

## DEBATE—continued

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### Menopause in crisis post-Women's Health Initiative? A view based on personal clinical experience

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**Menopausal women should not consider that hormonal treatment is an obligatory long-term commitment. Estrogen-based treatments are extremely effective for vasomotor symptom relief and for vaginal atrophy. HRT also is one of several effective methods for the primary prevention of osteoporosis. If trials were done early after the menopause when the endothelium is likely still to be intact, estrogen-based treatment might be shown to prevent coronary heart disease. However, greater efficacy is to be expected from smoking cessation, proper nutrition, exercise, moderate alcohol consumption, statins,  $\beta$ -blockers and angiotensin-converting enzyme inhibitors. The treatment options for a menopausal woman should include non-drug-related strategies, non-hormonal pharmaceutical therapies as well as hormonal treatments. The first objective of this contribution is to call to the attention of practising physicians the fact that the Women's Health Initiative (WHI) and Heart and Estrogen/Progestin Replacement Study (HERS) studies involved women much older than the early postmenopausal age groups for whom HRT is prescribed because of symptoms. The second objective is to emphasize that the attending physicians must not only treat the symptomatic women but also prevent the occurrence of diseases more prevalent after 60 years of age. Hormones can safely be used for the former, when not contraindicated, whereas for the latter non-pharmacological interventions and non-hormonal medications are preferable.**

*Key words:* cardiovascular/estrogens/HRT/menopause/Women's Health Initiative

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#### Introduction

A 'crisis' (from the Greek *krisis*, derived from *krinein*, to separate) is 'a crucial point or situation', 'a turning point' (American Heritage Dictionary, 1994). This is precisely what is happening with HRT. The management of menopausal women is now at a crucial point, a turning point. There are very few topics in the field of women's medicine that have attracted as much interest as hormonal treatment after the menopause and many critical interpretations have been published about the more recent studies (Blake *et al.*, 2002; Gambacciani *et al.*, 2002; Genazzani, 2002; Grimes and Lobo, 2002; Kelly, 2002; Neves-e-Castro, 2002a,b; Schneider, 2002; Speroff, 2002; Stefanick and Roussouw, 2002; Stevenson and Whitehead, 2002; Barlow, 2003; Genazzani *et al.*, 2003a; Goodman *et al.*, 2003; Grodstein *et al.*, 2003; Herrington and Klein, 2003; NAMS Report, 2003; Notelovitz, 2003; Shapiro, 2003; Solomon and Dluhy, 2003). This paper will show that the crisis is an over-reaction to a normal addition to our knowledge, an addition that permits adaptation of the best treatment strategies, non-drug and drug-related, with or without hormones.

In the late 1940s and early 1950s, knowledge of the endocrinology of the climacteric was not well developed. Osteoporosis was linked to the onset of the menopause and

women were known to have, prior to the menopause, less coronary heart diseases (CHD) than men, a difference that would fade after the spontaneous cessation of their menstrual cycles. The major concern, in those days, was the treatment of vasomotor symptoms, depressive mood, irritability, atrophic vaginitis and decreased libido, for which the available estrogens were very efficacious. In those days nobody thought about side-effects nor about disease prevention. With an increasing number of women being treated all over the world with high doses of often unopposed estrogens, and with further knowledge about the physiopathology of the menopause, it became apparent that serious side-effects such as cancer existed and that levels of endogenous and exogenous estrogens were causally linked to vasomotor symptoms, osteoporosis, CHD, mood, libido and vaginal atrophy. Thus, a new era opened with estrogen therapies not only for the treatment of climacteric-associated symptoms but also for the primary and, later, secondary prevention of CHD and osteoporosis. Few other drugs were then available with such effects.

In the last decades of the twentieth century new molecules were developed for the treatment and prevention of bone and cardiovascular diseases, such as bisphosphonates, statins,  $\beta$ -blockers and selective estrogen-receptor modulators (SERM),

which increased choice, and the objectives of effective prevention could thus be achieved differently, with fewer side-effects. For instance, in the Heart and Estrogen/Progestin Replacement Study (HERS) 'statin use was associated with lower rates of cardiovascular events, venous thromboembolic events and total mortality', providing 'strong support for statin use in eligible women with coronary disease' (Herrington *et al.*, 2002). 'HRT resulted in a significant increase in early risk for primary events in women who did not use statins but not in statin users' (Herrington and Klein, 2003). Thus it has been concluded that 'the favorable effects of statin therapy in women in clinical trials make a cholesterol-lowering drug preferable to hormone replacement therapy for CHD risk reduction' (NCEP adult treatment Panel III report, 2001).

### The medical care research evidence

With improvement in epidemiological study methodology, other HRT side-effects began to emerge and doubts were cast on the efficacy of estrogens in disease prevention. There was therefore the need to conduct well-designed randomized controlled trials. Many of the trials are well known, such as PEPI (Writing Group for the PEPI Trial, 1995), HERS I (Hulley *et al.* for the HERS Research Group 1998) and HERS 2 (Grady *et al.*, 2002; Hulley *et al.*, 2002), and ESPRIT (Khan *et al.*, 2000) but it is the largest, the Women's Health Initiative (WHI), which has caused profound concern amongst women, the medical profession and the pharmaceutical industry. Suddenly, estrogens were classified as carcinogens (Twombly, 2003) and very dangerous, with recommendations that estrogen be used very carefully, for specific indications, with the lowest possible doses, and for the shortest time (US Preventive Services Task Force, 2002). This was a reaction to the results of WHI showing that a specific dose of conjugated equine estrogens with medroxyprogesterone acetate given to asymptomatic allegedly healthy women, with a range of ages between 50 and 79 years, was associated with a slight increase in the absolute risks of stroke, heart attacks and breast cancer, of less than a tenth of 1% per year! (Writing Group for the Women's Health Initiative Investigators, 2002; Fletcher and Colditz, 2002). Additionally the estrogen-only arm of WHI in women with hysterectomy has not been suspended and continues because the balance of benefit and risk in that group of women is not yet clear.

The international interpretation of the WHI results must take into consideration the geographic epidemiology. For instance, ischaemic heart disease (IHD) is much more frequent in the USA than in Italy, whereas cerebrovascular disease is more common in Italy. Although breast cancer risk is similar in the two countries, IHD rates are so different that 'In the 40–49 age groups for each woman dying of IHD, 5 will die of breast cancer in Italy but only 2 in the USA (Ricci *et al.*, 2002). Even more intriguing is relative interpretation of the HERS and WHI results. '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' (Rossouw, 2002).

Women included in the observational studies and RCT are not comparable. In WHI, 66% of participants started taking the estrogen–progestin regimen at age  $\geq 60$  years and 21% began at age  $\geq 70$  years. Because the WHI cannot determine whether an estrogen–progesterone regimen initiated at the onset of menopause in symptomatic women increases or decreases the risk of CHD, the clinical implications of the WHI results are less dramatic than they appear (Michels, 2003). The Nurse's Health Study investigators (Hu *et al.*, 2000) reported that the reduction in CHD over a 14 year period was due to HRT in only 9%, to smoking cessation in 13% and to better nutrition in 16%; obesity increased CHD by 8%. Thus, hormonal therapy, if effective at all, seems to have no more than a minor role in the prevention of CHD (Mosca *et al.*, 1999) and the expectations of the WHI results were too high.

A recent meta-analysis of HRT trials is consistent with the overall results of the WHI (Beral *et al.*, 2002). The change in incidence of major potentially fatal conditions, in 1000 healthy menopausal women using HRT over 5 year period, was for women aged 50–59 years a total excess of 6/1000 (or 1/170 users), and for women aged 60–69 years a total excess of 12/1000 (or 1/80 users). As to the reduction of colorectal cancer and fractures of the neck of the femur, there is a total deficit of 1.7/1000 for women aged 50–59 years and 5.5/1000 in women aged 60–69, which is equivalent, respectively, to 1/600 users and 1/160 users. Therefore, the overall balance is a net excess of 1/230 users (aged 50–59 years) and 1/150 users (aged 60–69 years). Although these interpretations have been questioned by some (Stevenson, 2003), the analysis of two more recent studies supported the validity of the original report (Beral *et al.*, 2003).

In clinical practice, the number needed to treat (NNT) and the number needed to harm (NNH) are useful expressions of trial results (Cook and Sackett, 1995; Chatellier *et al.*, 1996; Altman and Andersen, 1999). For the average woman who may need a hormonal treatment between 50 and 59 years of age, the NNH is 170 and the NNT is 600, during 5 years of treatment, with a net excess (NNH) of 1/230. This suggests that the balance of benefit and risk is negative for the prevention of major potentially fatal conditions. Of course, if one calculates the NNT/year and NNH/year based on the results of the WHI, the figures are less impressive (Fahey *et al.*, 1995; Altman, 1998). The NNH are 1428 for CHD, 1250 for stroke, 588 for venous thromboembolism and 1250 for breast cancer. Thus, according to WHI, one would need to treat 1428 women during 1 year in order to find one additional CHD event compared with controls, and so on. As to the benefits the NNT are: 1667 for colon cancer and 227 for total osteoporotic fractures, thus suggesting that one must treat 1667 women to prevent one colon cancer and only 227 to prevent one osteoporotic fracture compared with controls.

The follow-up of the WHI Study (Manson *et al.*, 2003) confirms, as in the first report, that 'estrogen plus progestagen does not confer cardiac protection and may increase the risk of coronary heart disease among generally healthy postmenopausal women, especially during the first year after the initiation of

hormone use' and that 'this treatment should not be prescribed for the prevention of cardiovascular disease'.

A detailed analysis of this report shows the following. During the first year of treatment the NNH is 123 before one extra cardiac event is diagnosed in relation to the hormonal treatment; it rises to 300–400 from year 2 to 4, and to 1430 after the 6th year. The NNH for total women aged 50–59 years is 370. However, if they have hot flashes, night sweats or both, they are more protected from CHD (NNH 625 versus 196 for women with no vasomotor symptoms). The later after menopause the hormonal treatment is started the greater the CHD risk (NNH 1110, 454 and 140, for <10, 10–19 and  $\geq$ 20 years since menopause, respectively). Women with a body mass index (BMI)  $\geq$ 30 have 3-fold less risk than those with BMI <25. Women who use statins have a NNH 1010 compared to 370 in non-users (3-fold greater protection). The ratio for CHD is <1 if: total cholesterol <208 mg/dl; low density lipid (LDL) cholesterol <125 mg/dl; high density lipid (HDL) cholesterol >58 mg/dl; lipoprotein (Lp) (a) >31 mg/dl; C reactive protein >3.57 mg/l.

The likely conclusion is that the risk of CHD during the first year after the initiation of hormone use is probably abolished if treatment is started soon after the menopause (women aged 50–59 years), in women with BMI  $\geq$  30, who have vasomotor symptoms, who take statins, and who have the above-mentioned biochemical profile. If this will be the case it would be likely to assume that one would have to treat ~600 women before any extra cardiac event appears.

This is supported by the EPAT Study (Hodis *et al.*, 2001) which showed that 17 $\beta$ -estradiol therapy alone significantly slowed the progression of atherosclerosis relative to that in the women in the placebo group who did not receive lipid-lowering therapy, but had no demonstrable effects relative to that in the women in the placebo group who did receive such therapy'. This shows that 'unopposed 17 $\beta$  estradiol alone and lipid lowering therapy alone had similar effects on the progression of atherosclerosis'.

The WELL-HART Study (Hodis *et al.*, 2003) concludes that 'in older postmenopausal women with established coronary-artery atherosclerosis, 17 $\beta$ -estradiol either alone or with sequentially administered medroxyprogesterone acetate had no significant effect on the progression of atherosclerosis'. The mean age of the women was 65.5  $\pm$  6.5 years (range 48–75) and the mean time from menopause to randomization was 18.2 years (range 0.1–48.6). There was no evidence of an increase in the rate of coronary events during the first year of hormone therapy. An important detail of this study is that in all patients the LDL cholesterol level was reduced to a target of <130 mg/dl. The authors conclude that comparison with EPAT indicates that estrogen therapy may be effective in slowing the progression of atherosclerosis when it is initiated early in the menopause, while the vascular wall remains responsive to estrogen.

The mechanism for breast cancer harm suggested in a recent publication from the WHI Writing Group (Chlebowski *et al.*, 2003) is that 'estrogens plus progestin may stimulate breast cancer growth and hinder breast cancer diagnoses', due to increased mammographic density.

A recent study (Million Women Study Collaborators, 2003) on breast cancer involving more than one million UK women aged 50–64 years, in a non-randomized observation, concludes that 'current use of HRT is associated with an increased risk of incident and fatal breast cancer', and that 'the effect is substantially greater for oestrogen–progestagen combinations than for other types of HRT'.

'The breast cancers were diagnosed on average 1.2 years after recruitment'. The conclusion is that '5 years use of HRT beginning at age 50 is estimated to result in 1.5 (95% CI 0–3) additional breast cancer by age 65 years among 1000 users of estrogen-only preparations and 6 additional cancers among 1000 users of oestrogen–progestagen combination. 10 years use is estimated to result in 5 additional cancers in 1000 users of estrogen-only preparations and 19 additional cancers in 1000 users of combined HRT'.

It was also found that 'the only factor that modified the relative risk estimates was body-mass index, with the relative risk estimates being larger among the thinner women, i.e. those with a lower rather than a higher index'.

Thus, at the end of 10 years an estrogen-only treatment started at the age of 50 years results in five excess cancers per 1000 women and 19 excess cancers, for 10 years of use of estrogen–progestagen. In terms of NNH this means that one would have to treat 270 women during 10 years with an estrogen-only preparation and 76 with an estrogen–progestagen combination before one excess breast cancer would be diagnosed. These figures are slightly worse than those reported in the WHI and HERS Study (for estrogen–progestagen combination NNH was 384 and 370 respectively). Tibolone users had also an increased risk of developing breast cancer, although in a smaller percentage than with estrogen only or estrogen-progestagen preparations. The fact that with all preparations the increased risk became apparent within 1–2 years of starting treatment very strongly suggests that those preparations did not cause cancer; they most probably stimulated the growth of silent pre-existing cancers. (Neves-e-Castro, submitted; Neves-e-Castro, 2003; Speroff, 2003).

However, it should be made clear that these results apply to an older population, but not to a younger population represented by the vast majority of women who seek medical help for symptom relief. Nevertheless HRT is very much cost-effective, with a positive benefit/risk ratio, for the relief of vasomotor symptoms, treatment of vaginal atrophy and, altogether, for quality of life, when given early after the menopause. These benefits were not investigated in the above-mentioned trials.

The major difference between the observational studies and the WHI findings concerns the effect of HRT on heart disease. The good agreement between the observational studies and the trial endpoints other than CHD confirms the utility and validity of observational studies in the assessment of new preventive agents. Moreover, randomized clinical trials cannot evaluate the long-term effects of preventive agents' (Whittemore and McGuire, 2003). In relation to the discrepant CVS results between the major observational studies such as the Nurses Health Study and WHI there has been discussion that differences between the women who joined the studies may be a

factor (Grodstein, 2003) or that in examining the differences it may be that ‘estrogen, in pills, is not the chemical to focus on’ (Rossouw, 2003).

### Why all the noise?

I believe that this has been mainly because the conclusions of these trials were over-interpreted by the medical profession, the media and by the women themselves. It is relative risks which have been much publicized with the omission of the absolute risks. Everybody thought that those results applied to the individual woman rather than to an entire population. The relative risk increase was interpreted by many as representing an absolute risk increase!

This has raised concern amongst some physicians that women, who tend to be more concerned about breast cancer than about their heart, might take litigation against physicians who give them sex hormones for more than a few months even though properly indicated. ‘When the WHI documents were analysed using adjusted confidence intervals only the changes in incidence of thromboembolic diseases and total bone and other osteoporetic fractures were significant. The increase in breast cancer incidence did not reach statistical significance with either nominal or adjusted confidence intervals’ (Barber *et al.*, 2003). The absolute risks of hormone treatments are so very low in the individual middle-aged woman, that it is surprising how much impact these results have had in the minds of most of those who practice menopause medicine, whereas I personally did not have to fundamentally change any rules in the way I practice medicine. ‘There are no really ‘safe’ biologically active drugs. There are only ‘safe’ physicians’ (Kaminetzky, 1993). I perceive that the standard of good clinical practice is about to be lost due to the misinterpretation of what science is contributing to the art of medicine.

‘If you are a clinician, you must believe that you know what will help your patient, otherwise, you cannot counsel, you cannot prescribe’. ‘If you are a scientist, however, you must be uncertain—a scientist who no longer asks questions is a bad scientist ...’ (Pickering, 1964).

### Evidence-based medicine

Following the introduction of evidence-based medicine (EBM) philosophy in 1992, physicians have been expected to follow what is concluded in well-balanced randomized clinical trials. The concept has evolved and Haynes *et al.* (2002) have commented that EBM is ‘attempting to augment rather than to replace individual clinical experience and understanding of basic disease mechanism’. They also comment that ‘evidence from research can be no more than one component of any clinical decision’ and that ‘clinical judgment and expertise’ are viewed as essential to success. With the need to balance evidence from randomized trials with clinical experience and the demands of the clinical setting, they indicate that ‘clinicians must adopt not only the research evidence; they must also acquire and have the skills needed both to interpret the evidence and to apply it appropriately, doing the right

things’. They conclude that ‘the new look of EBM should be research enhanced health care’ (Haynes *et al.*, 2002).

We are nowadays facing an extremely difficult dilemma vis-à-vis the care of postmenopausal women. What is important is the best possible approach to preventive medicine in a middle-aged woman. The prescription of long-term hormonal treatments must depend always on a benefit/risk analysis in comparison with non-hormonal medications and strategies. It must be made clear that the concept of HRT does not mean that postmenopausal women must be always under hormonal treatments. Hormone treatments can be very good, but treatments without hormones can also be good (Neves-e-Castro, 2001a,b).

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 years. However, depriving a woman from the sound benefits of well-designed hormonal treatments because of the fear of relatively rare side-effects does not seem to be satisfactory medicine (Neves-e-Castro, 2000).

### Central nervous system

The central nervous system (CNS) is another important potential target for primary prevention in view of the nerve-growth-promoting effects of estrogens and their influence in neuromediation (Neves-e-Castro, 1999). However, a recent substudy of WHI suggests that estrogen plus progestin may increase the number of cases of Alzheimer’s disease in women aged  $\geq 65$  years (Shumaker *et al.*, 2003). The WHI investigators also concluded that ‘among postmenopausal women aged 65 years older, estrogen plus progestin did not improve cognitive function when compared with placebo’ (Rapp *et al.*, 2003). Nevertheless there is good evidence that ‘estrogens are potent neuroprotectants, demonstrating cell salvage from ischemic death pathways’ (McCullough, 2003).

The negative findings from the WHI trial are in marked contrast with the data presented in a recent review (Sherwin, 2003) showing that ‘an accumulating body of evidence is beginning to suggest that the immediate postmenopausal period may constitute a critical window for treatment with ERT that maximizes its potential to protect against cognitive decline with ageing and/or to reduce the risk of ageing dementia.

The conclusions of the WHI clinical trial do not apply to the vast majority of much younger women who need estrogens for the treatment of hot flashes, which, if not abolished, might cause brain cell lesions due to hyperthermia. Therefore, one may assume that estrogen treatment started early after the menopause may have protective effects on neural and endothelial cells if they are still undamaged. The future will show if the primary prevention of CNS, bone and cardiovascular diseases is a possibility when estrogen treatment is started at the time of the menopause (Mikkola and Clarkson, 2003). A recent position paper was published under the auspice of the International Menopause Society (Genazzani, 2003b).

## Personal experience

I believe that the time has come to slow down the discussions about the validity or lack of validity of the recent HRT studies. The trials are valid, although the results may not be directly relevant to younger women. What must be done now is to reflect on the best holistic management of women entering the menopause.

In the practice of medicine clinicians will interpret the best available published evidence in the light of their personal clinical experience. I have been involved in this approach for the past 40 years in my private clinic where adherence has been high and where the follow-up has been extended for several decades in a large number, allowing me to develop a good idea of their progress through longitudinal observation. In this experience I have diagnosed several breast, endometrial, ovarian and thyroid cancers and also a few CHD. Very few women had strokes. These problems were not related to past or current hormonal treatments but were diagnosed in the course of pre-treatment screening. I always encourage exercise, smoking cessation and proper nutrition. Many are put on low dose acetylsalicylic acid, statins, angiotensin antagonists or diuretics, when indicated. In hysterectomized women I never give progestagens.

I personally believe that hormonal treatments after the natural menopause are extremely important for symptom relief and for quality of life, for as long as women need them, with adequate controls of their health. I also believe that they may have positive effects in the primary prevention of CHD (Hodis *et al.*, 2001; Hu and Grodstein, 2002; Pines, 2002; Hodis *et al.*, 2003; Karas and Clarkson, 2003; Writing Group for the 3rd European Conference on Sex Steroids and Cardiovascular Diseases, 2003) if started early, when the endothelium is likely to be intact.

## Conclusions

It is of paramount importance to call to the attention of gynaecologists that they must be, above all, physicians with a good knowledge of internal medicine. One should never overlook the fact that physicians/gynaecologists are supposed only to give advice based on the best available evidence. Women are the decision-makers. Physicians advise and observe. Physicians/gynaecologists must also maintain a critical view of the claims of the pharmaceutical industry.

What clinicians must know is not the relative risk of an intervention out of context from the absolute risk. More meaningful is the NNT and the NNH. This is the information that is clearly important for a clinical decision-making, and to assess benefit/risk and cost/benefit. One must be expert in the practice of good medicine (Neves-e-Castro, 2002b,c), without forgetting that next to evidence-based medicine there is also a medicine-based evidence.

‘Without clinical expertise, practice risks becoming tyrannized by evidence ... without current best evidence, practice risks becoming rapidly out of date, to the detriment of patients’. ‘External clinical evidence can inform, but can never replace, individual clinical expertise, and it is this expertise that decides whether the external evidence applies to the individual patient

at all and, if so, how it should be integrated into a clinical decision’ (Sackett *et al.*, 1996; Writing Group for the 3rd European Conference on Sex Steroids and Cardiovascular Diseases, 2003).

Therefore, what at first sight might be considered to be a crisis is no more than a process of progress in our knowledge, an adaptation to the best strategies, non-drug and drug-related, with or without hormones.

The conclusions of these studies suggest that the profile for a woman (NNH: 600–1000 women) to ‘safely’ initiate HRT is between 50 and 59 years of age, with vasomotor symptoms, <10 years after the menopause, being treated with statins, with a good lipid profile and a body mass index >30 (to be protected from breast cancer). This is precisely the profile of the great majority of women who come for consultation after their menopause. Therefore it seems that what most gynaecologists are doing to their predominant population of patients is not unsafe and contributes not only to a good quality of life but also to prevention.

‘It ain’t so much what we don’t know that gets us into trouble as what we do know that ain’t so’ (Rogers, 1996).

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