22) Johnson J. W.: Proc. 10th International Conf. on Infertility and Sterility.
23) Oelsner G., Graebe R. A., Boyers S. P., Pan S., Barnea E. R., Cherney A. H.: *Am. J. Obst. Gyn., 154*, 569, 1986.
24) Jones H. W., Rock J. A.: Reparative and Constructive Surgery of the Female Generative Tract. Baltimore, Williams & Williams, 1983, 120.
25) Boeckx W., Gordts S., Vasquez G., Brosens I.: *Int. Surg., 66*, 47, 1981.
26) Candiani G. B., Fedele L., Zamberletti D., Vercellini P.: Scritti in onore del Prof. N. Vaglio, Monduzzi editore, Bologna, 1984.
27) Cittadini E., Quartararo P. *et al.*, in: « Fertilità e Sterilità». Atti IV Corso di Aggiornamento. Firenze 1977, COFESE Ed., Palermo, 1978.
28) Candiani G. B., in: «Fertilità e Sterilità». Atti del VI Corso di Aggiornamento. Firenze 1981, COFESE Ed., Palermo.

ADVANTAGE OF DESOGESTREL CONTAINING PILL IN ORAL CONTRACEPTION: INFLUENCE ON BLOOD LIPIDS AND LCAT ACTIVITY

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Summary: In the present study the effects of a combined oral contraceptive preparation containing 0.150 mg desogestrel and 0.030 mg ethinylestradiol on lipid metabolism were investigated.

In particular, we observed significant increase in HDL-cholesterol and apolipoprotein-A-I (apo A-I) and B (apo B). Triglycerides were not significantly modified. The cholesterol esterifying enzyme LCAT, assayed under "maximal" conditions against an exogenous substrate, was significantly decreased despite an increase in the physiological stimulator apo A-I. No changes were observed in the anti-atherogenic indexes apo A-I/apo B and HDL-cholesterol/LDL-cholesterol.

Thus, it appears that this combined oral contraceptive has the promising ability to increase the anti-atherogenic HDL-cholesterol particle without altering the atherogenic LDL-cholesterol.

Key words: oral contraceptives, desogestrel, HDL-cholesterol, LCAT.

INTRODUCTION

Relationships between blood lipids (and lipoproteins) and cardiovascular diseases (CVD) have been thoroughly investigated; in particular, an inverse relationship exists between HDL-cholesterol and the frequency of CVD ([1-5]). In addition the apolipoproteins (apo A-I and apo B) are considered as better discriminators for CVD ([3]).

In this respect the influence of sex steroids on blood lipids has been extensively investigated in women: this interest stems from the increased use of steroid based oral contraception and of the effects of hormones on lipid metabolism linked to cardiovascular disease.

A number of studies have demonstrated that estrogens and progestagens have op-

posite effects on total cholesterol and, most important, on the HDL-cholesterol, which is increased by estrogens and decreased by synthetic progestagenic compounds of the 19-norsteroid type ([6, 8]). Recently, a new progestagenic compound (desogestrel) has been introduced in clinical practice: this molecule has proved a potent progestagen, devoid of androgenic effects ([9, 10]). Data on the metabolic effects of 0.150 mg desogestrel (in combination with 0.030 mg ethinylestradiol) are conflicting, especially the data concerning the effects on HDL-cholesterol ([11-18]). For this reason we decided to investigate the properties of this OC combination on blood lipid metabolism including the assessment of LCAT activity (lecithin cholesterol acyl transferase).

MATERIAL AND METHODS

Tablets containing 0.150 mg desogestrel (17-ethinyl-18-methylene-4-estrene-17-ol) plus 0.030 mg ethinylestradiol were administered orally. We selected for this study 10 healthy women, aged 28-30 who had not been using oral contraceptives before this investigation and had no distory of hepatic or thromboembolic disease. Their informed consent was obtained. The subjects started treatment on the first day of menstruation. Every treatment cycle consists of 21 days of tablet intake and a 7-day pill-free period. The study lasted 3 cycles.

Blood samples were drawn in the morning after an overnight fast (12 h) during the secretory phase of the cycle (day 19-25) before starting therapy and after 3 months treatment. Serum samples were frozen and stored at −30 °C until analysis was performed. Serum levels of lipids and apolipoproteins were determined by established spectrophotometric and immunological procedures as described previously ([19]). The LCAT activity was determined as described by Alcindor ([20]), by measuring esterification of exogenous tritiated cholesterol, after delipidation of test-serum in the presence of Intralipide (Kabivitrum AB, Stockholm).

Statistical analysis was done using the paired Wilcoxon test.

RESULTS

In table 1 the mean value of the individual assays performed before and after treatment presented. Slight (non-significant) elevations are observed in the concentration of total cholesterol and VLDL-cholesterol. LDL-cholesterol was not altered during treatment, while HDL-cholesterol was significantly elevated. The triglycerides are increased but this is not significantly elevated. On the contrary, the main lipoproteins of HDL and LDL, apo A-I and apo B respectively, are both significantly increased during treatment. The mean levels of unesterified cholesterol, esterifield cholesterol and LCAT activity are presented in table 2. The values demonstrate a significant rise in esterified cholesterol and a significant decrease in the activity of the enzyme measured against an exogenous substrate.

Table 1. — *Comparison of blood lipids before and after three months of administration of a desogestrel containing pill.*

Parameters	Mean ± SD		Probability
	before	after	
Total cholesterol (mg/dl)	160±22	177±37	N.S.
HDL-chol (mg/dl)	45±11	51±10	$p<0.002$
LDL-chol (mg/dl)	99±25	104±39	N.S.
VLDL-chol (mg/dl)	17±5	21±6	N.S.
Triglycerides (mg/dl)	87±26	104±31	N.S.
Apo A-I (g/l)	2.70±0.42	3.25±0.47	$p<0.01$
Apo B (g/l)	0.80±0.18	0.98±0.30	$p<0.05$
Apo A-I/ Apo B	3.48±0.65	3.53±0.89	N.S.
HDL-chol/ LDL-chol	0.49±0.20	0.56±0.25	$p<0.05$

The significance of the difference between values before and after treatment was assessed by paired Wilcoxon test. N.S. = not significant.

DISCUSSION

The change from high to low estrogenic oral contraceptives has led to a decreased frequency of venous but not of arterial

Table 2. — *Influence of a desogestrel containing pill on fractional distribution and lecithin-cholesterol acyl transferase (LCAT).*

Parameters	Mean ± SD		Probability
	before	after	
Esterified cholesterol (mg/dl)	92±30	113±37	$p<0.05$
Free cholesterol (mg/dl)	61±13	64±5	N.S.
LCAT activity	4.9±2.0	3.3±1.1	$p<0.05$

The significance of the difference between values before and after treatment was assessed by paired Wilcoxon test. N.S. = not significant.

thrombotic accidents ([21]). In addition, there is evidence that proper composition of the pill can minimize the detrimental changes of lipid metabolism induced by sex steroid hormones ([22, 23]). The prominent alteration in lipid metabolism during contraception with a low estrogen pill is a decrease of HDL-cholesterol. This effect is due to the type and dose of the progestagen in the O.C. Estrogens are known to increase HDL-cholesterol ([7, 8, 22]), while progestagens with androgenic properties induce a decrease.

This observation led to the development of a new synthetic contraceptive progestagen with high progestogenic activity and low androgenic activity ([9, 10]), because the influence on HDL-metabolism is thought to be due to the intrinsic androgenicity of the progestagen. The active metabolite of desogestrel possesses a low androgenic activity, compared to other progestagens ([14]).

Contrasting results of the effects of this drug in combination with EE on lipid metabolism have already been reported ([11-18]). In this study we have extended the knowledge in this field by describing the effect on the activity of LCAT, a key-enzyme in the interconversions of circulating cholesterol ([24]).

The oral contraceptive combination 0.150 mg desogestrel plus 0.030 mg ethinylestradiol, leads to significantly increased levels in HDL-cholesterol, without significant changes in total cholesterol, LDL-cholesterol, VLDL-cholesterol and triglycerides. Furthermore, we observed significant increases in apolipoproteins A-I (apo A-I) and B (apo B). In particular, we observed parallel increase in both HDL-cholesterol and apo A-I the major protein of HDL. These effects may be due to the estrogenic component of the pill, since estrogens are known to increase the synthesis of apo A-I ([22, 25]). On the contrary, with regard to low density lipoproteins we observed increases in apo B without a significant change in LDL-cholesterol. The increase in apo-B is therefore probably due to an increase in apo-B from VLDL. Since VLDL synthesis and thus apo B of VLDL is under estrogenic regulation ([26]), even this effect could be due to the estrogenic component of the pill. In this study an increase in triglycerides is found; this was not significant due to large individual variations.

Thus, the administration of this oral contraceptive containing desogestrel has the main effect of altering lipoprotein metabolism by directing cholesterol to the non-atherogenic HDL-function, and confirms the results of previous studies ([13, 14, 16-18, 27]).

In the present study the effect of the combination on LCAT activity is rather surprising. This enzyme is biochemically strictly related to the esterification of HDL-cholesterol and thus to the transfer of the apolar cholesteryl ester to the inside of the lipoprotein particle ([24]). The *in vitro* measured activity of the enzyme LCAT was consistently decreased upon treatment, while the concentration of esterified cholesterol (the product of the enzyme) is increased *in vivo*. This discrepancy can either be explained on the basis of the increased level of the physiological activa-

tor Apo-A or, alternatively, as the results of further derangement of cholesterol ester turnover rate or volume of distribution. The decrease in maximal *in vitro* activity of the enzyme is likely to depend on a decreased number of circulating LCAT molecules, either because of an increased instability of the enzyme following therapy or a decreased secretion by the liver. It is noteworthy that similar devergence between *in vivo* and *in vitro* LCAT activity has already been reported ([28]).

In conclusion, because of the clear effects on blood lipid metabolism, our results confirm the advantage of therapy with a combined pill containing desogestrel over that containing levonorgestrel. However, further studies are needed to better clarify the modifications in key enzymes of lipid metabolism by combined oral controceptives.

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BIBLIOGRAPHY

1) Castelli W. P., Doyle J. T., Gordon T. *et al.*: *Circulation, 55*, 767, 1977.
2) Ishikawa T., Fidge N., Thelle D. S., Forde O. H., Miller N. E.: *Eur. J. Clin. Invest., 8*, 179, 1978.
3) Maciejko J. J., Holmen D. R., Kottke B. A., Zinsmeister A. R., Dinh D. M., Mao S. J. T.: *N. Engl. J. Med., 309*, 385, 1983.
4) Miller G. J., Miller N. E.: *Lancet, 1*, 16, 1975.
5) Gordon T., Castelli W. P., Hjortland M. C., Kamel W. B., Dawbeer T. R.: *Am. J. Med., 62*, 707, 1977.
6) Oster P., Arab L., Kohlmeier M., Mordasini R., Schellenberger B., Schlierf G.: *Am. J. Obst. Gyn., 142*, 773, 1982.
7) Knopp R. H., Walden C. E., Wahl P. W., Hoower J. J.: *Am. J. Obst. Gyn., 142*, 725, 1982.
8) Wynn V., Niththyanthan R.: *Am. J. Obst. Gyn., 142*, 766, 1982.
9) Cullberg G., Eriksson O., Knutsson F., Steffensen K.: *Acta Obst. Gyn. Scand.*, supp. III, 13, 1982.
10) De Jager E.: *Contracept. Deliv. Syst., 3*, 11, 1982.
11) Briggs M. H. in: "Symposium: New considerations in oral contraception". New York. Biomedical Information Corporation, 1981.
12) Cullberg G., Samsioe G., Andersen R. F. *et al.*: *Contraception, 26*, 229, 1982.
13) Samsioe G.: *Contraception, 25*, 487, 1982.
14) Bergink E. W., Borglin N. E., Klottrup P., Linklo P.: *Contraception, 25*, 477, 1982.
15) Briggs M. H., Briggs M.: Amsterdam Excerpta Medica, 22, 1983.
16) Wiseman A., Bowie J., Cogswell D.: *Marvelon. Br. J. Family Planning, 10*, 38, 1984.
17) Bergink E. W., Kloosterboer H. J., Lund L., Nummi S.: *Contraception, 30*, 61, 1984.
18) Crona N., Silfver G., Samsioe G.: *Contraception, 29*, 261, 1984.
19) Pansini F., Bergamini C., Bettocchi S. jr., Bassi P., Malfaccini M., Bagni B., Mollica G.: *Gyn. Obst. Invest., 18*, 134, 1984.
20) Alcindor L. G., Dusser A., Piot M. C., Infante R., Polomovski J.: *Scand. J. Clin. Lab. Invest., 38*, suppl. 150, 12, 1978.
21) Bottiger L. E., Boman G., Eklund G., Westerholm B.: *Lancet, 1*, 1097, 1980.
22) Patsch W., Kim K., Wiest W., Schonfeld G.: *Endocrinology, 107*, 1085, 1980.
23) Larsson-Cohn U., Fahraens L., Wallentin L., Zador G.: *Fertil. Steril., 35*, 172, 1981.
24) Frohlich J., McLeod R., Hon K.: *Clin. Biochem., 15*, 269, 1982.
25) Lin C. T., Chan L.: *Endocrinology, 107*, 70, 1980.
26) Capony F., Williams D. L.: *Endocrinology, 108*, 1862, 1981.
27) Gaspard U. J., in: "Advances in Fertility Control and the Treatment of Sterility". Special Symp. at XI World Congress on Fertility and Sterility, Dublin, R. Rolland ed., p. 81, 1983.
28) Ordovas J. M., Pocovì M., Grande F.: *Obst. Gyn., 63*, 20, 1984.