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Variation of Lipids and Lipoproteins in Premenopausal Women Compared With Men and Postmenopausal Women

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Numerous studies have reported cyclic fluctuations in lipids and lipoproteins as a function of the phase of the menstrual cycle. However, the reported patterns are quite variable and have led to an unclear picture of the influence of the menstrual cycle on the variability of lipids, and hence of the role of the menstrual cycle phase in the interpretation of serum lipids for premenopausal women. As part of the DELTA Study (Dietary Effects on Lipoproteins and Thrombogenic Activity), we evaluated the cyclic variation of circulating lipids and lipoproteins in 39 premenopausal women and compared intraindividual variances in these women, 18 postmenopausal women, and 46 men under conditions of tight dietary control. Cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, triglyceride, apolipoproteins A-1 (apo A-1) and B-100 (apo B-100), and lipoprotein (a) [Lp(a)] all demonstrated cycling in the premenopausal women. However, the observed cycling accounts for only a small fraction of the total biologic variability of lipids in premenopausal women. The magnitude of total intraindividual variability based on coefficient of variation (CV) for these lipids in premenopausal women (CV, 4% to 8.1%) was similar to that found for men (CV, 4.3% to 9.1%) and for postmenopausal women (CV, 3.7% to 6.7%). These results suggest that protocols for screening and monitoring of serum lipids in premenopausal women need not differ from those used for men or postmenopausal women.

PLASMA LIPIDS and lipoproteins have been reported to vary in premenopausal women in a cyclic pattern related to the hormonal influences associated with the menstrual cycle.[1-8] This cyclic variability, reported in some studies to be as high as 20%,[2,6] has made some investigators reluctant to include premenopausal women in observational studies and clinical trials. Their primary concern is that changes in lipid and lipoprotein outcome parameters might be obscured or exaggerated by large and seemingly unpredictable variations due to the menstrual cycle. Controlling for this putative variation would require including a larger number of women or collecting blood samples at specific points in the menstrual cycle.

Although numerous studies have reported cyclic fluctuations in one or more lipids,[1-10] the results are variable, with some studies reporting cyclic variations and others reporting no change or changes in the opposite direction. These contradictory results have led to an unclear picture of the influence of the menstrual cycle on lipids and lipoproteins.

In addition, most studies that have reported a variation of lipids and lipoproteins with the menstrual cycle have focused solely on premenopausal women. They have not included any control populations of men or nonmenstruating women to permit a comparison of the relative contribution of the menstrual cycle to the total intraindividual variation. Few studies have controlled for diet or even collected food intake data from the subjects.

In this study, we report our findings on the variation of cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, triglyceride, lipoprotein(a) [Lp(a)], and apolipoproteins A-1 (apo A-1) and B-100 (apo B-100) for a population of men, premenopausal women, and postmenopausal women enrolled in a multicenter study providing well-controlled diets. This experimental design allowed us to assess the variability in these endpoints based on measurements from 3 separate 4-week periods.

SUBJECTS AND METHODS

The current study is part of the multicenter DELTA Study (Dietary Effects on Lipids and Thrombogenic Activity). The purpose of the

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DELTA Study was to determine the effects of an increase in the fraction of calories from total and saturated fat on the concentration of blood lipids and coagulation factors. Briefly, subjects were studied over three 8-week periods during which they were fed different diets designed to provide 26%, 30%, and 37% of total calories as fat (with 5%, 9%, and 16% from saturated fat) and less than 300 mg cholesterol per day.[11,12] The design, methodologic details, and results of the DELTA Study are described more completely elsewhere.[12-16]

Subjects

The healthy normolipidemic adults (aged 22 to 67 years) included 39 premenopausal women, 18 postmenopausal women, and 46 men, 30 of whom were under 40 years of age. Of the subjects, 25% were black and 75% were white. Premenopausal women kept a menstrual calendar identifying the days of menses during each 8-week feeding period. Each subject signed a consent form to participate, and the projects were approved by the local Institutional Review Boards.

Measurements

Blood samples were drawn once per week during each of the last 4 weeks of each 8-week feeding period, allowing time for lipids to stabilize on each diet. A standardized protocol ensured that subjects had fasted for at least 12 hours. Serum was isolated and frozen at −80°C within 1 to 3 hours of collection.

Serum samples were analyzed for cholesterol, HDL-cholesterol, and triglyceride using enzymatic methods standardized through the Centers for Disease Control (CDC) Lipid Standardization Program. LDL-cholesterol values were calculated using the Friedewald formula.[17] Serum was analyzed for Lp(a) by enzyme-linked immunosorbent assay (Strategic Diagnostics, Newark, DE), and apo A-1 and apo B-100 were analyzed by immunonephelometry (Beckman, Brea, CA). All samples from an individual participant were thawed and analyzed immediately in a single analytic run. The analytic coefficients of variation (CVs) for cholesterol (1%), HDL-cholesterol (1.5%), and triglycerides (3.0%) are based on the within-run CVs determined by the CDC using challenge samples that validated both the accuracy and precision of measurements. CVs for apolipoproteins were determined from control materials analyzed multiple times (apo A-1, 1.8%; apo B-100, 1.0%; and Lp(a), 4.5%).

Serum samples from premenopausal women were also analyzed for estradiol, luteinizing hormone (LH), and progesterone by radioimmunoassay (Diagnostics Products, Los Angeles, CA).

Statistical Analyses

Circulating concentrations of lipids and lipoproteins were compared for premenopausal women, postmenopausal women, and men. Untransformed concentrations of total cholesterol, HDL-cholesterol, LDL-cholesterol, apo A-1, and apo B-100 were used for statistical analyses, whereas triglyceride and Lp(a) concentrations, which are not normally distributed, were transformed to the ln Trig and square root of Lp(a).

Two separate sets of linear mixed models were used, one to estimate components of variance in the absence of predictor variables for the menstrual cycle, and the other to compare phases of the cycle with respect to mean lipid levels and to estimate mean lipid levels as a curvilinear function of the day of the menstrual cycle. The family of curvilinear functions was defined in terms of a constant term plus lower-order sine and cosine functions as specified by the discrete Fourier transform [sin(2π day/28), cos (2π day/28), sin (4π day/28), cos (4π day/28)]. All of the fitted linear models assumed 3 components of variance: (1) intersubject deviation from the overall subpopulation mean, which reflects innate differences in baseline cholesterol values of individual subjects; (2) intersubject variation in response to the diet, which reflects the variation in the individual response to changes in the diet; and (3) residual intrasubject variation, which is the sum of the analytical and biological variances—in this case, a composite within-diet variance that does not include the effect of diet-to-diet changes since they are included in the variance of the individual response to the diet. Intraindividual variance may be represented as σ^2total = σ^2biol + σ^2anal.[18,19] The excellent assay precision, reflected by low within-run CVs for the analytical methods, results in the analytical variance contributing only a minor component to the total intraindividual variance. For example, for cholesterol for men, less than 2% of the total variance is from analytic sources. The biologic SD would be 9.97 mg/dL, as compared with the intraindividual SD of 10.1 mg/dL. The biologic CV would be 4.98%, as compared with the total intraindividual CV of 5.0%. Therefore, for this study, we report the total intraindividual variance with no adjustment for the contribution of analytical variance.

The phases of the menstrual cycle were defined by serum hormone levels and a self-reported menstrual calendar. Estradiol, LH, and progesterone concentrations were each fitted to a model that included a constant term plus lower-order sine and cosine functions as specified by the discrete Fourier transform. The phases of the menstrual cycle were chosen based on combinations of maxima and minima of hormone concentrations. Two-phase, 3-phase, and 4-phase models were all considered to allow a comparison of our results to other studies. A simple 2-phase model was based on low and high progesterone concentrations defining the follicular phase as days 1 to 14 and the luteal phase as days 15 to 28. A 3-phase model added an ovulatory phase defined as the time of elevation of LH, which yielded an early follicular phase (days 1 to 8), an ovulatory phase (days 9 to 18), and a late luteal phase (days 19 to 28). A 4-phase model, which is the most refined, distinguished a late luteal/menses phase reflecting a decrease to minima for all hormone concentrations (follicular, days 3 to 9; ovulatory, 10 to 16; midluteal, 17 to 23; and late luteal/menses, 24-28). Since the 4-phase model provides the greatest detail, the results presented herein are based on the 4-phase model.

RESULTS

The phases of cyclic variation for premenopausal women were defined using a combination of menstrual calendar data and statistical modeling of the serum concentration of 3 hormones—estradiol, progesterone, and LH. Table 1 is a summary of the mean concentration of these hormones for each phase of a 4-phase cycle, validating the cycle assignments.

The mean values for lipids and lipoproteins for each phase of a 4-phase cycle are shown in Table 2. All lipids and lipoproteins except apo B-100 showed a statistically significant pattern of cycling. Total cholesterol and LDL-cholesterol were lowest at

Table 1. Hormone Concentrations in Premenopausal Women During Different Phases of the Menstrual Cycle (mean ± SE)

Hormone	Follicular (days 3-9)	Ovulatory (days 10-16)	Luteal (days 17-23)	Late Luteal/ Menses (days 24-28)
Estradiol (pg/mL)	47.5 ± 7.06	118.1 ± 11.36	120.5 ± 12.58	95.06 ± 7.49
Progesterone (ng/mL)	1.27 ± 0.62	2.01 ± 0.57	8.48 ± 0.85	6.09 ± 0.69
LH (IU/mL)	2.24 ± 0.56	7.20 ± 0.58	3.60 ± 0.59	3.08 ± 0.58

NOTE. Days assigned to each phase represent that phase as determined by hormone cycling patterns of the best-fit curves. The values reported are taken from the best-fit curve. The follicular phase was defined by low progesterone and estradiol and increasing LH; the reported value is for day 6. The ovulatory phase was defined by low progesterone, high estradiol, and high LH; the reported value is for day 14. The luteal phase was defined as high progesterone, high estradiol, and decreasing LH; the reported value is for day 20.5. The late luteal/menses phase was defined by decreasing progesterone and estradiol and minimum LH; the reported value is for day 26.5.

Table 2. Lipid and Lipoprotein Concentrations in Premenopausal Women During Different Phases of the Menstrual Cycle (mean ± SE)

Parameter (mg/dL)	Follicular	Ovulatory	Luteal	Late Luteal/ Menses	*P*‡
Cholesterol*	171.2 ± 4.72	170.1 ± 4.71	169.0 ± 4.72	165.6 ± 4.71	<.001
HDL-cholesterol*	53.2 ± 2.30	54.1 ± 2.30	54.0 ± 2.30	51.8 ± 2.30	<.001
LDL-cholesterol*	104.4 ± 4.29	101.5 ± 4.28	101.0 ± 4.29	100.4 ± 4.28	.004
Apo A-1	138.3 ± 3.95	140.5 ± 3.94	141.0 ± 3.95	135.1 ± 3.95	<.001
Apo B	94.3 ± 4.62	93.4 ± 4.61	92.7 ± 4.62	91.7 ± 4.61	.118
Triglycerides†	68.0 ± 6.47	72.0 ± 6.81	70.0 ± 6.66	65.2 ± 6.21	<.001
Lp(a)†	30.2 ± 6.41	29.6 ± 6.36	31.2 ± 6.53	31.6 ± 6.55	.002

NOTE. The data are from 39 premenopausal women and 3 4-week periods.

*Cholesterol in mg/dL is multiplied by 0.0259 to convert to mmol/L.

†Triglycerides were transformed to ln Trig and Lp(a) to the square root of Lp(a) for statistical comparisons; the table shows the median rather than the mean.

‡*P* value for the test of the null hypothesis, ''the lipid level is not a function of the day of the menstrual cycle.''

menses and highest during the follicular phase. In contrast, HDL-cholesterol and triglycerides were highest during ovulation. A 2-phase model reflecting only the follicular and luteal phases and a 3-phase model with no distinct late luteal/menses phase failed to detect the cycling of many lipids and lipoproteins that was identifiable in the more refined 4-phase model.

Table 3 compares the total within-diet intraindividual variability of lipids and lipoproteins for premenopausal women, men, and postmenopausal women. Since the magnitude of the variance is influenced by the absolute concentration and the concentrations differ significantly for the 3 groups, we also computed intraindividual CVs (100 × SD/mean) for each analyte. Intraindividual CVs for our subjects were 4.9% to 5.7% for cholesterol, 6.7% to 8.2% for LDL-cholesterol, 5.6% to 6.6% for HDL-cholesterol, 3.7% to 4.9% for apo A-1, and 5.4% to 7.3% for apo B-100.

The intraindividual variation in cholesterol is compared with the variation in the population mean in Fig 1. The variations are reported as a function of time over 28 days. For premenopausal women, the index date (day 0) is the self-reported first day of the menstrual cycle. For postmenopausal women and men, the index date is a randomly assigned date within the last 4 weeks of the feeding period. The population means for cholesterol show a distinct cycling pattern in premenopausal women but not in postmenopausal women or men. The amplitude of cycling in premenopausal women (a change of 5.6 mg/dL or 0.14 mmol/L from the minimum at menses to the maximum during the follicular phase) is small compared with the magnitude of the intraindividual variation (range, 38.8 mg/dL or 1 mmol/L from −2 SD to +2 SD) (Table 3). Plots of the other lipids (not shown) are similar to the plot for cholesterol, with cycling evident only in premenopausal women and with a small magnitude relative to the total intraindividual variation.

Table 3. Intraindividual Variability of Lipids and Lipoproteins in Men and Women

Parameter	Women		Men
	Premenopausal	Postmenopausal	
Cholesterol			
Mean (mg/dL)*	169.2	208.4	200.5
Variance	93.4	106.3	101.5
SD (mg/dL)	9.7	10.3	10.1
CV (%)	5.7	4.9	5.0
HDL-cholesterol			
Mean (mg/dL)*	53.3	53.2	44.5
Variance	12.3	11.5	6.1
SD (mg/dL)	3.5	3.4	2.5
CV (%)	6.6	6.4	5.6
LDL-cholesterol			
Mean (mg/dL)*	101.9	136.9	135.4
Variance	71.2	83.7	87.7
SD (mg/dL)	8.4	9.2	9.3
CV (%)	8.2	6.7	6.9
Apo A-1			
Mean (mg/dL)	138.7	146.3	127.4
Variance	46.2	28.7	32.1
SD (mg/dL)	6.8	5.3	5.7
CV (%)	4.9	3.7	4.4
Apo B-100			
Mean (mg/dL)	93.2	120.5	126.9
Variance	46.0	48.7	47.0
SD (mg/dL)	6.8	7.0	6.9
CV (%)	7.3	5.8	5.4
Triglycerides Ln Trig			
Median (mg/dL)	68.7	85.7	95.5
Mean	4.230	4.451	4.559
Variance	0.028	0.031	0.038
SD	0.167	0.176	0.195
CV (%)	4.0	4.0	4.3
Lp(a) SQRT Lp(a)			
Median (mg/dL)	31.1	28.6	12.5
Mean	5.58	5.35	3.53
Variance	0.162	0.076	0.103
SD	0.40	0.28	0.321
CV (%)	7.2	5.2	9.1

Abbreviation: SQRT, square-root–transformed.

*Cholesterol in mg/dL is multiplied by 0.0259 to convert to mmol/L.

DISCUSSION

Biologic variability can be a major source of inaccuracy in the assessment of cardiovascular risk based on the measurement of lipids and lipoproteins. A single measurement of cholesterol or HDL-cholesterol can be quite different from the individual's mean value. Consequently, risk assignment based on a single measurement can be inadequate or incorrect. Likewise, assessing the success of an intervention such as diet or exercise by monitoring the changes in lipids and lipoproteins based on single measurements can misrepresent the impact of the inter-

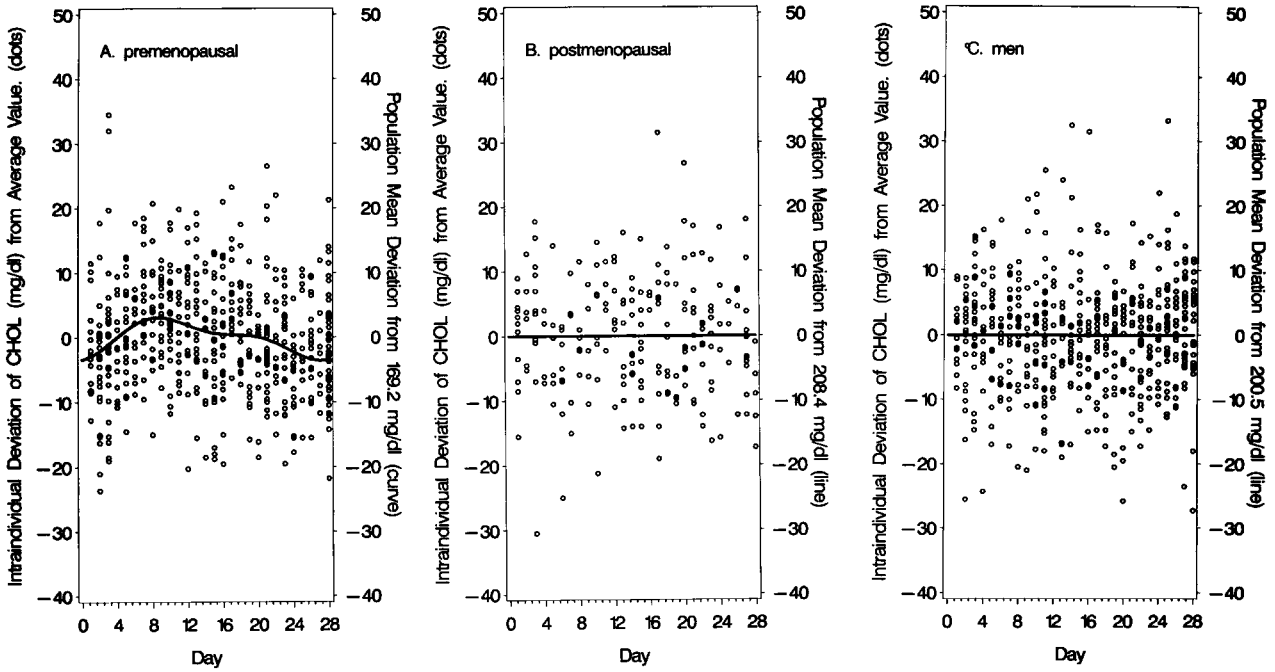

Fig 1. Variability of serum cholesterol. Data are displayed as the deviation from a reference value. The curve or line represents the deviation of the subpopulation mean for the analyte at that point in time compared with the overall population mean value for the entire period (shown on the right y-axis). Circles represent the deviation of a single measurement of cholesterol for an individual from the overall mean value of cholesterol for that individual. Intraindividual variations are computed independently for each diet period. For premenopausal women (A), the first day of menses was the index day—based on a self-reported menstrual calendar and confirmed by hormone concentrations (estradiol, progesterone, and LH). For postmenopausal women (B) and men (C), the index day was randomly selected for each subject.

vention. Characterizing the intraindividual variability in lipids and lipoproteins, as presented herein, is useful when assessing individual outcomes and when designing clinical trials that seek adequate power to detect expected changes in these endpoints.

Based on the analysis of serum samples for each of 103 individuals during three 4-week intervals spanning an 8-month time frame, we have demonstrated that the within-subject variance for serum lipids and lipoproteins is not markedly different for premenopausal women versus men or postmenopausal women. For example, the variance of cholesterol is lower in premenopausal women (93.4 mg/dL, 2.42 mmol/L) versus men (101.5 mg/dL, 2.62 mmol/L) or postmenopausal women (106.3 mg/dL, 2.75 mmol/L). This finding is similar to the findings of Ginsberg et al,[20] who reported that the within-subject variation for plasma cholesterol was lower in 13 young women (as reflected by the root mean square error of 0.148 mol/L) versus 20 young men (root mean square error, 0.257 mmol/L) enrolled in 2 controlled-diet studies of similar design.[21]

Since total cholesterol is lower in premenopausal women versus the other 2 groups, we adjusted for the differences in mean values by comparing the CVs. Premenopausal women demonstrated a lower intraindividual CV (4.9%) compared with men (5.0%) and postmenopausal women (5.7%). These CVs are somewhat lower than the intraindividual CVs of 6.7% to 7.8% reported by others.[18,19] Since our calculations are for within-diet variability, the discrepancy is likely to reflect the added contribution of dietary variation in the other studies, which did not control for diet.

The magnitude of changes from the lowest to the highest values during the menstrual cycle is more modest in this study than in many other studies. For example, our observed change in cholesterol between the follicular phase and late luteal/menses phase of −5.6 mg/dL (0.14 mmol/L) is less than the range of −10.9 to −13.5 mg/dL (0.28 to 0.35 mmol/L) reported by others.[1,4,7] The relatively small magnitude of the changes we observed may reflect the tightly controlled diets consumed by these participants such that the calorie, carbohydrate, protein, and fat intakes did not change.[10,22-23]

To ensure complete and accurate analysis, we examined our data using 2-, 3-, and 4-phase models, as well as a continuous-time cyclic model. We confirmed the assignment of day or phase of cycle for all participants by combining the first day of menses reported on the menstrual calendar with a fit to the cyclic models of each hormone level. Although each of our mathematical models confirmed some statistically significant changes, the 4-phase model gave the most complete reflection of variation across the cycle. Since the observation of differences may be masked by the choice of times during the cycle that values are observed, some discrepancies in the literature may derive from incomplete consideration of the entire cycle and inopportune comparison of 2 parts of the cycle wherein the lipid of interest is coincidently at the same level.

Since most other studies have not included men or postmenopausal women for comparison, the variation due to cycling has been interpreted as evidence that premenopausal women are a hypervariable subgroup and that some special consideration of this needs to be taken into account in both clinical and research settings. Our study suggests that men and postmenopausal women demonstrate the same biologic variability as premenopausal women. This implies that in a clinical setting, to correctly classify the risk of cardiovascular disease or to

correctly assess changes in risk based on serum lipids, premenopausal women may be monitored in the same way as men or postmenopausal women. For observational studies and dietary trials, the power to detect a difference should not be altered by the inclusion of premenopausal women in the subject population, nor should special protocols be needed to adjust monitoring to control for the phase of the menstrual cycle.

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