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PREMATURE MENOPAUSE AND ITS ASSOCIATION WITH DYSLIPIDEMIA

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ABSTRACT

Introduction: *Premature Menopause is defined as premature ovarian failure before the age of 40 years with a consecutive 12 months of amenorrhea. Menopause affects 1% of women under the age of 40 years. It is seen in 10-28% of primary amenorrhea and 4-18% of secondary amenorrhea. Estrogen deficiency occurring during premature menopause causes decrease in HDL level and increase in LDL, cholesterol and triglycerides levels thus causing dyslipidemia. Regardless of cause, women who experience estrogen deficiency at an early age before the natural menopause are now considered to be at increased risk for premature morbidity and mortality. The current study is aimed to find out the impact of premature menopause on the blood lipid level in the current population.*

Methods: *Ninety-six cases of premature menopause women were enrolled retrospectively for the study. Complete Lipid profile – Serum Total Cholesterol, Serum Triglyceride, Serum HDL, were measured in fully automated biochemistry analyzer and Serum VLDL and Serum LDL were estimated by Friedewald' Formula.*

Results: *The current study revealed the lipid profile status of premenopausal women. The prevalence of dyslipidemia was observed in 57 cases (59.4%) and remaining 39 cases (40.6%) were having normal lipid levels. On comparing the serum lipid levels statistical significance were observed in Total cholesterol (P value:0.00), Triglyceride (P value: 0.00), LDL-C (P value: 0.00), and VLDL-C (P value: 0.00). However, no statistically significant difference was observed in HDL cholesterol (P value:0.15).*

Conclusions: *Serum Lipid levels is deranged in the women with premature menopause (Age< 40 years) and thus dyslipidemia, particularly noticed with the Total cholesterol and triglyceride levels. The path-physiologylyingbehinddyslipidemiacanbecorrelatedtothepremature ovarianfailureandestrogendeficiency.*

Keywords: *Estrogen, Premature Menopause, Total Cholesterol, Triglycerides*

INTRODUCTION

Menopause is a state when a female individual has undergone12 consecutive months without a menstrual cycle. The time period leading up to menopause is called perimenopause or transition phase. This is when women may notice changes in their menstrual cycles or have symptoms like hot flashes and others. Menopause in women is either attained naturally due to ageing process or early (Age ≤ 45years) or prematurely (Age < 40 years).[1-3] Natural menopause is a spontaneous process that happens with the permanent ending of menstruation that doesn't happen because of any type of medical/surgical treatment. The study by Ahuja et al identified 46.2 ± 4.9 years as the age of natural menopause in India. The Indian women begin their perimenopausal stage, identified by irregular periods, by the age of 44.69 ± 3.79 years.[4]

The process of attaining menopause is gradual and happens in three stages, that are perimenopause, menopause and post-menopause. Perimenopause can begin eight to ten years prior to menopause when estrogen production gradually decreases. Secondly, menopause is the point of stoppage of menstrual periods due to stopped production of estrogen by ovaries. Its diagnosis is based on absence of menstrual period for 12 consecutive months. Moreover, post-menopause represents the time period of prolonged amenorrhea for an entire year.

Premature Menopause is defined as premature Ovarian failure before the age of 40 years with a consecutive 12 months of amenorrhea.[5,6] Premature Menopause affects 1% of women under the age of 40 years. It is marked by amenorrhea, increased gonadotropin levels in blood (FSH level >40 mIU/ml) and Estrogen deficiency (E2 level <20 pg/ml).[6] It is seen in 10-28% of Primary amenorrhea and 4-18% of secondary amenorrhea.[7,8,9]

It can be of spontaneous onset or of Induced type. The definitive etiology of Premature menopause is hard to determine but the identifiable causes can be distinguished.[9,10,11] The causes for premature ovarian failure can be idiopathic as well as due to genetic causes, infections, autoimmune disorders, enzyme deficiencies and metabolic syndromes.[12,13] Moreover, prematurely/ early induced menopause could be a result of medical or surgical interventions i.e. chemotherapy, hysterectomy and bilateral oophorectomy. Regardless of cause, women who experience estrogen deficiency at an early age before the natural menopause are now recognized to be at increased risk for premature morbidity and mortality.[14]

Women experience a number of hormonal changes throughout their lifetime including those changes associated with puberty, menarche, pregnancy and menopause. Each of these states during lifetime can cause alterations in serum lipid profile.[15,16] Because lipids such as cholesterol and triglycerides are insoluble in water these must be transported in association with proteins in the circulation. These called as, plasma lipoproteins are formed by the union of Cholesterol or Triglycerides in central core peripherally surrounded by free cholesterol, phospholipids and apolipoproteins. Plasma Lipoproteins are divided into 7 classes based on their size, lipid composition and apolipoproteins (Chylomicrons, Chylomicron remnants, VLDL, IDL, LDL (large and small), HDL (HDL_1 and HDL_2) and Lp(a). Based on their sizes from larger to smaller, Chylomicrons, Chylomicron remnants, VLDL, IDL, LDL (large and small) and Lp(a) belong to PRO-Atherogenic Lipoproteins and HDL (HDL_1 and HDL_2) belongs to ANTI-atherogenic lipoproteins.[17,18,19] Starting during puberty and continuing into adulthood, HDL-concentration decrease in men while staying constant in women.[20] After menopause, women experience serum lipid changes owing to a significant decrease in the sex hormone estrogen[21] and those post-menopausal women tend to have significantly different lipid profile. Their low-density lipoprotein cholesterol (LDLC), total cholesterol (TC), and triglycerides (TG) increase and high-density lipoprotein cholesterol l(HDL-C) decreases.[22]

In the Framingham Study an increase in cholesterol level has been documented that coincided with menopause suggesting a important role of menopause in altering lipid levels.[23] In addition menopause is also associated with a transition in LDL particles to more atherogenic smaller and more dense particles.[24] Total HDL cholesterol and HDL_2 also decrease in postmenopausal women.[25] Elevated Lp(a) levels have been associated with an increased CHD risk and has been further reported to increase in women following total hysterectomy and oophorectomy.[26,27] Elevated levels of LDL-C and triglycerides and low levels of HDL are independent risk factors for atherosclerotic heart disease in postmenopausal women and are believed to be responsible for the increased risk for cardiovascular events. While HDL and triglycerides are strong predictors of CVD death, LDL-C and total cholesterol are poor predictors in women. LDL particle size also appears to confer CHD risk in women (although similar to men). Young women with a predominance of small atherogenic LDL-C particles have been shown to have a significantly increased risk of early myocardial infarction.[28] Lp(a) is also shown to be an independent predictor of CHD risk in women.[29] Premature menopause is associated with an increased risk of ischemic heart disease and angina and the risk increases with an earlier age of ovarian failure.9,30 It is also associated with increased cardiovascular mortality and total mortality.[31,32,33] Estrogen deficiency occurs which increases the risk of ischemic heart disease and angina in a post-menopausal woman. Normally, Estrogen is cardio protective in nature.[34] [34] Estrogen increases HDL and decreases LDL, cholesterol and triglycerides. Estrogen receptors have been found throughout the cardiovascular system. A typical estrogen effect is a relaxation in arterial tone and a decrease in resistance.[35]

In Korea, dyslipidemia among women increased with age and showed a significant difference before and after menopause. The prevalence was 27.6% in women aged < 40 years, 55.9% in women aged 40–59years, and 64.6%in women aged≥60 years.[36,43] They experience changes in serum lipid levels, and there is a significant increase in the incidence of fatal cardiovascular disease.[21,37,38]

The natural menopausal age of a woman serves as a biomarker for subsequent disease prediction and mortality, while premature/early menopause are associated with an increased risk of cardiovascular disease and osteoporosis, and other complications.[1,2,3] The consequences of premature menopause can be divided into short-term and long-term consequences. The short-term consequences include vasomotor symptoms such as hot flushes, night sweats, palpitations and headaches, weight gain, vaginal dryness and dyspareunia, urgency and stress incontinence with psychological problems including irritability, forgetfulness, insomnia and poor concentration.[9,10] The long-term consequences of premature menopause include infertility, osteoporosis and an increased risk of premature death, cardiovascular diseases and stroke.[9,10]

As dyslipidemia usually has no clear symptoms, it is

difficult to make an early diagnosis. Even if it is confirmed through a health checkup, the level of awareness about the risk of disease is low. Hence, it is often left unattended, and people do not visit the hospital to receive an accurate diagnosis and treatment.[39]

MATERIALS AND METHODS

This is a cross-sectional observational descriptive study carried in the outpatient Department of General Practice and Emergency Medicine at National Medical College and Teaching Hospital, Birgunj, Nepal for a period of six months (20th December, 2022 to 20th June, 2023). Ethical clearance (Ref. F-NMC/619/079-080) from Institutional Review Committee (IRC), National Medical College was taken prior to the study. Proper consent was also taken with the participants.

STATISTICAL ANALYSES:

All the data were entered in the Microsoft Excel 2010, converted to SPSS version 22 accordingly. Frequency and percentage were calculated for descriptive statistics. Chi square test was applied to compare the categorical variables. Student's t test was used to compare mean between two groups. Continuous data were expressed in mean SD. P value <0.05 was considered as statistically significant.

RESULTS:

Our study covered the measurement of serum lipid levels (Total Cholesterol, TGA, LDL-C, VLDL-C and HDL) in the women achieving premature menopause (menopause at Age < 40 years). The sample size at the end of the study consisted of total 96 cases. The variables were expressed as mean and standard deviation as depicted in the table 1.

Table1: Descriptive statistics of the data (n=96)

Parameters	Mean	Std. Deviation
Age (Years)	38.20	1.270
Weight (Kg)	59.02	6.091
TC (mg/dL)	185.89	23.120
TG (mg/dL)	171.09	21.894
LDL-C (mg/dL)	116.17	23.474
HDL-C (mg/dL)	35.47	4.341
VLDL-C (mg/dL)	34.25	4.367

The total sample size was then further categorized on the basis of the presence of dyslipidemia in the group and the normal lipid levels in the groups. The normal levels for the lipid profile considered were (by NTCP recommendations) – Total Cholesterol < 200 mg/dL, TGA < 150 mg/dL, HDL > 60 mg/dL, LDL-C <100mg/dL, VLDL-C< 30mg/dL.

The prevalence of dyslipidemia in our study was found to be 59.4% of women with premature menopause and remaining 40.6% was contributed by women having normal lipid levels, as illustrated in the figure 1.

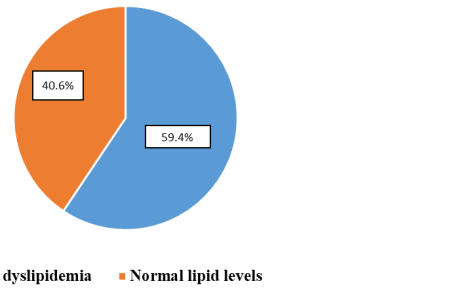

Figure1: Distribution of premature menopause women based on serum lipid levels (n=96)

Out of total 96subjects, 57 were having deranged lipid levels either for one or multiple parameters causing dyslipidemia and remaining 39 were having normal lipid levels for all parameters. There were significant differences in mean value and standard deviation of Total Cholesterol (p value – 0.00), TGA (p value - 0.00), HDL (p value -0.00), LDL-C (p value-0.00) and VLDL-C (pvalue-0.00) as depicted in table 2.

Table2: Comparison of variables between dyslipidemia and normal lipid levels in premature menopause women (n=96)

Variables	Serum Lipid Level	N	Mean ± Std. Deviation	P value*
Age(years)	Deranged Lipid Level	57	38.37±1.19	0.11
	Normal lipid Level	39	37.95±1.35	
Weight (Kg)	Deranged Lipid Level	57	60.54±6.43	0.00
	Normal Lipid Level	39	56.79±4.81	
Menopause Months	Deranged Lipid Level	57	7.81±2.94	0.66
	Normal Lipid Level	39	7.56±2.22	
Total Cholesterol (mg/dL)	Deranged Lipid Level	57	194.00±24.44	0.00
	Normal Lipid Level	39	174.03±14.57	
Triglycerides (mg/dL)	Deranged Lipid Level	57	178.18±19.05	0.00
	Normal Lipid Level	39	160.74±21.87	
HDL	Deranged Lipid Level	57	34.95±3.94	0.15
	Normal Lipid Level	39	36.23±4.80	
VLDL-C	Deranged Lipid Level	57	35.63±3.80	0.00
	Normal Lipid Level	39	32.23±4.39	
LDL-C	Deranged Lipid Level	57	123.42±25.12	0.00
	Normal Lipid Level	39	105.56±15.91	

DISCUSSION:

Dyslipidemia is significantly prevalent among women and premature menopause can prove itself to be an aggravating factor. The long-term consequences of premature menopause include infertility, osteoporosis sand an increased risk of premature death, cardiovascular diseases and stroke.[9,10] The management of dyslipidemia is a cornerstone in the prevention of both primary and secondary cardiovascular events, such as myocardial infarction, ischemic stroke, and coronary death. Interestingly, no clear association has been documented between natural menopause and changes in Lp(a) levels. In contrast with the surgical menopause data, Jenneret al showed that post menopausal women participating in the Framingham Offspring Study had 8% lipid levels than premenopausal women. The change in lipoprotein profile with the observed increase into cholesterol, transition to more atherogenic LDL particles, and reduction in HDL-C is believed responsible for the increased risk for cardiovascular events in women after menopause. [27]

Our study investigated the serum lipid level for given parameters (Total Cholesterol, TGA, HDL, VLDL and LDL) in the women with premature menopause. Premature menopause hereby, is defined as all women of age ≤ 40 years and in menopause proved clinically, and with amenorrhea of ≥ 1 years. Our study has included the individuals with no known chronic diseases and not taking any drug that could alter the serum lipid profile level and who have given the informed consent for the research purpose. It revealed that women with premature menopause are at risk to develop dyslipidemia more. It is evident that 57 cases out of total 96 cases of all with premature menopause, have deranged levels of Total Cholesterol with p-value0.00, TGA with p-value 0.00, VLDL with p-value 0.00 and LDL with p-value 0.00, which carry statistical significance for these four parameters and thus developed dyslipidemia. In our study Dyslipidemia in women with premature menopause is also has some association with body weight. However, no statistically significant differences were observed in HDL cholesterol level.

Consistent with results for menopausal status, observations in the highest estradiol quartile had the lowest levels of total cholesterol, low density lipoprotein cholesterol, and triglycerides, although the association with triglycerides was only marginally statistically significant. Compared with premenopausal women, premature and early menopausal women had a 2-fold risk of low-density lipoprotein (LDL-cholesterol) above the level recommended by the national guidelines.[40] The results of a previous study showed that the prevalence of dyslipidemia before menopause was 35.0%, which increased to as high as 65.2% after menopause.[22] An international study on obesity discovered that more than 39% of women experiencing menopause were either overweight or obese.[41,43] This status was due to weight gain because of changes in hormones and body fat distribution, in addition to unhealthy lifestyles. In this study, overweight and obese subjects accounted for 61.5% of those with dyslipidemia, which was much higher than the international study results.[42,43]

CONCLUSION

This study provides valuable information about the development of dyslipidemia in women in our study group with premature menopause (Age < 40 years). Regardless of the cause of development of premature menopause, these women are always at high risk to develop premature morbidity and mortality due to the cardiovascular diseases, osteoporosis, infertility, stroke. Interestingly, the awareness about development of dyslipidemia at an early age due to premature menopause is completely absent which could prove even more risky. This study may be helpful in terms of raising awareness about the risks of premature menopause and dyslipidemia.

LIMITATIONS

The study duration was short, the follow up of the patients was not done and the drug history of the patients were not recorded.

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