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Guidelines for the hormone treatment of women in the menopausal transition and beyond

Position Statement by the Executive Committee of the International Menopause Society

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 the estrogen + progestin arm had a mean age of 63.3 years and were, on average, 12 years postmenopausal (13 years since their last period). Few (~10%) of these women were in the critical first 5 years after menopause[8].
- The MWS is an observational study of UK women volunteering for a national breast-screening program. It reported that all types of HT regimens induce an increase in breast cancer risk, starting from the 1st year of use. In addition, the risk disappears from 1 to 5 years after the withdrawal of HT. The appearance of

significant risk in the 1st year strongly suggests that the surplus of breast cancers arose from observational bias and was not induced by the hormones[4,9].

- In considering apparent differences between the outcomes of the positive observational studies that inspired the present RCTs and the 'negative' findings of the RCTs themselves, the Executive Committee has identified crucial differences between the experimental populations in the two different types of studies, which tend to be neglected during minute consideration of the outcomes. *In the observational studies, the hormones were prescribed for women in the menopausal transition, most of whom were symptomatic, and who were generally 55 years of age or less at the time of starting treatment. On the contrary, in the three RCTs, the HT was started at 55 years or older in 89% of the subjects*[7,8]. Overall, the women in the observational trials were mainly patients in the menopausal transition who sought help for symptomatic hormone deficiency, while the women in the RCTs were, by design, recruited subjects who were largely past the point of being symptomatic, *indicating an altered physiological status that could be related to differences in outcomes. All in all, the age and condition of its subjects do not support contentions that the WHI is a primary prevention trial against cardiovascular outcomes or that it is testing HT in the same manner as the observational studies*. Rather, the WHI is a RCT on the effects of one particular regimen of combined estrogen + progestin on aging women, many of whom will have had sub-clinical vascular and cardiovascular disease at the time they entered the trial[10]. This is a major difference between the observational studies that showed a cardioprotective effect of HT and the RCTs that failed to show cardioprotection.
- A power analysis of the WHI showed that it was ten-fold underpowered to detect an early-estrogen cardioprotective effect of the magnitude reported in the observational Nurses Health Study[8,11].
- As is standard practice for the application of the results of RCTs, the results of the WHI may not be generalized to populations that it was not designed to study. This exclusion of comparisons pertains to the results of HT in observational trials in women in the menopausal transition symptomatic at the initiation of HT. *Therefore, at present, the only valid studies of HT for cardioprotection of women in the menopausal transition are the epidemiological and observational studies that generally agree with laboratory and animal studies, indicating cardioprotection by estrogen initiated in women during the menopausal transition.*
- *The possibility that contemporary HT causes an increase in breast cancer is not clarified by either the WHI or the MWS and remains to be resolved.*

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 counseled 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 life-style 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.

(c) *Appropriate and effective doses should be established 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.

(d) *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.

(e) The different types and regimens of HT do not have the same tissue and metabolic effects and should not be grouped together as having a class effect.

(f) *Progesterone/progestins are only required for protection of the endometrium*. This benefit has to be balanced against effects on other tissues and metabolic effects. Intrauterine delivery systems may have some advantages. The role of progesterone and progestins and the different routes of administration remain issues for study.

(g) Combinations of hormones with other treatment regimens may be of benefit.

(h) *Evidence from population studies cannot be directly generalized to individual patients*. However, such evidence can be used as general guidance in clinical decision-making, in which case the emphasis should be on absolute rather than relative risk.

There is a great body of important pre-clinical experimental evidence that bears on these matters. Clinical research, both observational and RCTs, should be encouraged to improve clinical practice. *The quality of experimental design is still a key factor in the evaluation and applicability of even the largest RCT*[9]. In this regard, the Executive Committee of the IMS supports the immediate release of the full database from the estrogen + progestin arm of the WHI and the MWS database for independent review.

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.

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References

1. Rossouw JE, Anderson GL, Prentice RL, *et al*. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *J Am Med Assoc* 2002;288:321–33
2. Manson JE, Hsia J, Johnson KC, *et al*. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;349:523–34
3. Chlebowski RT, Hendrix SL, Langer RD, *et al*. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. The Women's Health Initiative Randomized Trial. *J Am Med Assoc* 2003;289: 3243–53
4. Million Women Study Collaborators. Breast cancer and hormone replacement therapy in the Million Women Study. *Lancet* 2003;362: 419–27
5. Hulley S, Grady D, Bush T, *et al*. Randomized trial of estrogen plus progestin for secondary prevention of coronary disease in postmenopausal women. *J Am Med Assoc* 1998;280:605–13
6. Herrington DM, Reboussin DR, Brosnihan KB, *et al*. Effects of estrogen replacement on the progression of coronary artery atherosclerosis. *N Engl J Med* 2000;343:522–9
7. Hays J, Ockene JK, Brunner RL, *et al*. Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med* 2003;348:1839–54
8. Naftolin F, Taylor HS, Karas R. Early initiation of hormone therapy and clinical cardioprotection: the Women's Health Initiative (WHI) could not have detected cardioprotective effects of starting hormone therapy during the menopausal transition. *Fertil Steril* 2004: in press
9. Shapiro S. Effects of hormone replacement therapy on the risks of breast cancer and cardiovascular disease: the validity of the epidemiological evidence. In Schneider HPG, Naftolin F, eds. *Climacteric Medicine – Where Do We Go?* Proceedings of the 4th Workshop of the International Menopause Society. London: Parthenon Publishing, 2004:in press
10. Karas RH, Clarkson TB. Considerations in interpreting the cardiovascular effects of hormone replacement therapy observed in the WHI: timing is everything. *Menopausal Med* 2003; 10:8–12
11. Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000;133: 933–41
12. Grodstein F, Stampfer MJ, Colditz GA, *et al*. Postmenopausal hormone treatment and mortality. *N Engl J Med* 1997;336:1769–75
13. Joakimsen O, Bønaa KH, Stensland-Bugge E, Jacobsen BK. Population-based study of age at menopause and ultrasound assessed carotid atherosclerosis. *J Clin Epidemiol* 2000;53: 525–30
14. Hu FB, Stampfer MJ, Manson JE, *et al*. Trends in the incidence of coronary heart disease and changes in diet and lifestyle in women. *N Engl J Med* 2000;343:530–7
15. Mack WJ, Hameed AB, Xiang M, *et al*. Does elevated body mass modify the influence of postmenopausal estrogen replacement on atherosclerosis progression: results from the estrogen in the prevention of atherosclerosis trial. *Atherosclerosis* 2003;168:91–8
16. Adams MR, Kaplan JR, Manuck SB, *et al*. Inhibition of coronary atherosclerosis by 17β-estradiol in ovariectomized monkeys: lack of an effect of added progesterone. *Arteriosclerosis* 1990;10: 1051–7

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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