# Hormone Replacement Therapy 2004 – The Dilemma

Edith Flatau MD

Department of Internal Medicine B, Central Emek Hospital, Afula, Israel

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The average woman in the western world lives nearly 30 years after menopause, but these 'golden' years are often complicated by vasomotor symptoms, vaginal atrophy, decreased libido, as well as chronic diseases including cardiovascular disease, cancer, depression, osteoporosis, and cognitive decline. Estrogen therapy has been available to treat menopausal symptoms for more than 60 years, during which time many observational studies suggested additional beneficial effects of estrogen alone or combined with progestin in the prevention of cardiovascular disease, colon cancer, osteoporosis, depression and cognitive decline. Towards the end of the last millennium, approximately 38% of postmenopausal women in the United States were using hormonal replacement therapy; the main reason that prevented many women from using this 'panacea' was the fear of increased risk of breast cancer attributed to HRT. A meta-analysis of 51 studies published in 2001 suggested that only prolonged treatments (more than 5 years duration) were accompanied by increased risk for breast cancer [1], thus many physicians suggested the use of HRT for not more than 5 years after menopause. Recently, however, several randomized studies were published that shattered the belief that HRT was effective in primary or secondary prevention of cardiovascular disease [2,3]. Moreover, in the Heart and Estrogen/Progestin Replacement Study (HERS) there was a 50% increase in the risk of coronary events during the first year of the study [2]. The Women's Health Initiative (WHI) study was halted before completion due to increased risk of breast cancer as well as increased occurrence of cardiovascular events during the 5.2 years median duration of the study [3]. My colleagues will discuss the pros and cons of the use of HRT.

HRT = hormone replacement therapy

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**Correspondence:** Dr. E. Flatau, Head, Dept. of Internal Medicine B, Central Emek Hospital, Afula 18101, Israel.
email: flatau_ed@clalit.org.il

# HRT 2004: Where Do We Stand Now?

Amos Pines MD

Department of Medicine T, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

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Hormone replacement therapy, recently referred to as hormone therapy, has been used in postmenopausal women since the middle of the 20th century. HRT is indicated for vasomotor and other menopause-related symptoms, as well as for prevention/treatment of osteoporosis. Numerous studies support the above indications, obviating the need to further explore these beneficial effects. However, there has been a change leading to a negative attitude by both professionals and the lay public toward HRT during the past 5 years, following the publication of results of several randomized studies on cardioprotection by hormones (HERS trial, WHI study, etc). Before getting into details, it should be stressed that those studies were based on an assumption that gained popularity mainly

in the United States – that HRT might be prescribed in older women *solely* for primary or secondary prevention of cardiovascular diseases. The rationale for this hypothesis came from results of multiple large-scale observational studies (such as the Nurses' Health Study) showing that postmenopausal women using HRT had a better health status than those who were not taking hormones. There were also solid evidence-based data that demonstrated many positive metabolic effects of HRT, mainly related to cholesterol profile and endothelial function. While observational trials can examine any population (premenopausal, perimenopausal, early menopausal, postmenopausal), the randomized studies on cardiovascular endpoints had to select a higher risk population (women with coronary artery disease or with risk factors for CAD, or older women) in order to gain statistical power. By the same token, study protocol excluded women with moderate to severe vasomotor symptoms (to avoid a high dropout rate in the placebo group, and to keep the blinding). As a result, those randomized studies actually investigated the benefits and risks of HRT in women with an average age of 65–75, most of whom had never used hormones prior to their recruitment. The final conclusion of those randomized-controlled trials was that the standard dose of HRT did not confer any cardiovascular protection in the above-specified population. There seemed to be a slightly increased risk for cardiac and cerebral events among the older participants, and an increased risk for venous thromboembolism. On the other hand, there was a reduced risk for osteoporotic fractures, including hip fractures. The issue of breast cancer risk was more intriguing, since some studies did not demonstrate any effect: the estrogen-progestin arm of the WHI showed a borderline increase in risk, while the estrogen-only arm showed a borderline decrease in risk.

So where do we stand now? What are the lessons from those studies?

- It is accepted that HRT should not be prescribed in older women solely for prevention of cardiovascular disease. Is timing of initiation of HRT or age at the beginning of HRT important? It might be, but we still do not have good quality data on that. Many believe in the "window of opportunity" concept, which assumes that the protective effects of HRT are obtained only when treatment starts no later than the early years of menopause when arteries are still relatively free of atherosclerosis and the normal endothelial function is still relatively maintained. This concept is supported by elaborate studies in monkeys and other animals.
- We should not generalize the results of the randomized studies to all the clinical set-ups and all drug preparations, dosages and estrogen-progestin combinations. There is no class effect of HRT with regard to various metabolic parameters. Although there are insufficient data for many specific hormone products, this does not necessarily imply that all products are the same. We know that transdermal and oral estrogen might have completely different metabolic activities, and that the effect of low dose therapy may not be compatible with that of a standard dose or a high dose HRT.
- We should consider the absolute rather than the relative risks of HRT. Data from the randomized trials show that all major risks combined amount to an additional two to three events per year per 1,000 hormone users. When the positive effects (mainly on fracture risk and colon cancer risk) are deducted, the surplus of risk is very minimal or non-existent, and should not prevent prescribing the drugs when needed. There are no effective substitutes for HRT with regard to treatment of vasomotor and menopause-related symptoms.
- What would be the duration of treatment? My view is that there should not be a predetermined time limit. As long as a woman wishes to continue with hormones, based on treatment goals and her personal experience, this should be allowed. As mentioned earlier, long-term HRT may carry a very small risk, which grows with age and with years of use, and it is the duty of the prescribing physician to provide all relevant information to the woman prior to any decision. Also, as a rule of thumb in medicine, the minimal effective dose of hormones should be sought individually. Avoiding or reducing possible adverse effects should always be a major consideration.
- It is essential to clarify once again that the WHI study was designed to test the hypothesis that initiating HRT in elderly women may decrease the risk for cardiovascular events. The study was not aimed, and was not powered to examine symptomatic women at the menopause transition or at early menopause. The results of the WHI study therefore do not apply to the majority of women who seek consultation at the menopause clinics.

## Suggested reading


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**Correspondence:** Dr. A. Pines, Dept. of Medicine T, Tel Aviv Sourasky Medical Center, 6 Weizmann Street, Tel Aviv 64239, Israel.
Fax: (972-3) 696-2715
email: apines@netvision.net.il


CAD = coronary artery disease

# HRT: The Argument Against

Shlomo Berliner MD PhD

Department of Medicine D, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

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During the last two decades observational studies have suggested that hormone replacement therapy helps to prevent cardiovascular diseases, improves general health, prevents osteoporosis and suppresses the unpleasant symptomatology of the menopause. However, two randomized controlled trials – the Heart and Estrogen/progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) – refuted these notions. In fact, it was found that not only does HRT not prevent cardiovascular conditions but it might actually be involved in the occurrence of myocardial infarction, stroke, and episodes of venous thromboembolism. In addition, it became clear that this therapy might be associated with invasive breast cancers as well as gallbladder diseases. Clearly, therefore, HRT can no longer be prescribed for the prevention of cardiovascular diseases, which are now the leading cause of morbidity and mortality in the western world.

The HERS was a secondary prevention study in women with an established coronary heat disease [1]. This study was terminated earlier than scheduled due to the above-mentioned side effects, indicating that HRT should not be prescribed for the secondary prevention of heart diseases. Moreover, due to the excessive number of events during the first year after administration of these medications, it can be said that they are even contraindicated following acute ischemic coronary events. In this context, it should be mentioned that studies on the progression of atherosclerosis did not show any substantial evidence that these drugs prevent the progression of the disease, a prevention that was suggested in the past.

The second randomized large study that has changed our attitude towards HRT was the WHI [2]. This primary prevention study recruited 16,608 healthy women, the primary outcomes being coronary disease and invasive breast cancer. The results showed a high incidence of stroke and pulmonary embolism. It should be noted, however, that women on combined hormone therapy experienced less colorectal cancer and hip fracture. This trial, as well as the HERS, led to the current recommendations, which do not suggest that HRT use will prevent any disease, not only cardiovascular.

The findings of the HERS and WHI trials raise the obvious question: what indeed is the benefit of HRT? It appears that its sole advantage is the relief of bothersome vasomotor flushing. The prevention of osteoporosis can be effectively achieved with less harmful medications, and colon cancer is preventable by endoscopic or virtual colonoscopies. Prevention, both primary and secondary, of cardiovascular disease is no longer evidence-based medicine and the improvement of quality of life is restricted to women who have significant flushing [3]. Since local applications of estrogen can be used in cases of dry vagina, the use of HRT has decreased dramatically throughout the western world. Decreasing numbers of women prefer to risk invasive breast cancer, acute ischemic event or thromboembolism in order to attenuate the vasomotor symptoms. This therapy is therefore restricted to a limited number of women, following a thorough discussion regarding the potential hazards of these medications.

There is hope on the horizon though, and that is the transdermal approach. This too has to await large prospective and randomized trials before any conclusion can be reached. However, due to the low dose of the medication, it is conceivable that it might be less harmful. Only future trials will provide scientific information if this is indeed the case.

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**Correspondence:** Dr. S. Berliner, Director, Dept. of Medicine D, Tel Aviv Sourasky Medical Center, 6 Weizmann Street, Tel Aviv 64239, Israel.
Phone: (972-3) 697-3313
Fax: (972-3) 974-61
email: z@tasmc.health.gov.il

## Summary

The pendulum concerning HRT, which had swung higher and higher towards the end of the last millennium, dropped steeply following the recent publication of the HERS and WHI studies. However, as long as 50–80% of relatively young postmenopausal women continue to suffer from vasomotor symptoms, and in the absence of good alternative treatment, HRT will continue to be used by many millions of women. (We must bear in mind that the worldwide number of postmenopausal women currently approaches 1 billion). HRT is currently not recommended for chronic disease prevention in postmenopausal women. Recently, a few selected groups of women were identified who might react to HRT differently from the general population. These include women with increased cardiovascular risk due to elevated serum lipoprotein (a) levels [1,4] who may benefit from HRT, women with mutations in the prothrombin gene who are at increased risk of developing cardiovascular complication early in the course of HRT [5], and certain interleukin-6 gene variants (*IL-6-174C*) that cause increased mineral bone density in response to HRT [6]. A possible futuristic setup might enable us to perform personal genetic profiles that will help us decide the advantages vs. disadvantages of HRT in individual women. Until then, I believe we should adopt the current U.S. Food and Drug Administration recommendation for postmenopausal women to use HRT only for menopausal symptoms at the smallest effective dose for the shortest possible time [7].

**E. Flarau MD**