The menopause and HRT: where are we now?

In our ageing society, the management of menopausal health will take on an ever-increasing importance. Controversy surrounding hormone replacement therapy (HRT) has caused confusion over how best to deal with the effects of the menopause. Nick Panay assesses HRT use in the light of recent findings.

More than 50% of women are aged 50 or over. Maintenance of peri and postmenopausal health is therefore of paramount importance if we are to minimise the future economic impact on society. Recent adverse media on hormone replacement therapy (HRT), still the most effective treatment available for the alleviation of menopausal symptoms, could not have come at a worse time. Symptoms of the menopause, which can be debilitating, and long-term sequelae, such as osteoporosis, still need to be addressed.

Menopausal symptoms
Approximately 75% of Caucasian and Afro Caribbean women report troublesome symptoms during the menopause transition. In the short term, these predominantly consist of vasomotor symptoms such as hot flushes and night sweats, often leading to rebound insomnia and exhaustion. In the medium term, urogenital symptoms, such as vaginal dryness, urinary frequency and stress incontinence, and psychological symptoms including mood swings and depression, are reported by 50% of women. The effect of these and other symptoms is profound and often underestimated by health professionals, leading to a serious impairment of quality of life.

The role of HRT
Relief of hot flushes and night sweats are the most common reasons that women seek treatment with HRT. There is good evidence from clinical studies that oestrogen is effective in treating these vasomotor symptoms. Vaginal dryness, soreness, superficial dyspareunia, and urinary frequency and urgency also respond well to oestrogen therapy, given either topically or systemically. Libido may also be affected, particularly in younger women who have experienced a surgical (oophorectomy) or premature menopause. This can be improved with oestrogen but a significant proportion also needs testosterone replacement.

Recent studies
The results of the WHI (Women’s Health Initiative) and MWS¹ (Million Women Study) have focused attention on the increased risk of developing cancer and cardiovascular problems, yet HRT has beneficial effects in other conditions. For example, HRT has been found to achieve a 60% reduction in recurrent urinary tract infections and 35% reduction in the onset of diabetes. A meta-analysis of HRT studies³ speculates that the decrease in risk of death from causes other than heart disease or cancer may be due to the reduction in complications associated with hip fracture, diabetes and sepsis. This meta-analysis demonstrated a 39% reduction in mortality if HRT had been commenced before the age of 60.

Breast cancer
The WHI study was stopped prematurely by the data safety monitoring board after running a mean of 5.2 rather than 8.5 years. This was because it was deemed that the risk versus benefit statistic was exceeded due to an excess of breast cancer and coronary heart disease cases in the treatment arm (continuous combined conjugated equine oestrogens 0.625 mg and medroxyprogesterone acetate 2.5 mg). The data from the WHI study suggested an excess risk of breast cancer with combined hormone therapy of four cases per 1,000 women after five years.

The MWS, a large questionnaire survey by Cancer Research UK of women attending the NHS breast-screening programme,
reported an increased risk of breast cancer diagnosis with all HRT regimens (Relative Risk [RR] 1.66 95% CI 1.58-1.75); there was a statistically higher risk with oestrogen/progestogen HRT (RR 2.00 [1.91-2.09]) than that seen with oestrogen alone (RR 1.30 [1.22-1.38]) or tibolone (RR 1.45 [1.25-1.67]).

The press alarmingly reported this as evidence of HRT doubling the risk of breast cancer, failing to mention the absolute risk in terms of the actual case numbers. For oestrogen alone, the figures represent an additional 1.5 per 1,000 cases after five years of use and for oestrogen/progestogen, an additional six per 1,000 cases after five years of HRT. In women aged 50-64, whose baseline risk is 32 per 1,000, this translates to 33.5 per 1,000 and 38 per 1,000 cases respectively.

The higher risk estimates from the MWS compared to WHI may have been due to the observational nature of the MWS, which underestimated the duration of HRT usage, as it did not count the years of HRT exposure from baseline (filling in the questionnaire) to reporting breast cancer on the UK cancer registry. It is also unlikely that the cancers diagnosed after one year had developed de novo - it is more likely these cancers were missed by mammography at baseline and that HRT had acted as a promoter rather than an initiator.

On the positive side, a second WHI study in hysterectomised women using unopposed oestrogen reported that the rate of invasive breast cancer diagnosed was 23% lower in the conjugated oestrogen group compared to the placebo and this comparison narrowly missed statistical significance (p=0.06). This result was unanticipated and appears to suggest that it is the addition of progestogen to oestrogen which leads to the increased risk of breast cancer, not oestrogen alone.

Osteoporosis
For many years, bone marker and bone density data suggested HRT had a beneficial effect on the skeleton. Data from the WHI study finally provided strong (prospective randomized placebo controlled) evidence for the prevention of fractures. In its initial publication of results relating to the impact of HRT (combined oestrogen plus progestin), the WHI reported that the overall risks of HRT outweighed any benefits related to decreased risk of fracture.

A more recent report assessed whether a woman's risk of fracture influenced this balance of risks and benefits. Despite the good news regarding osteoporosis from the WHI study, the authors still felt that when considering the effects of hormone therapy on other important disease outcomes in a global model, there was no net benefit - even in women considered to be at high risk of fracture.

Cardiovascular
Initial cardiovascular data from observational studies suggested up to a 50% reduction in the risk of coronary heart disease in HRT users and a neutral effect on stroke. The WHI suggested that after a mean usage of five years there was an excess of heart disease cases in the active treatment arm of the study compared to placebo, and an excess of stroke. The cardiovascular risks in WHI were small, equating to an extra 7-8 cases per 10,000 women per year.

These were largely accounted for by an excess of cases in the first couple of years of use, probably due to an initial pro-throm-
Encouragingly, results from the conjugated oestrogen-only arm of the WHI study showed that there was no significant effect on CHD (primary outcome) compared with placebo (hazard ratio 0.91; 95% CI 0.72-1.15). This again suggests progestogen may be the problem with HRT.

Endometrial cancer
The MWS investigators recently published the analysis of the endometrial cancer data6, which showed a risk of three cases per 1,000 women after five years in non-HRT users. Encouragingly, sequential combined HRT appeared to have a neutral effect overall on the endometrium. The study confirmed that continuous combined HRT had a protective effect (two per 1,000 after five years) and that women using oestrogen alone had an increased risk (five per 1,000 after five years).

Surprisingly, there were also a larger number of endometrial cancers reported in the users of the tissue-selective agent tibolone (six per 1,000 after 5 years). This is possibly explained by the fact that higher risk women, ie, those with a family history of endometrial cancer or with previous bleeding problems, have preferentially been started on tibolone because it has been viewed as a lower risk product.

The results of a large (>3000 women) prospective randomised trial (THEBES), comparing the effect of tibolone to placebo, are awaited. The report is due at the end of 2005. The data safety monitoring board has encouragingly allowed the study to continue unchanged.

Venous thromboembolism (VTE)
Studies, including HERS & WHI, indicate a two- to threefold increase in the risk of venous thromboembolism with oral HRT, with the greatest risk occurring in the first year of use. However, recent data suggest that transdermal therapy may not increase the risk of VTE.7 There is biological plausibility for this; avoidance of hepatic first pass metabolism minimises adverse effects on clotting factors and the fibrinolytic system.

Colorectal cancer
The WHI study confirmed previous observational data for the beneficial effect of combined HRT in reducing the incidence of colorectal cancer (six less cases per 10,000 women per year), although interestingly not with oestrogen alone. There is still uncertainty as to the mechanism of action of HRT in reducing the risk of colorectal cancer. There may be an effect on the reduction of insulin, eg, growth factor production or bile acid secretion, but the jury is still out!

Impact of trials on HRT usage
Conflicting news about its safety has impacted severely on the number of women taking HRT. As a result of publicity arising from publication of the WHI and MWS studies and subsequent advice from regulatory authorities, there has been a significant downturn in HRT usage, by up to a half in some countries. However, there has been a stabilisation of HRT usage in the last year. Based on the fact that most of adverse reports from these studies are already in the public domain, it is unlikely that there will be a further downturn in usage.

Many women who came off their HRT are now asking to restart because of the return of severe symptoms, particularly muscular aches and joint pains. However, the recent labelling of the combined contraceptive pill and HRT as cancer-causing agents by the World Health Authority (WHO) has not been helpful.

HRT alternatives
There has been a move towards alternative therapies, eg, complementary medicines such as phytoestrogens. This is a largely unregulated area with products that often have little or no efficacy and may have questionable safety, eg, recent reports of liver failure in users of Black Cohosh. Some phytoestrogens, such as red clover isoflavones, can safely provide up to 50% symptom relief but this falls short of the 80 to 90% efficacy of traditional HRT.8 Many women are therefore in a difficult position; struggling with severe symptoms of the menopause, too frightened to use HRT and unable to find effective, affordable alternatives.9
View of advisory bodies
In December 2004, largely as a result of the WHI and MWS studies, the European Agency for the Evaluation of Medicinal Products (EMEA) advised that HRT should no longer be classed as first line for prevention of osteoporosis. The CSM (Committee on Safety of Medicines) in the UK also advised the MHRA (Medicines and Healthcare Products Regulatory Agency) that HRT should become second line for osteoporosis. NICE (National Institute of Clinical Excellence) are currently carrying out a technology appraisal for some of the alternatives to HRT, eg, bisphosphonates, raloxifene and parathyroid hormone. The guidelines on secondary prevention were published in January 2005 and those on primary prevention are still pending.

EMEA and the MHRA still advocate the use of HRT although they stipulate that it should be at the minimum effective dose for the shortest possible duration with annual re-evaluation. The RCOG recommends that "short-duration" HRT (ie, up to five years) may be considered for relief of menopausal symptoms in women in their early 50s. At a meeting of RCOG representatives with the BMS in November 2004 it was not possible to reach a unanimous consensus on HRT usage, as BMS council members felt that there should not be arbitrary time constraints placed on the duration of HRT usage.

The BMS view (BMS Website Consensus 2005) is that HRT still offers potential for benefit to outweigh harm, providing the appropriate regimen has been instigated in terms of dose, route and combination. The BMS also argues that the advice regarding HRT may be appropriate for women with no increased osteoporosis risk, as in the WHI study population, but the risk-benefit ratio changes favourably when targeting women who are at increased risk. There are already constraints placed on the duration of HRT usage.

My view is that decisions to prescribe and continue therapy should be individualised, taking into account each woman’s unique risk-benefit profile.

Conclusions
We must not underestimate women’s desire for a high quality of life in the menopause. Women will continue to demand HRT or a safe, effective alternative for their symptoms. It is therefore our duty to strive to provide the best therapy for women to achieve this goal. Unfortunately, it is difficult for the menopause specialist, let alone the average clinician, to keep up with the rapidly changing data regarding menopause therapies. With each new study there appears to be a change in advice given by the regulatory agencies as to how we should advise our patients, leading to a great deal of confusion.

In my opinion, current best practice should involve the following:

- Discussion of lifestyle measures, HRT and alternatives should take place from the outset.
- Management should be individualised, taking into account risks and benefits.
- The main indication for HRT use should be for symptom relief rather than for prevention of long-term problems.
- Low-dose HRT should usually be commenced, except in premature ovarian failure, and increased if necessary to achieve effective symptom relief.
- Rigid cut-offs in the duration of therapy should be avoided with regular reappraisal (at least annual) of the benefits and risks for each individual.
- Delivery of services should be from a multidisciplinary team if possible, with close liaison with allied specialties and experts.

It is unlikely the ultimate menopause therapy will ever be developed that truly provides all the benefits without any side effects and risks. Clinicians should therefore aim to provide the best evidence-based advice possible in order to allow women to make an informed choice as to how to manage their menopause transition and beyond.

REFERENCES


RESOURCES

British Menopause Society www.the-bms.org
Medicines and Healthcare products Regulatory Agency www.mhra.gov.uk
Menopause Matters www.menopausematters.co.uk
The Premenstrual Syndrome Website www.pms.org.uk
National Osteoporosis Society www.nos.org.uk
The North American Menopause Society www.menopause.org