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Hormone therapy and cardiovascular disease in the early postmenopause: the WHI data revisited

M. H. Birkhäuser

The publication of data from the Women's Health Initiative (WHI) study follows a certain pattern: first, we were given preliminary data[1,2] which provided the basis for stopping the study before the end of its scheduled follow-up period; then we received separate and detailed manuscripts on cardiovascular endpoints in its two arms (combined conjugated equine estrogens (CEE) + medroxyprogesterone acetate in women with an intact uterus[3] and CEE-only in hysterectomized women[4]); now, we are given a final manuscript[5] which recycles the previous information, but with a focus on age groups and time since menopause, including analyses for the two arms combined.

The practical, clinical message that came out of the preliminary data was so loud and clear that it was immediately adopted by many health authorities like the US Preventive Services Task Force (USPSTF) and the European Agency for the Evaluation of Medicinal Products (EMEA): the use of hormone therapy (HT) is dangerous at any age and therefore should be avoided, unless there is a substantial reduction in quality of life because of menopausal symptoms. Later on came the detailed articles on cardiovascular morbidity, which showed that the harm was actually confined only to older women, especially those recruited beyond the age of 70 years, and that there was even some cardiovascular benefit and reduced mortality in hormone users during the early postmenopause period. However, the apparent age-specific different risks, and the known fact that most women actually use HT only for a limited time in their late forties or early fifties, did not change the opinion of the health authorities in the US and Europe. Almost 5 years after the initial WHI publication comes the third and final chapter in the trilogy, saying that age matters in regard to the cardiovascular adverse effects of HT.

The International Menopause Society (IMS), in its Statement on HT in February 2004 (updated document released in February 2007), was the first organization to emphasize the importance of age in determining the risk profile of HT. But the IMS brought it one step further by taking a positive, rather than a defensive attitude toward the use of hormones in the menopause. HT is indicated primarily for symptoms that are related to estrogen deficiency and menopause, and there is no reason to withhold this therapy from women who need it. The absolute numbers of women who could benefit or be harmed by HT for the age group 50–59 years in the WHI study, as compared to the placebo group, were in the range of 0–1 extra case per 1000 women per year of hormone use. This defines those events as 'rare', according to standard nomenclature.

Therefore, the IMS believes that healthy women in their early postmenopause period should not be concerned because of the 'alleged risks' of HT. The cardiovascular risks (coronary artery disease and stroke), attributed by WHI investigators to HT back in 2002, now seem irrelevant, at least until the age of 59. The WHI data on breast cancer, which had initially a very alarming impact, were also re-analyzed recently. The WHI figures (from the controlled and observational studies) actually accord with previous data, reassuring women that there is no extra risk of breast cancer during the first 7 years' use of standard doses of estrogen/progestin and for as much as 15 years of estrogen-alone therapy. The IMS also emphasizes the importance of dosage, route of administration and type of hormone as possible determinants of the risk–benefit balance.

In our view, the WHI study did, however, provide one service to menopause medicine after all. The debate and turmoil which ensued following the WHI studies showed that we cannot discuss 'hormone therapy' as one entity, that there is no 'class effect' for the adverse reactions of hormones, and that referring to 'postmenopausal women' as a unified and homogeneous population is wrong. The critical period for hormone use is during the menopause transition and the first years after the menopause. Indeed, hormone replacement therapy (HRT) is important in the early postmenopause to improve quality of life. Furthermore, there are enough data to support its use as part of an overall strategy in maintaining the health of postmenopausal women. On the other side of the equation, serious risks are negligible in the early postmenopause. The IMS recommends that decisions on the use of hormones, or on the continuation of HT, should be individualized, taken at the discretion of the well-informed woman and her health professional.

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Amos Pines, President, David Sturdee, General Secretary and Martin Birkhäuser, Treasurer
Press Statement, April 3, 2007

Response to the Lancet paper on ovarian cancer in the Million Women Study

The Million Women Study (MWS) has reported new data on the risk of ovarian cancer in postmenopausal hormone users.[1] The study showed a 20% increase in risk when current users were compared with never users. No increase in risk was recorded in women using HRT for less than 5 years, and past users had the same risk as never users. Risk did not vary significantly with types of HRT.

While the data derived from the MWS are not much different from several other studies, such as the Nurses' Health Study, the Women's Health Initiative study did not show an increased risk of ovarian cancer.[2] The IMS would like to comment:

- Following the previous analysis of the MWS on breast and endometrial cancers, there were many reservations concerning the methodology and these are still pertinent.[3]
- Most epidemiologists would consider that a relative risk of 1.2 is of minimal clinical significance but will inevitably reach statistical significance with very large numbers.
- Risk is far better reported in absolute numbers rather than relative risk or percentage. The absolute risk for ovarian cancer in the MWS was only one extra case per 2500 women after 5 years and mortality was one per 3300 over 5 years.

It is most regrettable that the risks for all gynecological cancers have been added together to produce an estimated increase in risk of 62% for hormone users. Endometrial cancer should be prevented by combined hormone therapy, and adding percentages is inappropriate and will inevitably cause further unnecessary distress to the many women who are benefiting from HRT.

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Amos Pines, President, David Sturdee, General Secretary and Martin Birkhäuser, Treasurer
Press Statement, April 18, 2007

IMS reaction to a special report on breast cancer incidence in 2003 in the United States

A special report in the April 19 issue of the New England Journal of Medicine[1] brings initial analysis of data from the National Cancer Institute's Surveillance, Epidemiology and End Result (SEER) registries, showing that the incidence of breast cancer in women in the US fell by 6.7% in 2003, and stayed at the same level in 2004. The decrease was evident only in women who were 50 years of age or older, and solely involved cancers that were estrogen receptor-positive. The investigators suggested that a plausible explanation for the unexpected data is the concomitant sharp decrease in the use of postmenopausal hormones, which followed the first report from the Women's Health Initiative (WHI) study in mid-2002.

While being pleased with these new data on the incidence of breast cancer, the International Menopause Society (IMS) advises caution in linking these two parallel trends observed in the US. Any attempt to put both observations into one framework is premature and there is little scientific basis for such an assumption. In fact, the authors themselves mention in the manuscript that other factors might have contributed to these changes in breast cancer incidence. Nevertheless, the reader of the article still receives a clear message on the presumed association with hormone therapy (HT).

The IMS wishes to stress the following relevant facts:

- Despite a similar decrease in the use of HT in other countries as a result of the WHI results, such a decline in the incidence of breast cancer incidence in 2003 was not recorded by some other national cancer registries world-wide such as in the UK.
- According to Figure 1 in the article, a transient decrease in breast cancer incidence was observed also around 1987–9. There is no reason to associate that incidence with hormone use, which shows that other factors may play a role, or that unexplained epidemiological aberrations may occur.
- Possible confounders were not evaluated in this initial analysis of SEER data. Perhaps the most important ones are the rates of mammography and clinical breast exams. An abstract was presented in February 2007 by Dr Chagpar[2] at a congress of the Association for Academic Surgery and the Society of University Surgeons, showing that, according to data from the Centers for Disease Control and Prevention's National Health Interview Survey, both mammography and clinical breast cancer exam rates were significantly reduced in 2005 as compared to the 2000 figures. Thus, it remains unclear whether some or all the decline in breast cancer incidence observed in 2003 actually reflects an artifact caused by less screening.
- Current knowledge of the biology and development of breast cancer suggests that a 10% decrease in breast cancer incidence occurring within a year after cessation of estrogen therapy is unlikely.
- The WHI study has already provided very good epidemiological data on the association between HT and breast cancer risk. In the conjugated equine estrogen plus medroxyprogesterone acetate arm (5.2 years' follow-up), no risk was recorded for women who did not use HT prior to the study or were aged less than 60 years at randomization. The results in the conjugated estrogen-alone arm (6.8 years' follow-up) were more favorable, with fewer cases of invasive breast cancer in women entering the study before age 60. The availability of the results of the WHI study and other major observational studies (such as the Nurses' Health Study) makes the suggested link between a decrease in breast cancer incidence and the decrease in hormone use less important for the consumer, since risks of long-term HT can be reported accurately, based on the above randomized or cohort studies.

The IMS maintains its recommendation that HT should be prescribed whenever indicated. The use of hormones in early menopause and up to age 60 years has a very minor potential for harm, but carries substantial benefits. Women should decide annually whether they wish to continue treatment after consultation with their caregiver.[3]

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ISSUED ON BEHALF OF THE INTERNATIONAL MENOPAUSE SOCIETY BY
Amos Pines, President, David Sturdee, General Secretary and Martin Birkhäuser, Treasurer
Press Statement, April 19, 2007

THE INTERNATIONAL MENOPAUSE SOCIETY

The aims of the Society (IMS) are to promote knowledge, study and research on all aspects of aging in men and women; to organize, prepare, hold and participate in international meetings and congresses on menopause and climacteric; and to encourage the interchange of research plans and experience between individual members. The Society is a non-profit association, within the meaning of the Swiss Civil Code. It was created in 1978 during the first World Congress on the Menopause. In addition to organizing congresses, symposia, and workshops, the IMS owns its own journal: Climacteric. See website: www.imsociety.org

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