Introduction

Menopausal symptoms, which include vasomotor symptoms, vaginal atrophy, insomnia, depression, altered cognitive function, dementia and loss of muscle mass, can affect up to 80% of women during menopause, and may be severe in up to 20% of these women.1 The duration of these symptoms varies, with most women experiencing spontaneous cessation of symptoms within five years after onset. However, a substantial proportion of women continue to experience symptoms beyond five years.2

Hormone replacement therapy (HRT) remains the gold standard treatment for the management of moderate to severe menopausal symptoms, and should be recommended as a first option in cases where there are no contraindications to its use.3-4 HRT should be individualised, and is considered to be safe for short-term use at the lowest possible dose.2 The benefits derived from HRT generally outweigh the risks to women younger than 60 years of age, or within 10 years of the menopause. Starting HRT in women aged 60 years and older is not recommended.3-5 Table I lists the contraindications to HRT.

Indications

There is general consensus that HRT should be considered in:
- Women with premature menopause
- Women with significant vasomotor symptoms
- Women with symptomatic urogenital atrophy
- Women aged 50-60 years, when there are menopausal symptoms and an above-average risk of osteoporosis.

There is also agreement that HRT should not be recommended purely as a strategy to prevent coronary heart disease or osteoporosis. While HRT must not be initiated in women aged 60 years and older, some women who are 65 years and older may continue to use HRT for the management of vasomotor symptoms. Routine discontinuation of HRT is not recommended in these cases.

Recommended dosing

The dose and duration of treatment should be individualised and consistent with treatment goals and safety issues.3-5 Low-dose and ultra-low systemic doses of oestrogen are preferred, and appear to have a more favourable adverse effect profile than standard doses.2-4

Low- and ultra-low dose oestrogen and progestogen preparations are listed in Table II.

Once a decision has been made to initiate HRT, consideration should be given to the type of oestrogen, the route by which it is to be administered, and the presence of any progestogen. The selection of the type of oestrogen and progestogen should be based on the individual needs of the patient and the risks associated with each preparation.

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be given (oral or transdermal), as well as the need for progestogen and the most appropriate progestogen regimen, i.e. cyclical or continuous.3

In general, progestogen should be added to systemic oestrogen for all women with a uterus to prevent endometrial hyperplasia and cancer.3,4 If the last menstrual period occurred less than one year prior to starting HRT, a sequential combined regimen should be started, i.e. continuous oestrogen with progestogen for 12-14 days per month.4

After a minimum of one year of HRT, or one year after the last menstrual period (two years in premature ovarian insufficiency), women who wish to avoid a monthly withdrawal bleed may attempt a switch to a continuous combined regimen of oestrogen plus progestogen for 12-14 days per month.4

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Low-dose vaginal oestrogen formulations, e.g. cream, gel, a pessary or vaginal ring, are preferred for atrophic urogenital symptoms. There is no requirement to combine this with systemic progestogen therapy for endometrial protection as low-dose vaginal oestrogen preparations do not result in significant systemic absorption, and the use of progestogen to protect the endometrium from unopposed oestrogen stimulation is therefore not necessary.4

The transdermal delivery of HRT may be the preferred route of delivery for some patients as it exhibits a better safety profile than oral formulations.5,6

### Hormone replacement therapy and osteoporosis

According to the World Health Organization, 1% loss of bone mass per year is accepted as within the normal range as a result of the ageing process, but approximately one third of women suffer bone loss of up to 5%/year. Postmenopausal osteoporosis occurs when bones lose their mineral density owing to decreasing oestrogen levels, as seen during menopause.3 Women may lose 2% of bone annually in the interval around menopause.

Thereafter, bone loss slows to the rate associated with ageing, approximately 1-1.5% per year.5

HRT is effective and appropriate in preserving bone density and preventing osteoporosis in both the spine and hips, as well as reducing the risk of osteoporosis-related fractures in women with menopausal symptoms before the age of 60 years or within 10 years after menopause. However, oestrogen therapy, with or without progestogen, is not recommended as first-line treatment or as prophylaxis for osteoporosis.5

### Risks associated with hormone replacement therapy

Thromboembolic disease, strokes, cardiovascular disease, and breast and endometrial cancer, as well as gall bladder disease, are the main risks associated with the use of HRT.2 However, data accumulated from various studies over the past few years have shown that initiating HRT as early as possible in menopause will provide a favourable benefit to risk ratio. The benefits derived from HRT generally outweigh risks in the majority of women aged 60 years and younger, or those within 10 years of the menopause.

### Hormone replacement therapy and heart disease

Controversy exists over whether or not HRT has a cardioprotective effect. Clinical evidence suggests that women on HRT, whether on a combination of oestrogen and progestogen or oestrogen alone, gain protection against coronary heart disease.8 Evidence also suggests that women in early menopause, who are in good cardiovascular health and on HRT, whether on a combination of oestrogen and progestogen or oestrogen alone, gain protection against coronary heart disease.8 Further analysis of these data also suggests that HRT does not increase the risk of coronary heart disease in healthy women who have recently reached menopause. However, women who start HRT aged 60 years and older have an increased risk of coronary disease. According to this hypothesis, which is supported by substantial epidemiological data, oestrogen may offer protection when the arterial endothelium is still healthy and intact. However, oestrogen may destabilise an atherosclerotic plaque and precipitate an event in elderly women with established vascular disease.5,8

### Table II: Low- and ultra-low dose oestrogen preparations

<table>
<thead>
<tr>
<th>Oestrogen</th>
<th>Low dose</th>
<th>Ultra-low dose</th>
<th>Standard dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugated equine or synthetic oestrogen</td>
<td>0.3 or 0.45 mg</td>
<td>0.3 mg (every alternate day)</td>
<td>0.625 mg</td>
</tr>
<tr>
<td>Micronised 17 β-oestradiol</td>
<td>1 mg</td>
<td>0.5 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>Oestradiol valerate</td>
<td>1 mg</td>
<td>2 mg</td>
<td></td>
</tr>
<tr>
<td>Transdermal oestradiol</td>
<td>0.025 mg</td>
<td>0.05 mg</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progestogen (cyclical)</th>
<th>Low dose</th>
<th>Ultra-low dose</th>
<th>Standard dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norethisterone acetate</td>
<td>0.7 mg</td>
<td>0.7 mg</td>
<td>0.7-2.5 mg</td>
</tr>
<tr>
<td>Dydrogesterone</td>
<td>5 mg</td>
<td>5 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>5 mg</td>
<td>5 mg</td>
<td>5-10 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progestogen (continuous)</th>
<th>Low dose</th>
<th>Ultra-low dose</th>
<th>Standard dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norethisterone acetate</td>
<td>350 µg</td>
<td>350 µg</td>
<td>350-700 µg</td>
</tr>
<tr>
<td>Dydrogesterone</td>
<td>5 mg</td>
<td>5 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>2.5 mg</td>
<td>2.5 mg</td>
<td>2.5-5 mg</td>
</tr>
<tr>
<td>Drospirenone7</td>
<td>2 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Hormone replacement therapy and the risk of venous thromboembolism and strokes**

The risk of venous thromboembolism (VTE) is doubled with HRT.\(^5\) The effect is maximal in the first year of treatment, and more pronounced with advancing age, obesity, previous VTE, smoking and immobility.\(^5,6\) The VTE risk appears to be higher in users of oestrogen plus progestogen than in users of oestrogen alone.

It has been suggested that the effect of HRT on strokes may be dose related. Smaller doses are protective and larger doses are harmful. Transdermal oestrogen is thought to have a more favourable safety profile with regard to thrombotic risk.

The consensus as per the international menopause guidelines is that the relative risk of VTE and ischaemic strokes increases with oral HRT, but that the absolute risk is low in women aged 60 years and younger.

**Hormone replacement therapy and cancer**

Unopposed oestrogen therapy increases the incidence of endometrial cancer. Therefore, it is mandatory that women with an intact uterus who are prescribed HRT use a combination of oestrogen and progestogen, to eliminate the risk of endometrial cancer. The use of cyclical progestogen for at least 10 days per 28-day cycle appears to reduce this risk.\(^9\)

The risk of breast cancer associated with HRT in women aged 50 years and older is a complex issue. Treatment with oestrogen or progestogen regimens has been associated with a small but significant increase in the risk of breast cancer, but this may relate to duration of use.\(^5\) Oestrogen therapy alone does not appear to increase the risk of breast cancer, and may, in fact, reduce such risk. Combined HRT increases breast density and the risk of having an abnormal mammogram.

There is no evidence of an increased risk of breast cancer in women on HRT aged 50 years and younger compared with menstruating women of the same age.\(^5,8\)

**Practical advice for the patient**

A healthy lifestyle of a balanced, prudent diet and regular exercise is recommended to reduce the risk of cardiovascular disease in menopausal women.

Reasonable strategies to manage vasomotor symptoms include layering clothing and lowering the room temperature, as appropriate.

Women should be advised to try to avoid factors that might trigger vasomotor symptoms, such as spicy foods, alcohol, caffeine and stress.

Non-oestrogen, water-based vaginal lubricants and moisturisers may be useful in alleviating the pain and discomfort associated with vaginal dryness, or that associated with discomfort during intercourse.

**Conclusion**

HRT remains the most effective treatment for menopause symptoms. Its benefits outweigh the risks in most women. However, HRT is not recommended for long-term use or for the prevention of chronic diseases in women who reach the age of natural menopause with no associated symptoms. The HRT dosage, regimen and duration should be individualised, with an annual evaluation of benefits and risks. It is hoped that with the consensus reached by global menopausal societies, HRT will once again be used appropriately for the benefit of women who require it during the menopausal period.

**References**