THE BEST OF THE REST

A summary of some of the best recent landmark articles from the international journals.

The major journals have published much on replacement therapy after the menopause in 2007. It has been intriguing watching the pendulum swing, and the following summaries of what they printed give a good idea where the establishment now stands.

Transdermal estrogen HRT

Troublesome menopausal symptoms can be readily treated with estrogen therapy but there are concerns about dosages and methods of administration.

The shadow caused by the Women's Health Initiative study remains, so researchers are looking for the minimum effective dose of hormone in the hope of reducing breast cancer or thrombotic risk. Since estrogen-only HRT appears to be without breast cancer risk, its use in women with intact uteri is being explored.

Simon *et al.* (*Obstet Gynecol* 2007; 109: 588-596) gave recently menopausal, symptomatic women a new estrogen-only transdermal gel or placebo and monitored their response over 12 weeks. A dose of 0.87 g per day gave relief from hot flushes and vaginal dryness without endometrial hyperplasia, so the need for intermittent progestin treatment is questioned. The gel – Electrin (BioSanta Pharmaceuticals Inc.) – delivers a dose of 0.0125 mg of estradiol daily without adverse dermal effects.

Larger trials will be required, but these promising results from the USA indicate that the pendulum is swinging back towards HRT in women in their 50s who want 'relief without risk'.

Expect more trials of this nature in the journals in the near future.

HRT and breast cancer

Breast cancer risk is not increased in estrogen-only HRT, but when estrogens are combined with progestins, there is a raised risk that is cumulative. However, there is no evidence of increased mortality and after quitting HRT risk ratios return to normal.

If these data are correct, and if there is a causal or unmasking effect of hormonal therapy on breast cancer, then the rapid reduction in HRT use in America following the WHI trial results would have led to a concomitant reduction in cancers detected.

Ravdin *et al.* (*NEJM* 2007; 356: 1670-1674) report that such a drop in estrogen-receptor-positive breast cancers did occur in 2002 - 2003, as the number of prescriptions fell from about 50 million to 25 million. This change occurred in postmenopausal women only, strongly implying an association with hormone therapy. The change was of the order of 7% relative risk and the incidence levelled off thereafter.

These findings support a link between combined hormone therapy and breast cancer, but the interpretation should be cautious. The observations concern a particular set of products, a particular age group and a particular type of breast cancer.

The absolute risk of breast cancer for any woman considering hormonal therapy in America remains around 0.30% per annum, and this changes to 0.36% per annum on HRT and the effects are cumulative.

This sort of evidence moves our collective wisdom forward but does not answer other questions, such as will these incidences start to rise as the occult cancers reveal themselves later? Or will other forms of hormonal therapy remain free of breast cancer 'encouragement'?

So where is the evidence that taking HRT for 10 years after the menopause is harmful? Is this another example of a medical 'magic bullet' that is first hailed, then discredited, and finally finds its niche? JASS certainly believes that the notion of 'feminine forever' was a grossly optimistic concept but, equally, there has been an over-reaction to the harmful effects of HRT because of inappropriate hormones given to women long past their menopause – and who were not in the best of health.

Perhaps the pendulum is reaching sanity and hormonal therapy will be useful in the treatment of menopausal symptoms AND offer protection against chronic conditions if used appropriately in terms of initiation, dose, mode of delivery and duration, which may well turn out to be 10 years.

The bottom line in 2007 is that starting therapy at the menopause and continuing for a number of years carries little, if any, risk in healthy women. The experts appear in equipoise so it is up to women and their advisors to decide.

It seems clear that initiating combined HRT in women 10 years or more after their menopause does not turn back the clock and probably, on balance, does harm.

A new approach to incontinence

Tension-free mid-urethral tapes have become the fashionable surgical treatment of stress urinary incontinence. These measures deal with the mechanical causes of stress but a new approach focusing on the physiology of the urethral sphincter is now reported. The underlying principle is as follows:

Continence is mainly controlled by the urethral sphincter complex which in turn is dependent on smooth and striated muscle tone and supportive structures. The role of the striated sphincter, the rhabdosphincter, has received little attention, despite the fact that it forms a muscular coat that surrounds the urethra ventrally and laterally. Its function can be reduced by birth trauma, surgical injury, anatomical displacement and age.

Injecting myoblasts derived from the patient's own muscles has been an effective treatment of damaged muscles in other body tissues, such as the myocardium, so the concept of using a woman's own cells to reinforce the urethral sphincter has physiological precedent. Taking muscle and fibre cells from the woman's arm, growing them in culture and injecting them back into the rhabdosphincter is theoretically feasible and the first report from an Austrian group's research has been published (Strauss *et al.*, *Lancet* 2007; 369: 2179-2186).

The technique is sophisticated, using autologous myoblasts and fibroblasts prepared in cell culture, then injected trans-urethrally into the rhabdosphincter under ultrasonic guidance. These new cells regenerate the sphincter and combat atrophy of the urethral submucosa, allowing the normal mechanisms of continence to be restored.

In the trial reported, 42 patients received the cultured cell injections and 21 were injected with collagen which has some place in incontinence therapy. After one year, 90% of those receiving the cell injections were cured, that is they had no incontinence subjectively or objectively, whereas only 9% of those receiving collagen were cured. Contractability and mucosal thicknesses were also statistically significantly improved as were the quality-of-life scores. After 3 years, there were no serious side-effects and the continence levels maintained.

It remains to be seen whether this method will be a long-term cure and whether it could be used in tandem with reconstructive surgery. It certainly is a novel approach with impressive early results which could herald a new era in urogynaecology.

Neural tube defects and fortification

Supplementing a woman's diet with folic acid reduces her chances of having a child with a neural tube defect. This has been shown in experimental and observational studies and for the last 15 years all women have been encouraged to take folate periconceptually.

But this message has failed to have the desired effect, even in developed countries, so foodstuff fortification has been implemented by adding folic acid to staple foods such as flour, corn meal and pasta in the milling industry. In the case of Canada, this was a decade ago so data are now available showing the effects of this national intervention.

De Wals *et al.* (*NEJM* 2007; 357: 135-142) report a halving of the prevalence of neural tube defects after fortification. Dividing their results into regions, they noted that the largest reductions were in the previously worst affected area and these reductions coincided with the years when fortification was introduced around 1998. The actual figures for Canada dropped from 1.6 to 0.9 per 1 000 births.

They do not report untoward side-effects. Their results strengthen the argument for fortification policies or more imaginative methods such as adding folic acid to oral contraceptive pills.

These summaries were extracted from **Journal Article Summary Service (JASS)**, which can be accessed at **www.jassonline.com**

Athol Kent
Editor