Regardless of age, race, and ethnicity, cardiovascular disease is the number 1 cause of death for women, and its prevalence rises rapidly after menopause.1–4 This postmenopausal increase is believed to result from the loss of endogenous estrogen. Although estrogen replacement therapy (ERT) has long been thought to protect against menopause-associated cardiovascular anomalies, osteoporosis, hot flashes, and thinning of the vaginal epithelium,3–5 findings from the Heart and Estrogen/Progestin Replacement Study and the Women’s Health Initiative Study5 do not support the notion that ERT protects the cardiovascular system. Instead, the data indicate just the opposite, that is, increased risk of cardiovascular disease, in addition to the apparent higher risk of breast cancer and deep vein thrombosis.1,2,4

Although results from clinical trials have substantiated the beneficial role of ERT in the management of menopausal symptoms, the unexpected finding of exacerbated cardiovascular function after ERT has made women hesitant to initiate ERT after menopause.1 Further analysis of the clinical trials revealed that the age of a woman and especially the number of years after menopause onset may be primary factors that contribute to the ultimate cardiovascular outcome of ERT. Although estrogen-progesterone therapy was found beneficial in young postmenopausal women, it increased cardiovascular risk when initiated in older postmenopausal women with established coronary artery disease.2,4 It is, thus, recommended that ERT be limited to the shortest duration consistent with treatment goals (eg, relief of menopausal symptoms).1 In contrast to the generalized recommendation for short duration of menopausal hormone treatment,2,4 careful scrutiny of the data from the Women’s Health Initiative Estrogen Plus Progestin Trial revealed a reduced coronary heart disease risk after 5 to 6 years of ERT treatment. Accordingly, the overall effect of ERT on cardiovascular health in postmenopausal women is controversial, making it difficult to evaluate individualized care based on the risk:benefit ratio.

A number of studies have reported a potential link between reduced estrogen and the prevalence of metabolic syndrome, a complex, debilitating disorder that includes hypertension, diabetes mellitus, and dyslipidemia.3 However, a reduced incidence of type 2 diabetes mellitus and obesity was noted in otherwise healthy postmenopausal women who received estrogen.3 This inverse correlation between estrogen and metabolic syndrome suggests that estrogen deficiency that accompanies menopause may play a role in the onset and development of metabolic syndrome. Thus, despite the controversies regarding ERT, it appears that younger postmenopausal women with metabolic syndrome may benefit from ERT. However, there are still major gaps in our knowledge base. The pathophysiology of metabolic syndrome in perimenopausal and postmenopausal women is still not well understood, although ambient reproductive hormone levels are believed not to be the only variables that affect the frequency and severity of metabolic syndrome in women. It is particularly worrisome that some studies have indicated a potential tie between severity of menopausal syndrome (eg, hot flashes) and increased cardiovascular risk,1,3 suggesting that younger postmenopausal women with metabolic syndrome who most need ERT for symptom relief may be at a greater risk of adverse effects from ERT.

In this issue of Hypertension, Murase et al6 examined the effect of ERT on obesity, cardiac geometry and contractile function using a new model of metabolic syndrome, the DahlS.Z-Lepr+/Lepr+ (DS/obese) rats derived from a cross between Dahl salt-sensitive and Zucker rats.6 Animals ovarioectomized at 7 weeks of age received an estrogen pellet or placebo at 8 weeks. Age-matched female homozygous lean littermates (DahlS.Z-Lepr+/Lepr+ or DS/lean rats) of DS/obese rats served as controls. Ovx-DS/obese rats manifested hypertension at 7 weeks of age and thereafter and exhibited left ventricular fibrosis and diastolic dysfunction at 13 weeks of age. ERT attenuated hypertension in Ovx-DS/obese rats without affecting blood pressure in ovarioectomized DS/lean (Ovx-DS/lean) rats. ERT exacerbated left ventricular fibrosis and diastolic dysfunction and further increased cardiac oxidative stress and inflammation in Ovx-DS/obese and Ovx-DS/lean rats. Consistent with the reported beneficial effect of estrogen on metabolic syndrome,3 ERT reduced food intake, body weight, and visceral fat content in both Ovx-DS/obese and Ovx-DS/lean rats. These authors concluded that ERT may attenuate hypertension and obesity but exacerbated cardiac fibrosis and diastolic dysfunction in Ovx-DS/obese.
rats. These latter effects are thought to be mediated through increased cardiac oxidative stress and inflammation.

Collectively these findings revealed a detrimental effect of ERT on cardiac remodeling and function despite a beneficial protective effect against hypertension and obesity in metabolic syndrome. These harmful sequelae of ERT in the setting of obesity are distinct from those found in volume-overloaded cardiac hypertrophy where ERT delays the progression of adverse cardiac remodeling and dysfunction in volume-overloaded, ovariectomized rats. Further examination revealed that ERT protects against cardiac hypertrophy and dysfunction through improved tissue inhibitors of metalloproteinase 2/matrix metalloproteinase 2 and tissue inhibitors of metalloproteinase 1/matrix metalloproteinase 9 protein balance, restored estrogen receptor-α expression, and prevented matrix metalloproteinase 9 activation and perivascular collagen accumulation. These findings support the notion that estrogen limits undesirable extracellular matrix remodeling and ventricular dilation in volume-overloaded hearts. Similarly, female mice were found resistant to deoxycorticosterone acetate-salt–induced cardiac hypertrophy through estrogen receptor–induced adaptive stress signaling activation and inhibition of maladaptive calcineurin signaling in deoxycorticosterone acetate–treated female mice. Therefore, ERT may exert distinctive effects under different physiological/pathological conditions.

Several lines of evidence indicate that estrogen protects the cardiovascular system through modulation of neuronal and endothelial isoforms of NO synthase (NOS). However, it is noteworthy that the rodent ovariectomized model does not precisely mimic naturally occurring menopause in women. However, the phenotypic characteristics in rodents after depletion of ovarian hormones, including left ventricular hypertrophy and hypertension, are similar to the pathophysiological changes occurring in postmenopausal women. Nonetheless, caution has to be taken when extrapolating information derived from animal studies.

Last but not least, the development of selective estrogen receptor modulators has shown promise in minimizing the cardiovascular risk of estrogen. Selective estrogen receptor modulators generate ligand receptor complexes with a 3D conformation capable of activating cell functions, with a profile distinct from estrogen. Analysis from Multiple Outcomes of Raloxifene Evaluation and Continuing Outcomes Relevant to Evista trials have depicted little difference in the incidence of serious cardiovascular events, stroke, uterine cancer, endometrial hyperplasia, ovarian cancer, or postmenopausal bleeding between the raloxifene and placebo groups. These observations suggest that specific agonistic actions of some selective estrogen receptor modulators are capable of circumventing the adverse effects associated with estrogen. To optimize the beneficial effect of ERT for individual patients, new research is urgently needed to evaluate the cardiovascular effect of selective estrogen receptor modulators, as well as the influence of time, duration, dose, route of administration, and agents on ERT-related risks and benefits in patients with metabolic syndrome.

Disclosures

None.
References


Estrogen Replacement Therapy and Cardiac Function Under Metabolic Syndrome: A Treacherous Art
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