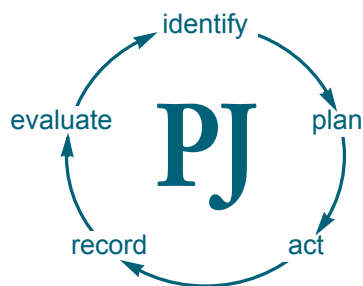


HORMONE REPLACEMENT THERAPY: (1) AN OVERVIEW

By Nuttan Tanna, PhD, MRPharmS

This article gives an overview of hormone replacement therapy in the United Kingdom so that the options open to patients can be explained



identify gaps in your knowledge

1. What important function does progesterone play in HRT?
2. List six different types of HRT that are licensed in the UK.
3. What oestrogen- and progesterone-related side effects can occur and how can they be managed?

Before reading on, think about how this article may help you to do your job better.

The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record," (available at: www.rpsgb.org.uk/education). This article relates to "common disease states and their drug therapies" (see appendix 4 of "Plan and record").

Around 25 per cent of women go through the menopause without suffering debilitating vasomotor symptoms and, generally, most symptomatic women become symptom free five years after the menopause. However, the symptomatic menopausal patient, with or without osteoporosis, will need to decide (based on an individualised risk-benefit evaluation) if hormone replacement therapy (HRT) is a good treatment option. With the recent publication of data from trials designed to assess the long-term risks and benefits of HRT, and which considered the associated risks of cardiovascular disease and breast cancer in particular, pharmacists will be approached by women with questions about the use of HRT. This article looks at the different types of HRT currently available. Next week's article will cover the evidence of risks and benefits of HRT.

THE MENOPAUSE

Natural menopause can only be established in retrospect, after 12 consecutive months of amenorrhoea. Most women go through the menopause at about the age of 51, although racial, genetic and socio-economic variations influence this average age. Vasomotor symptoms are experienced due to falling and fluctuating oestrogen levels. Classic cases present with hot flushes, night sweats and an erratic menstrual cycle. Menopausal women may complain of difficulty sleeping, irritability, headaches, palpitations, low energy levels and affected libido. Urinary problems are also common. In addition, during the climacteric (see Glossary), which generally occurs between the ages of 45 and 55 years, there may be accompanying family and social changes which can seriously influence psychosocial functioning.

Figure 1 (p616) shows hormonal changes during the climacteric. During the perimenopause (see Glossary), blood levels of follicle stimulating hormone (FSH) can be high but luteinising hormone levels can be normal so women still have a small possibility of conceiving. It is only after blood levels of FSH are shown to be consistently high (>30ng/ml) that pregnancy cannot take place and true menopausal status is confirmed. Current medical consensus on

contraception at the menopause is that women under the age of 50 need to use a non-hormonal contraceptive for two years after their last normal period. In women over 50 years, a non-hormonal contraceptive should be used for one year after their last normal period.

HORMONE REPLACEMENT THERAPY

The 50 or so different HRT formulations that are currently licensed in the United Kingdom offer many options to menopausal women. These range from oral and transdermal products to those administered intranasally and vaginally. Oestrogen implants are also available, but few general practitioners give them and patients using implants are usually managed by specialist clinics. Testosterone implants, licensed for menopausal libido problems, can also be used. Table 1 (p617) lists the advantages and disadvantages of different oestrogen formulations.

GLOSSARY

Pre-menopause The reproductive phase of a woman's life, characterised by normal, monthly menstrual cycles.

Perimenopause The time around the menopause when there are marked menstrual cycle changes (usually accompanied with hot flushes) but not yet 12 consecutive months of amenorrhoea.

Menopause The last vaginal bleed induced by the influence of ovarian hormones on the endometrium. The median age is 51 years.

Postmenopause The period of life after the menopause. The clinical definition is one year from the last menstrual period.

Climacteric The years of definitive changes taking place in a woman's body, linked to the ageing of the ovaries. The ovaries gradually become less responsive to stimulating hormones from the pituitary gland and secrete less oestrogen.

Premature menopause Menopause before the age of 45.

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If the aim of treatment is symptom control, HRT is given for two or three years. With short-term use for symptom relief, benefits are considered to outweigh the risks for most women. However, if the main aim is to prevent osteoporosis, treatment needs to last for at least five years. In these cases, patients should be aware of the increased incidence of some diseases and of alternatives for preventing osteoporosis. The patient's risks and benefits should be reappraised each year with continued HRT use.

The aim of HRT is to achieve the natural circulating oestrogen levels of the premenopause. Women who have had a hysterectomy can be prescribed oestrogen alone, but in women with an intact uterus, progestogens are needed for endometrial protection. Figure 2 shows a prescribing algorithm for the various HRT preparations.

Unopposed oestrogen (oestrogen-only treatment) is prescribed for a surgical menopause occurring after a total abdominal hysterectomy and bilateral salpingo-oophorectomy (removal of fallopian tubes and ovaries). In women who have kept their ovaries it is appropriate to wait until menopausal symptoms begin (suggesting ovarian failure) before oestrogen is prescribed.

Oestrogens Tablets containing conjugated equine oestrogens (sourced from pregnant mares' urine) are one of the most prescribed oestrogen formulations. These oestrogens are considered to be "natural" because they exert the same effects as endogenous human oestrogens. Other oestrogens used in HRT preparations include estradiol, estrone and estriol. Although these are manufactured for HRT, they are also classified as natural because the same oestrogens are produced by the ovaries. Estradiol is the most potent and estriol the least potent.

Progestogens Because the oral absorption of natural progesterone is poor, most of the progestogens used for HRT are synthetic. The progestogens used in HRT are classified as:

- The C19 or testosterone analogues, used orally or transdermally (eg, norgestrel, levonorgestrel and norethisterone)
- The C21 or progesterone analogues, used orally (eg, dydrogesterone and medroxyprogesterone)
- Natural progesterone, used vaginally (eg, in a gel formulation)

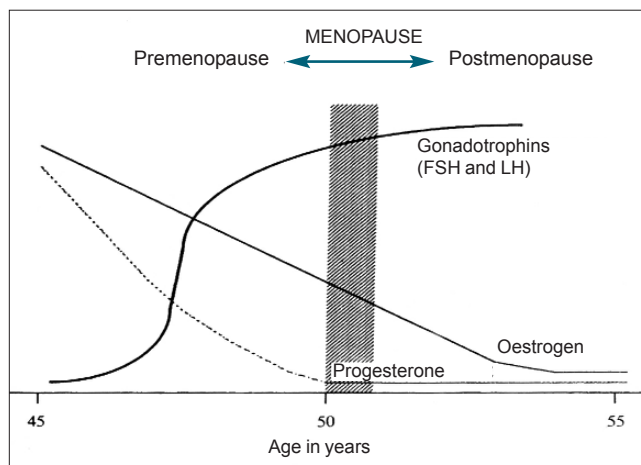


Figure 1: Hormonal changes during the climacteric

Generally, progestogens should be used with caution when the woman has a condition that can worsen with fluid retention, for example, epilepsy, hypertension, migraine, asthma or cardiac or renal dysfunction. High doses should be used with caution in individuals susceptible to thromboembolism, and care is needed in patients with liver impairment and in those with a history of depression. Progestogens can decrease glucose tolerance so women with diabetes should be monitored closely. However, progestogens are present in HRT preparations at lower doses than in other progestogen-containing products (eg, those used for dysmenorrhoea and infertility) and are generally not considered to make most of these disease states any worse, except in sensitive or high risk patients.

The testosterone analogues are more likely to cause androgenic side effects, such as acne and greasy skin and hair, but for patients with osteoporosis they provide enhanced bone density. Some patients report an increase in premenstrual syndrome side effects whereas others report mood improvement. Studies suggest that the progesterone analogue dydrogesterone may have the least impact on

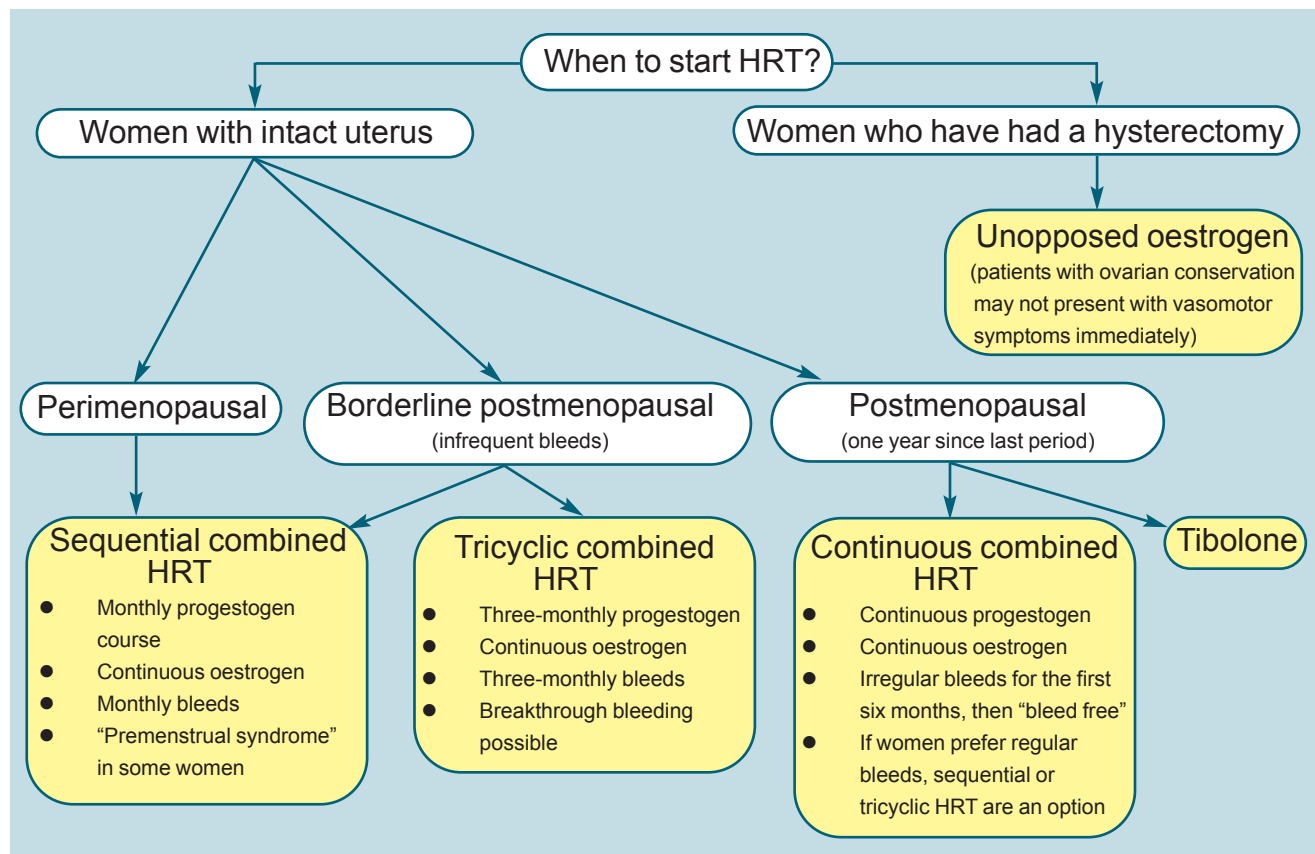


Figure 2: Prescribing algorithm for the various HRT preparations

TABLE 1: ADVANTAGES AND DISADVANTAGES OF HRT FORMULATIONS

Formulation	Advantages	Disadvantages
Tablets	Easy to take Easily reversible Comparatively cheap Cholesterol benefit	Need to be taken every day Nausea possible, especially with lactose intolerance
Patches	Convenient More natural delivery of hormone Easily reversible First line for patients with high triglycerides or gut problems	Can become detached Can irritate the skin Expensive Must be changed once or twice a week
Implants	100 per cent compliance More natural delivery of hormone Prolonged effect (four to eight months) Cheap	Small surgical procedure Not easily reversible Tachyphylaxis with unnaturally high levels of hormones Progestogens need to be continued for several months after last implant
Vaginal preparations	Greater effect if vaginal symptoms are the only problem Easily reversible	Oestrogen can enter the bloodstream (long-term use needs progestogen)
Nasal spray	Easy to use Easily reversible	Needs to be used daily Nasal irritation possible

lipid and insulin resistance profiles, so this may be the first line choice for patients with stable heart disease or with diabetes.

Sequential combined HRT The majority of sequential combined HRT regimens are designed to mimic the menstrual cycle and so result in monthly bleeds. Generally, original packs are based on a 28-day cycle. Oestrogen is taken continuously, with progestogen added for the last 12 to 14 days. Tridestra is the exception. It is a tricyclic or “long-cycle” regimen resulting in three-monthly bleeds usually prescribed to women at the “postmenopausal border”. These are women who have widely erratic bleeding that is likely to synchronise with three-monthly bleed patterns. In the early perimenopausal stages, some women bleed as frequently as every three to six weeks and the tricyclic regimen would not be appropriate.

Continuous combined HRT Continuous combined HRT is a “bleed-free” regimen in which oestrogen and progestogen are taken together daily, with no break. Products are licensed for postmenopausal women (see Glossary). An advantage of continuous combined HRT is the lower dose of progestogen used and, therefore, the lower risk of side effects (eg, premenstrual syndrome symptoms). Patients need to be warned that it can take up to six months for intermittent bleeds to stop with continuous combined HRT but to expect a lower incidence of breakthrough bleeding with time. Endometrial assessment should be considered if the bleeding becomes heavier rather than lighter, if it persists beyond six months, or if it occurs after a significant period of amenorrhoea. One in five patients fail to become bleed-free and may have to consider using a sequential combined treatment instead. Alternatively, the patient’s suitability for treatment with a gonadomimetic (see below) can be assessed, especially if the woman expresses a wish to take HRT but does not want bleeds. By the age of 54 years more than 80 per cent of women no longer have periods. Women who have been taking sequential combined HRT at perimenopause, and therefore cannot tell if they have been naturally bleed free for a year, can start using continuous combined HRT at the age of 55 years.

Vaginal oestrogen For symptoms of vaginal atrophy, vaginally administered oestrogens can be effective. These are available as creams, pessaries, vaginal tablets and rings. Long-term use may be associated with some absorption and endometrial stimulation and this should be borne in mind when considering endometrial safety. It should be noted that estradiol from the vaginal ring, Menoring, is systemically absorbed. It is licensed for the control of menopausal symptoms in women who have had a hysterectomy and not simply for localised vaginal symptom relief.

Gonadomimetic Tibolone (Livial) is the only gonadomimetic available in the UK. It is a synthetic steroid derivative of norethisterone, with mixed oestrogenic, progestogenic and androgenic

activity. It is licensed for use in postmenopausal women for menopausal symptoms and osteoporosis. In addition, tibolone can be used to treat low mood and libido problems. It provides an alternative to continuous combined HRT for postmenopausal women who do not wish to have withdrawal bleeds.

MANAGEMENT OF SIDE EFFECTS

Oestrogen-related side effects Women on HRT often suffer from oestrogen-related side effects such as mastalgia or breast tenderness. However, these are transient and women should be advised to persist with treatment for at least three months before considering a change of regimen or dose. At the clinic we have noted that evening primrose oil supplements can be useful for mastalgia. With the withdrawal of the product licence for Epogam because of poor evidence of efficacy, women wishing to use

evening primrose oil will have to buy supplements. Leg cramps can be helped with exercise. Women who take regular exercise find they cope better with both menopausal symptoms and HRT. If nausea or gastric upset occurs with oral oestrogens, patients should be advised to take the tablet after food and at night. Occasionally these symptoms may also indicate lactose intolerance. Management options also include changing the oestrogen or changing the route of delivery.

Progestogen-related side effects Progestogen-related side effects often resemble premenstrual symptoms. They are usually related to the type and dose of progestogen, and the duration of therapy. Management strategies include changing the progestogen type, reducing the dose (while taking care not to go below that recommended for endometrial protection) and changing the route of administration or duration of therapy.

action: practice points

Reading is only one way to do CPD and the Society will expect to see various approaches to CPD in a pharmacist’s portfolio.

1. Do you feel able to advise women prescribed an HRT product for the first time? Revise your knowledge of the products available and make a list of points to counsel on.
2. Discuss with a colleague how you would advise peri- and postmenopausal women on contraception. Explain why you would give such advice.
3. Each time you dispense HRT this week, have a look at the Monthly Index of Medical Specialities (MIMS). This presents the various HRT preparations in a quick-reference table, which defines preparations by the type of oestrogen and progestogen, the doses in each preparation, the type of formulation available and whether it is a “bleed” or “no bleed” regimen. What are the advantages and disadvantages of the preparation?

evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following three questions:

- What have you learnt?
- How has it added value to your practice? For example, have you applied this learning or had any feedback?
- What will you do now and how will this be achieved?