

Effects of Low Dosage Progestin-only Administration upon Plasma Triglycerides and Lipoprotein Metabolism in Postmenopausal Women

Bernard M. Wolfe and Murray W. Huff

Department of Medicine, University Hospital and The University of Western Ontario, London, Ontario, Canada N6A 5A5

Abstract

Oral administration to five postmenopausal women of *dl*-norgestrel (0.075 mg/d for 7 wk) reduced mean fasting plasma levels of triglycerides by 29% ($P < 0.001$), VLDL triglycerides by 39% ($P < 0.01$), and VLDL apo B by 26% ($P < 0.05$), while lowering mean total cholesterol by 7% ($P < 0.06$). To explain these observations the kinetics of VLDL and LDL apo B turnover were studied by injecting autologous ^{125}I -labeled VLDL and ^{131}I -labeled LDL under control conditions and again in the fourth week of a 7-wk course of *dl*-norgestrel. VLDL apo B pool size fell by an average of 27% (1.2 vs 1.7 mg/kg, $P < 0.06$) and production of apo B by 18% (18 vs 22 mg/kg per d, $P < 0.05$) with unchanged fractional catabolic rate. Production of LDL apo B increased 36% with *dl*-norgestrel (12 vs 9.4 mg/kg per d, $P < 0.05$), but this was compensated by a 36% increase in fractional catabolic rate of LDL apo B (0.33 vs 0.25 pools/d, $P < 0.005$), thereby maintaining pool size. Lipoprotein (a) fell by an average of 12% (16 vs 18 mg/dl, $P < 0.06$). *dl*-Norgestrel reduced VLDL triglycerides (40 vs 64 mg/dl, $P < 0.05$), intermediate density lipoprotein cholesterol (14 vs 19 mg/dl, $P < 0.02$), IDL apo B (5.3 vs 7.2 mg/dl, $P < 0.05$), and VLDL cholesterol (3.1 vs 5.1 mg/dl, $0.10 > P > 0.05$), in parallel with the reductions in VLDL apo B production and pool size. *dl*-Norgestrel significantly lowered the production rate of VLDL apo B, thereby decreasing plasma VLDL and intermediate density lipoprotein concentrations. (*J. Clin. Invest.* 1993; 92:456–461.) Key words: *dl*-norgestrel • lipids • estrogens • turnover • apolipoprotein

Introduction

The synthetic progestin *dl*-norgestrel is used widely pharmaceutically in combination with estrogen in the formulation of oral contraceptives (1) and has also recently been tested in continuous low dosage together with estradiol-17 β in the hormonal replacement of symptomatic estrogen-deficient postmenopausal women (2). Combined low dosages of *dl*-norgestrel and estradiol-17 β lower plasma cholesterol and triglycerides in postmenopausal women by increasing fractional catabolism of VLDL and reducing production of LDL (3). However, the specific contribution of *dl*-norgestrel to the ob-

served lowering of lipids is unknown. Although most reports find that oral contraceptives containing *dl*-norgestrel lower plasma triglycerides (4, 5), this has not been universal (6–8). Levonorgestrel, the active isomer of *dl*-norgestrel, lowers plasma total and VLDL triglycerides in intact female rats when given alone (9), but not when combined with estradiol (10). The reduction of VLDL apo B levels with levonorgestrel in intact female rats is attributable to enhanced fractional catabolism of VLDL (11). However, inhibition of hepatic triglyceride synthesis could also contribute to reduction of plasma triglycerides because levonorgestrel inhibits incorporation of labeled glycerol and fatty acids into rat hepatocyte triglycerides and reduces their incorporation into triglycerides released into the incubation medium (9). This appears to involve, at least in part, inhibition of the hepatic glycerol-3-phosphate acyltransferase (12). Prophylaxis against postmenopausal coronary heart disease, osteoporosis, endometrial cancer, and stroke (13–15) may be enhanced through improving compliance with female hormonal replacement regimens by administration of continuous low dosages of progestins, such as *dl*-norgestrel, along with estrogen and eliminating the main cause of non-compliance with such therapy which is the scheduled vaginal withdrawal bleeding induced by intermittent administration of progestin (2). To investigate the specific, individual effects of *dl*-norgestrel on plasma apo B in women with estrogen deficiency, we have examined the effects in postmenopausal women of continuous low dosage *dl*-norgestrel on (a) the kinetics of apo B metabolism of VLDL and LDL and (b) the concentration of plasma lipoprotein (a) [Lp(a)].¹ Lp(a) is closely related to apo B (16) and increases during the menopause (17), along with plasma cholesterol (18), thereby contributing to the loss of relative immunity from coronary heart disease enjoyed by premenopausal women compared with men of similar age (19).

Methods

Subjects. Five participants were recruited from University Hospital out-patient clinics (Table 1). Each had experienced typical menopausal symptoms and was amenorrheic for at least 6 mo. Serum follicle-stimulating hormone exceeded 110 U/liter before entering the study in all subjects. Baseline fasting plasma cholesterol concentrations during Phase I American Heart Association diets before entry into the study equaled or exceeded 200 mg/dl, the cut-point of eligibility for treatment recommended by the National Cholesterol Education Program (20). Subjects received no other medications known to affect lipid metabolism and intake of ethanol was < 30 ml/d for the month before each turnover study. All subjects had normal fasting concentrations of serum glucose, glutamic oxaloacetic transaminase, thyroxine, creatinine, calcium, albumin, sodium, potassium, chloride, and bicarbonate. Hematological and urine analyses were normal. The experimental pro-

Address correspondence to Dr. Bernard M. Wolfe, Division of Endocrinology and Metabolism, Department of Medicine, University Hospital, 339 Windermere Road, London, Ontario, Canada N6A 5A5.

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1. Abbreviations used in this paper: FCR, fractional catabolic rate; IDL, intermediate density lipoprotein; Lp(a), lipoprotein a.

Table I. Characteristics of Postmenopausal Subjects

Subject	Age	Height	Weight	Cholesterol		Triglycerides		Lp(a)	
				Control	Treated	Control	Treated	Control	Treated
	yr	cm	kg			mg/dl			
1	50	163	62	219	213	142	98	14	13
2	64	162	73	283	229	198	155	21	19
3	58	160	74	192	182	138	92	28	22
4	76	152	62	232	224	140	99	9.3	7.8
5	68	151	52	279	270	117	88	20	19
Mean	63	158	65	241	224*	147	106 [‡]	18	16*
±SE	4	3	4	18	14	14	12	3	3

Values for each subject are the mean of four fasting blood plasma samples obtained over 3 wk during each of the control and treatment periods.

* Different from control, $P < 0.06$ by sign test. [‡] Different from control, $P < 0.001$.

tocol approved by The Standing Committee on Human Research of The University of Western Ontario was explained to each subject and informed consent was obtained in writing.

Subjects were maintained on the modified fat diets containing ~30% of energy from fat (<300 mg cholesterol per d), 20% from protein, and 50% from carbohydrate. The ratio of polyunsaturated:monounsaturated:saturated fat was ~0.7:1.0:1.0. However, during admissions to hospital for the initial day of each turnover study, the subjects consumed low fat diets (<5 g fat/d, 62 g protein/d, and 378 g carbohydrate/d, consisting of 2% cottage cheese, cereals, juices, gelatin, and skim milk).

Samples of venous blood for determination of plasma total and HDL cholesterol, total triglycerides and Lp(a) concentrations were obtained from a forearm vein (after a 12-h fast) from each subject on four occasions at approximately weekly intervals (a) during the initial 3-wk control period before starting *dl*-norgestrel administration and (b) during the treatment period (weeks 3 to 6 of the 7-wk course of *dl*-norgestrel administration, 0.075 mg/d). Subjects underwent studies of the kinetics of VLDL and LDL apo B turnover during the control period and again during the last 16 d of *dl*-norgestrel administration. All subjects received 300 mg potassium iodide daily for 3 d before and 13 d after the reinjection of their radiolabeled lipoproteins.

Preparation of labeled lipoproteins and kinetic studies. Fasting blood plasma (1.5 mg EDTA/ml) for isolation of VLDL and LDL was obtained from each subject 6 d before each turnover study. The procedures used for the preparation of the labeled lipoproteins have been previously described (3, 11, 21–23). VLDL and LDL were radiolabeled with ¹²⁵I (Amersham, Oakville, Canada) and ¹³¹I (Merck-Frosst Canada Inc., Point Claire-Dorval, Canada), respectively. 96% of the radioisotope ¹²⁵I was bound to VLDL protein, 1% was associated with lipids, and 3% remained unbound; VLDL apo B accounted for 42% of the ¹²⁵I bound to VLDL protein. 98% of the radioisotope ¹³¹I was bound to LDL protein, 1% was associated with lipids, and 1% remained unbound; LDL apo B accounted for 90% of the ¹³¹I bound to LDL protein.

Experimental protocol. Each recipient was fasted 12 h before receiving serially 100 μ Ci of ¹²⁵I-labeled VLDL and 30 μ Ci of ¹³¹I-labeled LDL in 2–3 ml of normal saline over 2 min via a hand or forearm vein. Venous blood samples (each 25 ml, 1.5 mg EDTA/ml) were obtained over 16 d after injection at 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 48, 72, 120, 216, 288, and 384 h and placed on ice before immediate separation of plasma. Plasma VLDL (S_f 60–400), intermediate density lipoprotein (IDL) (S_f 12–60), and LDL (S_f 0–12) were fractionated (21, 24) and apo B isolated from each lipoprotein fraction by isopropanol precipitation and its specific activity determined as previously described (25).

Analyses. The structure of the kinetic model and equations used to calculate the kinetic parameters have been described in detail previously (11). The principal assumptions of this model are that (a) apo B

is an integral part of each of VLDL, IDL, and LDL, is nonexchangeable and therefore provides an accurate measure of the metabolism of these lipoproteins; (b) the metabolism of the tracer is identical to that of the tracee; (c) the production rate or flux of VLDL apo B is defined as representing input of apo B primarily into the larger, rapidly turning over, primary metabolic compartment (pool 1); (d) all apo B catabolism occurs from pool 1 either directly or after passing through either pool 2 or 3; (e) all subpopulations of VLDL are isolated for labeling and that the initial injected activity is proportional to the mass of apo B in each population; (f) the two-pool model used for LDL apo B analysis is characterized by a plasma compartment and extravascular exchange compartment; and (g) at the time of injection all LDL apo B radioactivity is introduced into the plasma compartment and irreversible loss of LDL apo B occurs from the same compartment.

As in earlier studies in humans and rats, the specific activity curves of VLDL apo B were best described by the three-pool model of Goodman et al. (26), modified according to Skinner (27), that provided a better fit by residual error testing than a two-pool model. The kinetic parameters of this model for VLDL were calculated as previously described (3, 11, 26). As in a previous study (3), there was no evidence for a third pool for LDL apo B and the specific activity curves of LDL apo B were analyzed and kinetic parameters calculated using the conventional two-pool model of Gurpide et al. (21, 28–30). This yielded values for flux rates through pool 1, irreversible fractional catabolic rate ($FCR = k_A$, assuming that catabolism from other pools is negligible) (28), and mass in pool 1.

The mass of plasma apo B in VLDL and LDL was determined by electroimmunoassay as previously described (31). Lp(a) was measured using Macra Lp(a) Kit obtained from Terumo Medical Corp., Elkton, MD. The intraassay coefficients of variation for apo B and Lp(a) were 4.5 and 4.7%, respectively. VLDL apo B pool size was determined independently from the plasma concentration of VLDL apo B (31) multiplied by the plasma volume taken as 36 mg/kg body wt (32). IDL apo B concentration was also determined by electroimmunoassay (31). The FCR was calculated as: $k_A = \alpha\beta/(\alpha + \beta - k_{AA})$ (28). The percentage of LDL apo B that was derived from IDL apo B was calculated as: $1 - (\text{area under the } ^{125}\text{I-LDL apo B specific activity curve} / \text{area under the } ^{125}\text{I-IDL apo B specific activity curve})$; (23, 33). Concentrations of cholesterol and triglycerides in the chloroform-methanol extract of whole plasma were determined as previously described (22), except that diagnostic kits from Boehringer Mannheim GmbH Diagnostica, Montreal, Canada (C-system kit for cholesterol and test combination kit for triglycerides) were used to measure cholesterol content of fasting plasma VLDL, IDL, and LDL and triglyceride content of VLDL during the turnover studies because of the small amounts of material available for assay. HDL cholesterol was measured after precipitation with heparin-manganese chloride (34). Values from control and treatment periods were compared using Student's

Table II. Effects of *dl*-Norgestrel on Fasting Levels of Cholesterol of Plasma Lipoproteins during Turnover Studies

Subject	Whole Plasma		VLDL		IDL		LDL		HDL	
	Control	Treated	Control	Treated	Control	Treated	Control	Treated	Control	Treated
<i>mg/dl</i>										
1	213	205	4.9	1.2	14	7.4	138	142	56	54
2	284	227	6.1	6.5	24	16	200	151	54	53
3	197	183	3.9	3.7	21	19	123	111	49	49
4	234	218	7.2	2.7	15	12	154	145	58	58
5	288	253	4.1	0.8	22	16	206	184	56	52
Mean	243	217*	5.2	3.0	19	14 [‡]	164	147	55	53
±SE	18	12	0.6	1.0	2	2	17	12	2	2

Values for each subject were based upon fasting blood plasma samples obtained immediately before injection of autologous labeled ¹²⁵I-VLDL and ¹³¹I-LDL at the beginning of each turnover study. * Different from control, $P < 0.05$. [‡] Different from control, $P < 0.02$.

paired two-tailed t test (35) or the nonparametric sign test (36) if the difference narrowly failed to achieve $P < 0.05$, as specifically noted.

Results

The oral administration of *dl*-norgestrel (0.075 mg/d for 7 wk) significantly lowered mean plasma triglycerides ($P < 0.05$, Table I), along with reductions in mean total cholesterol and Lp(a) ($P < 0.06$ by sign test). Based upon measurements on fasting blood plasma obtained during day 1 of the turnover studies, these changes were attributable to corresponding reductions in the concentrations of cholesterol in (a) VLDL, IDL, and LDL (Table II) and (b) VLDL triglycerides (40 ± 10 vs 64 ± 9 mg/dl, $P < 0.02$). Mean values for apo B were signifi-

cantly reduced during *dl*-norgestrel treatment versus control in plasma VLDL (3.3 ± 0.4 vs 4.4 ± 0.6 mg/dl, $P < 0.01$) and IDL (5.3 ± 0.2 vs 7.2 ± 0.7 mg/dl, $P < 0.05$), whereas LDL apo B was unchanged (47 ± 5 vs 49 ± 4 mg/dl, $P > 0.3$). Consistent with a steady state, there were no systematic changes during the turnover studies in plasma concentrations of the most readily quantified indices, namely total protein content of LDL (mean coefficient of variation of 10%, corresponding to a mean SD of 8 mg/dl, $n = 6$ paired studies) and VLDL (mean coefficient of variation of 22%, corresponding to a mean SD of 1.1 mg/dl, $n = 6$ paired studies). The ratio of triglycerides to apo B in plasma VLDL, IDL, and LDL was not significantly altered by *dl*-norgestrel treatment versus control (8.9 ± 1.5 vs 10 ± 1.8 , 3.9 ± 0.6 vs 3.8 ± 0.6 , and 0.29 ± 0.05 vs 0.32 ± 0.05 , respectively, $P > 0.2$).

Table III. Kinetic Parameters of Human ¹²⁵I-VLDL Apo B Turnover in *dl*-Norgestrel-treated Postmenopausal Subjects

Subject	Period	Half-life phase			Fractional catabolic rate	Pool size of VLDL apo B		Production rate [‡]
		I	II	III		Kinetic*	Mass [‡]	
		<i>h</i>				<i>mg/kg</i>		
1	Control	0.4	1.4	32	15	1.6	1.3	24
	Treated	0.5	1.9	35	22	0.8	1.1	18
2	Control	1.0	7.5	24	9.0	2.8	2.3	26
	Treated	0.4	1.0	16	17	1.0	1.7	18
3	Control	0.6	1.6	14	15	1.3	1.5	19
	Treated	0.7	2.7	17	12	1.2	1.0	15
4	Control	0.5	1.4	33	14	1.6	1.8	22
	Treated	0.7	1.7	38	15	1.5	1.2	22
5	Control	0.4	1.9	26	13	1.4	1.2	19
	Treated	0.5	1.6	33	13	1.3	0.9	17
Mean	Control	0.6	2.8	26	13	1.7	1.6	22
±SE		0.1	1.2	3	1.0	0.3	0.2	1.4
Mean	Treated	0.6	1.8	28	16	1.2	1.2 [†]	18 ^{**}
±SE		0.1	0.3	5	1.8	0.1	0.1	1.1

* Based upon kinetic analysis of ¹²⁵I-labeled VLDL apo B (see Methods). [‡] Mean values based upon plasma mass determined by electroimmunoassay on fasting specimens obtained daily during the first 4 d of each turnover study (31). Plasma volume was assumed to be 36 ml/kg (32).

[‡] Based upon product of fractional catabolic rate and radioisotopic determination of VLDL apo B pool size. ^{||} Different from control, $P < 0.06$ by sign test. [‡] Different from control, $P < 0.01$. ** Different from control, $P < 0.05$.

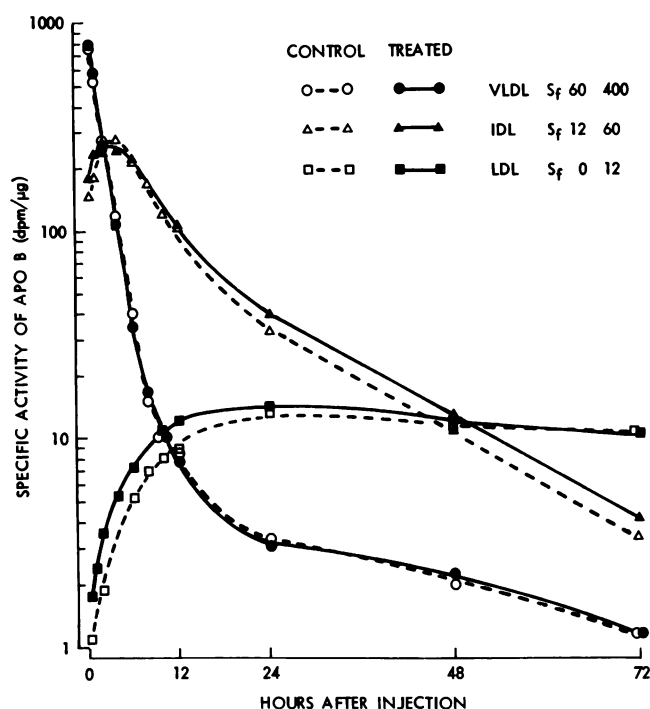


Figure 1. Specific activities of apo B of VLDL, IDL, and LDL after intravenous injection of autologous ^{125}I -labeled VLDL during control (open symbols) and treatment (closed symbols) for a representative subject.

Values for the specific activities of ^{125}I -labeled apo B in VLDL, IDL, and LDL over 72 h after injection of ^{125}I -labeled VLDL during *dl*-norgestrel treatment versus control are shown in Fig. 1. The kinetic parameters of VLDL turnover calculated from the ^{125}I -labeled VLDL apo B decay curves are shown in Table III. During the treatment versus control periods, there were no significant differences in FCR; however,

mean VLDL apo B production rate fell significantly by $18 \pm 5\%$ ($P < 0.05$) and mean VLDL apo B pool size determined by kinetic analysis fell by $27 \pm 12\%$ ($P < 0.06$ by sign test).

Fig. 2 illustrates the effect of *dl*-norgestrel administration on the percent decrease of the ^{131}I -labeled LDL apo B specific activity from the plasma for a representative subject. The kinetic parameters of LDL turnover calculated from the ^{131}I -labeled LDL decay curves using the two-pool model of Gurpide et al. (27) are shown in Table IV. Based on these curves the half-life of phase I, but not phase II, was significantly shorter during the treatment versus control (39 ± 4 vs 21 ± 2 h, $P < 0.01$). The FCR of LDL apo B was significantly increased by an average of $36 \pm 7\%$ during *dl*-norgestrel treatment versus control (0.33 ± 0.01 vs 0.25 ± 0.02 pools/d, $P < 0.005$). The enhancement of LDL apo B catabolism was not accompanied by any systematic change in pool size of LDL apo B because LDL apo B production rate increased reciprocally by an average of $36 \pm 13\%$ during *dl*-norgestrel treatment versus control (12 ± 1.4 vs 9.4 ± 1.7 mg/kg per d, $P < 0.05$).

Evaluation of product-precursor relationships (37) between lipoprotein fractions indicated that VLDL were the sole precursors of IDL. As illustrated in a representative subject (Fig. 1), the decay curves of VLDL apo B consistently intersected those of IDL apo B at their peaks during both treatment and control periods. However, the LDL apo B specific activity curves consistently reached their peaks before they were intersected by their corresponding IDL curves. This is consistent with LDL entering the circulation directly (33) and/or via small, a rapidly turning over, hepatogenous pool(s) of VLDL apo B (38) which is not traceable with exogenous iodine labeling (25). The relative importance of the two pathways in the present experiments could not be determined. Comparisons of the areas under the specific activity curve as described by Goldberg et al. (33) indicated that LDL production derived from plasma VLDL and IDL could account for up to half of total LDL apo B production during treatment versus control (50 vs

Table IV. Kinetic Parameters of Human ^{131}I -LDL Apo B Turnover in *dl*-Norgestrel-treated Postmenopausal Subjects

Subject	Period	Half-life phase		Fractional catabolic rate	LDL apo B	Production rate		Fraction of LDL apo B production derived from IDL apo B*
		I	II			Total	From IDL	
		h	h		mg/kg	mg/kg per d	mg/kg per d	
1	Control	29	72	0.29	32	9.2	3.9	42
	Treated	14	81	0.35	39	14	9.0	64
2	Control	45	150	0.22	33	7.3	4.0	55
	Treated	18	85	0.33	25	8.2	4.5	55
3	Control	29	132	0.30	20	6.0	3.4	57
	Treated	24	159	0.35	28	9.8	3.5	36
4	Control	45	156	0.22	39	8.4	4.2	50
	Treated	20	88	0.31	41	13	6.6	51
5	Control	47	153	0.21	77	16	5.0	31
	Treated	28	189	0.32	50	16	7.0	44
Mean	Control	39	133	0.25	40	9.4	4.1	47
±SE		4	16	0.02	10	1.7	0.3	5
Mean	Treated	21 [‡]	120	0.33 [§]	37	12	6.1	50
±SE		2	22	0.01	5	1.4	1.0	5

* Calculated according to method of Goldberg et al. (33). [‡] Different from control, $P < 0.01$. [§] Different from control, $P < 0.005$. ^{||} Different from control, $P < 0.05$.

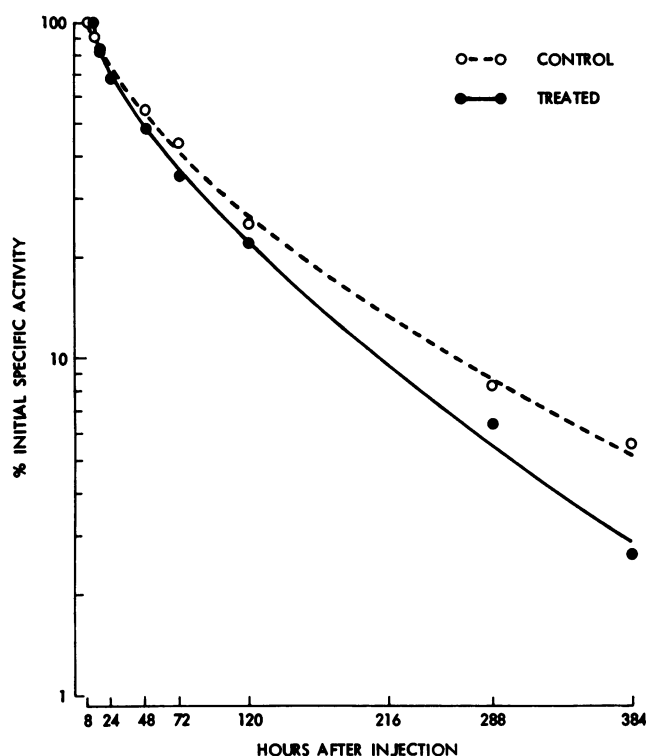


Figure 2. Specific radioactivity of LDL apo B expressed as percentage of the peak specific activity after intravenous injection of autologous ^{131}I -labeled LDL for a representative subject.

47%, respectively). The consistent increase in production of LDL derived from VLDL via IDL accounted for most of the increase in total LDL apo B production during treatment versus control (6.1 ± 1.0 vs 4.1 ± 0.3 mg/kg per d, $P < 0.05$, Table IV).

Discussion

The present studies provide new insights into the mechanisms whereby a continuous low dosage of the progestin *dl*-norgestrel alone can modulate the concentrations of plasma lipoproteins in women with estrogen deficiency due to primary ovarian failure. Whereas low dosage *dl*-norgestrel (0.075 mg/d) combined with estradiol-17 β (1 mg/d) increase the FCR of VLDL, thereby lowering VLDL triglycerides (2), low dosage *dl*-norgestrel alone significantly reduces VLDL apo B production rate and decreases mean VLDL apo B pool size (Table III). The reduction of plasma VLDL triglycerides during treatment with *dl*-norgestrel alone (Table II) is consistent with both reduced production of VLDL apo B and the previously demonstrated inhibition of triglyceride release from rat hepatocytes (9), likely involving, at least in part, inhibition of hepatic glycerol-3-phosphate acyltransferase, a key enzyme of triglyceride synthesis (12). In contrast, similar low dosages of *dl*-norgestrel combined with estradiol-17 β daily were found to lower VLDL triglycerides and VLDL apo B pool size by increasing FCR with unchanged production of VLDL apo B (3). Since VLDL were the sole precursors of IDL (see Results), the observed reduction in IDL cholesterol (Table II) and IDL apo B can be attributed, at least in part, to reduced rate of VLDL production during *dl*-norgestrel treatment. The consistent reduction of plasma total cholesterol (Table I, $P < 0.06$ by sign test) is attributable to the combined reduction in VLDL-, IDL-, and

LDL-cholesterol (Table II). Although low dosage *dl*-norgestrel had no detectable effect on HDL cholesterol during the 7-wk period of observation, combined administration of low doses of *dl*-norgestrel and estradiol-17 β was found to significantly lower HDL cholesterol (2), as have sixfold higher norgestrel doses (39).

The present finding of increased plasma LDL apo B turnover with constant plasma concentration during administration of *dl*-norgestrel alone (Table IV) strongly contrasts with the reductions in LDL apo B production and concentration that were observed when a similar dose of *dl*-norgestrel was given together with estradiol-17 β to postmenopausal women (3), but is consistent with enhanced production of LDL observed during progesterone treatment of female baboons (40). The low dosage *dl*-norgestrel given alone increased mean LDL catabolism to the same extent (i.e., 36%) as 2 mg/d estradiol in another study of postmenopausal women (41). Whereas estradiol increased LDL apo B production by only 21% and lowered LDL apo B (41), *dl*-norgestrel increased LDL apo B production by 36% maintaining its concentration (Table IV). The known effects of estradiol on lipoprotein metabolism (41, 42) fail to explain the differences in metabolic effects observed between administration of *dl*-norgestrel alone versus *dl*-norgestrel combined with estradiol-17 β (3) and the metabolic basis of the interaction of estradiol and *dl*-norgestrel in inhibiting LDL apo B production (3) remains unclear. It is conceivable that *dl*-norgestrel given alone could bind to estrogen receptors (43) and/or other estrogen- or progesterone-responsive elements of other genes and induce estrogen-like effects on LDL metabolism. Other mechanisms of hormone action may also be possible. For instance, antigluccorticoid effects have been attributed to progestin binding to glucocorticoid receptors (44). Levonorgestrel alone reduces plasma triglycerides in female rats in vivo and inhibits hepatocyte triglyceride synthesis in vitro, but not in the presence of estradiol (10). Nevertheless, plasma cholesterol is not reduced in the rat by either treatment.

The present finding of a slight, but consistent decrease in fasting plasma Lp(a) with administration of the present low dosage of *dl*-norgestrel could have implications for the reduction of coronary heart disease in postmenopausal women resulting from elevated plasma Lp(a) (16, 17). The change in Lp(a) concentration is in the same direction, though the changes are smaller than with an 80-fold higher dose of stanozolol (45). Although *dl*-norgestrel shares HDL lowering effects with stanozolol, the actual mechanism underlying the reduction of Lp(a) by these agents is unknown.

The present findings with low dosage *dl*-norgestrel in women with ovarian failure provide new insights into progestin effects on lipoprotein metabolism and may have implications both for the design of progestin-only and combined estrogen/progestin oral contraceptives for premenopausal women and the formulation of perhaps more widely acceptable continuous low dosage female hormonal replacement therapy in postmenopausal women (2), including those in whom moderate hypertriglyceridemia (46) may pose a risk of coronary heart disease and more severe hypertriglyceridemia may pose a risk of estrogen-induced pancreatitis (47, 48).

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