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Effect of oral contraceptives on serum apoprotein levels

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Abstract

The effect of oral contraceptives on serum lipoprotein concentrations, as assessed by their cholesterol content, is determined by the doses of estrogen and progestogen and the type of progestogen they contain. Assay of the apoprotein content, instead of cholesterol content, measures a different aspect of lipoprotein metabolism. Changes in serum concentrations of apoproteins A and B in women using oral contraceptives are similar to those obtained by measuring low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol.

Administration of estrogens or progestogens alone or in combination is known to affect the serum concentration of lipids. For the oral contraceptives (OCs), the magnitude of the effect depends on the dose and the nature of the estrogen and progestogen in the OC, as illustrated by the summary in Table 1 for four widely used OCs.

Table 1 Effect of oral contraceptives on low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C)

	LDL-C	*HDL-C*	*HDL-C/LDL-C*
EE30/LNG150	0+	0−	0−
Triphasic (EE + LNG)	0	0	0
EE30/DSG150	0	0+	+
EE35/NET1000	0+	0−	0−

EE = ethinyl estradiol; LNG = levonorgestrel; DSG = desogestrel; NET = norethisterone
All doses in μg
0 = no change; − = decrease; + = increase

These changes in lipids with OC use have assumed greater importance during the past few years, partly as a result of improvements in methodology that now

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permit the ready assessment of the levels of the major lipids, and particularly as the result of a large number of epidemiologic studies which have shown that the risk of developing cardiovascular disease is related to the blood lipid levels. Particular attention has been paid to HDL-C, since the epidemiologic studies and also a large number of investigative studies [1] have revealed an inverse correlation between the serum levels of HDL-C and the risk of developing cardiovascular disease. The major lipoprotein fractions, however, are heterogeneous, containing a number of subfractions, and are also in a state of constant change. In addition, measurements of HDL-C may be misleading since cholesterol accounts for only

Table 2 Composition of low density (LDL) and high density (HDL) lipoproteins

	LDL	*HDL*
Lipid content	75	48
Cholesterol	47	15
Protein content	25	50
Apoproteins	B (74%)	A-I (46%) A-II (23%)

Values for lipid, cholesterol and protein content are % of total mass
Values for apoproteins are % of protein content

about 15% (range 10–20%) of the HDL molecule (Table 2). Because of this, measurement of the protein part of the molecule, the apoprotein, may be more informative.

Although LDL and HDL contain a number of different apoproteins, both contain single apoproteins as the main constituent (Table 2). Apoprotein B accounts for about 20% of the molecule of LDL, and for HDL apoprotein A accounts for about 35%. Thus the apoproteins, particularly HDL, should provide a more reliable index of changes in the metabolism of the lipoproteins than estimation of lipoprotein cholesterol. A large number of reports have appeared which support this conclusion, and apoprotein levels may be a better indicator of subjects at risk of developing cardiovascular disease [2].

As in the case of the lipoproteins where the ratio of HDL-C to LDL-C may be a better indicator than the lipoprotein alone, the ratio of apoprotein A to apoprotein B may be an improvement over the measurement of the apoproteins alone. In a study of subjects with angiographically defined coronary artery disease, the ratio of A-1 to B gave a successful prediction rate greater than 80% [3]. Apoprotein A-1 levels increased more than those of HDL-C on estrogen administration [4] and the difference in apoprotein A-1 concentrations between women using OCs and control subjects was greater than the difference in HDL-C levels [5]. In view of these considerations the effect of OCs or apoprotein concentrations is important.

Information concerning the effect of different OC formulations provides some interesting conclusions. The formulations for which results have been published [6] are shown in Figure 1, which depicts the number of published studies reporting

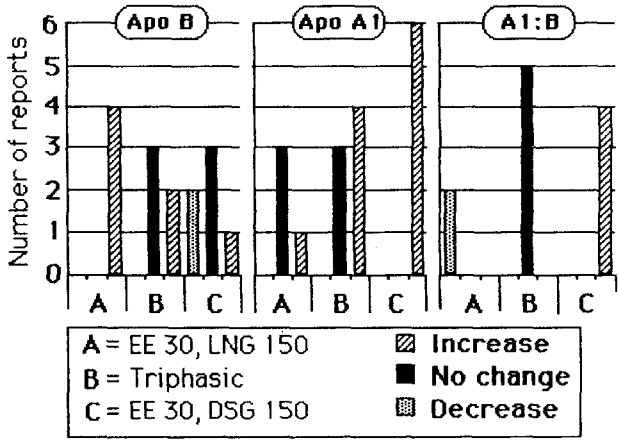

Figure 1 Number of published studies showing a decrease (▒), increase (▨) or no change (■) in serum apoprotein A-1 and B concentrations in women using oral contraceptives; A = EE 30 μg, LNG 150 μg; B = EE-LNG triphasic; C = EE 30 μg, desogestrel 150 μg

an increase, decrease or no change in the levels of the apoproteins in women using these formulations. For a number of reasons the quantitative aspects of the changes are not considered. The summary clearly shows that ethinyl estradiol 30 μg – levonorgestrel 150 μg (EE30/LNG150) increases apoprotein B without change in apoprotein A-1, and a consequent decrease in the A-1/B ratio. The triphasic formulation of EE and LNG has less effect in increasing apoprotein B and may slightly increase apoprotein A-1, but not sufficiently to produce a change in the A-1/B ratio. Ethinyl estradiol 30 μg – desogestrel 150 μg (EE30/DSG150) produces no change in apoprotein B but increases apoprotein A-1, leading to an increase in the ratio.

For comparison, Figure 2 shows information for LDL-C and HDL-C treated in

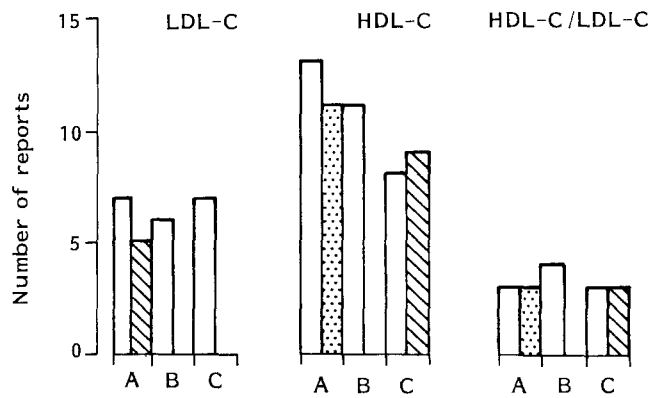

Figure 2 Number of published studies showing a decrease (▒), increase (▨) or no change (□) in serum LDL-C and HDL-C concentrations in women using oral contraceptives; A = EE 30 μg, LNG 150 μg; B = EE-LNG triphasic; C = EE 30 μg, desogestrel 150 μg

a similar way. EE30/LNG150 tends to increase LDL-C and to decrease HDL-C and the HDL-C/LDL-C ratio. Neither the triphasic nor desogestrel formulation alter LDL-C, but whereas the former does not change HDL-C levels, and therefore the ratio, the desogestrel formulation increases HDL-C levels with an increased HDL-C/LDL-C ratio. These changes are therefore in agreement with those observed in the apoproteins.

There appear to be only four reports regarding the effect of these formulations on HDL_2-C. HDL_2-C accounts for only about 30% of the cholesterol carried by HDL; the variation between subjects is wide (10–40%) so caution is necessary when interpreting the results. Preliminary studies suggest, however, that EE30/LNG150 decreases HDL_2-C levels whereas the triphasic and desogestrel formulations have no effect.

In prescribing OCs, clinicians seek those which produce an adequate contraceptive effect, minimal disturbance of the menstrual pattern, and no marked metabolic changes. Extrapolating (a) the epidemiologic findings of a direct correlation of the levels of LDL-C and aproprotein B, and (b) an inverse correlation of the levels of HDL-C and aproprotein A with the risk of developing cardiovascular disease to the changes produced in women using oral contraceptives, it appears that of the OCs considered above, the desogestrel formulation is the only one which produces beneficial changes in the lipoproteins.

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Resumé

L'effet des contraceptifs oraux sur les concentrations de sérum lipoprotéique, déterminé par la teneur en cholestérol, est fonction des doses d'oestrogènes et de progestogènes et du type de progestogènes qu'elles contiennent. L'évaluation chimique de la teneur apoprotéique,

et non pas de la teneur en cholestérol, permet de mesurer un aspect différent du métabolisme lipoprotéique. Les changements de concentration du sérum d'apoprotéines A et B chez les femmes qui utilisent des contraceptifs oraux sont du même ordre que ceux obtenus par la mesure du cholestérol à faible densité en lipoprotéines et à forte densité en lipoprotéines.

Resumen

El efecto de los anticonceptivos orales en concentraciones de lipoproteínas séricas, evaluados por su contenido en colesterol, es determinado por las dosis de estrógeno y progestágeno y el tipo de progestágeno que contienen. El análisis del contenido de apropoteína, en vex del contenido de colesterol, mide diferentes aspectos del metabolismo de las lipoproteínas. Los cambios en las concentraciones séricas de apoproteínas A y B en mujeres usando anticonceptivos orales, son similares a aquellas obtenidas midiendo el LDL y el HDL-colesterol.