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ALTERATIONS OF LIPID METABOLISM BY CONTRACEPTIVE STEROIDS

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SUMMARY

Estrogen administration leads to increased fasting serum triglyceride concentrations which appears to be due primarily to increased hepatic production of triglycerides. These changes are favored by the increase in circulating insulin and growth hormone concentrations and the blunting of aminogenic glucagon secretion often observed in users of birth control pills. Nortestosterone derivatives (but not 17α-acetoxyprogesterone derivatives) counteract the hypertriglyceridemic effect of estrogens. A small group of patients react dramatically to estrogens with the development of massive hypertriglyceridemia. This latter group of patients appears to be particularly susceptible to pancreatitis and to electrocardiographic changes compatible with coronary artery disease.

The changes in serum cholesterol concentrations induced by individual contraceptive steroids appear to be opposite in direction from the changes observed in triglyceride concentrations. When changes in circulating cholesterol concentrations occur, they appear to be much smaller than those observed with the triglycerides. Estrogen administration produces changes in cholesterol and bile metabolism which favors gall stone formation. It is significant that an increased incidence of cholelithiasis has been observed in users of contraceptive steroids.

Whether the modest changes in cholesterol and triglyceride metabolism have any effect on the development of atherosclerosis and coronary heart disease remains to be determined.

In an earlier review paper [1], the effect of contraceptive steroids on plasma or serum lipid concentrations in normal women was summarized as follows: Estrogen administration leads to a rise in fasting serum triglyceride concentrations. By contrast, nortestosterone derivatives (but not 17α-acetoxyprogesterone derivatives) counteract the hypertriglyceridemic effect of estrogens. Both of these effects seem to be dose-related. Only small changes in total serum cholesterol concentration are produced by birth control pills. When increases in serum cholesterol concentrations occur, they appear to be related to the amount of nortestosterone or progesterone derivative ingested in conjunction with a synthetic estrogen. These observations have been substantiated by a number of reports which have appeared subsequently in the world literature [2–12].

In this review we shall consider (1) the mechanisms underlying these changes in circulating triglyceride and cholesterol concentrations, and (2) the extent to which contraceptive steroids enhance those clinical pathologic disorders which are known to be related to disorders of lipid metabolism. Whenever possible we shall attempt to elucidate the specific effects of each major class of contraceptive steroids (derivatives of ethinyl estradiol, 19-nortestosterone, and 17α-acetoxyprogesterone, respectively) on triglyceride and cholesterol metabolism.

Triglyceride metabolism

Increased hepatic production of triglycerides appears to be a critical factor determining the increase in serum triglyceride concentrations observed during contraceptive steroid use. Kekki and Nikkila[13] have demonstrated that triglyceride turnover and removal rates are accelerated in women using nortestosterone plus mestranol (or ethinyl estradiol). These findings have been confirmed by Kissebah, Harrigan, and Wynn[14] who also demonstrated increased serum triglyceride turnover rates in women treated with estrogen alone, but not with progesterone or a 17α-acetoxyprogesterone derivative (megestrol acetate). These findings suggest that the increased serum triglyceride concentrations observed in patients treated with estrogen derivatives alone or in combination with nortestosterone derivatives are due to a rate of triglyceride synthesis which exceeds the removal rate. Rossner and coworkers [15] and Gustafson and Svanborg[16] have shown that the increase in serum triglyceride concentrations observed in women using contraceptive steroids appears predominantly in the very low density lipoprotein (VLDL) fraction, the lipoprotein fraction which is generally believed to be synthesized in the liver.

Do the hormonal changes produced by contraceptive steroids contribute to an increase in hepatic triglyceride synthesis? Numerous in vivo and in vitro studies have demonstrated that insulin stimulates triglyceride synthesis in the liver [17], using FFA as a substrate which has been mobilized from adipose tissue [18]. Growth hormone enhances adipose tissue lipolysis [19] and increases circulating FFA concentrations [20]. In women using combinations of ethinyl estradiol + nortestosterone derivatives, fasting circulating growth hormone [21–23] and insulin concentrations are elevated [24] and the insulin response

to glucose stimulation is also increased [24]. In addition, Azizi and coworkers[25] have reported that growth hormone administration increases plasma triglyceride concentrations in normal women, and that this increase is enhanced in young women using contraceptive steroids.

Nevertheless, several facts suggest the possibility that other hormonal changes may be involved in contraceptive steroid-induced increases in triglyceride synthesis. First, Spellacy and associates[26] have shown that elevation of serum insulin concentrations alone did not consistently result in altered basal triglyceride concentrations in women using norethindrone alone. Second, Heimberg, Weinstein and Kohout[27] and Poledne and Mayes[28] have shown in vitro that glucagon acts to shunt intrahepatic FFA into oxidative pathways and away from triglyceride synthesis. Moreover, this effect can be neutralized by insulin [28]. Schade and Eaton[29] have produced increased circulating β-hydroxybutyrate and acetoacetate concentrations in normal men treated with glucagon. Finally, Caren and Corbo[30] and Aubrey, Marcel and Da Vignon[31] have shown that exogenously administered glucagon acutely suppresses circulating triglycerides in man.

In collaboration with Dr. Eaton, we have examined whether contraceptive steroids suppress endogenous glucagon secretion. We have measured the glucagon response to arginine infusions in women using mestranol + norethindrone [32]. At comparable circulating amino acid levels, and in comparison with control tests in the same women, the glucagon response to i.v. arginine was significantly blunted after 2 weeks of treatment with mestranol + norethindrone. Moreover, the administration of this contraceptive steroid combination also blunted the usual rise in plasma glucose and plasma insulin following arginine administration. Finally, the plasma concentrations of triglycerides fell concurrent with the rise in plasma glucagon during the arginine infusions. These findings suggest the possibility that mestranol + norethindrone treatment leads to chronic blunting of dietary protein-stimulated glucagon secretion which would favor a chronic increase in hepatic triglyceride and lipoprotein synthesis.

Although the increase in serum triglyceride concentrations in most women using contraceptive steroids has been rather small, marked increases in serum triglyceride have been described in a few patients [33–36]. In a small subgroup of these patients, recurrent bouts of pancreatitis have been described which have disappeared following discontinuation of the contraceptive steroids [36]. Particularly disturbing is the high incidence of abnormal electrocardiograms of many of these patients with massive hypertriglyceridemia [34], since high circulating triglycerides appear to be an epidemiologic risk factor for coronary heart disease [37–39]. In addition, several reports suggest that the incidence of contraceptive steroid use is greater than would be anticipated in pre-menopausal women who develop myocardial infarction [40–45]. Nevertheless, these victims of coronary heart disease also have a greater incidence of other risk factors such as cigarette smoking, hypertension, and excess weight. Moreover, Irey and Norris have postulated that premenopausal women who develop cardiovascular disease may be more prone to develop intimal vascular lesions after exposure to contraceptive steroids [46]. Thus, the true risk of a moderate increase in serum triglyceride concentration (as seen in most women using contraceptive steroids) for the development of coronary heart disease and other atherosclerotic processes remains to be determined.

Cholesterol metabolism

Despite the small changes in circulating cholesterol concentrations observed in users of contraceptive steroids, recent data suggest that synthetic estrogens produce appreciable changes in the kinetics of cholesterol synthesis and disposal. As shown by Nestel, Hirsch, and Couzens[47], treatment of patients with coronary heart disease with 150 μg ethinyl estradiol daily leads to an increase in the rate of disappearance of radiolabeled cholesterol from the plasma and a concurrent decrease in the plasma concentrations of free and esterified cholesterol concentrations. If these changes were due to a decreased rate of entry of cholesterol into plasma, one might expect to see a decrease in the cholesterol content of circulating lipoproteins; such changes have been reported in the LDL serum fractions of post-menopausal women treated with ethinyl estradiol and conjugated estrogens [16, 48]. Alternately, if the plasma clearance of cholesterol were enhanced, one might expect to see an increase in the oxidation of cholesterol to cholic acid and an increase in biliary excretion of both of these substances. Recently, Pertsemlidis, Panveliwalla and Ahrens[49] have shown that there is an increase in the cholesterol concentration and a small, but insignificant, decrease in the bile acid concentration in the bile of women treated with conjugated estrogens and medroxyprogesterone acetate, a change which would favor gall stone formation [50]. These changes were accompanied by decreases in the pool size and the rate of synthesis of cholate, as determined by measuring the rate of disappearance of radiolabeled cholic acid from bile [49]. Clarification of these confusing data may be obtained from studies of cholesterol kinetics in the male rat treated with synthetic estrogens. Davis and coworkers[51, 52] have shown that the rate of bile flow and the rate of cholesterol degradation are significantly decreased in male rats treated with large doses of ethinyl estradiol; as in man treated with estrogens, there was a concurrent decrease in serum cholesterol and an increase in biliary cholesterol concentration without change in bile salt concentration in the bile of these animals. Since other workers have shown a decrease in the cholesterol content of plasma VLDL lipoproteins [53] and an increase in the hepatic cholesterol content of rats treated with estrogens [54–56]. Davis and Kern postulated that estrogen treatment produces an impair-

ment in the transport of newly synthesized cholesterol into the blood from the liver [57].

What is the clinical significance of these sex steroid induced changes in cholesterol metabolism? An increased risk of cholelithiasis is present in young women using oral contraceptives, according to a study from the Boston Collaborative Drug Surveillance Program [58]. Surgically proven gall stones were found twice as frequently (158/100,000) in women using contraceptive steroids as in women not using an ovulatory agent (70/1000,000). This epidemiologic finding is consistent with the thesis that the increased cholesterol saturation of bile produced by estrogen treatment favors gall stone formation.

It is tempting to speculate that the serum cholesterol-lowering effect of synthetic estrogens may neutralize the atherogenic potential of their hypertriglyceridemic effect. Assessment of this possibility, however, requires a more detailed knowledge of the importance of shifts in the proportionate concentrations of lipids in circulating lipoproteins and whether this has any effect on the development of lesions in arterial walls. Long-term epidemiologic studies of the survival rates of users of contraceptive steroids may provide an answer to this question.

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