Invited Editorial

The Women’s Health Initiative Conundrum

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Summary

The WHI has been designed to evaluate the metabolic risks and benefits of Estrogen/Progestagen Therapy (HT) or Estrogen Therapy (ET) in women in their later postmenopause. It has not been designed to study the effect of HT or ET on symptomatic peri- and early postmenopausal women. Furthermore, the selection criteria used in the WHI are not congruent with the profiles of women treated in daily medicine by HT or ET: women starting HT or ET in clinical routine are younger, less obese and healthier than the WHI population. Therefore, the results and the risk-benefit-conclusions of the WHI cannot be applied to normal symptomatic peri- and immediately postmenopausal women, and even less to women with early (40–50 years) or premature (40 yrs.) menopause.

Keywords: Menopause; estrogen therapy; hormone therapy; WHI; risks; benefits; climacteric symptoms; quality of life.

The Women’s Health Initiative (WHI) Study: General remarks

The WHI is the last of three recent RCT (Anderson et al., 2004; 2003; Cauley et al., 2003; Chlebowski et al., 2003; Hays et al., 2003; Manson et al., 2003; Rossouw et al., 2002; Herrington et al., 2000; Hlatky et al., 2002; Hulley et al., 1998) designed to evaluate the risk benefit ratio of hormonal treatment after menopause, particularly with respect to prevention of cardiovascular diseases, breast cancer risk and cerebral aging. It is an excellent trial for the population studied: elderly and mostly asymptomatic women taking hormone treatment (estrogen + progestagen, HT) or estrogen treatment (unopposed estrogen, ET) for prevention of metabolic diseases. However, the way the results of the WHI have been communicated to the medical community and to the world press, including the mass media, has raised confusion, concern and considerable fear not only in women taking HT, but also in doctors.

The WHI has been designed as a large, NIH-sponsored, randomised, multicenter-study. 27000 women have been included, aged 50–79 years (Ø ~63 years). The recruitment lasted from 1993 to 1998.

The hormone therapy subgroup consisted of a combined estrogen/progestagen arm (HT arm) and an estrogen-alone arm in hysterectomised women (ET arm). The aim of the trial has been to evaluate the risk/benefit ratio of the long-term results of an administration of ET and HT for the prevention of diseases. The primary benefit was coronary heart disease (CHD) and non-lethal myocardial infarction or death by coronary heart disease, the primary risk invasive breast cancer. A global index has been chosen to evaluate the sum of all risks and benefits. The end of the study has been planned for 2005.

However, the HT arm (Rossouw et al., 2002) was stopped in 2002 by the Data and Safety Monitoring Board (DSMB) because the sum of the risks exceeded the sum of the benefits (predetermined limits reached). The mean follow-up of the combined HT arm has been 5.2 years. In the HT arm, the treatment consisted in the combined administration of conjugated equine estrogens (CEE; 0.625 mg/d) + medroxyprogesterone acetate (MPA; 2.5 mg/d) (n = 8,506) or placebo (n = 8,102). The total dropout rate has been 42% in the HT arm and 38% in the placebo arm.

The ET arm has been stopped in February 2004 (Anderson et al., 2004). The mean follow-up of the estrogen-alone arm has been 6.8 years. In the ET arm, the treatment consisted in the administration of CEE
alone (0.625 mg/d) (n = 5,310) or placebo (n = 5,429). The characteristics of the participants in both arms are presented on Tables 1 and 2.

The age at recruitment has been unusually high: The volunteers for the WHI have been recruited about 12 years after their menopause. Therefore, the mean age of the women recruited for the WHI has been 63.2 years (HT arm) and 63.6 years (ET arm) at inclusion, bringing the mean age at termination of the trial up to 68 and 70 years. In contrast, women starting HT/ET in Europe and in other regions of the world are on the average more than 10 years younger (mean age 51–52 years) than the participants at the WHI (mean age 63.4 years).

Looking at general health at baseline, we are astonished to find a BMI ranging from overweight to frank obesity, an unusual high incidence of arterial hypertension at inclusion, particularly in the ET arm, and a high percentage of participants using aspirin or statins at inclusion. All these findings point to the presence of several cardiovascular risk factors in at least 50% of the study population. These women cannot be called “healthy”, as it is suggested by the title of the first publication (Rossouw et al., 2002).

The individual risk profile is decisive for each woman if she considers a hormonal treatment. For the mandatory full information about the risks and benefits of a HT or ET, the absolute and not the relative risks should be used, as it is unfortunately mostly done. The notion of the relative risk, used for the communication of the results to the mass media, has been the origin of most of the misunderstandings about the results of the WHI, as is illustrated by this example: In the first report from the HT arm of the WHI, it was stated that the risk of suffering from a cardiovascular event was increased by 29% in women using HT. However, the absolute risk of suffering a heart attack was 0.37% in the HT arm vs 0.30% in the placebo arm, or 37 vs. 30 events/year per 10,000 women, or a surplus of 0.7 events per 1000 women per year. Even more important, in women in their early postmenopause, the risk was not increased at all (Manson et al., 2003) Therefore, the absolute risk of having a serious complication induced by HT is extremely low in elderly women, and nil in younger women. However, the same has to be said about the absolute advantage of an HT/ET, such as the reduction of the risk of fracture.

**Hypothesis**

Our hypothesis is that there have been several selection biases, rendering the comparison with women at initiation of HT/ET in other regions of the world difficult if not impossible. These biases lead to a study design typical for a trial for secondary and not primary cardiovascular prevention. It might therefore be postulated that:

- The population studied in the WHI does not correspond to the postmenopausal women treated by HT/ET in daily medicine in Europe and in other regions of the world considering its age, its BMI and its pre-existing cardiovascular risk factors, such as the high incidence of arterial hypertension at inclusion.
- Because the WHI has been designed for the study of cardiovascular prevention in elderly women, the population recruited for the WHI has been essentially