7 Estrogen-based therapies

At a glance

- Estrogen-based therapies provide the most cost-effective treatment for menopausal symptoms.
- Progestogens are required in addition to estrogen if the uterus is still intact and in some women who have had sub-total hysterectomy or hysterectomy for endometriosis.
- Many types, doses and routes of estrogen and progestogen are available.
- Several changes in types, doses and routes may be required to provide optimum effect.
- In most women, treatment can be commenced using low-dose estrogen, with gradual increase in dose if required as determined by menopausal symptoms.
- Women should be offered to switch from sequential hormone replacement therapy (HRT) to continuous combined when it is likely that she is postmenopausal.
- There should be no arbitrary limits applied to recommended duration of therapy.
- Several types of vaginal estrogen are available to treat urogenital symptoms, for which long-term treatment is recommended.
- Vaginal estrogen can be used alongside systemic HRT.
- Testosterone may be required in addition to HRT in women who have had oophorectomy but no licensed testosterone products are currently available.

There are more than 50 estrogen-based preparations licensed worldwide, which feature different strengths, combinations and routes of administration. Various terms are used: hormone replacement therapy (HRT), hormone therapy, menopause hormone therapy, estrogen therapy, and estrogen and progestogen therapy for combined preparations – whether sequential or continuous combined. In the UK, the term HRT is still mainly used.

Components of HRT

HRT consists of an estrogen, either alone for women who have had a hysterectomy or combined with a progestogen if the uterus is still present. Progestogens are given cyclically or continuously with the estrogen, depending on the menopausal status of the woman. Different routes of administration are employed: oral, transdermal (patch and gel), subcutaneous and vaginal.

Estrogens

Two types of estrogen are available: synthetic and natural. Synthetic estrogens, such as ethinylestradiol in combined oral contraceptive pills, are generally considered to be unsuitable for HRT because of their greater metabolic impact, apart from their use in young women with premature ovarian insufficiency. The natural estrogens used in HRT include estradiol, estrone and estriol, which, although chemically synthesised from soybeans or yams, are molecularly identical to the naturally occurring human hormones. Conjugated estrogens, used in the Premarin® (Pfizer) range, contain about 50–65% estrone sulphate, and the remainder consists of equine estrogens – mainly equilin sulfate. Much confusion surrounds what constitutes a 'natural' estrogen. In this book, we have taken the view that a 'natural' estrogen is one that is found in normal physiology, irrespective of whether it has been prepared by chemical synthesis or extraction from a plant or animal source.

Progestogens

Unopposed estrogen use in women who have *not* had a hysterectomy is associated with an increased risk of endometrial hyperplasia and potentially carcinoma. Recommended practice is to use combined HRT (estrogen with a progestogen) in all women with a uterus. The progestogen can be used cyclically, in perimenopausal women, which will usually induce a withdrawal bleed, or continuously (continuous combined therapy) in postmenopausal women (more than 12 months after the last menstrual period). The protective effect of cyclical progestogens on the endometrium is less reliable after more than five years of use and consideration should be given to switching to a continuous combined therapy within five years of starting a cyclical preparation or once it can be assumed that the woman is postmenopausal. Continuous progestogens, in postmenopausal women, reduce the risk of endometrial carcinoma to lower than in postmenopausal women not taking HRT.

Irregular bleeding or spotting can occur during the first four to six months of continuous combined therapy and does not usually warrant investigation. Endometrial assessment needs to 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 (see Chapter 4). The incidence of irregular bleeding may be reduced by increasing the ratio of the progestogen to the estrogen. Lower doses of estrogen tend to be associated with better bleeding profiles.

The progestogens used in HRT are largely synthetic. They are structurally different from progesterone and are derived from plant sources. Currently, they are used mainly in tablet form, although norethisterone and levonorgestrel (LNG) are available in transdermal patches combined with estradiol (Box 7.1). The native molecule progesterone is also formulated in micronised form as an oral capsule, which is licensed for use as part of HRT, but its availability varies worldwide. A progesterone pessary to be used vaginally or rectally is also available but is not currently licensed for HRT.

Box 7.1

Classification of synthetic progestogens

Progestogens structurally related to progesterone

1 Pregnane derivatives:
   (a) acetylated (also called 17α-hydroxyprogesterone derivatives): medroxyprogesterone acetate, megestrol acetate, cyproterone acetate)
   (b) non-acetylated: dydrogesterone
2 19-norpregnane derivatives (also called 19-norprogesterone derivatives):
   (a) acetylated: nomegestrol acetate
   (b) non-acetylated: trimegestone

Progestogens structurally related to testosterone (also called 19-nortestosterone derivatives)

1 Ethinylated:
   (a) estranes: norethisterone, ethynodiol diacetate
   (b) gonanes: levonorgestrel, norgestrel, desogestrel, gestodene, norgestimate
2 Non-ethinylated: dienogest, drospirenone

The Mirena® (Bayer) intrauterine system, delivering 20 µg LNG daily to the endometrium, is also licensed to provide endometrial protection for four years in combination with systemic estrogen, although it is recognised as being effective for up to five years (see Chapter 6). It has the advantages of providing extremely effective contraception and good bleeding control, as well as being the only way in which a continuous progestogen can be used in perimenopausal women. A new low-dose system, delivering only 10 µg/day of LNG to the endometrium, is not currently licensed to be used for endometrial protection with estrogen therapy.

Tibolone

Tibolone is a synthetic steroid compound that is itself inert but, on absorption, it is converted to metabolites with mild estrogenic, progestogenic and androgenic actions. It is used in postmenopausal women who wish to maintain amenorrhoea. Classified as HRT in the *British National Formulary*, tibolone is used to treat estrogen deficiency symptoms and to prevent postmenopausal osteoporosis. The daily dose is 2.5 mg. It conserves bone mass and reduces the risk of vertebral and non-vertebral, but not hip, fractures.

Tissue-selective estrogen complex

The tissue-selective estrogen complex is a combination of a selective estrogen receptor modulator (SERM, bazedoxifene) and conjugated estrogens. It is suitable for postmenopausal women who have an intact uterus, and who are intolerant of progestogen. The SERM prevents estrogenic stimulation of the endometrium.

Delivery routes

Oral or parenteral administration

The main consideration in route of administration is whether to use oral or non-oral delivery. The latter avoids the gut and first-pass effects on the liver. After oral administration, the predominant circulating estrogen is estrone; after parenteral administration, it is estradiol.

Substances normally synthesised in the liver may be affected differentially by oral or parenteral delivery. For example, high doses of conjugated estrogens increase the production of renin substrate, although the type of substrate induced is not the one normally associated with hypertension.

The clinical significance is unclear, as blood pressure does not normally increase with this form of HRT. Oral estrogen also induces the hepatic production and release of sex hormone-binding globulin (SHBG). The route of administration may differentially affect the production of some coagulation factors and lipids and lipoproteins (Chapter 13).

Transdermal estrogens are associated with a lower risk of venous thromboembolism, stroke and gallbladder disease (see Chapter 8), although the risk with oral estrogen is still low. Furthermore, all estrogens, regardless of the route of administration, eventually pass through the liver and are recycled by the enterohepatic circulation. In routine clinical practice, therefore, either the oral or the transdermal route can be the first line of treatment, unless the woman has a specific indication to avoid oral use. This would include a perceived higher risk for thrombosis (including body mass index over 30), a pre-existing medical condition requiring minimal effect on thrombosis risk or a condition in which gut absorption may be affected. Some practitioners prefer to embark on transdermal treatment on the grounds that it more closely mimics the natural route of estrogen delivery in premenopausal women – when estrogen is delivered from the ovaries directly into the venous system. Similarly, women themselves may choose this route for the same reasons.

Non-oral routes

Transdermal patches and gels

Estradiol and progestogens can diffuse through the skin. Two transdermal systems are available: patch and gel. Most patches now use a matrix system in which the hormone is distributed evenly throughout the adhesive. This makes them amenable to cutting in half (or other variations) which can be useful in titrating doses. Patches are changed weekly or twice weekly according to manufacturer's instructions. Of the progestogens, currently only norethisterone and LNG can be delivered transdermally in patches combined with estrogen. Patch regimens of HRT are available as cyclical and continuous regimens, making them suitable for both peri- and postmenopausal women. Gel is available as estrogen only, so progestogen or micronised progesterone must be prescribed separately in women with an intact womb.

Implants

Estradiol implants are crystalline pellets of estradiol that are inserted subcutaneously under local anaesthesia and release estradiol over many

months. Implants are usually inserted every six months. Implants have the advantage that, once inserted, patients do not have to remember to take their medication. The implants achieve higher circulating estradiol levels than other treatments, which some women may find beneficial. However, the implants may continue to release estradiol for several years, which can lead to an accumulation of supraphysiological levels of estradiol, with unknown risks. Some women may also exhibit tachyphylaxis, which may be defined as a recurrence of menopausal symptoms while the implant is still releasing adequate levels of estradiol. A check on estradiol levels before reimplantation is advocated by some units, although there is no clear evidence as to what an appropriate level should be. Women with an intact uterus still need to take a progestogen and if estrogen should become contraindicated (for example, after thrombosis or hormone-sensitive cancer) the implant cannot easily be removed. There is currently a global difficulty in sourcing estradiol implants as the original manufacturer has ceased production.

Women who have undergone hysterectomy

In general, women who have undergone hysterectomy require estrogen-alone therapy and there is no requirement to add a progestogen. As combined HRT may entail a greater risk of breast cancer than estrogen alone (see Chapter 8), progestogen addition should only be considered in specific circumstances. Women who have had a subtotal hysterectomy may still have some remnants of endometrium in the cervical stump. The presence or absence of bleeding induced by monthly sequential HRT may be a useful diagnostic test and, if present, combined HRT should be used. Any unscheduled bleeding needs to be investigated. In women who have undergone pelvic clearance for extensive endometriosis, there is a risk that unopposed estrogen may reactivate residual micro-deposits. In such women, consideration should be given to using combined HRT or tibolone postoperatively to reduce this risk, at least for the first few years after surgery (see Chapter 13).

Endometrial ablation

Progestogens should usually be given to women who have undergone endometrial ablative techniques, as it cannot be assumed that all the endometrium has been completely removed – even if prolonged amenorrhoea has been achieved. Continuous combined therapy is usually sufficient.

Practical prescribing of systemic HRT

Starting therapy

Symptoms of estrogen deficiency, such as hot flushes, mood changes, tiredness, arthralgia and vaginal dryness, may start several months or years before periods stop; such a history in women older than 45 years is diagnostic of perimenopause (see Chapter 2). Amenorrhoea need not be awaited before HRT is started. For convenience, the woman should start her cyclical HRT at the beginning of a natural cycle, if present, so that the cycles are synchronised and irregular bleeding is kept to a minimum. If she has missed a few periods, she can start HRT at any time. The dose used should be sufficient to control the individual's menopausal symptoms, and control of symptoms can be used to establish the minimum required dose.

Dosage

There are generally accepted minimum bone-sparing doses of estrogen (Table 7.1). Lower doses may be sufficient to improve vasomotor symptoms and minimise the likelihood of any estrogenic adverse effects, and there is emerging evidence that lower doses may also be effective in conserving bone. In general, the lowest effective dose should be used, although young women who experience a surgical menopause may require higher than normal doses of estrogen to alleviate their symptoms. Conversely, older women maybe able to achieve symptom control with lower doses.

Table 7.1

Approximate minimum bone-sparing doses of estrogen

Estrogen preparation	Dose
Oral	1–2 mg
Patch	25–50 mg
Gel	1–2 mg (equivalent dose)[a]
Implant	25–50 mg
Conjugated estrogens	0.3–0.625 mg daily

[a] Depends on preparation: Oestrogel® (Besins Healthcare UK) 1 g/measure contains 600 µg estradiol; Sandrena® (Orion) 1 g/measure contains 1 mg estradiol

Choosing the right HRT combination

Standard cyclical HRT involves between 10 and 14 days of progestogen in a 28-day estrogen cycle, to mimic the normal menstrual cycle. Perimenopausal women should be started on cyclical therapy. No-bleed or continuous combined HRT involves continuous estrogen and progestogen. It is usually reserved for women who are clearly post-menopausal. Starting no-bleed HRT when a woman still has her own cycle may result in irregular bleeding.

Long-cycle HRT

Long-cycle HRT is continuous estrogen combined with a progestogen added for two weeks every three months. The less frequent addition of progestogen can be helpful for women who have significant adverse effects from progestogens or whose periods are becoming infrequent but who are not yet postmenopausal. However, irregular bleeding can occur during the estrogen-only phase and it is only suitable for short-term use, as prolonged use may be associated with increased risk of endometrial hyperplasia and carcinoma.

Switching to continuous combined HRT

Once a woman is postmenopausal, continuous combined therapy is recommended, as not only does it not cause any bleeding but it also reverses the small increased risk of endometrial cancer seen with more than five years of sequential therapy. Knowing when natural periods have stopped and it is suitable time to switch to continuous combined HRT is made difficult by the monthly withdrawal bleed achieved with sequential HRT. By the age of 54, 80% of women will be postmenopausal, so it is considered appropriate to switch around that time. The switching may be made earlier if it is suspected that spontaneous ovarian function has ceased. When switching to continuous combined therapy, it is advisable to complete the full cycle of sequential therapy before starting the continuous combined and warn the woman that irregular bleeding may occur in the first few months.

Managing the adverse effects of systemic HRT

Adverse effects can be related to either the estrogen or the progestogen, or both. Many of the adverse effects of HRT may be a result of the reintroduction of estrogen and/or progestogen after a period of relative lack

and may be worse after prolonged periods of hypoestrogenism. It is therefore generally recommended to start with a low-dose preparation and to discuss the possibility of early, transient adverse effects, which will usually resolve within the first few months of treatment. If unprepared for these start-up effects, some women may be alarmed and may discontinue their treatment. Persistent problems can be reviewed at the three-month follow-up appointment and the HRT dose adjusted accordingly. It is helpful to determine whether the adverse effects are estrogenic (occurring continuously or randomly throughout the cycle) or progestogenic (occurring in a cyclical pattern during the progestogen phase of sequential HRT).

Suggested management strategies that are useful in clinical practice are described below. It is helpful to consider which component of the treatment is causing the adverse effects and manage accordingly. None of these effects has been examined systematically in clinical trials, so the recommendations are based on extensive clinical experience and consensus.

Estrogen-related effects

Estrogen-related adverse effects include fluid retention, bloating, breast tenderness or enlargement, heightened nipple sensitivity, nausea, headaches, leg cramps and dyspepsia. These effects are often transient and resolve with increasing duration of use without any change in treatment. Women should be encouraged to persist with therapy for about 12 weeks to await resolution. The analogy with certain symptoms of early pregnancy may be useful. Women can be reassured and given appropriate advice to minimise these problems. Breast tenderness usually resolves with time and may be helped by the addition of gamolenic acid. Leg cramps can improve with lifestyle changes. Nausea or gastric upset with oral preparations may be alleviated by adjusting the timing of the dose or by taking the dose with food. Lactose intolerance should be considered. If the effects become persistent, options include:

- reducing the dose – the aims of treatment, such as symptom control and the prevention of osteoporosis, must be borne in mind
- changing the type of estrogen– estradiol or conjugated estrogens
- changing the route of delivery – oral, patch, gel or implant.

Progestogen-related effects

Typical progestogen-related adverse effects include fluid retention, breast tenderness, headaches or migraine, mood swings, depression, acne, lower abdominal pain and backache. Progestogenic adverse effects can be more

problematic because of the continuing need to provide endometrial protection. They are connected to type, duration and dose of progestogen. Once again, perseverance with therapy should be encouraged but difficult cases sometimes require specialist support. Useful strategies include:

- changing the type of progestogen – for example, from a 19-nortestosterone to a 17-hydroxyprogesterone derivative, or try micronised progesterone with a separate estrogen
- reducing the dose – but not below the recommended levels for endometrial protection
- changing the administration route – using transdermal, vaginal or intrauterine progestogen
- reducing the duration – progestogens are usually recommended for 10–14 days of each monthly sequential regimen. Lower durations, for example, seven days, may be considered but the potential for incomplete endometrial protection should be borne in mind.
- reducing the frequency – using long-cycle HRT that administers progestogen for 14 days every three months (this is suitable only for women with infrequent cycles and for short-term use; the long-term data suggest a possible increased risk of endometrial hyperplasia and cancer with this approach so it should be used with caution (see above)
- continuous low dose progestogen – giving the progestogen continuously allows a lower dose to be used and without the cyclical fluctuation it may reduce progestogenic adverse effects once established, but it is suitable only for postmenopausal women
- no progestogen – this is not recommended but in severe cases of progestogen intolerance can be considered with appropriate warnings and monitoring in place; hysterectomy must be considered only as a last resort
- use of tissue-selective estrogen complex (see Chapter 11).

Weight gain

Weight gain is often given as a major reason why women are reluctant to start or continue treatment. Weight gain and body fat redistribution commonly occur for many women through the menopause transition, regardless of whether or not they take HRT. Consistent weight gain (about 0.5 kg/year) is seen in women at midlife, which is associated with age and environmental factors, not menopause. While HRT may cause some shift in body fat distribution (reversing the effects of the menopause), randomised, placebo-controlled trials have repeatedly shown no evidence

of HRT-induced weight gain. Lifestyle advice should be offered to help achieve and maintain a healthy body mass index, including calorie restriction and increased exercise. Fluid retention and bloating, often associated, with the progestogen phase of treatment, should be managed as above.

Bleeding

Monthly sequential regimens should produce regular, predictable and acceptable bleeding, starting towards the end, or soon after, the end of the progestogen phase. If the bleed is prolonged or heavy, non-concordance with therapy, drug interactions (such as anti-epileptics and herbal remedies) and gastrointestinal upset, which can interfere with absorption, need to be excluded. Pelvic pathology will need to be excluded if the problem persists or does not respond to treatment (see Chapter 4). Useful strategies include:

- increasing dose or change type of progestogen in women with heavy or prolonged bleeding
- increasing dose or change type of progestogen in women with bleeding early in the progestogen phase
- changing the type of progestogen in women with painful bleeding
- changing the regimen or increase progestogen in women with irregular bleeding.

No bleeding usually reflects an atrophic endometrium and occurs in 5–10% of women but low estradiol levels, poor absorption and pregnancy should be considered in perimenopausal women or those with early ovarian failure. Breakthrough bleeding is common in the first three to six months of continuous combined and long-cycle HRT regimens but if it continues thereafter, it should be investigated as for postmenopausal bleeding (see Chapter 4).

Duration of systemic therapy

The duration of systemic therapy depends on the agreed endpoints of treatment but there is no finite limit as to how long HRT can be prescribed.

Treatment of vasomotor symptoms

Treatment with HRT may be continued for as long as it is clinically indicated, with no limitations simply because of duration of use.

Menopausal symptoms typically resolve within three to seven years, so for many women just a few years of treatment will be sufficient. Women can be reassured that this duration of treatment does not significantly increase their risk of breast cancer (see Chapter 8). However, some women continue to experience persistent troublesome symptoms for many years – even into their 70s and 80s (see Chapter 2). In this situation, the risks and benefits of continuing treatment should be assessed on an individual basis and reappraised at regular intervals taking quality of life and other risk factors into consideration. Guidance from the National Institute for Health and Care Excellence (NICE) emphasises that there is no absolute time limit on duration of therapy provided that the benefits are considered to outweigh the risks.[1]

Prevention or treatment of osteoporosis

The prevention of osteoporosis should be considered as a lifelong strategy. The role of HRT is discussed in more detail in Chapter 11. Women taking HRT for symptom relief will continue to gain skeletal benefits while they take it (provided that the dose is adequate). For asymptomatic women under the age of 60 with a low bone density and an increased risk of fracture, HRT should be considered a reasonable option that will conserve bone density for as long as it is taken. When it is discontinued, alternative preventative strategies should be implemented.

Premature ovarian insufficiency

Women who undergo an early menopause for whatever reason should be advised to continue with HRT at least until the average age of the natural menopause – that is, 51 years (see Chapter 12). Thereafter, the risks and benefits discussed in the following sections are relevant.

Stopping systemic HRT

Various strategies are used when stopping HRT, but none has been rigorously examined in clinical trials. NICE guidance suggests that the limited evidence available shows no clear advantage of stopping gradually or abruptly, although in practical terms it may make sense to reduce in a gradual way.[1] The main issue is a recurrence of menopausal symptoms, such as flushes and myalgia on stopping, as was reported by participants of the Women's Health Initiative study, who discontinued HRT suddenly. Anecdotally, older women need less estrogen to control their symptoms, and thus a lower dose can be tried before stopping. Reducing to alternate

day or even less frequent, oral treatment can be used in women who have had a hysterectomy, although there are some concerns that this could lead to irregular bleeding or insufficient progestogen in women whose uterus is intact, so this approach should be used with caution.

Longer-term treatment, in older women, should be reviewed annually and special consideration given to ensuring that each woman is on the safest and lowest dose of hormones that is appropriate for the indication for which she is taking it, especially in the over 60s. In general terms, non-oral estrogens are likely to be safer than oral estrogens and some progestogens (micronised progesterone and dydrogesterone) may have a preferred safety profile in relation to the breasts and lipids, than other progestogens.

Treatment of urogenital symptoms

For women who require relief of local symptoms only (Chapter 2) and who do not wish to take, or cannot tolerate, systemic HRT, local treatment with vaginal estrogens is usually sufficient. Treatment options include low-dose natural estrogens, such as vaginal estradiol administered by tablet or ring or estriol administered as a cream. The different preparations are:

- estradiol:
  - Estring® (Pfizer) vaginal ring (7.5 μg)
  - Vagifem® (Novo Nordisk) vaginal tablet (10 μg)

- estriol:
  - generic vaginal cream (0.01%)
  - Ovestin® (Aspen Pharma) vaginal cream (0.1%).

Systemic absorption with low-dose estradiol vaginal tablets or ring is very low and hormone levels remain within the postmenopausal range. Systemic effects are rarely seen and if the recommended topical estradiol and estriol preparations are used, there is no need to add a progestogen for endometrial protection. Vaginal estrogens can also be used in conjunction with systemic estrogens if women have refractory urogenital symptoms. NICE guidance supports the long-term use of low-dose local vaginal estrogen in women with no contraindications, without the need for progestogenic opposition or routine endometrial assessment.[1]

Androgens

There is a steady age-related decline in levels of testosterone and pre-androgens in women but the greatest decline is seen after bilateral

oophorectomy when around 50% of circulating testosterone is lost. The rest is produced via the adrenals. Up to 50% of women experience symptoms of loss of testosterone following oophorectomy, which can include low libido, low mood, loss of energy and headaches. All of these may respond to testosterone replacement, usually given in combination with an appropriate estrogen replacement. However, there are currently no licensed testosterone products for women in the UK. NICE guidance on diagnosis and management of menopause highlights options for women after oophorectomy, which includes off-label use of low doses of testosterone gels, currently only licensed for use in men.[1] Appropriate advice and warnings should be given if these products are prescribed. While some recent data have demonstrated the potential safety and efficacy of testosterone replacement in the absence of estrogen replacement and in women who have not had oophorectomy, current practice is to use testosterone replacement only in women who have had an oophorectomy and are already taking an estrogen replacement. Non-oral estrogens are preferred as oral estrogens increase SHBG production, which results in lower levels of free testosterone. The use of androgens should not be considered in isolation and additional management strategies such as vaginal estrogens, where there is vaginal dryness, vaginal moisturisers and lubricants and psychosexual counselling should be considered before and alongside testosterone replacement.

Dehydroepiandrosterone

Although there has been some recent interest in the use of the pre-androgen dehydroepiandrosterone, randomised controlled trials have shown no benefit over placebo and its efficacy and safety have not been confirmed.[2]

Bio-identical hormones

The term bio-identical literally means the product has the same molecular structure as the hormones produced in the body. In that respect, the estradiol and progesterone components of HRT are bio-identical. However, the term 'bio-identical hormone therapy' has been widely marketed as a 'natural' alternative to HRT. These products are an unregulated compounded mixture of various hormones put together in compounding pharmacies without the rigorous licensing standards which apply to normal pharmaceutical products. The Food and Drug Administration in the United States is concerned about the claims for safety, effectiveness and superiority of preparations that are made in

compounding pharmacies (Chapter 10). These products have no proven efficacy or safety and their use is not recommended. Women should be encouraged to use licensed, researched and regulated products. Those who are anxious about HRT being 'unnatural' or 'synthetic' should be reassured that the estradiol, progesterone and testosterone products used in HRT are bio-equivalent to those in the body.

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