ORAL CONTRACEPTIVES AND PLASMA LIPIDS

by

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Oral contraceptive steroids are most effective as a method of temporary contraception. Their effects on various metabolic processes in the body are being currently evaluated to prove their safety, especially after long term administration. Sex differences in the prevalence of atherosclerosis before the age of fifty suggested the influence of gonadal steroids in this condition, presumably through changes in plasma lipid components. The field of study received added impetus with developments in analytical techniques, especially in relation to identification and estimation of different types of lipo-proteins.

The present study relates to the effects of two types of oral contraceptive steroids on plasma lipid component in a group of healthy Indian women.

Material and Methods

A total of 45 women between 15-40 years of age attending gynaecological outpatient department of Nehru Hospital, Chandigarh, were selected for the study. Special attention was paid to exclude any contraindications for medication like diabetes, hypertension, chronic renal or liver disease. Fifteen subjects were placed according to medication given in each of the following groups for three consecutive cycles.

Group A.

Lynestrenol, 1 mgm. with mestranol 0.1 mgm. (Noracycline 1 mg), one tablet daily from 5th to 27th day in each cycle.

Group B.

Megesterol acetate, 4 mgm with ethinyl oestradiol, 0.05 mgm (Voldys), one tablet daily from 5th to 26th day in each cycle.

Group C.

Megesterol acetate 0.05 mgm. daily continuously for three months.

Fasting heparinised blood samples were collected on 23rd to 26th day of a control cycle before starting medication and subsequently in each of three consecutive cycles during medication between 23rd—26th day. Thus each subject served as her own control.

(i) Total plasma lipids (Bragdon, 1960). (ii) Total plasma cholesterol (Abel *et al.*, 1952). (ii) Beta lipo-protein cho-

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lesterol (Kumar *et al.*, 1963). (iv) Total phospholipids (extraction by method of King and estimation by method of Tausky & Shorr 1953). (v) Total lipo-proteins and percentage of lipo-proteins alpha and beta.

Observations

Table I shows that in the group using Noracyclin mean values for total lipids, phospholipids, cholesterol and beta lipoprotein—cholesterol did not show any change during the cycles observed as compared to values in control cycle. The lipoprotein fractions show a significant change (P 0.05) in that there is a rise in beta lipo-proteins with a corresponding decline in alpha lipo-proteins. This change is noticed in the first cycle with medication and values continued at same level in subsequent cycles.

No significant changes were seen in the group using Voldys in total lipids or lipid fractions studied during the three cycles of medication (Table II).

No changes were seen in the group using Megesterol Acetate in any of the parameters studied during the three months of medication (Table III).

Discussion

The effects of the three types of oral contraceptive schedules on the major components of plasma lipids were studied for three consecutive cycles in fifteen selected subjects each. A significant change was found only in the group taking Lynestrenol (19-norsteroid compound) with 0.1 mgm. of mestranol where the beta lipo-proteins showed a rise with a corresponding decline in alpha lipo-proteins even during the first cycle of administration. No changes were demonstrable in total lipids or cholesterol levels probably because of the small doses of constituents used in these formulation. The reports in literature appear confusing and contradictory because of the extreme variations in doses, types of drugs and schedule and periods of administration. The changes in the alpha and beta lipo-proteins observed with Lynestrenol

TABLE I

Effect of Noracycline on Plasma Lipids

Parameters	Control	1st cycle	2nd cycle	3rd cycle
Total lipids mg.%	450.6 ± 50.27 (289-536)	449.7 ± 33.05 (395-525)	473.3 ± 29.17 (420-525)	470.1 ± 37.45 (440-521)
—Phospholipids mg.%	160.8 ± 24.98 (136-216)	159.8 ± 13.42 (143-190)	159.8 ± 10.63 (149-177)	162.8 ± 10.68 (145-183)
—Cholesterol mg.%	136 ± 9.91 (120-157)	137.4 ± 7.83 (120-146)	138.5 ± 4.66 (128-148)	134.4 ± 6.34 (122-144)
—beta-lipo-protein cholesterol mg.%	100.2 ± 15.06 (77-128)	102 ± 14.74 (80-128)	104.8 ± 7.13 (94-118)	100.9 ± 9.8 (89-118)
—Lipo-proteins %				
alpha	28.1 ± 7.14 (15-38)	20.1 ± 6.48 (8-29)	20 ± 5.72 (10-29)	22.4 ± 6.71 (10-31)
beta	71.9 ± 7.14 (62-85)	79.9 ± 6.48 (71-92)	80 ± 5.72 (71-90)	77.6 ± 6.71 (69-90)

TABLE II

Effect of Voldys on Plasma Lipids

Parameters	Control	1st cycle	2nd cycle	3rd cycle
Total lipids mg.%	460 ± 34.48 (420-505)	461.4 ± 33.16 (416-512)	454.3 ± 20.56 (420-501)	464.3 ± 29.1 (420-519)
—Phospholipids mg.%	162.6 ± 11.75 (145-183)	158.5 ± 6.66 (150-169)	160.5 ± 9.59 (143-174)	163.6 ± 6.13 (151-175)
—Cholesterol mg.%	142.6 ± 6.1 (128-154)	139.7 ± 7.19 (130-154)	139 ± 7.29 (121-146)	139 ± 3.17 (134-144)
—beta-lipo-protein cholesterol mg.%	103.6 ± 6.96 (92-115)	98.4 ± 10.09 (85-118)	104 ± 5.6 (92-114)	102.2 ± 8.48 (89-114)
—Lipo-proteins %				
alpha	26.7 ± 3.33 (22-35)	27.4 ± 4.32 (20-35)	26.3 ± 3.22 (20-36)	26.3 ± 5.04 (18-35)
beta	73.3 ± 3.3 (65-78)	72.6 ± 3.7 (65-80)	73.7 ± 4.18 (64-80)	73.7 ± 5.04 (65-82)

TABLE III

Effect of Megesterol Acetate on Plasma Lipids

Parameters	Control	First cycle	2nd cycle	3rd cycle
Total lipids mg.%	460.5 ± 20.51 (434-498)	471.2 ± 28.22 (434-513)	465.7 ± 14.76 (433-489)	468.7 ± 19.15 (433-499)
—Phospholipids mg.%	164.5 ± 6.80 (150-173)	163.2 ± 5.52 (150-170)	162.9 ± 6.25 (155-175)	163.1 ± 4.90 (153-172)
—Cholesterol mg.%	136.3 ± 6.09 (126-144)	137.6 ± 12.13 (125-144)	134 ± 6.09 (125-151)	135.7 ± 9.23 (126-154)
—beta-lipo-protein cholesterol mg.%	99.9 ± 9.82 (84-116)	98 ± 6.94 (89-112)	97.8 ± 8.18 (86-112)	97.7 ± 5.74 (86-107)
—Lipo-proteins %				
alpha	30.86 ± 6.76 (18-46)	30.73 ± 6.54 (18-40)	31.2 ± 5.64 (22-40)	30.3 ± 4.54 (21-38)
beta	69.13 ± 6.76 (60-82)	69.26 ± 6.59 (60-82)	68.83 ± 5.62 (60-78)	69.7 ± 4.54 (62-79)

and Mestranol combination are the result of 19-norsteroid (Lynestrenol) modifying the effect of the oestrogen (Mestranol).

The second type of combination used in this study consisted of Megesterol Acetate (17-alpha hydroxyprogesterone derivative) which in the dosage used (4 mgms) did not produce any significant changes in lipids or lipid/lipid fractions. The oestrogen used in this combination was ethinyl oestradiol in the dose of 0.05 mgm. being only half of that in the former preparation. The daily continuous "micro dose" of progestogen (Megesterol Acetate 0.5 mgm) in the third group of subjects as expected did not show any changes in lipid patterns over three

months. No significant changes were observed in mean levels of phospholipids before and during medication with all the three schedules. Triglycerides were not included in this investigation. Phospholipids and triglycerides are reported to be elevated with several types of combined oestrogen progestogen including Volidan, Ovulen and Provest (Bierman, 1969).

Elevation of serum lipids and lipo-proteins during oral contraceptive medication has been reported by several workers like Wynn *et al.*, (1966); Aurell *et al.*, (1966); Brody and co-workers (1968) and Gershberg *et al.*, (1968). The effects of oestrogens, androgens and progestogens on total lipids, cholesterol, and the three major groups of lipo-proteins, have been clearly identified by several groups of workers. The three major groups of lipo-proteins of interest are (i) beta or low density lipoproteins (LDL) carrying most of the plasma cholesterol, (ii) alpha or high density lipoproteins (HDL) carrying additional cholesterol and most of the phospholipids and (iii) prebeta or alpha two or very low density lipoproteins (VLDL) which is the triglyceride rich fraction. Total serum lipids and the major fractions vary with the menstrual cycle. During pregnancy the total cholesterol, phospholipids and triglycerides increase from the 15th—18th week Adlercouentz *et al.*, (1967). Lewis, *et al.*, (1951) observed that women have higher concentration of HDL and lower concentration of LDL than men of comparable age. Havel and co-workers (1955) similarly noted that a greater proportion of plasma lipids was transported as HDL in women. Relevant literature regarding the influence of different gonadal steroids on lipids can be summarised as follows:

Oestrogens: (i) Decrease in total cholestrol, but the change is relatively slight due to reciprocal changes in HDL and LDL fractions; (ii) change in cholesterol phospholipids ratio by increase in serum phospholipids as well as decrease in cholesterol; (iii) increase in alpha lipoproteins (HDLP) which are rich in phospholipids; (iv) increase in VLDL rich in triglycerides. These effects may be primary or related to the elevated levels of circulating thyroxine, cortisone, and growth hormones and impaired carbohydrate tolerance with raised insulin levels.

Androgens

They have a variable effect on cholesterol levels but lower triglycerides and phospholipids and have effect on lipoproteins opposite to that of oestrogens.

Progestogens

Reports are unanimous that these have little or no effect, except in case of agents metabolised to derivatives with androgenic or oestrogenic action. When used in combination with oestrogens, as in most of the oral contraceptives, the results are variable, as all combinations do not produce similar effects. Bierman, (1969) pointed out that in general, progestogens appear to neutralise the effect of oestrogens on circulating cholesterol resulting in no change in cholesterol levels but do not affect the oestrogen induced increase in phospholipids or triglycerides. Thus, the oestrogen-progestogen combination type of oral contraceptives do not affect the cholesterol rich beta or low density lipoproteins but produce marked changes in the triglyceride rich very low density lipoproteins and perhaps on the alpha or high density lipoproteins as well. The mechanism of production of increased circulating triglycerides has been attributed variously to increased

synthesis by the liver and decreased removal by the tissues due to impairment of lipoprotein lipase activity (Wynn and Doar, 1969).

It is evident from the foregoing discussion that in view of the known relationship between elevated serum lipids and lipoproteins with atherosclerosis, the risks of long term administration of the combination type of oestrogen-progestogens for contraception cannot be as yet accurately assessed. As such, if the desired efficacy and minimum clinical side effects can be obtained, either progestogens alone or progestogens with as small a dose of oestrogen as is compatible with efficacy should be the choice of medication.

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