HRT and heavy-handed headlines: do new studies change anything?

Controversy surrounding the pros and cons of hormone replacement therapy (HRT) has been exacerbated recently by a study suggesting it may increase the risk of ovarian and breast cancers,[1] and a reopened debate on its cardiovascular effects.[2] Nick Panay considers the implications for treatment of menopausal symptoms

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UNTIL FIVE YEARS ago, hormone replacement therapy (HRT) was used by more than one-third of postmenopausal 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 (WHI) and Million Women studies (MWS) in 2002/03, there was a significant downturn in HRT usage, which dropped by up to 50% in some countries.[3–6]

The last couple of years had seen stabilisation of usage following recent favourable data on cardiovascular and breast cancer risks and life expectancy.[7] Encouraged by clinicians and the menopause societies, around one-third of the women who came off their HRT asked to restart because of a return of their symptoms.[8]

Most recently, menopausal women and their GPs have been confronted with further confusing data and the resultant media headlines. First, falling breast cancer rates in some areas of the USA were equated to falling HRT usage rates since 2002.[9] This extrapolation was criticised by the menopause societies, who 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 (CHD) 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.[2] 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]

A few weeks later, further news came from the MWS, which suggested that HRT may increase the risk of ovarian cancer diagnosis and mortality. The data were alarmingly represented by Cancer Research UK and the media as the total number of ovarian cancer cases (1,300) linked to HRT usage over 14 years. Data were only collected for five 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 one case per 2,500 users and one death per 3,300 users.[1] 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, eg, the 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 re-evaluation of the guidelines, which will be released in the next few months.

Changes in prescribing of HRT and alternative therapies

New data suggest that the benefits of HRT can be maintained with lower doses than

previously used while minimising risks and possibly side effects. A recent study showed preservation of osteogenic benefits at a dose as low as 0.5 mg of 17β oestradiol.[11] 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, eg, complementary medicines such as phytoestrogens. This is a largely unregulated area, with products that often have little or no efficacy and questionable safety – for instance, there have been recent reports of liver failure in users of Black Cohosh. However, there are more promising data for some red clover and soy products.[12]

Key take-home messages

Despite the most recent new data, current best practice has not significantly changed since the author's previous publication,[13] and 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 should be for symptom relief, rather than for the prevention of long-term problems, until we have better data on primary prevention.
- Low-dose HRT should usually be commenced, except in premature ovarian failure, and increased if necessary to achieve effective symptom relief.
- Rigid cutoffs in 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.

INGRAM

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RESOURCES

British Menopause Society
www.thebms.org.uk

International Menopause Society
www.imsociety.org

Medicines and Healthcare products Regulatory Agency
www.mhra.gov.uk

Menopause Matters
www.menopausematters.co.uk

National Osteoporosis Society
www.nos.org.uk

North American Menopause Society
www.menopause.org