Hormone replacement therapy: latest evidence and treatment recommendations

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Summary

- HRT is indicated for the treatment of moderate to severe vasomotor and urogenital symptoms associated with menopause.
- HRT is not recommended for primary prevention of disease because of increased risk of other adverse events.
- The use of HRT increases the risk of stroke, venous thromboembolism (VTE) and gall bladder disease and combined oestrogen progestogen therapy is also associated with an increased risk of breast cancer and dementia (women >65).
- Individual risk assessment is essential before starting HRT therapy. For women younger than 50, or those at low risk of cardiovascular disease, stroke, or breast cancer, the absolute risk from HRT is likely to be small.
- HRT should be prescribed at the lowest effective dose for the shortest duration possible. Other treatments should also be considered. Regular monitoring is necessary, along with attempted withdrawal after one to two years.

Definitions

HRT	Hormone replacement therapy (oestrogen only or combined therapy)
Oestrogen therapy	Oestrogen only
Combined therapy	Oestrogen + progestogen
Continuous combined therapy	Oestrogen + progestogen administered daily
Continuous sequential therapy	Oestrogen daily + progestogen (10–14 days each month)
Progestogen	Progesterone or progestin
Perimenopause	Period of approximately three to six years during which menstrual cycles become erratic and oestrogen levels fall, ending with the cessation of menstruation
Postmenopause	One year without menstruation

Treatment and management recommendations

Although most women manage menopause themselves, around 10% seek help from a GP or specialist.[1] Hormone replacement therapy (HRT) was very popular until 2002 when evidence began to emerge of significant risks. However, HRT remains the most effective treatment for symptoms of menopause and may be used with minimal risk by some women.

Risk-benefit assessment

When deciding whether to prescribe HRT, first consider treatment goals, benefits and risks for the individual woman.[2] HRT improves quality of life in women experiencing moderate to severe menopausal symptoms.

Factors to consider;[2]

- Time of menopause
- Impact of symptoms on quality of life
- Underlying risk of CVD, stroke, VTE, cancers and other conditions
- Suitability of other treatments

The decision to treat is based on what level of individual risk (and benefit) is acceptable to both patient and doctor.

Table 1 (over page) summarises the risks and benefits associated with HRT use.

Contraindications for HRT

HRT should not be used for women with the following risk factors:

- Previous breast cancer
- Previous or high risk of cardiovascular disease
- Previous or high risk of VTE
- Dementia

HRT is not recommended for prevention of chronic illness.

Indications for HRT

Adapted from "Managing the menopause", Dr Helen Roberts (2007).[1]

The primary indications for HRT are **hot flushes, night sweats** and **urogenital symptoms.** The patient's perception of severity of their symptoms should guide treatment, not hormone levels as they tend to fluctuate throughout peri-menopause. There is little evidence that **mood symptoms** are worsened during menopause and this is not an indication alone for HRT therapy.

Improvements in **hot flush** and **night sweat** symptoms may be seen within four weeks of beginning therapy. Short term use of HRT (one to two years) is appropriate as flushes disappear within a few years of menopause in about two thirds of women.

Urogenital symptoms, e.g. dryness, soreness, dyspareunia (painful sexual intercourse) and increased urinary frequency and urgency, occur in around 50% of women after menopause. Topical vaginal oestrogen may provide benefit in dyspareunia and decrease recurrent UTIs in susceptible women. Response can take several months and longer term treatment is often needed. Systemic absorption is minimal so the risks from oral oestrogen do not apply and concurrent progestogen is not required for women with a uterus.

Management and dosing regimens for HRT

There are no specific data on individual forms of HRT and whether their safety profile differs. Most of the major trials have tested conjugated equine oestrogens alone or with medroxyyprogesterone acetate. Recommended treatment regimens are listed in Table 2 (over page)

Women with **premature menopause** may have more severe symptoms, requiring higher doses of HRT.

Adverse effects of HRT include irregular bleeding with combined regimens, nausea and breast tenderness. These symptoms usually decrease over time, but lowering the dose of the hormones may reduce these effects.

Table 1: Summary of risks and benefits of HRT

	Risks	Benefits
Combined treatment (oestrogen plus progestogen)	Breast cancer Coronary heart disease (first year of use) Dementia and cognition (>65 years) Gallbladder disease Stroke VTE ? Ovarian cancer	Vasomotor symptoms e.g. hot flushes Urogenital symptoms e.g. dryness Sleep disturbances Osteoporotic fracture Colorectal cancer ? Diabetes
Oestrogen only treatment	Endometrial cancer (if uterus present) Gallbladder disease Stroke VTE ? Ovarian cancer	Vasomotor symptoms e.g. hot flushes Urogenital symptoms e.g. dryness Sleep disturbances Osteoporotic fracture Colorectal cancer ? Depression ? Diabetes

Table 2: Recommended treatment regimens

"Use the lowest effective dose, for the shortest duration possible"

Women beginning treatment	0.3 mg conjugated equine oestrogen or 0.5 – 1.0 mg 17-β-oestradiol or oestradiol valerate (low dose). Doses can be increased after a few weeks if symptom relief is not adequate.
Women who have had a hysterectomy	Oestrogen only
Women with a uterus	Add progestogen to protect endometrium (tablets or intrauterine system). Low dose prepacked regimens can be used initially (e.g. Kliovance), or progestogen doses can be extrapolated from these regimens and progestogen only pills containing norethisterone or levonorgestrel can be used. The intrauterine system (Mirena) may be a good option for perimenopausal women as it also offers contraception.
Perimenopausal or recent menopause	Combined sequential treatment (oestrogen daily with progestogen 10 – 14 days per month). For women still menstruating, oestrogen should be started on the first day of menstrual bleed and progestogen given 14 days later, withdrawal bleeding should then start at the time that the next period would be expected.
Postmenopausal for greater than one year (over two years since last menstrual period)	Combined continuous treatment (oestrogen and progestogen daily). May cause irregular bleeding in first 6 – 12 months of use.

Monitoring and investigation

Before beginning treatment with HRT, evaluation includes a cardiovascular risk assessment and up to date breast and cervical screening. Referral for bone densitometry is determined on a case by case basis.[2] Endometrial investigation (ultrasound) is not normally required unless there has been bleeding between periods or bleeding after one year with no periods.[1]

After treatment with HRT has commenced, review regularly based on individual need. Blood pressure measurement is recommended at each review. Other investigations should be done as indicated. Cervical smears should be performed based on national screening recommendations and mammograms performed every two years from age 45 to 69.[3]

How to discontinue HRT

Approximately 75% of women stop HRT within two years, usually without seeing their doctor. Attempted withdrawal is appropriate after one or two years, to see if symptoms have resolved.[1] Symptoms have an approximately 50% chance off reoccurring if treatment is stopped, regardless of age, length of treatment or method of withdrawal.[2]

Experts are divided in their opinion on whether HRT should be abruptly withdrawn or slowly tapered; women can be given the choice.

Dr Helen Roberts offers a best practice tip: If after a trial withdrawal, the patient experiences a severe return of symptoms, then HRT could be restarted but the dose slowly decreased over the next three to six months. Non-hormonal treatments could also be added that help flushes. Women with long term debilitating symptoms will need to balance symptom relief with ongoing risks from therapy.[1]

Alternatives to HRT

Life style factors such as stress reduction, regular exercise, weight management, diet, avoidance of smoking, excessive caffeine and alcohol intake can be helpful.[1, 3]

Other medications that may be effective for mild menopausal symptoms, include SSRIs (fluoxetine, paroxetine and venlafaxine have all shown benefit in reducing hot flushes) and clonidine.[1,3]

Tibolone is a synthetic steroid with weak oestrogenic, progestogenic and androgenic effects. It may be used as an alternative to HRT for women more than 12 months post menopause for the treatment of hot flushes and vaginal dryness. Randomised controlled trials show that tibolone is not associated with any change in mammographic density or any increased risk of VTE. The risk of breast cancer, stroke and cardiovascular disease is thought to be similar to standard hormone treatment.[1, 3] Tibolone is registered for use in New Zealand but currently not available.

Alternative therapies are commonly used to treat menopause symptoms. A large scale systematic review concluded that although individual trials suggest possible benefit of some products, overall there is no evidence to suggest that any alternative therapies are effective for treating the symptoms of menopause.[4] Use of alternative products is an individual choice and may be appropriate in women for whom HRT is contraindicated or not tolerated.

Evidence shows that soy products, dong quai, evening primrose oil, red clover, black cohosh and ginseng have no significant impact on hot flushes or sleep disturbances.[4, 5]

Transdermal wild yam creams are promoted as a natural source of progesterone. They contain diosgenin, a steroid with no hormonal activity, which can be synthesised into progesterone in a laboratory setting. However the human body is unable to do this. Wild yam cream appears to have little effect on menopause symptoms and should not be used in place of progestogen treatment.[6]

Progesterone creams have limited evidence of effectiveness. There is no assurance that these creams would provide adequate protection of the endometrium for women using oestrogen, therefore they are not recommended in place of other forms of progestogen.[1]

Evidence of risks and benefits

** Hazard ratios for women aged 50 – 79 using HRT, calculated based on results from the WHI study.[1] A hazard ratio of 1.25 would mean that risk is increased by a further 25% of baseline risk e.g. baseline risk = 5%, hazard ratio for treatment = 1.25, therefore new risk = 5 x 1.25 = 6.25%. It is important to interpret risk in relation to baseline risk, which can vary with the individual.*

Risks and benefits of HRT for specific outcomes

Osteoporosis: There is strong evidence that HRT is beneficial in reducing the risk of postmenopausal osteoporotic fracture and increasing bone density.[2] Although some evidence suggests that a few years treatment around the time of menopause can be beneficial in fracture reduction,[7] it is generally agreed that life long use of HRT is required to prevent bone fractures. HRT is however not first line treatment for women with low bone mineral density due to the increased risk of other negative outcomes.

Hazard ratio for increased risk of fracture (95% CI): Combined treatment 0.76 (0.69 – 0.85). Oestrogen only treatment 0.70 (0.63 – 0.79).

Coronary Heart Disease: There is conflicting evidence of the effect of HRT on cardiovascular risk. The timing hypothesis may explain this conflict. It theorises that oestrogen in recently menopausal women could prevent the development of coronary artery plaque but would have no effect, or even cause harm if given to older women with compromised plaque.[8]

The Women's Health Initiative trial (WHI) found an overall increase in coronary heart disease in the first year of use of combined HRT.[9] However, overall a non-significant reduction in the risk of coronary heart disease was observed in women aged 50–59 years (oestrogen only trial) and in women for whom menopause had occurred within the previous ten years (combined trial).[10]

An increased risk of cardiac events was observed in the Women's International Study of Long Duration Oestrogen (WISDOM), in women using combined treatment. However, most of these women were over 64 years at trial entry and had one or more cardiovascular risk factors.[11]

Hazard ratio for increased risk of coronary heart disease (95% CI): Combined treatment overall 1.24 (1.00 – 1.54), first year of use 1.81(1.09-3.01). Oestrogen only treatment 0.95 (0.70 – 1.16).

Stroke: An increased rate of stroke was observed in the WHI study, with both combined treatment and oestrogen only treatment. The absolute risk of stroke was lower for women under 60 or in whom menopause had occurred within the previous five years.[2]

Hazard ratio for increased risk of ischaemic stroke (95% CI): Combined treatment 1.41 (1.07 – 1.85). Oestrogen only treatment 1.39 (1.10 – 1.77).

Dementia: HRT does not prevent cognitive decline in older postmenopausal women.[12] There is some evidence that HRT may increase the risk of dementia when given to women over 65 years of age.[2] A beneficial effect on cognition has been observed when HRT is used in younger women, however evidence is inconsistent. In the WHI study, a two-fold increase in dementia was found in women over 75 years taking HRT.[7]

Hazard ratio for increased risk of dementia (>65 years) (95% CI): Combined treatment 2.05 (1.21 –3.48). Oestrogen only treatment 1.49 (0.83 – 2.66).

Ovarian cancer: Although evidence is conflicting, it has been concluded that HRT, especially oestrogen only therapy is associated with an increased risk of ovarian cancer.[13, 14] A meta analysis found that the risk was increased by 1.28 with oestrogen therapy and 1.11 with combined therapy.[14]

Venous thromboembolism (VTE): a significant increase in the risk of VTE has been observed in post menopausal women using HRT. The risk appears to be greatest during the first one to two years of treatment and decreases over time.[2, 7] Although HRT increases the risk of VTE up to two-fold, the absolute risk is small, with a baseline risk of 1.7 events per 1000 women over 50 not taking HRT.[7]

Younger age, lower HRT doses, transdermal HRT and oestrogen treatment alone may also be associated with less risk.[2, 5, 7] Women who have previously suffered a VTE event have an increased risk of recurrence in the first year of HRT use.[7] Older age, obesity and underlying thrombotic disorders also significantly increase risk.[2]

Hazard ratio for increased risk of DVT (95% CI): Combined treatment 1.95 (1.43 – 2.67). Oestrogen only treatment 1.47 (1.06 – 2.06).

Breast cancer: Combined treatment with oestrogen and progestogen increases the risk of breast cancer diagnosis or recurrence. Oestrogen treatment alone does not appear to increase this risk. The greatest risk is with use of combined treatment for more than five years, when treatment is started over 50 years of age, increasing with duration of use. It is not known if the risk is different for continuous or sequential use of progestogen.[2, 5, 7]

In the WHI study, an increase in invasive cancers was observed in women using combined treatment for five or more years and a non-statistically significant decrease in those using oestrogen alone, after an average of 7.1 years. There is limited observational data that oestrogen use for more than 15 years may be associated with increased risk of breast cancer.[2]

Combined HRT treatment and to a lesser extent, oestrogen only treatment, increases breast cell proliferation, breast pain and mammographic density and may impede the diagnostic interpretation of mammograms.[2]

Hazard ratio for increased risk of breast cancer (95% CI): Combined treatment 1.24 (1.01 – 1.54). Oestrogen only treatment 0.77 (0.59 – 1.01).

Summary

HRT is associated with the greatest risk when it is taken for more than five years, in women over 60 years of age. However the highest risk of VTE occurs within the first year of treatment. Short term HRT is appropriate in a healthy woman, within five years of menopause, experiencing moderate to severe symptoms. Careful consideration should be given to using HRT for more than five years or in women with risk factors for other conditions.

Useful website:

The US National Institutes of Health website is a good resource for HRT information.

http://health.nih.gov/result.asp/961

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