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The view of The International Menopause Society on the Women's Health Initiative

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BACKGROUND/INTRODUCTION

At a press conference of the National Heart, Lung, and Blood Institute (NHLBI) at Washington, July 9, 2002, Claude Lenfant, Director of the NHLBI, in his welcome address, reported on the estrogen plus progestin component of the Women's Health Initiative or WHI. This clinical trial was designed to examine the effect of estrogen plus progestin on the prevention of heart disease and hip fractures, and to identify any associated risk for breast and colon cancer. It has been stopped early due to an increased risk of invasive breast cancer and evidence that overall health risks exceed benefits.

Since its creation in 1991, the WHI has been recognized as one of the most important – and certainly one of the largest – prevention studies ever conducted. WHI has focused on strategies for preventing heart disease, breast and colorectal cancer, and osteoporosis in menopausal women. In addition, the National Cancer Institute, the National Institute of Arthritis and Musculo-Skeletal and Skin Diseases, the National Institute on Aging and the Office of Research on Women's Health have all collaborated and provided valuable input to the NHLBI since the WHI began.

Jacques Rossouw, acting Director of the Women's Health Initiative at NHLBI, in referring to the original article on 'Risks and benefits of estrogen plus progestin in healthy postmenopausal women'[1], pointed out that the results that he was going to present were of tremendous importance to women. Choosing whether or not to take postmenopausal hormone therapy would be one of the most important health decisions that women face. While much more remains to be learned, today the WHI would finally begin to offer some guidance.

The primary objective of the WHI was to assess the major health benefits and risks of the most commonly used combined hormone therapy in the United States, with the primary outcome measure being coronary heart disease (CHD). The WHI clinical trial was designed in 1991–92; recruitment started in 1993. A total of 16 608 participants were postmenopausal women aged 50–79 years who had an intact uterus. These volunteers were recruited at 40 clinical centers across the United States. They were randomly assigned to receive either continuous combined conjugated equine estrogens (CEE) 0.625 mg and medroxyprogesterone acetate (MPA) 2.5 mg daily (8506 women) or placebo (8102 women). A substantial number of women had stopped taking the study drugs at some time (42% of the CEE/MPA group and 38% of the placebo group). A third group of 10 739 hysterectomized women received 0.625 mg CEE (without progestin).

Throughout the trial, a high priority was placed on monitoring and maintaining participant safety, as well as on insuring that all participants were well informed about any potential risks associated with the study. The trial was overseen by an independent data and safety monitoring board, or DSMB. The 12 members of this board, who were appointed by the NHLBI, were individuals with expertise in clinical trials, statistics, ethics and all of the relevant areas of medicine.

The DSMB met every 6 months to review the emerging results. A plan established in advance was used to guide the board in interpreting the data. This plan was established primarily to ensure clear answers to the primary questions about heart disease and breast cancer; the potentially important effects of CEE/MPA on other

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diseases were also to be reviewed. Thus, the effects on hip fracture, pulmonary embolism, stroke, endometrial cancer and colorectal cancer were determined; designated outcomes required monitoring, based on findings from other studies of HRT, such as the Collaborative Analysis on Hormonal Factors in Breast Cancer[2] and the HERS[3], in particular.

To weigh the observed risks and benefits to participants' health, the DSMB used a 'global index', a multiple testing procedure for clinical trials first described by O'Brien and Fleming[4]. The monitoring plan allowed for a variety of possible scenarios and indicated how the DSMB might evaluate the data. The benefit for one study aspect, such as prevention of heart disease, had to be coincident with a beneficial global index for the DSMB to consider recommending that the study be stopped, because the benefits of hormone would have been adequately determined. However, the converse situation was observed because women on CEE/MPA had an increased risk of invasive breast cancer (hazard ratio, 1.26; 95% confidence interval (CI), 1.00–1.51) and the overall measure suggested that the treatment was causing more harm than good (global index, 1.15; 95% CI, 1.03–1.28). The decision to stop the trial occurred after an average follow-up of 5.2 years, when the results met predetermined levels of harm for breast cancer.

No study of the size and scope of WHI will be free of criticism. However, we have particular concerns about the design of the WHI and the interpretation of the results. The entry criteria chosen for the WHI study do not reflect the standard practice in the clinical selection of the women for HRT. Eminent statisticians, bioepidemiologists and scientists designed the study, but there was little attention to the clinical issues related to the selection of patients, so the population may not be representative of those who commonly use HRT. The 'healthy postmenopausal women' were enrolled using selection criteria which excluded severe hypertension of over 200/105 mmHg, prior osteoporotic fracture, breast cancer in the past, including *in situ* and invasive cancers or abnormal mammograms; not excluded were prior cardiovascular disease (CVD) events except during the last 6 months. The age of the participating women in the beginning of the study ranged between 50 and 79 years (average age 63.3 years); of these 33% were 50–59 years, 45% ranged between 60 and 69 years, and 21% had an age of 70–79 years. Thus, 66% of the women were older than 60 years and 21% older than 70 years; two-thirds of these were first-time users of HRT. Preferential selection of older first-time users of HRT unfairly biases the study against beneficial HRT effects because of increasing prominence of the age-dependent cardiovascular, thromboembolic and neoplastic events. Pre-existing atherosclerosis in a relatively large proportion of these women is most likely. This is confirmed by the proportion of women with a positive history of myocardial infarction (1.7%), stroke (0.8%), thromboembolic events (0.9%), coronary artery bypass graft (CABG) and percutaneous coronary revascularization (PCR) (1.3%); transient ischemic attacks (TIA) (2.8%), diabetes mellitus (4.4%), hypertension (36%) and hypercholesterolemia (12.7%). In total, 6.9% of all women were on statins and 19% on aspirin. A total of 16% of all women had a female relative with breast cancer and 10% were nulliparous. According to the Gail model[5], their risk for breast cancer over 5 years ranged between 1 and 2%.

COMMENTS

Biostatistics

There was a high differential unblinding rate of 40.5% in the HRT versus 6.8% in the placebo arm, mostly due to bleeding. Differential unblinding of such magnitude has the power to gradually destroy every randomized double-blind design from study inception, effectively converting parts of the trial into an uncontrolled observational trial. Failure to preserve the blind leaves a trial vulnerable to information bias, which alone could account for most, if not all 'significant' study outcomes. It is regrettable that the authors failed to address the impact of this differential unblinding on their study, as well as high drop-out and drop-in rates.

Multiple comparisons of related outcomes generally do not require correction for multiple testing. Such a correction is needed when measuring unrelated outcomes, e.g. breast cancer and coronary heart disease (CHD), as in this trial. Failure to adjust for multiple testing will, on average, produce one false-positive result in 20 tests on the 5% significance level by chance alone. After adjusting for multiple testing, the number of 'significant' outcomes dramatically dwindled. Until these issues are resolved, the 'significant' WHI results remain subject to misinterpretation.

Breast cancer

There was no difference between active and placebo arms for carcinoma *in situ*. However, the hazard ratio of invasive breast cancer for this active group was 1.26, the nominal 95% CI 1.00–1.59, and the adjusted 95% CI 0.83–1.92. The increased risk did not appear for 4 years. The calculated absolute risk in the CEE/MPA arm with respect to the annual incidence of breast cancer was 3.8 per 1000 women, as compared to 3.0 in the placebo arm. Women who had used the hormone therapy before entering the study (26% of participants) were more likely to develop breast cancer. Those women who did not use HRT before (74% of participants) did not experience an altered risk (hazard ratio 1.06).

From previous experience, even more breast cancers could have been expected in the treatment group. In the collaborative re-analysis of HRT and breast cancer studies in 1997[2], a 35% increased risk (relative risk of 1.35) was found, which was lost 5 years after stopping HRT. In this Oxford study, the additional cases were less aggressive, had less lymph node spread and, altogether, an improved prognosis. These observations were confirmed by other investigators and, in conjunction with the WHI's missing effect on carcinoma *in situ*, would infer that HRT promotes growth and development of pre-existing breast tumors such that these will be diagnosed at an earlier stage.

An observation period of 5.2 years is too short for CEE/MPA to be implicated as a carcinogen, e.g. as inducing breast tumors. Clinical and subhuman primate investigations have shown an incremental proliferative effect of CEE on breast ductal epithelia when continuously combined with MPA, which was unexpected[6].

Colorectal cancer

The risk of colorectal cancer in the CEE/MPA group was reduced with a hazard ratio of 0.63, nominal 95% CI 0.43–0.92 and adjusted 95% CI 0.32–1.24. This risk reduction of 37% is in concordance with other epidemiological investigations.

Endometrial cancer

The hazard ratio was 0.83, with nominal 95% CI of 0.47–1.47 and adjusted 95% CI of 0.29–2.32. It was to be expected that continuous addition of MPA would abolish the estrogen-dependent increased risk of endometrial cancer.

Cardiovascular disease

In the treatment arm with CEE/MPA, the hazard ratio for CHD, predominantly non-fatal, was 1.29, with a nominal 95% CI of 1.02–1.63 and an adjusted 95% CI of 0.85–1.97. Mortality from myocardial infarction, as well as the incidence of CABG or PTCA, were not increased with CEE/MPA. In absolute terms, there was an annual incidence of CHD of 3.7 per 1000 women taking CEE/MPA, as compared to 3.0 cases of CHD per 1000 women taking placebo. To confirm the accuracy of diagnosis, the clinical interpretation of the local groups and the study center were compared, with the result of 84% agreement in the definition of myocardial infarction.

In the HERS[3], postmenopausal women with pre-existing myocardial infarction or other serious heart disease were treated with the same preparation of CEE/MPA versus placebo, and, in the WHI investigation, there were also women with pre-existing serious CHD. As reported in the introduction, some women participating in the WHI trial had risk factors for cardiovascular disease, and many should have been redefined as a subgroup of secondary prevention. There is reason to believe (particularly because of data on subprimate investigations) that prevention of CHD by estrogens is effective only when started in individuals without signs of progressive atherosclerosis[7]. This was highlighted at the Consensus Workshop of the International Menopause Society on Cardiovascular Disease and Hormone Replacement Therapy[8]. Investigations of hypercholesterolemic postmenopausal women have shown that 1 mg of estradiol (without a progestin) prevents the development of atherosclerosis in a similar manner to a statin[9]. Also, low-dose conjugated equine estrogens seem to have more favorable effects when given alone[6].

So the implications of the type of additional progestin should also be considered. Primate research again has shown that MPA may attenuate the protective effect of estrogens on atherosclerosis and vasodilatation[10,11]. One possible reason may reside in the partial glucocorticoid effect of MPA which results in upregulation of the thrombin receptor in the arterial wall[12]. A first interim report on the WHISP study, as presented at the 10th World Menopause Congress 2002 in Berlin, demonstrated that, in women with a coronary syndrome and at least 3 months post-myocardial infarction, a combination of 1 mg estradiol and 0.5 mg norethisterone acetate would not coincide with any incremental cardiovascular events; rather a tendency to reduced CHD was

apparent in this secondary prevention analysis. Even when considering the rather short observation period of WHISP, providing no definitive answers, the data in conjunction with the HERS analysis – additional cardiovascular events with CEE/MPA culminated in the first 4 months of treatment – one might consider differences with different types of HRT preparations at least with respect to CHD prevention.

Stroke and venous thromboembolism

In the CEE/MPA arm, the hazard ratio for stroke was 1.41 with a nominal 95% CI of 1.07–1.85 and an adjusted 95% CI of 0.86–2.31. The hazard ratio for venous thromboembolic disease was 2.11, with a nominal 95% CI of 1.58–2.82 and an adjusted 95% CI of 1.26–3.55. These results are consistent with data from other epidemiological investigations.

Fractures

For hip fracture, the hazard ratio in the treatment arm was 0.66, with a nominal 95% CI of 0.41–0.98 and adjusted 95% CI of 0.33–1.33. The corresponding figures for vertebral fractures were 0.66, with nominal 95% CI of 0.44–0.98 and adjusted 95% CI of 0.32–1.34. For other osteoporotic fractures, the hazard ratio was 0.77, with nominal 95% CI of 0.69–0.86 and adjusted 95% CI of 0.63–0.94. Thus, the risk of vertebral fractures and hip fractures was reduced by 34%. These data are in accord with observational studies, but for the first time demonstrate clear evidence of total osteoporotic risk reduction with HRT (hazard ratio 0.76, nominal 95% CI 0.69–0.85 and adjusted 95% CI 0.63–0.94).

Mortality

Mortality was not increased in the CEE/MPA group with a hazard ratio of 0.98 and a nominal 95% CI of 0.82–1.18 and adjusted 95% CI of 0.70–1.37. It remains to be seen whether the intended follow-up of approximately another 5 years produces similar results. Mortality is the ultimate end-point and is what concerns every clinician when considering the overall safety aspects of any type of therapy. General trends of breast cancer mortality are not consistent with the media-born gloom that the termination of the WHI study arm has cast on women and their doctors world-wide. As everybody is aware, cancer in general but breast cancer in particular has always been the major concern of at least every other aging woman.

CONCLUSIONS

(1) The authors of WHI interpret from their data that women should not start or continue to use continuous combined treatment of 0.625 mg CEE together with 2.5 mg MPA as therapy for primary prevention of coronary heart disease. Heart attacks, stroke, breast cancer and blood clots reportedly increased during the period of WHI investigation. Thus, it is recommended that women should discuss with their doctors possible effective and safe alternatives. These would include lifestyle changes and drugs such as cholesterol-lowering statins and blood pressure medication. Women should keep to the regular schedule of mammograms and breast self-examinations in order to detect breast cancer early.

(2) In contrast to these assumptions, one should, however, emphasise that HRT still has its primary indication for relief of climacteric symptoms (hot flushes, sweats, insomnia, urogenital atrophy, etc.). There are no equally effective alternatives. The re-analysis of 1997 did not demonstrate any increased breast cancer risk up to a treatment period of 5 years. Therefore, after 4–5 years of continuous combined HRT, each individual woman should, after consultation with her doctor, reconsider for herself the merits of continuing.

(3) Primary prevention of CHD, as indicated by a reduction of myocardial infarction, was one of the main objectives of the WHI investigation. The terms primary and secondary prevention of CHD are potentially misleading since one-half of those postmenopausal women who die suddenly from myocardial infarction may never have experienced symptoms such as pectoral angina before the event. Atheroma begins very early in life and the majority of plaques that result in events are small. Thus, the term of risk-dependent intervention has been suggested; the stratification of individual risk should be based on classical risk factors and algorithms (www.chd-taskforce.de). It is stabilization of plaque that is all important; this is almost certainly what statins do. All statin studies in groups comparable to WHI demonstrate their

efficacy in this regard while the investigated type of HRT does not appear to be effective. Hormone replacement should remain a focus of CHD trials, particularly as timely substitution of properly dosed estrogen may be efficient.

(4) The results of the WHI study do not give any indication of the possible effects of other hormone doses, routes of administration, formulations or the use of progestins alone. With respect to most other combinations of estrogens and progestins, there are no equivalent epidemiological investigations at hand.

(5) Doctors should counsel their patients on an individual basis. The IMS Council of Affiliated Menopause Societies has developed a brochure *Adult Women's Health Plan*. A print of this booklet is in preparation. For further details, visit http://www.imsociety.org/pages/menuframeset.html.

(6) At a meeting in mid-July, an independent safety panel for the Women's International Study of Long Duration Oestrogen after Menopause (WISDOM) unanimously concluded that WHI's evidence that hormone replacement therapy raises the risk of heart disease is not convincing. The trial's steering committee, equally skeptical, decided to forge ahead with WISDOM. The US researchers 'have not determined the size of the risks reliably', says the Chair of the steering committee, Oxford epidemiologist Rory Collins. This split, according to many observers, reflects a difference between cultures as much as a disagreement over the science[14].

(7) The WHI authors interpreted their data and released their results in the media: HRT is dangerous for women's health. Jacques Rossouw stated that the WHI results are going to have tremendous importance to women in choosing whether or not to take postmenopausal hormone therapy, and offering some guidance in this important health decision. Around the world, the physicians prescribing HRT may also express their concern as to the design of this WHI study and may want to follow their clinical conscience and experience. Clinicians select the HRT type on the basis of women's characteristics, needs and preferences. In clinical practice, the vast majority of women with the characteristics of the WHI women are not treated with that particular HRT preparation. The WHI results, and particularly the data on cardiovascular disease risk, should only be related to the continuous combined treatment of 0.625 mg CEE together with 2.5 mg MPA, prescribed to elderly, obese women with characteristics similar to those depicted in the WHI study.

This document has been approved by the Executive Committee and other Expert Members of the IMS.

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