Benefits versus risks — the rise and fall of hormone replacement therapy

In this month’s article on landmark drugs, Jenny Bryantakes a look at hormone replacement therapy’s rapid rise in popularity in the 1990s and its subsequent decline in popularity after studies linking it to breast cancer were published

In the 1990s celebrities queued up to extol the virtues of hormone replacement therapy (HRT) and as much as 40 per cent of menopausal women in the UK used pills and patches to control their symptoms and protect their bones. But two major studies linking HRT to breast cancer, published in 2002 and 2003, halved HRT use in the UK and dramatically reduced the global HRT market.

“There will always be a core of women with severe menopausal symptoms whose quality of life is significantly impaired and who are very distressed, and can benefit from HRT. But a lot of GPs won’t consider prescribing it [because] they are very blinkered about the data,” explains David Sturdee, president of the International Menopause Society and a spokesman for the Royal College of Obstetricians and Gynaecologists.

GPs were equally reluctant to prescribe HRT when Mr Sturdee ran one of the first menopause clinics in the UK over 30 years ago: “There was very little treatment for menopausal symptoms before HRT, so there was no shortage of women seeking help. But I questioned whether it was a good career move [because] it was seen as a bit ‘way out’. We had to close the clinic for a while to clarify what we were doing with local doctors,” he recalls.

First steps to HRT

Early efforts to treat menopausal symptoms with hormones date back to the isolation of oestrogen from the urine of pregnant women by biochemist Edward Doisy at St Louis University, Missouri, in 1929. Having patented the methodology, the University licensed Parke-Davis (now part of Pfizer) and other pharmaceutical companies to sell the product as oestrone or theelin. Canadian firm Ayerst launched a rival oestrogen product called Emmenin in 1934, but later replaced this with conjugated oestrogens obtained from the urine of pregnant horses, marketed as Premarin (PREGnant MARe’s urINe) in 1942.

Premarin became the most widely prescribed form of HRT, but its method of production led Ayerst — and later Wyeth, which took over the Canadian company — into ongoing criticism from animal welfare groups over the need for large numbers of horses to have frequent pregnancies and to be restrained for urine collection.

In 1938, scientists at German pharmaceutical company, Schering, developed another type of oestrogen, ethinylestradiol, which formed the basis of some subsequent brands of HRT and many oral contraceptives.

Numerous European and US companies jumped on the HRT bandwagon during the next two decades, developing further types of oestrogen-based treatment.

The first HRT scare

Extensive publicity in the US hinting at the youth-restoring properties of HRT ensured rapidly increasing sales. But, in 1975, two case control studies published in the same issue of the New England Journal of Medicine demonstrated that women taking oestrogen therapy were at least four times more likely to get endometrial cancer than those who had not used oestrogen, and that there was a 14-fold increased risk in women who continued treatment for seven or more years.1,2 “In the UK, gynaecologists weren’t surprised that unopposed oestrogen increased the risk of endometrial cancer because we had always thought it was unphysiological to give oestrogen alone. Studies showed that adding a progestogen kept the lining of the womb healthy and prevented hyperplasia, so there was a gradual increase in the range of combination products available,” says Mr Sturdee.

A year after the endometrial cancer papers came research showing a link between five years and more of unopposed oestrogens and breast cancer.3 But it was hoped that this, too, would be a problem only for oestrogen-only brands of HRT, especially since many other observational studies at this time showed no increased breast cancer risk with HRT.
Cancer generally prevailed during the 1990s, outweighing their potential for causing breast osteoporosis and cardiovascular disease, but accumulated during the 1980s, which showed risks versus benefits sequential HRT,” he adds. “Continuous combined HRT caused quite a stir [because] people took time to accept the idea of not having a withdrawal bleed. But it has made a big difference for women because they get all the beneficial effects of HRT on their symptoms without cyclical symptoms and bleeding,” says Mr Sturdee. “We now recommend that women switch to continuous treatment once they are past the menopause [since] there is a slight increased risk of endometrial cancer with long term use of HRT,” he adds.

From pills to patches

The next major step forward in HRT came in the 1980s with the first hormone patch, Estraderm, by Swiss pharmaceutical company Ciba Geigy (now part of Novartis). Mr Sturdee explains that, by avoiding the first-pass effect through the liver that occurs with oral formulations of oestradiol, it became possible to achieve more consistent hormone concentrations in the circulation.

“The early patches were quite bulky [because] they contained a reservoir of hormone in a gel, which was released through a rate-limiting membrane into the skin and then into the peripheral circulation. But the current brands use matrix systems which enable the hormone to be absorbed more efficiently, directly from a single adhesive membrane,” he says.

Initially, women still had to take the progestogen component orally but, by the early 1990s, both hormones were incorporated into a single patch. Also available was the first bleed-free treatment, tibolone, which mimics the action of oestrogen, progesterone and testosterone. Used continuously, tibolone and other bleed-free brands of HRT relieve menopausal symptoms but, in contrast to conventional forms of HRT, are best started 12 months or more after a woman’s last period.

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Risks versus benefits

Alongside developments in HRT formulations, a growing body of evidence accumulated during the 1980s, which showed additional benefits of treatment for prevention of osteoporosis and cardiovascular disease, but the spectre was also being raised of an increased risk of breast cancer.

The view that the beneficial effects of HRT on osteoporosis and cardiovascular disease outweighed their potential for causing breast cancer generally prevailed during the 1990s, although a large analysis of epidemiological data published in 1997 showed an increased risk of breast cancer after five or more years of HRT use.4 However, it was the results of the Women’s Health Initiative (WHI) study in the US5 and the Million Women Study (MWS) in the UK6 that appear to have changed attitudes for good.

Fateful years for HRT

The WHI study, which was a randomised placebo-controlled trial, showed that combined HRT used by healthy postmenopausal women increased coronary events, strokes, breast cancer and pulmonary embolism, and decreased osteoporotic fractures and colon cancer.7 MWS, which was an observational study of women attending breast screening clinics, showed that current users of combined HRT were twice as likely to get breast cancer as non-users and that the risk was greater than for those using oestrogen-only brands.8 The methodology of both studies has been criticised.

“The WHI study chose women who were too old. Their average age was 63, which isn’t an age that you normally start women on HRT and, after five years’ treatment, they would have been 68. So it wasn’t surprising that they ran into problems,” explains Mr Sturdee.

He adds that the observational design of the Million Women study raises doubts over some of its findings, and concludes that the small increase in breast cancer consistently seen with HRT should still be set against the proven benefits of treatment.

“I’m not sure that the two studies really changed anything that we already knew about HRT, but it is very distressing that there has been such an over-reaction to the data. The bad news is what people remember, and they forget that the WHI study confirmed that HRT reduces hip fractures and colon cancer. “The effect on breast cancer was comparable to what had been seen before and the increase in heart disease only occurred in women who were well past their menopause when they started HRT. In younger women who started HRT at the menopause, heart disease was actually reduced.”

Mr Sturdee points out that subsequent analysis of the WHI data has shown that the timing of initiation of therapy is critical and that, when started within 10 years of the menopause, the risks of HRT in an otherwise healthy woman are low.9 He also draws attention to the fact that many women are being denied relief from the discomfort of vaginal atrophy, which can be simply and safely achieved with local oestrogen treatment to the vagina, which avoids systemic effects.9

Current recommendations

Following the WHI study and MWS, the Medicines and Healthcare products Regulatory Agency recommended that the benefits and risks of HRT be considered for every woman before treatment is prescribed and that the lowest effective dose should be used for the shortest time.4 HRT is only recommended for osteoporosis prevention in women who cannot use other treatment options. Mr Sturdee explains that such recommendations led to the next major change in HRT, with lower dose brands containing as little as 0.3mg of conjugated oestrogens or 1mg oestradiol launched in the UK.

“The low dose products still provide a very effective reduction in hot flushes and improved quality of life, and they have much less effect on breast density than higher doses of HRT, so it’s plausible to think that, by reducing the dose, we are reducing the risks,” he says.

Mr Sturdee regrets the demise of HRT in the UK, given the continuing needs of the small proportion of menopausal women who are seriously distressed by their symptoms, and is pessimistic about the outlook. “There is a chance that HRT will gradually make a comeback, but it could take a generation. Pharmaceutical companies have withdrawn their sales forces, and funds for research and education about the menopause were [dwindled]. GPs should be able to manage the menopause in primary care, without menopause clinics. But they need to get the risks into perspective, and read what the experts are writing in the journals, not the scare stories that appear in the newspapers.”

References