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

Position Statement by the Executive Committee of the International Menopause Society

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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, care-givers 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 International Menopause Society (IMS) has considered position statements presented at the Fourth Workshop of the IMS, December 2003 and reviewed all presently available information from observational studies, randomized controlled trials (RCTs) and pre-clinical research, and wishes to point out the following:

- Administration of hormones to symptomatic, estrogen-deficient women such as those in the observational studies is referred to as hormone replacement therapy (HRT). Administration of hormones to asymptomatic women such as those in the recent RCTs is referred to as hormone therapy (HT)[5,6]. In general, the administration of hormones to menopausal women is referred to as menopausal hormone treatment (MHT).

- The WHI is the most recent of several RCTs undertaken to test the validity of the cardioprotective effects of HRT 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 ability of these HT RCTs to reveal effects of HRT. Because of the potential for breast cancer induction by HRT, the MWS[4], a recent prospective cohort analysis, was also included in our considerations. Guidelines are suggested for clinical practice regarding HRT 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 (DSMB) 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 thromboembolic event frequency, coronary heart disease, stroke and pulmonary embolism. *A subsequent analysis by the WHI of the full estrogen plus progestin study period has already shown that in year five there was an unexplained transient fall in the rates of these events/diagnoses in the* placebo group*, rather than a rise in the estrogen + progestin group*[1,7]. In any case, the small differences in absolute numbers of events between groups during the trial makes conclusions regarding the possible 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 estrogen-only arm in post-hysterectomy women was stopped in the 7th year by the National Institutes of Health (NIH) (not the DSMB). The decision was based upon lack of proven cardioprotection and higher incidence of stroke, as in the estrogen + progestin arm. In contradistinction to the estrogen + progestin arm, the women taking only estrogen had a 23% lower incidence of new invasive breast cancers than did the placebo group ($p < 0.06$)[8].

- The general applicability of the results of RCTs such as the WHI's estrogen + progestin- and estrogen-only arms, the HERS[9] and ERAS[10] trials has been reviewed. *The WHI's publication indicated that, by design, symptomatic women were limited to ~10% of the study population*[11]. *The HERS and ERAS trials, by design, excluded younger women. The average ages of women in the WHI, HERS and ERAS trials were 63, 67 and 65 years, respectively*[1,8–10]. *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). The women in the estrogen-only arm were the same age on average, but the length of time since hysterectomy (± ovariectomy) is not known. They had somewhat higher indices of heart disease and predisposing factors at the outset, perhaps reflecting the longer period of diminished estrogen. Few (~10%) of these women were in the critical first few years after menopause[12].

- 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[4,7,13].

- In considering apparent differences between the cardioprotective outcomes of the observational studies that inspired the present RCTs and the 'negative' findings of the recent RCTs, 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*[8,11,12]. 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. This contention may be supported by a recently published review of two HRT RCTs studying relief of menopausal symptoms in which a younger population received HRT or placebo without an increase in cardiovascular events in comparison to subjects receiving placebo*[14]. This is consistent with the findings of the WHI, that the occurrence of venous thromboembolism is age-dependent[15].

- *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 HRT, as was the case in the observational studies*. Rather, the WHI is a RCT on the effects of one particular regimen of combined daily, as opposed to cyclic, estrogen + progestin or estrogen-only HT on aging women, many of whom will have had sub-clinical vascular and cardiovascular disease at the time they entered the trial[11,16]. This is a major difference between the observational studies that showed a cardioprotective effect of HRT and the RCTs that failed to show cardioprotection by HT.

- A power analysis of the WHI estrogen + progestin arm showed that it was ten-fold underpowered to detect an early-estrogen cardioprotective effect of the magnitude reported by the observational Nurses Health Study[12,17]. There was therefore no likelihood that this arm of the WHI could be sufficiently powered to reveal a statistically significant difference between treatment and placebo in women starting treatment during the menopausal transition[12]. Nevertheless, analysis of such women who started estrogen-only between the ages of 50 and 59 years suggested a different effect with three *fewer* cases of CHD and only one extra case of venous thromboembolism and 0.1 of stroke/10,000 women[8]. The relationship of age to venous thromboembolism has been documented by the examination of the WHI data[15].

- As is standard practice for the application of the outcomes of RCTs, the results of the WHI may not be generalized to populations that it was not designed to study. This exclusion of comparisons extends to the results of observational trials in women in the menopausal transition who were symptomatic at the initiation of HRT. *Therefore, at present, the only valid studies of MHT 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 MHT causes an increase in breast cancer is not clarified by either the WHI or the MWS and remains to be resolved[1-3,8].

In summary: The HT RCTs reported to date cannot indicate whether contemporary estrogen or estrogen + progestin treatment started during the normal or induced menopausal transition (HRT; 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 **HT** RCTs do not have the statistical power to test the outcomes of **MHT** starting during the menopausal transition. *In the absence of new, relevant information on **HRT** started in the menopausal transition (the positive data from the younger women in the estrogen-only arm of the WHI notwithstanding), 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 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[18,19] and the loss of cardioprotection after stopping **MHT**[17], such cessation may even be harmful. The conflicting data from the WHI on breast cancer incidence do not clarify this area of concern.

III. *Each patient must be counseled about the current data on the risks and perceived benefits of **HRT** 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 other screening protocols.

IV. *The risk of complications of **MHT** remains an important clinical issue; there are no general guidelines that apply, except to indicate that **MHT**, both estrogen + progestin*

and estrogen-alone, has been associated with a small absolute increase in deep venous thrombosis with subsequent stroke and pulmonary embolism. The WHI continues the trend of conflicting effects on breast cancer (a small absolute increase in the estrogen + progestin arm and decreased risk in the estrogen-only arm) and reduction in the risk of colorectal cancer and bone fractures, including hip fractures[1,3,8]. 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 **MHT**. *However, cancer, metabolic diseases, vascular disease and brain dystrophy are not only the concerns of women on **MHT**, but are of universal concern to women past the age of reproduction.*

V. 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[20].

(b) *There is no evidence that **HT** is beneficial for existing heart disease or dementia, but the initiation of **HRT** during the menopausal transition appears to provide protection against complications of the climacteric such as fractures and potentially heart disease and brain disease*[21-23]. This conclusion remains based on observational studies[14] and pre-clinical research[24], since no RCTs have adequately addressed women starting treatment during the menopausal transition. Specifically, a WHI-derivative study on dementia is not considered of value in this decision because of the late start of HT, the lack of changes in minimal cognitive dysfunction and the possibility that subjects in this thromboembolism-prone group developed vascular dementia rather than Alzheimer's disease[15,25].

(c) *Appropriate and effective doses should be established for each of the systems to be treated/protected. The dose and regimen of* ***HRT*** *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 **HRT** do not necessarily have the same tissue and metabolic effects and should not be grouped together as having a class effect. Ideally, good-quality data should have been obtained for each hormonal preparation, but, since this is not feasible, not having such data does not imply that information on other products could be automatically extrapolated.

(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. Direct genital 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 patient*s. 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 studies 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[13]. 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, HRT 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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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, UK.

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