Hormone Replacement Therapy (including Benefits and Risks)

Approximately 80% of menopausal women experience symptoms. While a quarter of those are thought to have severe symptoms, only a small proportion of menopausal women currently take hormone replacement therapy (HRT).

Symptoms of the menopause last far longer than most women anticipate. Frequent menopausal vasomotor symptoms, including night sweats and hot flushes, persist in more than half of women for more than seven years. HRT is an effective treatment for the typical menopause-related symptoms. There are also other long-term health problems associated with the menopause - the risk of osteoporosis, cardiovascular disease and stroke all increase after the menopause. HRT can also have a positive influence on these health problems.

This article discusses HRT in detail. The separate Menopause and its Management article discusses menopausal symptoms, differential diagnosis and possible investigations (although the diagnosis is usually clinically based on the typical symptoms). It also discusses health problems associated with the menopause and gives an overview of management.

See also separate HRT - Initial Consultation, HRT - Follow-up Assessments and HRT - Topical articles.

Indications for hormone replacement therapy

Current guidelines advise that HRT should be considered for troublesome vasomotor symptoms in perimenopausal and early postmenopausal women without contra-indications and after individualised discussion of likely risks and benefits. Starting HRT in women over the age of 60 years is generally not recommended.

For women with premature (age <40 years) or early (<45 years) menopause, current guidelines recommend sex steroid replacement until the age of 51 years for the treatment of vasomotor symptoms and for bone and cardiovascular protection.

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), even if they are asymptomatic.
- For those women under 60 years who are at risk of an osteoporotic fracture in whom non-oestrogen treatments are unsuitable.

Benefits of hormone replacement therapy

The benefits of HRT outweigh the risks for many women aged under 60 years.

Benefits of HRT include:

Reduction in vasomotor symptoms

- HRT is the most effective treatment at reducing vasomotor symptoms.
- Vasomotor symptoms are usually improved within four weeks of starting treatment and maximal benefit is gained by three months.
- There has been shown to be a significant mean reduction in the frequency of hot flushes by around 18 a week and in the severity of hot flushes by 87% compared with placebo.

Improvement in quality of life

HRT can also improve sleep, muscle aches and pains and quality of life in symptomatic women.

Improvement in mood changes

- HRT can improve mood and also depressive symptoms.
- HRT should be considered to alleviate low mood that arises as a result of the menopause. Cognitive behavioural therapy may be beneficial too.
Improvement of urogenital symptoms

- Various studies have shown that HRT significantly improves vaginal dryness and sexual function.
- HRT is effective in improving the symptoms related to vaginal atrophy.
- HRT can also relieve the symptoms of urinary frequency, as it has a proliferative effect on the bladder and urethral epithelium.
- Topical oestrogen is effective in improving symptoms in menopausal women[7].
- Vaginal symptoms are improved, vaginal atrophy and pH decrease and there is improved epithelial maturation with topical oestrogen preparations compared to placebo or non-hormonal gels[8].

Reduction in osteoporosis risk

- Oestrogens are the most effective way of increasing bone mineral density (BMD) and also preventing osteoporotic fractures in women[9].
- HRT is the first-line treatment for the prevention and management of osteoporosis in women with menopausal symptoms who are under the age of 50 years.
- HRT should be considered in those women at high risk of fracture if there are no contra-indications to HRT.
- The bone protection qualities of HRT are dose-related. However, even low doses of oestrogen give some bone protection.
- HRT rapidly normalises turnover and preserves BMD at all skeletal sites, leading to a significant reduction in vertebral and non-vertebral fractures[10, 11].
- Women taking HRT have a significantly decreased incidence of fractures with long-term use[12].
- Although bone density declines after discontinuation of HRT, some studies have demonstrated that women who take HRT for a few years around the time of the menopause may have a long-term protective effect for many years after stopping HRT[13].

Reduction in cardiovascular disease

- The relation between HRT and cardiovascular disease is controversial but the timing and duration of HRT, as well as pre-existing cardiovascular disease, are likely to affect outcomes[14].
- Taking HRT can reduce the risk of cardiovascular disease[15].
- Taking HRT has been shown to reduce the incidence of coronary heart disease by around 50%, if it is started within ten years of the menopause[16].
- Generally, oestrogens have favourable effects, raising HDL-cholesterol levels and lowering LDL-cholesterol levels. Progestogens are either neutral or oppose oestrogen effects, depending on their dose and androgenicity[17].
- The National Institute for Health and Care Excellence (NICE) states that HRT does not increase cardiovascular risk when started in women aged under 60 years and does not affect the risk of dying from cardiovascular disease[18].
- The presence of cardiovascular risk factors is not a contra-indication to HRT, as long as any risk factors are optimally managed[2].

Lower risk of colorectal cancer

- The Women's Health Initiative (WHI) trial showed that colorectal cancer risk was reduced in women taking combined conjugated equine oestrogens and medroxyprogesterone acetate[18].
- The use of oestrogen alone in postmenopausal women with prior hysterectomy has not been shown to influence the incidence of colorectal cancer[19].
- Other studies have demonstrated a reduction in risk of colorectal cancer with use of oral combined HRT[20].

Other benefits

- HRT has a positive effect on collagen as well as bone. Taking HRT leads to a decreased osteoclastic resorption[21].
- There is evidence to support the beneficial effects of HRT on the maintenance and enhancement of muscle mass, strength and connective tissue in women[22].
- Both systemic and topical oestrogens have positive effects on hormonal ageing, increasing skin collagen content, thickness, elasticity and hydration[23]. HRT may also improve wound healing and reduce the incidence of wound complications.
- There is a possible reduction in the long-term risk of Alzheimer's disease and all-cause dementia in those women who take HRT[24].
- Women with migraines often find their migraines worsen during their menopause. The hormonal fluctuations which are attributable to this can be stabilised with HRT, often leading to improvements in their migraine symptoms[25]. Transdermal preparations are preferable for these women.

Risks associated with hormone replacement therapy

The principal risks of HRT are thromboembolic disease (venous thromboembolism (VTE) and pulmonary embolism), stroke, breast and endometrial cancer, and gallbladder disease.

Large studies, including the WHI and the Million Women Study (MWS), raised concerns and controversy over the use of HRT[18, 26].

However, data accumulated from the WHI and other studies over a period of a decade have shown that, in women with symptoms or other indications, initiating HRT near menopause usually provides a favourable benefit:risk ratio[2].
The type, dose and delivery system of both oestrogen and progestogen influence the risk of thromboembolic disease.

Oral HRT (combined oestrogen and progestogen, and oestrogen-only) increases the risk of VTE.

The risk of VTE is increased two to three times with oral HRT.

These risks increase with age and with other risk factors, such as obesity, previous thromboembolic disease, smoking and immobility.

In healthy women aged under 60 years, the absolute risk of thromboembolic disease is low and mortality risks from VTE are low.

Transdermal HRT should be given for those women with an increased risk of VTE.

**Stroke**

The risk of ischaemic (but not haemorrhagic) stroke:

- It is associated with a small increased risk in women taking oral oestrogen-only or combined HRT.
- There is no evidence that transdermal preparations are associated with an increased risk of stroke.
- The effects of HRT on stroke may be dose-related and so the lowest effective dose should be prescribed in women who have significant risk factors for stroke.
- Tibolone increases the risk of stroke in women aged over 60 years.[27]

**Breast cancer**

- Data regarding the true effect of HRT on the incidence of breast cancer are still contentious.
- Some studies have failed to demonstrate any increased risk of breast cancer with HRT.[28]
- Combined HRT increases the risk of breast cancer.[29] However, the absolute risk is small at around one extra case of breast cancer per 1,000 women each year.
- This increased risk:
  - Is greatest in lean women (BMI <25).
  - Is similar in magnitude to the risk associated with late menopause, early menarche or nulliparity.
  - Is also similar in magnitude to drinking two to three units of alcohol daily or from being overweight or obese.
  - Returns to that of a non-user after of stopping HRT.
- There is no increased risk of dying from breast cancer by taking HRT.[2]
- Among women with prior hysterectomy, randomised clinical trial evidence has shown that oestrogen alone reduces breast cancer incidence and deaths from breast cancer.[30].
- Combined HRT also increases breast density and the risk of having an abnormal mammogram.[31]. It is important that women are informed about this.
- There has been a decline in breast cancer incidence since 2002 which some people have attributed to the reduction in HRT prescribing since this time. However, the reduction in breast cancer rates started to reduce before the publication of the WHI trial.[32]

**NB**: there is no evidence of an increased risk of breast cancer in women on HRT under the age of 51 years compared with menstruating women of the same age.

**Endometrial cancer**

- Oestrogen-only HRT substantially increases the risk of endometrial cancer in women with a uterus.
- The use of cyclical progestogen for at least ten days per 28-day cycle lowers this risk. Switching to continuous combined HRT after one year removes the risk.

**Ovarian cancer**

- Current data on the role of HRT and the risk of ovarian cancer are still currently conflicting.
- One meta-analysis showed an increase in ovarian cancer rate of 1 in 10,000 women but other studies have not demonstrated this.[33].

**Investigations before starting hormone replacement therapy**

Investigations are not usually necessary before starting HRT unless:

- 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 NICE guidance on familial breast cancer[34].
- The woman has arterial disease or risk factors for arterial disease - consider checking lipid profile.
Prescribing hormone replacement therapy

It is important that an individualised approach is undertaken at all stages of diagnosis, investigation and management of menopause.[2]

The dose, regimen and duration of HRT need to be individualised. There is no maximum duration of time for women to take HRT. Discussion with women who continue to have symptoms generally show their benefits from HRT usually outweigh any risks. Systemic HRT should not be arbitrarily stopped at age 65 years; instead treatment duration should be individualised based on patients' risk profiles and personal preference.[35]

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.[36] There is only one currently available to prescribe in the UK.

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.

Which preparation - cyclical or continuous systemic or local?

- Women should be prescribed sequential combined HRT if:
  - Their last menstrual period was less than one year previously.

- Women can be prescribed continuous combined HRT if:
  - They have received sequential combined HRT for at least one year; or  
  - It has been at least one year since their last menstrual period; or  
  - It has been at least two years since their last menstrual period if they had a premature menopause.

- 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.
- Erratic bleeding can be common in the first 3-6 months after starting HRT.
- Women with persistent vaginal bleeding after six months of starting HRT need to have further investigations.
- 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 7-10 days.
- Fewer progesteronic side-effects occur with micronised 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.
- Topical oestrogen is advisable as first-line for women with vaginal atrophy.
- However, around 10-25% of women still have symptoms with topical oestrogen so will require HRT in addition.

Which delivery route?

Delivery routes include:

- Continuous or cyclical oral therapy.
- Patches.
- Creams or gels.
- Nasal sprays.
- Local devices such as the progestogen-releasing IUS.
- The oestrogen-releasing vaginal ring.

The choice of delivery route depends partly on patient preference but there are also other advantages to certain delivery routes.

By avoiding the first pass metabolism through the liver, non-oral preparations (ie patches or gels):

- Have less effect on clotting factors.
- Reduce triglycerides.
- Are are often more suitable for:
  - Women who experience side-effects such as nausea with oral preparations.
  - Women with liver disease or gallstones.
  - Women with a history of malabsorption.
  - Women who are at risk of thrombosis.
  - Women with diabetes.
  - Women with a BMI >30 kg/m².
  - Women taking enzyme-inducing drugs.
  - Those women with a history of migraines (the bolus effects of oral medication can trigger migraines in some women).

Other considerations

- Low-dose vaginal oestrogen (tablet, cream, pessary, or vaginal ring) may be preferred if symptoms are primarily urogenital.
- The levonorgestrel-releasing IUS plus oestrogen component may be used if:
  - Progestogen side-effects are experienced with other progestogen preparations and delivery routes.
  - Contraception is still needed.
  - There is persistent heavy bleeding on cyclical combined HRT and normal investigations.

- The progesterone component of HRT may be progesterone or a progestogen (which binds to the progesterone receptor).
- 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.[5]

**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.
- Randomised controlled trials suggest it may be helpful in improving sexual function and vasomotor symptoms[37].
- There may be a small increased risk of stroke, endometrial cancer and breast cancer (including breast cancer recurrence) with tibolone.
- Tibolone is less effective than combined HRT in alleviating menopausal symptoms.

**Side-effects of HRT**
- Oestrogen: breast tenderness, leg cramps, bloating, nausea, headaches.
- Progestogen: premenstrual syndrome-like symptoms, breast tenderness, backache, depression, pelvic pain.
- Bleeding: monthly sequential preparations should produce regular, predictable and acceptable bleeds starting towards the end, or soon after, the progestogen phase. Breakthrough bleeding is common in the first 3-6 months of continuous combined and long-cycle HRT regimens.

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

**Starting hormone replacement therapy**
See separate HRT - Initial Consultation article.

**Follow-up of a woman taking hormone replacement therapy**
- The separate HRT - Follow-up Assessments article gives advice about following up women taking HRT and when to stop HRT.
- Initial follow-up after starting HRT should occur at about three months. Most symptoms are likely to have responded to oestrogen in this time period and any residual problems may require alternative management.
- Frequency of follow-up thereafter is controversial and not evidence-based. Drug manufacturers vary in their recommendations but consensus appears to be a minimum of annual checks.

**Hormone replacement therapy and contraception**
- 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 separate Contraception from 40 to the Menopause article.

**Further reading & references**

- Menopause: diagnosis and management; NICE Guidelines (Nov 2015)
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