

Practical recommendations for hormone replacement therapy in the peri- and postmenopause

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INTRODUCTION

The following recommendations provide guidance to medical practitioners in the appropriate use of estrogen and progestogen therapy in peri- and postmenopausal women. They are derived from a meeting in February 2004 of internationally recognized experts who reviewed results of the recent clinical trials, the conclusions of which have led to much confusion and alarm among women and their doctors. These trials, in particular the randomized, controlled trials of continuous combined hormone treatment within the US Women's Health Initiative (WHI), have provided estimates of benefit and risk which are incorporated in these recommendations. Care should be exercised in distinguishing absolute risk/benefit from relative risk/benefit, which is expressed as a percentage increase or decrease in absolute risk (e.g. the reported 26% increase in the relative risk of breast cancer in the WHI is actually an absolute excess of four breast cancers for 1000 women treated for 5 years, or less than one excess case per 1000 women per year of treatment).

Middle-aged women often approach their doctor seeking information on hormonal therapy because of typical menopausal symptoms such as hot flushes, sweating, insomnia and vaginal dryness or urinary frequency. Up to 75% of menopausal women experience one or more such symptoms. They are a direct consequence of a

decrease in estrogen levels. Therefore treatment with estrogens is logical and, because of its efficacy, is the therapy of choice. Estrogens also improve mood, well-being and quality of life. The prevention of postmenopausal bone loss and reduction of fracture risk have been demonstrated in randomized, placebo-controlled trials in menopausal women.

INDICATIONS FOR HRT

Menopausal symptoms

Autonomic disturbances such as hot flushes, sweating, insomnia and palpitations can be relieved by hormone replacement therapy (HRT). Other symptoms such as fatigue, irritability, nervousness and depressed mood may be improved. In this way, the quality of life is maintained. Progestogens can potentiate or oppose the action of estrogens.

Urogenital atrophy

- Atrophic changes in the urogenital tract and their consequences (e.g. vaginal dryness, dyspareunia, urinary frequency and urgency) are improved by estrogen therapy.
- When prescribing *solely* for the treatment of such symptoms, topical low-dose vaginal products are the treatment of choice.

Prevention and treatment of postmenopausal osteoporosis

- Necessary but not sufficient measures in the prevention and treatment of postmenopausal osteoporosis include regular weight-bearing exercise, cessation of smoking, adequate calcium intake and insuring normal levels of vitamin D.
- Estrogens prevent postmenopausal bone loss and reduce fracture risk (as shown in randomized, controlled trials).
- Some progestogens potentiate the action of estrogens.
- Low-dose HRT prevents the loss of spinal and hip bone mass in elderly patients, as well as in recently postmenopausal women. Standard-dose HRT, additionally, has been shown to lower the risk of spine, hip and forearm fractures.
- In symptomatic women treated with HRT, the effect on bone mass is a major additional benefit.
- HRT may be an initial option for osteoporosis prevention and for fracture risk reduction in the asymptomatic woman at significantly increased fracture risk. Such treatment would be the first phase of a long-term program which may involve the subsequent use of selective estrogen receptor modulators (SERMS) and/or bisphosphonates and teriparatide when indicated.

Premature menopause

Premature menopause is associated with an accelerated risk of osteoporosis and probably coronary heart disease. Women who have undergone premature menopause should normally be offered HRT at least until the average age of menopause (51 years).

OTHER EFFECTS

- The increase in body weight observed in postmenopausal women is associated with aging and is not related to the use of HRT. Increases in body weight are less pronounced in women on HRT.
- Low libido may improve with estrogen alone, but oophorectomized women, in particular, may require the addition of an androgen, e.g. testosterone. The value of androgens in non-oophorectomized women remains unclear.

- Estrogens delay the development of atheromatous plaques in oophorectomized primate models. Clinical studies have demonstrated positive effects of estrogen on cardiovascular risk factors and vascular function in non-atherosclerotic vessels.
- The effect of various progestogens on vascular function has not been clarified. There are preliminary data from *in vitro* and *in vivo* experiments that different progestogens (e.g. medroxyprogesterone acetate (MPA) vs. norethisterone/norethindrone acetate (NETA)) may have different effects on the vascular system.
- Where there is pre-existing cardiovascular disease (either subclinical atherosclerosis or a history of angina pectoris or myocardial infarction), initiation of HRT may precipitate an increase in risk of cardiac events in the first year of therapy, especially in women many years after menopause. Currently available data indicate that HRT is not suitable for secondary prevention of coronary heart disease. If severe menopausal symptoms occur in such patients, low-dose HRT may be considered.

HRT ALTERNATIVES

When estrogen therapy is not tolerated or is contraindicated, a number of alternative therapies can be considered.

- Some herbal extracts may improve menopausal symptoms, although such improvement may be similar to that seen with placebo. Some extracts contain significant amounts of substances with estrogenic properties (phytoestrogens), the actions of which have not been sufficiently investigated. Neither organ nor herbal extracts are adequate alternatives to HRT.
- Phytoestrogens may slow the rate of bone loss, but fracture risk reduction has not been demonstrated.
- α -Adrenergic agonists such as clonidine are moderately effective in relieving hot flushes.
- High doses of progestogens (5–10 mg NETA, 20–40 mg MPA or megestrol acetate/day) effectively reduce hot flushes. Long-term safety including effects on the breast has not been demonstrated.
- Tibolone is a synthetic steroid described as a pro-drug with progestogenic, androgenic and estrogenic activity. It relieves menopausal

sal symptoms and conserves bone, but has not as yet been shown to decrease fracture risk.

- Neuroactive drugs, e.g. selective serotonin receptor inhibitors (SSRIs), are able to relieve vasomotor symptoms with moderate efficacy and may be tried for short periods when HRT is contraindicated or an alternative is desired, as in symptomatic patients who have been treated for breast cancer. Prescribers should be aware of the potential side-effects of such drugs and the need for gradual withdrawal of therapy.
- Recent reports suggest that gabapentin reduces hot flushes.
- Bisphosphonates can be used to treat osteoporosis, especially in older postmenopausal women with a history of osteoporotic fracture. In younger postmenopausal women, their long-term effects have not been adequately investigated. There are no data demonstrating a reduction in hip fracture risk in younger postmenopausal women (<65 years) treated with bisphosphonates.
- SERMs are licensed for the prevention and treatment of spinal osteoporosis in postmenopausal women. They have not been shown to reduce hip fracture risk. In early postmenopausal women, SERMs are not able to relieve climacteric symptoms and may make them worse. Preliminary evidence suggests that they may reduce breast cancer risk.

PROGESTOGEN USE

In women with an intact uterus and treated with estrogens, progestogens should be used to protect the endometrium. They are generally not required in women following hysterectomy.

Progestogens are used to protect the endometrium at times of unopposed estrogen stimulation. Sporadically unopposed endogenous estrogen levels are seen in the pre- and perimenopause when the corpus luteum is not functioning or is functioning inadequately, and excess endogenous estrogen is found in obese postmenopausal women. Together with the prolonged use of unopposed estrogen, these states are associated with an increased risk of endometrial hyperplasia and/or carcinoma. Progestogen, given sequentially or continuously as a component of HRT, prevents endometrial hyperplasia and endometrial carcinoma.

Protection against endometrial hyperplasia in patients treated with HRT can be achieved only by sequential or continuous progestogen administration. With sequential treatment, the progestogen should be given in an adequate dosage for 10–14 days each month. There are inconsistent long-term data on endometrial protection with long-cycle progestogen (every 3 months for 14 days). Local intrauterine administration has not been evaluated adequately. Low-dose unopposed estrogen is not recommended because of the increased risk of endometrial hyperplasia and cancer.

Progestogens do not protect against breast cancer and may increase this risk compared to estrogen alone.

CONTRAINDICATIONS (AS SPECIFIED BY REGULATORY AUTHORITIES)

HRT should generally not be prescribed in the following circumstances:

- Current, past or suspected breast cancer,
- Known or suspected estrogen-dependent malignant tumors (e.g. endometrial cancer),
- Undiagnosed genital bleeding,
- Untreated endometrial hyperplasia,
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism),
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction),
- Untreated hypertension,
- Active liver disease,
- Known hypersensitivity to the active substances or to any of the excipients,
- Porphyria cutanea tarda (an absolute contraindication).

INITIATION OF TREATMENT

As a general principle, HRT should be initiated when menopausal symptoms occur.

Perimenopause

Treatment will be dictated by the type of symptom. Hormonal treatment includes the following:

- Progestogens during the second half of the cycle, if menstrual disturbances are the main symptom;

- HRT, if vasomotor symptoms have begun or cycle regulation is needed;
- Oral contraceptives (preferably low-dose), if contraception is also required.

During the menopausal transition, endogenous estrogens may be produced irregularly. Sequential preparations, which are preferably progestogen-dominant, should be chosen to achieve regular withdrawal bleeding. Later, a bleed-free continuous combined estrogen/progestogen therapy can be recommended. When changing from sequential to continuous combined HRT, which should be done at the end of withdrawal bleeding, the aim should be to fulfil the following criteria:

- The patient is likely to be postmenopausal (age \geq 50 years);
- The patient should have had regular withdrawal bleeding and no irregular bleeding while taking sequential HRT

or

- The patient had no bleeding on sequential HRT.

The majority of metabolic changes, e.g. the increase of bone resorption, start during the perimenopause.

Postmenopause

Early initiation of HRT in symptomatic patients is of major importance; it enables both relief of menopausal symptoms and protects against the consequences of estrogen deficiency.

HRT DOSE RECOMMENDATION

The dose of estrogen should be the lowest needed to relieve symptoms effectively. Recommended starting doses include:

- 0.5–1 mg 17 β -estradiol
- 0.3–0.45 mg conjugated equine estrogens
- 25–37.5 μ g transdermal (patch) estradiol
- 0.5 mg estradiol gel
- 150 μ g intranasal estradiol

Symptoms should be reassessed after 8–12 weeks of treatment and the dose adjusted if necessary. In about 10% of patients, a higher dose may be required. The need for higher doses should be reassessed from time to time with a reduction of

dose where possible. Women with premature ovarian failure may need a higher dose than older menopausal women. In young women, a combined contraceptive preparation is often suitable.

DURATION OF TREATMENT

The duration of HRT is based on the indication for treatment.

- The appropriate indication, dose and type of HRT should be re-evaluated annually.
- The need for continuing treatment to relieve menopausal symptoms can be determined only by temporarily discontinuing therapy. In general, this can be considered after 2–3 years. If symptoms do not recur, HRT does not need to be reinstated.
- For the prevention or treatment of osteoporosis only, long-term therapy is effective. HRT may be an appropriate initial option in younger postmenopausal women at increased risk, and could be followed by SERMs and/or bisphosphonates.
- Similarly, long-term therapy, usually topical, may be required for ongoing relief from the symptoms of urogenital atrophy.

ROUTES OF ADMINISTRATION

The non-oral route of administration may offer advantages and disadvantages. Because of the lack of the first-pass effect on the liver, the non-oral route of administration may be preferable in women with hypertriglyceridemia, liver disease, migraine headaches and increased risk of venous thrombosis.

For women with symptoms of urogenital atrophy alone, low-dose vaginal estrogen is recommended. Some women on systemic therapy continue to experience urogenital symptoms and, for them, additional vaginal therapy is recommended. In women with an intact uterus using vaginal estrogen, consideration should be given to monitor or evaluate them annually for evidence of endometrial stimulation.

MONITORING TREATMENT

Pretreatment assessment should include history and physical examination with measurement of weight and blood pressure. The history should be directed, in particular, to potential indications and contraindications for HRT, including menopausal symptoms, menstrual history, personal and/or

family history of osteoporotic fracture, venous thromboembolism, breast cancer and cardiovascular disease. Additional investigations would be guided by this evaluation. Patients should be re-evaluated annually.

Additional assessments that may be required include:

- Mammography (frequency according to local guidelines): some women may develop increased mammographic density, particularly on higher doses of continuous combined HRT. To avoid diagnostic difficulties in such patients, discontinuation of HRT for 2–4 weeks before mammography can be considered.
- Vaginal ultrasound and/or endometrial biopsy:
 - Patients on continuous combined HRT often bleed during the first 3–6 months of treatment. If bleeding persists beyond this time or is excessive or prolonged, appropriate investigation is required according to local practice.
 - Abnormal vaginal bleeding in patients on sequential HRT requires investigation. Patients who do not bleed on sequential HRT do not require investigation.
- Bone mineral density measurement based on local guidelines.

The indication for HRT should be reconsidered at the annual check-ups (see Duration of treatment above). If HRT is continued, a further reduction in dose may be considered. Osteoporosis management should be continued independently of management of menopausal symptoms in patients at high risk for osteoporosis and fracture.

HRT AND CANCER

Sex steroids influence the behavior of neoplasms in varying ways. The risk of breast cancer diagnosis may be increased by long-term HRT use, while colorectal cancer is reduced. However, most women fear breast cancer more than any other cancer and this affects their willingness to use HRT.

Unopposed estrogens increase the risk of endometrial cancer and this persists for many years after cessation. The risk of endometrial cancer is minimized by the concomitant administration of progestogens (see Progestogen use above).

Other neoplasms, including cervical and ovarian carcinoma, are not a contraindication to the use of HRT.

Breast cancer

Breast cancer risk is influenced by the total duration of exposure to endogenous and exogenous estrogens and progestogens. Progestogens increase the estrogen-dependent proliferation of mammary tissue. The reported small increase in the incidence of breast cancer found in women on long-term HRT with estrogens or estrogen/progestogen combinations has not been associated with an increased mortality in most studies. There is no definite evidence of any differences between the various estrogens and progestogens in terms of their effect on the risk of breast cancer. It is also reported that tibolone increases this risk.

- Before starting HRT, the advantages must be balanced against possible risks. This is particularly important if the therapy is continued beyond 4–5 years.
- The risk of the diagnosis of breast cancer is increased with use of estrogen and, to a greater extent, with estrogen/progestogen treatment beyond about 5 years. However, the announcement of the termination of the estrogen-only arm of the WHO hormone therapy trials stated that there was no increase in breast cancer risk in women treated with estrogen alone for an average of 7 years (a full report is expected later in 2004). On the basis of randomized, controlled trial evidence, for combined therapy the absolute increase in breast cancer risk is up to four extra cases per 1000 women for 5 years of treatment.
- To place the above in perspective, the increased risk of diagnosis of breast cancer with HRT is similar to the increased risk of breast cancer associated with such factors as an early menarche (before age 11 years), a late first pregnancy (over 35 years), nulliparity and moderate alcohol consumption (≥ 20 g/day). It should be noted that the risk of breast cancer increases with increasing age.
- The increased risk attributed to HRT is much less than that associated with obesity. In this context, it has been reported that the increased risk of breast cancer with long-term HRT use is seen predominantly in women of normal (< 24 kg/m²) rather than increased body mass index.
- The increased risk of breast cancer returns to that of the never-user of HRT within 5 years of discontinuation of treatment.
- Most observational studies have reported that the breast cancers associated with HRT have a

better prognosis than tumors arising in non-users. The WHI reported that tumor size was slightly greater and lymph node metastases were more frequent in hormone users than in non-users.

- The type of hormones (both estrogens and progestogens), route of administration and the HRT regimen (sequential, continuous combined) seem to be associated with similar increases in breast cancer risk. Tibolone, like conventional HRT, is also reported to show an increased breast cancer risk.
- Different regimens of HRT (unopposed, sequential, continuous combined) lead to different frequencies of increased mammographic density (approximately 5%, 15%, 30% of patients, respectively). This increase may reduce the sensitivity of mammographic diagnosis. There are no data demonstrating a relationship between increased mammographic density due to HRT and breast cancer risk.
- Low-dose vaginal estrogen treatment has not been reported to increase breast cancer risk.
- Findings with regard to the relative risk for breast cancer in large, randomized, clinical trials and in observational epidemiological studies are listed in Tables 1 and 2.

HRT AND CARDIOVASCULAR RISK

- Various observational and interventional studies have shown that HRT increases the risk

of venous thromboembolic disease by a factor of 2–3. As calculated from the WHI randomized, controlled trial, the number of additional cases of venous thromboembolism over a 5-year period is approximately 2–6 per 1000 women aged 50–59 years. With transdermal estrogen therapy, it is reported in one observational study that the risk of thromboembolic disease is not increased or is only slightly increased. If there is a history of venous thrombosis, HRT is usually contraindicated, because the risk of recurrence is significantly increased.

- The WHI reported a significant increase in cardiovascular events in the first year of treatment with the combination of conjugated equine estrogens (CEE) 0.625 mg and MPA 2.5 mg (an absolute increase of two additional events per 1000 women in that first year). There was an absolute increase of 3.5 extra cases per 1000 women (statistically not significant) for 5 years of treatment. It is not known whether this risk also applies to lower doses, other therapeutic combinations and/or routes of administration. Whether such risk estimates are applicable in general to women in whom treatment is initiated around the time of menopause is unclear, since the WHI reported no increase in cardiovascular disease risk in women who were less than 10 years since their last menses.
- There is a reported small increased risk with HRT for ischemic stroke. For the combination

Table 1 Findings of the randomized, clinical trials for the relative risk of breast cancer

<i>Group investigated</i>	<i>Relative risk</i>	<i>Confidence intervals</i>	<i>Statistically significant</i>
WHI*	1.24	1.01–1.54	yes
WHI*, no prior hormone use	1.09	0.86–1.39	no
WHI*, prior hormone use < 5 years	1.70	0.99–2.91	no
WHI*, prior hormone use ≥ 5 years	2.27	1.00–5.15	no
HERS**	1.30	0.77–2.19	no
HERS II***	1.08	0.52–2.24	no

WHI, Women’s Health Initiative; HERS, Heart and Estrogen/progestin Replacement Study
 Treatment duration with continuous combined HRT: * 5 years; ** 4 years; *** 6.8 years

Table 2 Findings of two recent observational epidemiological studies of the relative risk of breast cancer with HRT

<i>Group investigated</i>	<i>Relative risk</i>	<i>Confidence intervals</i>	<i>Statistically significant</i>
Collaborative Group*	1.35	1.21–1.49	yes
Million Women Study**	1.66	1.58–1.75	yes

*Treatment duration 5 years; **treatment duration at recruitment was approximately 6 years for women on continuous combined treatment

of CEE 0.625 mg and MPA 2.5 mg in the WHI, the absolute excess risk of stroke was four extra cases per 1000 women for 5 years of treatment.

- Epidemiological results suggest a relationship between estrogen dose and risk for thromboembolic events, as well as for stroke: a decrease in dose results in a decrease in the respective risks.
- HRT should not be used for secondary prevention of cardiovascular disease, i.e. for reducing the risk of cardiovascular events in women with clinical or subclinical atherosclerosis. The role of low-dose therapy is unclear.
- The development of atherosclerosis in postmenopausal women, and hence the risk of coronary heart disease, correlates with the duration of estrogen deficiency. Estrogens may have a favorable effect on the arteries if HRT is initiated soon after menopause. Currently, primary prevention of coronary heart disease is not an indication for HRT.

CONCLUSION

HRT should only be prescribed when it is clearly indicated, primarily for symptom relief. In this context, there is no effective alternative to estrogen or estrogen/progestogen treatment. HRT may be an initial option for fracture risk reduction in women at significantly increased fracture risk and has numerous other beneficial effects. It involves some additional risk of venous thromboembolic disease, stroke and breast cancer after long-term therapy. The need to continue with treatment should be reviewed regularly. For this reason, the indications for HRT should be reconsidered regularly when used in the long term.

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