

A Practical Guide to Prescribing Hormone Replacement Therapy

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Abstract

Over the past 20 years there has been increasing interest in the menopause and hormone replacement therapy (HRT). More recently, postmenopausal HRT has been seen as a specific treatment for symptoms in the short term and preventative therapy in the long term. Women must be counselled regarding the risks and benefits of HRT according to the best available evidence. The patient should also be actively involved in the decision regarding HRT therapy, which should then improve patient compliance.

Generally, an appropriate regimen of HRT can be formulated for the majority of patients. Progestogen should be added to therapy in women with an intact uterus in a cyclical or continuous regimen. The management of common estrogenic and progestogenic adverse effects is important in improving compliance. At present, new drugs are being developed for the management of the menopause

(selective estrogen receptor modulators and phytoestrogens). Obviously, further research will be necessary to determine whether these drugs have advantages over regular HRT.

By offering postmenopausal women HRT an attempt is made to optimise their physical and psychological well-being. However, HRT is not without adverse effects, the most worrying of which is the possible increase in breast cancer risk with long term use. However, with patient education efforts, treatment regimens acceptable to both patient and practitioner can be initiated; in this regard, the aim of the practitioner should be to help the menopausal woman make the decision which is the most appropriate for her.

Over the past 20 years there has been enormous interest in both the menopause and hormone replacement therapy (HRT). Most recently, the role of the menopause in the aetiology of major age-related disease in women has become apparent. Postmenopausal HRT can be seen as a specific treatment for symptoms in the short term and preventative therapy in the long term. The perception of the menopause as a problematic time for almost all women is changing and it seems that it is no longer viewed as a negative experience by the majority of women.^[1] Unfortunately, data from randomised, controlled clinical trials on the impact of HRT on women's health are still lacking. To this end, we await the completion of the Women's Health Initiative in the US and the Medical Research Council trial which has just commenced in the UK. Definitive answers on questions such as the possibility of increased breast cancer risk in patients on long term HRT should then be available. Until that time, treatment recommendations are based on results from observational studies.

1. The First Clinic Attendance

At initial assessment women must be counselled regarding the risks and benefits of HRT based on the best available evidence. Physical examination, which should be carried out, should include height, bodyweight, arterial blood pressure and breast and pelvic examination, including cervical smear if indicated. After discussion with the patient, a decision regarding HRT can be made. Close patient involvement in that decision will improve patient compliance.

1.1 Screening

Patients are advised to have 3-yearly mammography screening, which is offered after the age of 50 years in the UK. Older women (>64 years) are outside the screening programme and should be advised to continue with the 3-yearly screening programme.

2. Contraindications to Postmenopausal Hormone Replacement Therapy (HRT)

2.1 Absolute Contraindications

Absolute contraindications to HRT are rare, and many patients are told that they must not receive such therapy when this is not actually the case. Severely impaired liver function and acute vascular disease (including embolus and thrombosis) should be considered as absolute contraindications to HRT. Women with slight or moderate impairment of liver function may benefit from HRT as they are at higher risk of osteoporosis (due to decreased bone formation and less commonly osteomalacia) as well as elevated cholesterol (especially cholestatic liver disease).^[2] Women who are heterozygous for mutant factor V Leiden (approximately 6% of Caucasian women) have a 5-fold increased risk of thrombosis (primarily venous). With the addition of HRT, the risk of thrombosis is increased to 50 times that of the general public and is also associated with osteonecrosis.^[3,4] If fasting triglyceride levels are >500 mg/dl, estrogens should be avoided as the risk of acute pancreatitis is very high.^[5]

2.2 Relative Contraindications

Close surveillance is indicated for patients with familial hyperlipidaemias and migraine headaches. Patients with migraine headaches often have reduced symptoms if a daily continuous combined estrogen/progestin HRT is used, eliminating a cyclic change in hormone levels that may trigger headaches. Serum lipid changes due to HRT administration are discussed in section 3. Conditions that do not represent contraindications include controlled hypertension, ischaemic heart disease, otosclerosis, obesity, benign breast disease, diabetes mellitus and varicose veins.

2.2.1 Venous Thromboembolism

Three studies published in a recent issue of *The Lancet*^[6-8] suggested that postmenopausal HRT was associated with a 2- to 3-fold increased risk of venous thromboembolism. When a venous thrombotic episode is related to trauma, prolonged bed rest or surgery, estrogen therapy is well tolerated. However, the risk in women with either a past history of spontaneous thromboembolism or thromboembolism in association with oral contraceptive use is not known. Investigations to exclude inherent coagulation abnormalities (these include antithrombin III, protein S and protein C resistance) should be followed by a careful assessment of individual risks and potential benefits before commencing estrogen therapy. If protein C resistance is abnormal, screening for mutant factor V Leiden trait, which is the most common cause of venous thromboembolism in Caucasian women, should be done.

2.2.2 Patients with a Past Medical History of Cancer

Hysterectomised women who have had stage I adenocarcinoma of the endometrium may use estrogen therapy without fear of recurrence, but the combination of estrogen-progestin is recommended in view of the potential protective action of the progestin.^[9] There are no data about the risk in women with more advanced disease. However, if the tumour is estrogen receptor-positive, a period of approximately 5 years without recurrence

of the cancer may indicate that hormone therapy can be used. However, even after this time period it would be difficult to actually confirm that there would be no risk of recurrence and that HRT administration would be problem-free. A similar approach should be used in patients previously treated for endometrioid tumours of the ovary.

In patients with previously treated breast cancer there is a lack of epidemiological evidence on the effects of HRT. Two small series in which women with previously treated breast cancer were given HRT indicated that the recurrence rate was no greater than expected for the stage of their disease.^[10,11] However, with only limited data available these patients must take an unknown risk if they want the benefits of HRT. Tamoxifen may be considered as an alternative to HRT for women with a history of breast cancer due to its antagonism of estrogen action on the breast combined with its agonistic estrogenic actions in other tissues. Tamoxifen is associated with estrogenic effects on bone density and cardiovascular disease but the impact may not be equal to that of hormone treatment in postmenopausal women.^[12,13] Vasomotor symptoms occur in 25% of women on tamoxifen and may actually be exacerbated by this treatment.^[13]

3. Methods of HRT

Until data become available documenting the degree of impact of the various routes of administration on actual clinical events (fractures and cardiovascular disease), it would seem reasonable to select an oral programme which has epidemiological support. Oral estrogen is subject to first-pass metabolism in the liver; therefore, subcutaneous or transdermal administration more closely reflects endogenous hormone activity. It is now thought that the correct oral dose has no effect on arterial hypertension; therefore, the transdermal method is of no benefit with regard to safety in hypertensive patients and is also less cost effective.^[14,15] Because estrogen increases triglyceride levels, women with elevated triglycerides should be treated with an estrogen-progestin combination

(progestins lower triglycerides) with monitoring of triglyceride levels. If fasting triglyceride levels increase to ≥ 2.8 mmol/L, a non-oral route of administration should be considered. Oral administration would be preferred in women with hypercholesterolaemia as it is less expensive and has epidemiological support while transdermal therapy may have theoretical advantages in cholestatic liver disease.

3.1 Patches or Tablets?

Oral estrogen is the most commonly used form of HRT in the UK. However, many women prefer the patch regimen and it has become increasingly popular although it is more expensive. The estrogen is delivered through the skin at a constant rate and is absorbed into the circulation. The patch must be changed once or twice weekly and some women find this regimen easier to comply with than a daily oral treatment. The older transdermal reservoir patches contain 17β -estradiol dissolved in alcohol in a circular, multilayered patch with an outer impermeable membrane. The drug reservoir delivers estradiol to the skin surface at a fixed rate determined by the patch area. As the alcohol medium becomes absorbed, the estradiol absorption from the patch decreases, so the patch needs to be changed after 3 to 4 days. Skin irritation has occurred in approximately 5% of women and may be minimised by changing the patch application site.

However, the newer matrix patches appear to produce less skin irritation. They are applied directly to the skin with alcohol-free adhesive. They are available in a variety of strengths that release from 25 to 100 μ g of estradiol per 24 hours, which allows greater flexibility for treatment. Many postmenopausal women have problems with estrogenic adverse effects and therefore it may be beneficial to commence treatment with lower doses before increasing to therapeutic levels. Alternatively, in younger women following a surgical menopause, higher estrogen doses may be required initially to provide symptomatic relief. Progestogens are also available in a patch form and can be

administered in a sequential or continuous method combined with the estrogen patches.

3.2 Percutaneous Estrogen

The administration of percutaneous estrogen can be accomplished by application of an alcohol-based gel to the skin over the abdomen or thighs. The preparation is packaged in a canister which dispenses 1.25mg of gel containing estradiol 0.75mg. The daily dose is 2 measures delivering estradiol 1.5mg, which produces blood concentrations of estradiol ranging from approximately 350 to 450 pmol/L (higher and more variable than those obtained with standard oral regimens). Usually this dose gives good symptomatic relief; however, there are no available data on prevention of osteoporosis or cardiovascular disease. It may also be useful for the management of patients with implants who have tachyphylaxis until they are weaned off the implants.

3.3 Local Estrogen

Local estrogen preparations are useful for relieving symptoms due to urogenital atrophy. They are often administered before vaginal surgery to improve healing in those women with epithelial atrophy. A variety of preparations is available, such as creams and pessaries, and this use should reflect both the woman's personal preference as well as her ability to administer the preparation. The creams do produce pharmacological estrogen concentrations in the systemic circulation; therefore, women with an intact uterus will require progestogen for 10 to 14 days each month to provide endometrial protection. Vaginal tablets, containing estradiol 25 μ g in disposable applicators, can be inserted using a regimen of 1 tablet daily for 2 weeks followed by 1 tablet twice weekly for 3 months. They appear to have a negligible systemic absorption, so that endometrial hyperplasia does not appear to be a problem.

Some women find the creams and pessaries messy and inconvenient. An alternative is Est-ring[™], which is a silicone ring impregnated with estradiol, delivering 7.5 μ g per 24 hours and lasting

for 3 months. It can be easily inserted and removed by the patient. It provides improvement in vaginal dryness and urogenital symptoms. However, there is little or no useful systemic absorption of the estrogen.

3.4 Estradiol Implants

Estradiol implants are available in doses of 25, 50 and 100mg for subcutaneous administration twice yearly. The implants are usually inserted into the subcutaneous fat of the lower abdominal wall or the upper outer quadrant of the buttock. It is an easy, quick and painless procedure carried out under local anaesthetic. Complications are rare, with the most common being bleeding at the insertion site a few hours after implantation. There may be some bruising and occasionally the implant may become surrounded by fibrous tissue and blood clots, forming a palpable lump. This may lead to a slower release of the hormone. Infection at the implantation site is extremely rare, as is implant extrusion.

The 25mg implant provides blood concentrations in the range of 150 to 220 pmol/L, which is comparable with concentrations obtained with the standard oral dose.^[16] However, the effect is cumulative and after several years the measured blood concentrations are 2 to 3 times those obtained with an oral regimen. In nonhysterectomised women progestins are required for 14 days each month. Some women request repeat implants for symptomatic relief at increasingly frequent intervals although their hormone levels are in the premenopausal range or above.^[17] This is caused by falling estrogen concentrations rather than a deficiency of estrogen. This tachyphylaxis is the major drawback to implant therapy. Pretreatment counselling and monitoring of estradiol concentrations before implant insertion may decrease its incidence. If the estradiol concentrations are high a further implant should be postponed and the patient treated with estrogen gel or patches until the concentrations fall. It may well be more suitable to wean these patients off the implants altogether and commence them on an alternative form of estrogen therapy.

These patients are very difficult to manage as they often experience severe vasomotor symptoms.

3.5 Testosterone Implants

Testosterone implants are available in 100mg and 200mg sizes. After menopause the circulating levels of androstenedione and testosterone are decreased by approximately 50%. Androgen therapy may improve psychological well-being and libido but these effects have only been shown at high doses.^[18] Any benefit must be balanced against the negative effects of such high androgen doses, such as an adverse effect on the lipoprotein profile. The implant is inserted in a similar way to the estradiol implant every 6 months, starting with a 100mg dose. Complications following implantation are infrequent. However, rejection and extrusion of the implant occur in 1% of patients. Adverse effects such as hirsutism or acne are rare.

3.6 Tibolone

Tibolone is a synthetic progestogen which combines estrogenic and progestogenic activity with weak androgenic activity. It does not stimulate the endometrium, and therefore does not cause a monthly bleed. It is suitable for women who are at least 12 months past the menopause. If used in the premenopause stage it may cause irregular vaginal bleeding. It relieves vasomotor symptoms and protects against the development of osteoporosis but has not been shown to be cardioprotective. Adverse effects, such as headaches, dizziness, bodyweight gain and mild androgenic effects, are usually minimal. If patients are switched to tibolone from an estrogen/progestogen regimen, irregular vaginal bleeding may occur.

4. Alternative Treatments for Vasomotor Symptoms

Clonidine,^[19] bromocriptine and naloxone given orally are only partially effective for the relief of vasomotor symptoms and require high doses with resultant adverse effects. Methyldopa, in doses of 250 to 500 mg/day, has some effect but

there have been no randomised controlled clinical trials with this drug in this indication. Propranolol appears to be ineffective.

5. Treating the Healthy Woman Who Wants HRT

Patients can conveniently be grouped into those with and without an intact uterus.

5.1 Patients with a Uterus

Estrogen normally promotes mitotic growth of the endometrium. One year of treatment with unopposed estrogen will produce a 20% incidence of endometrial hyperplasia.^[20] Abnormal progression of growth through simple hyperplasia and atypia to early carcinoma has been associated with unopposed estrogen. The endometrium can be protected by the addition of progestogen for a minimum of 10 days per month^[21] or continuously. Patients who are less than 1 year postmenopausal can take cyclical progestogen for 10 to 14 days each month with continuous estrogen; problems with this sequential regimen include mastalgia, bloating, fluid retention and depression. However, compliance remains poor because of fear of cancer and failure to tolerate monthly withdrawal bleeding, which occurs in 90% of cases.^[22] A recent alternative is a new regimen of estradiol valerate 2mg for 84 days with 20mg medroxyprogesterone (medroxyprogesterone acetate) added for the last 14 days. This produces withdrawal bleeds every 3 months and may be useful in those women who wish to have less frequent withdrawal bleeds but are not suitable for a continuous combined regimen.

The continuous/combined method of treatment evolved to improve patient compliance by avoiding a monthly withdrawal bleed and is most suitable for women who are at least 1 year *post* menopause. The continuous presence of progestin allows the use of lower doses which will often ameliorate progestogenic adverse effects. Light bleeding or spotting occurs in 40 to 60% of patients in the first 6 months of treatment but this decreases to approximately 20% after 1 year of use.^[23] Women should be counselled to anticipate this bleeding and

encouraged to continue on treatment. However, if bleeding persists after the first 6 months of treatment, hysteroscopy can be performed to exclude endometrial pathology. Unfortunately, there is no effective method of drug alteration to manage such breakthrough bleeding, which is a frequent cause of poor HRT compliance.

It is also important to establish that the woman is not perimenopausal as residual endogenous ovarian activity can cause irregular bleeding. The date of the last natural menstrual period may be difficult to determine, especially if the woman has been having regular withdrawal bleeds on a sequential HRT. Follicle-stimulating hormone (FSH) levels are of little value as they often fluctuate markedly in the perimenopause. If there is clinical doubt that a woman is in fact menopausal, and she presents with breakthrough bleeding, she should be changed to sequential HRT for at least a year before restarting the continuous combined HRT.

Unfortunately, there remains a group of patients who continue to bleed. This is more likely to occur if a patient is having withdrawal bleeds either because she is still perimenopausal or has been taking a sequential HRT preparation. For this small number of patients who have persistent breakthrough bleeding it may be more acceptable to the patient to return to sequential HRT in order to have a regular withdrawal bleed instead of irregular bleeding.

5.2 Treating the Hysterectomised Woman

Patients who have undergone hysterectomy are usually commenced on unopposed estrogen therapy. There is no evidence at present to suggest that one form of estrogen is superior to another. The specific estrogen is not as important as the duration and dose of treatment. Exogenous estrogens may be delivered orally or parenterally. Transdermal administration of an estradiol patch of 50µg twice a week is as effective on bone density and lipids as oral conjugated estrogens 0.625mg.^[24,25] The ability of these methods to produce short term benefits such as symptom relief or long term benefits is related to the plasma concentrations achieved.

However, there are some conditions which warrant a combined estrogen-progestin regimen in hysterectomised women, such as stage I adenocarcinoma of the endometrium or previously treated endometrioid tumours of the ovary. If the women have a history of endometriosis, a combined estrogen-progestin regimen is recommended to prevent potential cancer development in residual or recurrent lesions exposed to unopposed estrogen. Hysterectomised women at high risk for osteoporosis also benefit from the combination of estrogen and progestin, as this has a greater positive impact on bone density than estrogen alone.

6. Managing Common Adverse Effects

6.1 Progestogenic Adverse Effects

Progestogen treatment may cause breast tenderness, a bloated feeling, nausea and abdominal cramps. Psychological complaints are often similar to the symptoms of premenstrual syndrome (PMS) of younger women and include depression, anxiety and irritability. The C19 nortestosterone derivatives (norgestrel and norethisterone) seem to have a higher risk of adverse effects than the less androgenic C21 derivatives (medroxyprogesterone and dydrogesterone).

Some patients can alleviate adverse effects by taking the progestogen in divided daily doses or at bedtime. It may be of value to change from one type of progestogen to another or to reduce the dose (as in continuous combined regimens). The newer progestogens, such as gestodene or desogestrel, may well produce fewer adverse effects. In women with heavy withdrawal bleeding or breakthrough bleeding, endometrial resection may eliminate or reduce the bleeding. Another option deserving consideration is the progestin intrauterine device. The local release of progestin provides endometrial protection and avoids the systemic adverse effects of progestogens. Hysterectomy may also be a valid option for women who need estrogen therapy but are unable to tolerate progestogens.

6.2 Estrogenic Adverse Effects

Estrogenic adverse effects such as breast tenderness/enlargement, leg cramps, bloating, nausea and headache may adversely affect compliance. In the majority of cases these adverse effects resolve with time (usually within 2 months) and the women should be supported and encouraged to remain on HRT. Evening primrose oil capsules can help alleviate breast symptoms and bloatedness.^[26] The estrogen dose can be reduced or the route of administration altered. It may also be beneficial to change the type of estrogen administered. In older women especially, it can be of value to commence therapy with a low dose regimen, increasing the dose slowly to the required level.

7. Prolonged Usage of HRT

There is an increasing number of women who have been on HRT for more than 10 to 20 years. There would appear to be no contraindication to allowing these patients to continue on treatment. However, they should be advised that there is evidence suggesting a relationship between duration of use and breast cancer risk. A recent report^[27] suggests there are an extra 12 cases of breast cancer by the age of 70 for every 1000 women who start taking hormones at the age of 50 and continue to do so for 20 years. When counselling women about these risks it is important to balance them against the impressive evidence on the long term benefits of HRT against osteoporosis and cardiovascular disease: estrogen therapy will stabilise the process of osteoporosis or prevent it from occurring^[28], and this reduction is primarily seen in women who take estrogen for more than 5 years. Postmenopausal HRT appears to reduce the incidence of coronary heart disease by 40% or more.^[29]

8. The Future

At present 2 groups of new drugs are being developed for the management of the menopause: selective estrogen receptor modulators (SERMs) and phytoestrogens. SERMs include such agents as raloxifene and droloxifene, which were previously

called antiestrogens. These drugs bind to the estrogen receptor and have both agonistic (estrogenic) and antagonistic (antiestrogenic) actions in certain tissues. The bone and arterial effects of these drugs would indicate estrogenic activity whereas their antiestrogenic effects would prevent endometrial proliferation and stimulation of breast tissue.^[30] The phytoestrogens are compounds derived from plants and have a weak affinity for the estradiol receptor compared with estradiol itself. They appear to compete with estradiol for the estrogen receptor and have both agonistic and antagonistic actions.^[31]

9. Conclusion

By offering postmenopausal women HRT an attempt is made to optimise their physical and psychological well-being. However, this treatment is not without adverse effects, the most worrying of which is the possible increase in breast cancer risk with long term use. Patients must be advised and educated as to the risks and benefits of HRT such that a rational treatment plan, acceptable to both patient and practitioner, can be agreed upon. Only then will the opportunity for optimal treatment benefits from HRT present itself.

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Errata

Vol. 54, No. 4, page 574: In figure I, the dosage of furosemide in the 'Ascites grade 3' and 'Refractory ascites' columns should read 40-160 mg/day and 160 mg/day, respectively.

[Bataller R, Ginès P, Arroyo V. *Practical recommendations for the treatment of ascites and its complications*. *Drugs* 1997 Oct; 54 (4): 571-80]

Vol. 55, No. 6, page 762: In the first paragraph of section 2.2, some reference citations were inadvertently omitted. Lines 8 to 16 of that paragraph should read: 'Early clinical studies with live oral heterologous (bovine or rhesus) vaccines showed good efficacy against severe rotavirus gastroenteritis in Scandinavia and the US,^[15,16] but the protection was insufficient in developing countries.^[17] Therefore, these vaccines were not developed further. Similarly, human rotavirus (neonatal) strains also failed to induce protection against diarrhoeal illness when used as vaccines.^[18]'

[Eskola JJ. *Childhood immunisation today*. *Drugs* 1998 Jun; 55 (6): 759-66]