

Principles of management of the menopause

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Abstract

The decision to treat a postmenopausal woman with hormone replacement therapy should be made on an individualized basis. The major indications for treatment are either the presence of acute menopausal symptoms or to provide prophylaxis against the long term risk of developing either osteoporosis or cardiovascular disease. Women without a uterus may be treated with oestrogen alone, but those with an intact uterus should receive regular progestogens to protect the endometrium against the development of hyperplastic changes. Oestrogens can be administered orally, as a transdermal patch or a percutaneous gel, by subcutaneous implants or by vaginal tablets or creams. Progestogens are usually prescribed in an oral form. Natural oestrogens taken in low doses are associated with minimal side effects and there are few absolute contraindications to their use.

Keywords: Menopause; Hormone replacement therapy

Introduction

Differences in approach to the menopause and the prescription of hormone replacement therapy (HRT) to postmenopausal women have been shown to exist between populations. A recent survey amongst four European countries demonstrated a variation in current use of HRT which ranged from 3% of postmenopausal Italian women to 25% of German women.¹ The administration of HRT is influenced by the severity of symptoms in the postmenopausal population and also by the awareness of both patients and doctors of the potential reduction in the incidence of osteoporosis^{2,3} and cardiovascular disease^{4,5} that HRT may provide.

Factors influencing the decision to prescribe HRT

Of major importance in determining whether a postmenopausal woman is prescribed HRT is the attitude and level of knowledge of the medical practitioner towards the menopause and the therapeutic options available.⁶ Extremes of opinion exist, with some medical practitioners regarding the menopause as a physiological event for which reassurance

should be provided, whilst others treat it as an endocrine disease and use long term hormone replacement in all cases except those where an absolute contraindication to treatment exists. A balance of these opposing views and an individualized approach to treatment is more reasonable.

There are now few absolute contraindications to the use of HRT,⁷ with natural oestrogens being prescribed in low doses having far fewer metabolic side effects than the synthetic oestrogens used in oral contraceptives.

Routes of administration of HRT

In the majority of cases, the choice of route of administration of oestrogen can be determined according to the preference of the patient. Oestrogens may be administered orally, or as a percutaneous gel, a transdermal patch, a subcutaneous implant or as vaginal tablets or cream. The non-oral routes avoid the 'first pass' effect on the liver, and this form of administration may be more suitable when there is glucose intolerance or a history of thromboembolism, or in the few cases where hypertension develops whilst taking HRT. For the majority of women, however, the method of administration is unimportant, and allowing them to choose the method themselves is likely to result in greater compliance.

(1) Oral administration

Oral oestrogens are available in either synthetic or

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natural form. The synthetic oestrogens are more potent, and use is made of this in oral contraceptives to suppress ovulation. The synthetic oestrogens have greater metabolic side effects, and are now infrequently used for HRT. The natural oestrogens are oestradiol, oestrone and oestriol. Conjugated equine oestrogens are also usually included in this category.

Oral oestrogens are easy for the patient to administer, and have a short half life. Their hepatic effects produce a beneficial change in cholesterol and lipoprotein levels, but they may also have the opposite effect on triglycerides,^{8,9} although other studies suggest no change¹⁰ or a lowering of triglyceride levels.¹¹ Compliance may also be a problem, with nausea and breast tenderness being the most common complaints at the commencement of treatment. Oral oestrogens produce wider fluctuations in plasma levels than is associated with the parenteral route.¹² Although the risk may be more theoretical than actual, the non-oral route may be preferable for patients with abnormal glucose tolerance or those at risk from thromboembolic disease.¹³

(2) The transdermal patch

The patches are usually applied to the lower abdomen, buttocks or thighs, being changed alternately every third and fourth day. Skin reactions are not uncommon,¹⁴ and are more severe in warmer and more humid climates. The patch has little effect on lipids and lipoproteins,¹⁵ and may be preferable to oral treatment if triglyceride levels are elevated.

(3) The percutaneous gel

The gel is supplied in 80 g tubes, one of which lasts approximately one month. The tube is supplied with a spatula containing a groove upon which the daily dose can be measured. The gel is applied to the skin away from the breasts or vulva, and takes three to four minutes to become properly absorbed. Dermatological side effects are uncommon, but if the gel is not rubbed well into the skin, some transfer onto clothing may occur. Effects on lipids and triglycerides are similar to those of the transdermal patch.

(4) Subcutaneous implants

The implants are supplied as 25, 50 or 100 mg pellets, and are usually inserted beneath the skin of the lower abdomen under local anaesthesia. The duration of action is stated to be from four to eight months, but depot release may occur over longer periods of time. It is difficult to accomplish abrupt withdrawal of treatment using this route of administration.

(5) Vaginal administration

The vaginal route is usually less acceptable to women

than the methods mentioned above, and absorption may not be as reliable. Despite the introduction of vaginal tablets as an alternative to vaginal creams, this method of administration is infrequently used as a form of HRT. The vaginal route is still commonly used to treat local symptoms, but it should be remembered that systemic absorption will occur, which increases as the mucosa becomes less atrophic.

The prescription of progestogens

Progesterone is the only natural progestogen, and the synthetic progestogens may be classified into either those structurally resembling progesterone, or those related to testosterone. Oral progesterone is rapidly metabolized, and must be given in high doses to produce the required effect on the endometrium. In these doses drowsiness is a frequent side effect. For those women who have not had a hysterectomy, a progestogen should be added to the oestrogen regimen for 12 days each month to prevent hyperplastic changes from developing in the endometrium due to the effect of unopposed oestrogen administration.¹⁶ The addition of progestogens has been shown to have little effect on the beneficial influence of oestrogen on the cardiovascular system,^{17,18} and some studies have suggested that the addition of progestogens may lead to a replacement of osteoporotic bone.¹⁹ Epidemiological evidence concerning the effect of progestogens on breast tissue is contradictory,²⁰ and in view of the uncertainty, it would seem wise to withhold progestogens in those women who have had a hysterectomy.

Treatment regimens

Oestrogens may be administered in a continuous or a cyclic manner. For those women who have had a hysterectomy, continuous rather than cyclic treatment is likely to produce the best compliance, and there is no physiological reason why the treatment needs to be interrupted. In some cases, such an interruption can result in the recurrence of distressing vasomotor symptoms.

For those women with an intact uterus, cyclic administration of a progestogen for 12 days each month is recommended. This may be prescribed for the first 12 days of each calendar month, or may already be included with an oestrogen in a pack similar to those used for oral contraceptives. If prescribing progestogens on a cyclic basis in an HRT regimen, it is important to write clearly that the tablets should be taken on the first 12 calendar days of the month rather than the first 12 days of each cycle, otherwise irregular bleeding may occur. Withdrawal bleeding will

occur in approximately 80% of cases using 12 days of a progestogen each month. The absence of withdrawal bleeding is not an indication for endometrial biopsy.

Two other treatment options are suitable for those women who have been menopausal for some years at the time of commencement of treatment. Neither of these methods of treatment tend to stimulate the endometrium sufficiently to cause withdrawal bleeding, and this factor is usually attractive to postmenopausal women who are often reluctant to commence a treatment which will cause the resumption of menstrual bleeding. If these methods are instituted too close to the perimenopausal period, however, irregular bleeding may be a problem.

The first of these methods is a continuous combined regimen of oestrogen and progestogen. The oestrogen is given in a standard dose, but usually a lower dose of the progestogen can be used than in a cyclic regimen (e.g. 2.5 or 5 mg of medroxyprogesterone acetate rather than 10 mg). If irregular bleeding occurs, it may be worthwhile changing to a twice daily dose of the progestogen before discontinuing treatment. Otherwise, if the patient is willing to persist, amenorrhoea is likely to occur within eight months of commencing the continuous combined regimen.

A newer drug, tibolone, is weakly oestrogenic, progestogenic and androgenic, and is effective in reducing menopausal symptoms and preventing bone loss²¹ without initiating withdrawal bleeding. It has also been shown to have beneficial effects on the lipid profile.²² Its main disadvantage is that it is more expensive than the other methods of treatment previously described.

HRT — relative and absolute contraindications

(1) Breast carcinoma

There is no data to support the suggestion that a history of carcinoma of the breast is an absolute contraindication to treatment. However, given that the risk of a postmenopausal woman developing breast carcinoma with prolonged use of oestrogens is slightly higher than that of the background population, it would seem logical to withhold treatment in these women. If, however, symptoms are severe, and the disease has shown no evidence of recurrence after a period of years, then HRT may be considered in selected cases after appropriate counselling. Studies are in progress in other countries which are evaluating the use of HRT in women who have a past history of breast cancer but have been disease free for at least five years.

(2) Endometrial carcinoma

In the limited studies available, no increase in the risk

of recurrence of endometrial cancer has been demonstrated in those cases where HRT was prescribed after adequate treatment of the disease in its early stages.²³ However, as with breast cancer, there are many who would regard treated endometrial cancer as an absolute contraindication to treatment.

(3) Ovarian and cervical carcinoma

There is no evidence that HRT has any effect on either of these malignancies, and HRT may be used for patients who have been treated for these conditions.

(4) Thromboembolic disease

Unlike the data for the oral contraceptive, oestrogen replacement therapy has not been shown to increase thromboembolic risk in the normal population.^{17, 24} There are no studies on whether the risk is increased in that group of women who are predisposed to this condition. If HRT is to be used in a woman who is at risk, then the non-oral route should be used.

(5) Diabetes

Both oestrogen and progestogens can alter glucose tolerance, although low dose natural oestrogens have little effect on carbohydrate metabolism. Diabetics can be prescribed HRT, and in view of their increased cardiovascular risk, many would regard it as an important part of their management. Insulin dosage should be more carefully monitored in the first few months of treatment until the HRT dose has been fixed.

(6) Gallstones

Oral oestrogens should be used with care in patients with gallstones, and this is another condition where the non-oral route is preferable.

(7) Otosclerosis

Otosclerosis has been shown to worsen during pregnancy²⁵ but to date there is only anecdotal evidence that it may progress in women using HRT.

(8) Epilepsy

Anticonvulsant drugs, apart from sodium valproate, enhance oestrogen metabolism by increasing glucuronidation in the liver.²⁶ The choices, therefore, are sodium valproate with an oral oestrogen or else parenteral oestrogen with one of the other anticonvulsants.

Individualizing treatment

Whilst vasomotor symptoms are common accompaniments of both a physiological and a surgical

menopause in Caucasian women,^{27, 28} studies quoted in the article on menopausal symptoms in this issue of the Journal, as well as those conducted within our own Department, have demonstrated that hot flushes and sweating occur less frequently amongst Chinese women in Hong Kong. Nevertheless, there are still many women who suffer distressing vasomotor symptoms, and there is clear evidence that the majority of these women benefit from the administration of oestrogens.²⁹ If acute menopausal symptoms are the major complaint, then in the absence of absolute contraindications, HRT should be administered. The duration of treatment will depend upon patient preference and the presence of other risk factors. For the individual who has only a small risk of developing cardiovascular disease, who has good bone density and who prefers not to be using any treatment, then after two years the HRT may be slowly withdrawn, although these symptoms may persist for more than five years in over 25% of women.²⁷

In the absence of symptoms, the current level of education received by the majority of women in Hong Kong makes it unlikely that they will present requesting prophylaxis against the long term complications of the menopause. The attitude and level of education of the medical practitioner is then of major importance in providing satisfactory counselling for the patient so that she can decide whether to initiate treatment. Whatever method of administration is chosen by the patient, there will be some degree of inconvenience caused through taking the medication, and the degree of inconvenience will be greater if she still has a uterus and must also receive a progestogen. Withdrawal bleeding on a combined regimen of treatment may be inconvenient enough to interfere with compliance or to cause the cessation of treatment altogether. If the patient has no postmenopausal symptoms, she should still be advised of the potentially beneficial effects of HRT on bone metabolism and on the cardiovascular system. Her risk of developing osteoporosis may be assessed according to various lifestyle factors, and her bone density may be measured quantitatively in a non-invasive manner. Her cardiovascular risk can also be judged on the basis of lifestyle factors and family and past medical history. Measurement of cholesterol and lipoproteins will also assist in determining whether to proceed with treatment. In some cases, the medical practitioner may choose to provide a greater influence on the patient's decision. For a woman who has had either a premature physiological or surgical menopause, in the absence of absolute contraindications, she is likely to benefit in the long term from HRT administration. In these cases, counselling is especially important, as a young asymptomatic woman may find it difficult to understand why she is being persuaded to begin a prolonged course of hormonal

treatment. On the other hand, few would advocate the use of HRT for a woman with a past history of breast cancer, and the presence of a relative contraindication to treatment will also influence the final decision.

In summary, by balancing the severity of symptoms and the risk factors for osteoporosis and coronary artery disease against inconvenience and possible side-effects of treatment, it is possible for a well informed postmenopausal woman to come to decision about whether she wishes to embark upon a long term course of treatment. HRT should be offered to all postmenopausal women, and the decision to proceed with this treatment should be made after consideration of the relative advantages and disadvantages in each individual case.

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