HRT - follow-up assessments

HRT reviews[1] [2]

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). At each review:

- Reinforce information and lifestyle advice.
- Assess the efficacy and tolerability of treatment(s).
- Assess for bothersome adverse effects or persistent symptoms, and offer to adjust the HRT dose or preparation if appropriate. Options include:
  - Reduce the dose of oestrogen.
  - Change the dose or type of progestogen.
  - Alter the route of administration - for example, switch from oral to transdermal.
  - Switch to a combined oestrogen/bazedoxifene acetate preparation (a selective oestrogen receptor modulator), if progestogen-containing therapy is not appropriate.
- If there is a sudden change in menstrual pattern, intermenstrual bleeding, postcoital bleeding, or postmenopausal bleeding - assess appropriately and arrange an urgent two-week referral if a gynaecological cancer is suspected.[3]
- If there are persistent symptoms despite adjustment of the HRT dose or preparation, consider an alternative cause for symptoms.

Review the duration of HRT treatment:

- If HRT was started in the perimenopause, discuss the option of changing the treatment regimen and/or reducing the dose of oestrogen.
- Support the woman to make an individual decision on when and how to stop HRT. Advise that:
    - HRT should be continued for as long as benefits of symptom control and improved quality of life outweigh any risks, and there is no arbitrary limit for duration of HRT use.
    - For vasomotor symptoms, most women require 2-5 years of treatment, but some women may need longer.
    - Women with premature menopause or premature ovarian insufficiency (POI) should take HRT up to 50 years in the UK, after which the need for ongoing HRT should be reassessed.
    - HRT may be gradually reduced over 3-6 months, or stopped suddenly, depending on the woman's preferences. However, gradual reduction is preferable (see 'Stopping HRT' below).
    - Symptoms may recur in the short term after stopping treatment, particularly if HRT is stopped suddenly.
- If troublesome symptoms recur, options include restarting HRT at a low dose, or considering alternative non-hormonal treatments.
- Vaginal oestrogen preparations may be required long term, but regular attempts to stop treatment, such as annually, can be made.

HRT assessment[1]

Components to a follow-up assessment:

- A three-month trial of HRT is suggested to achieve maximum effect.
- Improvement of symptoms should be noted and women should be asked about any residual symptoms.

Where a patient remains symptomatic, consider:

- Poor absorption - for example, due to bowel disorder.

- Drug interactions reducing bio-available oestrogen - for example, carbamazepine and phenytoin.
- Problems with patch adhesion.
- Incorrect diagnosis - hypothyroidism or diabetes may mimic some features of menopause.
- Patient expectations - these may also need to be addressed.
- The dose of oestrogen in HRT may be too low.

Altering the HRT product or delivery method may help address some of these problems. The oestrogen dose may need to be increased. For example, vaginal oestrogen cream can be added if urogenital symptoms are poorly controlled.[4]

A regular review should include the following:

- Check for side-effects - eg, breast tenderness or enlargement, nausea, headaches or bleeding - and manage appropriately (see 'Management of side-effects', below).
- Check blood pressure and weight.
- Encourage breast awareness and participation in screening mammography and also cervical screening if appropriate for age.
- A review and discussion of an individual's risk:benefit ratio concerning HRT should occur at least annually.
- If appropriate, consider switching from cyclical HRT to continuous combined HRT (see below).

The decision on whether to advise continuation of HRT should be based on symptoms and ongoing risks and benefits, rather than a set minimum or maximum duration of therapy. Cessation of HRT leads to recurring symptoms for up to 50% of women. Consider the potential impact of these symptoms on quality of life.

The merits of long-term HRT use should be assessed for each individual woman, and the lowest dose of HRT which controls symptoms should be used.

Management of HRT side-effects[1]

Side-effects may be oestrogen-related (occurring continuously or randomly through a cycle) or progestogen-related (occurring cyclically during the progestogen phase).

Oestrogen-related side-effects

These are usually transient and may resolve spontaneously with increasing duration of use. Encourage patients to persist with a particular therapy for at least 12 weeks. Side-effects are more likely to occur or be problematic where there has been a longer interval since ovarian failure.

Oestrogen-related side-effects include:

- Breast tenderness or enlargement - this usually settles after 4-6 weeks of taking HRT. The oestrogen dose could be reduced and then increased very gradually. A change in progestogen can sometimes be beneficial. Evening primrose oil is no longer recommended.
- Leg cramps - suggest exercise and calf stretching.
- Nausea and dyspepsia - adjust time of dose and administer with food.
- Headaches - try transdermal oestrogen, as this usually produces more stable oestrogen levels.

Progestogen-related side-effects

These may be more problematic and are usually connected to the type, duration and dose of progestogen.

Progestogen-related side-effects include:

- Fluid retention.
- Headaches or migraine.
- Breast tenderness.
- Mood swings and depression.
- Symptoms of premenstrual syndrome.
- Acne.

- Lower abdominal and back pain.

Again encourage perseverance, as symptoms may improve over three months. If there is no improvement at that point strategies include:

- If bleeding is heavy or irregular on sequential combined HRT then the dose of progestogen can be doubled or increased in duration to 21 days. Alternatively the type of progestogen can be changed.
- Erratic bleeding can be common in the first three to six months after starting HRT.
- Women with progestogen side-effects (eg, fluid retention, mood swings, weight gain) can have the progestogen dose halved or the duration of taking progestogen reduced to seven to ten days.
- Fewer progestogenic side-effects occur with progesterone and dydrogesterone. The intrauterine system (IUS) can be used as an alternative for endometrial protection. Its licence for this use is four years.
- Drospirenone has anti-androgenic and anti-mineralocorticoid properties.
- 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, venous thromboembolism (VTE), probably stroke and even breast cancer, but these data are from observational studies only and they have a higher risk of endometrial hyperplasia.[5] There is only one currently available to prescribe in the UK.
- Micronised progesterone can be prescribed with oral or transdermal oestrogen. It is commonly prescribed at a dose of 200 micrograms a day for two weeks followed by a two-week break for those women who are still having periods.

- For 'continuous' micronised progesterone use, the dose recommended in the BNF is days 1-25, with a 3-day break, rather than continuous use. This may reduce the chances of breakthrough bleeding compared to continuous use. However continuous is commonly used in practice, is generally well tolerated, and is easier for women to remember.

Weight gain

This is often given as a major reason for why women discontinue HRT but there is no randomised controlled trial evidence of HRT-induced weight gain. Reassure the patient that weight gain is common at this time of life and counter with dietary and lifestyle advice.[6]

Bleeding

Monthly sequential preparations should produce regular, predictable and acceptable bleeds starting towards the end, or soon after, the progestogen phase. This pattern may be altered by:

- Non-concordance.
- Drug interaction.
- Gastrointestinal upset.

Breakthrough bleeding is common in the first three to six months of continuous combined and long-cycle HRT regimens. Unscheduled bleeding in the first six months of HRT use does not need investigation, but investigate new-onset or persistent bleeding to exclude pelvic disease.

Where pelvic pathology is excluded, strategies for tackling bleeding problems include:

- Heavy or prolonged bleeding - increase dose, duration or type of progestogen. Consider the use of the levonorgestrel-releasing IUS (LNG-IUS) combined with oral or transdermal oestrogen.
- Bleeding early in the progestogen phase - increase the dose or change the type of progestogen.
- It can be useful for some women with bleeding when taking a continuous combined regime to revert back to a cyclical regime for a few months.

- Painful bleeding - change the type of progestogen.
- Irregular bleeding - change the regimen or increase progestogen.
- No bleeding - this occurs in 5% of women and is due to an atrophic endometrium. It is necessary to exclude pregnancy in perimenopausal women and to ensure compliance with the progestogen element of the HRT regimen.

Switching from cyclical HRT to continuous combined HRT

Women should be prescribed cyclical/sequential combined HRT if their last menstrual period was less than one year previously, or if they are significantly symptomatic but still having periods.

Cyclical HRT can be changed to continuous combined HRT when the woman is considered to be postmenopausal. This is advantageous to the woman as it removes the risk of endometrial hyperplasia. The woman may also no longer want to have to deal with a bleed.

Women can be prescribed continuous combined HRT if they have received sequential combined HRT for at least one year; **or i**t has been at least one year since their last menstrual period.

A woman may be reasonably sure that she is postmenopausal by the age of 54 years. The problem with starting continuous combined HRT before a woman is postmenopausal is the increased frequency of irregular bleeding, which may need further investigation, such as ultrasound assessment of endometrial thickness.

HRT referral[2]

At the time of review, consider arranging referral to a healthcare professional with expertise in menopause if:

- The woman has ongoing symptoms and lifestyle measures, hormonal, non-hormonal, or non-drug treatments are ineffective.
- The woman has persistent, troublesome adverse effects from treatment.

- 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.
    - Consider referral for psychosexual counselling, depending on the woman's wishes.
- There is a sudden change in menstrual pattern, intermenstrual bleeding, postcoital bleeding, or postmenopausal bleeding - assess appropriately and arrange an urgent two-week referral if a gynaecological cancer is suspected.[3]

Stopping HRT[1]

Menopausal symptoms (hot flushes and sweats) last on average between two to five years but there is considerable individual difference and symptoms may last decades in some women.

A trial of withdrawal of HRT could be considered:

- In those women symptom-free on HRT after one to two years.
- In women who have been on HRT for longer than five years.
- After the age of 51 for women who were started on HRT for premature menopause.

Alternatives to HRT are discussed in the separate Menopause and its Management article.

Abrupt cessation or gradual withdrawal of HRT?

When stopping HRT, it is generally recommended that the dose of HRT should be reduced gradually over three to six months, to minimise the chance of oestrogen deficiency symptoms returning.

On initial cessation of therapy, symptoms may return fairly soon but then resolve. Ideally, staying off treatment for two to three months should be considered before deciding whether or not to recommence.

However, if the vasomotor symptoms are severe after stopping HRT, restarting treatment may be the most appropriate course of action. The lowest dose to improve symptoms should be given.

Reasons HRT must be stopped[7]

Hormone replacement therapy should be stopped (pending investigation and treatment) if any of the following occur.

- Sudden severe chest pain (even if not radiating to the left arm).
- Sudden breathlessness (or cough with blood-stained sputum).
- Unexplained swelling or severe pain in the calf of one leg.
- Severe stomach pain.
- Serious neurological effects including:
    - Unusual severe, prolonged headache, especially if for the first time or that is getting progressively worse.
    - Sudden partial or complete loss of vision.
    - Sudden disturbance of hearing.
    - Other perceptual disorders or dysphasia.
    - Bad fainting attack or collapse or first unexplained epileptic seizure.
    - Weakness, motor disturbances.
    - Very marked numbness suddenly affecting one side or one part of body.
- Hepatitis, jaundice, liver enlargement.
- Blood pressure above systolic 160 mm Hg or diastolic 95 mm Hg.
- Prolonged immobility after surgery or leg injury.

- Detection of a risk factor which contra-indicates treatment.

Further reading

- Cobin RH, Goodman NF; American Association of Clinical Endocrinologists and American College of Endocrinology Position Statement on Menopause - 2017 Update. Endocr Pract. 2017 Jul;23(7):869-880. doi: 10.4158/EP171828.PS.
- HRT - Guide; British Menopause Society (2020)

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