HRT - initial consultation

The publicity that has accompanied studies, including the Women's Health Initiative (WHI) and the Million Women Study (MWS), and the results of a 2019 systematic search published in the Lancet, has understandably led to many women being concerned about the potential risks of hormone replacement therapy (HRT).[1] [2] [3]

It is therefore very important to explore a woman's fears and understanding of the menopause and her expectations for HRT.

See also the separate Menopause and its Management, Hormone Replacement Therapy (including Benefits and Risks), HRT - Follow-up Assessments and HRT - articles.

The following outlines assessment and discussion points in an initial consultation about HRT.

Patient assessment

History

- Confirm the menopause if possible, as the diagnosis is usually clinical.
- Discuss the symptoms being experienced - consider whether they are likely to respond to HRT. Establish how much they are affecting the woman's life.
- Bleeding - ask whether the woman is still having periods. If not, ask when her last period occurred. The majority of women notice irregularities in their cycle around the menopause: the cycle may lengthen to many months or shorten to 2-3 weeks; a slight increase in the amount of menstrual blood loss is common.

- Postmenopausal bleeding is vaginal bleeding occurring after 12 months of amenorrhoea and needs urgent investigation. Enquire about postcoital bleeding. Any abnormal bleeding pattern should be investigated before starting HRT.
- Age:
    - The average age of the menopause in the UK is 51 years.
    - To have a menopause up to five years younger or older than this is within the normal range.
    - Early menopause relates to those women aged <45 years.
    - Premature ovarian insufficiency occurs in women aged under 40 years.
- Uterus - cyclical progestogen must be added for those women who have not had a hysterectomy, to prevent endometrial cancer.
- Explore risk factors for osteoporosis, breast cancer and coronary heart disease (CHD).

Examination

- Blood pressure.
- Height and weight.
- Other examination as indicated by the history (routine vaginal/bimanual examination is not required).

> Women who would like HRT but have a contra-indication to it, such as current breast cancer, should be referred for specialist advice.

Health promotion

There is some evidence that healthy lifestyle behaviours can improve vasomotor symptoms.[4] In addition, weight loss, mindfulness and cognitive behavioural therapy can have a mild-to-moderate effect on these symptoms.[5]

Discuss with women any modifiable risk factors for cardiovascular disease, such as alcohol, smoking, diabetes and hypertension control.

Take the opportunity for health promotion and offer lifestyle advice:

- Smoking and alcohol.
- Diet and exercise.
- Check cervical smear is up to date.
- Discuss breast self-examination and breast cancer screening.

HRT and comorbidities[6]

Offer hormonal, non-hormonal, or non-drug treatment options depending on the risks, benefits, adverse effects, and contra-indications. If there is any uncertainty about appropriate management, seek specialist advice from a healthcare professional with expertise in menopause or refer to the relevant specialist team.

Women with, or at high risk of, breast cancer

- Stop systemic HRT in women who are diagnosed with breast cancer.
- Do not offer HRT routinely to women with menopausal symptoms and a history of breast cancer.
- Seek specialist advice if a woman wishes to consider the use of hormonal therapy, such as treatment with low-dose vaginal oestrogen.
- Advise on lifestyle measures, and non-hormonal and non-drug treatment options for symptom relief.
- Advise that women taking tamoxifen should not use fluoxetine or paroxetine, as they may inhibit the effect of tamoxifen.
- Do not recommend the use of isoflavones, red clover, black cohosh, vitamin E, or magnetic devices to treat menopausal symptoms in women with breast cancer.
- St John's wort may interact with other drugs such as tamoxifen, anticoagulants, and anticonvulsants. In addition, there is uncertainty about the appropriate dose, and possible variation of potency of over-the-counter preparations.

Women with increased risk of venous thromboembolism (VTE)

- Consider the use of transdermal rather than oral HRT for women at increased risk of VTE, including women with a BMI over 30 kg/m^2.
- Consider referring women at high risk of VTE (eg, strong family history of VTE or a hereditary thrombophilia) to a haematologist for assessment before considering the use of HRT.

Women with increased risk of cardiovascular disease (CVD)

- Manage any cardiovascular risk factors before considering the use of HRT.
- The presence of cardiovascular risk factors is not a contra-indication to taking HRT as long as they are optimally managed.
- Consider the use of transdermal rather than oral HRT for women at increased risk of CVD.

Women with type 2 diabetes

- Consider the use of HRT after taking any other comorbidities into account.
- HRT is not associated with an adverse effect on blood glucose control.

Women with hypothyroidism

Thyroid-stimulating hormone (TSH) levels should be monitored regularly (for example, 6-12 weeks after starting oral HRT), to ensure that levels remain in the acceptable range, as the dose of levothyroxine (LT4) medication may need to be increased.

Investigations before starting hormone replacement therapy[6] [7]

Blood tests such as follicle-stimulating hormone (FSH) are not routinely required to diagnose perimenopause or menopause in otherwise healthy women (who are not using hormonal contraception) aged over 45 years, with typical menopausal symptoms.

Serum FSH measurements may be considered (provided not taking combined hormonal contraception or HRT) if:

- Aged over 45 years with atypical symptoms.
- Aged 40-45 years with menopausal symptoms, including a change in menstrual cycle.
- Younger than 40 years with a suspected diagnosis of premature ovarian insufficiency.
- Over 50 years of age using progestogen-only contraception, including depot medroxyprogesterone acetate (DMPA).

If the FSH level is in the premenopausal range, the woman should continue contraception and the FSH level should be rechecked in one year.

The Faculty of Sexual and Reproductive Healthcare (FSRH) states that a single elevated serum FSH level (more than 30 IU/L) indicates a degree of ovarian insufficiency, but not necessarily sterility.[8]

The British Menopause Society (BMS) recommends checking for an elevated FSH level on two blood samples taken 4-6 weeks apart.

Investigations may also be necessary before starting HRT if:

- There is sudden change in menstrual pattern, intermenstrual bleeding, postcoital bleeding, or postmenopausal bleeding - refer for endometrial assessment.
- There is a personal or family history of VTE - a haematology opinion may be helpful.
- There is a high risk of breast cancer - consider mammography or MRI scan; refer to National Institute for Health and Care Excellence (NICE) guidance on familial breast cancer.
- The woman has arterial disease or risk factors for arterial disease - consider checking lipid profile.

See the separate Menopause and its Management article for more information.

Counselling

Explain indications for HRT

For women with premature (age <40 years) or early (<45 years) menopause, current guidelines recommend HRT for women without contra-indications, until the age of 51 years for the treatment of vasomotor symptoms, and bone and cardiovascular protection.[7] [9]

Current indications for the use of HRT are:

- For the treatment of menopausal symptoms where the risk:benefit ratio is favourable, in fully informed women.
- For women with early menopause until the age of natural menopause (around 51 years).
- For those women under 60 years who are at risk of an osteoporotic fracture in whom non-oestrogen treatments are unsuitable.

Starting HRT in women over the age of 60 years is generally not recommended.

Discuss potential benefits and risks

See the separate article Hormone Replacement Therapy.

Discuss alternatives to HRT

See the paragraph at the bottom of the separate Menopause and its Management article.

Prescribing hormone replacement therapy[6] [7]

It is important that an individualised approach be undertaken at all stages of diagnosis, investigation and management of menopause.

Micronised progesterone is a natural, 'body-identical' progestogen, devoid of any androgenic as well as glucocorticoid activities but being slightly hypotensive due to anti-mineralocorticoid activity. It may be the optimal progestogen in terms of cardiovascular effects, blood pressure, VTE, probably stroke and even breast cancer but this evidence is only from observational studies. There is only one currently available to prescribe in the UK (Utrogestan®).

As transdermal oestrogen is associated with fewer risks than oral HRT, a transdermal route may be preferable for many women. This route is also advantageous for women with diabetes, history of VTE and also those with thyroid disorders. In addition, transdermal HRT is preferable to those women with a history of migraine or gallbladder problems.

Contra-indications and cautions for hormone replacement therapy[6]

Do not prescribe hormone replacement therapy (HRT) in women with:

- Current, past, or suspected breast cancer.
- Known or suspected oestrogen-dependent cancer.
- Undiagnosed vaginal bleeding.
- Untreated endometrial hyperplasia.
- Previous idiopathic or current venous thromboembolism (deep vein thrombosis or pulmonary embolism), unless the woman is already on anticoagulant treatment.
- Active or recent arterial thromboembolic disease (for example, angina or myocardial infarction).
- Active liver disease with abnormal liver function tests.
- Pregnancy.
- Thrombophilic disorder.

Prescribe HRT with caution in women with:

- Porphyria cutanea tarda.
- Diabetes mellitus (increased risk of heart disease).
- Factors predisposing to venous thromboembolism.
- History of endometrial hyperplasia.
- Migraine and migraine-like headaches.
- Increased risk of breast cancer.

Which preparation?[6] [7]

The dose, regimen and duration of HRT need to be considered for each individual. Use the **lowest effective dose of HRT for the minimum duration** to control symptoms. The dosage and type of HRT should be tailored to symptoms and possible side-effects. Start with a low-dose oestrogen and consider gradually increasing the dose after four to six weeks if vasomotor symptoms persist.

Choice of systemic oestrogen

'Natural' oestrogens are found in normal physiology (may be manufactured chemically, or extracted from a plant or animal source), such as conjugated oestrogen, estradiol, estrone, and estriol, and are generally used in systemic hormone replacement therapy (HRT) preparations.

'Synthetic' oestrogens, such as mestranol or ethinylestradiol, are generally not used, except in women with premature ovarian insufficiency (POI) in certain circumstances, due to their greater metabolic impact.

Choice of progestogen

The progesterone component of HRT may be progesterone or a progestogen (which binds to the progesterone receptor).

The progestogens most commonly used in combined oral HRT are almost all synthetic and include dydrogesterone, medroxyprogesterone, norethisterone, levonorgestrel, norgestrel, and drospirenone. Women vary in their tolerance to progestogens, and changing the progestogen component of combined HRT may be needed if progestogenic adverse effects occur:

Combined HRT patches only contain norethisterone or levonorgestrel.

- Medroxyprogesterone, dydrogesterone, and drospirenone may be better tolerated than norethisterone or levonorgestrel, because they are less androgenic.
- Drospirenone also has aldosterone antagonistic activity and is useful for women who have fluid retention during the progestogen phase.
- Micronised progesterone or dydrogesterone may be preferred in women with hypertriglyceridaemia due to their neutral effect on lipid profile.

The levonorgestrel-releasing intrauterine system (LNG-IUS) is an alternative route of delivery of progestogen, which provides endometrial protection locally, resulting in low systemic levels of levonorgestrel. It may be useful in women:

- With persistent progestogenic adverse effects with other progestogen preparations and delivery routes.
- With troublesome or heavy withdrawal bleeds taking cyclical HRT and normal investigation results.
- If contraception is still needed.

Women may use a levonorgestrel-releasing intrauterine system (LNG-IUS) with oestrogen for up to five years for endometrial protection, as part of an HRT regimen (licensed for four years but may be used for up to five years off-label). Women using LNG-IUS for this purpose must have the device changed every five years.

Mirena® is the only IUS licensed in the UK for HRT. Levosert® is the same dose and, although not licensed in the UK, is used by some specialists.

Combined oestrogen/bazedoxifene acetate (a selective oestrogen receptor modulator) oral preparation may be an option for women with a uterus (with at least 12 months since the last menstrual period), if progestogen-containing therapy is not appropriate.

Some observational studies have shown that HRT containing micronised progesterone or dydrogesterone may be associated with a lower risk of breast cancer, cardiovascular disease and thromboembolic events.

Which regimen?[6] [7]

The hormone replacement therapy (HRT) regimen used depends on whether the woman is perimenopausal or postmenopausal, the route of adminstration, and the woman's wishes.

Combined HRT can be prescribed as a:

- **Monthly cyclical regimen**:
    - Oestrogen is taken daily and progestogen is given at the end of the cycle for 10-14 days, depending on the type of progestogen.
    - The suggested dose of progestogen given in a continuous combined HRT regimen is a minimum of 0.5 mg/day of norethisterone or 2.5 mg/day of medroxyprogesterone acetate.
    - For low-dose sequential regimens, norethisterone a minimum of 1 mg/day given for 10 days a month, oral micronised progesterone 200 mg/day for 12 days a month, medroxyprogesterone acetate 10 mg/day for 10-14 days a month or dydrogesterone 10 mg/day for 14 days a month are suitable options.
- **Three-monthly cyclical regimen**:
    - Oestrogen is taken daily and progestogen is given for 14 days every 13 weeks.

- **Continuous combined regimen**
    - Oestrogen and progestogen are taken daily.
    - Bijuve® has been approved as the first oral combined HRT with bioidentical hormones for use in the UK. It is taken as a continuous combined oral tablet: 1 mg estradiol with 100 mg micronised progesterone.

Perimenopausal women

Monthly or three-monthly cyclical regimens may be used.

- A three-monthly regimen may be more suitable for women with infrequent periods or who are intolerant to progestogens. See the section on adverse effects for more information.
- A monthly regimen produces monthly bleeding whilst a three-monthly regimen produces a bleed every three months.
- A continuous combined regimen is not suitable for use in the perimenopause or within 12 months of the last menstrual period.

The absence of bleeding whilst taking a cyclical regimen reflects an atrophic endometrium.
Exclude pregnancy in perimenopausal women or women with premature ovarian insufficiency. Check compliance with therapy if the progestogen component is taken separately.

If HRT was initiated in the perimenopause, consideration should be given to switching from monthly or three-monthly cyclical regimens to continuous combined regimens after the woman becomes postmenopausal.

Postmenopausal women

Monthly or three-monthly cyclical regimens, or a continuous combined regimen may be used.

- A continuous combined regimen may be preferred as it does not produce withdrawal bleeding.
- A continuous combined regimen may produce irregular bleeding or spotting for the first 4-6 months of treatment. If bleeding persists beyond six months, becomes heavier, or occurs after a spell of amenorrhoea, endometrial pathology should be excluded.

Vaginal oestrogen[6] [7]

Low-dose vaginal oestrogen (tablet, cream, pessary, or vaginal ring) may be preferred if symptoms are primarily urogenital.

Vaginal oestrogen therapy regimens depend on the vaginal preparation used:

- One vaginal tablet daily for two weeks, then reduced to one vaginal tablet twice weekly.
- One applicatorful daily for 3-4 weeks, then reduced to one applicatorful twice weekly, to be applied at bedtime, for cream and gel preparations.
- One pessary daily for three weeks, then reduced to one pessary twice weekly, to be inserted at bedtime.
- One vaginal ring inserted into the upper third of vagina and worn continuously, to be replaced at three months. Maximum duration of continuous treatment is two years.

Which delivery route?[6] [7]

Hormone replacement therapy (HRT) is available as oral or transdermal preparations, depending on the woman's preferences.

Oestrogen-only preparations are given to women without a uterus, and combined oestrogen and progestogen preparations are given to women with an intact uterus.

Transdermal preparations may be appropriate if the woman has:

- Persistent troublesome symptoms with oral treatment.
- Troublesome adverse effects with oral treatment.
- A history of, or increased risk of, venous thromboembolism.
- Cardiovascular risk factors, such as obesity, uncontrolled hypertension, or hypertriglyceridaemia.
- Concomitant hepatic enzyme-inducing drug treatment (for example, carbamazepine).

- A gastrointestinal disorder that may affect absorption of oral treatment.
- A history of migraine or gallbladder disease.
- Lactose sensitivity (most HRT oral preparations contain lactose).

Transdermal preparations are available as a gel (oestrogen only), patch (oestrogen only or combined oestrogen and progestogen), or spray (oestrogen only).

If the woman is using combined HRT, the progestogen component may also be given separately as an oral tablet or as the levonorgestrel-releasing intrauterine system (LNG-IUS).

Low-dose vaginal oestrogen is available as a vaginal tablet (Vagifem®), creams (Ovestrin® or Gynest®), gel (Blissel®), pessary (Imvaggis®), and vaginal ring (Estring®), depending on the woman's preferences. A progestogen is not needed for endometrial protection, as systemic absorption of vaginal oestrogen is minimal.

Side-effects of HRT[6]

Hormone replacement therapy (HRT) may cause a variety of adverse effects.
Oestrogen-related adverse effects include:

- Fluid retention, bloating, breast tenderness or enlargement, nausea, headaches, leg cramps, and dyspepsia.
- Exogenous oestrogens may induce or exacerbate symptoms of hereditary and acquired angio-oedema.

Progestogen-related adverse effects include:
Fluid retention, breast tenderness, headaches or migraine, mood swings, premenstrual syndrome-like symptoms, depression, acne vulgaris, lower abdominal pain, and back pain. They tend to occur in a cyclical pattern during the progestogen phase of cyclical HRT.

Vaginal bleeding problems
Unscheduled vaginal bleeding is a common adverse effect of HRT within the first three months of treatment.

Monthly cyclical regimens should produce regular withdrawal bleeding towards the end of the progestogen phase.

Continuous combined HRT commonly produces irregular breakthrough bleeding or spotting in the first 4-6 months of treatment. If bleeding persists beyond six months, becomes heavier, or occurs after a spell of amenorrhoea, endometrial pathology should be excluded.

Unpredictable or unexpected bleeding may also be due to non-adherence with treatment, drug interactions, or a gastrointestinal disorder (which may affect drug absorption).

If serious gynaecological pathology has been excluded, altering the progestogen part of the regimen may improve bleeding problems. Options include increasing the duration or dose of the progestogen, or changing the type of progestogen, for example switching to the levonorgestrel-releasing intrauterine system (LNG-IUS) combined with an oral or transdermal oestrogen preparation.

See the separate HRT - Follow-up Assessments article for a discussion of how to manage these side-effects.

HRT and contraception[6]

Contraception is needed along with HRT. HRT is not a contraceptive and a woman is considered potentially fertile for two years after her last menstrual period if she is aged under 50 years and for one year if she is aged over 50 years.

For many women oestrogen HRT and an IUS are an optimal combination.

Alternatively, the progestogen-only contraceptive pill can be given to women who are taking cyclical combined HRT.

Women aged 50 years and over should not be prescribed the combined oral contraceptive pill. See the separate Contraception from 40 to the Menopause article.

Tibolone

Tibolone is a selective oestrogen receptor modulator (SERM) which combines oestrogenic and progestogenic activity with weak androgenic activity. It can be used in women with an intact uterus who have had no bleeding for more than one year, without the need for cyclical progestogen.

A Cochrane review found (much of the evidence was of low or very low quality):[10]

- Moderate-quality evidence suggests that tibolone is more effective than placebo but less effective than HRT in reducing menopausal vasomotor symptoms, and that tibolone is associated with a higher rate of unscheduled bleeding than placebo but with a lower rate than HRT.
- Compared with placebo, tibolone increases recurrent breast cancer rates in women with a history of breast cancer, and may increase stroke rates in women over 60 years of age.
- No evidence indicates that tibolone increases the risk of other long-term adverse events, or that it differs from HRT with respect to long-term safety. Limitations included high risk of bias and imprecision.

Testosterone

Testosterone is not licensed for use in women in the UK. However, it does have a role for those women who have low libido despite receiving HRT. Testosterone has been shown in many studies to improve mood, energy and libido in menopausal women.[11]

Referral[6]

If a woman has menopausal symptoms, consider arranging referral to a healthcare professional with expertise in menopause if:

- There is uncertainty about the most suitable treatment option - for example, if the woman has comorbidities and/or contra-indications to treatment.

- The woman has persistent altered sexual function and hormonal and/or non-hormonal, or non-drug treatments are ineffective:
    - Seek specialist advice regarding the use of testosterone supplementation (off-label use).
    - Consider referral for psychosexual counselling, depending on the woman's wishes.
- There is uncertainty about diagnosing premature ovarian insufficiency, or specialist advice is needed to manage the condition.
- There is a sudden change in menstrual pattern, intermenstrual bleeding, postcoital bleeding, or postmenopausal bleeding. Arrange an urgent two-week referral if a gynaecological cancer is suspected. [12]

Follow-up[6]

Arrange to review the woman after three months if HRT has been started or changed, then at least annually thereafter, unless there are clinical indications for an earlier review (such as treatment ineffectiveness or adverse effects).

Further reading

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