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S 04 (LS 2)

Heterogeneity of the Cardioprotective Effect of HRT

Jay M. Sullivan, M.D.*

In 1993, more women than men died of cardiovascular disease in the United States. There has been a decline in the death rate from cardiovascular disease (CVD) and stroke. Studies show that in postmenopausal women the rate of CVD increases regardless of the age at which menopause takes place. Hospital-based and population-based case-control studies of the effect of estrogen replacement therapy (ERT) on CVD have yielded inconsistent results, while prospective cohort studies have found a protective effect. The Nurses Health Study demonstrated a reduction in the relative risk of cadiovascular disease to 0.56 (0.40-0.80) in current users of ERT. In a separate study of corornary artery stenosis, estrogen use was reported by fewer postmenopausal women with positive coronary angiograms. Analysis showed that ERT had an independent protective effect against coronary atherosclerosis. Generally, studies have found that the apparent cardioprotection in estrogen users is relatively greater in women with cardiovascular risks. One of the beneficial effects of estrogen involves lipids. After menopause, serum HDL levels fall as LDL levels rise. Studies demonstrate that ERT reverses this pattern, although when a progestational agent is used, the elevation of HDL is less than that with estrogen alone. It was initially suggested that the effect of ERT on cardiovascular events was associated solely with the effect on HDL. However, recent analyses suggest that changes in HDL cholesterol account for no more than 33% to 50% of the reductions in CV events. Other studies comparing ERT and HMG-CoA reductase inhibitors report that the effect of estrogen on HDL was equal to or greater than that of a statin, but the statins were more potent LDL-lowering agents. Statins lower triglycerides, while estrogen increases triglycerides. Importantly, estrogen lowers LP(a), while the statins do not. There is increasing evidence that estrogens directly affect blood vessel walls by other mechanisms, such as increasing fibrinolysis and decreasing fibrinogen and plasminogen activator inhibitor.

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S 05 (LS 2)

Vascular Effects of Estrogen

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Sex hormones have vasoactive properties that can directly affect the vasculature of many systems in addition to those of the reproductive organs. Estrogen relaxes animal and human coronary and cerebral arteries, which may contribute to the cardioprotective role of hormone replacement therapy (1-3). A number of mechanisms have been proposed to explain the vascular effects of estrogen. Calcium antagonistic properties of estrogen have been observed in uterine arteries (4), cardiac myocytes (5), and vascular smooth muscle (6). Long-term calcium antagonist treatment is known to decrease the progressing of minimal arteriosclerotic lesions when given to patients with established coronary heart disease ((no 7),8,9) ; therefore, estrogen may be cardioprotective *via* a beneficial effect on atheroma progression *in vivo* due to calcium antagonism. In addition, estrogen may attenuate the effects of vascular constrictor factors such as endothelin -1 (10) and angiotensin II (11). Estrogen may also be cardioprotective by stimulating nitric oxide production from the vascular endothelium (12). There is evidence that estrogen mediates nitric oxide synthase, and subsequently the presence of the estrogen receptor in female human coronary arteries has recently discovered - ERß. The significance concerning CHD is unknown (14). In humans, there are data to support a role for the endothelium in the mediation of estrogen-induced coronary and peripheral vessel relaxation (15 (no 16) 17, 18). Vasorelaxation may also be enhanced by stimulatory effects on endothelial prostacyclin production (19). Estrogen can affect coagulation, possibly resulting in a tendency toward a decrease in thrombotic events (20). All these mechanisms may contribute to the reduced degree of myocardial ischemia found in estrogen-treated postmenopausal women with coronary heart disease (21-24). The data argue against a single mechanism accounting for the beneficial cardiovascular activity of hormone replacement therapy. More likely, there is a synergistic interaction between a number of mechanisms to explain the favorable vascular effects of estrogen.

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S 06 (LS 3)

Livial for the Tissue Specific Treatment of Postmenopausal Hormone Deficiency States

Ernst J. Johannes*

Different body systems or organs may respond in a specific way to one and the same agent. This has led to the development of compounds that may exert "estrogen agonistic or stimulating" effects in one tissue while in other tissues the same compound exerts no estrogenic effects or even an estrogen antagonistic, a progestogenic or an androgenic effect. The first compound with such tissue specific effects used for the treatment of postmenopausal sex hormone deficiency states is tibolone. Tibolone is a steroid hormone with a molecular structure closely resembling the natural sex hormones. However, due to a chemical modification of the molecule it cannot be classified as either an estrogen nor a progestogen or an androgen. *In vitro* and *in vivo* studies have demonstrated that the 3α and 3ß-OH-tibolone metabolite predominantly bind to the estrogen receptor and the △4-isomere has a preference for the progestogen or androgen receptor, A tissue specific conversion of tibolone into one of its active metabolites could explain the potent estrogenic effect seen with tibolone on climacteric symptoms and bone comparable to that of estradiol, while on the other hand no endometrial stimulation is found and low bleeding rates are reported. The local, tissue specific, modification of tibolone into its △4-isomere can explain the absence of endometrium stimulation. This unique feature of tibolone demonstrates the progression in drug designing since it selectively prevents undesirable proliferative stimulation of the endometrium in postmenopausal women while preserving its benefical estrogenic effects on other tissues, including bone.

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S 07 (LS 3)

Tibolone : A Unique Form of Hormone Replacement Therapy

Christian Egarter*

Tibolone (Livial®) is an innovative synthetic steroid analogue for the treatment of postmenopausal climacteric symptoms which, in contrast to classical hormone replacement therapies, reacts with both estrogen, gestagen, and androgen receptors. This is mainly due to free metabolites of tibolone, the 3α and 3ß hydroxy metabolite and the △ 4 isomer.

One significant advantage of tibolone over conventional hormone replacement therapies is the low rate of vaginal bleeding. One of our own investigations in 129 postmenopausal patients treated with either tibolone or conjugated estrogens plus medrogestone showed significantly lower bleeding rates in the tibolone group, with 10-15% of patients in the tibolone group experiencing vaginal bleeding in the first three months treatment; after that, vaginal bleeding was very rare. The vital lack of endometrial stimulation of tibolone is thought to due to be the presence of a 3 ß hydroxysteroid dehydrogenase in the endometrium. This enzyme is responsible for the transformation of tibolone to the △ 4 ismomer, which exhibits mainly progestogenic activity.

Another study was designed to assess the tolerability and side effects of tibolone after four months of treatment in a large collective of patients, 189 postmenopausal patients were included in this study, tibolone significantly relieved all of the classical menopausal complaints. The proportion of patients with bleeding problems dropped significantly from 15.9% to 6.8%. Other complaints, such as headache, nervousness, and breast tenderness what also significantly less frequent than before treatment. Only 14.4% of women discontinued treatment prematurely. The use of tibolone in the postmenopause is only rarely associated with vaginal bleeding, a side effect of hormone replacement therapy which traditionally has kept many postmenopausal women

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