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Research Article

COMPARISON OF EFFECTS OF HORMONE REPLACEMENT THERAPY ON SERUM LIPID PROFILE & LIPOPROTEIN(A) IN POSTMENOPAUSAL WOMEN IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Objective: The study was used to compare the effects of combined estrogen–progestogen therapy and estrogen alone on serum lipid profile and lipoprotein (a).

Methods: A prospective longitudinal study was conducted on the patients attending the Gynecology OPD at the All India Institute of Medical Sciences, New Delhi. Thirty women, who have attained spontaneous or surgical menopause, were selected as cases. All the women with natural menopause received combined estrogen-progestogen therapy (CEE, 0.625 mg and medroxyprogesterone acetate 2.5 mg daily) for 6 months. On the other hand, the women who underwent surgical menopause received only estrogen (CEE 0.625 mg) daily for 6 months lipid profile parameters and lipoprotein (a) were measured using commercially available kits before commencement of treatment and on follow-up (at 3 and 6 months).

Results: There was a 30% decrease in serum lipoprotein (a) level following 6 months of Hormone replacement therapy. This finding confirms with the positive cardioprotective effects of estrogen.

Conclusion: The beneficial effects of estrogen on lipids and lip (a) got partially attenuated when progesterone was added to estrogen.

Keywords: Lipid profile, Lipoprotein (a), Hormone replacement therapy, Estrogen, Progestogen.

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INTRODUCTION

"Menopause" is derived from the Greek words, "Men" (month) and "Pauo" (to stop) and refers to the permanent cessation of menstruation due to loss of ovarian follicular activity [1].

Menopause results in a number of problems in women such as a change in self-image sexual dysfunction, atrophic changes, osteoporosis, and coronary artery disease [2]. During the reproductive period of life, women are protected from coronary artery disease. Hormone replacement therapy (HRT) is currently prescribed for the relief of menopausal symptoms and prevention of both postmenopausal osteoporosis and coronary heart disease as a cup benefit [2].

The cardioprotective effects of exogenous estrogen have been attributed to various factors such as effects on lipid profile, carbohydrate metabolism, vascular interactivity blood pressure, endothelial function, and coagulation cascade. Postmenopausal women have an atherogenic lipid profile. There is a rise in total cholesterol, triglycerides, and very low-density lipoprotein (VLDL). The rise in total cholesterol is associated with a parallel increase in low-density lipoprotein (LDL), which increases faster in postmenopausal women than in men of a similar age group. High-density lipoprotein (HDL) levels however are not affected by natural menopause and their level continues to be higher in women than in men [3].

Estrogen increases HDL while it decreases LDL and lipoprotein (a). Monotherapy with estrogen is associated with the risk of endometrial hyperplasia and subsequent endometrial cancer. Therefore, the addition of progestin, either periodically or continuously is recommended.

Progestogens are most commonly prescribed on a cyclical basis for 10–14 days each month, although in women with established menopause, they may be given in continuous combined regimens without causing withdrawal bleeding. Depending on the androgenic potency of the progestin and on the dose used, these compounds may negate the estrogen-induced beneficial changes in plasma lipids in HDL. Hence, progestogens which are less androgenic are used in the preparations [4].

Presently, there are very little data available on the newer markers such as lipoprotein (a) and LDL subtraction profile. Over the past 20 years or more, a large study of evidence has accumulated to indicate that high levels of lipoprotein (a) are associated with atherosclerosis. Most of this evidence has come from case–controlled studies and also from prospective studies. The balance of evidence from these studies suggests that lipoprotein (a) is an important predictor of coronary heart disease. Most of the pharmacological agents that are effective in lowering LDL levels have little effect on lipoprotein (a). Postmenopausal estrogen therapy has been shown to have a minor effect on this marker, while the androgenic progesterone norethisterone markedly reduces the levels. Studies on the effects of estrogen combined with medroxyprogesterone acetate, which has low androgenic activity have produced inconsistent results.

Although it has not been demonstrated as yet that lowering lipoprotein (a) levels reduces the risk of cardiovascular disease, it seems likely that such a reduction would be beneficial and knowledge of the effect of hormone replacement therapy regimens on this risk marker would improve our ability to decrease their likely effect on cardiovascular disease.

In this study, we propose to monitor lipoprotein (a) levels in a group of postmenopausal women treated with estrogen alone or in combination with progesterone.

Aims and objectives

1. To compare the effects of hormone replacement therapy on serum lipid profile.
2. To compare the effects of combined estrogen-progestogen therapy and estrogen alone on serum lipid profile and lipoprotein (a).

METHODS

Study design

A prospective longitudinal study.

Settings

Patients attending the Gynecology OPD at the All India Institute of Medical Sciences, New Delhi.

Subject

Thirty women, who have attained spontaneous or surgical menopause.

Eligibility criteria

Postmenopausal women with

a. Physiological menopause
   - age >45 years
   - No menstruation for the past 6 months
   - Not taking hormone replacement therapy for the past 3 months
b. Surgical menopause
   - Post-hysterectomy with bilateral salpingo-oophorectomy.

Exclusion criteria

Postmenopausal women with

- H/o breast carcinoma
- H/o endometrial carcinoma
- Active thromboembolic disease
- Liver disease
- Renal disease
- Intake of drugs known to affect lipoprotein metabolism
- Smokers.

Patients were subjected to the following:

1. Informed written consent was taken from all the women.
2. Detailed history
3. Clinical examination
   - General physical examination e.g., height, weight, blood pressure, thyroid examination, breast examination, examination of chest and cardiovascular system.
   - Pelvic examination.
4. Baseline investigations.
   - Blood sugar (fastinai postprandial)
   - Liver function tests
   - Kidney function tests
   - ECG
   - Pap smear
   - Endometrial aspiration
   - Mammography- only in high-risk patients, i.e., history of breast carcinoma in the family, presence of any lump.

Baseline record of postmenopausal symptoms and scoring of the complaints

a. Mild: Does not disturb the routine activity of the patient
b. Moderate: Disturbs the routine work of the patient and is relieved by medication.
c. Severe: Patient is disturbed even at rest during either the daytime or at night.
5. Before commencement of treatment:
   a. Lipid profile: Serum cholesterol, LDL, HDL, VLDL, triglycerides
   b. Lipoprotein (a): Fasting blood sample (2 mL) taken and serum level measured on follow-up
   c. Serum FSH and serum estradiol.

On follow-up:

- Assessment of post-menopausal symptoms done at 3 and 6 months.
- Estimation of serum lipid profile and lipoprotein (a) done 3 and 6 monthly.
- Estimation of serum FSH and estradiol done after 6 months of treatment

Biochemical analysis

1. Estimation of lipid profile
   a. Triglycerides and total cholesterol were estimated by fully enzymatic methods using commercially available kits (Randox, UK).
   b. LD1 and HDL were selectively precipitated from serum. The cholesterol was then estimated by the enzymatic method used for total cholesterol assay.
2. Estimation of lipoprotein (a)
   Lipoprotein (a) levels were assayed by immunological techniques (immunoturbidimetry) using commercially available kits, in Boehringer, Germany.

Statistical analysis

This was performed with the BMDP statistical software. Values are expressed as a mean±SD. Differences between pre and post-treatment values were calculated using Wilcoxon's signed rank test and comparison of data between the groups by Mann–Whitney non-parametric test. Correlation between variables was assessed using Perason's correlation coefficients.

RESULTS

A total of 30 postmenopausal women were included in this study.

They were divided into two groups. Patients in group I (with natural menopause) were given oral conjugated equine estrogen (0.625 mg/day) and medroxyprogesterone acetate (2.5 mg/day). Patients in group II (with surgical menopause) were given only conjugated equine estrogen (0.625 mg/day). Patients were followed at baseline, 3 months, and 6 months of therapy.

Patients' characteristics

The mean age of the patients in this study was 48.26±5.47 years with a range of 37–65 years. The mean age in groups I and II were 48.46±6.18 years and 48.06±4.86 years respectively. There was no difference in the two groups in regard to age (Table 1).

Indications of surgery in patients with surgical menopause

In patients with surgical menopause, the indication of surgery has been depicted in the table (Table 2).

Table 1: Distribution of patients in various age groups

Age range (years)	NM Group I (*n*=15)	SM Group II (*n*=15)	Total (*n*=30)
35–40	0	1	1
41–45	3	2	5
46–50	6	7	13
51–55	3	2	5
56–60	2	3	5
61–65	1	0	1

NM: Natural menopause, SM: Surgical menopause

Table 2: Indications of surgery

Indications	No. of patients (%)
Fibroid uterus	7 (46.66%)
Dysfunctional uterine bleeding	4 (26.66%)
Utero-vaginal prolapse	3 (20.0%)
Cervical infra-epithelial neoplasia	1 (6.66%)

DISCUSSION

Hormonal replacement therapy is prescribed more and more frequently to increase quality of life and decrease the symptomatic and organic consequences of menopausal status. There is substantial epidemiological evidence suggesting that this treatment protects women against cardiovascular disease and osteoporosis.

With sequential therapy, approximately 80–90% of women experience monthly withdrawal bleeding. With continuous, combined estrogen-progestin therapy, one can expect 40–60% of patients to experience breakthrough bleeding during the first 6 months of treatment; however, this percentage decreases to 10–20% after 1 year. This percentage of amenorrhea with continuous combined therapy is a grafting accomplishment [5].

A review of case–control studies in the literature finds overwhelming support for reduced risk of coronary heart disease in estrogen users. Current postmenopausal hormone users have reduced risk of mortality, due largely to protection against coronary heart disease, an effect that was still present after adjusting for dietary factors, alcohol intake, vitamin or aspirin use, and exercise [6].

The protective effects of estrogen were initially thought to be due to its effect on lipid profile, but the Lipid Research Clinics reported that less than half of the arterial disease protection afforded by the use of estrogen replacement could be explained as a result of a change in lipid and lipoprotein metabolism [7]. Thus, other mechanisms that have beneficial effects are as follows:

- A direct antiatherosclerotic effect in arteries.
- Augmentation of vasodilating and antiplatelet aggregation factors, specifically nitric oxide and prostacyclin (endothelium-dependent mechanism).
- Direct inotropic actions on the heart and large blood vessels.
- Antioxidant activity.
- Inhibition of macrophage foam cell formation.
- Reduction of P-selectin levels.
- Reduction of homocysteine levels.

There are a number of issues that are yet to be determined such as (i) will the addition of progesterone negate the effects of estrogen replacement (ii) for how long HRT should be continued (iii) how the protective effect is mediated.

In the present study, 30 postmenopausal women were studied with respect to the effect of HRT on postmenopausal symptoms, hormonal profile, lipid profile along lipoprotein (a).

Age at menopause
The mean age at menopause in our study was 48.06±4.86 years with a range of 37–60 years. Although the mean age at menopause is reported to be 51 years.

Menopausal symptoms
There is wide variation in the frequency of different characteristic climacteric symptoms as seen in the West and India.

The vasomotor flush is viewed as the hallmark of the female climacteric, experienced to some degree by most postmenopausal women. Although the hot flush is the most common problem of the postmenopause, it presents no inherent health hazard. A striking and consistent finding in more studies, dealing with menopause and hormonal therapy is a marked placebo response in a variety of symptoms including flushing. We observed a higher percentage of women reporting vasomotor symptoms.

Hormonal profile in postmenopausal women

S-FSH
After menopause, serum FSH level rises rapidly and reaches the maximum at 2–3 years. There is a 10–20-fold increase in FSH and 3-fold increases in LH. FSH levels are higher than LH because LH is cleared from the blood much faster, and perhaps, there is no specific negative feedback peptide for LH like inhibition. This rise is due to increased gonadotropin-releasing hormone pulses in both the amount and frequency.

In our study, the mean serum FSH in the group I was 84.60 and in group II was 46.93. Only eight out of 30 (27%) patients had serum FSH <40 mIU/mL.

S. Estradiol
In menstruating women, normal estradiol level ranges from 50 to 300 pg/mL. The circulating estradiol level after menopause is approximately 10–20 pg/mL, most of which is derived from the peripheral conversion of estrone, which in turn is mainly derived from the peripheral conversion of androstenedione. In our study, the mean serum estradiol level in group I was 42.66±45.4 and in group II was 44.13±43.8 pg/mL. Only 8 patients in this study had serum estradiol levels <20 pg/mL. The serum estradiol level is on the higher side of the normal range can be explained on the basis of alternative sources of estrogen production, such as the peripheral conversion of androstenedione, which is produced primarily by the adrenal gland and in smaller amounts of the ovary in postmenopausal women.

Effect of HRT on hormonal profile in postmenopausal women
After estrogen supplementation, there was a significant fall in serum FSH levels in group I ($p<0.01$). This finding is consistent with the physiological feedback inhibition of FSH by circulating estradiol. In group II, the fall in serum FSH level was not significant.

In our study, after estrogen supplementation for 6 months, there was a 33% increase in group I and an 8.5% increase in group II of serum estradiol level. After sudden cessation of estrogen production from its main source, ovary in case of surgical menopause, the peripheral production of estrogen takes time to reach its level similar to that of patients having natural menopause. Upon this ground, our results are consistent.

Lipid profile in postmenopausal women
Dyslipidemia is a common cardiovascular risk factor in menopausal women. Statins and other lipid-lowering medications may be prescribed to manage dyslipidemia and reduce cardiovascular risk [8].

Effects of HRT on lipid profile in postmenopausal women
Estrogen has been found to play a protective role by regulating lipid metabolism. It is shown that Estrogen-based menopause hormone therapy (MHT) could influence lipid profile in postmenopausal women. It has been reported that MHT is the most effective treatment for menopause-related symptoms caused by the loss of estrogen [9].

We chose the dose of oral estrogen to be 0.625 mg daily based on the observation of no significant difference between 0.625 mg and 1.25 mg of conjugated estrogen in lipoprotein concentration.

Estrogen replacement by oral route affects almost all the components of the lipid profile favorably. In our study, the patients of group I had a 3.14% increase and group II had a 3.55% decrease in serum cholesterol after 6 months of HRT. The decrease in serum LDL-C in various studies varies from 5 to 19%. In our study, serum LDL-C decreased by 15%. The increase in serum HDL-C was as observed by various authors is 5.6–40%. In our study, in group I there was no change and in group II it was increased by 15.55%.

Serum triglycerides are an important risk factor for coronary heart disease in women; however, an increased rate of cardiovascular disease is observed only when increased triglyceride levels are present in association with low HDL-C levels [10]. We observed a decrease of 7.01% in group I and 5.95% in group II. Usually, there is an increase in triglyceride levels following oral estrogen therapy. This has been

attributed to the "first pass" through the liver which results in pronounced hepatic enzymatic induction and thus changes in increased triglyceride synthesis. However, in our study, there has not been a generalized increase in triglyceride levels in all the patients of groups I and II. There has been an increase in six patients of group I, and seven patients of group II i.e., roughly an increase in 50% of patients of both the groups.

The beneficial effect of postmenopausal estrogen in preventing the hyperinsulinemia associated with aging is present with a dose of 0.625 mg conjugated estrogens but lost with a dose of 1.25 mg. The effect of estrogen on arterial thrombosis is dose related. Sharing the results of the measurement and the concern regarding high doses of estrogen administration helps patients accept the recommendation to keep the blood level of estradiol below 200 pg/mL and preferably, below 100 pg/mL.

Effect of HRT on Lipoprotein (a)

Lip(a) is an independent marker of cardiovascular disease which is relatively unresponsive to treatment with most of the commonly prescribed lipid-lowering agents. Endogenous estrogen appears to lower levels of lip (a) since postmenopausal women have higher lip (a) concentration than premenopausal women, a difference that has been attributed specifically to menopause rather than aging.

In our study, the percentage decrease in lip (a) level was lesser in group I than that in group II. There was a substantial decrease in lip(a) level after 3 months of therapy and after 6 months of HRT, there was a slight decrease in lip(a) level. The effect of HRT on the lip (a) on a long-term basis is yet to be established.

This study suggests that on this regimen, lipid values do not fluctuate greatly between the estrogen and combined regimen of HRT. Although no significant differences were present, there was a trend toward a more atherogenic lipid profile during combined treatment. The mean concentration of serum cholesterol, LDL, and triglycerides tended to be higher and those of HDL lower during the combined regimen of HRT. Lip (a) values tended to be lower when patients were taken estrogen alone.

While the beneficial effect of combined HRT on the basic lipid pattern [11] is well recognized, these data confirm that this treatment is also effective in reducing concentrations of lip(a). These results provide further strong support for the cardioprotective action of HRT in postmenopausal women.

CONCLUSION

Contrary to popular opinion, menopause isn't a signal of impending decline, but rather, a wonderful phenomenon that can signal the start of something positive, a good health program. Postmenopausal hormone therapy is an option that should be considered by virtually all women as a legitimate part of their preventive health program.

Although the effect of HRT including both the regimens on serum lipid profile and lipoprotein (a) was not found to be statistically significant, the patients in group II who were on estrogen alone therapy were found to have an increasing trend in HDL, decreasing trend in LDL/HDL ratio and decreased serum lip (a) level following 6 months of HRT.

The beneficial effects of estrogen on lipids and lip (a) got partially attenuated when progesterone was added to estrogen. This study consisted of a small number of patients on HRT for a short period only and did not achieve statistically significant results which might be overcome by a large, long-term trial.

AUTHORS CONTRIBUTION

Dr Sachi Prasad Basu: Data collection. Dr Koustuv Chowdhury: Statistical analysis. Dr Arindam Sur: Manuscript writing.

CONFLICTS OF INTEREST

The authors would like to state that there were no conflicts of interest in this study.

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