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ESTIMATION OF SERUM LIPID PROFILE IN OOPHORECTOMIZED PREMENOPAUSAL WOMEN AFTER ESTROGEN ADMINISTRATION

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ABSTRACT

Introduction: Premenopausal women suffer less from CVD as compared to men. Women with spontaneous or surgically induced menopause (Oophorectomy) have increased serum lipids and thus increased risk of IHD. Substitution therapy with estrogens to reduce the menopausal symptoms in such subjects may reduce serum lipid levels but the association between exogenous estrogen use and cardiovascular disease is controversial.

Material & Methods: The study was conducted in a tertiary care hospital of Western Uttar Pradesh for a period of one year on 60 premenopausal women who were subjected to oophorectomy due to various reasons. The patients were divided into 2 groups after one month post operatively, with 30 subjects in each. Group 1(control) with less post-menopausal symptoms after operation and were not treated with estrogen. Group 2(test), with more pronounced menopausal symptoms post operatively were given estrogen (0.3mg daily). The blood samples were collected for a period of 6 months at monthly intervals for estimation of serum lipid profile.

Observations and Results: After one month, there was a highly significant increase in Total Serum Cholesterol, TG, LDL and a decrease in HDL cholesterol values. Most of the patients developed postmenopausal symptoms of different intensity like episodes of hot flushes, sweating, irritability and behavioural changes etc. And patients were now divided into two subgroups Gr1 and Gr 2. Group1 did not have intolerable menopausal symptoms and were not given estrogen therapy while Group2 received estrogen therapy (0.3mg daily). In Group 1 patients the serum lipids increased significantly throughout the period of study while in Group 2 with estrogen administration besides allaying the severe menopausal symptoms also reduced lipid profile significantly in 2nd and 3rd month then it stabilised in the subsequent period of study.

Conclusion: Estrogen administration can be beneficial after oophorectomy and protects the women against premature cardiovascular disorders. However, further studies are required for a longer duration to ascertain its efficacy as the prolonged use of estrogens can give rise to many adverse effects.

KEYWORDS : Premenopausal Women, Oophorectomy, Hyperlipidaemia, Lipoproteins, Estrogen

INTRODUCTION

Ischemic Heart Disease (IHD) is one of the major causes of morbidity and mortality all over the world and in India. Women in the reproductive age group suffer less from IHD than do men[1] and it has been suggested to be due to the protective effects of oestrogen [2]but this advantage declines in women with advancing age and finally disappears after menopause, because it is thought that the functioning ovaries provide protection against IHD by producing oestrogens and by lowering lipid levels [3].

There are large number of risk factors for cardiovascular disease (CVD) among these, the three most important are (1) abnormal lipid levels, (2) hypertension, and (3) cigarette smoking and tobacco chewing. The other risk factors include diabetes mellitus, blood coagulation defects for example fibrinogen, factor VII, plasminogen activator inhibitors, and some new factors like apolipoprotein E4 and homocysteine, which are known to increase the risk of developing CVD for example myocardial infarction. Women with spontaneous or surgically induced menopause (removal of ovaries with or without removal of fallopian tubes and uterus) have increased serum lipids and thus increased risk of IHD[4].On being given substitution therapy with estrogens the level of lipids may return to normal [5]but prolonged estrogen administration causes weight gain and water retention and increased blood sugar level, which may induce IHD and can lead to type 2 diabetes mellitus.

The association between exogenous estrogen use and cardiovascular disease is controversial. According to some studies, exogenous estrogen use increases the risk of cardiovascular disease while other studies have reported that estrogen use protects against the development of cardiovascular diseases by changing the lipid levels. Evidence from animal and autopsy studies show that exogenous estrogens may inhibit the development of atherosclerotic coronary lesions. Furthermore, the majority of studies of non-contraceptive estrogen use in women suggest that estrogens either protect against or do not increase the risk of cardiovascular disease [6,7].

So, the present research study is undertaken to observe the effect of estrogen administration on blood lipids in post oophorectomized premenopausal women.

MATERIAL & METHODS:

This is a prospective observational study conducted in a tertiary care hospital of Western Uttar Pradesh over a period of one year on total 60 premenopausal women (38 to 48 years of age) who were non diabetic, non-hypertensive, with no malignancy or inflammatory disease and undergoing oophorectomy (with or without salpingectomy and hysterectomy) were included in the study. The study was done after taking approval from the Institutional Ethics Committee (IEC) and written consents from the patients included in the study, each patient was followed for 6 months from the time of admission.

The subjects were divided into two groups after one month post-operatively when they developed the post-menopausal symptoms.

Group 1 (control) having 30 patients, who did not receive any estrogen post-operatively as these patients had minimal postmenopausal symptoms after oophorectomy.

Group 2 (test) having 30 patients received estrogen therapy (Tab Premarin) 0.3mg daily orally after one month of operation and had intolerable postmenopausal symptoms.

At the time of admission in the hospital, a thorough general systemic examination of the patients was done.

For performing the investigations (lipid levels) blood samples from the subjects of both groups were collected before surgery and after a week post oophorectomy. The follow up was done at monthly intervals for a period of 6 months. At each follow up blood samples were collected for the estimation of lipid levels. The patients were also enquired about whether they experienced any side effects after taking the medication.

The total cholesterol was measured by:
Cholesterol Oxidase/ Peroxidase Method (CHOD – POD Method) [8]
HDL Cholesterol was measured by Direct Enzymatic Method [9]
LDL Cholesterol was measured by Friedewald Equation: LDL = TC – (HDL + TG/ 5) [10]

Serum Triglycerides were measured by:
Glycerol – 3 – Phosphate Oxidase Method (GPO)[11]

The statistical analysis was done using Two Way ANOVA and Tukey (post hoc analysis).

OBSERVATION AND RESULTS:
Some patients (50%) complained of minimal post-menopausal symptoms like hot flushes, sweating, irritability, giddiness, palpitations, forgetfulness and mood swings etc. occasionally while rest of the patients had developed severe menopausal symptoms viz frequent and intolerable episodes of hot flushes and flashes, sweating, insomnia, depression and behavioural changes.

The blood samples were collected for the estimation of the lipid profile. The mean initial lipid profile of the selected subjects was found to be in normal range that is Mean Total Serum Cholesterol 162mg/dL ±5.3, Triglycerides (TG) 76 mg/dL ±7.4, HDL 48mg/dL±6.3 and LDL102mg/dL±9.4.(Table 1,Fig.1-4).

Table 1. Effect of oophorectomy on lipid profile in premenopausal women (N=30) Group 1 (control). All values are mean ±S.E. statistically significant p<0.0001 Two way ANOVA and Tukey(post hoc analysis).

Name of the lipoprotein	Before Operation (Zero Day)	After Operation						
		1 Week	1 Month	2 Month	3Month	4Month	5Month	6 Month
Total Serum Cholesterol (mg/dL)	162±5.3	166±5.5	266±12.7	291±12.8	316±12.9	320±13.3	309±12.9	325±14.4
Serum Triglycerides (mg/dL)	76±8.4	75±5.8	275±11.9	298±15.5	320±12.5	314±14.6	310±17.1	301±14.8
Serum High Density Lipoproteins (mg/dL)	48±6.3	45± 4.9	32±3.5	26±3.2	27±2.9	30±4.1	28±3.7	25±4.6
Serum Low Density Lipoproteins (mg/dL)	102±9.4	106±7.8	147±8.9	190±13.3	203±14.1	216±13.8	220±15.3	205±16.4

Table 2. Effect of estrogen (Primarin) 0.3mg daily administration on lipid profile in premenopausal women after oophorectomy (N =30) Group 2. All values are mean ±S.E. statistically significant p<0.0001 Two way ANOVA and Tukey(post hoc analysis).

Name of the Lipoproteins	Before Operation	After Operation						
	Mean Initial Values	1Week	1 Month	2 Months	3 Months	4 Months	5 Months	6 Months
Total Serum Cholesterol (mg/dL)	162±5.3	166±5.5	266±12.7	190±8.2	185±4.5	170±9.4	178±10.2	174±8.9
Serum Triglycerides (mg/dL)	76±7.4	75±5.8	275±11.9	175±7.8	108±3.5	98±7.5	86±9.5	94±7.5
High Density Lipoproteins (HDL) (mg/dL)	48±6.3	45±4.9	32±3.5	48±2.2	49±3.6	46±6.2	50±4.5	55±5.1
Low Density Lipoproteins(LDL)(mg/dL)	102±9.4	106±7.8	147±8.9	120±6.9	110±6.8	107±9.7	111±10.2	104±11.3

Post operatively after one week, the lipid profile was estimated again and no significant change was found in the lipid profile as Mean Total Serum Cholesterol 166mg/dL±5.5, Serum TG 75mg/dL±5.8, HDL45mg/dL±4.9 and LDL106 mg/dL±7.8 in comparison to the initial values(Tab 2,Fig1-4). All the patients were followed postoperatively and their blood samples were collected at monthly intervals for 6 months. A highly significant($p<0.0001$) increase was found in Mean Total Serum Cholesterol 266mg/dL±12.7, TG 275mg/dL±11.9, LDL147mg/dL±8.9, and a significant decrease in HDL32mg/dL±3.5 levels after one month of oophorectomy in all the subjects (Tab 1,2; Fig.1-4).

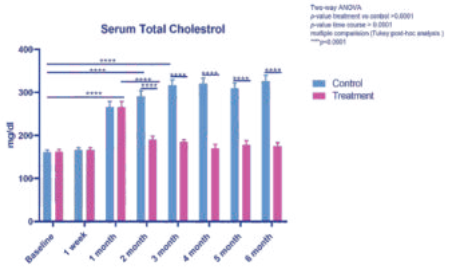

Fig 1: Effect of estrogen administration in oophorectomized premenopausal women and its comparison with the control group (N=30 in each group) on mean total serum cholesterol. ****p = < 0.0001

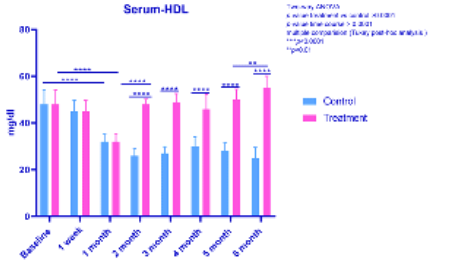

Fig 2: Effect of estrogen administration in oophorectomized premenopausal women and its comparison with the control group (N=30 in each group) on mean HDL cholesterol. ****p= < 0.0001, p = < 0.01**

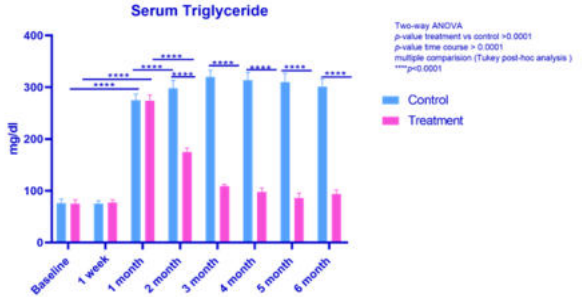

Fig 3: Effect of estrogen administration in oophorectomized premenopausal women and its comparison with the control group (N=30 in each group) on mean serum triglyceride ****p = <0.0001

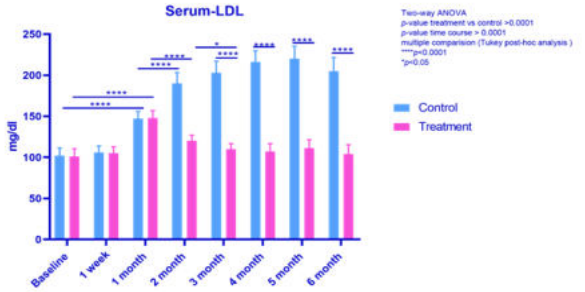

Fig 4: Effect of estrogen administration in oophorectomized premenopausal women and its comparison with the control group (N=30 in each group) on mean serum LDL ****p = <0.0001 , *p=<0.05

In Control (Group 1), in the subsequent months (2nd,3rd,4th,5th,6th) a highly significant ($p<0.0001$) increase was observed in the Mean Total Serum Cholesterol, Serum TG and Serum LDL and a highly significant ($p<0.0001$) decrease in Serum HDL Level in comparison to the first month values (Tab1,2; Fig 1-4).

In Group 2, a highly significant($p<0.0001$) decrease in lipid profile was noted after the administration of estrogens in second month as the

Total Serum Cholesterol (190mg/dL±8.2),Serum TG (175mg/dL±7.8), HDL(48mg/dL±2.2) and LDL(120mg/dL± 6.9) levels were observed in comparison to the values of lipids after the first month(Tab1,2;Fig.1-4).Only significant ($p<0.05$) decrease was noted in the third month as the Mean Total Serum Cholesterol (185 mg/dL± 4.5),Mean TG (108mg/dL±9.5) ,Mean LDL(110 mg/dL±3.8), and an increase in Mean HDL (40 mg/dL±3.6) (Tab 1,2; Fig 1-4) were noted in comparison to the value of the second month. In the fourth, fifth and sixth month no significant ($p>0.05$) change was noted in the lipid profile (Tab1,2; Fig 1-4) in comparison to the 3rd month and the initial values. The post-menopausal symptoms of patients subsided after estrogen therapy.No significant change was found in their blood pressure and weight. The patients were also questioned about any other complaints like headache, nausea, flushing, dizziness, breast discomfort etc as the adverse effects of estrogen administration.

DISCUSSION:

The present study was undertaken with a view to analyse the effect of estrogen administration on lipid profile in premenopausal women (38 to 48 years)who had undergone bilateral salpingo-oophorectomy or bilateral salpingo-oophorectomy with hysterectomy(surgically induced menopause) due to various other conditions (like ovarian cyst, endometriosis, adenomyosis ,uterine fibroid ,benign tumours, dysfunctional uterine bleeding etc). There is still controversy if menopause increases the risk of IHD or not [7]. However, epidemiological evidence indicates an association between premature loss of ovarian function and increased risk of CHD with increased serum lipid profile[4].

Cholesterol and TG levels are influenced by several factors such as: diet, life style, age, sex and hormonal changes[12]. The women's lipid profile is highly influenced by hormonal change, since physiological fluctuations in menstrual cycle changes the lipidogram and glycaemic index[13].Surgical menopause is sudden in onset as opposed to normal menopause which occurs naturally in women as part of the aging process is slow in onset and ovaries continue to secret low levels of hormones long after menopause[14].When ovaries are removed a women is at a higher risk of cardiovascular diseases[14-16].

In the present study, the lipid profile of 60 women who went through surgical removal of ovaries has been estimated. Postoperatively, after a month, most of the subjects developed menopausal symptoms of different intensities like episodes of hot flushes, sweating, nightmares, irritability and behavioural changes. Only 30 women did not require any hormonal treatment since they did not experience these intolerable symptoms. So, these 60 patients after one month were divided into two groups. Group 1 patients without estrogen therapy and Group 2 was treated with estrogen 0.3mg/day to alley the menopausal symptoms. Blood samples were also collected from both the groups at monthly intervals for a period of 6 months post oophorectomy to see the effect of estrogens on lipid profile.

Effect of Estrogen Therapy on Total Serum Cholesterol

There was no significant effect on serum cholesterol in both groups after one week of oophorectomy in comparison to the baseline value.[Fig.1 Tab.1,2] but there was a highly significant($p<0.0001$) increase after one month in both the groups. On estrogen (Premarin 0.3mg) administration orally to Group 2 subjects produced a highly significant($p<0.0001$) decrease in serum cholesterol level in second month and a significant decrease($p<0.05$) after third month in comparison to the first month level and no significant change was observed after the 4th,5th,6th months. Our results are in accordance to that of Parrish et al[14],Rivera et al [16], A. Flöter et al[17],Godsland IF[18], Rosenberg et al[19], Castelo-Branco et al [20] reported that total serum cholesterol levels remained unaltered after giving estrogen therapy to oophorectomized women. However, in Group 1 patients the Total Serum Cholesterol increased significantly in the subsequent months during the period of study.

Effect of Estrogen Therapy on Serum Triglycerides

In this study the mean TG level in both the groups before operation and after one week of surgery showed no significant change. But after one month there was a highly significant increase in TG level in comparison to the baseline value. Similar findings have also been reported by Li PC.[21](Fig 3,Tab 1,2).

However, after estrogen administration to Gr 2 subjects the TG level decreased significantly in second and third month. Similar results have been reported by Nanda S. et al [22] after transdermal estrogen application to the patients but on oral administration the TG levels did not change.

Punnone [23] reported that serum triglyceride tends to increase postoperatively peaking at one month but it subsequently declines to preoperative levels in the following 6 months similar to our findings but in Gr 1 subjects who were not on estrogen therapy, a marked increase was noted in their TG levels.

Effect of Estrogen Therapy on Serum HDL Cholesterol

The serum HDL cholesterol value showed a significant decrease after one month while, Punnonen and Rauramo [23] reported that HDL remained unchanged after oophorectomy. On estrogen administration the HDL cholesterol significantly increased in second and third month and no significant change was observed in the subsequent fourth, fifth and sixth month, showing a protective effect of estrogen administration for IHD (Fig 2,Tab 1,2).Our findings are similar to that of Castelo-Branco et al [20] and Nanda S. et al [22].In Gr 1 subjects HDL Cholesterol kept on decreasing which shows that these patients were more prone to IHD(Tab 1,2;Fig 1-4).

Effect of Estrogen Therapy on Serum LDL Cholesterol

The serum LDL cholesterol level increased significantly after one month of oophorectomy (Fig 4).These findings are similar to that of Natalia et al [24] who also reported marked increase in serum LDL cholesterol post oophorectomy. On estrogen administration to Gr 2 patients, after one month of operation, the serum LDL cholesterol decreased highly significantly after second and significantly after third month and it remained stationary after the fourth, fifth and sixth month. In comparison to baseline value estrogen has a protective role against IHD, it is further confirmed by our results of Gr 1 where the LDL cholesterol kept on increasing throughout the period of study (Table1,2; Fig 4).

Our findings are in accordance with the findings of Castelo-Branco et al [20] and Ida Gregersen et al [25]

Other occasional complaints reported by the patients of Gr 2 post operatively were hot flushes and sweating. Some patients reported palpitation episodes while other patients mentioned about behavioural changes and irritability but all these symptoms subsided after few months of estrogen therapy.

Estrogen administration itself produced certain adverse effects like five patients mentioned about nausea and dizziness, and six patients had mild weight gain otherwise there were no complaints reported since it was in a very low dose.

In conclusion the above study indicates that estrogen administration can be beneficial after oophorectomy. However, further studies are required for a longer duration to ascertain its efficacy for prolonged use since estrogens can cause many adverse effects.

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