Turbulent Times for Hormone Replacement Therapy: Is There a Way Out?

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Key Words

Menopause · Hormone replacement therapy ·
Estrogen insufficiency · Androgen insufficiency ·
Ovarian hormone insufficiency syndrome

Abstract

The long-awaited results of the large Women's Health Initiative (WHI) trial on the effects of combined estrogen-progestin hormone replacement therapy (HRT) in postmenopausal women show that the overall benefits are smaller than the risks. Herein I argue that many of the findings could be predicted from earlier observational studies. Although the WHI trial will rightly reverse the soaring HRT use of the last decades, there is unquestionably a future for HRT. A consensus is growing that postmenopausal women may be treated with HRT only when seeking help for disturbing symptoms of the ovarian hormone insufficiency syndrome, rather than be treated for menopause per se. The ovarian hormone insufficiency syndrome comprises conditions of estrogen and/or androgen insufficiency; at this time, the diagnosis of these clinical entities is based largely on symptomatology. Future research should disclose why the deprivation of ovarian hormones has a variable impact on women's functioning, and further trials ought to reveal effective and safe treatments for women suffering from this syndrome.

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History of a Downfall

It is incorrect that the first results of the large Women's Health Initiative (WHI) randomized trial, published in July 2002, came with such brusqueness as to be regarded as the 'September 11th of hormone replacement therapy' (HRT) [1]. In fact, many of the major findings were not unexpected in view of data that had been accumulating over the last 5 years.

Ten years ago, the prevailing view was that the risk-benefit balance of HRT was tilted in favor of the benefits (fig. 1, left). HRT provided not only relief against vasomotor symptoms, but at that time was also one of the few options to prevent or treat postmenopausal osteoporosis. The widely known results of the Nurses' Health Study opened further perspectives: the risk of coronary heart disease in HRT users was found to be reduced by 35–40%, which was translated into a comparable reduction in the risk of death; interestingly, the mortality risk reduction was most pronounced in HRT users with coronary risk factors [2]. In addition, the majority of the studies showed that HRT improves cognition and may also reduce the risk of dementia [3].

Much less interest was given to the side effects and risks of HRT, until recently. Bleeding was and is unanimously regarded as a bothersome 'side effect', and innovative ways of administering HRT were attempted, in-

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0378-7346/03/0561-0043\$19.50/0

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Fig. 1. The benefit-risk balance of hormone replacement therapy (HRT) in 1993 (left) and 2003 (right).

cluding HRT with a continuous combination of estrogens and progestins, interrupted HRT regimens, and low-dose HRT. Although more than 80% of women have no bleeding in the 13th cycle of combined HRT with low doses of estrogens and progestins [4], the disappointing key message to women still is that the guaranteed bleed-free HRT regimen does not exist. In the early days of HRT, breast discomfort was often dismissed as minor and temporary, but the randomized PEPI trial has shown that, compared with the placebo group, breast discomfort is about twice as common with standard HRT regimens that contain progestins on a sequential or continuous basis [5]. In addition, mammographic breast density increases in women taking estrogen-progestin therapy, but not in women taking estrogen alone [6].

As for the vascular risks of HRT, it was assumed 10 years ago that there was an accrued risk of venous thromboembolism, but that the risk would probably be lower than that associated with the use of oral contraceptives, given that HRT contains lower doses of 'natural' estrogens. However, observational studies have demonstrated since that HRT entails a 2- to 3-fold increased risk of venous thromboembolism [7], not much lower than the 3- to 4-fold increased risk with oral contraceptives [8]. The risks of coronary and cerebrovascular disease were examined in recent randomized trials in women with established coronary heart disease. The results of these trials (HERS, ERA) are well known, and show that there is no benefit of HRT on cardiovascular events and mortality, and that the risk of a coronary event is increased during the first year of treatment. The significant trend for a low-

er risk of coronary events with longer treatment duration, documented in the HERS trial [9], was not confirmed in the follow-up analysis (HERS II) [10]. The HERS trial also confirmed an overall 2-fold increased risk of venous thromboembolism, which was highest in the first year of treatment [11]. Although some critics blamed the continuous addition of a progestin for the negative results, in the smaller ERA trial neither estrogen alone nor estrogen and progestin affected the progression of coronary atherosclerosis assessed by angiograms [12], and in the ESPRIT trial, estrogen alone did not prevent further coronary events in women who had survived a first myocardial infarction [13]. However, since these trials were carried out in women who were, on average, 10–15 years past the menopause, many practitioners felt that these trials on secondary cardiovascular prevention were not necessarily representative of the main group of women receiving HRT in clinical practice, i.e., women in the perimenopause and early postmenopause.

Regarding the cancer risks, the general view on endometrial cancer 10 years ago was that standard estrogen-only therapy increases the risk dose- and duration-dependently [14], but that the excess risk is reversed by the addition of a progestin either on a continuous basis or on a sequential monthly basis, provided that the progestin is added for a sufficient number of days. Observational studies have upheld that view for continuously combined HRT, but in one well-publicized study, the risk of endometrial cancer was still significantly increased in women using sequential HRT with the progestin added for 10 days or more per month, if the hormonal treatment was

continued for 5 years or more [15]. And in another study, low-potency estrogens (estriol 1–2 mg), widely prescribed in Europe for the alleviation of mild menopausal symptoms and urogenital atrophy, were found to result in a 2-fold increased risk of endometrial cancer, even within the first 5 years of treatment [16].

But the biggest blow to HRT was the re-analysis of a large number of breast cancer studies, coordinated from Oxford [17]. Although some of the larger observational studies which reported an increased risk of breast cancer [18] had found their way into the media, before 1997, the effect of HRT on breast cancer was very much in doubt. From the contradictory data, practitioners could pick out their ‘favorite’ view, and patients were often given muddled or partisan information. According to the Oxford re-analysis, the risk of breast cancer increases by 2.3%/year of treatment, much the same as the risk conferred by the delay of natural menopause; 5 years or more of HRT increases the overall risk by 35%. Another interesting finding is that the excess risk was observed only in women who are not overweight or obese, a finding that was confirmed in later observational studies; alcohol intake may also interact with the risk of breast cancer during HRT. Regarding the type of treatment, the Oxford reanalysis was unable to produce any conclusions, but subsequent observational studies are in line with the breast discomfort and mammographic density data of the PEPI randomized trial, mentioned earlier, showing that the risk of breast cancer is higher in women using both estrogens and progestins: in one of these studies, the excess risk was calculated to be 1%/year for estrogen-alone therapy and 8%/year for estrogen-progestin therapy [19]. It comes as a relief that death from breast cancer does not appear to be increased among HRT users, with some studies even showing a beneficial effect of HRT [20]. The improved survival after a breast cancer diagnosis in HRT users has been attributed to various factors: more favorable histologic types and smaller cancers less likely to have spread beyond the breast; possibly a better surveillance of HRT users (who, on average, have a higher socio-economic status), and the temporary regression of the tumor resulting from stopping the hormonal treatment.

The WHI Trial: Setting the New Standard for HRT

In the randomized WHI trial, more than 16,000 women aged 50–79 years with an intact uterus were assigned to placebo or HRT, consisting of continuously combined

estrogens (conjugated equine estrogens, 0.625 mg/day) and progestins (medroxyprogesterone acetate (MPA) 2.5 mg/day); in addition, more than 10,000 hysterectomized women were assigned to placebo or conjugated estrogens alone. As is well known by now, the first arm of the trial was stopped after an average follow-up of 5–6 years instead of the projected 8.5 years, whereas the second arm is still continuing and due to end in 2005. The principal clinical outcome data of the estrogen-progestin arm were published concurrently with the medical and lay press release concerning the trial stop [21], and several more detailed analyses have now been published or will be published in the near future.

The clinical outcome study shows that the risk-benefit ratio of HRT is, in fact, tilted toward the risks (fig. 1, right). In terms of benefits, the WHI trial is the first randomized trial that unequivocally shows that HRT reduces the risk of both vertebral fractures and hip fractures by 35%, which is comparable with the effect of raloxifene, a selective estrogen receptor modulator, on vertebral fractures, and with the effect of bisphosphonates such as alendronate and risedronate on vertebral and nonvertebral fractures [22]. In addition, the WHI trial corroborates other data, accumulated from recent observational studies, that the risk of colorectal cancer is 37% lower in HRT users. But HRT is unlikely to be used as a method to prevent colorectal cancer, for which other strategies (dietary and other) are being pursued.

The risks, on the other hand, include an increased risk of breast cancer and cardiovascular events. The breast cancer data show that the risk is increased by 26% after an average of 5.2 years, or an excess risk of 5%/year; this figure is consistent with earlier data from observational studies using combined HRT. However, there can be no doubt now that this excess risk is the result of the HRT itself, and not the consequence of earlier diagnosis in HRT users due to surveillance bias. Regarding the cardiovascular event data, the risk of venous thromboembolism is predictably 2- to 3-fold increased, but also the risk of cerebrovascular events (stroke) is significantly increased by 41%, and the risk of coronary events by 29%. A subsequent analysis showed that it is ischemic but not hemorrhagic strokes that occur more frequently among estrogen-progestin users [23]. The stroke data are at odds with early observational studies and other randomized trials that found a beneficial or no effect [24]; recently, the Nurses’ Health Study also reported a 45% increased risk of ischemic strokes in estrogen-progestin users [25]. But the coronary event data of the WHI trial are in sharp contrast with the Nurses’ Health Study data as well as data from

other observational studies, and because there was no coronary benefit in the WHI trial, there was predictably no benefit on the overall risk of death. The reasons for the discrepancy regarding coronary events and mortality are unclear, but many interesting points have been raised by the Nurses' Health Study investigators [26]. They submit that both methodological and biological differences may be relevant. Methodologically, they point to a number of biases inherent to the study of women who choose to take HRT in the real world (healthy user bias, compliance bias) and, importantly, to the incomplete capture of early complications in observational studies. Biological differences include the potential impact of progestin previously alluded to, and the fact that the women in the WHI trial were, on average, older (means of 63 years) and more overweight than in the Nurses' Health Study. The age effect is an important issue because it asks this question: is there a difference between the effects of HRT on primary and secondary atherosclerosis prevention? Some data obtained in primates are consistent with such a divergent effect, and whereas estrogens do not affect the progression of coronary atherosclerosis in women with established heart disease [12], the EPAT randomized trial demonstrated slower progression of carotid artery atherosclerosis in healthy but hyperlipidemic women taking low-dose estrogens [27].

Many practitioners suspect that the results of the WHI trial might have been different if a different type of HRT had been used (e.g. transdermal or percutaneous instead of oral estrogens, micronized progesterone instead of MPA, lower doses of estrogens and progestins). Certainly, cardiovascular markers are different during transdermal estrogen treatment: for example, C-reactive protein levels are elevated during oral but not transdermal estrogen treatment [28]. And in the PEPI trial, progesterone did not antagonize the beneficial effect of estrogens on HDL-cholesterol levels, in contrast to MPA [29]. However, until clinical outcome data for HRT preparations other than those studied in the WHI trial become available (not in the foreseeable future [24]), clinicians should respect the new standards set by the WHI data.

How to Envisage the Future of HRT?

As a result of the trial, many societies and task forces have revised their recommendations. In the USA, the US Preventive Task Force recommends against the use of estrogens and progestins for the prevention of chronic conditions in postmenopausal women, and withholds a

recommendation on estrogen-alone therapy until this arm of the WHI trial has been completed [30]. The North American Menopause Society provides practitioners with amended recommendations [31].

There can be no doubt left that combined HRT must not be used in the primary or secondary prevention of cardiovascular disease in postmenopausal women. In addition, if any clinical cardiovascular event occurs, the treatment should be stopped at once, and be reinstated only after careful re-assessment of benefits and risks, and with the informed consent of the patient. In patients undergoing surgery, HRT should be stopped temporarily.

Although the WHI trial has demonstrated a beneficial effect of HRT on fractures, anti-osteoporosis treatment should ideally be long-term, since stopping antiresorptive drugs such as HRT results in rapid bone loss [32], in fact there is some evidence that bone loss after discontinuing HRT may be more pronounced than that after stopping alendronate [33]. And data from observational studies indicate that the beneficial effect on the incidence of non-vertebral fractures wanes rapidly after stopping HRT, even after long-term treatment [34]. The breast cancer data, however, argue against long-term HRT. Hence, other strategies must be employed to prevent and treat postmenopausal osteoporosis, including screening selective groups of postmenopausal women for osteoporosis by bone densitometry. Various advisory panels and organizations, including the US Preventive Services Task Force [35], recommend screening in all women 65 years of age and older, and in younger women at increased risk for osteoporotic fractures. Although there is no consensus as yet on the definition and threshold of these risk factors, this is a fast-moving research area and answers will be forthcoming in the next few years; low body weight will undoubtedly be recognized as one of the most important clinical risk factors. When osteoporosis is diagnosed on bone densitometry [bone mineral density (BMD) T-score ≤ -2.5 SD], antiresorptive drug treatment is recommended because the risk of fractures is increased fourfold compared to women with normal BMD [36]. The non-HRT antiresorptive drugs approved for osteoporosis treatment include raloxifene (60 mg/day) and bisphosphonates such as alendronate (10 mg/day or 70 mg/week) or risedronate (5 mg/day or 35 mg/week). In the near future drugs that stimulate bone formation, such as teriparatide (recombinant human parathyroid hormone₁₋₃₄), will become available for clinical use in a selected group of osteoporotic patients.

But there is a future for HRT! Practitioners know that many women are seeking help for genuine and bother-

Table 1. Symptoms and diagnosis of the estrogen and androgen insufficiency syndromes in women

	Estrogen insufficiency syndrome	Androgen insufficiency syndrome ¹
Symptoms	Vasomotor symptoms (hot flashes/flushes and night sweats) Sleep difficulties Mood swings and low mood Memory and concentration difficulties Disturbed sexual arousal (impaired lubrication)	Decreased well-being and low mood Persistent, unexplained fatigue Disturbed sexual arousal (low sexual drive and receptivity)
Diagnosis	On basis of symptoms	On basis of symptoms, but only in adequately estrogenized women Free testosterone level at or below the lowest quartile of the range in women 20–40 years of age

¹ Adapted from Bachmann et al. [38].

some symptoms in the peri- and postmenopause, and that HRT relieves these symptoms. These symptoms can be caused by estrogen deprivation or/and androgen deprivation. Estrogen insufficiency syndrome can be diagnosed in late perimenopause, when estrogen levels are erratic and hypo-estrogenic periods may alternate with hyper-estrogenic periods [37], and during the early postmenopausal years. Clinicians know that these symptoms occur more frequently after abrupt estrogen withdrawal (e.g. after bilateral oophorectomy or radiotherapy). The ‘female androgen insufficiency syndrome’ was recently defined through a consensus statement [38]: the symptoms are summarized in table 1. The androgen insufficiency syndrome may occur in women with pituitary or adrenal pathology, but most frequently it is the result of (functional) ovarian ablation (surgical, radio- or chemotherapy). In the latter group of women, the estrogen and androgen insufficiency syndrome may coexist, which is defined herein as the ‘ovarian hormone insufficiency syndrome’ (fig. 2). Through its effect on sex hormone binding globulin levels, estrogen therapy may lower free testosterone levels, potentially giving rise to the androgen insufficiency syndrome.

The symptoms of the estrogen insufficiency syndrome are also shown in table 1. The potentially disruptive effect of vasomotor symptoms on women’s lives is well recognized. Sleep difficulties are also more common in peri- and postmenopausal women, allowing for age, and are believed to be related to the occurrence of vasomotor disturbances [39]. Estrogen therapy reduces the number of movement arousals during sleep and improves subjective sleep quality, again especially in women with vasomotor symptoms [40]. Perimenopausal women with vasomotor

Fig. 2. Ovarian failure can result in symptoms of the estrogen insufficiency syndrome, the androgen insufficiency syndrome, or both (the ovarian hormone insufficiency syndrome).

symptoms are also 4 times more likely to report symptoms of depression in a primary care setting [41]; in addition, there is preliminary evidence that abrupt hypo-estrogenism in premenopausal women, resulting from GnRH agonist treatment, may induce depressive mood symptoms [42]. Interestingly, a small randomized trial documented improvement in mood with estrogen treatment in women presenting with depressive symptoms associated with the perimenopause [43]. The WHI Memory Study failed to show any benefit of combined estrogen-progestin use on global cognitive function or the incidence of mild cognitive impairment, and even showed a harmful effect on the incidence of dementia [44, 45]. However, abrupt hypo-estrogenism in premenopausal women appears to exert a negative effect on cognitive function, particularly

on short-term memory, which is reversed by estrogen treatment [46]. Also, functional magnetic resonance imaging studies show that estrogen therapy alters brain activation patterns during memory tasks in postmenopausal women [46, 47].

It is unknown why some postmenopausal women develop symptoms which are disruptive for their quality of life, whereas many others have no symptoms at all. Possible explanations could be: individual differences in endogenous estrogen levels (routine estradiol assays are not helpful, since most postmenopausal women have undetectable values), or/and differences in the genomic or non-genomic action of estrogens in the central nervous system. Some data point to an interaction between estrogen receptor- α polymorphisms and cognitive function in postmenopausal women [48], but more research on this topic is urgently needed.

How to square the above data on menopausal symptoms with the findings from the WHI trial that HRT does not affect quality-of-life measures [49]? In effect, the trump card of HRT 'believers' in any discussion on HRT 10 years ago was that it would improve the psychological, sexual and social functioning of postmenopausal women. The WHI data prove this assumption to be wrong, and lead to the firm conclusion that HRT should not be imposed on asymptomatic postmenopausal women because of putative quality-of-life benefits. In counterpart, the data are not inconsistent with the view that bothersome symptoms of the estrogen insufficiency syndrome are effectively relieved by HRT. At randomization, most women in the WHI trial had a low menopausal symptom score (an average of 2.3 on a 0–15 score), and most were satisfied with their sexual functioning. In the subgroup of women aged 50–54 years with moderate-to-severe vasomotor symptoms, these symptoms were improved as well as sleep disturbances, buttressing previous data. Also, the trial excluded perimenopausal women, in whom menopausal symptoms appear to be the most distressing.

Hence, hormonal treatment should be focused to women who are seeking help for disturbing symptoms of the ovarian hormone insufficiency syndrome. But what is appropriate hormonal treatment since the WHI trial? I believe that these women should receive the lowest dose of hormones to suppress bothersome symptoms to an acceptable level. For estrogens, lower than standard doses (e.g. 0.3 mg conjugated equine estrogens, or 1 mg micronized estradiol) have been reported to be effective against vasomotor symptoms in the large majority of women [50]. Women should be told to return in 12 weeks; if the prescribed dose is then deemed to be insufficiently effica-

cious by the patient, the dose can be augmented after reassessment of the benefits and risks. The patient is told that the treatment would preferably be stopped within a maximum of 5 years. Women without a uterus should receive estrogens alone [31], and women with an intact uterus the lowest effective dose of estrogens and progestins. If a diagnosis is made of the androgen insufficiency syndrome (table 1), there is some evidence that androgens may be helpful, but such treatment remains controversial and is not approved for this indication. In one well-publicized study, transdermal testosterone (300 μ g/day) improved sexual function in oophorectomized women with impaired sexual function, but at the expense of supra-physiological testosterone levels and facial hirsutism [51]. Intramuscular testosterone injections are even more likely to produce unwanted side effects, let alone their negative effect on lipid metabolism. In Europe, many practitioners would consider prescribing tibolone in women presenting with symptoms of the ovarian hormone insufficiency syndrome. Tibolone is an analogue of the progestin norethynodrel; it is metabolized into 3 α - and 3 β -hydroxy-tibolone which binds to the estrogen receptor, and into a Δ_4 isomer which binds to the progesterone and androgen receptors [52]. As a result, tibolone acts in a tissue-specific manner, much as the selective estrogen receptor modulators do. But, in contrast to the latter, tibolone provides relief against vasomotor symptoms, prevents urogenital atrophy, and improves sexual function [53]. In symptomatic women, a dose of 2.5 mg is recommended to prevent early drop-outs due to insufficient effect [54]. In addition, tibolone does not cause breast tenderness [53], or increase breast density on mammography, and in vitro data as well as in vivo data in animals provide no evidence for a breast-stimulating effect. Although tibolone results in more bleeding episodes than does a placebo, clearly the bleeding rate is lower with tibolone than with estrogen-progestin treatment [53]. Finally, tibolone causes an increase in bone density at the spine and the hip of about 2% after 2 years [52]. Although tibolone certainly is one of the most promising molecules to date, we need definitive data on long-term clinical outcome measures such as fractures, cardiovascular disease, and endometrial and breast cancer. Until such time, tibolone can be recommended only for the short-term alleviation of symptoms that can be ascribed to the ovarian hormone insufficiency syndrome.

Although the challenges have clearly changed, the future of HRT is as exciting as before the WHI trial. To move forward, both drug companies and the research community need to be as innovative as ever, and clini-

cians need to carefully weigh the information obtained from randomized trials against the genuine problems encountered in daily practice. Peri- and postmenopausal women deserve no less.

Financial Disclosure

The author received honoraria for consultancy and lectures on menopause-related issues from Eli Lilly, Novo Nordisk, Organon and Solvay.

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