HRT: Clarity after Controversy

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The Problem in Perspective

The 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. We live in an era when the population is ageing; at the time of writing more than 30% of women are aged 50 years of age or over. Maintenance of peri and postmenopausal health is therefore of paramount importance if we are to minimise the economic impact on society in this and future millenia. The controversy surrounding the pros and cons of HRT has left menopausal women, health professionals and society in general, confused as to how best to deal with both the short and long term sequelae of the menopause. The immediate symptoms, often debilitating and the long term sequelae such as osteoporosis, still need to be dealt with, and will take on ever increasing importance because of our ageing society.

The Controversy

Until five years ago, Hormone Replacement Therapy (HRT) was used by over a third of post menopausal women for symptoms and prophylaxis against the long term sequelae of the menopause. However, as a result of adverse publicity on the possible risks of HRT (breast and cardiovascular) arising from publication of the Women's Health Initiative and Million Women studies in 2002/3, there was a significant downturn in HRT usage which dropped by up to 50% in some countries.[1-4] The last couple of years had seen stabilisation of usage following recent favourable data on cardiovascular and breast cancer risks and life expectancy.[5] Encouraged by clinicians and menopause societies, about a third of women who came off their HRT asked to restart because of a return of their symptoms. [6-7]

Just as the dust was starting to settle, menopausal women and their GPs were confronted with further confusing data and the resultant media headlines. Firstly, falling breast cancer rates in some areas of the USA were equated to falling HRT usage rates since 2002.[8] This extrapolation was criticised by the menopause societies; they pointed out that the fall in rates may not have been in ex - HRT users, rates were starting to fall prior to 2002 anyway and this may have occurred because less women were attending for breast screening having come off HRT.

In April 2007, data from the reanalysis of the joint data from the combined and estrogen alone WHI studies were published. These data showed that there was no increase in coronary heart disease risk for the youngest cohort of participating women (50 – 59 years) and a 30% decrease in all cause mortality, significant at the $p<0.05$ level.[9] These data supported the concept that HRT does not cause harm, and may even be protective, when given to younger women in whom the arterial endothelium is still intact.[10] In the last few weeks a cross sectional study was published in the New England Journal of Medicine looking at the degree of coronary artery calcification by computerised tomography in women from the youngest cohort (50-59 years) of the unopposed estrogen arm of the WHI study. There was a statistically significant lower calcification score in women on active therapy compared to those on placebo (83.1 v 123.1 $p=0.02$ by rank test) supporting a potential cardioprotective effect of estrogen.[11]

Further analysis of data from the Million Women Study (MWS) suggested that HRT may increase the risk of ovarian cancer diagnosis and mortality. The data were alarmingly represented by Cancer Research UK in The Lancet and consequently the media, as the total number of cases of ovarian cancer (1300) linked to HRT usage over 14 years. Data were only collected for 5 years from 1996 – 2001 by the MWS but controversially, extrapolation was carried out using HRT usage rates from 1991 – 2005. The absolute risk was rather less alarming at 1 case per 2500 users and 1 death per 3300 users.[12] The observational questionnaire methodology of the MWS once again came in to question as the randomised prospective WHI study had not indicated a problem with ovarian cancer.

Regulatory Authorities and Societies

Although the regulatory authorities e.g. Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK and the European Agency for the Evaluation of Medicinal Products (EMEA) still advocate the use of HRT they stipulate that it should be at the minimum effective dose for the shortest possible duration with annual re-evaluation. The guidelines have not changed since October 2004 but following the most recent data, the MHRA have indicated that there will be a revision of the guidelines in the near future.

Practical Implications for GPs

New data suggest that the benefits of HRT can be maintained with lower doses than previously used whilst minimising risks and possibly side effects. A recent study showed preservation of oestrogenic benefits at a dose as low as 0.5mg of 17β oestradiol.[12] The importance of androgen replacement is also evolving with the recent licensing of the first transdermal testosterone preparation for surgically menopaused women with distressing low libido. There has also been a move towards alternative therapies e.g. complementary medicines such as phytoestrogens. This is a largely unregulated area with products that often have little or no efficacy and questionable safety e.g. recent reports of liver failure in users of Black Cohosh. However, there are more promising data for some red clover and soy products.[13]

Key Take Home Messages

Current best practice in the management of the menopause should involve the following:

1) Discussion of lifestyle measures, HRT and alternatives at initial consultation.

2) Management should be individualised taking into account risks and benefits.

3) The main indication for HRT should be for symptom relief rather than for prevention of long term problems until better data exist on primary prevention.

4) Low dose HRT should usually be commenced, except in premature ovarian failure, and increased if necessary to achieve effective symptom relief.

5) Rigid cut off's in duration of therapy should be avoided with regular reappraisal (at least annual) of the benefits and risks for each individual.

6) Delivery of services should be from a multidisciplinary team if possible with close liaison with allied specialties and experts.

Key Websites

- www.thebms.org
- www.womens-health-concern.org.uk
- www.menopausematters.co.uk
- www.menopause.org
- www.imsociety.org
- www.mhra.gov.uk

Key References

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