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Results from WHI and HERS II - Implications for women and the prescriber of HRT

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1. Background

Placebo controlled randomised clinical trials are considered to be the gold standards to assess the real risks and benefits of chronic treatments. This was the case with the WHI, a study aimed at the primary prevention of cardiovascular diseases in healthy postmenopausal women.

The WHI safety committee [1,2] decided to interrupt one arm of the study because women on the combined estrogen-progestin, at the end 5.2 years, had an increase in the relative risks for cardiovascular events and breast cancer, though with a lesser risk of osteoporotic fractures and colon cancer. However, interim reports on women on estrogens alone did not show adverse CV or breast cancer crossing the predetermined safety boundaries, and this part of the trial thus continues.

The order of magnitude of the relative risks is impressive. However, absolute risks are small per 10 000 woman / year, an abstract figure of extrapolation that does not reflect the actual results: at the end of 5.2 years there were 7968 women in the treated group and 7608 in the placebo group. Therefore, if the absolute risks are plotted as percentages, instead of the additional 8 strokes, 7 heart attacks and 8 breast cancers per 10 000 woman / year one would have, respectively, 0.8, 0.7 and 0.8 cases per 1,000 woman / years a figure that is easier to interpret. It would suggest that if 1000 women were treated during one year there would be less than one woman with an adverse effect.

As the WHI investigators say 'the increased risk of breast cancer for each woman in the WHI study who was taking the estrogen plus progestin therapy was actually very small: less than a tenth of 1 percent per year' [3]. This is more realistic than the reported relative risk increase of 26% for breast cancer.

It is reassuring that there was 'no difference in total mortality of all causes' and it is also a very important conclusion that only 2.5% of women in the estrogen plus progestin, had those health events [4]. Thus, 'the absolute risk of the study arm to an individual woman is small' [2]. 'The absolute excess risk events included in the global index was 19 per 10 000 person/years' [1]; that is to say that 1000 women would have to be treated during one year in order to cause two events. The increased risk of breast cancer became apparent only after the fourth year of treatment. These cancers were invasive. In the protocol of the study it is mentioned that women had to have a base line mammography [5].

Another puzzling aspect of this study is the high drop out rate of 42% in the estrogen plus progestin group that, over time, has exceeded the design projections. At the time of this report clinical

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gynaecologists had been unblinded to treatment assignment for 3444 (40.5%) women in the estrogen plus progestin group and 548 (6.8%) women in the placebo group, primarily to manage persistent vaginal bleeding. During the trial 248 women in the estrogen plus progestin group and 183 in the placebo group had an hysterectomy [1]. This is a sign of excessive dose for women between 60-69 (45.3%) and 70–79 (21.3%). No information is available about which of the age groups had more vaginal bleeding. Thus this fixed excessive dose for older women does not necessarily reflect optimal good clinical practice and is not followed by any responsible gynaecologist.

The findings in WHI for stroke are consistent with, but somewhat more extreme than, those of HERS [1]. This is puzzling since the HERS participants where definitely sicker (CV) than those in WHI, supposed to be CV disease free. Unlike HERS which showed no benefit or harm after 6.8 years of hormone use, WHI found more heart disease in women taking the combined therapy after 5.2 years. This is a key finding because WHI results apply to healthy women while HERS involve women with heart disease [3].

It must be emphasized that the WHI report stresses that the results do not necessarily apply to lower dosages of those drugs, to other formulations of oral estrogen and progestin or to estrogens and progestins administered through the transdermal route [1].

It seems that the recommendations of the WHI writing group are mainly focused on public rather than individual health, since they say that, even small individual risks over time, and on a population-wide basis, add up to ten's of thousands of those serious adverse health events and becomes an important public health concern. Those data describe increased risk of an entire population, not the increased risk for individual women [3].

2. Comments

The results reported in clinical trials are sometimes difficult to interpret. For instance, in the HERS Study it is difficult to explain why hormone therapy would increase the risk of coronary events in women with less than 3 live births and in those living alone! The observed lower event rate in smokers compared with non-smokers in the hormone group is intriguing. There is a higher event rate among users of digitalis in the hormone group compared with the placebo groups [6]. The authors of these re-analyses of the HERS Study conclude that they did not identify any sub-groups of HERS participants in which postmenopausal treatment was clearly beneficial or harmful.

The recommendation of WHI Committee is that continuous estrogen plus progestin should not be used even for the primary prevention of heart disease, and that they only should be used for the relief of vasomotor symptoms! In a re-analysis of HERS follow-up during 6.8 years of hormone therapy (HERS II) it was concluded that lower rates of CHD events among women in the hormone group in the final years of HERS did not persist during additional years of follow up [7].

3. Clinical implications

It is not an easy task to opt between results of observational and clinical trials. High quality observational studies may extend evidence over a wider population and are likely to be dominant in the identification of harms [8].

Let us go back to the WHI clinical trial and to the recommendations to stop its estrogen+progestin arm.

The incidence of side effects was really very, very small in terms of *individual* health. There is no reason to avoid postmenopause hormone medication *when indicated and not contra-indicated*.

Second, it must be stressed that the main goal is women's health and not hormonal therapies. The Nurses Health Study [9] has shown that between 1980 and 1994 there was a 31% reduction in CHD. Better nutrition, cessation of smoking, and hormonal treatments in the menopause, were responsible for the 18%, 13% and 9% reduction, respectively.

Third, the results of a crucial study should preferably be expressed in such a way that practitioners may use them for their practice to inform users. A very useful way is the Number Needed to

Treat (NNT) and the Number Needed to Harm (NNH) which are respectively the reciprocals of *absolute risk reduction* and *absolute risk increase*. These are expressions that are easier to extrapolate into clinical practice.

We are nowadays facing an extremely difficult dilemma vis-à-vis the care of postmenopausal women. The important issue after all is not the improperly named hormone replacement therapy [10]. What is important is the best possible approach to preventive medicine in a mid-aged woman. The prescription of long-term hormonal treatments for osteoporosis must depend always on a benefit/risk analysis in comparison with non-hormonal medications and strategies. At present, in some European countries the indication for prevention of postmenopausal osteoporosis by HRT will be re-assessed according to public statements of drug licensing authorities. It must be made clear that the concept of HRT does not mean that all postmenopausal women must be always under hormonal treatments [11,12].

Our main goal, as attending physicians of postmenopausal women, is the maintenance of their health and the primary and secondary prevention of the diseases, which are more prevalent after age 50 [13].

> Preventing a woman from the benefits of a sound postmenopausal hormone therapy because of the fear of rare side effects does not seem to be satisfactory Medicine... *Primum, non nocere*, neither by excess nor by abstention, as well... [14].

4. Conclusions and Recommendations

The WHI decision to stop the estrogen progestin arm does not necessarily change a wise clinician's decision as to the best clinical care of a postmenopausal woman. However, we all have learnt now to be ever more cautious in discussing risks and benefits of estrogen and progestin treatment. More recent epidemiological studies continue to supply evidence that long-term postmenopausal hormone therapy may reduce the risk for CAD in healthy women. The Nurses' Health Study and studies from Europe, where estradiol is the commonly prescribed form of estrogen, suggest that the estrogen at lower doses may confer similar benefit'' [15].

Luckily one has nowadays an ample choice of strategies and drugs (hormonal and non-hormonal) that enable a conscientious physician to do his best to restore the confidence of those women who have sought his help.

The WHI is an important study. It was meant to prove the clinical effectiveness of ONE specific estrogen and progestin to prevent heart disease. This concept failed in this specific, large group of women studied. WHI does not introduce new rules to good clinical practice.

Given these latest additions to our overall knowledge the policy of EMAS wil be to:

1) Recommend the use of any HRT to women with climacteric symptoms likely to impact on quality of life and to re-emphasize that topical use of low dose vaginal estrogens can be used by any woman carrying an indication for such therapy.
2) To reassess the need of HRT after four years of therapy and not recommend HRT for the sole purpose of preventing chronic disease, such as cardiovascular disease or osteoporosis as other alternatives are available.
3) To promote the use of additional and alternative non-hormonal strategies for maintaining health and preventing disease in symptom free women of middle age and beyond.

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