

Cyclic Changes in Lipoprotein and Apolipoprotein Levels During the Menstrual Cycle in Healthy Premenopausal Women on a Controlled Diet

RICHARD A. MUESING, MICHELE R. FORMAN, BARRY I. GRAUBARD,
GARY R. BEECHER, ELAINE LANZA, PATRICIA A. MCADAM,
WILLIAM S. CAMPBELL, AND BEATRIZ R. OLSON

Lipid Research Clinic, Department of Medicine, The George Washington University Medical Center, The George Washington University (R.A.M.), Washington, District of Columbia, 20037; National Cancer Institute, Cancer Prevention and Control Branch, National Institutes of Health (M.R.F., B.I.G., E.L., W.S.C.), Bethesda, Maryland 20892; Human Nutrition Research Center, United States Department of Agriculture (G.R.B., P.A.M.-A.), Beltsville, Maryland 20705; and Moynahan Medical Center (B.R.O.), Waterbury, Connecticut 06702

ABSTRACT

Lipoprotein, apolipoprotein (apo), and hormone levels were measured in 12 healthy women over three consecutive menstrual cycles; one free-living and two under controlled dietary conditions. Serum hormone levels were measured to identify menstrual cycle phases (menses, early follicular, late follicular, and midluteal). After stabilization for one cycle on the controlled diet, ANOVA modeling of the second controlled-diet cycle revealed that low-density lipoprotein (LDL) cholesterol levels in the midluteal phase were significantly lower (by 7%) than in the early follicular phase. High-density lipoprotein (HDL) cholesterol levels during the late follicular phase were higher (by 6%) than menses levels. Differences in the HDL-cholesterol

and apoA-I fluctuations resulted in a higher proportion of HDL-cholesterol to apoA-I during the late follicular phase than that during the menses phase. The ratios of LDL cholesterol/HDL cholesterol and apoB/apoA-I in the early follicular phase were greater by 5.6% and 6.0%, respectively, than those in the midluteal phase. Fluctuations in total cholesterol, triglyceride, apoA-I, and apoB did not reach significance. Thus, the cyclic fluctuations of LDL and HDL cholesterol need to be considered in the screening and medical monitoring of women with borderline lipoprotein levels, as well as in the design and the interpretation of results of studies involving premenopausal women. (*J Clin Endocrinol Metab* 81: 3599–3603, 1996)

ORAL ESTROGEN and progestogen administration in pre- and postmenopausal women have pronounced effects on lipoprotein levels. Estrogens decrease levels of low-density lipoprotein (LDL) cholesterol and apolipoprotein (apo) B, and increase high-density lipoprotein (HDL) cholesterol and apoA-I (1, 2). These changes are associated with a decreased risk of cardiovascular disease (3). On the other hand, progestogens tend to reverse these favorable effects (1, 4).

Among the studies that have examined fluctuations of lipoprotein levels by phase of the menstrual cycle, Kim and Kalkhoff (5) were the first to report changes in apolipoprotein as well as lipoprotein levels in the free-living (FL) state. Total and LDL cholesterol and apoB levels during the luteal phase were 10–25% lower than during the follicular phase. Results from subsequent studies have been inconsistent. Some investigators have reported that total cholesterol, LDL cholesterol, or apoB levels during the luteal phase were lower than levels during the follicular phase (5–10), whereas others found either no change or fluctuations that did not reach significance (11–14). Follicular HDL cholesterol and/or

apoA-I levels were reportedly higher than menses (MEN) levels in some investigations (7, 10, 13, 15, 16), but not others (8, 9, 12, 14). Finally, significant elevations in triglycerides have been reported during midcycle in some studies (6, 8, 12), but not in others (5, 7, 9, 11).

Only a few studies (10, 15) have measured hormone and lipid levels with sufficient frequency to adequately assess lipoprotein levels by phase of the menstrual cycle. Further, diet is known to affect lipoprotein levels. Thus, it is important to examine changes during the menstrual cycle under controlled dietary (CD) conditions. In one CD study (6), significant fluctuations were found in total and HDL cholesterol, and changes in triglyceride levels appeared to be dependent on the level of fat in the diet. In a second CD study, fluctuations in total and lipoprotein cholesterol failed to reach significance, but triglycerides were increased during the ovulatory phase (12). Thus, the large majority of the research has not been conducted under CD conditions nor with frequent blood draws to identify menstrual cycle phase.

The current study was designed with frequent measurements of serum hormone levels to precisely identify menstrual cycle phase, and concomitant lipid/apolipoprotein measurements during one menstrual cycle in the FL state followed by two cycles under CD conditions. The first two study cycles were designed to confirm that participants experienced an ovulatory cycle in the FL state, and place the participants on a CD regimen for one cycle (CD1) to stabilize

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Address all correspondence and requests for reprints to: Michele R. Forman, National Cancer Institute, Cancer Prevention and Control Branch, National Institutes of Health, Executive Plaza North, Suite 211, 6130 Executive Boulevard, Bethesda, Maryland 20892-7326.

plasma lipoprotein levels. The objective of this report is to describe the fluctuation in the levels of cholesterol, triglyceride, and LDL and HDL cholesterol and their protein moieties, by phase of the cycle during the second CD cycle (CD2) in 12 normal healthy premenopausal women.

Methods

Study subjects

Twenty healthy premenopausal women met the following study criteria: 1) aged 20–34 yr; 2) nonsmokers; 3) normal range for plasma cholesterol, triglycerides, and hemoglobin; 4) not pregnant, using hormone preparations, or breastfeeding for the last 12 months; 5) a reported menstrual cycle length of 26–32 days; 6) an abstainer from alcohol or a drinker of less than 6 drinks/week and less than 2 drinks/day, and willing to stop alcohol intake during the controlled feeding study; 7) not following a restricted diet, or regularly using vitamin-mineral supplements and willing to stop supplementation; and 8) within 20% of weight for height using age and gender based on the 1983 Metropolitan Life Insurance Table (17). Informed consent was obtained from all subjects, and all procedures were approved by the institutional review boards of the George Washington University and National Cancer Institute.

The study was designed with a FL phase for one menstrual cycle ($n = 20$) followed by a CD phase for two menstrual cycles ($n = 13$). Before the FL cycle, each participant attended a half-day session of training in food record completion and familiarity with a chart that identified blood specimen collection days by phase of the cycle. It was emphasized that the late follicular phase (LF) of blood drawing would begin on MEN day 11 and stop at ≥ 1 day post-LH surge. Midluteal blood draws would always be 7–8 days post-LH surge.

FL phase

The first day of the FL cycle began on MEN day 1. Subjects kept daily food records indicating time, place, portion size, description of each food ingredient, and whether intake was at the usual level. Food records were reviewed daily by a registered dietitian, with questions about intake during the past 24 h answered in person or by phone. The food records were sent to the University of Minnesota Nutrition Coordinating Center for nutrient analysis (18).

CD phase

The CD phase began on the first MEN day following the FL cycle. The CD phase was conducted at the United States Department of Agriculture-Beltsville Human Nutrition Research Center (BHNRC). All meals were prepared at the BHNRC and consisted of a 7-day menu cycle. Breakfast and dinner were eaten at the facility with monitoring by a study team member. Lunches and weekend meals were prepared for carry-out; uneaten portions were returned. Analyzed composites of the CD meals contained 36% of calories from fat (36.8% as saturated fat; P:S ratio = 0.53) and 19% from protein, and 8.4 g total dietary fiber, and 177 mg cholesterol/1000 kcal.

To maintain constant weight, caloric intake was increased or decreased in increments of 200 kcal if a woman lost ($n = 1$) or gained greater than 1 kg and maintained that weight for at least 3 days. Physical activity was monitored weekly with a self-reported questionnaire throughout CD1 and CD2. No subject changed her physical activity on a low, medium, or high activity scale based on a ranking of her actual activity(s) and time.

Measurement of serum hormone and plasma lipoprotein concentrations

All blood samples were collected between 0600 and 0700 h from women who had fasted for more than 10 h. Blood samples were collected during MEN (MEN days 1–2), during the early follicular phase (EF) (MEN days 4–6), during the LF (MEN days 11 through ≥ 1 days postovulation based on serum LH levels and until progesterone levels were ≥ 1 ng/mL), and during the midluteal phase (LUT) (days 7 and 8 post-LH surge).

Blood samples for lipoprotein analyses were collected in Vacutainer tubes (Becton Dickinson, Rutherford, NJ) containing solid EDTA. Aliquots of plasma obtained after centrifugation at 4 C were delivered on ice to the George Washington University Lipid Research Clinic Laboratory (Washington, D.C.). The HDL fractions were isolated on the day the samples were drawn using the heparin-MnCl₂ precipitation procedure (19). Aliquots of plasma and the HDL fractions were promptly placed at -70 C in Nunc vials (A/s Nunc, Roskilde, Denmark). All samples from an individual were analyzed sequentially as a set at the end of the study. Cholesterol and triglycerides were determined enzymatically as previously described (20). Coefficients of variation for analysis of total cholesterol, triglyceride, and HDL cholesterol averaged 1.5%, 1.8% and 3.3%, respectively. Total plasma apoA-I and apoB were determined by rate nephelometry (20). LDL cholesterol levels were derived using the equation of Friedewald *et al.* (21).

Measurements of serum hormone levels, typically on samples from greater than 16 days of a cycle, were performed by the Immunoassay Laboratory of the Genetics & IVF Institute (Fairfax, VA) on the day the samples were drawn. Estradiol and progesterone were measured by RIA (Diagnostic Products Corp., La Jolla, CA), and LH by monoclonal immunoradiometric assay (Serono, Randolph, MA) (22). Intraassay coefficients of variation were 7.0%, 5.8%, and 11.4%, respectively, and interassay coefficients of variation were 8.1%, 11.7%, and 13.3%, respectively.

Statistical analysis

Among the 20 normolipidemic women who entered the FL phase, 2 dropped out. Of the 18 completing the FL cycle, 2 declined to participate in the CD phase, 3 dropped out because of health problems, and 1 subject had highly elevated apoA-I levels (23). Therefore, the data analyses were based on values of 12 women who completed all three menstrual cycles.

ANOVA modeling was used to compare mean concentrations by phase of the menstrual cycle, and least square means (24) were determined for each phase. The ANOVA analysis included a separate intercept for each individual to take into account the correlation among the repeated measurements over the cycle. The analysis adjusted for different multiples of consecutive days of plasma concentrations for each person, because the number of days that blood was drawn varied by phase. All findings that were statistically significant at a P -value of < 0.01 are described in *Results* as a means of adjusting for multiple comparisons.

Results

Subject characteristics

The 12 study subjects had a mean age of 27 ± 3 yr, body mass index of 21 ± 2 , average menstrual cycle of 27 ± 2 days, and an average educational level of 13 ± 2 yr.

The average reported macronutrient levels during the FL cycle were 33% of the calories as fat (11.1% saturated) with a P:S ratio of 0.60, compared with 36% fat and a P:S ratio of 0.53 during the CD1 and CD2 cycles.

Hormone levels

Serum estradiol levels during the LF phase were 6-fold higher than those during the EF phase and were reversed approximately 50% in the LUT phase (Table 1). Progesterone concentrations increased over 11-fold from the LF to LUT phase, and the peak LH concentration was 84 mIU/mL at the LH surge.

Lipoprotein / apo levels

In the LUT phase of CD2, LDL cholesterol concentrations were 7% lower than the EF levels (Table 2). ApoB levels closely followed those of LDL cholesterol, but the fluctuations did not reach significance. Similar patterns and mag-

TABLE 1. Hormone concentrations by phase of menstrual cycle during second CD cycle^a

	MEN	EF	LF	LUT
Estradiol	114 ± 33	117 ± 26	731 ± 217	389 ± 103
Progesterone	ND	ND	4.1 ± 2.2	47.1 ± 15.6
Peak LH	ND	ND	84 ± 34	ND

^a Estradiol (pmol/L) and progesterone (nmol/L) least square mean ± SE; peak LH (IU/L) ± SD. MEN (days 1-2), EF (days 4-6), LF (days 11+), and luteal (days 7-8 postovulation). ND, not determined.

TABLE 2. Lipoprotein and apo during second CD cycle

	MEN	EF	LF	LUT
Lipoprotein/apo levels ^a				
Cholesterol	4.34 ± 0.07	4.38 ± 0.03	4.36 ± 0.04	4.28 ± 0.04
Triglycerides	0.59 ± 0.04	0.58 ± 0.02	0.54 ± 0.02	0.56 ± 0.02
LDL cholesterol	2.67 ± 0.05	2.70 ± 0.03	2.61 ± 0.04	2.58 ± 0.04 ^{bc}
ApoB	0.58 ± 0.01	0.60 ± 0.01	0.58 ± 0.01	0.57 ± 0.01
HDL cholesterol	1.41 ± 0.02	1.42 ± 0.01	1.50 ± 0.01 ^{de,be}	1.45 ± 0.02
ApoA-I	1.45 ± 0.02	1.44 ± 0.01	1.46 ± 0.01	1.47 ± 0.01
Lipoprotein/apo ratios				
HDL cholesterol/apoA-I	0.38 ± 0.006	0.38 ± 0.003	0.40 ± 0.004 ^{de}	0.38 ± 0.004 ^{fe}
LDL cholesterol/HDL cholesterol	1.92 ± 0.04	1.95 ± 0.02	1.80 ± 0.03 ^{be}	1.84 ± 0.03 ^{be}
ApoB/ApoA-I	0.40 ± 0.01	0.42 ± 0.01	0.41 ± 0.02	0.40 ± 0.02 ^{be}

^a Lipoprotein-cholesterol (mmol/L), triglyceride (mmol/L) and apo (g/L) levels, and lipoprotein/apo ratios (wt/wt) during menstrual cycle. Least square mean ± SE.

^b vs. early follicular.

^c P < 0.01.

^d vs. menses.

^e P < 0.005.

^f vs. late follicular.

nitude of change were found during the FL and CD1 cycles; both shifted to higher levels after initiation of the CD (Fig. 1). Concentrations at the MEN phase during the CD2 were used as a reference because any diet-induced influences on lipoprotein levels would be minimal. The HDL cholesterol level in the LF phase was 6% higher than in the MEN phase (Table 2). In contrast, peak apoA-I levels appeared in the LUT phase. However, the changes were smaller than those of HDL cholesterol and did not reach statistical significance. The differences in the HDL cholesterol and apoA-I patterns

(Fig. 2) resulted in significant cyclic changes in the ratio of HDL cholesterol to apoA-I (Table 2). The ratio peaked during the LF phase and was lowest during the MEN phase. A similar significant change appeared in the CD1 cycle (not shown). Ratios of LDL cholesterol/HDL cholesterol and apoB/apoA-I during the EF phase were significantly greater than those during the LUT phase.

Discussion

This two-cycle CD study was designed to assess hormone and lipoprotein changes across the menstrual cycle while minimizing possible effects of dietary fat on cyclic fluctuations in lipoprotein levels (6, 25), and allowing sufficient time for the lipoprotein levels to stabilize at a new steady state (26). Hormone levels were frequently analyzed to precisely identify the phases of the cycle. Results from this study demonstrate cyclic fluctuations in lipoprotein levels under these stabilized CD conditions.

After stabilization, LDL cholesterol (and apoB) peaked during the EF phase and were at their lowest levels during the LUT phase. Thus, levels of both LDL cholesterol and apoB were at a minimum when estrogen and progesterone levels were high. On the other hand, HDL cholesterol levels were highest in the LF phase when estrogen levels were at a maximum. Changes in apoA-I levels were markedly smaller than those of HDL, and levels peaked in the LUT phase.

The cyclic change in LDL cholesterol is in accord with prior studies (5-10). An identical fluctuation in LDL cholesterol (0.1 mmol/L) was reported in one of the two CD studies (12). Similar fluctuations in HDL cholesterol (0.05-0.10 mmol/L) were found in both studies (6, 12), but fluctuations in LDL and HDL cholesterol did not reach significance in one of the

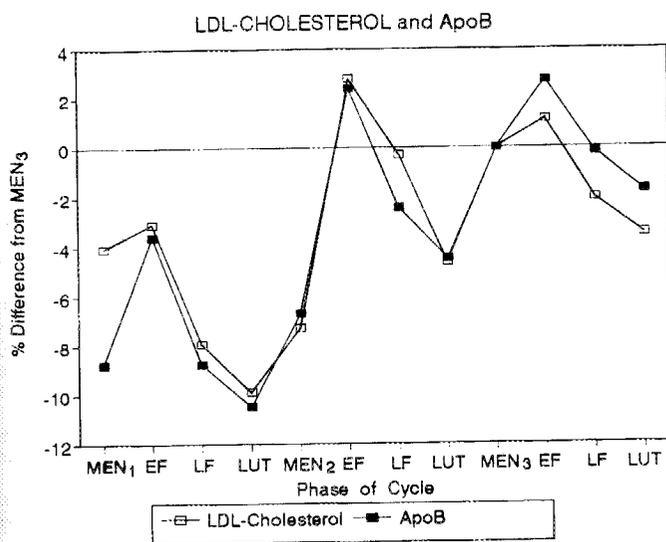


FIG. 1. Percent changes in LDL cholesterol and apoB compared with MEN concentrations during second CD cycle. MEN₁, MEN of FL cycle; MEN₂, MEN of first CD cycle; and MEN₃, MEN of second CD cycle.

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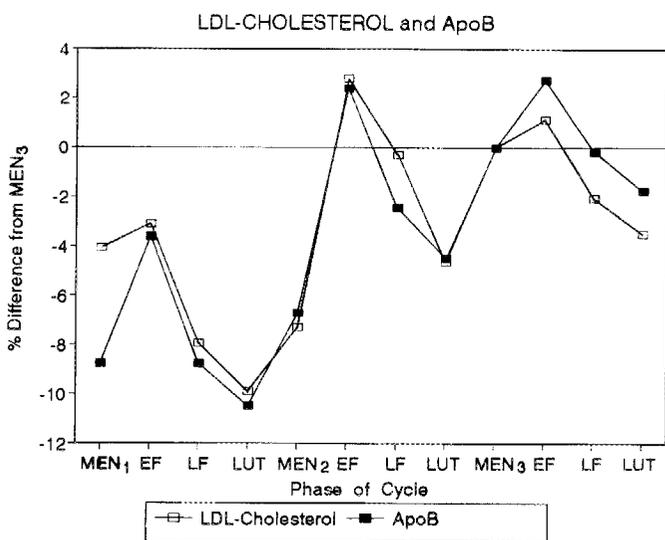


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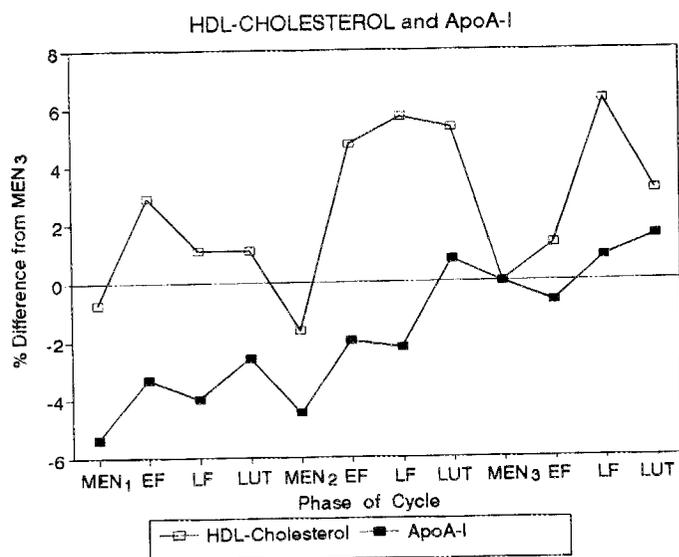


FIG. 2. Percent changes in HDL cholesterol and apoA-I compared with MEN concentrations during second CD cycle. MEN₁, MEN of FL cycle; MEN₂, MEN of first CD cycle; and MEN₃, MEN of second CD cycle.

studies (12). Possible reasons for not achieving significance are: 1) variable recoveries of LDL in ultracentrifugation fractions, 2) single samples were analyzed from each of the phases, 3) day-to-day variations in analyses, and 4) the SES were double those in the current study.

The suppression of LDL levels during the phases when estradiol levels are high is consistent with the established decrease in LDL levels by exogenous unopposed estrogens (1, 2). Presumably, the decrease in LDL could be attributed to an estrogen-induced increase in hepatic LDL-receptor activity during the LF and LUT phases (27). In addition, the demands of growth of the endometrial lining and steroid hormone synthesis during the follicular and LUT phases of the cycle could contribute to the decrease in LDL during these phases. The LDL receptors of the corpus luteum peak during the LUT phase (28), and granulosa cells reportedly assimilate LDL for progesterone synthesis (29). A reported rate of progesterone secretion of 40 mg/day (0.12 mmol/day) by the corpus luteum (30) is nearly one-half of the reduction in LDL cholesterol (assuming a 2.7 liter plasma volume) during the LUT phase.

Differences in the HDL cholesterol and apoA-I fluctuations resulted in a higher ratio of HDL cholesterol to apoA-I in the LF phase, indicative of an alteration in HDL composition. Azogui *et al.* (13) recently reported an increased HDL cholesterol/apoA-I ratio at day 23 after MEN (midluteal) compared with the ratio at days 1 (EF) and 14 (LF) of the cycle. The study was in a FL population, and the menstrual cycle phases were not clearly described to assure that days 14 and 23 truly reflected the respective LF and LUT phases. These methodological issues may have contributed to the apparent discrepancy with the current findings. The LF increase in HDL cholesterol and in the proportion of HDL cholesterol to apoA-I is likely caused by an increase in the HDL_{2a} subfraction (31), and thus, an increase in the HDL lipid content after midcycle. These changes may be caused by

a decrease in hepatic lipoprotein lipase activity during the LUT phase of the cycle (32), resulting in a decrease in the removal of cholesterol from HDL and in the conversion of HDL₂ to HDL₃.

In summary, under CD conditions and with precise identification of phases of the menstrual cycle, significant cyclic fluctuations were found in LDL and HDL cholesterol, the ratios of LDL cholesterol/HDL cholesterol and apoA-I/apoB, and the cholesterol content of HDL. The cyclic fluctuations in lipoprotein levels need to be taken into consideration in the screening and medical monitoring of lipoprotein levels in premenopausal women. Further, failure to take these cyclic changes into account could confound the results of studies involving premenopausal women.

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