A Clinician's Opinion

Estrogen, Lipids, and Coronary Heart Disease

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Two questions regarding atherosclerosis in females have long puzzled physicians. They are: (1) Why is the premenopausal woman immune from atherosclerosis, and (2) will estrogen replacement therapy (ERT) prevent the estrogen-deficient woman from developing atherosclerosis?

The answers lie in the effect of hormones on lipoprotein levels. The relationship between coronary heart disease (CHD) and increased levels of plasma cholesterol and triglycerides has been clearly established. Enhanced risk is now known to be due to a disproportionate increase in serum low-density lipoproteins (LDL) and a decrease in the serum high-density lipoprotein (HDL). A recent report from Finland on the treatment of 17 postmenopausal women with type II hyperlipoproteinemia showed that daily treatment for 6 months with a "natural" estrogen (estradiol valerianate, 2 mg) resulted in an 18 per cent decrease in the mean LDL cholesterol concentration and a 30 per cent increase in the mean HDL. These changes were reflected in an overall reduction of plasma cholesterol by 10 per cent, with no change in plasma triglycerides. There is good epidemiological data to suggest that similar lipoprotein changes decrease the risk of CHD.

Atherosclerosis is a multifactorial disease, with an early stage characterized by endothelial desquamation, exposure of the underlying intimal connective tissue, and adherence of platelets to this area. Platelet factor(s) interact with plasma constituents in the arterial wall, stimulating smooth-muscle cell proliferation and cholesterol-ester deposition within these cells. Regression of the proliferative lesions may occur if the source of injury is removed. If secondary factors such as hypertension and hypercholesterolemia persist, the lesions will become permanent and lead to the later stage, complicated by fibrosis, further platelet deposition, and the formation of mural thrombi.

The smooth-muscle cells of the arterial wall play a central role in the atherogenic process. These cells take up and degrade LDL at a high rate and this avid metabolism of LDL is accompanied by a net increase in the cell cholesterol content. The progression of atherogenesis is slowed at this point. It has quite recently been shown that HDL has protective mechanisms that slow this atherogenic process: HDL competes with and binds to the surface of arterial smooth-muscle cells thereby decreasing the internalization and deposition of LDL; and secondly, HDL facilitates the uptake of cholesterol from peripheral tissues (including the arterial wall) and transports it to the liver for catabolism and excretion.

In young women, plasma LDL concentrations and total cholesterol levels are lower than in young men. The increase in LDL levels as middle age approaches is, however, much greater in women and, above the age of 45, their mean LDL concentrations exceed those of men. The menopause, whether surgically induced at an early age or naturally achieved during the middle years, is associated with a dramatic change in the lipoprotein moiety; HDL concentrations decrease and LDL cholesterol increases. This is a biological and *not* a chronological event. A recent Swedish study compared women aged 50 or more who were still menstruating with others who had already reached the menopause; serum cholesterol and triglycerides were significantly higher in the postmenopausal group and this seemed to increase with postmenopausal age.

Exogenous estrogens whether in oral contraceptives or used for replacement in postmenopausal women

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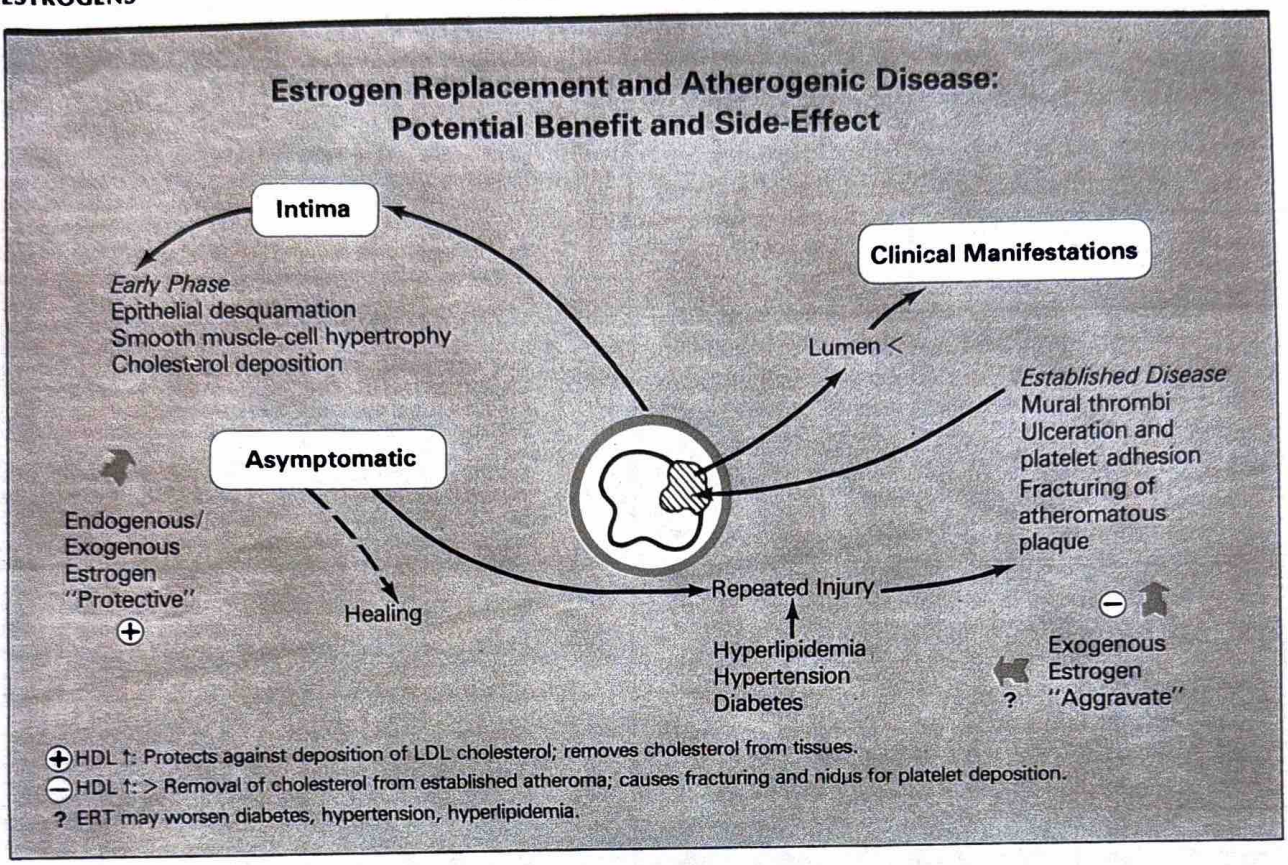

also affect lipoprotein levels. A recent study has shown that the level of HDL-cholesterol in women taking oral contraceptives varies with the type and dose of the component steroids: HDL increases with increasing doses of estrogen and decreases with increasing potency of added progestin. Thus, the net effect of a combination oral contraceptive on HDL depends on its formulation.

From the clinician's viewpoint, the available epidemiological evidence has not been very useful; some reports support and others are against the protective effect of estrogens on CHD. For example, it is accepted that castration before the age of 40 is associated with an excess of atherosclerosis, especially in individuals who survive for 14 or more years beyond the surgery. Estrogen substitution in this group is associated with a decrease in the morbidity and mortality from atheroma-related disease. On the other hand, the results of the Coronary Drug Project have revealed that men who had had established coronary artery disease and were treated with 5 mg of conjugated estrogens per day, had twice the mortality of a similar, but placebo-treated group.

This apparent paradox may be explained by the fact that estrogen affects preexisting atherogenic vascular disease, not a healthy system. An understanding of this fact aids the clinician in making appropriate use of hormonal therapy. Coronary thrombosis is rare in the absence of an underlying atheromatous ulcer; estrogen, by mobilizing, softening, and reducing the size of a preexisting atheromatous plaque dislocates and fractures the overlying fibrohyaline cap. The resulting ulcer provides the necessary nidus for the development of a mural thrombosis. This concept has been well documented in experimental studies: When estrogens are introduced simultaneously with a high atherogenic diet, ulcer-prone atheroma has no chance to develop and hence no ulcerations are seen. When animals are fed on an atherogenic diet without estrogens, atheromatous plaques do develop with time. Once these plaques are present, later treatment with estrogens produces typical ulcerations. Autopsy findings support this concept.

The risk of developing estrogen-induced ulcerations in preexisting atheromatous plaques is higher in persons who have major coronary heart disease risk factors such as diabetes mellitus, hypertension, and hyperlipidemia. The danger is greater in older premenopausal women than in younger women; however, it still is less than in men. Based on some of the investigations published to date, it appears that the precipitation of atheromatous ulceration must be dose dependent: excess levels of estrogens are required whether their origin is endogenous or exogenous.

Since atherosclerosis is a multifactorial disease, it

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would be simplistic to suggest that this disease could be prevented or induced by the use or misuse of estrogens. Important factors such as cigarette smoking and stress need to be considered along with the potential role of estrogen in inducing hypertension and an increased coagulability. However, the effect of estrogens on the lipid component of atherogenic disease is most important. The normal production of endogenous estrogen in healthy younger women affords some protection from coronary atherosclerosis.

In this context, the need to preserve endogenous ovarian steroidogenesis by limiting the practice of premenopausal oophorectomy cannot be overemphasized. The protective effect of estrogen replacement therapy still needs to be proven although there is good evidence to support ERT in agonadal females and women subject to an early menopause. The usefulness of ERT in older postmenopausal women is more controversial and is difficult to assess since the risk:benefit ratio of this treatment will be dependent on the presence of preexisting atherogenic disease and other risk factors.

There is a close corollary between estrogen replacement and coronary heart disease and between estrogen use and osteoporosis. Estrogen is most effective in preventing osteoporosis, but not in treating the condition once it has developed. In this author's opinion, the same might be true for estrogens and coronary heart disease. □

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