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Postmenopausal Hormone Therapy

Lessons from Observational and Randomized Studies

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The effect of estrogen replacement therapy (ERT) and hormone replacement therapy (HRT) for cardioprotection in postmenopausal women remains controversial. Observational studies conducted in the past two decades have suggested an average risk reduction of 50% for the primary prevention of CAD, these findings, however, have not been confirmed by recent randomized clinical trials (RCTs). The discrepancies in results between observational and randomized studies are related to several differences in patient selection, hormone regimen, and biological effect of hormones in different periods of women's life. In an attempt to justify the use of hormone replacement therapy against the mounting contraindications for any use by several opinion leaders and scientific societies, several authors have criticized the design and the results of the randomized clinical trials as the cause of the unexpected results. The randomized clinical studies were conducted exceptionally well; therefore, methodologic issues are not the problem. The main difference between the observational and randomized studies, which may fully explain the discrepancies between these studies, are the women under study and their reasons for taking hormone therapy. In the observational studies women choose to take ovarian hormones initially for menopausal symptoms and then may have decided to continue for other reasons, while in the randomized studies the absence of menopausal symptoms was a pre-requisite for inclusion in the study. This apparently small difference has important implications because symptomatic women are younger and have clinical symptoms that suggest the lack of estrogen effect on several organs or systems. In conclusion, several biological reasons may have contributed to the divergent findings from observational studies and RCTs. Clearly time elapsed since menopause seems to be an important one for its effect on vascular responsiveness to ovarian hormones and to prothrombotic effects. In the meantime, a role remains for combined estrogen and progestin supplementation in the treatment of menopausal symptoms.

Key Words: Hormone replacement therapy; postmenopausal; epidemiology; postmenopausal trials; clinical cardiovascular disease; clinical pharmacology.

Introduction

Estrogen replacement therapy (ERT) and hormone (estrogen/progestin) replacement therapy (HRT) have long been prescribed for the relief of menopausal symptoms, and especially in the United States their use had been extended to several years after the menopause for the prevention of osteoporosis and in the recent decades also with the understanding that both replacement regimens might reduce the occurrence of cardiovascular disease (CVD) *(1)*. This latter belief was based on the findings of observational studies, almost all suggesting a significant reduction in cardiovascular events with ERT and HRT, and on a large body of evidence suggesting a protective activity of estrogen on the vascular system (including an increase in nitric oxide synthase with subsequent vasodilation, decrease of atherosclerotic plaque formation, favorable effect on lipid pattern, fibrinolytic activity, and endothelial function) *(1–13)*. The belief in the cardioprotective effect of ERT/HRT has recently been challenged after the somewhat surprisingly results of two randomized studies that have shown no beneficial effects of postmenopausal hormone therapy on the prevention of cardiovascular disease and have, on the other hand, suggested that ERT/HRT may *increase*, rather than decrease, CVD risk *(14–15)*.

Observational epidemiologic studies have suggested that ovarian hormone use reduced the incidence of CHD, fractures, and colorectal cancer but may increase breast cancer, stroke, and venous thromboembolism and that estrogen only use may increase the incidence of endometrial cancer in women with a uterus *(16–18)*. The results of the randomized studies found largely concordant results with the observational studies except for the divergent findings about CHD. Therefore, it is important to find the reason(s) for the widely divergent findings on the cardiovascular effects of observational studies and RCTs.

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The divergent results of observational and randomized studies on cardiovascular end points have led many authors to stress the superiority of randomized clinical trials over observational studies but have not solved the dilemma of the cardiovascular effect of hormone therapy. The discrepancies in results between observational and randomized studies are related partially to the interpretation of data by the authors of the randomized studies but mainly to several differences in patient selection, hormone regimen, and biological effect of hormones in different periods of a woman's life between the two different type of studies. There are many reasons to still consider cardiovascular benefits from hormone therapy for postmenopausal women providing that this therapy is given to the right women at the right dose and at in the right period of their life.

Although several authors have claimed methodologic issues to explain the divergent effect of hormone therapy between observational and randomized studies, they are unlikely to explain fully the divergent results of observational studies and clinical trials with regard to coronary disease. The randomized clinical studies were conducted exceptionally well; therefore, methodologic issues are not the problem. The main difference between the observational and randomized studies are the women under study, because in the observational studies women choose to take ovarian hormones for menopausal symptoms and then they decided to continue, while in the randomized studies the absence of menopausal symptoms was a prerequisite for inclusion in the study. This apparently small difference has important implications because symptomatic women are younger and have clinical symptoms that suggest the lack of estrogen effect on several organs or systems. The absence of symptoms indicates a physiological adaptation to ovarian hormone deprivation, because of the slow decline in estrogen levels or because of the long time lapsed from menopause, and therefore a new homeostasis. Thus, it is also important to consider biologic explanations for the divergent results of observational and RCTs.

Aging and Cardiovascular Response to Estrogens

Several studies evaluating the effect of hormone therapy on intermediate markers of coronary heart disease in women and in nonhuman primates indicated substantial benefits (e.g., improved lipid profile and enhanced endothelium-dependent vasodilation), although they also suggested some adverse effects (e.g., higher levels of C-Reactive Protein, inflammatory markers and coagulation factors) *(11,12,19–21)*. Clinical and experimental evidence suggest that many of the cardioprotective and anti-atherogenic effects of ovarian hormones are receptor-mediated and endothelium-dependent *(8)*. Both estrogen receptors and endothelial function are markedly influenced by time of estrogen deprivation and progression of the atherosclerotic injury.

Recent evidence suggests estrogen receptor expression in the arterial wall is sharply diminished with increasing age as suggested by the significant age-related rises in methylation of the promoter region of the estrogen receptors and by the methylation of the estrogen receptors in vascular areas with atherosclerosis *(22)*. After a prolonged period following menopause, estrogens are associated with a reduced protective effect on atherosclerosis, while their unfavourable effects on coagulation remain unaltered. Therefore, in early postmenopausal women, like the ones included in the observational studies, ovarian hormone replacement may be cardioprotective because of the responsiveness of the endothelium to estrogens, while in late postmenopausal women ovarian hormones have either a null effect or even a detrimental effect because of the predominance of the procoagulant or plaque-destabilizing effects over the vasculoprotective effects. It is therefore likely that hormone therapy may be beneficial in younger women but may not inhibit progression of atherosclerosis and progression of complicated plaques leading to coronary events in older women. This hypothesis had already been suggested by randomized studies of postmenopausal, cynomolgus monkeys in which estrogens had no effect on the extent of coronary-artery plaque in monkeys assigned to estrogen alone or to estrogen combined with medroxyprogesterone acetate beginning 2 yr (approximately six human years) after oophorectomy, while hormone treatment resulted in a 50% reduction in the extent of plaque when given to younger monkeys soon after oophorectomy *(23)*.

The effect of the presence of atherosclerosis and aging on the vascular responsivenes to ovarian hormones has also been analyzed in several clinical studies. In the Cardiovascular Health Study, women with established cardiovascular disease had a flow-mediated vasodilator response that was equivalent among women who used hormones and those who did not, while among women without cardiovascular disease, hormone users had a 40% better response than that of nonusers *(24)*. In the Estrogen Replacement and Atherosclerosis trial *(25)*, a randomized trial involving women with documented coronary disease, no effect of estrogen alone or of estrogen combined with progestin on the diameter of coronary arteries was found, while in the Estrogen in the Prevention of Atherosclerosis Trial *(26)*, in which younger women without cardiovascular disease were randomly assigned to estrogen alone or placebo, the average rate of progression of carotid atherosclerosis was slower in women assigned to estrogens.

Hormone Regimen

It has been suggested that a possible explanation for the conflicting findings of the observational and randomized studies may be related to the dose and regimen of estrogen used. It seems obvious that the dose of ERT/HRT that is

adequate for an early postmenopausal woman is too high to start a late postmenopausal woman on without serious consequences. In all the randomized studies the dose of conjugated estrogens used was similar for the 50-yr-old as for the 75-yr-old women. Furthermore, in observational studies, most women used estrogens alone. The few studies including combined therapy with estrogen and progestins have reported protection against coronary heart disease *(4–6)*, even if only a small percentage of women took continuous combined hormone regimens. In contrast, both HERS and the WHI studied daily therapy with a combination of estrogen and a progestin. Therefore, although the regimens used in the randomized studies differed from those used in the observational studies, it is likely that the dose of estrogen used might have been of major importance. After the publication of the HERS and WHI trial results, most authors blamed conjugated estrogens and medroxyprogesterone. We have to take into account that if one is going to blame these two hormones, then one has to negate any cardioprotective effect of ovarian hormones because almost all studies suggesting such a protective effect had been conducted with these two substances.

Characteristics of the Study Populations

Patient populations included in the observational and randomized studies are very different, women included in the observational studies were younger, leaner, and with a less compromised cardiovascular system compared to those included in the randomized studies. As mentioned above, age and the number of years since menopause are important factors in modifying the cardiovascular effect of ovarian hormones.

In the Nurses' Health Study, women ranged in age from 30 to 55 yr at enrollment, and nearly 80% of them began to use hormones within 2 yr after menopause. Although analyses including older women found cardiovascular protection *(27)*, most older women had used hormones for a long time, beginning at menopause. In contrast, the mean age of participants was 63 yr in the WHI and 67 yr in HERS; thus, these women had generally been postmenopausal for at least 10 yr at the time of enrollment.

Although the WHI investigators reported no protection against coronary heart disease (RR = 0.89) among women within 10 yr of menopause, this cohort of women accounted for less than a third of the study population and therefore the subanalysis did not have power to detect a protective effect of ovarian hormones because few of these younger women had coronary events. However, even in this subgroup of younger women, a substantial number of subjects would have been assigned to hormone treatment at least 6 yr after menopause.

Some evidence suggests that the vascular effects of hormones may differ in women with different clinical characteristics. As suggested by Cardiovascular Health Study women with cardiovascular risk factors seem to have a reduced vascular response to estrogens. Women recruited in the randomized studies had a high incidence of uncontrolled risk factors such as arterial hypertension compared to women included in the observational studies *(24)*, thus reducing the effectiveness of the cardioprotective effect of estrogens and increasing the likelihood of potential cerebrovascular side effects related to the mineralocorticoid effect of the progestins and their consequent effect upon blood pressure. Body-mass index is an important marker of endogenous estrogen levels in postmenopausal women and has been associated with cardiovascular risk especially when >25 kg/m^2. In a very large cohort of 290,827 postmenopausal women *(28)*, the coronary benefits of hormone therapy exclusively affected women with a lower body-mass index. The mean body-mass index in the WHI was 28.5, while in the Nurses' Health Study it was 24.3.

Furthermore, it is interesting to note that the analysis of the cardiovascular data from RCTs conducted primarily for gynecologic endpoints in menopausal women do not reach the same conclusions as the WHI and HERS in which an increased cardiovascular risk was suggested. Indeed, Lobo has recently reported the comparison of the results of HERS and WHI with the findings of HOPE Study and The Menopause Study Group, two large, randomized clinical trials in which different dosages and combinations (including those used in HERS and WHI) of conjugated equine estrogens (CEE) and MPA were used and found that there was no increased risk for CHD-related death nor acute myocardial infarction in subjects taking HRT *(29–31)*. The overall event rates for stroke, pulmonary embolism, deep vein thrombosis and transient ischemic attack were not increased in the HRT group compared with placebo group. The mean ages of the HOPE and Menopause Study Group women were 53.4 and 54.0, respectively, compared with 63.3 for WHI and 66.7 for HERS. Thus, the results of these two studies differ significantly from HERS and WHI findings. There could be various explanations for this discrepancy. First, women in WHI did not suffer from neurovegetative symptomatology, while women in the HOPE and Menopause Study Group trials were symptomatic; this observation suggests a group of women characterized by a lower menopausal age (that is, women in the HOPE and Menopause Study Group trials were more close to the time of menopause at the start of hormone therapy). Second, the age differences suggest a different anatomic and functional status of arteries between the two groups of populations, with the HERS and WHI populations likely having atherosclerotic vessel walls with subsequent atherosclerotic plaque rupture and thrombotic mechanism activation. It is also important to remember the age-related exponential increase of thrombotic diseases that may have an important effect on increasing the risk for elderly women taking menopausal hormones.

In conclusion, several biological reasons may have contributed to the divergent findings from observational studies and RCTs. Clearly, time elapsed since menopause seems to be an important one for its effect on vascular responsiveness to ovarian hormones and to prothrombotic effects. In the meantime, a role remains for estrogen and combined estrogen and progestin supplementation in the treatment of severe menopausal symptoms. The suggestion that hormone therapy should involve the lowest effective dose makes clinical sense, but the suggestion that it should be prescribed for the the shortest duration does not, since it is in the very first months that, if an increased risk is present, it becomes manifest. At present, the suggestion that menopausal hormones should not be initiated or continued only for primary or secondary prevention of cardiovascular disease comes from the results of RCTs that have included only a minority of those women in whom menopausal hormones are and have been prescribed in the past on clinical grounds.

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