OPINION

Oestrogens in the postmenopause – taking stock of the options

Does the road wind uphill all the way?

Yes, to the very end.

Will the journey take the whole long day?

From morn to night, my friend …

C G Rossetti

Use of oestrogen for the treatment of menopausal symptoms and to prevent bone loss (the only two licensed indications) has altered greatly since the publication of data[1] from the Women's Health Initiative (WHI) study in the USA – and, it is to be hoped, is about to alter again. Gynaecologists are frequently asked for advice on this subject and need to know where the shifting sands of opinion currently lie.

The following should be regarded as a personal view only and as an encouragement for your own examination of the literature.

Throughout the English-speaking world there was a cataclysmic reaction by endocrinologists, rheumatologists and regulatory authorities to the clear observation, in the large and well-conducted WHI study, that American women, mean age 64, given conjugated equine oestrogen (CEE) plus medroxyprogesterone acetate, exhibited a higher rate of breast cancer, coronary heart disease (CHD) events and stroke than placebo-treated controls. The WHI study was designed to ask a highly necessary question – does HRT provide primary heart disease prevention in this population? – since a secondary prevention trial, the Heart and Estrogen/progestin Replacement Study (HERS), had failed to demonstrate any benefit from oestrogen therapy[2] in women with established CHD.

The answer from WHI was a resounding *no*. However, the problem arose when these results were applied to, or rather flung across, all forms of HRT and directed at all populations of women. In vain gynaecologists pointed out that the WHI authors themselves had stressed in their paper[1] that these results did not necessarily apply to other populations of postmenopausal women – or to other formulations of HRT. Family practitioners and physicians were stampeded – and many patients were panicked – into stopping oestrogen treatment forthwith. Thousands of US, UK and South African women in their 50s receiving oestrogen for menopausal symptom control were left high and literally dry as HRT was withdrawn on the grounds of safety. The press lost its collective head with large headlines proclaiming the results in percentage values – forgetting, as usual, that when absolute changes are small, quoting them as percentage values can be highly misleading. A breast cancer rate going up from 32 to 38 per 10 000 per annum was presented as a '26% increase' – which, technically, it is. It is also highly inflationary.

'The gentle Christ', I told my BBC radio interviewer on the national news, 'was betrayed by no less than 8.33% of the disciples.'

'But surely it was only Judas?' said the interviewer.

Exactly. One of twelve – 8.33%. Women deserve to be told the truth about the risks and benefits of treatments. But they deserve to be told the *absolute* truth, not a *relative* truth from an RR (relative risk) value or, even worse, a percentage of the truth. Every gynaecologist should now consider having, on his or her desk, one of the charts showing the background rate of, for example, breast cancer and how the number will change with oestrogen exposure. As we shall see now in respect of oestrogen alone, there may be no change at all. Recently, Grodstein and colleagues[3] prospectively examined the relation of oestrogen therapy to heart disease according to the timing of oestrogen exposure relative to age and time since menopause. Participants were postmenopausal women in the Nurses' Health Study, with follow-up from 1976 to 2000. Women beginning oestrogen near menopause, that is, in their 50s, had a significantly reduced risk of CHD (RR 0.66, 95% confidence interval (CI) 0.54 - 0.80) for oestrogen alone, the risk also being lower (RR 0.72, 95% CI 0.56 - 0.92) for oestrogen with progestin. Intriguingly, among women who began taking hormones after 60 years, they found no relation between current use of oestrogen alone and CHD.

Could the progestogen have been the problem in WHI, then? One way to approach this is to look at the results of the oestrogen-only arm of WHI, reported by Anderson *et al.*[4] and involving some 10 739 hysterectomised women randomly assigned to receive either 0.625 mg/d CEE or placebo. The relative risks (expressed as a hazard ratio or HR) were as follows: for CHD, 0.91 (0.75 - 1.12); for breast cancer, 0.77 (0.59 - 1.01) – in other words, no significant risk of either of these two major outcomes. There was a significant increase in stroke risk, with an HR of 1.39 (1.10 - 1.77), but in absolute oestrogen terms again, this only represented 1.2 additional strokes per 1 000 person-years. There was no increase in pulmonary

embolism, and a reduction in the risk of fracture and colon cancer. Total mortality was unaltered.

We therefore badly need a good randomised trial of early intervention with low-dose oestrogen to ascertain once and for all whether its use is safe in the decade of the 50s when gynaecologists are normally asked to consider it. However, such is the climate of fear generated by our regulatory authorities that recruiting such a study would be far from easy. At least the Americans are having a go. The Kronos Early Estrogen Prevention Study (KEEPS) is a multicentre, 5-year clinical trial that will evaluate the effectiveness of 0.45 mg CEE *or* 50 µg daily transdermal oestradiol (both with cyclic oral, micronised progesterone, 200 mg for 12 days/month) and placebo in preventing progression of cardiovascular disease. In 2005 it was planned to enrol a total of 720 women aged 42 - 58 years who were within 36 months of menopause.[5] While we wait for KEEPS, gynaecologists should give consideration to the most encouraging data on the use of transdermal oestrogen, probably the safest route of delivery, with the 'medical hysterectomy' achievable with a levonorgestrel-releasing IUS delivering 20 µg/day to the endometrium, the only tissue requiring progestogen cover in the postmenopause.[6] Now we have good trial evidence that low doses of transdermal oestrogen will also prevent bone loss,[7] the patch/IUS combination looks to be another step in the right direction along this long, winding and uphill road – which will indeed take all day and night, my friend.

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