South African Menopause Society Council Revised Consensus Position Statement on Menopausal Hormone Therapy

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The Council of the South African Menopause Society (SAMS) revised the 2004 statement[1] on menopausal hormone therapy (HT) at a consensus meeting held on 25/26 November 2006. The revision incorporated not only new evidence but also the re-evaluated evidence used in the previous statement.

Clinicians are 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 – for example, a weak association between postmenopausal HT and breast cancer may be more important to women and the lay press than a possibly stronger association between HT and thrombo-embolic disease.
- The side-effects of preventive medicine in healthy individuals have to be viewed differently from the side-effects resulting from treatment for disease.
- New results are being published at an increasingly rapid rate and this may complicate choices regarding treatment options.
- For many years HT use was based on the results of observational trials; however, the results of large randomised trials are now also available.
- 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.

Clinical guidelines will not be able to cater for all situations, as there are still major gaps in our present knowledge. The final decision must be a joint decision between the health care provider and an informed patient, based on the relevant current clinical factors and ongoing new scientific evidence.

Estrogen alone will be referred to as ET and estrogen in combination with a progestogen as EPT. The term hormone therapy (HT) refers to either ET or EPT.

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Position statement on present knowledge regarding menopausal HT

Systemic HT improves vasomotor symptoms and associated sleep disorders of early menopause

HT remains the only treatment that has consistently had a greater effect than placebo in published controlled trials. It has been found that after 5 years the incidence of hot flushes is low in untreated patients, but follow-up of women who stopped EPT in the Women's Health Initiative (WHI) trial showed that 55.5% of women suffering from vasomotor symptoms at the start of the study, relapsed after cessation of treatment.[2] ET is effective even in low dosages and the effect is enhanced by the addition of a progestogen. EPT did not improve quality of life (QOL) in mostly asymptomatic menopausal women in the WHI trial,[3] but this may be a result of the specific instrument used to measure QOL. It is recommended that in clinical practice the individual patient herself judge the effect on QOL.

Systemic or local HT is effective in the prevention and treatment of vulval and vaginal atrophy

In cases of severe atrophy, initial combination of systemic and local therapy may be followed by local therapy alone. When correctly used, local estrogen preparations generally do not result in sufficient systemic absorption to warrant the use of progestogen for endometrial protection. The use of conjugated equine estrogen vaginal cream appears more likely to predispose to endometrial proliferation. At present there is not enough evidence to mandate progestogen use in women who persist with any local intra-vaginal estrogen preparations beyond 6 months.

HT is effective in preventing bone loss associated with menopause

The increased rate of bone resorption immediately after menopause clearly indicates a hormonal influence on bone density in women.

HT is effective in decreasing the incidence of all osteoporosis-related fractures, including vertebral and hip fractures, even in patients at low risk for fractures.

The protective effect of HT on bone mineral density is lost at an unpredictable rate after cessation of therapy. Although some degree of fracture protection may remain after cessation of HT, the patient at risk for fracture should receive additional therapy with proven bone-sparing medication.[4]

EPT is associated with a small increase in the risk of invasive breast cancer, if used for more than 5 years

Although the relative risk (RR) is in the order of 1.35, the absolute increase in risk is small (e.g. in the WHI study the risk was found to be 8/10 000 per year or less than 0.1% per year), but this increases with the duration of treatment if initiated after age of 50 years. 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. As the biological behaviour of breast cancer has not been adequately studied, firm conclusions cannot be drawn. The effect of EPT is more pronounced in lean patients. The increased risk disappears 5 years after cessation of therapy.

ET does not increase the risk of breast cancer

The increased risk of breast cancer shown with EPT is associated with the addition of progestogen and is absent when estrogen is used alone. The initial report on the estrogen-only arm of the WHI concluded that there was a non-significant ($p < 0.06$) decreased risk for breast cancer in ET users, but subgroup analyses now reveal that first lifetime exposure to ET at the trial was associated with significantly fewer breast cancer cases when compared with placebo (hazard ratio (HR) 0.76, 95% confidence interval (CI): 0.58 - 0.99; $p < 0.05$). Women who took ET had significantly fewer breast cancers with localised disease and significantly fewer breast cancers with ductal carcinoma (HR 0.71, 95% CI: 0.52 - 0.99). Furthermore, women who were adherent to study medications had significantly fewer invasive breast cancers (HR 0.67, 95% CI: 0.47 - 0.97).[5] Having no first-degree relatives with breast cancer or personal history of benign breast disease was also associated with significantly fewer breast cancers in the ET users compared with the control group.

HT in standard doses increases breast density

This may lead to more breast biopsies and it may therefore be advisable to stop HT 2 - 4 weeks before mammography.

EPT reduces the risk of colorectal cancer

In the EPT arm of the 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 incidence of colorectal and uterine cancer. Likewise, the all-cause mortality figure was the same in both groups. The reduction in risk of colorectal cancer was not shown in the ET arm of the WHI.

HT does not offer secondary protection against coronary heart disease (CHD)

The WHI study failed in the primary endpoint to demonstrate a reduced risk of CHD in HT users. In the EPT arm, a significant increase in non-fatal CHD was found only in the first year, with a significant downward trend thereafter in women started on HT more than 10 years after the start of menopause (absolute risk 7/10 000 women per year). It can be speculated that an inappropriate population was used in the study considering their age, time since menopause and other risk factors for CHD.

HT may offer primary protection against CHD if started soon after menopause

The concept of an early window of opportunity is based on the assumption that estrogen offers protection only when the arterial endothelium is still intact and is supported by epidemiological studies, animal models and the ET arm of the WHI.[6] There was an insignificant increase in CHD events, only in women older than 70 years at the beginning of the study, and in those who had been menopausal for at least 20 years. However, in the younger women (50 - 59 years) there were fewer CHD events in the hormone users compared with women in the placebo arm, although the data were not statistically significant because of a relatively small sample size and the low incidence of CHD in this age group.

Additional evidence comes from the most recent analysis of the Nurses' Health Study. With large subjects numbers the study was able to demonstrate that women starting HT near the menopause had a significantly reduced risk of CHD on ET (RR 0.66, 95% CI: 0.54 - 0.80) and on EPT (RR 0.72, 95% CI: 0.56 - 0.92).[7] Also, in a subgroup of women demographically similar to those in the WHI, there was no significant relation between HT and CHD among women who initiated therapy at least 10 years after the menopause using ET (RR 0.87, 95% CI: 0.69 - 1.10) or on EPT (RR 0.90, 95% CI: 0.62 - 1.29).

There is not enough evidence to support any firm conclusion regarding the effect of HT on stroke

The WHI study reported an increased risk of thrombotic stroke (HR 1.39). This is consistent with results from the Nurses Health Study. In contrast to venous thromboembolism (VTE), the effect was not confined to the first year, but was maintained throughout the study. However, the Danish Nurses Study[8] found that in 13 122 healthy postmenopausal women followed for 5 years, unopposed estradiol 1 mg daily was not associated with an increased risk of stroke (HR 0.80 (CI: 0.40 - 1.61). It is

possible that the effect of HT on stroke is dose related. Smaller doses may be protective and larger doses harmful.[9]

HT is not indicated for the treatment of Alzheimer's disease

Early commencement of HT will have no detrimental effect and could possibly be beneficial in certain domains of cognitive performance. However, commencement of HT after 65 years of age may have detrimental effects.

HT increases the risk of VTE

The relative risk of VTE is doubled with HT, but the absolute risk of VTE is increased by only 22 cases per 10 000 women per year. The effect is maximal in the first year of treatment and more pronounced with advancing age, obesity, previous VTE and underlying thrombophilia. The risk of VTE in the 50 - 60-year age group is very small, but increases 4-fold in the 60 - 69-year and 7-fold in the 70 - 79-year-old age groups. The route of delivery will impact on risk, with the highest risk being with EPT orally, then ET orally and least risk with the transdermal route.

ET increases the risk of endometrial cancer

The risk is significantly reduced with the addition of progestogen. The primary indication for progestogen use in women on HT is for endometrial protection and it should not be used in women who have had a hysterectomy.

HT should be offered to patients with premature menopause

Although this issue has not been addressed directly in recent studies, patients should be offered HT or low-dose combined hormonal contraception until at least 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 should be supplemented with special investigations. These may include a fasting lipogram, blood glucose, mammography, thyroid function test and bone densitometry. Investigations for hypercoagulability states should only be undertaken in patients at risk (personal or family history of VTE) before instituting HT.

Lifestyle modifications such as the cessation of smoking, a healthy diet, and the maintenance of appropriate body mass index, exercise and stress reduction should be discussed. Treatment of dyslipidaemias, hypertension, diabetes and other medical conditions should be optimal.

HT should only be initiated for specific proven indications, provided there are no contraindications, and should be individualised according to each patient's needs.

Indications

1. Treatment of vasomotor symptoms and associated sleep disorders.

2. Symptomatic urogenital atrophy.

3. Prevention of bone loss in women with premature menopause, secondary amenorrhoea and women with osteopenia at risk for fracture.

4. The treatment of osteoporosis in women in the 50 - 60-year age group at risk of fracture, with or without vasomotor symptoms. If HT is considered for the sole purpose of the prevention or treatment of osteoporosis, then other proven bone-specific therapies should be considered.

Contraindications

HT should generally not be prescribed where there is:

- current, past or suspected breast cancer
- known or suspected estrogen-dependent malignant tumours
- undiagnosed genital bleeding
- untreated endometrial hyperplasia
- previous idiopathic or current VTE
- known arterial CHD
- active liver disease, or
- porphyria cutanea tarda (absolute contraindication).

General guidelines

1. The duration of HT should be based on the indication for treatment.

2. The indication for therapy should be reviewed on an annual basis. The decision to determine whether to continue treatment for the relief of climacteric symptoms may be made by temporarily discontinuing treatment. If symptoms do not recur, HT does not have to be resumed. Topical therapy for relief of urogenital atrophy symptoms may need to be continued long term. Only long-term therapy is effective for the prevention or treatment of osteoporosis. Long-term HT can still be considered for bone effects, weighing its benefit and risks against those of alternative therapies. At present there is no compelling evidence to restrict duration of treatment as long as treatment goals are maintained.

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

4. Until further evidence is available all estrogens and progestogen formulations, including tibolone, should be considered similar in terms of clinical risks and benefits.

5. 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 and in smokers.

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

7. Low-dose therapy has been shown to be effective in symptom control and the prevention of bone loss; therefore the principle of lowest effective dose should be adhered to.

8. It is recommended that before commencing HT, all patients should be advised to undergo breast screening, including mammography. Ideally, all menopausal women should have regular mammography.

9. Studies on phyto-estrogens and botanicals have shown inconsistent results. Most good studies show no clear benefit and some potential for harm. Further research is required in order to make firm recommendations. Patients should be made aware of this.

10. Unfortunately no published data exist on the use of traditional African medicine for menopausal symptoms.

11. No therapy for menopausal symptoms should be initiated without proper clinical assessment, including breast and pelvic examination.

It is concluded that every practitioner needs to be aware of the latest evidence on HT in order to assist patients in making informed decisions on menopausal management. It is anticipated that HT in conjunction with lifestyle modifications will remain the treatment of choice for acute menopausal symptoms in the immediate future. It is to be 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.

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