

Hormone replacement therapy (HRT) – a change of heart



Attitudes regarding HRT changed significantly in 2002, after the publication of the first results of the Women's Health Initiative study (WHI). The fear of a reported increased risk of coronary artery disease (CAD) and breast cancer resulted in a 50% decrease in the use of HRT. The message delivered to a captive worldwide audience was simple and clear: HRT may only be used for the treatment of severe menopause-related symptoms, for the shortest possible time and at the lowest effective dose. HRT was not to be used for the prevention of chronic diseases of old age such as CAD and osteoporosis. This was in stark contrast to the prevailing mood of the day, which offered most menopausal women HRT not only for symptomatic relief but also for the prevention of CAD, stroke and osteoporosis and to delay onset of Alzheimer's disease (AD). The finger was pointed directly at menopause societies and opinion leaders, who were accused of neglecting their duty of first doing no harm. As can be expected, most menopause societies and opinion leaders such as the South African Menopause Society (SAMS) and the North American Menopause Society (NAMS) endorsed restricted indications based on the evidence as presented by the WHI investigators. The International Menopause Society (IMS) was more cautious in their initial reaction to the WHI data. Following American recommendations, it was decided to drop the R (replacement) in HRT and to instead use the term menopausal hormone therapy (HT). In 2007, all three societies revised their guidelines independently and all supported a less restricted and more pragmatic approach to the use of menopausal HT. This change of heart was prompted by the availability of more detailed data from WHI, including central adjudication of endpoints, the publication of the estrogen alone (ET) arm data as well as pooled data from both arms, and the publication of new sub-studies.

A secondary analysis of the combined estrogen alone (ET) and combination therapy (EPT) arms of WHI concluded that women who initiated hormone therapy closer to menopause tended to have reduced CAD risk compared with the increase in CAD among women more distant from menopause.¹ The same investigators revealed in a secondary analysis of the ET arm of the WHI that patients treated with estrogen in the age group 50 - 59 years, when compared with placebo-treated patients, were 42 - 61% less likely to have significant arterial calcification (as measured by computed tomography).² These publications are in stark contrast to earlier publications by the same



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investigators that implied HT as a cause of CAD, without taking into account that this did not apply to the typical patient, who initiates HT at the age of 50 - 59 years.³

Present knowledge, based on the latest SAMS recommendations, can be summarised as follows.⁴

The use of HT for the treatment of early menopausal vasomotor symptoms and genital atrophy is well accepted and based on solid evidence.

The effect of HT on the cardiovascular system must be seen in context of age and time since menopause, at initiation of therapy. There are good animal data, randomised control study (RCT) data as well as epidemiological data pointing to an early window of opportunity for HT. If HT is initiated in the age group 50 - 60 years, it will indeed offer primary protection to blood vessels, without increasing the risk of CAD, stroke or DVT. HT does not offer secondary protection to compromised arteries and should not be initiated in patients at risk of CAD or after the age of 60 years. HT is not promoted for the sole use of cardiovascular protection, in view of other proven therapies. As in the case of CAD, HT has no effect on established AD, but may delay the onset of AD if initiated near the start of

menopause. In the older patient, HT may increase the risk of stroke, but this effect may be dose related. The risk of venous thrombotic events (VTE) is slightly raised in the older patient, but this risk decreases after the first year of treatment. The risk can be reduced further by screening patients for a family history of VTE or by using the transdermal route of administration.

HT helps prevent osteoporotic fractures, even in patients at low risk of fracture. The use of HT for fracture prevention is limited by the need for long-term therapy and there are other drugs with proven efficacy.

Knowledge regarding the relationship between HT and breast cancer has surprisingly not changed significantly on the basis of the WHI data. The previously known slight increase in breast cancer incidence related to duration of use is supported by findings in patients treated with a combination of estrogen and progestin. In contrast, a significant reduction of breast cancer was found in certain subgroups of patients using estrogen alone. The significance of these findings still needs to be fully explained, but strong evidence points to HT not being an initiator of new cancer, but rather a stimulant of pre-existing tumours.

There is no compelling evidence to restrict the duration of HT to a predetermined time period. Continued use of HT after the age of 60 must be individualised and be consistent with the aim of treatment. The lowest effective dose is encouraged, with consideration of the transdermal method of application in patients at higher risk of thromboembolic events.

Judging by the present knowledge, it is clear that the scare produced by the initial reports that led to an estimated 1 million women abandoning HT was unfounded and misleading. Even today, many women with severe debilitating vasomotor symptoms

in early menopause are denied the use of HT, based on data derived from a much older population. The main lesson learned from this debacle pertains to the role of randomised controlled trials as the highest level of evidence-based medicine. The inappropriate extrapolation of data obtained from patients at a much older age than the age where most patients use HT, is the single biggest problem. The use of intention-to-treat analyses in a long-term study with a high drop-in and drop-out rate is highly questionable. The publication of controversial conclusions based on incomplete data without central adjudication of all primary endpoint events is irresponsible. The saddest aspect of this saga remains the flow of information pertaining to the results of the study. This was done directly to the media and lay public in a sensational way, with disregard for the main prescribers of HT. In the interests of our patients and the trust that the public has in medical research, I hope that these lessons have been learned and that the same mistakes will not be made again. Now is the time to put the R back into HRT.

The views expressed in this editorial are those of the author and nor necessarily those of the SAJOG Editorial Board or SAMS.

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