity of the MWS.

What is the current thinking on HRT?

All these data make it difficult for everyone to come to a consensus on what the implications of these studies are for the use of HRT. The government watchdog, the committee on safety of medicines (CSM), has advised that HRT is the best treatment for the relief of menopausal symptoms, but that it should be used at the lowest dose that is effective and for the shortest time necessary. Such advice is not particularly helpful, as there are wide variations in the duration of menopausal symptoms, and some women need to continue taking treatment for many years. However, new lower dose regimens are becoming available and it is advisable for women to be on the lowest suitable dose. Generally the dose can be adjusted with age, with younger women needing the higher doses.

Alternative non-hormonal therapies are available for the prevention of osteoporosis, but most of these have only been studied in women well beyond menopausal age. For those at risk of significant bone loss caused by hormonal change, HRT appears to be the most suitable and effective option.

Premature menopause

It is particularly important that women who undergo the menopause early should have oestrogen replacement therapy, at least until the normal age of the menopause. These include those who have a premature menopause (before age 45 years) and those who have had a medical or gynaecological condition that required removal or destruction of the ovaries. Young women who develop Hodgkin's disease or other blood disorders need adequate oestrogen to ensure their long-term health and skeletal

development. There is no evidence that such replacement will have a harmful effect or increase the risk of breast cancer or stroke in these women. All the data referred to above are only relevant for women at or after the normal age of the menopause.

Conclusion

HRT is not suitable for or wanted by every woman. However, most women request HRT for the relief of menopausal symptoms and improvement in quality of life. There are some risks associated with treatment, which need to be put into perspective, but every woman should be given the opportunity to discuss their situation, the potential benefits and risks, and to make an informed decision with a suitably trained and experienced medical advisor.



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