Dealing with the HRT dilemma

We should not be afraid of hormone replacement therapy, but instead take each patient with their individual symptoms and risk factors and prescribe accordingly, writes Claire McNicholas

HORMONE REPLACEMENT THERAPY (HRT) has been available for over 50 years and has had its fair share of controversy. Initially, the controversy was to do with prescribing unopposed oestrogen and the associated link with endometrial hyperplasia and, in some cases, endometrial carcinoma.

More recently there has been controversy over the increased risk of breast cancer and the risk of thrombosis. This evidence led many prescribers and patients to re-assess the need for HRT with a subsequent fall in prescribing rates. However, recently a new HRT drug with a more user-friendly progestogen was launched. This may increase confidence in prescribing patterns.

What are the indications for HRT?

The primary indication for prescribing hormone replacement therapy is for the relief of menopausal symptoms. These include hot flushes, night sweats, insomnia and sometimes palpitations. Other symptoms that women present with at this time include fatigue, irritability, mood changes and urogenital atrophy. The latter may present as dryness of the vagina, dyspareunia and urinary frequency or urgency.

HRT may be prescribed for the prevention and treatment of post-menopausal osteoporosis. In some patients it is believed that earlier treatment may give later benefit. However, HRT is not considered as first-line treatment and risks must be balanced against benefits for each individual patient when prescribing.

Premature menopause

It is believed that women with a premature menopause may experience an accelerated risk of developing osteoporosis and perhaps coronary artery disease. Women who have had a premature menopause should normally be offered HRT until approximately 50 years of age.

Contraindications to prescribing HRT include:
- Current, past or suspected breast cancer
- Known or suspected oestrogen-dependent malignant tumours, eg. endometrial cancer
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous idiopathic or current venous thromboembolism (deep vein thrombosis [DVT] or pulmonary embolism)
- Active or recent arterial thromboembolism, (eg. angina or myocardial infarction)
- Untreated hypertension
- Active liver disease
- Known hypersensitivity to any of the active substances in the prescribing drug.

When to start HRT

Usually it is started when women present with their symptoms. If a woman presents with irregular bleeding, progestogen may help in the latter part of the cycle.

Combined oestrogen and progestogen (HRT) is indicated for vasomotor symptoms. Some women who present early with irregular bleeding and symptoms may also need contraception. Combined oral contraception may be prescribed.

It is probably best to start with a sequential form of HRT, since in the early part of the menopause endogenous oestrogen may still be produced, however irregularly. This will achieve a regular withdrawal bleed. At a later stage a woman can be changed to a continuous preparation and then would expect no bleed.

Routes of administration

HRT is available in oral, transdermal, local and implant forms. The dose of oestrogen used should be the lowest needed to relieve symptoms effectively. Women who have had a hysterectomy do not need progestogen.
Duration of treatment
Most women take HRT for 18 months to three years on average. When treatment is stopped and symptoms recur HRT may need to be re-started.

Treatment of osteoporosis
HRT may be considered in an overall treatment plan for the prevention of osteoporosis in people at high risk. The anti-fracture effect of HRT is proven but would involve longer-term treatment. It may be considered initially at a young age and then with a switch to SERMS or bisphosphonates at a later stage.

Risks in prescribing HRT
The two main risks in prescribing HRT are breast cancer and cardiovascular disease.

• HRT and breast cancer risk
   It has been well established that there is a small increase in the risk of developing breast cancer with long-term use of HRT. It is thought there is no increased risk if duration is less than two years. But the advantages must be balanced against the possible risks in all cases.

   It must be noted that various factors affect the development of breast cancer, including a total duration of exposure to endogenous and exogenous oestrogen and progesterone. Thus an early menarche, a late first pregnancy over 35 years, nulliparity and moderate alcohol consumption, ie. over 20g per day, may all be a factor.

   Randomised controlled trials have shown that combined HRT increases the absolute risk of breast cancer by four extra cases per 1,000 women over five years of treatment. This may be a similar risk to the other risk factors mentioned above.

   It has also been noted that the increased risk of breast cancer returns to that of the never-user of HRT within five years of quitting the treatment. Equally, breast cancers diagnosed whilst on HRT seem to show a better prognosis than those diagnosed in non-users. Also, the type and route of HRT does not affect the outcome.

   However, the different regimes of HRT prescribed, eg. unopposed, sequential, or continuous types, have been shown to produce different densities on mammographic examination; the most dense being in patients on continuous combined regimes. This in itself may lead to reduced sensitivity in interpreting mammograms.

   The Million Women Study1 was linked with the National Health Service Breast Screening Programme, with women aged 50 to 65 in the UK invited for routine mammography every three years. The study concurred with some of the above findings which were published in 2003.

• HRT and cardiovascular risk
   There has been great interest and controversy in recent years regarding HRT and coronary heart disease. Two large trials—the Heart and Oestrogen-Progestogen Replacement Study (HERS) trial2 and The Women’s Health Initiative (WHI) study—revealed some interesting findings. These trials did not reveal major new information but largely confirmed existing knowledge, which is essentially that HRT is not cardio-protective. But HRT was never licensed as treatment for cardio-protection.

   The HERS study looked at 2,763 women with coronary heart disease at a mean age of 67 years, using conjugated equine oestrogen and medroxyprogesterone acetate. The

   The principal findings of this study were that there was no difference detected in overall mortality between those taking the combined HRT preparation and those taking placebo. Combined HRT used in healthy post-menopausal women increases the risk of cardiovascular disease and is not cardio-protective.

   The study confirms that HRT reduces the risk of fractures and colorectal cancer and increases the risk of breast cancer and venous thromboembolism. Looking at figures, it might seem that the percentage difference is large - in actual fact the number of cases is small. To put things in perspective, if you have 10,000 women taking HRT over one year compared with placebo there will be:
   • Seven more coronary heart disease events
   • Eight more strokes
   • Eight more pulmonary embolisms
   • Eight more invasive breast cancers
   • Six fewer colorectal cancers
   • Five fewer hip fractures.

   This study was only looking at one continuous combined preparation, and this particular formulation was never marketed in Ireland. It is somewhat similar to what we know as Premique 5 but in different dosages. It finds us in a difficult scenario as to how to extrapolate these findings to other HRT products used.

Advice to patients
So overall what advice do we give our patients with regard to HRT? Much has been teased out re all the above findings by various working groups and the advice is short-term use in the main.

Firstly, women who are very symptomatic may be given a trial of HRT for a period of 18 to 36 months, with regular follow-up. Quality of life is a very important issue. Longer use must be monitored closely and benefits versus risks closely assessed.

Long term use of HRT, ie. greater than five or 10 years, will increase risks, however relative these risks are. Patients must be counselled carefully regarding same. Equally, we must advise women that sudden cessation of HRT may cause rebound occurrence of their symptoms. A gradual weaning off HRT is advisable when women do choose to stop. As can be seen, HRT is a much studied drug and we await future studies. We should not be afraid of it – but take each patient with their individual symptoms, their risk factors and prescribe accordingly.

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References
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2. Principal results from HERS research group randomised trial JAMA 2002; 288: 49-57