Study of Lipid Profile during Late Reproductive Phase, Perimenopause and Postmenopause in North Indian Women

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Abstract

Background: Perimenopause or menopausal transition is the phase which precedes menopause and is characterized with fluctuation in estrogen levels. Several studies have been done to investigate the changes in lipid profile in premenopausal and postmenopausal women. Studies regarding the changes in lipid profile during perimenopause are scanty. This study was done to study the lipid profile in reproductive or premenopausal, perimenopausal and postmenopausal women. **Materials and method**: A case control study was done on 60 late reproductive phase, 60 perimenopausal and 60 postmenopausal women. Total cholesterol (TC), serum triglyceride and High Density Lipoprotein – Cholesterol (HDL-C) were determined with a fasting venous blood sample. Low Density Lipoprotein – Cholesterol (LDL-C) was calculated by Friedwald's formula. TC/HDL cholesterol ratio and LDL/HDL cholesterol ratio were calculated and compared. Data was analyzed using Statistical Package for Social Sciences (SPSS) 17.0 version (SPSS Inc., Chicago, IL, USA). **Results**: Statistically significant increase in the total cholesterol, serum triglyceride and HDL-C levels and LDL/HDL cholesterol ratio in the perimenopausal was observed when compared with women in late reproductive age group. LDL- C and the TC/HDL-C ratio although increased was statistically not significant. Postmenopausal women showed statistically significant increase in TC, serum TG, LDL-C, TC/HDL-C ratio and LDL/HDL-C ratio. **Conclusion:** Adverse changes seen in the lipid profile during post menopause begins during the perimenopause. As the perimenopause phase is a period of varied length, it is the optimal time for lifestyle style modification and preventive intervention in order to prevent cardiovascular risk in future.

Keywords: Atherogenic Index, Dyslipedemia, Perimenopause

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Introduction

Throughout their reproductive life women have a lower incidence of Coronary Artery Disease (CAD) when compared with men [1]. These women seem to tolerate classical cardiovascular (CVD) risk factors such as smoking, high levels of cholesterol, hypertension, and excessive weight better than men do [2]. Menopause is the permanent cessation of menstruation resulting from the loss of ovarian follicular activity with subsequent hormonal changes. Perimenopause or menopausal transition refers to the phase immediately before menopause when the menstrual cycle is irregular or when there is a long period of amenorrhoea of minimum three months but not more than 12 months.

Amenorrhoea beyond 12 months is referred to as postmenopause phase [3]. After menopause, the levels of lipids and their transporting lipoproteins are altered resulting in an increase in the incidence of CAD [1]. Women who undergo surgical menopause or experience premature ovarian failure and not treated for estrogen deficiency, are characterized by a two-fold risk of coronary artery disease than the women attaining menopause by around 50 years [4]. All this has been seen as evidence that estrogens protect women from CAD.

Average age of menopause in India is 47.5 years compared to 51years in western countries [5]. In present era with increased life expectancy, women are likely to face long periods of menopause accounting to

approximately a third of her life. In addition to this, there is an increased incidence and prevalence of premature menopause and ever increasing burden of surgical menopause. This has resulted in a woman today spending almost a third of her life in menopause and that too with distressing clinical problems [6-10]. It is therefore critical to understand the influence of menopause on lipid profile in order to enhance our ability to identify targets for effective preventive measures.

Data regarding changes on lipid profile during perimenopause is very little as earlier studies focus mainly on changes in lipid profile in women in their reproductive phase and postmenopausal women. In view of this, our study was done to identify the changes in the lipid profile during the period of perimenopause and compare it with the changes seen in late reproductive phase and after menopause in order to identify the risk factors at a very early stage and subsequently prevent life threatening complication.

Material and method

Study design

This case control study was carried out at a tertiary care hospital in Patna on patients attending Gynaecology OPD for treatment of menopausal complains. The study was approved by the Institutional Ethics Committee and consent was obtained from the patients to participate. 180 patients between 35 to 56 years of age were included in the study. Based on the menstrual history and STRAW +10 criteria, they were divided into 3 groups: Group I (late reproductive phase group) with regular menstrual cycles, Group II (perimenopause group) with irregular menstrual cycles and Group III (postmenopause group) with amenorrhoea over a year [3]. Each group had 60 participants. Patients with

undiagnosed vaginal bleeding, cardiac disease, liver disorder, diabetes mellitus, breast tumour or other malignancies, history of stroke or transient ischemic attack, history of hormonal treatment or soya bean derived products in previous 12 months were excluded from the study.

Biochemical analysis

A venous blood sample was collected after a fasting period of 10 – 12 hours. Sample was then centrifuged and serum was used for the analysis. Lipid profile was determined by Erba 360 auto nalysed by using enzymatic methods such as CHOD-PAP method for total cholesterol (TC), GPO-PAP method for triglycerides (TG) and enzymatic method for High Density Lipoprotein – Cholesterol (HDLC-C). Low Density Lipoprotein – Cholesterol (LDL-C) was calculated by Friedwald's formula.

Statistical analysis

Statistical analysis was done using the statistical package for social sciences (SPSS) version 17.0. Data was nalysed using one way analysis of variance (ANOVA).The mean of the three groups was compared using multiple comparison post hoc test. P value of < 0.05 was considered statistically significant.

Results

Figure 1 show the mean age of the women in the three groups. The women had a mean age of 38.23 ± 6.73 in the late reproductive group, 43.43 ± 2.04 in perimenopausal group and 48.48 ± 2.36 years in the postmenopausal group.

Figure 1: Age distribution of women in late reproductive phase, perimenopause and postmenopausal group
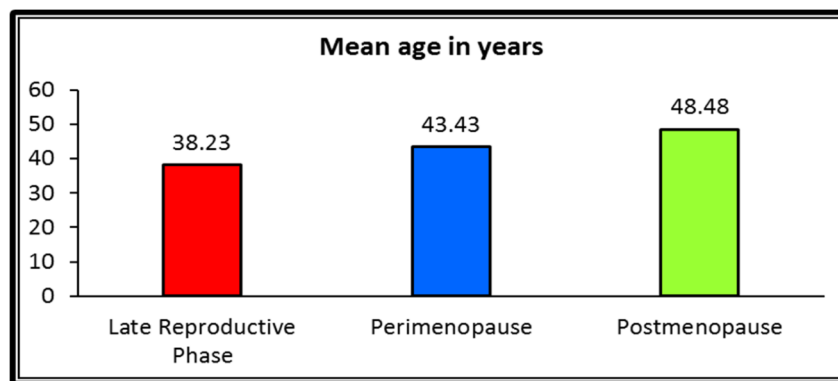

Table 1: Table showing the lipid profile, LDL/HDL cholesterol ratio and TC/HDL cholesterol ratio in the three study groups

	Late Reproductive Phase (n=60)	Perimenopause (n=60)	Postmenopause (n=60)
Total Cholesterol (mg/dL)	160.97 ± 22.42	196.92 ± 29.30**	211.67 ± 21.35*
Triglyceride (mg/dL)	118.26 ± 28.62	136.26 ± 27.23*	142.36 ± 42.22
HDL-Cholesterol (mg/dL)	50.76 ± 4.40	54.76 ± 5.10*	45.75 ± 4.02*
LDL-Cholesterol (mg/dL)	97.56 ± 24.63	114.20 ± 27.16	137.65 ± 21.03**
LDL/HDL Ratio	1.75 ± 0.54	2.09 ± 0.83*	3.00 ± 0.85***
TC/HDL Ratio	3.18 ± 0.93	3.64 ± 0.86	4.65 ± 0.97**

* P value < 0.05 ** P value < 0.001 *** P value 0.001

Table 1 shows the lipid profile of the women in the three groups. The postmenopausal women had a statistically significant increased levels of TC, LDL-C and significantly decreased levels on HDL-C when compared to women in late reproductive phase. The serum TG levels although increased in postmenopausal women but statistically not significant. The women in the perimenopausal group showed a statistically significant increase in the levels of TC, serum TG and HDL when compared to women in Group 1. TC/HDL cholesterol ratio and LDL/HDL cholesterol ratio was higher in perimenopausal women in comparison to late reproductive age group women. However they were further elevated in postmenopausal women. Elevation in these ratios was within the acceptable range. Apart from the increased TC/HDL cholesterol ratio in perimenopausal women, all the other changes in these ratios were statistically significant.

Discussion

Data from various studies have concluded that postmenopausal women are four to eight times more likely to die of CAD than of any other disease [11]. Lipids and lipoproteins are the established surrogate markers of vascular risks. The desirable levels for fasting lipid profile set by the National Cholesterol Education Programme (NCEP) is total cholesterol below 200 mg/dL, serum triglyceride levels below 150 mg/dL, serum HDL cholesterol levels more than 60 mg/dL and LDL cholesterol level less than 100 mg/dL. Apart from the lipid profile, the total cholesterol/high-density lipoprotein (HDL) cholesterol ratio, and the LDL/HDL cholesterol ratio are also used as an indicators of vascular risk as their predictive value of which is greater that isolated parameter. LDL/HDL ratio more and 3.0 and TC/HDL-C ratio greater than 4.5 indicates average cardiovascular risks in females [12].

According to the Stage of Reproductive Aging Workshop (STRAW) adult female are divided into three broad phases: reproductive, the menopausal transition, and postmenopause. These three phases included a total of seven stages centred on the FMP. The reproductive phase was divided into early, peak, and late. The menopausal transition phase consisted of early phase and late phase. Similarly postmenopause phase consisted of early and late [3].

Perimenopausal phase or the menopausal transitional phase begins with the first features of irregular menstrual cycle until the final menstrual period (FMP).

This ranges from 2 to 7 years averaging to about 4 years [13]. During this phase the FSH levels are rise to low normal levels of estrogen with intermittent fluctuation. Data pertaining to changes in lipid profile is scanty in the perimenopausal phase as most of the studies are carried out in women in their reproductive phase and postmenopausal women [14].

With the intention to study the changes of lipid profile in perimenopausal women and comparing it with late reproductive age group and postmenopausal women, this research was carried on a total of 180 women. Each of late reproductive age, perimenopause and postmenopause group consisted of 60 women. As age could be a confounding factor which alters the lipid profile, we included women of higher age before the onset of menopausal features and postmenopause women who recently attained menopause (Figure 1).

Several studies such as those by Bade *et al.,* Swapnali *et al.* and Carr *et al.* were conducted on premenopausal i.e reproductive age and postmenopausal women which demonstrated changes in lipid profile [15-17]. Their study showed that postmenopausal women had higher levels of total cholesterol, triglyceride and LDL-C. Our study also showed that the total cholesterol, triglyceride and LDL-C levels were increased in postmenopausal women as compared to late reproductive age women (Table 1). Although the increase in total cholesterol (P <0.05) and LDL-C ($P < 0.01$) was significant, the increase in triglyceride was not significant. This study

also determined the lipid profile of women during their menopausal transition phase. We observed that their total cholesterol levels and the serum triglyceride levels were significantly elevated when compared with women in late reproductive phase ($P < 0.01$ and $P < 0.05$ respectively) (Table 1). Similar observation was made by Berg et al. in their study [18]. The LDL-C which is atherogenic was comparable in the group 1 and perimenopausal group and hence was not significant. Similar observation was made by Kim et al. in a study carried out on 1679 women [19].

HDL-C has a protective function due to its anti atherogenic activity. Data on HDL-C levels in postmenopausal women have been inconsistent as HDL-C has been reported to remain unaffected by some [18, 20] and decreased by others [1, 21, 22]. In this study we observed that the HDL-C was slightly elevated in perimenopausal women which was statistically significant ($P < 0.05$). However as the women progressed to menopause, there was a statistically significant ($P < 0.05$) decrease in the HDL-C on comparison with premenopausal women (Table 1).

Two lipid ratios, Total/HDL cholesterol (atherogenic index) and LDL/HDL cholesterol were calculated to assess the cardiovascular risk in women in all the three groups. Individuals with a high Total/HDL cholesterol or LDL/HDL cholesterol ratio have greater cardiovascular risk owing to the imbalance between the cholesterol carried by atherogenic and protective lipoproteins. As the numerator of both these ratios contains the atherogenic component and the denominator contains the anti-atherogenic component, increase in these ratios indicates higher cardiovascular risk [12]. In our study the women in the post menopause group had the highest TC/HDL ratio and LDL/HDL ratio, both of which was statistically significant ($P < 0.01$ and $P < 0.001$). Similar observation was made in other studies [22-24]. The women in the perimenopausal group showed a statistically significant increase in the LDL/HDL ratio ($P < 0.05$) when compared to the women in their late reproductive phase. However this increase was clinically not significant as the ratio was below 3.0. There was an increase in the TC/HDL ratio in the perimenopause women which is neither clinically nor statistically significant (Table 1).

Alteration in the lipid profile mainly higher total cholesterol, triglyceride LDL-C and the atherogenic index may be attributed to the hormonal changes and failure of the follicular development due to reduced levels of estradiols in the postmenopausal phase [21].

Estrogen regulates the activity of lipoprotein lipase (LPL) which catalyzes the hydrolysis of Very Low Density Lipoprotein to form Intermediate Density Lipoprotein (LDL) and later LDL. During the menopause due to deficiency of estrogen, increased activity of plasma LPL and hepatic TG lipase causes elevation of LDL-C along with down regulation of LDL receptors.

During perimenopause, the level of estradiol fluctuates. Alteration in the activity of LPL may begin with this fluctuation resulting development of dyslipidemia as seen in our study. Non-significant elevation of LDL/HDL cholesterol and LDL-C accompanied by higher levels of HDL-C in perimenopausal than women in late reproductive phase and then a lower level of HDL-C and significant elevation of the indexes in postmenopausal women points that major alteration in the lipoprotein metabolism occurs during the perimenopausal phase. The comparable levels of LDL-C and LDL HDL cholesterol in the perimenopausal women could be explained by the increased HDL-C which scavenges cholesterol esters, reducing its availability for LDL-C formation [16].

Conclusion

To summarize, during the reproductive phase of life, circulating estrogen plays a cardio-protective role. However, during menopause, the circulating level of estrogen falls making them prone for CVD. These adverse changes seen during postmenopause begins during the menopause transition phase i.e. the perimenopause.

As the perimenopause phase is a period of varied length, it is the optimal time for lifestyle style modification and preventive intervention in order to prevent cardiovascular risk in future. Moreover a larger population based prospective study on changes lipid profile during the early and late perimenopause would provide beneficial to improve the quality of life of women entering the postmenopausal phase.

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