



## CLINICAL PRACTICE

## Hormone replacement therapy — differing guidelines

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Position statements have been issued by the International Menopause Society (IMS)<sup>1</sup> and the South African Menopause Society (SAMS)<sup>2</sup> in response to publication of the Heart and Estrogen/Progestin Replacement Study (HERS),<sup>3</sup> the Estrogen Replacement and Atherosclerosis (ERA) study,<sup>4</sup> the Women's Health Initiative (WHI) oestrogen-plus-progestin arm,<sup>5,7</sup> the Million Women Study (MWS)<sup>8</sup> and the oestrogen arm of the WHI.<sup>9</sup>

These papers caused major concern among women, dismay among medical and nursing experts and opinion leaders and confusion among general practitioners.

The trials and response of *inter alia* the American Food and Drug Administration (FDA) and the European Medicine Evaluation Agency were evaluated against observational studies, meta-analysis and pre-clinical research by the IMS.

Randomised controlled trials (RCTs) are the gold standard, but their results must not be generalised to populations they were not designed to study. By design the WHI<sup>5</sup> limited the intake of vasomotor symptomatic women in the early years of the menopause to less than 10%. This highlights a major difference between RCTs and observations trials. Symptomatic women seek help and choose observational trials, while asymptomatic women are willing to participate in RCTs.

The menopause transition, namely the first 5 or maximum 10 years of the menopause, may well be the 'window of opportunity' for cardiovascular disease and dementia protection using hormone replacement therapy (HRT).

The HERS<sup>3</sup> and ERA<sup>4</sup> studies are secondary prevention trials. Over 40% of the cohort of the two WHI trials<sup>5,9</sup> were at high risk of cardiovascular disease and two-thirds were over the age of 60 years.

In the WHI trial<sup>5</sup> the ratio of disease outcome for coronary heart disease, venous thromboembolism (VTE), stroke and breast cancer shows impressive increases from year 4 to 5, and even larger reductions from year 5 to 6 and later. The significance of this unsustainable rise in year 5 is uncertain. The changes correlate more closely with the placebo outcome inversely than with treatment incidence. The year 6 and later

drop is discounted by the writers: 'the narrowing of the difference by year 5 is because HR [hazard ratio] estimates tend to be unstable beyond 6 years after randomization'. No references are given. The planned duration of the trials was 8.5 years. Over 25% of subjects had used HRT before the start of the trial! The oestrogen arm<sup>9</sup> was stopped in the 7th year because of lack of cardiovascular protection and increased stroke risk.

The HR of venous thromboembolic disease in the WHI trial is over 2.00<sup>5</sup> and is the only clinical outcome not to show a weak association (HR between 1.00 and 2.00) and to have a statistically significant nominal 95% confidence interval (CI).

The data for the risks of HRT and breast cancer are inconsistent.

In a recent review in the *Journal of Internal Medicine* (2004; **19**: 791-804) of 30 clinical studies involving 25 000 women, Salpeter found that women under the age of 60 years on HRT had a 39% lower death rate than non-users and that in the over-60 age group the death rate was similar in users and non-users.

The media, both medical and lay, should be careful about publishing comments on trials until they have been peer reviewed, otherwise incorrect conclusions will be published, as with the WHI on a trial that was outdated when published as it applied to treatment schedules from 1992. By 2002 HRT was no longer prescribed for women of all ages, only to those in the early years of the transition, which according to WHI data may be beneficial for cardiovascular and Alzheimer's disease.

### HRT and menopausal disease

HRT is acknowledged as the best treatment for two conditions, namely vasomotor symptoms and atrophic vaginitis. For other conditions it is preventive or possibly preventive.

#### Vasomotor symptoms

Vasomotor symptoms may cause sleep disorders and secondary depression.

#### Atrophic vaginitis

Atrophic vaginitis causes symptoms of vaginal dryness and dyspareunia. The oestrogen receptor only responds to systemic oestrogens in 70% of women and local oestrogen therapy may be preferred or necessary. Unopposed local

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oestrogen may cause endometrial hyperplasia and yearly ultrasound, endometrial biopsy or progesterone challenge should be performed.

## Osteoporosis

Osteoporosis prevention and hip and lumbar vertebral fracture reduction are the commonest indications for HRT.

## Colorectal cancer

Most trials, including the WHI<sup>5</sup> but not the oestrogen arm of the WHI,<sup>9</sup> found that HRT reduces incidence of colorectal cancer.

## Cardiovascular disease

Both the IMS and SAMS disagree with the National Institute of Health (NIH) that the oestrogen-plus-progestin arm of the WHI<sup>5</sup> is a primary prevention trial.

The menopause transition, namely the first 5 or maximum 10 years of the menopause without atherosclerosis and hypertension may well be the 'window of opportunity' for cardiovascular protection using HRT. This has been suggested by surrogate markers, animal studies,<sup>10</sup> observational trials<sup>11</sup> and at least 4 meta-analyses.

Evaluation of cardiovascular events in the Women's Hope Study and the Menopause Study Group<sup>12</sup> using varying doses of conjugated equine oestrogen and medroxyprogesterone acetate in healthy, early menopausal women (average age 53 and 54 years) showed no increased risk of cardiovascular events in the first year of use, unlike the WHI<sup>5</sup> and HERS.<sup>3</sup>

Both the HERS<sup>3</sup> and the ERA study<sup>4</sup> are secondary prevention trials. Although claiming to be a primary prevention trial, the WHI<sup>5</sup> limited the intake of symptomatic women in the early years of the menopause to less than 10%.<sup>13</sup> A power analysis of the WHI showed that it was 10-fold underpowered to detect an early oestrogen cardioprotective effect<sup>13</sup> of the magnitude reported in observational studies such as the Nurses Health Study.<sup>11</sup>

In the WHI trials the relative risk (RR) for coronary heart disease was 0.9 for the first 10 years since commencement of the menopause<sup>6</sup> but 1.29 in the entire trial overall,<sup>5</sup> and 0.56 for women aged 50 - 59 years and 0.91 overall.<sup>9</sup> The RR for starting HRT early in the menopause is similar to that in many observational trials including a meta-analysis<sup>14</sup> based on observational studies up to mid-1997 (RR 0.70, 95% CI: 0.65 - 0.75) for oestrogen-only users, and 0.66 (95% CI: 0.53 - 0.84) for 7 studies reporting on cyclical oestrogen-plus-progestin use. The WHI<sup>5,9</sup> and HERS<sup>3</sup> show no increased risk with duration of use.

SAMS suggests that cardiovascular disease has not been sufficiently studied in RCTs to allow any firm conclusion, while the IMS states that HRT appears to provide protection against

potential heart disease if started early in the menopause.

## Stroke

According to SAMS primary prevention of stroke has not been sufficiently studied in RCTs to allow a firm conclusion.

The two WHI trials<sup>5,9,15</sup> and HERS<sup>3</sup> involve older women. The Women's Estrogen Trial for stroke (WEST),<sup>16</sup> a secondary prevention trial on 71-year-old women, showed an increased rate of fatal stroke and an unsustained increase in overall stroke rate in the first 6 months.

The WHI paper<sup>15</sup> states that prior studies have given conflicting results in relation to stroke risk, 4 showing decreased risk, 3 no effect and 3, including a recent meta-analysis, increased risk. Analysis of women who started oestrogen only between the ages of 50 and 59 years have only 0.1 extra cases of stroke per 10 000 women.<sup>9</sup>

## Dementia

Dementia risk was increased in the 65-year-old group in the WHIMS studies.<sup>17,18</sup> In the Cache County Study,<sup>19</sup> where women were a mean age of 73.2 years, HRT users had a reduced risk of Alzheimer's disease (HR 0.59, 95% CI: 0.36 - 0.96). Only long-term current users (more than 10 years) appeared to benefit (HR 0.41, 95% CI: 0.17 - 0.86), probably representing women starting HRT in the early menopausal years. These results are consistent with those of 2 other prospective studies.<sup>20,21</sup>

## Breast cancer

The data on HRT and breast cancer are inconsistent and pre-2000 results are best summed up in the conclusions of Bush *et al.*<sup>22</sup> and the Collaborative Group.<sup>23</sup> 'The evidence did not support the hypotheses that estrogen use increases the risk of breast cancer and that combined hormone therapy increases the risk more than estrogen only. Additional observational studies are unlikely to alter this conclusion. Although a small increase in breast cancer risk with hormone therapy or an increased risk with long duration of use (15 years or more) cannot be ruled out, the likelihood of this must be small,<sup>22</sup> and 'little information was available about long duration of use of any specific preparation'.<sup>23</sup> The post-2000 results are similarly inconsistent (Table I).

The modest increased risk of invasive breast cancer after 5 years of HRT use in some studies is, as suggested by SAMS, probably promotion of a pre-existing subclinical cancer not the initiation of a malignant mutation.<sup>29</sup>

SAMS quotes no increase in carcinoma *in situ* as a reason for the promotion theory and this is supported by a statistical analysis of breast cancer risk for duration of use and the following 10 years. Breast cancer takes 7 - 10 years to grow to a clinically or radiologically detectable size.<sup>30</sup> The 5-year increased risk is 2 - 5 years less than would be expected if HRT

**Table I. Relative risk of HRT and breast cancer — post-2000 trials and studies**

	Oestrogen replacement therapy	Oestrogen-plus-progestin therapy	Any HRT
Women's Health Initiative (WHI) <sup>9</sup>	0.77	-	-
Million Women's Study <sup>8</sup>	1.30	2.00	-
Ross <i>et al.</i> <sup>24</sup>	1.06	1.38 (sequential) 1.09 (continuous combined)	1.10
Schairer <i>et al.</i> <sup>25</sup>	1.1	1.3	-
Weiss <i>et al.</i> <sup>26</sup>	0.84	0.96 (sequential) 1.35 (continuous combined)	-
Moorman <i>et al.</i> <sup>27</sup>	0.8	-	0.8
Heart and Estrogen/ Progestin Replacement Study (HERS) <sup>3</sup>	-	1.27 (continuous combined)	-
WHI <sup>5</sup>	-	1.26 (including previous users) 1.06 (excluding previous users)	-
De Ligneres <i>et al.</i> <sup>28</sup>	-	-	0.98

initiated breast cancer. The risk disappears 5 years after stopping HRT<sup>23</sup> and is followed by a further slight reduction over the next 5 years.<sup>23,25,27</sup>

All types of HRT in the MWS<sup>8</sup> induced an increased breast cancer risk starting from the first year of use, suggesting that breast cancer was present at the start of therapy and was not induced by hormones.

The review by Bush *et al.*<sup>22</sup> consistently noted a reduced risk of death from breast cancer in hormone users compared with non-users. The WHI<sup>7</sup> reported that tumour size was slightly greater and lymph node metastases more frequent in hormone users than non-users.<sup>7</sup> This must be assessed against the knowledge that 19.7% were past and 6.4% current HRT users at baseline and that the HR dropped from 1.26 to 1.06 if baseline current users were excluded.<sup>7</sup> Baseline users were not excluded from the statistics in the report by Chlebowski *et al.*<sup>7</sup>

### Venous thromboembolism (VTE)

The risk using conjugated equine oestrogen 0.625 mg and medroxyprogesterone acetate 2.5 mg in older women in the HERS<sup>3</sup> and WHI<sup>5</sup> trials was nearly doubled, but with the oestrogen-only arm<sup>9</sup> it was only 1.33 (95% CI: 0.99 - 1.77). The risk reduced with duration of use. Oestrogen plus progestin increased the risks associated with age, overweight, and factor V Leiden in the WHI<sup>31</sup> and showed only 1 extra VTE per 10 000 women in the 50 - 59-year age group.<sup>9</sup>

Full haematological screening will establish who is at high risk of the disease. At a presentation in Cape Town L Speroff (2004) agreed that a previous challenge using the combined oral contraceptive for a reasonable duration of time (more than 2 years) would probably exclude the majority of women at high risk.

### Age of commencement of HRT

Both societies agree that premature ovarian failure requires HRT until the average age of the menopause, namely 51 years.

The WHI confirmed the impression suggested by the HERS<sup>3</sup> and the ERA study<sup>4</sup> in which Herrington *et al.* state that 'another possible explanation for our results are that estrogen is more effective in preventing atherosclerosis than in slowing the progression once it is established'. HRT should be started in the first 5 or maximum 10 years of the menopause.

### Indications for HRT

SAMS state that HRT should only be initiated for specific proven indications, as discussed above, provided there are no contraindications. These include vasomotor symptoms and/or associated sleep disorders of early menopause. Systemic and local HT is effective in the prevention and treatment of vulval and vaginal atrophy, decreasing the incidence of vertebral and hip fracture and EPT for reducing the risk of colorectal cancer.<sup>7</sup> The statement 'HT (HRT) is effective in preventing the bone loss associated with early menopause' requires explanation. Does 'early menopause' mean only in association with premature ovarian failure or only in the early transition? The WHI has shown a preventive effect at all ages.

'The effect of HT on primary prevention of CHD and stroke has not been sufficiently studied in RCTs to allow any firm conclusion' and 'HT is not indicated for the prevention or treatment of Alzheimer's disease'.<sup>2</sup>

The IMS guideline agrees with the SAMS indications for HRT use but differs in its review with regard to heart and brain disease: 'initiation of HRT during the menopausal transition appears to provide protection against complication of the climacteric such as fracture and potentially heart disease and brain disease'.



## Duration of use

The IMS and SAMS are in total disagreement on duration of HRT use.

According to the IMS guidelines 'There are no new reasons to place mandatory limitations on the length of treatment, including arbitrary cessation of HRT in women who started replacement during the menopausal transition and remain symptom-free while on hormones. Judging from the accelerated rate of cardiovascular events after premature menopause and the loss of cardioprotection after stopping HRT, such cessation may even be harmful.'

According to the SAMS statement, '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. The decision is best left in the hands of the menopausal expert and the informed patient.' This statement is difficult to understand – as SAMS are unable to suggest guidelines, who are the menopause experts in South Africa?

The statistics of the WHI and HERS show little change in risk with duration of use other than reduction in total death<sup>3,9</sup> and coronary heart disease death.<sup>32,33</sup> The risk increases with duration of HRT use only in stroke patients.<sup>9</sup>

The effect of duration of HRT use and breast cancer can be assessed from Table II. Although inconsistent it would suggest promotion of a pre-existing breast cancer and not initiation of a new cancer.

## HRT dose

The lowest effective dose should be the objective. Early in the menopause and with premature ovarian failure higher doses may be required, but these can be reduced slowly.

## Route of administration

Non-oral oestrogens lack first-pass effect on the liver and are recommended in women with liver disease, raised triglyceride levels (at baseline or after oral oestrogen use), increased risk of venous thrombosis and high risk of breast cancer especially in the presence of excessive breast sulphatase activity.<sup>34</sup>

Women with high cholesterol, low high-density lipoprotein (HDL) and normal triglyceride levels will benefit more from oral oestrogens. Oral oestrogens increase sex hormone-binding globulin (SHBG) via hepatic stimulation and the same amount of free oestradiol is available from 2 mg 17-β-oestradiol and a 50 µg oestradiol patch.

## Types of HRT, tibolone and raloxifene

In the clinical guidelines section, SAMS states that 'These statements are currently applicable to all estrogens and progestins as well as tibolone'. The IMS disagrees – 'The different types and regimens of HRT do not necessarily have the same tissue and metabolic effects and should not be grouped together as having a class effect.'

Only one paper, the MWS,<sup>8</sup> has suggested that tibolone (Livifem) increases the risk of breast cancer. This is thought to be due to preferential prescribing for high-risk breast cancer patients, as biologically it has been called a selective oestrogen enzyme modulator and should reduce the risk of breast cancer. HDL is reduced by tibolone but according to David Cook this may not increase the risk of cardiovascular disease. An example is Tangiers disease. RCTs are ongoing and are necessary for this product.

Interestingly, SAMS has not mentioned raloxifene (Evista) which increases the risk of VTE, flushing and cramps but reduces breast cancer risk within 40 months.<sup>35</sup> This suggests inhibition of existing breast cancer. What is the prognosis when raloxifene is stopped? How long can raloxifene be used for?

**Table II. Effect of duration of HRT use (plus 5 years) on breast cancer\***

	Increased risk	Risk unchanged	Reduced risk	Risk -1 (less than placebo)
Oestrogen replacement	2 (8) (25)	1 (25)	1 (24)	3 (9) (26) (27)
Oestrogen progestin	4 (8) (24) (25) (26)	1 (25)	1 (33)	1 (27)
Any HRT	2 (24) (28)	1 (27)	0	0

\* Number of published papers. The numbers in brackets refer to the references in this article.



## Conclusions

Both the IMS and SAMS recommend HRT for premature ovarian failure, vasomotor symptoms, atrophic vulval and vaginal pathology (often local oestrogen with regular check-ups with regard to endometrial safety), and prevention of osteoporosis and hip and vertebral fractures, and advise starting HRT in the first 5 or 10 years of the menopause. HRT reduces the risk of colorectal cancer but this reduction was not shown in the oestrogen arm of the WHI trial.<sup>9</sup> The dosage should be the lowest that is effective.

SAMS feels that no firm conclusion can be made on the primary prevention of cardiovascular disease or stroke using HRT and that HRT is not indicated for the prevention and treatment of dementia.

The IMS quotes many studies and trials to suggest the opposing view and states that during the menopausal transition HRT provides protection against complications such as heart and brain disease. HRT promotes breast cancer minimally and possibly more with opposed than unopposed oestrogens.<sup>29</sup> HRT users have reduced mortality and improved survival rates.<sup>22</sup> A 5-year moratorium is not justified on statistical grounds as only breast cancer possibly increases with duration of use and this is due to promotion of an existing breast cancer with improved prognosis. For possible cardiovascular and dementia prevention and reduced risk of VTE, starting age should be early in the menopause.

Hopefully this paper will give our health care providers an unbiased view. Over the past 7 years recommendations have swung from use for all, to no use at all, to use of low dose early in the menopause to protect against conditions of old age. More trials are required to establish disease outcome and contraindications to treatment.

I personally use the IMS guidelines as reasons are given for duration of use and prevention of cardiovascular disease and dementia. Explanation of both recommendations will help women make an unbiased decision.

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