



## South African Menopause Society Council consensus statement on menopausal hormone therapy

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The modern clinician is expected to practise in accordance with the findings of evidence-based medicine. This implies that the clinician is familiar with the strongest evidence available. The latter is difficult for the following reasons:

- The results of a given clinical trial can only be applied to the specific population and circumstances as applicable to the study in question.
- A small group of individuals may react in a unique way to medication.
- Statistical significance does not always equate to clinical significance.
- Different methods of defining statistical significance may yield different answers when applied to the same data.
- Publications often only quote relative risks and ignore the clinically more relevant absolute risks.
- The perception of the patient is always relevant. A weak association between hormone therapy (HT) and breast cancer may be more important to women and the lay press than a strong association between HT and thrombo-embolic disease.
- The side-effects of preventive medicine in healthy individuals have to be viewed differently to side-effects resulting from treatment for disease.
- New results are being published at an increasingly rapid rate and this may compound choices regarding treatment options.
- The practice of HT was for many years based mainly on the results of observational trials. These have now been supplemented with the results of large randomised trials.
- Cancer, metabolic diseases, vascular disorders and brain ageing are not only the concerns of women on HT, but are of universal concern to women past reproductive age.

With the aforementioned in mind, the South African Menopause Society (SAMS) has decided to formulate a position statement based on present knowledge regarding menopausal hormone therapy and provide guidelines for clinical practice. Clinical guidelines will not be able to cater for all situations, as there are still major gaps in our present knowledge. The situation is unlikely to improve in the near future. The final decision must be a joint decision between the health care provider and an informed patient, based on the

relevant current clinical factors.

Oestrogen alone will be referred to as ET and oestrogen in combination with a progestogen as EPT. HT refers to both forms of treatment.

### Position statement on present knowledge regarding menopausal HT

**Systemic HT improves vasomotor symptoms and/or associated sleep disorders of early menopause.** It remains the only treatment that consistently has a greater effect than placebo in published controlled trials. The incidence of hot flushes in the untreated patient after 5 years is low, but the incidence of hot flushes after cessation of HT has not been adequately studied. ET is effective even in lower dosages and the effect may be enhanced by the addition of a progestogen. EPT did not improve quality of life (QOL) in mostly asymptomatic menopausal women in the Women's Health Initiative trial (WHI), but this may be a result of the specific instrument used to measure QOL. It is recommended that in clinical practice the effect on QOL can best be judged by the individual patient herself.

**Systemic and local HT is effective in the prevention and treatment of vulvar and vaginal atrophy.** In cases of severe atrophy, initial combination of systemic and local therapy may be followed by local therapy alone. Local oestrogen preparations, as available in South Africa, when correctly used, do not result in sufficient systemic absorption to warrant the use of progestogen for endometrial protection.

**HT is effective in preventing the bone loss associated with early menopause.**

**HT is effective in decreasing the incidence of vertebral and hip fractures, even in patients at low risk for fractures.** This effect is only present while on therapy and is fairly rapidly lost after cessation of therapy.

**EPT is associated with a modest increase in risk of invasive breast cancer, if used for more than 5 years.** Although the relative risk is in the order of 1.35, the absolute increase in risk is small (e.g. WHI: 8/10 000 per year or less than 0.1% per year), but increases with duration of treatment if treatment is initiated after the age of 50. It is possible that this does not imply causality, but rather modification of pre-existing malignancy. Carcinoma *in situ* has not been shown to increase in any study. The biological behavior of breast cancer has not been adequately studied to make firm conclusions. The effect is

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more pronounced in lean patients. The increased risk disappears 5 years after cessation of therapy. The increased risk is associated with the addition of progestogen and risk is apparently not increased when oestrogen is used alone (WHI: no increased risk on ET up to 7 years). HT may impede the diagnostic interpretation of mammography by increasing breast density, so it may be advisable to stop HT 2 - 4 weeks prior to mammography.

**EPT reduces the risk of colorectal cancer.** In the EPT arm of WHI the overall incidence of newly diagnosed malignancies was equal in the treated and untreated groups, as the increase in breast cancer was offset by the reduction in colorectal and uterine cancer. Likewise the all-cause mortality figure was the same in both groups. The reduction of risk of colorectal cancer was not shown in the ET arm of WHI.

**HT does not offer secondary protection against coronary heart disease (CHD) or stroke.** EPT (not ET) is associated with an increase in non-fatal CHD in patients started on HT more than 10 years after start of menopause (WHI: excess cases of CHD 7/10 000 per year). HT increases the risk of ischaemic stroke but not haemorrhagic stroke (WHI: excess cases of stroke 8/10 000 per year). The effect of HT on primary prevention of CHD and stroke has not been sufficiently studied in randomised clinical trials (RCTs) to allow any firm conclusion.

**HT is not indicated for the prevention or treatment of Alzheimer's disease (AD).** It is acknowledged that primary prevention has not been adequately studied in RCTs but epidemiological studies have found that ET causes a delay in onset of AD. EPT in patients older than 75 increases the risk of AD.

**The risk of venous thrombo-embolism (VTE) is doubled with HT.** The absolute risk of VTE is increased by 18 cases per 10 000 women per year (EPT arm WHI). The effect is maximal in the first year of treatment and more pronounced with advancing age, obesity and previous VTE.

**ET increases the risk of endometrial cancer.** The excess risk is reduced by the addition of progestogen. The primary menopause-related indication for progestogen use is endometrial protection from ET in the patient with a uterus.

**Premature menopause has not been addressed in recent studies and patients should be offered HT until the expected age of normal menopause (approximately 51 years).**

## Clinical guidelines regarding menopausal HT

The menopausal transition should be utilised as a window of opportunity to assess and manage specific, as well as general, health related matters. Medical history and examination can be supplemented by special investigations. These may include a

fasting lipogram, blood glucose, mammography and DEXA bone densitometry. Lifestyle modifications such as the cessation of smoking, diet, and the maintenance of appropriate body mass index, exercise and stress reduction should be discussed. Medical treatment of dyslipidaemias, hypertension and diabetes should be optimal. Investigations for hypercoagulability states should only be undertaken in patients at risk, before instituting HT.

HT should only be initiated for specific proven indications, as discussed above, provided there are no contraindications.

HT should be individualised according to each patient's needs.

If HT is considered for the sole purpose of the prevention or treatment of osteoporosis, other proven therapies should also be considered.

The need for continuation of HT should be re-evaluated annually. The need for continuing treatment of menopausal symptoms can be determined by temporarily discontinuing therapy after about 4 - 5 years. As a general rule, the risks involved with EPT for the first 5 years after menopause and with ET for the first 10 years after menopause are very small. **Treatment for periods exceeding these limits or the age of 60 years must be individualised in terms of risk and benefit. This decision is best left in the hands of the menopausal expert and the informed patient.**

**HT should in general not be initiated after the age of 60 years.**

The general pharmacological principle of the smallest effective dose for the shortest required time is applicable to HT.

Should EPT be required for longer than 5 years, it is recommended to convert from sequential HT to continuous combined HT.

**These statements are currently applicable to all oestrogens and progestogens as well as tibolone.** Although it has been suggested that tibolone has minimal effect on the breast, there is at present not sufficient evidence to support this in clinical decisions. Several RCTs are currently in progress that will better define the role of tibolone.

**These statements are applicable to all routes of administration including transdermal application.** The non-oral route avoids the first-pass effect on the liver and may be preferable in conditions of hypertriglyceridaemia, liver disease, migraine, glucose intolerance and increased risk of VTE.

All patients should be re-evaluated annually.

It is recommended that ideally all postmenopausal women should be encouraged to undergo yearly mammography, whether on HT or not.

It is concluded that every practitioner needs to be aware about the present status of knowledge regarding HT in order to assist the patient in making informed decisions about menopausal management. It is anticipated that HT in



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conjunction with lifestyle modifications will remain the treatment of choice for acute menopausal symptoms for the immediate future. It is hoped that future research will be able to identify a patient profile or method of application where longer use of HT is without risk. This will unlock the true potential of HT in the prevention and treatment of osteoporosis and allow new research on the role of HT in primary prevention.

## Key reading

1. Barret-Connor E, Slone S, Greendale G, *et al.* The postmenopausal Estrogen/Progestin Intervention Study: primary outcomes in adherent women. *Maturitas* 1997; **27**: 261-274.
2. Cardoza L, Bachmann G, McClish D, *et al.* Meta-analysis of estrogen therapy in the management of urogenital atrophy in menopausal women: second report of the Hormones and Urogenital Therapy Committee. *Obstet Gynecol* 1998; **92**: 722-727.
3. Chlebowski RT, Hendrix SL, Langer RD, *et al.* Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. *JAMA* 2003; **289**(24): 3243-3253.
4. Hulley S, Grady D, Bush T, *et al.*, for the Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998; **280**: 605-613.
5. MacLennan A, Lester S, Moore V. Oral oestrogen replacement therapy versus placebo for hot flushes. *Cochrane Database Syst Rev* 2001; **1**: CD002978.
6. Manson JE, Hsia J, Johnson KC, *et al.* Women's Health Initiative Investigators. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003; **349**: 523-534.
7. Shumaker S, Legault C, Rapp SR, *et al.* Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003; **289**: 2651-2662.
8. Warren MP. A comparative review of the risks and benefits of hormone replacement therapy regimes. *Am J Obstet Gynecol* 2004; **190**: 1141-1167.
9. WHI Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. *JAMA* 2004; **291**(14): 1701-1712.
10. Writing Group for WHI Investigators. Risks and benefits of estrogen and progestin in healthy postmenopausal women. *JAMA* 2002; **288**: 321-333.

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