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Cardiovascular Risk Factors and Menstrual Cycle Phase in Premenopausal Women

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Abstract

Background—Exogenous estrogens have been shown to affect markers of cardiovascular risk in women.

Aim—The objective of this study was to determine the effect of menstrual cycle phase on markers of cardiovascular risk in young, healthy women with regular menstrual cycles.

Subjects and Methods—This prospective cohort study examined 20 healthy premenopausal women at two time points in the menstrual cycle, in early follicular phase and early luteal phase.

Results—In the early luteal phase, levels of estrogen, progesterone, luteinizing hormone, total cholesterol and HDL were significantly higher, compared with the early follicular phase. In contrast, there were no significant differences in LDL or triglyceride levels between the two phases. Furthermore, there were no significant effects of menstrual cycle phase on glycemic indices (fasting blood glucose, HbA1c or $HOMA_{IR}$), markers of inflammation (CRP, sCD40L, ICAM, VCAM, or adiponectin), or vascular function, as measured by brachial artery reactivity.

Conclusions—Although menstrual cycle phase affects total cholesterol and HDL levels, it does not affect other markers of cardiovascular risk in young women with regular menstrual cycles.

Keywords

Cholesterol; insulin sensitivity; menstrual cycle; CD40 ligand; brachial artery reactivity

INTRODUCTION

Young healthy women are used as a comparator group for women with cardiovascular disease states throughout the literature and also serve for the establishment of normative ranges for clinical care. Since young healthy women are subject to hormonal variations within the menstrual cycle, it is important to determine whether phase of the menstrual cycle affects levels of cardiovascular risk factors.

It is clear that exogenous estrogens affect markers of cardiovascular risk.[1-3] However, studies of the effects of endogenous estrogens and menstrual cycle phase on cardiovascular risk have not shown a consistent pattern.[4-6] Prior studies have suggested that the process of ovulation is similar to an inflammatory reaction[7] and may result in vascular changes, the expression of chemokines, and the expression of cell adhesion molecules.[8] In this study, we sought to determine if specific, well-established markers of cardiovascular risk were

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affected by varying estrogen and progesterone levels in the early follicular and early luteal phases of the menstrual cycle.

MATERIALS AND METHODS

Study Population

Twenty healthy, nonpregnant premenopausal women were studied at two sites, Brigham and Women's Hospital or the Joslin Diabetes Center, both in Boston. The institutional review committees at both hospitals approved the study protocol, and all women provided written, informed consent prior to participating in the study. All women met the inclusion criteria of regular menstrual cycles, (defined as 26 to 32 day intervals), for the previous six months. No subject had used hormonal contraception or tobacco products for 3 months prior to enrollment in the study. All subjects also denied any history of diabetes, hypertension, or other current medical illness. No subjects were taking prescription medications, aspirin or nonsteroidal anti-inflammatory medications at the time of study.

Subjects were studied after a 10-hour overnight fast in the outpatient clinical research center in two phases: early follicular phase (within three days of onset of menstruation) and again in early luteal phase (within two days of ovulation). Ovulatory and menstrual onset visits were performed in random order, with the first visit determined by a coin toss. Subjects were provided with the ovulation test kits and instructed to begin daily urine testing on day 9 of their cycle. The kit detects the urinary LH surge by ELISA and at a level of 40 mU/mL with 99% accuracy (Inverness Medical Ovulation Test Kit, Waltham, MA). At the study visit, after 30 minutes of rest, supine blood pressures (Dinamap Pro-100; General Electric Healthcare), and fasting blood samples were obtained in both phases of the menstrual cycle. In addition, brachial artery reactivity was measured in both phases of the menstrual cycle as described below.

Measurement of Brachial Artery Reactivity

Analysis of brachial artery reactivity was performed using high resolution ultrasonography of the brachial artery (Digital Toshiba Power Vision 8000, Toshiba American Medical Systems, Armonk, NY). In brief, flow-mediated dilation (FMD) was assessed by a trained ultrasonographer according to published protocol.[9] The ultrasonographer was blinded to the menstrual phase of the study subjects. Subjects were placed in a supine position in a controlled environment after a 10-hour overnight fast. FMD was defined as the brachial artery diameter 1 min after cuff deflation or for 5 minutes continuously after sublingual administration of 0.4mg nitroglycerin. Brachial artery diameter was calculated prior to and after reactive hyperemia or nitroglycerin, and the change in diameter was expressed as a percent change of brachial artery diameter over baseline.

Laboratory Assays

Blood samples were collected on ice and centrifuged in a refrigerated centrifuge. Follicle stimulating hormone (FSH) and luteinizing hormone (LH) were measured with the chemiluminescence method (Beckman Access Immunosystem, Fullerton, CA). Estradiol was measured using double antibody radioimmunoassay (RIA) and progesterone was measured using single antibody RIA (Diagnostics Products Corporation, Los Angeles, CA).

Glucose was measured by glucose oxidation, total cholesterol and high density lipoprotein (HDL) were measured by a cholesterol esterase assay, triglycerides were measured via hydrolysis to glycerol and free fatty acids (FFAs) (Beckman Synchron CX3 Delta and CX9; Beckman Coulter, Brea, CA), and glycohemoglobin (Hb A1c) was measured by high-performance liquid chromatography (Tosho 2.2; Tosoh Bioscience, San Francisco, CA). The

Homeostatic Model Assessment of Insulin Resistance ($HOMA_{IR}$) was calculated as: [(Fasting plasma insulin (in μU/mL) ×Fasting plasma glucose (in mg/dL)/405].[10] Low density lipoprotein (LDL) levels were calculated from measured total cholesterol, HDL and triglyceride levels using the Friedewald equation.[11] Immunoassays were performed using commercial assays including radioimmunoassays for insulin (Diagnostic Systems Laboratories, Webster, TX) and adiponectin (Linco Research, St. Charles, MO), and enzyme-linked immunoabsorbent assays for vascular cell adhesion molecule-1, VCAM, and intercellular adhesion molecule-1, ICAM (R&D Systems, Minneapolis, MN). C-reactive protein (CRP) was analyzed by immunoturbidometry (Immulite, Siemens USA, Deerfield, IL). Serum sCD40L was measured using a high sensitivity ELISA kit with detection limit 0.005 ng/mL and intra-assay coefficient of variation of 5.5% (Bender Medical Systems, Vienna, Austria).

Statistical Analysis

The Shapiro-Wilk Test was used to test for normal distribution. For normally distributed data, the paired T test was used to perform two-group comparisons of blood pressures, hormone levels, lipid measures, inflammatory markers and glycemic parameters between the early follicular phase and early luteal phase. For non-normally distributed data, the Wilcoxon Rank Sum test was used. Data are expressed as mean ± standard error of the mean (SEM). Comparisons of inflammatory markers and lipid levels to hormone measurements were performed individually by calculation of Pearson's correlation coefficient. Non-normally distributed data were log-transformed for correlation. Statistical analyses were performed using SAS version 9.1 and JMP version 7.0.1 (SAS Institute, Inc., Cary, NC). Two-tailed significance tests were used and a p-value of less than 0.05 was considered significant.

RESULTS

Subject Demographics

The mean age of the subjects was 25.3 ± 0.9 years, and mean body mass index (BMI) was 23.5 ± 0.6 kg/m^2 at the screening visit. Study subjects were healthy with no physical limitations. Of the twenty subjects studied, 16 were Caucasian, three were Asian and one was Hispanic. All subjects were studied in the earlier follicular phase, 2.7 ± 0.1 days within onset of menses, and again in the early luteal phase, 2.2 ± 0.2 days within ovulation.

Hormone Levels

Estradiol, progesterone, and LH levels were all significantly higher in the early luteal phase, compared with the early follicular phase (Table 1). In contrast, FSH levels did not differ significantly between the menstrual cycle phases at the time points measured.

Lipid Profile Levels

Total cholesterol and HDL concentrations were both significantly higher in the early luteal phase, compared with the early follicular phase (Table 1). Calculated LDL levels trended higher in the early luteal phase, but this did not reach statistical significance (p=0.07). In contrast, neither triglyceride levels nor the LDL to HDL ratio were significantly different between the two phases of the menstrual cycle. In addition, there was no correlation of HDL or total cholesterol with estrogen or progesterone levels in either the early follicular or early luteal phases.

Glycemic Indices and the Menstrual Cycle

Fasting blood glucose did not vary significantly between the early follicular phase and the early luteal phase (83 ± 2 vs. 82 ± 2 mg/dL, respectively). Likewise, fasting insulin levels did not differ significantly between the two menstrual cycle phases (4.4 ± 0.4 vs. 5.3 ± 0.5 μU/mL, respectively). Furthermore, the following estimates of insulin resistance also did not differ significantly between the early follicular versus early luteal phase: $HOMA_{IR}$ (0.89 ± 0.1 vs. 1.08 ± 0.1), fasting glucose to insulin ratio (21.0 ± 1.6 vs. 18.1 ± 1.7), and hemoglobin A1c (4.9 ± 0.1 vs. 4.9 ± 0.1%).

Inflammatory Markers and the Menstrual Cycle

Subjects demonstrated no differences in markers of inflammation between phases of the menstrual cycle (Table 2). Specifically, concentrations of CRP, sCD40L, ICAM, VCAM and adiponectin did not differ between the early follicular and early luteal phases.

Vascular Function and the Menstrual Cycle

All subjects demonstrated normotensive blood pressures in both the early follicular phase and the early luteal phase (Table 3). Baseline brachial artery diameter did not vary significantly between early follicular and early luteal phase. In addition, FMD did not change significantly between menstrual phases, either in terms of absolute measurement or percent of baseline brachial artery diameter. In a smaller subset of subjects (n= 12), nitroglycerin induced dilation was measured and also did not vary significantly with phase of menstrual cycle.

DISCUSSION

Young, premenopausal, healthy women with regular menstrual cycles demonstrated significant differences in lipid parameters, with significantly higher HDL and total cholesterol levels in the early luteal phase, compared with levels measured in the early follicular phase. In contrast, LDL and triglyceride levels did not vary with menstrual cycle phase. In addition, despite significant changes in estradiol and progesterone, measures of vascular function, markers of inflammation and glycemic indices also did not vary significantly between the early follicular and early luteal phases.

Young healthy women are used as a comparator group for women for cardiovascular disease states throughout the literature and also serve for the establishment of normative ranges for clinical use. Since young healthy women have menstrual cycles, it is important to determine whether phase of the menstrual cycle affects cardiovascular risk factors. As a result, understanding the baseline pattern of various accepted markers of cardiovascular risk across the menstrual cycle is important when interpreting cardiovascular risk data in women. The present study explored various markers of vascular function, inflammation and insulin resistance and found no differences between the early follicular and early luteal phases.

Studies have shown variable effects of menstrual cycle phase on lipid parameters, with some studies showing higher cholesterol levels during the follicular phase[4,12] and others showing no differences in lipid parameters across the menstrual cycle.[5,13-15] However, these previously published studies were not all performed in the early follicular or early luteal phases. The effect of estrogen on lipid measures is also debated, as randomized trials have demonstrated that exogenous oral estrogen improves lipid profiles, despite increasing cardiovascular risk.[2,3] Estrogens are hypothesized to improve lipid parameters by increasing the synthesis of very low density lipoprotein (VLDL), inhibiting hepatic lipoprotein lipase activity and upregulating the expression of LDL receptors.[1,16,17] In addition, endogenous estradiol may affect HDL metabolism through the SR-BI receptor.[18]

In our study population, we sought to understand the effect of varying levels of endogenous estrogen on lipid parameters. In our subjects, total cholesterol and HDL levels did differ significantly between the early follicular and early luteal phases. We found that HDL is significantly higher in the early luteal phase, just after ovulation, similar to a recently published study.[19] This recently published study indicated that more women demonstrate lipid profiles above the desirable range, as defined by criteria of the National Cholesterol Education Program (NCEP), in the follicular phase of the menstrual cycle compared with the early luteal phase.[19] In contrast, despite the fact that our subjects were studied at similar time points, our study did not demonstrate similar findings.

Some studies have demonstrated increases in insulin resistance in the luteal phase,[20-22] while others did not demonstrate differences in insulin resistance between the follicular and luteal phases, as measured by the euglycemic insulin clamp technique.[23,24] Another study, using $HOMA_{IR}$ as an estimate of insulin resistance, also did not find variations between the mid-follicular and mid-luteal phases.[25] Our study did not demonstrate differences in fasting glucose, fasting insulin, $HOMA_{IR}$ or HbA1c between the early follicular and early luteal phases. However, compared with other previously published studies, our subjects were relatively young with lean BMI, which may have affected our ability to detect changes in insulin resistance with menstrual cycle phase. In addition, the timeframe in which our subjects were studied was likely too brief to observe a change in HbA1c. To our knowledge, no studies have examined the effect of menstrual cycle phase on HbA1c in non-diabetic women.

Previous studies have reported variable effects on menstrual cycle phase on levels of CRP, with some studies showing higher CRP levels in the follicular phase,[26] higher in the luteal phase,[27] or no differences at all between menstrual cycle phases,[6,28] despite similar sample sizes, and similar time points of study. Our study demonstrates that CRP levels do not vary significantly between the early follicular and early luteal phases. sCD40L is an inflammatory marker expressed in the endothelium.[29] Elevated levels of sCD40L in apparently healthy women were shown to be associated with increased risk of early cardiovascular disease.[30] A relationship between gonadotropic hormones and sCD40L was suggested when hCG administration was shown to increase sCD40L levels in women undergoing in vitro fertilization. The relationship between estrogen and progesterone and sCD40L levels is less clear. Our study demonstrated no difference in sCD40L levels between the early follicular and early luteal phases, similar to one previously published study that studied regularly menstruating women during similar phases of the menstrual cycle.[31] Other serum markers of inflammation, including ICAM-1 and VCAM-1, also did not vary with menstrual cycle phase, consistent with previously published studies.[32] Adiponectin, which is associated with decreased inflammation and increased risk for atherosclerosis,[33] exists in higher levels in women compared with men, suggesting that adiponectin secretion may be regulated by gonadal steroids.[34-36] However, our study found no variation of adiponectin between the early follicular and early luteal phases, despite significant changes in levels of estradiol and progesterone levels, which confirms findings of previously published studies.[37,38]

Our study also demonstrated that measures of vascular function, including systolic and diastolic blood pressures and brachial artery reactivity, do not change significantly with menstrual cycle phase. Baseline brachial artery diameter in our study subjects was within the expected range for young menstruating women.[39] Although the relationship between increased vascular reactivity and estrogen has been suggested in older women, studies of younger, spontaneously menstruating women indicate that brachial artery reactivity does not vary with menstrual cycle phase.[39-41] Compared with our study, these studies were performed at similar times during the menstrual cycle and had similar sample sizes.

Our study has several strengths. Measures of vascular function, inflammation and insulin resistance were determined simultaneously in the fasting state, in the clinical research center, at two specified, confirmed time points during the menstrual cycle. In addition, our sample size was larger than many similar, previously published studies.[26,27,31,40] However, our sample size was still relatively small. In addition, study time points were limited to two specific times in the menstrual cycle, early follicular and early luteal phase. As a result, it is possible that differences may be detectable at other time points in the menstrual cycle and that our study was not able to identify these differences.

In conclusion, this study examined the effects of endogenous estrogen and progesterone on a variety of accepted markers of cardiovascular risk simultaneously in a cohort of healthy, premenopausal women. We found that a majority of these markers do not vary significantly between the early follicular and early luteal phases, with the exception of total and HDL cholesterol levels, which were higher in the luteal phase. However, given that young healthy women serve as a valuable reference group for women with cardiovascular disease states, it is reassuring that variations in the menstrual cycle do not affect many commonly accepted markers of cardiovascular risk.

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Table 1

Hormone and Lipid Levels

	Early Follicular Phase (n=19)	Early Luteal Phase (n=19)	p-value
Estradiol (pg/mL)	40.8 ± 9.2	122.2 ± 17.3	0.002
Progesterone (ng/mL)	1.5 ± 0.6	3.7 ± 1.1	0.001
LH (mU/mL)	4.2 ± 0.4	19.2 ± 3.8	<0.0001
FSH (mU/mL)	6.6 ± 0.5	9.0 ± 1.2	NS
Total Cholesterol (mg/dL)	149 ± 6	162 ± 5	0.003
HDL (mg/dL)	54 ± 3	61 ± 3	<0.0001
LDL (mg/dL)	82 ± 4	87 ± 4	0.07
LDL/HDL ratio	1.6 ± 0.1	1.5 ± 0.1	NS
Triglycerides (mg/dL)	68 ± 5	71 ± 5	NS

Mean ± SEM

Table 2

Markers of Inflammation

Parameter	Early Follicular Phase	Early Luteal Phase	p-value
CRP (mg/dL) *	0.06 ± 0.02	0.05 ± 0.01	NS
sCD40L (ng/mL)	7.0 ± 1.5	7.1 ± 1.5	NS
sICAM-1 (ng/mL) †	189.7 ± 13.9	201.6 ± 15.3	NS
sVCAM-1 (ng/mL) ‡	441.6 ± 24.4	463.4 ± 22.1	NS
Adiponectin (ng/mL)	19582.5 ± 1683	20087.5 ± 1706	NS

* n= 18 for both phases

† n = 17 for both phases

‡ n=19 for both phases Mean ± SEM

Table 3

Vascular Function

Parameter	Early Follicular Phase (n=20)	Early Luteal Phase (n=20)	p-value
Systolic BP (mmHg)	106 ±2	105 ± 2	NS
Diastolic BP (mmHg)	69 ± 2	67 ± 1	NS
Baseline brachial artery diameter (mm)	3.14 ± 0.1	3.12 ± 0.1	NS
Flow-induced dilation, absolute FMD (mm)	0.38 ± 0.05	0.34 ± 0.05	NS
Flow-induced dilation, percent FMD (%)	12.4 ± 1.7	11.1 ± 1.6	NS
Nitroglycerin-induced dilation, absolute (mm) *	0.77 ± 0.06	0.86 ± 0.09	NS
Nitroglycerin-induced dilation, percent (%) *	23.2 ± 2.0	27.0 ± 3.0	NS

Mean ± SEM

* n=12 subjects who received nitroglycerin

NS, not significant