The clinical and biochemical effects of two combination oral contraceptive agents

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Summary

A comparison of the effects of two low-dose oral contraceptives on lipid metabolism was undertaken in an open-group comparative design study at the Family Planning Clinic, Groote Schuur Hospital, Cape Town. Sixty healthy women aged 18 - 35 years requesting oral contraception were allocated alternately to use a monophasic oral contraceptive containing 30 μg ethinyloestradiol and 150 μg desogestrel (Marvelon, group A), or a triphasic oral contraceptive containing 30 - 40 μg ethinyloestradiol and 50 - 125 μg levonorgestrel (Triphasil, group B). The changes in the lipoprotein profile elicited by the two preparations differed significantly. Group A subjects had a much greater triglyceridaemic response (42,4%) than group B (14,6%) and had a significant increase in high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-1 (Apo-A1). In group B, HDL-C decreased and Apo-A1 showed little change. Non-HDL-C (NHDL-C) and Apo-B levels hardly changed in either group. The atherogenic ratios, NHDL-C/HDL-C and Apo-B/Apo-A1 were higher in group B.

This study confirmed a significant difference in the response of plasma lipoproteins to the two oral contraceptive preparations. The evidence suggests that the desogestrel-containing oral contraceptive elicits a less atherogenic lipoprotein profile than does the levonorgestrel-containing preparation. Although unsupported by direct clinical evidence that changes in the lipoprotein pattern induced by oral contraceptives cause atherosclerosis, these effects should be considered when prescribing oral contraceptives for women who have risk factors for cardiovascular disease.

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The adverse cardiovascular effects of oral contraceptives have been well documented.[1,2] These are probably mediated through changes in the plasma lipoprotein profile,[3-5] in the blood coagulation[6] and fibrinolytic systems,[7] and through effects on blood pressure[8] and carbohydrate metabolism.[9] The risk of coronary artery disease is exacerbated by smoking, especially in women over the age of 35 years.[10]

Steroid-induced changes in plasma lipoprotein transport have received considerable attention due to the established role of lipoproteins in atherogenesis and as a risk factor for coronary artery disease.[11] Oral contraceptive preparations containing 50 μg ethinyloestradiol are associated with a significantly increased risk of thrombo-embolic events, hypertension, weight gain and with hyperinsulinism and impaired glucose tolerance.[12] Oestrogens also enhance plasma triglyceride and high-density lipoprotein cholesterol (HDL-C) levels, more specifically the HDL_2 subfraction; the latter effect is seen as beneficial. Low-dose preparations containing 30 - 35 μg ethinyloestradiol are associated with a significant reduction in the adverse oestrogenic effects[13,14] and may even be beneficial in certain categories of women as far as coronary artery disease is concerned.[15]

It has become apparent that the progestogen in oral contraceptives potentiates some of the adverse actions of oestrogens and may counteract the beneficial effects.[16] Progestogens have androgenic as well as progestational properties and, in addition, may possess anti-androgenic and anti-oestrogenic actions. The effects of any combined oral contraceptive preparation will therefore depend on the nature and relative biological activity of the oestrogen and progestogen used, as well as the absolute dose, and the characteristics of the recipient.[17] In this connection, the increased risk of coronary artery disease associated with oral contraceptive use is mainly, although not entirely, confined to women over the age of 35 years, and especially current smokers.[10] In developing new oral contraceptives attention has been directed towards minimising risks by dose reduction, and by modification of the progestogen component, while maintaining contraceptive efficacy.

In this study a monophasic oral contraceptive preparation (A) (Marvelon; Donmed) containing 30 μg ethinyloestradiol and 150 μg desogestrel was compared with a triphasic preparation (B) (Triphasil; Akromed) containing ethinyloestradiol 30 - 40 μg and levonorgestrel 50 - 125 μg in two groups of women. Both preparations contain low-dose ethinyloestradiol and differ primarily in the amount and nature of the progestogen.

Subjects and methods

This was an open group-comparative study involving 62 healthy women who requested oral contraceptives, and gave informed consent for this clinical study. They were alternately allocated to group A (the monophasic preparation) or group B (the triphasic preparation), except that current cigarette smokers (5 in each group) were allocated to each group alternately in equal numbers. Only the research sister knew which oral contraceptive constituted group A or B until the data were computerised.

The study period lasted 4 months and included 2 visits in the pre-treatment month and 3 follow-up visits between day 18 and day 21 of the treatment cycles 1, 2 and 3. At each visit, blood was collected after a 12-hour fast. Tablets were checked at each visit to ensure compliance, and subjects were reminded to continue on their normal diet and other lifestyles.

All women selected were between 18 years and 35 years of age, were normolipidaemic, and were healthy on routine questioning and clinical examination. None took any hormonal preparation or other medication in the 2 months before inclusion in the study or during the trial itself, except for the prescribed oral contraceptive. Standard contraindications to oral contraceptives were applied. In addition, women with an intake of more than 2 glasses of alcohol per day and also those weighing over 80 kg or following a diet, and those who were less than 3 months postpartum or post-abortion, were excluded.

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TABLE I. PRETREATMENT CLINICAL AND BIOCHEMICAL FEATURES OF GROUPS A AND B (MEAN±SD)

Group (*N*)	Age (yrs)	BMI	CHOL	HDL-C	NHDL-C	Triglycerides	Apo-A1	Apo-B
A (30)	**22,6 ± 3,10**	**23,2 ± 3,2**	**4,43 ± 0,64**	**1,59 ± 0,28**	**2,84 ± 0,65**	**0,64 ± 0,23**	**149 ± 22,0**	**80,2 ± 18,0**
B (30)	**22,0 ± 4,40**	**22,0 ± 2,9**	**4,30 ± 0,70**	**1,46 ± 0,24**	**2,84 ± 0,70**	**0,69 ± 0,18**	**141 ± 22,8**	**78,2 ± 22,6**

Lipid and apolipoprotein values represent the mean of the first 2 visits.

The two groups were similar in age, body mass index, as well as in dietary, smoking and alcohol consumption habits. The basal lipid and apolipoprotein values of the two groups were comparable (Table I).

Laboratory investigations

Blood was taken without venestasis, placed in tubes containing ethylenediaminetetra-acetic acid and centrifuged within 1 hour at 4° to separate cells from plasma. Lipid assay was performed immediately or within 4 days. Apolipoprotein assay was batched and carried out on samples stored at −70°C for less than 3 months.

Total plasma cholesterol was estimated enzymatically using a commercial kit (Boehringer-Mannheim CHOD-PAP High Performance kit) and triglyceride was similarly determined (Clinical Colorimetric Enzymatic Method, Carlo Erba, Milan). HDL-C was measured after precipitation of the low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) by means of heparin-manganese according to the Lipid Research Clinics protocol.[18] VLDL-C plus LDL-C levels were estimated by subtracting HDL-C from total plasma cholesterol. This product, termed non-HDL-cholesterol (NHDL-C), represents the cholesterol associated with the two atherogenic apo B-containing fractions. Apolipoprotein A-1 (Apo-A1) was determined by rate nephelometry on a Beckman ICS system according to the method of Weinstock *et al.*[19] and Apo-B by an immuno-electrophoretic (rocket) procedure.[20]

Statistical analysis

Within-group comparisons of basal values with levels achieved in the course of oral contraceptive therapy were made by a procedure that is essentially a paired test, with allowance being made for the co-variates age and smoking. Between-group comparisons were made by two sample tests, that is ANOVA, again with allowance for co-variates. The statistical methods were implemented by means of the general linear model procedure of Statistical Analysis System.[21] All ANOVA and regression procedures were performed on actual observed changes. In some summaries percentage change values are shown so as to facilitate interpretation. One patient from each of the two groups dropped out of the trial after the 4th visit for personal reasons. They were omitted from the statistical analysis, which was thus performed on 30 individuals in each group.

Results

The percentage change in plasma lipid and apolipoprotein levels in the two groups is illustrated in Fig. 1. The effects of the two oral contraceptives differed strikingly in the direction of the HDL fraction change as well as in the extent of the hypertriglyceridaemic response.

Preparation A elicited a significant increase in both HDL-C (7,9%) and Apo-A1 (13%) whereas preparation B caused a

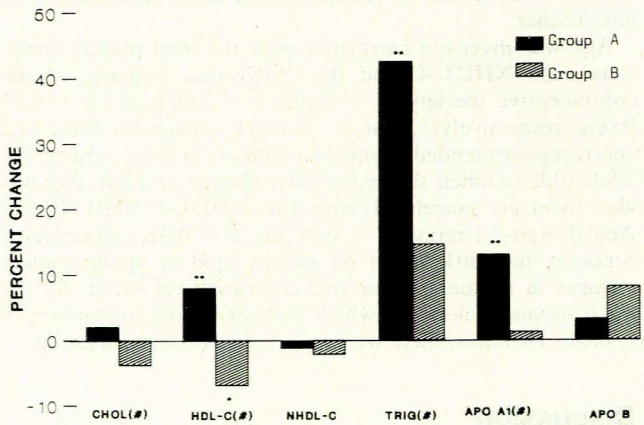

Fig. 1. Changes in plasma lipid and apolipoprotein levels in response to oral contraceptives A and B.

6,9% fall in HDL-C without significantly affecting Apo-A1 levels. The responses of the two groups were significantly different from one another at $P = 0{,}001$ and $P = 0{,}003$ for HDL-C and Apo-A1, respectively. Both preparations A and B elicited an increase in plasma triglyceride levels. Group A subjects showed a 42,4% rise whereas triglyceride levels rose by 14,6% in group B subjects. The triglyceridaemic responses of the two groups differed significantly ($P = 0{,}0003$) from one another.

In contrast to the striking changes in HDL and triglyceride concentrations, total plasma cholesterol and NHDL-C levels altered relatively little. Both groups showed a small, non-significant fall in NHDL-C concentration whereas group A showed a slight rise (2,1%) and group B a slight fall (−3,8%) in total plasma cholesterol, presumably reflecting changes in the HDL-C values. Apo-B rose by 3,7% and 8,1% in groups A and B, respectively, but these changes also did not achieve statistical significance, and the two groups did not differ significantly from one another.

The ratio of NHDL-C/HDL-C and Apo-B/Apo-A1 may be taken as a reflection of atherogenic potential. These ratios were reduced by 8,7% ($P = 0{,}04$) and 10,4% (non-significant)

TABLE II. CHANGES IN LIPOPROTEIN COMPOSITION AND LIPOPROTEIN RATIOS IN RESPONSE TO ORAL CONTRACEPTIVES A AND B

Group	NHDL-C*** / HDL-C	Apo-B / Apo-A1	Apo-B / NHDL-C	Apo-A / HDL-C
A	**−8,7**	**−10,4**	**4,1**	**5,1***
B	**+3,5**	**+5,9**	**10,9***	**8,7****

*$P < 0{,}05$.
**$P < 0{,}001$.
*** Significant difference between groups ($P < 0{,}05$).