Contraception and dyslipidemia

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The risks of cardiovascular disease associated with dyslipidemia differ in women and men, being more strongly associated with triglyceride/high-density lipoprotein in middle-aged women than in men. Although the incidence of heart disease is lower in women because they live longer, over a lifetime, cardiovascular disease in women is equal to that in men, with the greatest incidence after age 65 years. Major coronary events are rare among reproductive-age women who use oral contraceptives and are related to the concomitant effects of age, smoking, diabetes, hypertension, and obesity. Low estrogen-progestin dose oral contraceptives appear not to promote cardiovascular disease and can be used in women with controlled cholesterol elevations. Alternative contraceptive measures should be considered for patients with severe uncontrolled hypercholesterolemia or a lipid disorder that carries a high risk of coronary heart disease. In these conditions, thrombotic propensity associated with supraphysiologic doses of estrogen in oral contraceptives might accelerate coronary thrombosis should an arteriosclerotic plaque rupture. Treatment of hypercholesterolemia should follow the guidelines of the National Cholesterol Education Program and emphasize hygienic measures. Contraceptive selection in hyperlipidemic patients should reflect a balance between the risks—and their management—of developing cardiovascular disease versus the risks of pregnancy. (Am J Obstet Gynecol 1993;168:1994-2005.)

Key words: Cardiovascular disease, contraception, dyslipidemia, National Cholesterol Education Program, sex hormones

Although 5 to 6 million women of reproductive age in the United States have some form of lipid abnormality,[1] most are unaware of potential health risks associated with that abnormality. Among women interviewed in a 1990 Gallup poll, less than 20% knew that heart disease is the most common cause of death in women more than 50 years of age, even though approximately 80% had had a serum cholesterol determination in the previous 2 years. Many of these women who are potentially at risk for developing cardiovascular disease (CVD) later in life are currently of reproductive age and actively seek contraception without any knowledge that exogenous hormones may be important modifiers of coronary disease risk.

Whereas most of the data linking lipid abnormalities with coronary heart disease (CHD) have been derived from large-scale studies involving men or women more than 35 years of age,[2, 3] CHD in women of younger reproductive age is not uncommon. The annual mortality rate is approximately 20 times that of the death rate from maternal causes.[4] Furthermore, with convincing evidence that atherosclerosis begins early in life,[5] good preventive medicine dictates the use of risk reduction strategies in younger patients in an effort to avoid CHD later in life. In women who seek contraception, a careful assessment of CVD risk must be balanced with the risks of unplanned pregnancy to the mother and the fetus.

This article presents an overview of lipid abnormalities, related risk factors for CVD, and risk reduction strategies in relation to considerations for women seeking contraception. In the absence of guidelines in the literature, recommendations are given for use of currently available, reversible, and effective contraceptive options in women with abnormal levels of plasma lipoproteins.

Dyslipoproteinemia

The term dyslipidemia encompasses the disorders of lipoprotein metabolism that lead to atherosclerosis. These abnormalities arise from genetic and secondary disorders and are caused by excessive entry of lipoproteins into the bloodstream, their impaired removal, or both.

Excessive entry of apoprotein B particles results in increased levels of very low-density lipoprotein, intermediate-density lipoprotein, also called *remnant* particles, and low-density lipoprotein (LDL). Familial combined hyperlipidemia is the characteristic disorder of excess entry and can appear with an elevation of any one or a combination of these lipoproteins. Familial combined hyperlipidemia is the most common dyslipi-

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demia and the one most frequently associated with CHD.

Impaired remnant removal also contributes to abnormally high plasma levels of the remnant. Because remnant removal is mediated by the LDL receptor, it accumulates in the plasma in the presence of apoprotein E_2, which is poorly recognized by the LDL receptor.

Impaired removal of low-density lipoprotein cholesterol (LDL-C) is associated with classic familial hypercholesterolemia, with reduced LDL receptor activity. The same effect can be achieved by a diet rich in saturated fats, which downregulate hepatic LDL receptors. A small percentage of patients with hypercholesterolemia, perhaps 5% to 10%, have familial defective apoprotein B, which presents like familial hypercholesterolemia but is caused by an abnormal apoprotein B that is not recognized by the LDL receptor.

Low levels of high-density lipoprotein (HDL) result from diminished production of HDL or its increased removal from the bloodstream. The disorder may involve a structural defect in apoprotein A-I the major HDL apoprotein, and other regulatory defects. In some cases, low serum levels of HDL cholesterol (HDL-C) are associated with hypertriglyceridemia or secondary causes, such as obesity or diabetes, when multiple regulatory abnormalities exist. In some hypertriglyceridemias, the number of HDL particles is normal but the core cholesterol is replaced with triglyceride.

Effects of estrogen

Estrogen exerts several favorable actions on circulating lipoproteins. Estrogen increases LDL receptor activity, thereby enhancing removal of both LDL and remnants. Estrogen also increases the amount of apoprotein A-I in HDL by enhancing the synthesis or impairing the catabolism of apoprotein A-I or both, thus increasing the number of HDL particles and the level of HDL-C.[6]

Differences in lipoproteins between men and women

LDL-C levels are reportedly lower in women than in men until ages 50 to 54 years, and then higher subsequently (Fig. 1).[7] Perhaps this is because of decreased estrogen secretion by women later in life. Levels of HDL-C appear to decline slightly in postmenopausal women but continue to rise slightly in men (Fig. 1), which may relate to a postmenopausal decline in estrogen in women and an age-related decline in testosterone in men, as well as excess mortality in men with low levels of HDL.

Several qualitative differences are found in the circulating lipids in women and men, in addition to quantitative differences in serum levels. More apoprotein is found in the HDL of women and significantly more total cholesterol, cholesterol ester, and phospholipid is found in the fraction of HDL that contains only apoprotein A-I (Table I).[8] This fraction comprises the majority of HDL_2. As the menstrual cycle progresses, serum levels of HDL rise slightly, whereas those of LDL decrease.[9] The incidence of β-migrating very low-density lipoproteins, a manifestation of the remnant, is highest in men, intermediate in women who do not take hormones, but almost absent from women who take hormones (Table II).[10]

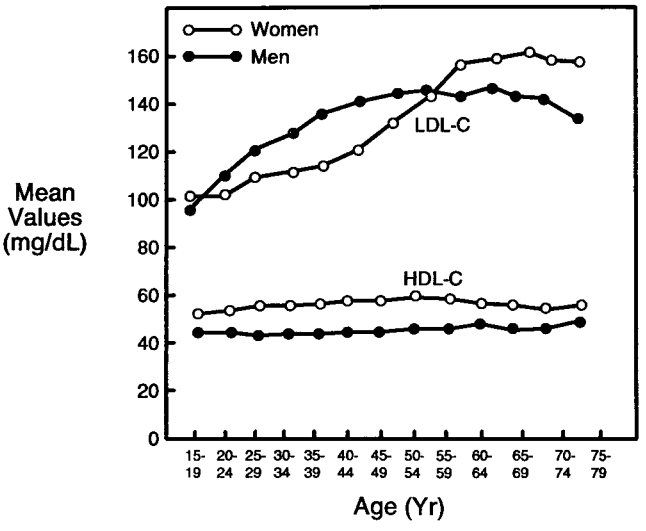

Fig. 1. Lipoprotein cholesterol fractions and age trends in women and men. (Modified from Kannel WB. Nutr Rev 1988;46:68-78.)

Lipid risk factors and age

Cholesterol. During an entire lifetime, the incidence of CVD in women and men is similar and that of myocardial infarction (MI) is slightly lower in women.[11] If the data are adjusted for age to reflect the greater life span of women, the incidence of both is lower in women—approximately half that of men (Table III).[11] Despite the fact that the baseline CHD rate for women is lower than that for men, high serum cholesterol levels predict a higher risk of CHD in women and men (Table IV).[2] Because of the effect of age, the relative CHD risk associated with high cholesterol declines with increasing age, but less so in women than in men. Thus the increase in CVD risk from high versus low cholesterol at age 65 years is approximately twofold for women, considerably more than the 23% increase for men the same age. These and other data indicate that in older age, cholesterol is a stronger risk factor in women than in men. On the basis of these types of data, the National Cholesterol Education Program (NCEP)[12] has promulgated guidelines that designate cholesterol levels of 200 to 240 mg/dl as "borderline" and those more than 240