Effects of danazol and lynestrenol on serum lipoproteins in endometriosis

The treatment of endometriosis with danazol or lynestrenol decreased cholesterol content of plasma high-density lipoproteins by 50% and 32%. There were simultaneous increases in low-density lipoprotein cholesterol content of 51% and 19%. We suggest that changes induced by lynestrenol are due to progestational activity, while in the case of danazol both antigonadotropic and androgenic activities are involved.

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Endocrine factors, especially gonadal steroids, play an important role in lipoprotein metabolism, but the mechanisms by which they influence lipoproteins are poorly understood. Recent recognition of the important role of plasma high-density lipoprotein (HDL) cholesterol in the pathogenesis of atherosclerotic processes highlights the need for better understanding of the endocrine and metabolic processes regulating plasma lipid patterns.

To eluicidate in greater detail the action of such gonadal steroids on lipoprotein metabolism, we studied the effect of inhibiting endogenous ovarian function in young women suffering from endometriosis by treatment with a recently introduced antigonadotropin, danazol,[2] or with the progestin lynestrenol, both of which are derivatives of ethisterone.

Patients and methods

Six patients with recurrent endometriosis were treated with danazol (Danocrine) 600 mg daily for 3 to 6 mo and another similar group with lynestrenol (Orgametril) 5 to 10 mg daily for 6 mo. The groups were matched with respect to age (31 ± 2.0 and 31 ± 4.4 yr, $\bar{x}$ ± SD), relative body weight, and severity of the disease. Apart from endometriosis all subjects were clinically healthy, with normal values of routine hematology and on tests of hepatic, renal, thyroid, adrenal, and ovarian function.

Blood for lipid analysis was drawn after an overnight fast on two occasions 1 wk apart before drug treatment to determine basal levels and thereafter once a month during the treatment. Lipoproteins were separated by ultracentrifugation using the swing-out technique.[12] Cholesterol was determined by the ferric chloride method. Changes in the lipoprotein fractions were confirmed by agarose-gel electrophoresis and by precipitating plasma very low-density lipoproteins (VLDL) and low-density lipoproteins (LDL) with PEG-6000.[11]

Results

The initial levels of total cholesterol, LDL cholesterol, and high-density lipoprotein (HDL) cholesterol were in the same range and within

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normal limits in both groups. As shown in Fig. 1, danazol increased LDL cholesterol after only 1 mo of treatment from 2.9 ± 0.16 ($\bar{x}$ ± SD) to 4.4 ± 0.72 mmole/*l*, a rise of 51% ($p < 0.001$) and decreased HDL cholesterol from 1.8 ± 0.18 to 0.9 ± 0.04 mmole/*l*, a fall of 50% ($p < 0.001$). A small simultaneous increase was detected in the total cholesterol, but it was not significant until after 3 mo of treatment ($p < 0.05$). Lynestrenol increased LDL cholesterol from 3.1 ± 0.32 to 3.7 ± 0.33 mmole/*l* (19%) ($p < 0.01$) and decreased HDL cholesterol from 1.5 ± 0.12 to 1.0 ± 0.06 mmole/*l* (32%) ($p < 0.001$). There were no significant changes in total cholesterol concentration.

The ratio of HDL cholesterol to total cholesterol is given in Fig. 2. The proportion of HDL decreased in both groups in 1 mo (lynestrenol, $p < 0.05$; danazol, $p < 0.001$). In both groups, plasma total triglycerides remained within normal range and did not change significantly. Initial lipid levels were regained within 1 to 3 mo of discontinuation of the treatment.

There were no obvious clinical side effects attributable to danazol or lynestrenol during the treatment. No weight changes occured and aminotransferases remained within normal limits.

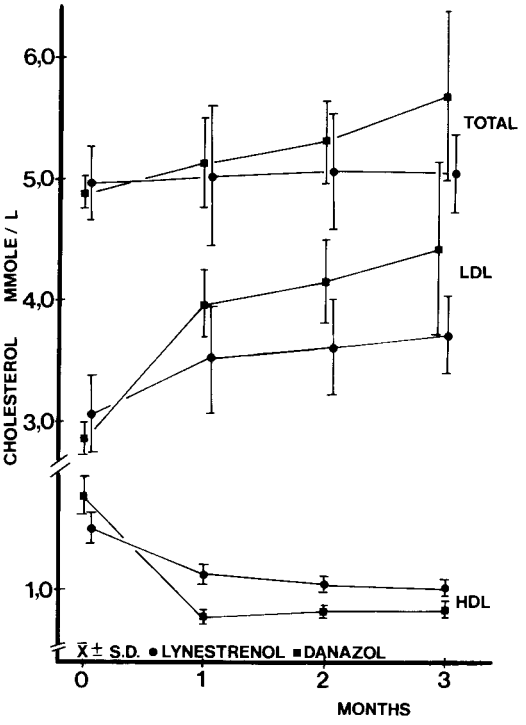

Fig. 1. Changes in plasma total cholesterol and LDL and HDL cholesterol during 3 mo of treatment with danazol or lynestrenol.

Discussion

Lynestrenol, a progestin, and danazol, an antigonadotropin, both decrease estrogen excretion and induce therapeutic amenorrhea. Estrogen deficiency and progestin administration are both known to decrease plasma HDL cholesterol,[3, 5, 10] which would explain the lowering reported here.

Progestins induce alterations of varying magnitude in plasma lipoproteins, depending on their androgenic and progestational as well as on their estrogenic and antiestrogenic activity.[1] Both lynestrenol and danazol have some androgenic activity, but androgenic side effects due to danazol are the more obvious clinically. Androgens given to men, with or without simultaneous estrogen, are known to decrease plasma HDL substantially and to elevate LDL concentration. Such alterations are opposite to those due to estrogen alone.[8] Danazol also seems to have some anabolic activity.[14] Thus the rapid and pronounced lipoprotein changes caused by danazol are apparently not entirely the result of an estrogen deficiency due to its antigonadotropic effects. Increased androgenic and anabolic activities appear to be contributory factors. This suggestion is reinforced by the finding that during sequential postmenopausal replacement therapy with estradiol valerate, medroxyprogesterone acetate (a 17-α-OH-progesterone derivative without androgenic activity) did not decrease HDL cholesterol. In contrast, two other progestins, norethisterone acetate and norgestrel (both 19-nortestosterone derivatives with androgenic activity), brought about such a fall.[4]

The decrease in estrogen excretion brought about by the antigonadotropic action of danazol presumably involves hypophyseal regulation of lipid metabolism. Hypophyseal control of lipoproteins has been suggested on the basis of results in hypophysectomized rats[6] and in men on antiandrogen therapy.[13] But both Solyom[9] and Nikkilä,[7] in reviewing the endocrine control of lipoprotein behavior, noted that the biochemical mechanisms involved are still largely unknown

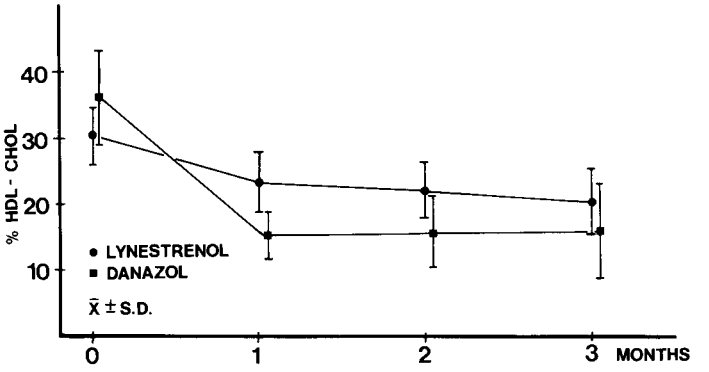

Fig. 2. Alterations in percentage HDL cholesterol of total cholesterol.

and results so far published show considerable disagreement. More extensive and well-designed studies are obviously needed to determine the physiologic and biochemical regulatory mechanisms involved. Despite these uncertainties, our study establishes that both lynestrenol and danazol have profound effects on lipoprotein metabolism in man. Since some of these effects may be undesirable clinically, they should be taken into account.

Our results show the importance of lipoprotein fractionation when the effect of various hormones on lipids is being assessed; drastic changes may occur in different components without indication in total lipid values. The properties of the hormones in question should be accurately described.

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