

Cardiovascular CORNER

Window of Opportunity for the Vascular Effect of Estrogens: Implications for HT

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Since the late 1970s and until the publication of the Women's Health Initiative (WHI), estrogen therapy (ET) and hormone therapy (HT) have been widely prescribed to early postmenopausal women for the relief of menopausal symptoms. In the 1990s their use was extended, particularly in the US, to several years after menopause, with the understanding that both replacement regimens might reduce the occurrence of cardiovascular disease (CVD). This belief was supported by the large body of evidence demonstrating a favorable effect of ovarian hormones on lipid profiles and vascular function, and by several observational studies showing a significant reduction in cardiovascular events with ET and HT in early postmenopausal women.¹⁻⁵ However, findings from recent randomized controlled trials that failed to show a cardioprotective effect of ET or HT in predominantly late postmenopausal women altered that practice.⁶

An important difference between the observational studies and randomized trials is defined by the characteristics of the cohorts recruited. Women included in the observational studies could choose to take ovarian hormones because of menopausal symptoms; on the contrary, in the randomized trials the absence of menopausal symptoms was a prerequisite for inclusion. The lack of symptoms indicates a physiologic adap-

tation to ovarian hormone deprivation (due to a slow decline in estrogen levels and/or to the long time lapsed from menopause) and corresponds with the development of a new homeostasis. The NHANES III study reported that in the US during the period of recruitment for the WHI, HT was largely prescribed to women within 5 years since menopause.⁷ Reports from Europe suggest that less than 1%–4% of women attending menopause clinics and taking HT had features similar to those included in the randomized trials.⁸ This suggests that the results of the WHI cannot be fully translated to clinical practices in which symptomatic women are treated within a few years since menopause.

The timing of HT initiation is of pivotal importance in explaining the differences in outcomes between observational and randomized studies. Indeed, the WHI showed that although ET and HT do not reduce cardiovascular events in late postmenopausal women, they reduce total mortality and show a trend toward a reduction in coronary events by an extent similar to that in observational studies in early postmenopausal women (within 10 years since menopause).⁹ The overall results of the WHI study on cardiovascular outcomes and on time to initiation of HT since menopause are further supported by a meta-analysis of all available randomized studies, showing that ET/HT reduces cardiovascular events in women under 60 years of age, while having no cardioprotective effect if started in women over age 60.^{10,11} Therefore, data obtained from the randomized studies, together with the evidence gathered from mechanistic studies, suggest that estrogen has a time-dependent effect on cardiovascular functions, and that there is a "window of opportunity" for maximizing the cardiovascular effect of HT.

Vascular Effect of Estrogens

It has long been suggested that ET and HT exert their cardioprotective effect mainly through lipid lowering. This concept has now been revised and it is widely believed that a direct effect of estrogens and progestins on the vascular bed is the most important explanation for the cardiovascular benefits of ovarian hormones. A large body of evidence suggests that endothelial

dysfunction is an initial step in the development of atherosclerosis, and that it is associated with future cardiovascular events in subjects with increased cardiovascular risk and in patients with CVD. Endothelial function is influenced by cardiovascular risk factors and genetic predisposition, as well as by aging and sex hormone

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deficiency. In women, ovarian hormone deficiency occurring after natural or surgical menopause is associated with an impairment of endothelial function,^{12,13} and several studies have shown that ET and HT may restore, at least in part, the impairment of endothelial function related to the cessation of menses.¹⁴⁻¹⁶ Most of the anti-atherogenic effects of ovarian hormones are receptor-mediated and endothelium-dependent. Both estrogen receptors and endothelial function are markedly influenced by duration of estrogen deprivation and progression of the atherosclerotic injury.¹⁷

Experimental studies conducted on monkeys indicated that estrogen administration delays atherosclerosis progression if given immediately after ovariectomy.¹⁸ The finding that the protective effect vanishes when the therapy is introduced at a later time suggests an extremely different condition in states of prolonged ovarian hormone deprivation. These results are paralleled in humans; in women, estrogen loss occurring after either natural or surgical menopause is associated with greater progression of atherosclerosis, and ET/HT started early after menopause reduces this progression,¹⁹⁻²¹ whereas ET started late after menopause has no effect on atherosclerotic progression.^{22,23} These findings are further supported by the results of the recent WHI Coronary Artery Calcium Study, which found that estrogens substantially reduced coronary artery calcification (an excellent marker of atherosclerosis and predictor of future CVD

events) in women in the WHI who were 50 to 59 years old at inclusion.²⁴

Although ovarian hormones have a direct antiatherogenic effect, their action upon the cardiovascular system is multifaceted and related principally to their direct action within the vessel wall. Ovarian hormones affect endothelial function and vascular tone through both genomic and non-genomic pathways that are mainly receptor-mediated.²⁵ The genomic effects of estrogens involve changes in vascular-cell gene and protein expression mediated by the two known estrogen receptors, and are involved in both improvement of endothelial function and in the arterial wall response to injury and development of atherosclerosis.²⁵

The expression of estrogen hormone receptors may vary depending upon gender, status of the gonads and the degree of vascular atherosclerosis. Differences in vascular response to estrogens may well be related, in part, to the level of estrogen receptors in vascular tissues. It has been shown that women who have been postmenopausal for several years have a reduced number and reduced activity of vascular estrogen receptors.^{17,25} Thus, women who have been postmenopausal for more years are clearly exposed to a longer period of estrogen loss, which may lead to reduced numbers and activity of vascular estrogen receptors and, ultimately, to a reduced vascular effect of estrogens.

In accordance with these considerations, there is evidence to support a time-dependent effect of ET/HT on the cardiovascular system.²⁶ Our group has shown that age (time since menopause) influences vascular response (measured as flow-mediated dilatation) to estrogens, and that estrogens have a significantly greater effect in improving endothelial function if they are administered within 5–10 years since menopause (50–59 years of age) (Figure).²⁷ We have also shown that endothelial function correlates inversely with age ($r = -0.43$; $P < 0.05$) and time since menopause ($r = -0.67$); $P < 0.001$) in postmenopausal women who have never received HT in the past, and that past hormone use reduces the detrimental effect of aging on vascular reactivity and improves the endothelial response to estradiol administration.²⁷ These findings suggest

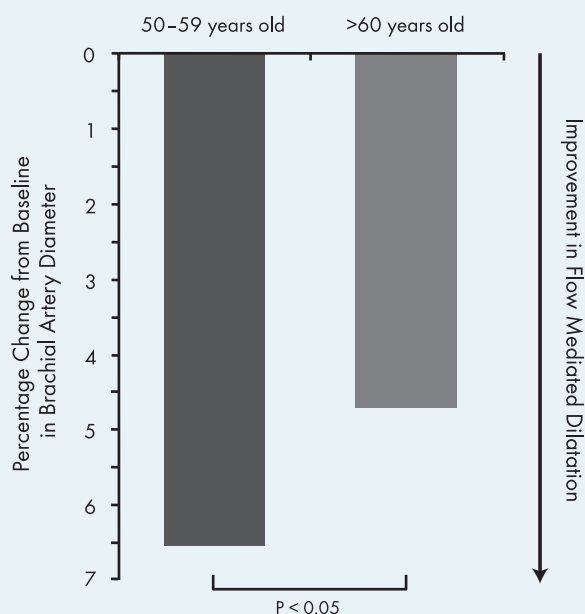


Figure. Effect of HT by age 50–59 years (close to menopause) and >60 years (distant from menopause) on endothelial function, measured as flow-mediated dilatation (percentage change from baseline in brachial artery diameter).

that postmenopausal HT use buffers the detrimental effect of ovarian hormone deprivation on endothelial function. We have also shown that in women over age 60, ET/HT may increase the vascular inflammatory response, which, in turn, may reduce the endothelium-mediated vasodilation induced by estrogens.²⁸

The results of our studies—showing that the vascular effect of postmenopausal HT is time-dependent and is reduced by longer time lapsed since menopause—suggest that the physiologic effect and the balance between favorable and unfavorable vascular effects of exogenous estrogens differ according to time since menopause and suggest a window of opportunity for ET/HT.

Conclusions

In conclusion, basic science and animal studies are concordant with clinical investigations in suggesting that a long time since menopause is associated with a reduced protective effect of estrogens. In early postmenopausal women included in the observational studies, ET/HT may be cardioprotective because of the favorable responsiveness of the endothelium to estrogens. To

the contrary, in late postmenopausal women ovarian hormones have an indifferent or even detrimental effect because of the procoagulant or plaque-destabilizing effects, which predominate over the vasoprotective effects. ■

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(continued on page 32)

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Cardiovascular Corner

(continued from page 29)

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