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VARIATION OF LIPID PROFILE IN PHASES OF MENSTRUAL CYCLE IN WOMEN OF REPRODUCTIVE AGE GROUP: A PROSPECTIVE ANALYTICAL STUDY

Physiology

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ABSTRACT

The sex hormone which is secreted in minute quantities undergoes changes in levels according to different phases of menstrual cycle. They play an important role in lipid metabolism, especially oestrogen. In our study 50 women of reproductive age group (15-49years) were recruited. Lipid profile was measured during all the four phases of menstrual cycle and it was found that HDL was highest in ovulatory phase, and LDL and total cholesterol was lowest in luteal phase, as compared to other phases of menstrual cycle. There are gender differences in plasma lipid profiles, and that women are relatively protected against coronary heart disease (CHD) relative to their male counterparts. Furthermore, steroid hormones play an important role in the determination of lipid profile concentrations. Based on these facts co-relation between different phases of menstrual cycle and lipid profile is established in our study.

KEYWORDS

menstruation phases, lipid profile

INTRODUCTION

Coronary heart disease (CHD) is the most prevalent manifestation of disease resulting in nearly 50% of all cardiovascular death in the world. Many risk factors for developing CHD have been identified, like family history of CHD, older age, male sex; diet, cigarette smoking, hypertension, diabetics, and high serum cholesterol level have been identified.

Among those risk factors, serum lipid and lipoprotein levels are considered to be a primary cause of pathogenesis of this disease [3]. The association between serum cholesterol levels and risk of CHD has been demonstrated.[1]. Recently several line of research have demonstrated that in addition to total amount of circulating cholesterol, the manner in which this amount of cholesterol is distributed and classified into specific lipoprotein (LDL,HDL,VLDL,TG),is particularly important[2] . Studies indicate that there is substantial difference in lipoprotein level among different gender .Men have higher level of TG & LDLC associated with higher risk of CHD, where as women have higher level of HDLC associated with protection from CHD.[4] Oestrogen appeared to affect lipoprotein in that HDLC is raised & LDLC is lowered.[5]

Due to cyclic nature of circulating sex hormone in premenopausal women and their possible impact on level of lipid and lipoprotein, and CHD risk, it is important to determine how this level varies between phases of menstrual cycle.

MATRIAL & METHORDS

SOURCE OF DATA: The study was conducted in the Department of Physiology, Biochemistry & Radio diagnosis, SCB Medical College,

STUDY PERIOD: September 2014 to September 2015

STUDY DESIGN: Prospective analytical study

50 women of reproductive age group (15-49years) were recruited in the study from the community after getting ethical clearance from the ethical committee of the institute. Routine physical examination and anthropometric measurement was done. Subjects were followed up for 3 months.

In first month--determination of cycle length and basal body temp (BBT).

2nd month-- the determination of ovulation (By I KNOW Ovulation kit) and Ultrasonography (TVS- in case of married females and TAS in case of unmarried ladies).Features of ovulation in USG are, 1. Non-visualisation of previously visible dominant follicle and 2. Mild fluid in pouch of douglas.

In 3RD month- fasting blood sample were collected during the phase's menstrual cycle for evaluation of lipid profile as MENSTRUAL PHASE-Day 1or 2 of bleeding ,FOLLICULAR PHASE-Within 3 to 9day of cycle, OVULATORY PHASE-Within 24 hr of ovulation by use of ovulation kit & BBT & ultrasound, LEUTAL PHASE-Within 10 to 12 day after ovulation.

The subjects were included in the study basing upon the following inclusion and exclusion criteria. Women having regular menstruation for three months ,not taking any OCP or any hypolipidemic drugs for last 6 months were selected into study .

LIPID PROFILE ANALYSIS

It includes

1. Total cholesterol (TC)
2. Triglycerides (TG)
3. High density lipoprotein cholesterol(HDL-C)
4. Low density lipoprotein cholesterol(LDL-C)

The levels were determined by **enzymatic method.**
Determination of total plasma cholesterol and triglyceride was performed with automated enzymatic methodology with DIMENTION XPAND PLUS ANALYSER. Sampling, reagent delivery, mixing, processing and printing of results are automatically performed by the Dimension® system..

STASTICAL ANALYSIS

The obtained data were analyzed by using a software statistical package for the social science (SPSS version 20). Frequency and descriptive analyses were used to describe the data. Paired samples t-test was also used to differentiate between two numerical data of two phases. Any difference or correlation was considered significant if p value less than 0.05 ($P<0.05$).

RESULTS

I. TABLE-A.Anthropometric data

CATEGORY	MEAN S/D
AGE (YEAR)	25.62±4.7
WEIGHT(KG))	54.62±5.4
HEIGHT(Mt)	1.53±.29
BMI(Kg/m2	23.05±2.3

1. This table shows the anthropometric data of the study subjects with a mean age of 25.6 yr, weight 54.7 kg , height 1.5 mt. and BMI 23.05 kg/m^2.

2. TABLE –B: BMI of study subjects

CATEGORY	NUMBER	PERCENTAGE
UNDERWEIGHT	1	2%

NARMAL	38	76%
OVERWEIGHT	11	22%

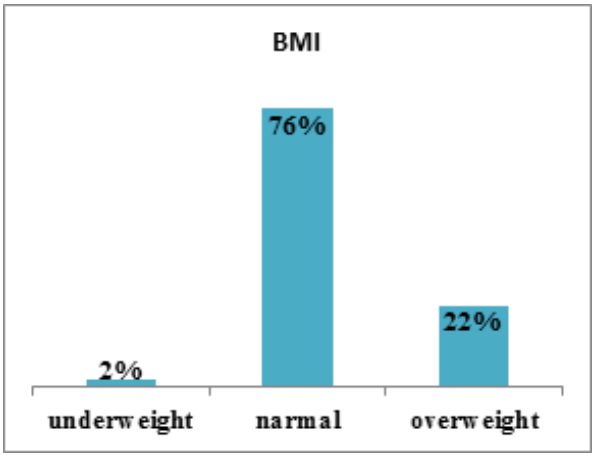


Table B is represented by the above diagram—DIAGRAM .1

2. This data shows the BMI values, it was found that most of the subjects (around 76%) are in normal range (18.5-24.9) .;[6]

3. TABLE - C

Age of menarche	Number	percentage
10	3	6
11	11	22
12	18	36
13	10	20
14	7	14
15	1	2

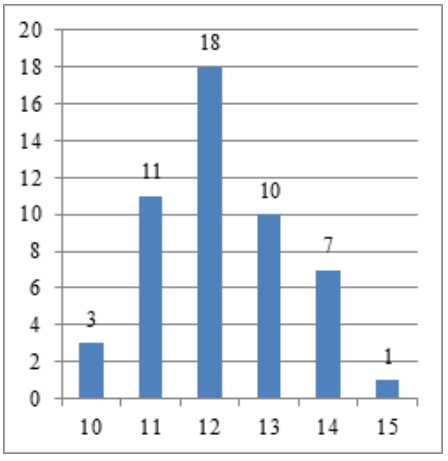
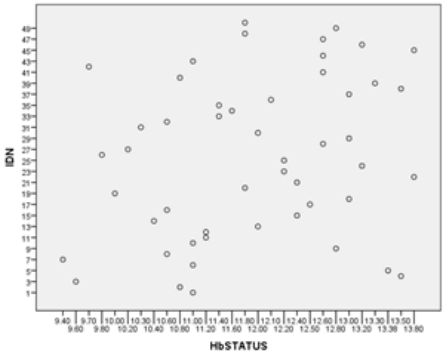


Table C is represented by the above bar diagram—DIAGRAM.2

DIAGRAM-3



The scatter diagram shows that the Haemoglobin status of all the study subjects was within the normal range 9.4mg/dl to 13.6mg/dl. ;[6]

4. TABLE-D *LIPID PROFILE VALUE IN PHASES OF MENSTRUAL CYCLE OF STUDY SUBJECTS*

Category	Menstrual phase	Follicular phase	Ovulatory phase	Luteal phase
TC(mg/dl)	157.56	159.44	139.99	120.8
TG(mg/dl)	109.76	110.57	108.41	108.53
HDL(mg/dl)	44.4	45.67	66.49	58.32
LDL(mg/dl)	93.7	94.4	82.5	65.40
VLDL(mg/dl)	26.91	26.43	27.15	28.5

This table shows the lipid profile value of all the phase of menstrual cycle, with HDL value highest during ovulatory phase and gradually declining levels of TC & LDL value from follicular to luteal phase.

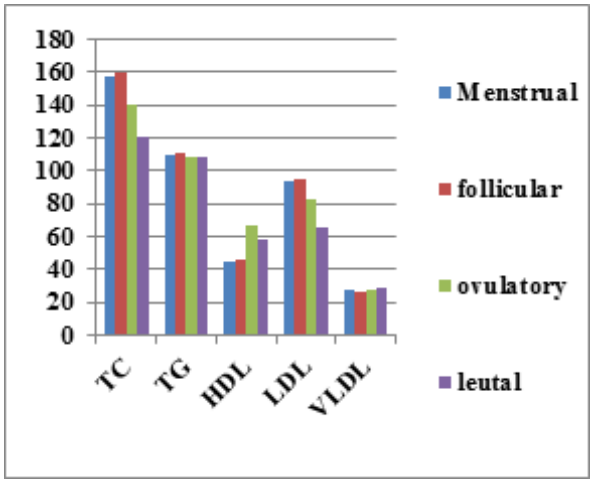


Table D is represented by the above diagram—DIAGRAM .4

5. TABLE E: RATIO OF TC TO HDL

TC-F/HDL-F	3.5	.74
TC-O/HDL-O	2.2	.73
TC-L/HDL-L	2.1	.75
TC-M/HDL-M	3.6	.84

p value <.001,found in paired t test, significant

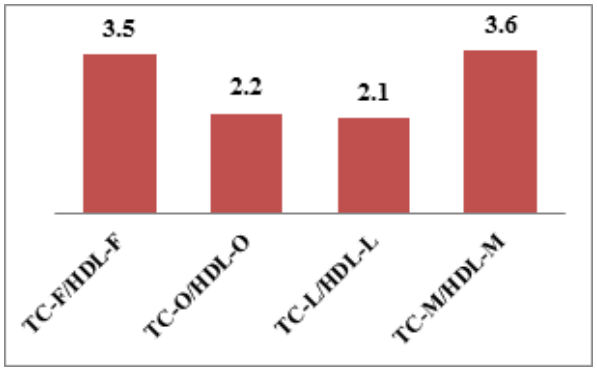


Table-E is represented by the above diagram-DIAGRAM.5

DISCUSSION

The results of the present study are addressed with emphasis on the mechanisms by which the corresponding endogenous gonadal steroid hormones exerted their effects on plasma lipid and lipoprotein modifications throughout the different phases of the normal menstrual cycle.

On anthropometric study it was found that most of the study subjects were within normal range of BMI (Table –A & B) ;[6]

The age of menarche was found to be between 10 to 15 years with peak at 12 years. (Table-C)

Average cycle length was 28.5±2.1 days in the study subjects.

Blood parameters showed that no one was anaemic. (Diagram-3)

EFFECT OF THE MENSTRUAL CYCLE PHASES ON PLASMA LIPID PROFILE

(I) Plasma High Density Lipoprotein Cholesterol (HDL-C):

In the present study it was found that HDL increased by 45.58% in ovulatory phase, 27.69% in luteal phase and 2.7%in menstrual phase and as compared to follicular phase (table D). This suggests that HDL-C values fluctuate significantly throughout the phases of the normal menstrual cycle. High Density Lipoprotein Cholesterol levels were significantly elevated during the Luteal and ovulatory phase compared to the Follicular phase. The significant elevation in HDL-C concentrations during the ovulatory phase could be due to expected increased levels of estrogen during ovulatory phase of menstrual cycle as compared to follicular phase [9]

Similarly A.R. Saxena, E.W. Seely, and A.B. Goldfine et al in the year 2012 conducted a study on Cardiovascular Risk Factors and Menstrual Cycle Phase in Premenopausal Women taking 20 healthy premenopausal women, found that in the early luteal phase, levels of estrogen, progesterone, luteinizing hormone, total cholesterol and HDL were significantly higher, compared with the early follicular phase.

Contrary to above it was reported by Kim and Kalkhoff (1979) that an increase in HDL-C levels in menstruating women was observed during the luteal phase of the cycle but this difference was not significant when compared with the follicular and ovulatory phases.

However, Tikkanen et al. (1986) and Gorbach et al. (1989) demonstrated a significant elevation in HDL-C levels in the follicular phase compared to the luteal phase of the cycle, which is dissimilar with the results of present study. .

Contrary to the above results, other investigations reported no significant changes in HDL-C concentrations in premenopausal women during the phases of the normal menstrual cycle (de Mendoza et al., 1979; Kim & Kalkhoff, 1979, Demacker et al., 1982; Hemer et al. 1985; Lebech & Kjaer, 1989; Lebech et al., 1990; Schijf et al., 1993; Hemer et al., 1985; Woods et al., 1987 Jones et al., 1988).

The differences in these results could be due to variation in timing of blood sampling during phases of menstrual cycle, parameter adopted, and other factors such as controlled diet physical activity etc.

(II)Plasma Low Density Lipoprotein Cholesterol (LDL-C)

The value of LDL cholesterol has decreased by 12.62% in ovulatory phase, 30.74% in luteal phase &1.3% in menstrual phase a as compared to follicular phase (Table-D). The reduction in plasma LDL-C levels during the luteal phase of the cycle occurred because progesterone level was expected to peak and estrogen was on average higher level.(de Mendoza et al., 1979).

Present study findings are comparable with the study conducted by Sunni L Mumford, Sonya Dasharathy, Anna Z Pollack, and Enrique F Schisterman,; Clin Lipidol. 2011 April 1; 6(2): 225–234. doi:10.2217/clp.11.9, with study title 'Variations in lipid levels according to menstrual cycle phase: clinical implications' where it was found that total cholesterol and LDL-C tend to be highest during the follicular phase and to decline during the luteal phase.

A possible explanation or mechanism for these observations may be the increased suppression in the activity of the Hepatic lipase (HL) enzyme (Tikkanen et al., 1986), which is induced by the concentrations of estrogen secretion during the luteal phase, and causes lower levels of LDL-C as well as lower total plasma cholesterol concentrations.

Another possible mechanism for the reduction in LDL-C levels as a result of the rise in plasma estrogen concentrations in the luteal phase is suggested by Kovanen, Brown & Goldstein (1979), who reported that pharmacologic doses of estrogen resulted in the increase of hepatic LDL receptor synthesis in experimental animals.

In addition, estrogen administration causes an increase in the catabolism of LDL by increasing hepatic LDL receptor activity. Since the major site for the uptake of LDL occurs primarily in the liver, and the rise in estrogen secretion enhances the uptake process, it may be suggested that the effects of estrogen are manifested through HL activity and consequently on hepatic degradation of LDL levels.

The following studies differ from present one.

1. The Gorbach et al.(1989) observed a significant decrease in LDL-C levels during the follicular phase compared to the luteal phase, which is not in accordance with the finding of the our study.
2. Barclay et al. (1965) observed insignificant variations in plasma LDL-C levels during the phases of the menstrual cycle.
3. Moreover, de Mendoza et al. (1979) found that LDL-C values were not significantly different during the follicular and the luteal phases of the normal menstrual cycle, in agreement with Demacker et al. (1982).
4. Lebech and Kjaer, 1989; Lebech, Kjaer & Lebech, 1990; Woods et al., 1987 reported no significant variations in the concentrations of LDL-C in premenopausal women during the different phases of the menstrual cycle.

(III) Plasma Total Cholesterol (TC)

There was a significant reduction in plasma total cholesterol concentrations during the luteal phase compared to both the ovulatory and the follicular phases. The total cholesterol value has decreased by 12.1% in ovulatory phase, 24.23%in luteal phase, 1.2%in menstrual phase as compared to follicular phase (Table-D)

The reduction in total plasma cholesterol during the luteal phase of the cycle occurred when progesterone levels were expected to peak and estrogen was on the average higher levels.[9]

The decreased total cholesterol values observed during the luteal phase of the present study is in agreement with the results of other investigators as follows, Hemer et al., 1985; Kim & Kalkhoff, 1979; Mattsson et al., 1984; Schijf et al., 1993; Tikkanen et al., 1986, Sunni Mumford, Sonya Dasharathy, Anna Z Pollack, and Enrique F Schisterman; Clin Lipidol.2011 Apr 1;6(2):225-234.and Pt. B D Sharma et al , 1998. Kirti Gupta et al, Sch J .App Med Sci July 2015.

(IV)Plasma Triglycerides (TG)

The levels of triglycerides decreased by 2.7% during the ovulatory phase as compared to the follicular phase and a little change in the levels had been observed by 1.7% during the luteal phase of the cycle and by 0 .7% in menstrual phase.(table-D)

The following studies have similar results with the present study-

Kirti Gupta et al , Sch J .App Med Sci July 2015 also showed small change in values of TG during the luteal phase.

De Mendoza et al., 1979; Jones et al. 1988;Tikkanen et al., 1986) found a small change of TG levels in luteal phase as compared to follicular phase.

Mattsson, Silfverstolpe, & Samioe, 1984; Woods et al. 1987) demonstrated a decrease in TG levels in ovulatory phase compared to the follicular phase.

The possible explanation for the findings of our study and the above studies is that oestrogen increases the removal rate of triglycerides.

However,Lebech, Kjaer & Lebech, 1990; Lussier-Cacan et al., 1991; Schijf et al., 1993; Tangney, Brownie & Wu, 1991; Wender, Kastner & Schmahl, 1992) found that triglyceride levels did not vary significantly during the phases of the normal menstrual cycle. These results are not in agreement with the results of the present study.

(V) VLDL –very low density lipoprotein

In this present study VLDL value increased 2.3% in ovulatory phase, 4% in luteal phase, and 1.9% in menstrual phase as compared to follicular phase.

Similar results were observed by Kirti Gupta et al , Sch J .App Med Sci July 2015 in values of VLDL during the luteal phase, which may be due to the favourable effect of oestrogen on lipid metabolism that increases VLDL synthesis subsequently decrease in LDL and HDL. Oestrogen increases the light subtype of VLDL that decreases the artherogenicity leading to overall beneficial effects.

The evidence presented here suggests that elevations in the secretion of

gonadal steroids at specific times and phases of the cycle induce favourable fluctuations in the plasma lipid and lipoprotein concentrations

(VI) RATIO OF TOTAL CHOLESTEROL WITH HIGH DENSITY LIPOPROTEIN (TC/HDL)

TC/HDL ratio was found to be 3.5, 2.2, 2.1, and 3.6 respectively in follicular ovulatory luteal and menstrual phase. The ratio had decreased significantly in luteal and ovulatory phase as compared to follicular phase in our present study.

The following studies are in agreement with the finding of the present study.

1. Kriti gupta et al (2015) demonstrated that TC/HDL ratio declined significantly in luteal phase as compared to follicular phase.
2. K.Devi et al had described the similar results.

This may be due to increase of HDL levels, decrease TC levels in luteal and ovulatory phase as compared to follicular phase which is due to increase estrogen and progesterone levels in luteal phase than in follicular phase.

At sub cellular level; Oestrogen exerts a favourable effect on lipoprotein metabolism by various mechanisms:[7],[8]

1. **Increasing VLDL-C synthesis leading to subsequent decrease in LDL-C and increase in HDL-C**
2. **Up regulate the LDL receptors.**
3. **Up regulate ATP Binding Cassette Transporter-A1 (ABCA1) and Apolipoprotein-A1 (APOA1, a most important HDL protein, which enhance HDL production).**
4. **Suppress hepatic Scavenger Receptor Class B Type 1 (SR-BI) activity leading to reduced hepatic cholesterol uptake from HDL-C**

But it has been observed that the hormone progesterone counters the stimulating effect of oestrogen or has inert effect on lipoprotein [10]

SUMMARY

It is known that endogenous sex hormone levels and plasma lipoprotein concentrations are interrelated since the incidence of atherosclerosis and coronary heart disease is higher in men than in age-matched premenopausal women.

The previous early and recent studies on the relationships between plasma lipid and lipoprotein concentrations and plasma endogenous sex hormone levels in premenopausal women during the menstrual cycle have given somewhat significant results and regular patterns have been established.

In our study 50 premenopausal women were taken as subjects. They had mean age 25.62 yr, mean weight 54.62 kg , mean height 1.53 meters and BMI 23.05 kg/m^2.

The subjects had age of menarche between 10 to 15 with a peak at 12 years and their Lipid profile analysis (TC, TG, LDL, HDL, and VLDL) was done.

The mean HDL value during menstrual, follicular, ovulatory and luteal phase was 44.40, 45.67, 66.49, 58.32 mg/dl respectively.

The mean LDL value during menstrual, follicular, ovulatory and luteal phase was 93.10, 94.44, 82.52, 65.40 mg/dl respectively.

The mean total cholesterol value during menstrual, follicular, ovulatory and luteal phase was 157.56, 159.44, 139.99, 120.80 mg/dl respectively.

The mean TG value during menstrual, follicular, ovulatory and luteal phase was 109.76, 110.57, 108.41, 108.83 mg/dl respectively.

The mean VLDL value during menstrual, follicular, ovulatory and luteal phase was 26.94, 26.43, 27.17, 28.50 mg/dl respectively.

The results of the present study demonstrate the effects of the different phases of the normal menstrual cycle on plasma lipid and lipoprotein concentrations .

1. *During the follicular phase of the normal menstrual cycle there was a significant increase in plasma total cholesterol and LDL-C concentrations compared to both the ovulatory and the luteal phases of the cycle.*
2. *During the follicular phase of the normal menstrual cycle there was a significant decrease in plasma HDL-C concentrations compared to the luteal phase of the cycle.*
3. *During the ovulatory phase of the normal menstrual cycle there was a significant increase in plasma total cholesterol compared to the luteal phase of the cycle.*
4. *During the ovulatory phase of the normal menstrual cycle there was a significant increase in plasma HDL-C concentrations compared to the luteal phase of the cycle.*
5. *Plasma triglyceride concentrations show a decreasing trend from follicular to luteal phase.*
6. *Plasma VLDL levels show increasing trend from follicular to luteal phase.*
7. *Minimum variation was seen in the levels of TG, TC, LDL, HDL, VLDL during menses as compared to follicular phase.*

CONCLUSION

The overall results show fluctuations in plasma lipid and lipoprotein concentrations throughout the normal menstrual cycle in healthy premenopausal eumenorrheic women.

Estrogen has definite protective effect against CHD.

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.

Both women and physician should take menstrual cycle phases into account when interpreting a woman's cholesterol measurement.
Cyclic variation also have implications on the design and interpretation of studies in women of reproductive age.

LIMITATION OF THE STUDY—*serum estrogen and progesterone level has not been estimated.*

FUTURE PROSPECTIVE–

Although recent studies have elucidated the hormonal effects on lipoprotein metabolism, of great interest is the role of androgens in this setting as androstendione and testosterone are both precursors of estrogen and thus vary 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.

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.

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