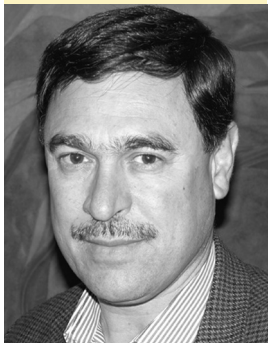
FEMININE FOREVER?

As populations age, the number of women living for many years after menopause is increasing.



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The life expectancy of men and women has increased significantly over the past century. This has resulted in an increased incidence of age-related conditions such as coronary arterial disease (CAD), cerebrovascular incidents, dementia and malignancies. It also means that the female population living after the menopause has increased significantly. The menopause is unique to women. At about the age of 12 years, the female ovaries start cyclical production of the reproductive hormones oestrogen and progesterone. This process unlocks the reproductive potential, which is terminated around the age of 51 years, when the production of the two hormones in question has ceased. In the previous century, few women lived long after the menopause. In spite of the significant increase in life expectancy over the past century, the average age of menopause has stayed constant at 51 years. This means that the average woman can expect to live for about one-third of her life after the menopause. During this period, the absence of the hormone oestrogen has certain specific direct and indirect negative effects on the general health, morbidity and mortality of elderly women.

Oestrogen has been commercially available for more than 50 years, and the concept of 'feminine forever' was advocated by Wilson in 1966. This was previously known as menopausal hormone replacement therapy. In this article, oestrogen therapy alone will be referred to as ET and oestrogen in combination with a progestogen as EPT. Hormone therapy (HT) refers to both forms of treatment. The promise of HT is the prevention of hormone-related problems in older women. This concept became popular, backed by the beneficial effects of oestrogen on secondary markers of disease such as lipids and bone mineral density (BMD) as well as epidemiological evidence on disease endpoints such as CAD and osteoporosis-related fractures. This led to the spectacular growth of the HT market. However, the publication of the results of the randomised trial of oestrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women (HERS) in 1998, failing to support the secondary protective effect of EPT on CAD, reversed the growing trend. The decline in the use of HT was further fuelled by the early termination of both the EPT and the ET arm of the Women's Health Initiative (WHI) study, when the investigators concluded that disadvantages of HT outweighed the advantages. Initial reaction to these studies led to a very restricted indication for the use of HT and many patients discontinued therapy. This article reviews the advantages and disadvantages of menopausal HT and the promise of 'feminine forever'.

PROVEN ADVANTAGES OF HT

Treatment of vasomotor and associated symptoms

Hot flushes are symptoms of vasomotor instability. These usually occur in the first 5 years after menopause, and in a minority may last for years. In 25% of women who have recently gone through menopause, hot flushes are severe enough for the women to seek medical attention. Sleep disturbance frequently results from severe vasomotor symptoms, which remain the most important indication for systemic HT. It is the only form of treatment that consistently and significantly relieves vasomotor symptoms when compared with placebo in randomised trials. No alternative or complementary medication has ever been shown to reduce the

vasomotor symptoms of menopause consistently and significantly above the level shown for placebo. Vasomotor symptoms are generally confined to the first 5 years after menopause, so it should be possible to discontinue HT after 5 years. Whether this is possible in practice will be discussed below.

PREVENTION AND TREATMENT OF UROGENITAL ATROPHY

Some degree of urogenital atrophy is present in all menopausal women and will increase with age. This neglected gynaecological syndrome of older women can be prevented and treated successfully and safely with either systemic or topical vaginal therapy. Typical symptoms are dryness, itching and irritation of the vulva or vagina; discomfort during sexual intercourse; bladder symptoms such as urgency and stress incontinence; pelvic relaxation and symptoms of genital prolapse. Significant urinary stress incontinence and genital prolapse need to be treated surgically, but all other symptoms can be successfully treated by either systemic or local HT. Local oestrogen applications available in South Africa do not result in sufficient systemic absorption to warrant the use of progestogen for endometrial protection.

PREVENTION AND TREATMENT OF OSTEOPOROSIS-RELATED FRACTURES

Lack of oestrogen after menopause causes accelerated bone loss, in addition to normal age-related bone loss, resulting in an increased risk of osteoporosis-related fractures. The most common are fractures of the distal forearm, vertebral fractures and hip fractures. Both vertebral and hip fractures are associated with significant morbidity and mortality. Although the beneficial effect of oestrogen on bone loss as measured by BMD has been recognised for many years, a significant reduction in all osteoporosis-related fractures was documented for the first time in the WHI study. However, the beneficial effect of HT on bone is only present while the patient is on therapy. Bone loss after cessation of therapy is rapid and returns to pre treatment levels within 1 year, resulting in an increased risk of fracture. Protection against osteoporosis implies long-term therapy, with the attendant potential risks such as a possible increase in the relative risk of breast cancer. This needs to be weighed against the use of other proven therapies such as the selective oestrogen-receptor modulators (SERMs) or bisphosphonates.

EPT REDUCES THE RISK OF COLORECTAL CANCER

A significant reduction in colorectal cancer in HT users was documented in the EPT arm of the WHI study. How this effect can be utilised in clinical practice is currently unclear. However, it is important to consider this effect when judging the oncological implications of HT. In the EPT arm of the WHI study the overall incidence of newly diagnosed malignancies was equal in the treated and untreated group because 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.

PROVEN DISADVANTAGES OF HT

Increased risk of venous thrombo-embolism (VTE)

The absolute risk of VTE is increased by a factor of 2 - 3. In the WHI study, this translated to 2 - 6 extra cases per year per 1 000 women aged 50 - 59 years. The effect is maximal in the first year of treatment and more pronounced with advancing age, obesity and previous VTE. This risk was documented in many epidemiological studies. In the EPT arm of the WHI study the risk was significant for both deep venous thrombosis (DVT) and pulmonary embolism (PE), while in the ET arm it was significant only for DVT. Patients considering the initiation of HT with a personal or familial history of VTE should be tested for predisposing haematological factors. All patients on HT should be warned about the symptoms and be instructed to seek medical attention immediately. It has been suggested that the risk of VTE may be less if HT is given transdermally.

Increased risk of stroke

HT was previously considered possibly to be protective against stroke. However, the WHI trial suggested that HT increases the risk of ischaemic stroke, but not haemorrhagic stroke. The absolute excess risk of stroke in the EPT arm was 4 extra cases per 1 000 women for 5 years of treatment. The risk was increased in all years of treatment.

No secondary protection against CAD

CAD in premenopausal women is less common than in men. After menopause, CAD is the most common cause of death in women. HT has proven beneficial effects on risk markers for CAD at both arterial and extra-arterial levels. Observational studies have consistently supported a beneficial effect of HT on CAD, with the incidence of CAD reported as lowered by up to 50% in HT users. It was suggested that these favourable results might have been false because of the healthy user effect. This argument implies that healthier people chose to use HT and therefore have a lower incidence of CAD anyway. However, the HERS trial in 1998 conclusively proved that EPT was not effective in the prevention of secondary CAD and may in fact be the cause of an increased incidence in the first year of treatment. The WHI trial was designed to address the problem of primary prevention. However, the average age of participants was 64 years and significant numbers were obese and smokers. Both the ET and EPT arms of the WHI trial failed to show a reduction in CAD and possible harm was demonstrated in the EPT arm.

The difference between the results of observational studies and RCTs may be explained by the fact that most patients in observational trials started HT immediately after menopause, thus representing true primary protection. It

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has been shown in animal studies that the beneficial effect of oestrogen on arteries is lost after the arteries have been damaged. The effect of HT on CAD in humans when initiated immediately after the start of the menopause has not been studied in RCTs and probably will not be as other effective ways of preventing CAD are currently available. These include changes of lifestyle as well as agents such as statins and proper control of hypertension and diabetes. HT should not be used for the prevention of CAD.

Diagnosis of invasive breast cancer increases after 5 years of EPT

The absolute increase in risk of breast cancer is small (WHI: 8/10 000 per year or less than 0.1% per year), but increases with duration of treatment if initiated after the age of 50. Possibly this does not imply causality, but rather modification of pre-existing malignancy. However, the biological behaviour of such tumours and their associated mortality has not been adequately studied. The effect is more pronounced in lean patients. The increased risk disappears 5 years after cessation of therapy, is associated with the addition of progestogen and is greatly reduced when oestrogen is used alone. In the ET arm of the WHI study, the incidence of invasive breast cancer was indeed lowered to nearly insignificant levels. HT may impede the diagnostic interpretation of mammography and it is advisable to stop HT for 10 days before mammography.

HT should not be used in the treatment of Alzheimer's disease (AD)

Observational studies have suggested that HT may help to preserve memory and delay brain ageing and dementia. However, HT has not been shown to be effective in the treatment of established AD. The WHI trial failed to show any significant effect of HT on mild cognitive impairment and indeed the risk of AD was increased in patients after the age of 71 years. It is attractive to speculate that as with the cardiovascular system the beneficial effects of HT on the brain are confined to primary protection if taken from the start of the menopause. However, this needs investigation.

CONCLUSION

The promise of 'feminine forever' has proved more complicated than initially thought, but the concept of menopausal HT is still alive and well, provided it is only used when clearly indicated. Patients should be informed about possible disadvantages, but the absolute risk rather than relative risk should be used as illustration. This will provide a better platform from which the patient and health care provider can make a combined informed decision about the initiation or continuation of HT.

CLINICAL GUIDELINES FOR THE USE OF HT

- Only use HT for proven indications.
- Progestogen should only be used in the patient with a uterus to protect against endometrial cancer.
- The lowest effective dose for the specific indication should be used.
- The need for continuation of HT should be re-evaluated annually. The need for continuing treatment of vasomotor symptoms can be determined by temporarily discontinuing therapy after about 3 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.
- HT should not be initiated after the age of 60 years.
- Statements made are currently applicable to all oestrogens and progestogens as well as tibolone. Although it has been suggested that tibolone has minimal effects on the breast, there is currently not sufficient evidence to support this in clinical decisions. Several RCTs are at present in progress that will better define the future role of tibolone.
- Statements are applicable to all routes of administration. Non-oral routes avoid the first-pass effect on the liver and may be preferable in conditions of hypertriglyceridaemia, liver disease, migraine and increased risk of VTE.

MORE ABOUT HT AND QUALITY OF LIFE

Most gynaecologists with extensive experience in the use of HT are convinced that HT significantly improves quality of life (QOL) in addition to known positive effects on vasomotor symptoms and symptoms due to vaginal atrophy. The scientific proof of this concept is troubled by lack of validat-

ed instruments to measure QOL in controlled trials. In a subgroup of the WHI study QOL was not significantly improved by EPT if used for 3 years. This is probably due to the fact that the average patient in this subgroup had no QOL problems at the start of the study. The concept of improved QOL is very important in the decision to continue HT after the first 5 years. Considering the lack of evidence, it is better to leave the decision about QOL in the hands of the patient. This can be determined by temporarily discontinuing therapy. Most experts agree that the patient should be gradually weaned from therapy. If QOL is not affected, HT need not be reinstated.

Further reading

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.

WHI Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. *JAMA* 2004; **291** (14): 1701-1712.

Writing group for WHI investigators. Risks and benefits of estrogen and progestin in healthy postmenopausal women. *JAMA* 2002; **288** (3): 321-333.

IN A NUTSHELL

HT is the only proven therapy for the treatment of vasomotor symptoms of menopause.

Systemic or local HT prevents and treats urogenital atrophy.

HT prevents the early bone loss of menopause and associated fractures.

HT is associated with a lowered risk of colorectal cancer.

HT increases the risk of VTE and stroke.

HT should not be used for the prevention of CAD.

EPT is associated with an increased risk of invasive breast cancer after 5 years of therapy.

Progestogen is only added in the presence of a uterus in order to protect against endometrial cancer.

Use the lowest dose of HT for the shortest period of time.

SINGLE SUTURE

TV AND PREMATURE PUBERTY?

It seems that children who spend too much time in front of the TV screen may run the risk of premature puberty, according to research by Robert Salti of the University of Florence, Italy. Extra exposure to light lowers production of melatonin, believed to hold back puberty. Salti's team found that melatonin levels in children denied access to TV for a week rose on average by 30%. However, this result is not accepted by everyone. Paul Kaplowitz of the Children's National Medical Centre in Washington, DC says that there is limited published evidence that melatonin is a major factor in regulating puberty in humans. It could also be that extra exercise results in an increase in melatonin levels, so being active would in itself potentially delay puberty. This is the view of Marcia Herman-Giddens of the University of North Carolina, who first published evidence that puberty is occuring earlier.

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