WHAT'S NEW IN HORMONE REPLACEMENT THERAPY?

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There has been a rapid increase in the number of Hormone Replacement Therapy (HRT) preparations available. Are they useful new products or dreary "me-toos"? Before looking at this, it is worth considering how the indications and contra-indications to HRT have changed. Many contraindications listed in data sheets and textbooks only relate to the highly potent synthetic oestrogens in the oral contraceptive pill and should not prevent the use of HRT. Table 1 shows a list of conditions that should no longer be regarded as contraindications. If a woman has a family or personal history suggestive of thrombophilia, it is always worth considering a full thrombophilia screen after discussion with a gynaecologist and/or a haematologist.

Controlled hypertension
Mild angina
Family history of ischaemic heart disease (unless due to specific heritable problem, see text)
Varicose veins
Smoking
Obesity
Otosclerosis
Migraine
Malignant melanoma
Elective surgery planned
Previous cervical cancer or dysplasia
Previous ovarian cancer unless endometrioid

Table 1 – Ex-contraindications to HRT

Table 2 shows a list of relative contraindications, where other tests and specialist consultation are needed, or particular formulations should be chosen.

Previous DVT/pulmonary embolism/CVA
Diabetes
Gallstones
Mild or past liver disease
Fibroids

Table 2 – "Proceed with caution" with specialist consultation

The remaining absolute contraindications are in Table 3.

Acute phase myocardial infarction, pulmonary embolism or DVT
Breast or endometrial cancer
Pregnancy
Undiagnosed abnormal vaginal bleeding
Undiagnosed breast lump
Severe liver disease

Table 3 – Contraindications to HRT

Cardiovascular mortality after the menopause is less for oestrogen users than non-users. Probably some of this decrease in mortality is due to HRT users being more healthy to start with, and then seeing more of their doctors. Nevertheless, survival is prolonged on HRT even with risk factors or established coronary disease. It will probably take some time for patients to accept that concerns over the cardiovascular safety of the contraceptive pill are wholly irrelevant to HRT.

I shall now consider the new treatments, mentioning which are well established enough to use today and which should be left to specialists for now. I shall also comment on which are overpriced.

OESTROGEN PREPARATIONS

Much the most potent natural oestrogen is oestradiol, and the value of adding oestriol or oestrone to it in HRT is not clear to me. Oestradiol can be given orally, transdermally, as an implant, or topically into the vagina.

Oral oestrogens

The long-established conjugated equine oestradiol and oestradiol valerate have been joined by micronised 17β oestradiol. No particularly impressive differences between them have been shown, but micronised 17β oestradiol (Zumenon) appeals due to its similarity to endogenous oestradiol. The synthetic mestranol (Menophase) is no longer considered appropriate for use in HRT by most practitioners.

Transdermal oestrogen

Transdermal oestrogen therapy has several theoretical advantages over the oral route. There is no first pass through the liver, so it is the route of choice when there is mild liver disease or a history of DVT. It should also be used if there is familial hypertriglyceridaemia. The patches are changed twice a week. The original transdermal oestrogen (Estraderm) is a reservoir patch. Although the introduction of transdermal HRT was a considerable advance at the time, Estraderm caused unacceptable skin irritation for many users. The newer preparations use a matrix patch, which is thinner, more adherent, less irritant, and makes fewer crinkly noises. There is an ever-growing number of matrix patches, including one that lasts a week, and they are available in various doses. Most women will start on a 50 microgram/24 hours patch and adjust as necessary. Patches cost two to three times as much as tablets so many will use them only in the circumstances listed above. The other development in transdermal oestrogen is Oestrogel, an oestradiol gel in a pressurised container which is smoothed into the skin. It might be preferred by a well-motivated woman who wishes to show no sign of needing oestrogen replacement.

Implants

There have been some reports of tachyphylaxis (requiring ever-increasing doses to obtain symptom relief) with implants, but this seems a rare problem. This route would not be a good choice when relative contraindications to HRT are present, as the implants cannot readily be removed.

Topical

The topical or intravaginal route is appropriate when the predominant symptoms are due to vaginal dryness or urinary urgency, and systemic oestrogen is either unwanted or contraindicated. Vaginal creams have been available for years, but have the disadvantages of being messy and sometimes difficult for patients to apply. They are also not metered in their dose so with oestradiol creams (Dienoestrol or Premarin) there is a risk of giving enough oestrogen to stimulate the endometrium and cause bleeding or hyperplasia. Ovestin (oestriol) is less potent and so is less hazardous to the endometrium. The most interesting new products in this field are Vagifem, an oestradiol tablet with an applicator that avoids mess and gives a controlled dose, and Estring. Estring is a silicone ring that releases oestradiol at a controlled rate for three months. It is the most acceptable topical treatment to most patients and highly effective for urogenital symptoms. Unfortunately the price is three to four times that of oral tablets or vaginal creams and 50% more than the price of patches.

PROGESTOGENS

There has been no recent change in the recommendation that all women with a uterus require progestogen to oppose the effect of oestogen on their endometrium. Natural progesterone is not absorbed orally, and there are two main groups of progestogen in common therapeutic use. Progestogens with 21 carbon structures such as dydrogesterone and medroxyprogesterone acetate are not androgenic and do not affect lipids. Those with 19 carbons such as levonorgestrel and norethisterone acetate are androgenic, but their effects on lipids are small at low doses such as are found in most HRT preparations.

The 21 carbon progestogens are a little more expensive but the difference is small. Although these hormones are new to HRT there is very extensive experience with dydrogesterone and medroxyprogesterone acetate in gynaecology and general practice so the natural hesitation about using a new drug need not apply here.

The only transdermal progestogen is norethisterone, which is only available in a reservoir patch. The pharmacokinetics of transdermal progestogen seem very difficult, and it may be some time before there is much progress.

A levonorgestrel releasing IUD is now available. It releases a much lower dose of progestogen into the general circulation than oral preparations, but the local delivery protects the endometrium. It will be discussed below.

NO BLEED AND LONG CYCLE COMBINATIONS

A lucky 5 to 15% of women on traditional sequential cycle HRT will be amenorrhoeic. To try to avoid periods for the others, there has been research into the effects of continuous combined HRT for the last 10 years, and the first products are now commercially available. Most experience is with oral preparations. These tend not to be successful at producing amenorrhoea until about a year after the last spontaneous period, or if cyclic treatment has already been started, the age of 54 is suggested for a change to continuous combined. There is a high rate of erratic bleeding for the first few months of treatment. For this reason, the drop-out rate in published studies is 30-40%. Of the two-thirds that persist, 95% of postmenopausal women are amenorrhoeic by one year. It is usual to allow six months of abnormal bleeding on continuous combined HRT before checking the endometrium with hysteroscopy or ultrasound and biopsy. Inexplicably, the two preparations now available, Kliofem and Premique, are only liable for a single prescription charge, while the cyclic ones cost two charges. It is also strange that Kliofem, with its less lipid-friendly progestogen, should cost more than Premique.

For many women, the levonorgestrel IUD (Mirena) is the ideal route of progestogen administration, as it usually causes amenorrhoea and has the additional advantage of providing safe and effective perimenopausal contraception. Its value for money depends on the indication for which it is used. It provides endometrial protection for 3 years so is not an expensive way of opposing oestrogen therapy, while avoiding any adverse effects of systemic progestogen on symptoms or lipid metabolism. It is very cheap viewed as an alternative to hysterectomy. As an IUD it is very dear.

Long cycle HRT

Another potentially attractive new development is long cycle HRT, giving unopposed oestrogen for 10 weeks, followed by two weeks of combined oestrogen and progestogen, then a pill free week (Tridestra). Some women develop proliferative or hyperplastic endometrium towards the end of the unopposed oestrogen, but after the progestogen these rates drop. The bleeding appears acceptable too, with breakthrough bleeding rarer than on continuous combined therapy. My only caveat is that little of the work on this drug has appeared in a peer-reviewed journal. I think it is wiser to wait until it does before prescribing it outside the setting of a specialist menopause clinic.

CONCLUSIONS

The arrival of many new products should make it easier to start a woman on a treatment that she will find satisfactory and which will have few adverse metabolic effects. This has decreased the need to put bespoke combinations of drugs together. The older preparations I would now abandon are Menophase, for the reason given above, and Cyclo-progynova. Cyclo-progynova gives seven oestrogen-free days during which symptoms can recur, and has a relatively high dose of an androgenic progestogen.

I would choose Femoston 2/10 as a standard cyclic treatment for women who are still menstruating or are within a year of the last period. Premique is the cheapest and least androgenic continuous combined HRT for the older woman. Matrix patches have such a clear advantage over the reservoir patch that they could reasonably be offered to a woman who had been intolerant of Estraderm. The levonorgestrel IUD is a good choice for a woman who requires contraception, or one whose periods are troublesome but is too young for continuous combined HRT. If the promise of Tridestra is fulfilled, this should be the alternative for a perimenopausal woman who wishes to have as few periods as possible but wants to avoid a coil.

Declaration of interest

I spent nine months in 1991 as a research fellow funded by Solvay (Duphar).