Effects of Low Dose Oral Contraceptives on Very Low Density and Low Density Lipoprotein Metabolism

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Abstract

Oral contraceptives (OC) raise plasma triglyceride and VLDL levels, which may be of concern, since some conditions characterized by elevated triglycerides are associated with atherosclerosis. To identify the responsible mechanism, we studied 11 healthy premenopausal women, 5 of whom were taking OC containing 0.035 mg ethinyl estradiol, and 6 of whom were not. Their rates of VLDL and LDL metabolism were measured by endogenously labeling apoB, the protein component of VLDL and LDL, by an intravenous infusion of deuterated leucine. OC use had the greatest effect on the large, triglyceride-rich VLDL subfraction (Sf 60–400), increasing plasma levels threefold and production rates fivefold ($P < 0.05$). Among OC users, small VLDL (Sf 20–60) levels were 2.2 times higher, and production rates were 3.4-fold higher ($P < 0.05$). The fractional catabolic rates of large and small VLDL were similar among OC users and nonusers. LDL levels and metabolic rates were not significantly different between the two groups. Thus, contemporary low dose OC substantially raise VLDL levels by increasing the production rate of large, triglyceride-rich VLDL, and not by slowing VLDL catabolism. Since VLDL catabolism is not impaired, we speculate that the hypertriglyceridemia induced by OC may be less atherogenic than that of hypertriglyceridemia resulting from impaired lipolysis. This may explain why long-term OC use does not appear to promote atherosclerosis. (*J. Clin. Invest.* 1993. 91:2126–2132.) Key words: estrogen • cholesterol • triglyceride • apolipoprotein B • hormones

Introduction

Women who use oral contraceptives (OC)[1] have higher levels of plasma triglycerides, the majority of which are carried by VLDL. The estrogen component of OC is believed to be responsible for this effect, and appears to raise triglyceride levels in a dose-dependent manner (1). This increase in triglycerides may be of concern, since some conditions characterized by elevated

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1. *Abbreviations used in this paper:* D_3, trideuterated leucine; FCR, fractional catabolic rate; OC, oral contraceptives; Sf, Svedberg units of flotation.

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triglycerides are associated with atherosclerosis (2). However, the development of atherosclerosis may not be due to the elevated triglycerides per se, but may depend upon the nature of the primary metabolic derangement which caused the high triglyceride levels to occur. For instance, hypertriglyceridemia resulting from increased VLDL synthesis may be less harmful than that resulting from impaired VLDL catabolism. This is supported by the observations that postmenopausal estrogen replacement (3), moderate alcohol consumption (4), and cholestyramine, a bile acid sequestering resin (5), all of which raise triglycerides by increasing VLDL synthesis, have not been found to promote atherosclerosis and in fact appear to lower the risk of coronary heart disease (6–8). In contrast, endogenous hypertriglyceridemia, in which VLDL levels rise principally due to impaired catabolism of VLDL (9), has been associated with cardiovascular disease (10). The lipoprotein abnormalities that result from impaired VLDL catabolism may be the factors which are atherogenic, such as the cholesterol ester enrichment of VLDL, or the reduced levels of HDL.

Since millions of women currently use OC it is important to delineate the metabolic alterations responsible for the elevation of triglycerides. Prior work evaluated very high dose OC which are uncommonly used today; one study found OC to both increase triglyceride synthesis as well as impair triglyceride clearance (11), whereas another study found OC to increase VLDL apoB production only (12). Furthermore, these studies did not evaluate the effect of OC on different subpopulations of VLDL particles, which may be important, since VLDL consists of a heterogenous spectrum of particles with varying triglyceride content and, perhaps, different atherogenicity (13, 14). There has been no work evaluating the effect of OC on LDL metabolism. We therefore studied the metabolism of individual VLDL subfractions and of LDL in nonusers and users of contemporary low dose OC's, to identify the mechanisms by which OC use raises plasma VLDL and triglyceride levels. The rates of VLDL and LDL synthesis and catabolism were measured by endogenous labeling of their primary protein component, apoB, with a nonradioactive amino acid tracer, trideuterated leucine (D_3-leucine).

Methods

Subjects. 11 healthy premenopausal women, ages 22–27, were enrolled into this study. Nine were dieticians, and two were research associates. The first six subjects (three OC users, and three nonusers) had been randomly selected to participate in a pilot study of lipoprotein metabolism. After marked differences in VLDL metabolism were noted between the OC users and nonusers, an additional five subjects (two OC users and three nonusers) were recruited to complete the final study group. The five OC users had all taken oral contraceptives containing 0.035 mg ethinyl estradiol for more than 1 y. Four of the five OC users took oral contraceptives containing norethindrone, given as 1 mg daily for 21 d (Ortho-Novum 1/35; Ortho Pharmaceutical Corp., Raritan,

NJ) for subjects 1 and 4; or given as 0.5 mg, 0.75 mg, and 1.0 mg given sequentially for 7 d each (Ortho-Novum 777; Ortho Pharmaceutical) for subjects 2 and 3. The fifth OC user took an OC containing ethyno-diol diacetate, given as 1 mg daily for 21 d (Demulen; Searle Pharmaceuticals Inc., Skokie, IL) for subject 5. The other six subjects (6–11) were not taking OC and had regular menstrual cycles. No subjects used any other prescription drugs or tobacco, nor consumed more than 15 g of ethanol daily. The composition of their usual diet was analyzed by a semiquantitative food frequency questionnaire (15). Subjects recorded the duration of exercise performed over one month's time. Subjects gave informed consent, and the study was approved by the Committee for the Protection of Human Subjects at Brigham and Women's Hospital. All 11 subjects completed the entire study.

Protocol. The subjects were admitted to the Clinical Research Center at Brigham and Women's Hospital, after a 12-h overnight fast. The metabolism of VLDL subfractions and of LDL was studied once in all 11 subjects. The first six subjects were studied twice 28 d apart, to determine measurement reproducibility: LDL and unfractionated VLDL metabolic rates were measured during the first admission, and LDL and VLDL subfractions were measured during the second admission. They maintained their usual diet and exercise patterns between admissions. They recorded all foods eaten during the 24 h before the first admission and replicated this diet the day before the second admission. OC users were studied during the same day of their monthly oral contraceptive cycle; nonusers, during the same day of their natural menstrual cycle. The subsequent five subjects were admitted only once.

During each admission, the metabolism of LDL and VLDL was evaluated by endogenously labeling their primary protein component, apoB, by a constant 16-h intravenous infusion of a nonradioactive isotope, trideuterated leucine (L-leucine, 5,5,5-d_3; Tracer Technologies, Cambridge, MA), delivered at a rate of 4.7 μmol/kg per h after a priming dose of 4.2 μmol/kg. This rapidly achieved and maintained the plasma leucine enrichment at ~4.5% (Fig. 1). D_3-leucine is incorporated by the liver into apoB, which is assembled into VLDL and secreted into the circulation; as VLDL is converted into LDL, the label appears in LDL apoB (Fig. 1). Blood specimens were obtained through a second intravenous catheter in the contralateral arm every 15 minutes for the first 2 h, and hourly thereafter. For the first 4 h, subjects were restricted to noncaloric and noncaffeinated fluids. This was followed by a standardized fat-free and leucine-free diet containing 60% of the total daily calories required for maintenance, served as lunch (at 4 h), dinner (at 10 h), and evening snack (at 13 h). The diet was leucine free to prevent "dilution" of plasma leucine enrichment by the intake of unlabeled (dietary) leucine. The isotopic enrichment curves of VLDL subfractions and unfractionated VLDL during the fasting period were used to determine their metabolic rates. In this way, the

measurement of VLDL metabolism would not be altered by any acute effect of feeding on VLDL production or clearance. Plateau enrichments were unaffected by meals since steady-state enrichment had already been achieved.

Specimen analysis. Blood was collected into tubes containing disodium EDTA, 1.5 mg/ml; aprotinin, 0.01 mg/ml; PMSF, 17.5 μg/ml; and gentamicin, 0.05 mg/ml. Blood specimens were then centrifuged to separate plasma. VLDL (density < 1.006 g/ml) was immediately prepared from plasma overlayered with 2 ml NaCl 0.9%, and spun in a type 70.1 Ti rotor at 70,000 rpm in an L8-70M instrument (Beckman Instruments, Palo Alto, CA) for 2.5 h. During one of each subject's admissions, VLDL subfractions were prepared from a second aliquot of plasma: large (Svedberg units of flotation [Sf] 60–400) and small (Sf 20–60) VLDL were isolated by cumulative-rate, density-gradient ultracentrifugation (16) using a type 41 SW rotor (Beckman Instruments). LDL (density, 1.019–1.063 g/ml) was isolated by sequential preparative ultracentrifugation at 25,000 rpm for 26 h, in a type 25 rotor (Beckman Instruments) adjusting plasma density with potassium bromide (17). High density lipoprotein was separated from plasma by precipitation after the addition of dextran and magnesium chloride (18). Cholesterol and triglyceride concentrations were determined by enzymatic methods (19) (Boehringer-Mannheim, Indianapolis, IN). ApoB concentrations were measured by a direct ELISA using a polyclonal antibody (obtained from Dr. Peter Herbert, Brown University, Providence, RI) and an alkaline phosphatase conjugate of the same antibody. VLDL-apoB subfraction concentrations, measured by ELISA, were validated by determining the apoB concentrations by gas chromatography/mass spectroscopy (GC/MS) which uses the peak area of leucine from hydrolyzed apoB. Linear regression analysis of ELISA measurements on gas chromatography/mass spectroscopy measurements demonstrates a slope of 0.94 for apoB in large VLDL and 1.04 for apoB in small VLDL. The intraassay coefficients of variation for "blinded" control samples was 1.2% for cholesterol, 2.7% for HDL cholesterol, and 6.4% for apoB.

ApoB was precipitated from fractionated lipoproteins by isopropanol and washed three times (20). We and others (20, 21) determined by polyacrylamide gradient gel electrophoresis that the isopropanol precipitate after appropriate washing is free of apoproteins other than apoB. ApoB was hydrolyzed into component amino acids by heating at 120°C with 6 N hydrochloric acid for 16 h. Free amino acids were isolated from plasma by chromatography on AG50W-X8 resin (Bio-Rad Laboratories, Richmond, CA). All amino acids were converted to heptofluorobutyric acid derivatives. The proportion of D_3-leucine in each specimen was measured using a 5890 gas chromatograph with a 5988A mass spectrometer (Hewlett Packard, Palo Alto, CA).

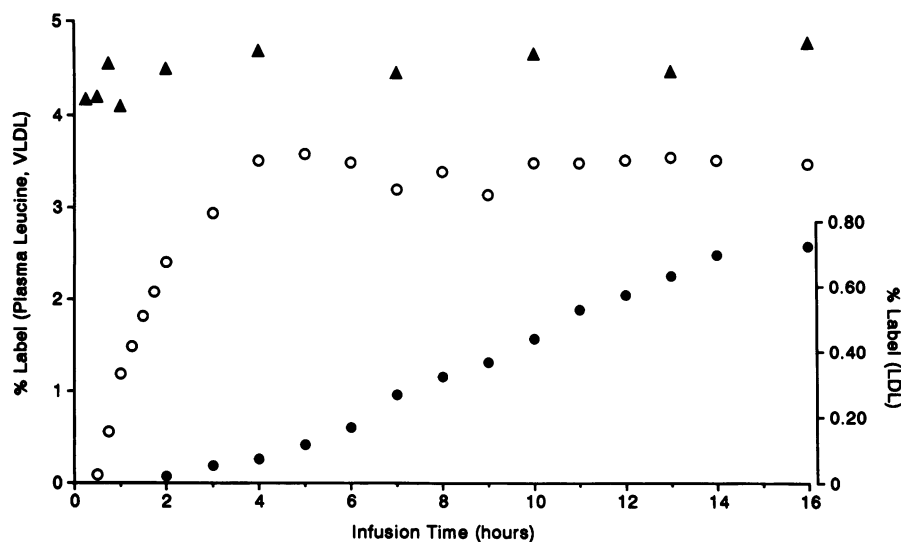*Calculation of metabolic rates.* The fractional catabolic rate (FCR)

Figure 1. Isotopic enrichment of leucine in plasma (*triangles*), VLDL apoB (*open circles*), and LDL apoB (*closed circles*) during intravenous infusion of trideuterated leucine for subject 2, study 1.
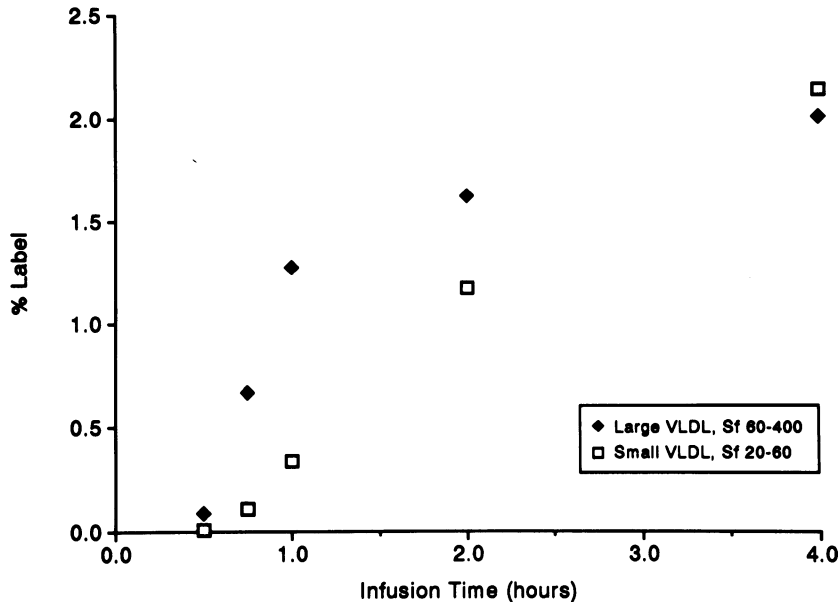
Figure 2. Isotopic enrichment of leucine in large VLDL apoB (Sf 60–400) and small VLDL apoB (Sf 20–60) during intravenous infusion of trideuterated leucine, for subject 2, study 2.

of LDL was calculated according to the theoretical principle that FCR is equal to the initial rate of appearance of label in a product (LDL apoB) divided by the precursor enrichment (VLDL apoB) if the precursor enrichment is constant (22). This approach was valid for LDL since the enrichment in VLDL-apoB was constant after 5 h (Fig. 1). This approach could not be used to analyze VLDL subfractions since the initial appearance of label in small VLDL occurs before the enrichment in large VLDL reaches steady state (Fig. 2). We therefore calculated the metabolic parameters of VLDL subfractions by computer modeling using the National Institutes of Health SAAM-30 (simulation, analysis, and modeling) software program. This program uses the rates of appearance of deuterated leucine in apoB of large VLDL and small VLDL, and their plasma pool sizes to calculate metabolic rates. We used a model (Fig. 3), which allowed for: (*a*) secretion into plasma of both large and small VLDL, (*b*) conversion of large VLDL to small VLDL, (*c*) clearance of large VLDL independent of conversion to small VLDL, and (*d*) clearance of small VLDL.[2] Production rates were calculated as the products of FCR and pool size. Pool size was calculated by multiplying plasma volume (body wt [kg] times 0.44) by plasma concentrations.

Statistical analysis. All VLDL concentrations and production rates underwent logarithmic transformation before statistical analysis to approximately normalize their distributions. Comparisons between mean values in OC users and nonusers were made with Student's unpaired *t* test (two-tailed with 9 degrees of freedom), after averaging LDL data for the six subjects studied twice. There was no significant time trend in the metabolic data measured in the six subjects who were studied twice.

Results

Study groups. The OC users and nonusers were similar in terms of age, height, weight, duration of exercise, alcohol consumption, and dietary intake (Table I). As may be expected for

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dieticians, these subjects consumed a diet low in total fat, saturated fat, and sucrose; and high in fiber and complex carbohydrates.

Lipoprotein levels. The mean plasma concentrations of all measured VLDL components (measured during all metabolic studies for each subject) were significantly greater in OC users (Table II): VLDL cholesterol, 1.6 times higher ($P < 0.05$); VLDL triglyceride, 1.7 times higher ($P < 0.05$); and VLDL apoB, 2.4 times higher ($P < 0.05$). Of note is that VLDL in OC users is not enriched in cholesterol or triglyceride; the molar ratio of VLDL cholesterol to VLDL apoB is 4,200 in OC users and is 6,400 in nonusers; the molar ratio of VLDL triglyceride to VLDL apoB is 6,900 in OC users and is 9,800 in nonusers. In addition, each subject had VLDL apoB subfractions measured during one metabolic study, and the higher level of VLDL apoB in OC users was found to be distributed between both VLDL subfractions: large VLDL apoB (Sf 60–400) was 3.0 times higher ($P < 0.05$) and small VLDL apoB (Sf 20–60) was 2.2 times higher ($P < 0.05$) compared to OC nonusers (Table III). The mean plasma concentrations of total cholesterol, HDL cholesterol, LDL cholesterol, and LDL apoB were not significantly different between the two groups.

Reproducibility of metabolic measurements. LDL fractional catabolic rates were highly reproducible when measured twice, 1 mo apart in six subjects: the intraindividual coefficient of variation was only 3.4%. Thus both methodologic and biologic variability is quite low. Methodologic variability may have been minimized by the multiple measurements obtained: LDL FCR is calculated using both (*a*) the slope of the initial linear appearance of label in LDL, determined from measurements obtained during at least 10 different times; and (*b*) the precursor (i.e., VLDL) enrichment at plateau, determined by averaging typically 8–10 measurements. The reproducibility of the metabolism of VLDL subfractions was not determined since isolation of VLDL subfractions was performed during only one of each patient's metabolic studies. However, we have previously found that the intraindividual CV were 35% and 47% for large and small VLDL, respectively, in a group of postmenopausal women (3).
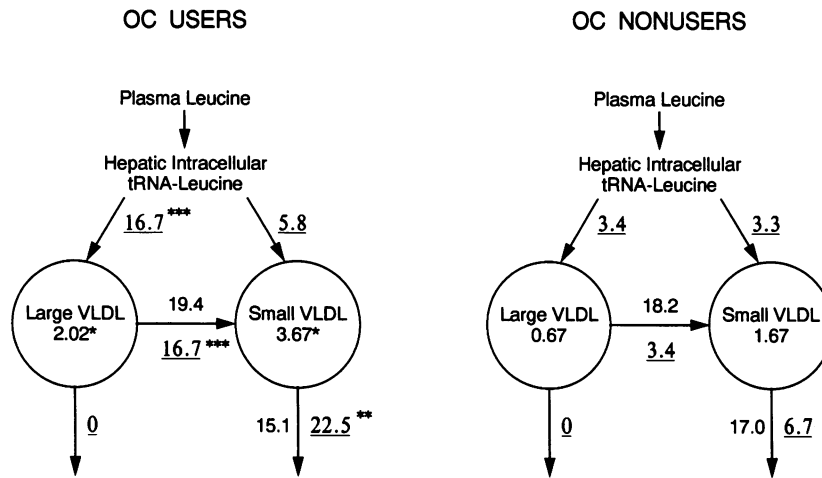
OC USERS

OC NONUSERS

Figure 3. Multicompartmental model used to analyze the appearance of trideuterated leucine infused intravenously as it shifts from the plasma leucine pool, to the intracellular hepatic tRNA leucine pool, the VLDL apoB (Sf 60–400) pool, and/or to the VLDL apoB (Sf 20–60) pool. Numbers inside the circles indicate apoB concentrations (nmol/liter); nonunderlined numbers beside arrows are fractional catabolic rates (pool/d); underlined numbers are absolute production or catabolism rates (nmol/kg per d). The figure on the left displays the mean values of the five oral contraceptive users; on the right, the mean values of the six nonusers. Users vs. nonusers, $*P < 0.05$, $**P < 0.01$, and $***P < 0.005$.

The values for LDL and VLDL metabolic rates of OC nonusers, measured by endogenous stable isotope labeling, are comparable to those obtained in studies by reinfusion of lipoproteins exogenously labeled using radioiodination (Table IV). LDL measurements are similar to those obtained in a study of five postmenopausal women (23); large VLDL measurements are similar to those obtained in a study of seven healthy subjects, ages 22–48 (9). To our knowledge, there is no single metabolic study of VLDL subfractions and LDL in normolipidemic young women that used radioidinated lipoproteins that would be directly comparable to the present study.

Metabolic measurements. OC users had significantly greater rates of VLDL apoB production compared to nonusers (Fig. 4): for large VLDL (Sf 60–400) it was 4.9 times higher ($P < 0.01$); and for small VLDL (Sf 20–60) it was 3.4 times higher ($P < 0.05$). The mean production rates of unfractionated VLDL isolated by fixed angle ultracentrifugation were also significantly higher among OC users: 21 nmol/kg per d, vs. 11 nmol/kg per d for nonusers ($P < 0.05$). There was no overlap between groups for large VLDL production rates. Exclusion of

the subject who took the OC which contained ethynodiol diacetate did not alter our results.

In contrast, the two groups did not have significantly different FCR for large VLDL, small VLDL, and LDL (Fig. 4). Although the mean production rate of LDL was 15% higher in OC users, this difference was not statistically significant ($P = 0.77$).

Discussion

We found that women who use contemporary low dose oral contraceptives, which contain 0.035 mg ethinyl estradiol, have significantly higher plasma levels of VLDL triglyceride, apoB, and cholesterol. We further found that these greater VLDL levels are due to increased VLDL production, and are not the result of reduced VLDL clearance. In particular, OC use has the greatest effect on large, triglyceride-rich VLDL, increasing its plasma concentration threefold, and production rate fivefold. The increases in small VLDL concentrations and production rates were statistically significant but smaller in magnitude

Table I. Characteristics of Oral Contraceptive Users and Nonusers

Subject	OC Users						OC Nonusers						
	1	2	3	4	5	mean±SD	6	7	8	9	10	11	mean±SD
Age (yr)	24	23	22	22	23	23±1	27	23	24	26	23	23	24±2
Height (cm)	165	173	166	160	157	164±6	167	163	157	149	164	165	161±7
Weight (kg)	66.9	64.6	56.8	60.1	54.4	60.6±5.2	68.1	56.6	50.5	53.1	60.5	71.6	60.1±8.4
Quetelet's index*	2.45	2.16	2.06	2.35	2.21	2.24±0.15	2.44	2.13	2.05	2.39	2.25	2.62	2.31±0.21
Exercise (h/wk)	4.0	5.0	3.0	2.0	6.0	4.0±1.6	2.0	10.0	4.5	6.0	3.0	6.0	5.3±2.8
Dietary intake													
Calories per d	1,313	2,558	2,702	1,936	2,033	2,110±550	1,410	2,902	1,731	2,030	2,194	1,972	2,040±500
Protein (% calories)	14	23	17	15	19	18±4	16	16	21	18	15	20	18±2
Fat (% calories)	33	28	26	18	17	24±7	17	20	26	22	24	23	22±3
Saturated	12	10	9	6	5	8±3	5	9	10	6	8	9	8±2
Polyunsaturated	7	6	5	4	4	5±1	5	3	4	4	4	3	4±1
Monounsaturated	12	10	9	5	5	8±3	6	7	9	7	8	8	8±1
Carbohydrate (% calories)	48	50	55	71	67	58±10	67	64	52	62	63	58	61±5
Sucrose	10	10	7	14	8	10±3	11	16	13	9	11	9	12±3
Cholesterol (mg/d)	163	327	250	57	167	193±102	61	216	256	213	160	335	207±92
Fiber (g/d)	14	28	28	23	44	27±11	21	20	22	33	42	28	28±9
Alcohol use (g/d)	4.6	2.9	12.6	1.1	3.9	5.0±4.4	5.7	6.9	8.3	7.2	4.8	5.8	6.5±1.3

* (Weight [kg]/height [cm]^2) × 1,000.
All differences not statistically significant.

Table II. Lipoprotein Concentrations of Oral Contraceptive Users and Nonusers

Subject	OC Users						OC Nonusers						
	1	2	3	4	5	mean±SD	6	7	8	9	10	11	mean±SD
Cholesterol (mmol/liter)													
Total	3.79	3.91	4.18	3.56	3.63	3.81±0.25	5.05	3.27	4.24	3.09	3.58	3.56	3.80±0.72
HDL	1.31	1.16	1.31	1.24	1.26	1.25±0.06	1.83	1.05	1.26	1.11	0.88	1.19	1.22±0.33
LDL	2.14	2.53	2.65	2.11	2.22	2.33±0.25	3.09	1.93	2.86	1.86	2.53	2.27	2.42±0.50
VLDL	0.34	0.23	0.21	0.21	0.21	0.24±0.06	0.13	0.28	0.08	0.10	0.18	0.13	0.15±0.07*
Triglyceride (mmol/liter)													
VLDL	0.50	0.38	0.32	0.49	0.24	0.39±0.11	0.15	0.41	0.11	0.19	0.34	0.18	0.23±0.12*

Compared with OC users, $*P \leq 0.05$.
To convert values for cholesterol to milligrams per deciliter, multiply by 38.8.
To convert values for triglyceride to milligrams per deciliter, multiply by 87.5.

(2.2-fold and 3.4-fold, respectively). Thus, the mechanism by which oral contraceptives raise triglyceride levels appears to be fundamentally different from that of endogenous hypertriglyceridemia, although both are characterized by high concentrations of large VLDL. In many individuals with endogenous hypertriglyceridemia, the conversion of large VLDL to small VLDL is retarded (9). This impaired lipolysis prolongs the residence time of large VLDL, so that it may acquire cholesterol ester from HDL (24). Cholesterol ester–rich VLDL from normolipidemic (13) and hyperlipidemic persons (25) may be atherogenic, since it promotes cholesterol ester formation in macrophages. In addition, impaired VLDL catabolism may decrease the formation of HDL in the circulation and accelerate HDL catabolism, leading to lower HDL concentrations which in turn may promote atherogenesis. In marked contrast, VLDL catabolism appears to be unaffected by OC use. Normal VLDL catabolism in OC users may contribute to the normal HDL levels and lack of cholesterol enrichment of VLDL. For these reasons, we speculate that the observed increase in triglycerides produced by OC would not contribute to atherosclerosis. Our observations may therefore offer a possible biochemical explanation for why long-term OC use does not appear to increase the risk of cardiovascular disease later in life, despite increased triglyceride levels (26).

The increase in VLDL production induced by OC's is most likely due to its estrogen component, ethinyl estradiol. Schaefer et al. (12) found that a high dose of ethinyl estradiol, 0.100 mg, elevated the VLDL-apoB levels of three premenopausal women by doubling the rate of VLDL apoB production, from 8.6 to 16.0 mg/kg per d. This increase in VLDL production rates is comparable to that seen in the present study of ethinyl estradiol, 0.035 mg: 6.7 mg/kg per d for OC nonusers, and 22.5 mg/kg per d for OC users (Fig. 3). In contrast, micronized estradiol 2 mg, a less potent estrogen dose than ethinyl estra-

Table III. Apolipoprotein B Metabolic Rates of Oral Contraceptive Users and Nonusers

Subject	OC Users						OC Nonusers						
	1	2	3	4	5	mean±SD	6	7	8	9	10	11	mean±SD
LDL (1.019 < d < 1.063)													
Concentration (nmol/liter)	940	1,190	1,470	1,160	1,080	1,170±200	1,670	1,040	1,180	780	1,220	830	1,120±320
Production rate (nmol/kg per d)	17.4	23.0	24.3	16.7	22.8	20.8±3.5	33.3	10.3	21.0	16.3	11.0	13.6	17.6±8.6
FCR (pool/d)	0.43	0.45	0.37	0.32	0.49	0.41±0.07	0.45	0.23	0.42	0.48	0.21	0.38	0.36±0.11
Large VLDL (Sf 60–400)													
Concentration (nmol/liter)	23.9	35.1	8.3	25.3	8.3	20.2±12.0	4.3	17.5	1.3	3.1	10.5	3.6	6.7±6.2*
Production rate (nmol/kg per d)	12.3	23.9	17.6	17.4	12.5	16.7±4.7	3.0	3.9	1.3	2.8	5.3	4.1	3.4±1.4‡
FCR (pool/d)	12.2	18.7	24.0	15.6	26.4	19.4±5.9	15.6	10.8	22.8	22.2	11.5	26.4	18.2±6.5
Small VLDL (Sf 20–60)													
Concentration (nmol/liter)	25.3	33.7	42.7	52.5	29.1	36.7±11.0	14.5	48.9	4.2	7.4	21.6	3.6	16.7±17.1*
Production rate (nmol/kg per d)	14.5	28.9	25.3	32.2	11.3	22.5±9.1	7.0	7.8	4.2	4.1	12.1	5.2	6.7±3.0§
FCR (pool/d)	13.7	20.4	13.4	13.9	13.8	15.1±3.0	11.0	7.7	24.0	12.9	12.7	33.6	17.0±9.8

Compared with OC users, $*P \leq 0.05$, $§P \leq 0.01$, $‡P \leq 0.005$.
To convert values for apoB concentrations to milligrams per deciliter, divide by 18.1.
To convert values for apoB production rates to milligrams per kilogram per day, divide by 1.81.

diol, 0.035 mg, has been reported to increase large VLDL pro-
duction rates of healthy postmenopausal women only 1.8-fold
(3), as compared to the fivefold higher rates seen in the present
study. Thus, lower doses of estrogen may increase VLDL pro-
duction rates in a dose-dependent fashion, until a biologic
maximum is reached, beyond which no further increases are
possible.

The present study did not find OC's to increase VLDL cata-
bolic rates. Such an increase might be expected, based on the
work of Kissebah et al. (11) who studied women using OC
containing 0.050 mg ethinyl estradiol with varying progestins.
They found that VLDL triglyceride levels were twofold higher
in OC users due to both twofold higher production rates and
45% higher catabolic rates. They attributed the latter effect to
the progestin component of the OC, since their comparison
group of estrogen-only users did not show increased rates of
VLDL catabolism. That the present study did not find an in-
crease in VLDL catabolic rates may be due to the lower dose of
progestins currently used. Alternatively, a modest effect of the
progestin component on FCR (in contrast to the several-fold
effect of estrogen on VLDL production) might not have been
detected, since this study had sufficient statistical power (80%)
to detect changes in VLDL FCR of only 50% or more.

OC users and nonusers had similar rates of LDL produc-
tion and catabolism, in contrast to the marked differences in
their rates of VLDL metabolism. This study had adequate sta-
tistical power (80%) to detect a change in LDL FCR of 27% or
greater. However, increases in LDL FCR of this magnitude
might be expected, since 2 mg micronized estradiol (which is
far less potent than ethinyl estradiol) given to postmenopausal
women increased the FCR of LDL by 38%, from 0.24 to 0.33
pool/d (3). Two explanations for the apparent lack of effect of
OC's on LDL metabolism may be offered: (a) An increase in
LDL catabolism induced by ethinyl estradiol may have been
negated by the progestin component of the OC. (b) Young
women, having relatively high LDL FCR's, may be at a "bio-
logic maximum" for LDL catabolism (possibly 0.45 pool/d)
beyond which no additional increases with OC use are possible.
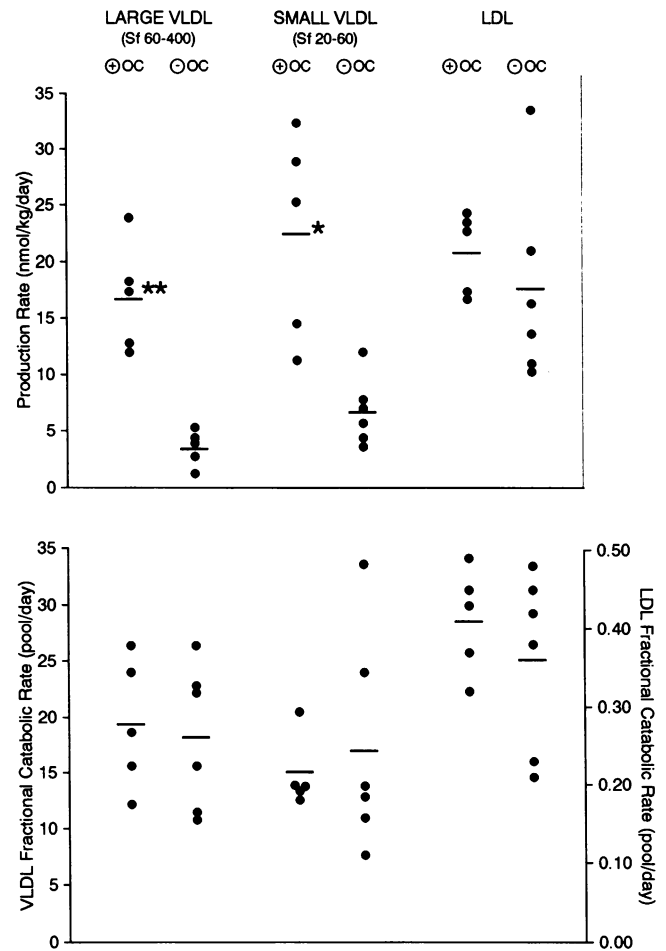

Figure 4. The production rates (nmol/kg per d) and fractional cata-
bolic rates (pool/d) of large VLDL apoB (Sf 60–400), small VLDL
apoB (Sf 20–60), and LDL apoB ($d = 1.019–1.063$), for oral contra-
ceptive users ($+OC$) and nonusers ($-OC$). Each point shows the
data of one patient. Horizontal bars show the means of each group.
Users vs. nonusers, $*P < 0.01$ and $**P < 0.005$.

Table IV. Comparison of Metabolic Data Obtained by
Endogenous Stable Isotope Labeling (Present Study) and by
Exogenous Radioiodination

	Exogenous labeling by radioiodination	Endogenous labeling by stable isotope
	$n = 5$ (Reference 23)	$n = 6$
LDL		
FCR (pool/d)	0.31 (0.28–0.33)	0.36 (0.23–0.48)
Production rate		
(mg/kg per d)	11 (8–12)	10 (6–18)
(nmol/kg per d)	19 (14–22)	18 (10–33)
	$n = 7$ (Reference 9)	$n = 6$
Large VLDL		
FCR (pool/d)	21 (9–50)	18 (11–26)
Production rate		
(mg/kg per d)	*	1.9 (0.7–2.9)
(nmol/kg per d)		3.4 (1.3–5.3)

Values are listed as means (range).
* Not reported by investigator.

Acknowledgments

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