Guidelines for the Hormone Treatment in Women in the Menopausal Transition and Beyond. Position Statement by the Executive Committee of the International Menopause Society

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Guidelines for the Hormone Treatment of Women in the Menopausal Transition and Beyond*

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Recent communications regarding estrogen or estrogen + progestin treatment and clinical cardioprotection, breast cancer risk and cerebral aging have produced considerable confusion and concerns among women, caregivers and the media. The actions of the United States’ Food and Drug Administration (FDA) and other National Safety of Medicine Boards, such as the European Medicine Evaluation Agency (EMEA), in response to publication of data from the Women’s Health Initiative (WHI) [1–3] and the Million Women Study (MWS) [4], have also raised concerns. The Executive Committee of the IMS has considered position statements presented at the Fourth Workshop of the International Menopause Society (IMS), December 2003, reviewed available information from observational studies, randomized clinical trials (RCTs) and pre-clinical research, and wishes to point out the following:

- The WHI is the most recent of several RCTs undertaken to test the validity of the cardioprotective effects of hormone treatment (HT) shown by observational trials. Others include the Heart and Estrogen/progestin Replacement Study (HERS) and the Estrogen Replacement and Atherosclerosis Study (ERAS), which utilized the same hormonal regimen, and which had the common underlying premise that the study of women beginning HT well beyond the menopausal transition is an acceptable design for this purpose. This statement also addresses the validity of these RCTs. Because of the potential for breast cancer induction by HT, the MWS [4], a recent prospective cohort analysis, was also included in our considerations. Guidelines are suggested for clinical practice regarding HT for women going forward from the menopausal transition.
- The WHI is an ongoing RCT on the effects of HT in women aged from 50 to 79 years. Few of these women were in the critical first years after menopause. The full results of the trial will not be available for some time. At the end of the 5th year, the independent drug safety monitoring board terminated the estrogen + progestin arm of the study because of an apparent increase in the risk of breast cancer and an apparent adverse global index. The factors included in the index, in addition to an increased risk of breast cancer, were coronary heart disease, stroke and pulmonary embolism. While the complete results of the larger trial will not be available for some time, a subsequent analysis by the WHI of the full 5-year period has already shown that there was not a statistically significant increase in breast cancer and the apparent increase in the cardiovascular hazard risk in year five had occurred because of a transient fall in the rates of these events/diagnoses in the placebo group, rather than a rise in the estrogen + progestin group [1]. In any case, the lack of statistically significant differences between groups after the full duration of the WHI trial makes conclusions regarding the value of HT highly uncertain and devalues or invalidates the conclusions from the initial publication from which so many clinical implications have been drawn.
- The general applicability of the results of RCTs such as the WHI’s estrogen + progestin arm, the HERS [5] and ERAS [6] trials was reviewed. The WHI’s publication indicated that, by design, symptomatic women were limited to ~10% of the study population [7]. The HERS and ERAS trials, by design, excluded younger women. The average ages of women in the WHI, HERS and ERAS trials were 63.3, 67 and 65 years, respectively [1, 5, 8]. Results in such populations cannot, and should not, be generalized to women who are unlike those tested (i.e. younger women early in menopause). Women in

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In summary: The RCTs reported to date cannot indicate whether contemporary estrogen or estrogen + progestin treatment started during the menopausal transition (the great majority of its use) is effective for primary prevention of cardiovascular disease or other long-term consequences of sex steroid withdrawal.

With the above in mind, the Committee proposes the following guidelines for addressing these issues for women during the climacteric.

I. Available RCTs do not have the statistical power to test the outcomes of HT starting during the menopausal transition. In the absence of new, relevant information on hormonally treated women undergoing menopause, the Executive Committee recommends the continuation of presently accepted global practice, including the use of estrogen + progestin, or estrogen alone in the case of women who have undergone hysterectomy, for the relief of menopausal and urogenital symptoms, avoidance of bone-wasting and fractures, and atrophy of connective tissue and epithelia. Possible clinical benefits in the prevention of cardiovascular disease and nervous system protection seem likely but have yet to be confirmed.

II. There are not new reasons to place mandatory limitations on the length of treatment, including arbitrary cessation of HT 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 [12, 13] and the loss of cardioprotection after stopping HT [11], such cessation may even be harmful. Each patient must be counselled on the current data on the risks and perceived benefits of HT so that she can make appropriate, informed, individual decisions about continuing or stopping treatment. Such discussions could be part of the annual risk–benefit analysis undertaken with each patient and in the context of timely mammographic and genital cancer studies.

III. Although the risk of complications of HT remains an important clinical issue, there are no general guidelines that apply except to indicate that HT, especially the use of estrogen + progestin, has been associated with a small absolute increase in deep venous thrombosis and pulmonary embolism, an apparent smaller absolute increase in breast cancer and reduction in the risk of colorectal cancer and bone fractures [1, 3]. These issues remain subjects for discussions between individual patients and their care-givers. None of these generalities should preclude regular testing of the involved systems, regardless of the decision whether or not to begin or continue HT. However, cancer, metabolic diseases, vascular disease and brain dystrophy are not only the concerns of women on HT, but are of universal concern to women past the age of reproduction.

IV. The use of hormones/hormone substitutes as part of the care of the aging population will be a subject of increasing importance in both sexes. Governing principles for enhancing the length and quality of life are emerging:

(a) Prevention, not treatment, is the most feasible goal. Use of hormone/substitutes should be part of an overall strategy including lifestyle modification and other preventive measures, especially cessation of smoking and alcohol abuse [14].

(b) There is not evidence that HT is beneficial for existing heart disease or dementia, but the initiation of hormones during the menopausal transition appears to provide protection against complications of the climacteric such as fractures and heart disease [15]. This conclusion remains based on observational studies and pre-clinical research [16], since no RCTs have adequately addressed women starting treatment during the menopausal transition.
Preventing illness and maintaining quality of life in this population; therefore, it must be the subject of continuing and dietary management, HT remains a principal tool in prevention by changes in life-style evidence that bears on these matters. Clinical research, both observational and RCTs, should be encouraged to influence the vascular, musculoskeletal and nervous systems, as well as the role of hormones and hormone-like compounds in carcinogenesis and prevention. We are facing a tide of post-reproductive women generally require lower doses than younger women. Intrauterine delivery systems may have some advantages. The role of progesterone and progestins and the different routes of administration remain issues for study. The dose and regimen of HT need to be individualized for each of the systems to be treated/protected. The dose and regimen of HT need to be individualized. Older menopausal and postmenopausal women generally require lower doses than younger women. The effect of the route of administration remains an issue. Avoidance of the first-pass effects of oral therapy may be advantageous, especially for those with increased risk factors for venous thrombosis. More long-term data are required on the clinical outcomes of non-oral routes of administration. The IMS particularly supports the expansion of research into the effects of hormones on the vascular, musculoskeletal and nervous systems, as well as the role of hormones and hormone-like compounds in carcinogenesis and prevention. We are facing a tide of post-reproductive women and men. In addition to prevention by changes in life-style and dietary management, HT remains a principal tool in preventing illness and maintaining quality of life in this population; therefore, it must be the subject of continuing scientific investigation.

February 13, 2004

References


Note: Further detailed information and guidelines will be found in The Health Plan for the Adult Woman: Management Handbook, to be published on behalf of the IMS by Parthenon Publishing in May 2004.
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