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ORIGINAL ARTICLE

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Effect of menopausal hormone replacement therapy on fibrinogen and antithrombin III levels

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OBJECTIVE(S) : To study the effect of hormone replacement therapy (HRT) on fibrinogen (1+2) and antithrombin III levels.

METHOD(S) : Forty consecutive consenting menopausal (surgical menopause 20 and natural menopause 20) women were recruited for this study. Fibrinogen and antithrombin III levels were determined before, and 3 and 6 months after initiation of HRT. Paired t- test was used to study the alterations with time.

RESULTS : Though, the subject characteristics in both groups were similar, the preHRT lipid profile of those with natural menopause had significantly higher triglyceride (159 $\pm$ 27 vs 138+31; $P<0.05$) and lower high-density lipoprotein levels (44$\pm$7 vs 54$\pm$9; $P<0.01$) than those of the subjects with surgical menopause. Both groups showed significantly increased fibrinogen values at 6 months of HRT use and the rise in levels appeared to increase significantly with duration of use whereas antithrombin III levels showed significantly decreasing trend with the duration of use of HRT.

CONCLUSION(S) : In the early part of use of HRT, alterations in fibrinogen and antithrombin III levels, towards more thrombogenic state occur.

Key words: menopausal changes, hormone replacement therapy, fibrinogen levels, antithrombin III levels

Introduction

There have been numerous studies establishing the risks and benefits of hormone replacement therapy (HRT) which produces significant changes in the hemostatic system. Some of these changes would appear to be associated with a reduction and others with an increase in thrombotic risk. Although studies have established a link between postmenopausal doses of estrogens and venous thrombosis [1,2] there have been reports of no increased risk[3] as well. Some studies have demonstrated reduction in fibrinogen[4,5] as well as antithrombin activity [6] after HRT whereas, other reports[7] have shown an increase in the fibrinogen level.

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Since the effect of postmenopausal HRT on thrombosis remains controversial, the present study was undertaken to determine alterations in the fibrinogen and antithrombin III levels after intake of HRT.

Methods

This study was conducted by the 1st Author, at the Postgraduate Institute of Medical Education and Research, Chandigarh, as a postgraduate student. Forty consecutive menopausal women (surgical menopause 20 and natural menopause 20) attending the menopause clinic of a tertiary care hospital were recruited for the study after obtaining their consent. Cases with surgical menopause were the ones who had undergone total hysterectomy with bilateral adnexectomy for benign gynecological conditions at least 8 weeks prior to recruitment and were $\geq$40 years of age. A woman was considered to have had natural menopause if there was cessation of menstruation for at least 1 year and had negative progestational challenge response

(no withdrawal bleed within 2 weeks after oral adminisration of 10 mg of medroxyprogesterone acetate daily for 5 days).

Women with history of episodes of postmenopausal bleeding, venous thromboembolism, cerebrovascular disease, cardiac disease, coagulopathy, vasculitis, recent fractures, injuries, malignancy, and endocrine disorders were excluded from the study. The protocol was approved by the institutional thesis committee. Transvaginal pelvic ultrasound examination was carried out in all the cases for endometrial thickness and ovarian size using a 7.5 MHz transducer, and Pap smear evaluation was done in women with natural menopause.

All women were treated with oral conjugated equine estrogen 0.625 mg and elemental calcium 1000 mg daily. Women with natural menopause were prescribed oral medroxyprogesterone acetate 2.5 mg daily, in addition. Levels of fibrinogen and antithrombin III were estimated before initiation of HRT, and 3 months and 6 months after continuous HRT intake. Fibrinogen (1+2) level was measured by salt precipitation method [8]. Antithrombin III level was estimated by clotting method [9].

Statistical analysis using the paired t- test was performed to study the significance of alteration in the coagulation profile with time after intake of HRT within each group.

Results

All women completed the study. Age, duration of menopause, body mass index, blood pressure records, hemoglobin status and blood sugar profile of the women in the two groups were similar. But, the preHRT lipid profile of the women with natural menopause had significantly higher triglyceride and lower high density lipoprotein levels than those in the women with surgical menopause (Table 1).

The preHRT fibrinogen levels in the two groups were comparable, although in women with surgical menopause apparently higher values were noted. Both groups showed significantly increased fibrinogen values at 6 months of HRT use. Rise in levels of fibrinogen appeared to increase significantly with duration of use of HRT (Table 2) whereas antithrombin III levels showed significantly decreasing trend with the duration of use of HRT. This observation was more marked in women with natural menopause who were on progestins in addition (Table 3).

Table 1. Subject characteristics.

Characteristic	Group I (Mean + SD) (n=20)	Group II (Mean+ SD) (n=20)	p value
Age (years)	46 ± 3	48 ± 3	NS
Duration of menopause (years)	2.8 ± 3.2	4.5 ± 4.1	NS
BMI (kg/m^2)	25 ± 2	26 ± 2	NS
Systolic blood pressure (mmHg)	129 ± 7	125 ± 8	NS
Diastolic blood pressure (mmHg)	80 ± 4	78 ± 7	NS
Hemoglobin (g/dL)	11 ± 1	11 ± 1	NS
Fasting blood sugar (mg/dL)	87 ± 9	85 ± 7	NS
Postprandial blood sugar (mg/dL)	120 ± 20	120 ± 14	NS
Cholesterol (mg/dL)	199 ± 36	215 ± 35	NS
Triglycerides (mg/dL)	138 ± 31	159 ± 27	<0.05
HDL (mg/dL)	54 ± 9	44 ± 7	<0.01
LDL (mg/dL)	130 ± 37	139 ± 27	NS

SD - Standard Deviation NS - Not significant
BMI - Body Mass Index
HDL - High Density Lipoprotein LDL - Low Density Lipoprotein

Table 2. Effect of HRT on fibrinogen

Duration of HRT	Group I (Mean ±SD) (mg%)	Group II (Mean±SD) (mg%)
Before HRT	360 ± 77 [c]	345 ± 99 [a,c]
3 months	378 ± 111 [b]	426 ± 91 [a,b]
6 months	495 ± 95 [b,c]	510 ± 66 [b,c]

[a,b,c] P < 0.01
HRT - Hormore replacement therapy
SD - Standard Deviation

Table 3. Effect of HRT on antithrombin III.

Duration of HRT	Group I (Mean+SD) (%)	Group II (Mean+SD) (%)
Before HRT	96+26	99+16 [a,c]
3 months	98+22 [d]	93+11 [a,b]
6 months	92+19 [d]	86+8 [b,c]

[a,b,d] P <0.05 [b] P <0.01

HRT - Hormone replacement therapy.
SD - Standard Deviation

Discussion

Previous reports regarding the effects of HRT on thrombosis included coagulation tests such as factor levels, inhibitor levels and clot based tests. Measuring hemostasis markers helps to evaluate thrombosis risk. In this study, the coagulation markers characterizing the last steps of coagulation were chosen. Particularly fibrinogen is known to be an independent predictor of risk and this marker is influenced by HRT. By its conversion to fibrin, fibrinogen (1+2) is the ultimate natural substrate of the coagulation system. Antithrombin III is perhaps the principle natural inhibitor of thrombin and factor Xa, and plays a central role in the prevention of intravascular clotting. Because factor levels at any time result from the balance between production and consumption, low factor levels could be because of either decreased production or increased consumption. In contrast, high fibrinogen levels indicate in vivo generation of factor Xa, whereas elevated thrombin antithrombin III complex levels are indicative of in vivo thrombin generation.

The finding of increased fibrinogen level is consistent with the significant increase in mean fibrinogen levels reported by Caine et al [7] who observed significant increase in those receiving conjugated equine estrogens for 3 months as compared to those receiving placebo though the study did not compare the levels with those receiving both estrogen and progestogen. There have been studies [10] showing no alteration in the fibrinogen levels while other studies [11,12] have shown decline in fibrinogen levels in those receiving HRT. The Finrisk Hemostasis Study [12] has found decreased fibrinogen levels in those who received HRT as compared to those who did not, only after a longer follow up of 3 years. Lowe et al [11] included younger subjects in whom the fibrinogen levels are comparatively lower as compared to those in the elder women participating in the present study. The user group in these studies comprised women who were already receiving HRT irrespective of the number of years they had received it before and it was not known whether they received estrogen alone or estrogen combined with progestin. Thus long term effect of HRT in these studies might differ from the short term effect seen in the present study. Studies have shown that increased risk of deep venous thrombosis was confined to early use and the risk lowered to nonsignificant level after 1 year [1,2].

Decline in antithrombin III levels was similar to the results observed in other studies [5,13]. The Writing Group for the Estradiol Clotting Factors Study [5] used transdermal estradiol in postmenopausal women and found a significant decline in antithrombin III levels after 6 months and 12 months and thus found association with deep vein thrombosis. Saleh et al [13] did not find any significant difference in the levels of antithrombin III between HRT users and control group. There was however, statistically significant difference in age, with the control group being much younger ($P<0.01$) than the user group when the antithrombin III levels were found to be lower as compared to those in older women[11].

The finding of increasing fibrinogen with lowering of antithrombin III in women with natural menopause receiving both estrogen and progesterone as compared to the group receiving estrogen alone could probably be because of their increased triglyceride and decreased HDL levels prior to initiation of HRT. It is worth recalling that activated blood coagulation is demonstrated in hyperlipidemic subjects in whom fibrinogen levels are strongly associated with serum triglycerides [14,15]. It is likely that the progestin component also may be adding to the risk of thrombosis. We did compression ultrasonography of the calf veins for detection of deep vein thrombosis prior to, as well as 3 and 6 months after start of HRT using a 5 MHz linear transducer. No case of deep vein thrombosis was demonstrated at any time.

Though it might be too premature to conclude that HRT is associated with increased risk of thrombotic state, the observations based on the present study indicate that atleast in the early part of the use of HRT, alterations towards thrombogenic state viz., increased fibrinogen and lowered antithrombin III levels, are noted. Effect of progestin component needs to be further evaluated with stringent patient selection and the study designed for that purpose.

Conclusion

Within 6 weeks of HRT use fibrinogen levels rise and antithrombin III levels fall leading to a thrombogenic state.

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