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Variations in lipid levels according to menstrual cycle phase: clinical implications

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Abstract

Understanding variations in lipoprotein cholesterol levels throughout the menstrual cycle is important because there may be clinical implications regarding the appropriate timing of measurement and implications on the design and interpretation of studies in women of reproductive age. Our objective was to review the evidence comparing lipoprotein cholesterol levels throughout the menstrual cycle among premenopausal women. Overall, lipoprotein cholesterol levels were observed to vary in response to changing estrogen levels. Taken together, the evidence suggests that total cholesterol and LDL-C tend to be highest during the follicular phase and to decline during the luteal phase, with HDL C highest around ovulation. Based on these findings, the menstrual cycle phase should be taken into account when evaluating lipoprotein cholesterol levels among reproductive-aged women. Measuring cholesterol levels during menses is recommended for consistent comparisons as this phase can be more reliably identified than other phases, although women within National Cholesterol Education Program acceptable ranges, but near the boundaries when tested during menses, should undergo additional tests.

Keywords

cholesterol; estrogen; lipoprotein; menstrual cycle

According to the National Cholesterol Education Program (NCEP) guidelines, total blood cholesterol levels greater than or equal to 200 mg/dl put the average US adult at elevated risk for coronary heart disease (CHD) [1]. High lipoprotein cholesterol is one of the primary risk factors for heart disease, the leading cause of death among women [2]. Interestingly, the prevalence of cardiovascular disease (CVD) among women aged 20–39 years is half of that for men in the same age group (women: 7.8%; men: 15.9%). The sex disparity in CVD narrows with increasing age as the prevalence among women increases, leading researchers to consider estrogen as a potential modifying factor in CVD risk. As increasing evidence shows that estrogen levels impact various metabolic systems in the body, guidelines may need to be tailored separately to men and women. However, NCEP blood cholesterol guidelines are not sex-specific, despite the differences in health and risk factors between men and women.

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Based upon the increased risk for CVD for postmenopausal women when compared with premenopausal women, hormone therapy (HT) was recommended to postmenopausal women as a means of cardioprotection [3–6]. Concurrently, randomized controlled clinical trials were implemented to further examine the cardioprotective effects of HT. While the Women's Health Initiative (WHI) trial [7] and the Heart and Estrogen/Progestin Replacement Study (HERS) [8] found an antiatherogenic lipid profile among women using exogenous estrogens, estrogen plus progestin therapy was associated with increased rates of CHD. Although these studies may not demonstrate a direct relationship between lipid levels and CHD due to potential confounding by age and duration and indication of treatment, these results support the cardioprotective properties of HT, and especially estrogen-only HT. Furthermore, while estrogen-only HT showed the largest improvements in lipid levels among postmenopausal women [7–10], there is also evidence to suggest that exogenous estrogens in the form of oral contraceptives also improve the lipid profile among premenopausal women, although results depend upon the formulation and dose [11–14]. The effects of endogenous estrogens on the lipid profile are less clear, although there are strong biological mechanisms to support a beneficial role of estrogen in lipoprotein metabolism [15,16]. Conversely, progesterone is thought to oppose the stimulatory effects of estrogen or have a neutral effect on lipoprotein metabolism [13]. Thus, any antiatherogenic effect of reproductive hormones on lipid levels is usually attributed to estrogen.

Despite the increases in CHD among post-menopausal women on HT, questions regarding the role of endogenous estrogens on lipoproteins in premenopausal women remain. Understanding the impact of endogenous estrogens is critical for proper management of lipid levels, which are an important contributor to atherosclerosis. Furthermore, the effects of endogenous and exogenous estrogens may vary, and evaluation of the role of endogenous estrogens on lipoprotein metabolism may help to elucidate the role of estrogen in protecting premenopausal women against CHD. Lastly, understanding variations in lipoprotein cholesterol levels is important because there may be clinical implications regarding the appropriate timing of measurement during the cycle and implications on the design and interpretation of studies in women of reproductive age.

Therefore, our objective was to review the epidemiological evidence comparing lipoprotein cholesterol levels across the menstrual cycle among premenopausal women, highlight results from a recent large prospective study and discuss potential clinical implications regarding these findings.

Epidemiological evidence

Numerous epidemiological studies have evaluated the role of endogenous estrogens in lipoprotein metabolism. These studies yielded conflicting results, with some observing fluctuating plasma lipid levels throughout the menstrual cycle [17–32], while others found a lack of variation in lipid levels over the menstrual cycle [33–40]. These differences could be due to study design differences including small sample size, follow-up for only a single menstrual cycle and/or timing of sample collection, heterogeneity in markers of ovulation or inconsistencies in the timing of lipoprotein and hormone measurements. Various methods of timing of lipoprotein cholesterol measurements to menstrual cycle phase were implemented, including determining hormone levels by basal body temperature methods [22,37], ovulation charts [18] or blood samples [18,22,23,25,27–29,34,35,37,41]. Most studies typically only compared lipoprotein cholesterol levels between the follicular and luteal phases of the cycle, and did not estimate associations between hormone levels and lipoproteins at multiple points during the cycle. Many studies found that only certain component measures of lipoprotein cholesterol (total cholesterol [TC], HDL-C, LDL-C or triglycerides) differ between cycle phases.

Lipoprotein cholesterol levels varied across the menstrual cycle. Specifically, TC and LDL-C were most often lower during the luteal phase, corresponding to the time of the menstrual cycle when estrogen and progesterone levels are high compared with the follicular phase. Furthermore, HDL-C levels were typically highest during the late follicular and periovulatory phases, a finding that tended not to be observed in studies that only compared measurements during the follicular and luteal phases. The increases in TC and LDL-C immediately prior to ovulation, and peak levels of HDL-C at ovulation, are of great physiological importance as cholesterol, and VLDL-C in particular, constitutes the precursor for steroid synthesis and needs to be dramatically increased should a pregnancy occur. Table 1 summarizes the results of studies that compared levels between phases. The mean changes in TC levels across the menstrual cycle varied between 4 and 10%, LDL-C between 4 and 12.5% and HDL-C by 11% across the studies evaluated. The mean intraindividual variability reported for TC ranged from 8 to 19%. Triglyceride levels did not vary cyclically throughout the cycle. Certain studies also reported various lipoprotein particle subfractions, although further work is needed in this area.

Not only do lipoprotein cholesterol levels differ between the follicular and luteal phases, but they have been shown to vary on a day-to-day basis throughout the cycle. In the largest study to date, hormones and lipoprotein cholesterol were measured at up to eight visits per cycle, for up to two cycles in a cohort of 259 healthy, regularly menstruating women [42]. Collection of these fasting blood samples was timed to specific phases of the menstrual cycle using fertility monitors. These multiple measurements enabled evaluation of the patterns of means and the variability of lipoprotein cholesterol levels across the cycle. As shown in Figure 1, TC and LDL-C follow a similar pattern across the menstrual cycle, with levels increasing rapidly after menses, peaking during the follicular phase and then declining throughout the luteal phase. The peak levels of TC and LDL-C were observed during the follicular phase prior to the rise and peak of estrogen, with TC and LDL-C levels declining during the luteal phase, corresponding to rising and peak concentrations of estrogen and progesterone. HDL-C levels were highest around ovulation, corresponding to high levels of estrogen, whereas triglyceride levels varied without a consistent pattern across the cycle. Interestingly, variability in lipoprotein cholesterol measurements fluctuated across the cycle (Figure 2). Minimum variation in TC, LDL-C and triglycerides was observed during menses and around ovulation, with HDL showing the most variability around ovulation. Many of the other studies reviewed observed similar variation in lipoprotein levels (standard errors or variance) during the follicular and luteal phases of the cycle, while some did not report the levels of variability. Among the studies reporting measurements during menses [18,24,27,29,39], most detected a decrease in the variability of TC levels [18,24,39], while an increase in variability in HDL levels around ovulation was observed in one other study [29].

Owing to the observed day-to-day changes in both the mean and variability of lipoprotein cholesterol levels, studies have analyzed the association between estrogen and lipoprotein cholesterol levels across the cycle (Table 2). Positive correlations and associations between HDL and estrogen levels were observed. TC and LDL-C levels were inversely associated with estrogen levels, although findings were not statistically significant in all of the studies. In the most recent study, endogenous estrogen was also positively associated with TC and HDL-C and inversely associated with LDL-C in acute effects models (which consider hormones and lipoprotein cholesterol measured on the same day), and significantly and inversely associated with TC and LDL-C levels during the cycle in persistent effects models (which consider hormones measured at the visit immediately prior to measurement of lipoprotein cholesterol levels) [42]. These models took into account repeated measurements across the cycle, levels of other circulating reproductive hormones and other factors known to impact these associations, such as age and BMI [42]. Further adjustment for physical

activity and dietary intake did not alter the results. These findings suggest that estrogen has a rapid effect on increasing TC and HDL-C levels and decreasing LDL-C levels, as well as nonacute effects on decreasing LDL-C, which lead to decreases in TC.

Taken together, these studies show cyclic changes in lipoprotein cholesterol levels during the menstrual cycle, which are associated with circulating estrogen levels. The changes in lipids between different days of the menstrual cycle are fairly small, but should be taken into account when evaluating lipoprotein cholesterol levels among reproductive-aged women, particularly in light of the corresponding differences in lipid variability observed over the course of the menstrual cycle.

Biological rationale

Changes in lipoprotein cholesterol levels during the menstrual cycle in response to fluctuating estrogen levels are well supported by the available biological evidence. Initially, the rates of formation of all lipoprotein fractions increase to some degree under the influence of estrogen, but their removal rates are variably increased or decreased [15]. There is growing evidence that improvements in the atherogenic nature of the plasma lipid profile in response to endogenous or exogenous estrogen consist of increasing VLDL synthesis, which subsequently increases HDL and decreases LDL. These changes depend upon an elegant interaction of many components. The upregulation of the LDL receptors increases clearance of LDL-C, while upregulation of the ATP-binding cassette transporter and apoA-I increases HDL synthesis, and the suppression of hepatic class B scavenger receptors expression leads to decreased hepatic selective cholesterol uptake from HDL and further effects on LDL [43–45]. The evidence reviewed supports these findings in that endogenous estrogen improves the lipid profile by elevating HDL levels and lowering LDL levels. Alternatively, fluid retention and hemodilution during the luteal phase induced by rising progesterone levels could potentially account for a portion of the reduction in lipoprotein cholesterol levels during the luteal phase. However, some studies demonstrate that the cyclic changes in lipoprotein cholesterol levels are greater than the accompanying changes in plasma volume [18,27,46].

Clinical implications

Based on these findings, menstrual cycle phase should be taken into account when evaluating lipoprotein cholesterol levels among reproductive- aged women in order to improve interpretation in clinical settings and in future research.

Although the changes observed in mean levels by cycle phase were modest (only 5–8% on average), these differences have potential clinical implications for reproductive-aged women. In fact, women crossed clinical boundaries of acceptable lipoprotein cholesterol levels when tested at different phases of the menstrual cycle. Specifically, fewer women were classified as having high cholesterol when measured during the luteal phase compared with the follicular phase (TC: 7.9 vs 14.3%; LDL: 10.5 vs 17.8%) [42]. Based on these findings, the mid-follicular phase may be the best phase for measurement to reduce false negatives if we assume that management of a woman’s cholesterol should be based on a level outside the NCEP guidelines at any point during the cycle. While treatment decisions regarding the lipid profile may still require repeated samples above the recommended level, standardizing the timing of lipid measurements may improve the interpretability of results and consequently reduce the overall number of tests. Notably, the observed changes occurred among healthy women. It is possible that variability in lipoprotein cholesterol levels over the course of the menstrual cycle could be even greater among other groups of women.

While the best time to measure cholesterol during a woman's cycle has yet to be established, measurements should be made at the same time each month for consistent comparisons. Even measurements taken a week or two apart may be quite different solely because of changing estrogen levels. Both women and physicians should take menstrual cycle phase into account when interpreting a woman's cholesterol measurement. Measurements during menses consistently had the least amount of variability in several studies, and given the difficulties in timing clinic visits to other phases of the cycle, we recommend measuring cholesterol levels during menses to ensure consistent comparisons. However, due to menstrual cycle variability, any woman that is within NCEP acceptable ranges but near the boundaries during menses should undergo additional tests.

Conclusion

Overall, lipoprotein cholesterol levels have been observed to change over the menstrual cycle in response to changing reproductive hormone levels. TC and LDL-C tend to be highest during the follicular phase and to decline during the luteal phase. HDL-C is most often highest during the late follicular and periovulatory phases. Based on these findings, the menstrual cycle phase should be taken into account when evaluating lipoprotein cholesterol levels among reproductive-aged women. Testing during menses is recommended to facilitate consistent comparisons due to reduced variability during this time and because this menstrual cycle phase can be more reliably identified than others. Implementation of uniform timing of cholesterol testing in reproductive-aged women would improve interpretation in clinical settings as well as future studies. These findings are important in that they show that the standard of care based on men are not necessarily appropriate for women, and that women need to be studied directly. Thus, considering menstrual cycle phase in the development of clinical guidelines for reproductive-aged women could improve the current standard of care.

Future perspective

Although recent studies have elucidated the hormonal effects on lipoprotein metabolism, many questions remain. Of great interest is the role of androgens in this setting as androstendione and testosterone are both precursors of estrogen and thus covary with estrogen levels during the menstrual cycle. It is hypothesized that androgens oppose the stimulatory effects of estrogen, and future studies need to take circulating estrogens, progesterone and testosterone into account. This may further elucidate the suggestion of an association between polycystic ovary syndrome and CHD. In addition, thyroid hormones and insulin metabolism are intricately connected to lipoprotein metabolism, and future research should evaluate the interplay between these systems in a comprehensive manner. Furthermore, now that the importance of menstrual cycle phase has been introduced, the particular times in the cycle that should be measured remain unclear. It is unknown whether measurements at different phases are more or less correlated with long-term outcomes. Based on future studies of these effects, re-evaluation of the recommended TC levels for reproductive-aged women may be justified to take timing and menstrual cycle variability into account.

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Executive summary

- The role of endogenous hormones on lipoprotein cholesterol levels has not yet been clearly defined.
- Epidemiological evidence suggests that lipoprotein cholesterol levels vary during the menstrual cycle and are significantly associated with endogenous reproductive hormone levels. Total cholesterol and LDL-C tend to be highest during the follicular phase and decline during the luteal phase. HDL-C tends to be highest around ovulation.
- Both women and physicians should take menstrual cycle phase into account when interpreting a woman's cholesterol measurement. Cyclic variations also have implications on the design and interpretation of studies in women of reproductive age.
- Measuring cholesterol levels during menses is recommended for consistent comparisons due to reduced variability in cholesterol levels during this phase and because this phase can be more reliably identified and scheduled than others. Any woman within the National Cholesterol Education Program acceptable ranges, but near the boundary when measured during menses, should undergo additional testing.

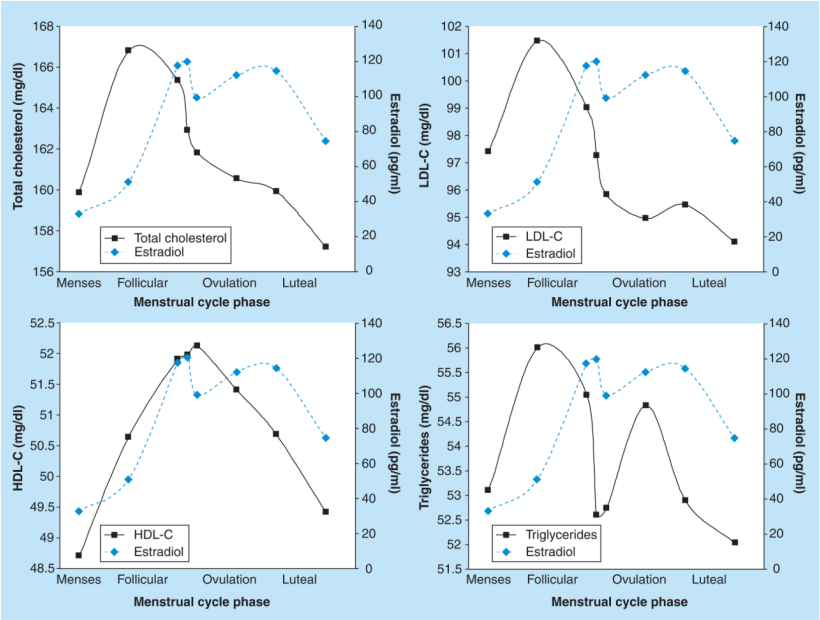

Figure 1.
Mean levels of total cholesterol, LDL-C, HDL-C, triglycerides and estrogen levels across the menstrual cycle among 259 women enrolled in the BioCycle Study.
Data taken from [42].

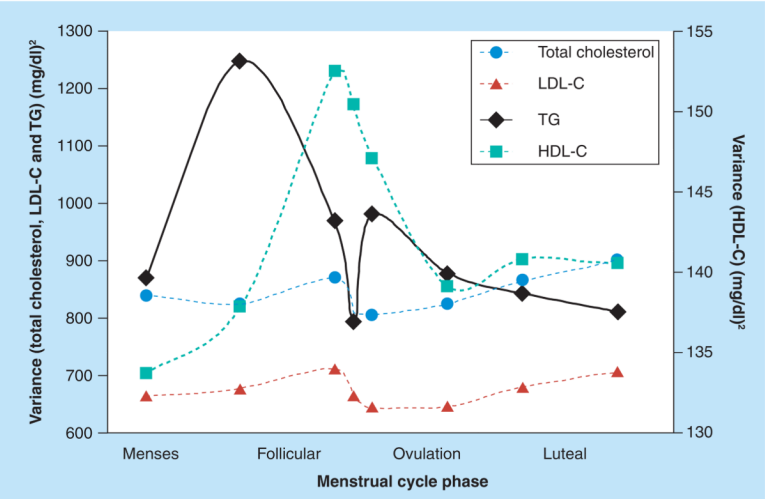

Figure 2.

Variance in lipoprotein cholesterol measurements during different phases of the menstrual cycle among 259 women enrolled in the BioCycle Study.

TG: Triglyceride.

Data taken from [42].

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Table 1

Summary of findings by selected studies evaluating cyclic changes in lipoprotein cholesterol levels across the menstrual cycle[†].

Study (year)	n (age in years)	Cycle, measurements	Changes from follicular to luteal phase (lipids and lipoprotein levels)[‡]	Statistical tests used	Ref.
Barnett *et al*. (2004)	44 (26.8 ± 4.1)[§]	One cycle, two blood samples (follicular and luteal phases)	LDL-C: decrease (6.2%; p = 0.015) TC/HDL-C: decrease (5.1%; p = 0.0006) LDL-C/HDL-C: decrease (8.4%; p = 0.002)	Paired t-test	[34]
Muesing *et al*. (1996)	12 (27 ± 3)[§]	Three cycles, four blood samples per cycle	LDL-C: decrease (4%; p < 0.01) LDL-C/HDL-C: decrease (6%; p < 0.005)	ANOVA	[25]
Tonolo *et al.* (1995)	16 (30 ± 1)[§]	One cycle, two during menses and daily thereafter	TC: decrease (9.3%; p < 0.05) LDL-C: decrease (12.5%; p < 0.05) HDL-C: increase (11.4%; p < 0.05) ApoA-I: increase (p < 0.05) ApoB: NS	Paired t-test and ANOVA	[29]
Lussier-Cacan *et al.* (1991)	18 (23–38)[¶]	Three cycles, blood samples taken at determined intervals	TC and TG: NS	ANOVA	[39]
Schijf *et al.* (1993)	54 (28 ± 4.7)[§]	One cycle, two blood samples (follicular and luteal phases)	TC: decrease (6.4%; p < 0.01) LDL-C: decrease (12%; p < 0.01) LDL-C/HDL-C: decrease (12.5%; p < 0.01) TC/HDL-C: decrease (7.3%; p < 0.01) ApoB: decrease (1.3%; p < 0.01) TG, HDL-C and apoA-I: NS	Wilcoxon signed rank test	[41]
Azogui *et al*. (1992)	18 (19–44)[¶]	One cycle, three blood samples (early follicular, preovulatory and mid-luteal phases)	ApoA-I/HDL-C: increase (11%; p < 0.05) LDL-C, TC, TG, VLDL-C and apoB: NS	Paired t-test	[33]
Elhadd *et al.* (2003)	20 (34 ± 1)[§]	One cycle, three blood samples (early and mid-follicular and luteal phases)	TC, LDL-C, HDL-C, TG, apoA-I, apoB and Lp(a): NS	Paired t-test	[36]
Jones *et al.* (1988)	31 (20–40)[¶]	Three cycles, two blood samples (mid-follicular and mid-luteal phases)	TC: decrease (6%; p < 0.05) TG and HDL-C: NS	Paired t-test	[37]
Kim and Kalkhoff (1979)	14 (33 ± 2)[§]	Three cycles, blood samples taken every 3–5 days	TC: decrease (10%; p < 0.01) TG, LDL-C, HDL-C and HDL-C/LDL-C: NS	Paired t-test	[22]
Barclay *et al*. (1965)	11 (25–44)[¶]	Approximately three cycles, 12 blood samples taken weekly	HDL-C2: increase at ovulation (49%; p = 0.05)	ANOVA	[30]
Basdevant *et al*. (1981)	8 (25–30)[¶]	18 cycles, three blood samples (menses, follicular and luteal phases)	TC, TG and HDL-C: NS	Paired t-test	[47]
Mattsson *et al*. (1984)	22 (18–35)[¶]	One cycle, four blood samples	LDL-C: decrease (10%; p < 0.05) HDL-C: increase (11%; p < 0.05) TC/HDL-C: decrease (12%; p < 0.01) LDL-C/HDL-C: decrease (18%; p < 0.01)	Paired one-sample Wilcoxon rank test	[48]
Woods *et al.* (1987)	15 (24.2 ± 7.5)[§]	One cycle, three blood samples (follicular, ovulatory and luteal phases)	TC, TG, VLDL-C, LDL-C and HDL-C: NS	ANOVA	[40]

Study (year)	n (age in years)	Cycle, measurements	Changes from follicular to luteal phase (lipids and lipoprotein levels)‡	Statistical tests used	Ref.
Lebech and Kjaer (1989)	37 (19–36)¶	One cycle, three blood samples	TC, TG, LDL-C and HDL-C: NS	ANOVA	[38]
De Leon *et al.* (1992)	29 (20–26)¶	One cycle, blood samples collected every other day during the first and last weeks, daily during middle period	TC: decrease (4%; $p < 0.05$) TG: decrease (17%; $p < 0.05$) HDL-C: NS	Paired t-test	[35]
Nduka and Agbedana (1993)	14 (20–30)¶	One cycle, 20 blood samples	TC: decrease (5%; $p < 0.03$) HDL-C: increase (11%; $p < 0.03$)	Multivariate repeated measures	[26]
Oliver and Boyd (1953)	12 (mean: 22)	One cycle, two blood samples per week for 5 weeks	TC: lowest point at ovulation (5% decrease from menses); no p-values presented	NA (only descriptive analysis performed)	[32]
Lyons Wall *et al.* (1994)	12 (19–37)¶	One cycle, 20 blood samples	HDL-C: increase (12%; $p < 0.001$) TC: increase (9%; $p < 0.005$) LDL-C: increase (11%; $p < 0.025$) TG: NS	ANOVA	[24]
Larsen *et al.* (1996)	19 (21–39)¶	Two cycles, two blood samples per week for 9 weeks	TC: decrease (~8%; $p < 0.001$) LDL-C: decrease (~10%; $p < 0.001$) Changes from ovulation to late luteal phases: HDL-C: decrease (~8%; $p < 0.001$)	Wilcoxon signed rank test	[23]
Adlercreutz and Tallqvist (1959)	29 (20–41)¶	One cycle, blood samples taken at timed visits	TC: decrease ($p < 0.01$)	ANOVA	[31]
Haines *et al.* (1997)	47 control (33.7 ± 4.8)§ 43 study (35.1 ± 3.1) §	One cycle, two blood samples for control cycles and one blood sample for study cycles	Ovary not being stimulated: Lp(a): increase (5.6%; $p < 0.05$) TC, LDL-C, apoB, HDL-C, apoA-I and TG: NS Ovary hyperstimulation: Lp(a): increase (14.2%; $p < 0.05$) TC: decrease (6.9%; $p < 0.001$) LDL-C: decrease (11.7%; $p < 0.0001$) TG: increase (10.4%; $p < 0.05$) ApoB, HDL-C and apoA-I: NS	Wilcoxon signed rank test	[49]
Ahumada Hemer *et al.* (1985)	114 (mean: 24)	One cycle, one blood sample	TC: increase in the late follicular phase compared with early phase ($p < 0.05$) VLDL-C: increase ($p < 0.05$) LDL-C: decrease ($p < 0.005$) HDL-C and TG: NS	ANOVA	[50]

†Selected only to show the varied findings by various authors.

‡As defined by the authors.

§Mean ± standard deviation.

¶Range.

ANOVA: Analysis of variance; NA: Not applicable; NS: No significant change; TC: Total cholesterol; TG: Triglyceride.

Table 2

Selected studies evaluating the association between lipoprotein cholesterol levels and estrogen.

Study (year)	n (age in years)	Cycle, measurements	Association between lipoprotein cholesterol levels and estrogen	Statistical tests used	Ref.
Lyons Wall *et al.* (1994)	12 (19–37)†	One cycle, 20 fasting blood samples on alternate days (for 5 weeks); ovulation timed by hormone measurements; divided into six phases	HDL-C and estrogen: r = 0.75 ($p < 0.01$) during ovulation TC and estrogen: r = 0.27; across cycle: NS LDL-C and estrogen: r = -0.02; across cycle: NS Mean intraindividual variation: TC: 7.8% HDL-C: 8.3% LDL-C: 11% TG: 14.9%	Linear regression	[24]
Lamon-Fava *et al.* (1989)	60 Caucasian (26.2 ± 5.7)† 117 African– American (25.5 ± 5.2)†	Cross-sectional	HDL-C (square root transform), estrogen (log transform): $\beta = 0.163$ ($p < 0.03$) adjusted for age, BMI, waist:hip ratio and ethnicity	Multiple linear regression	[51]
Gorbach *et al.* (1989)	24 healthy (premenopausal)	Single follicular phase sample between days 4 and 6	HDL-C and estrogen (partial r = 0.57; p = 0.02) VLDL-C and estrogen (partial r = 0.63; p = 0.01) LDL-C and estrogen (partial $r = -0.77$; $p < 0.001$)	Multiple linear regression	[20]
Mumford *et al.* (2010)	259 (27.3 ± 8.2)†	Two cycles, eight fasting blood samples per cycle timed using fertility monitors	TC and estrogen: $\beta = -0.0173$ ($p < 0.0001$) HDL-C and estrogen: $\beta = 0.0186$ ($p < 0.0001$; acute) LDL-C and estrogen: $\beta = -0.0228$ ($p < 0.0001$) TG and estrogen: $\beta = -0.0410$ ($p < 0.0001$) Mean intraindividual variation TC: 19%, 27.7 mg/dl	Weighted linear mixed effects models	[42]
Reed *et al.* (2000)	39 (premenopausal)	Three cycles (dietary intervention), blood samples drawn once per week	Amplitude of cycling 5.6 mg/dl from menses to follicular phases; intraindividual variation (range: 38.8 mg/dl)	Linear mixed models	[28]

† Mean ± standard deviation.

NS: No significant change; r: Correlation coefficient; TC: Total cholesterol; TG: Triglyceride.