

# COMPARING THE EFFECT OF TWO DIFFERENT HORMONAL THERAPY REGIMENS ON THE ACTIVITY OF COAGULATION FACTORS VII, VIII, IX AND SERUM LIPIDS IN MENOPAUSAL WOMEN

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## Abstract

**INTRODUCTION:** During extrinsic coagulation pathway, a complex is developed between factor VII, calcium and tissue factor (a cell membrane lipoprotein that is exposed after cell injury). Factor VII needs calcium and vitamin K for its biologic activation. Coronary artery disease (CAD) can be induced by increased level and activity of the coagulation factors VII, VIII and IX. In postmenopausal women, estrogen decreases blood lipids and thereby decreases risk of CAD. However, the exact effects of the estrogen on the other predisposing factors of CAD are unknown. This study was conducted to evaluate the effects of oral hormone therapy regimen on fibrinogen and other coagulation factors.

**METHODS:** Sixty menopausal women with history of hysterectomy were randomly allocated in 2 groups. One group was treated with conjugated estrogen 0.625 mg/day and the other group was treated with conjugated estrogen 0.625 mg/day and medroxyprogesterone 2.5 mg/day. Serum fibrinogen level and activity of coagulation factors VII, VIII and IX and blood lipids level were checked before and 3 months after treatment.

**RESULTS:** In the group treated with estrogen alone, mean factor VII activity showed significant increase 3 months after treatment as compared to before hormone therapy ( $P < 0.05$ ). There were no significant changes in mean activities of coagulation factors VIII, IX and serum fibrinogen level in patients treated with estrogen or estrogen/medroxyprogesterone after treatment ( $P > 0.05$ ). In both groups, hormone therapy significantly decreased serum cholesterol level and LDL-C and increased HDL-C ( $P > 0.00$ ), but serum triglyceride level increased in the group only treated with estrogen.

**DISCUSSION:** Significant increase of coagulation factor VII and serum triglyceride in estrogen-treated patients is logical. This study confirms that hormone therapy with this protocol does not change mean serum fibrinogen levels and activity of coagulation factor VIII and IX. This may be a genuine finding or may be due to inadequacy of samples, given the wide normal range of coagulation factors and serum fibrinogen. Studies with more prolonged follow-up or more samples are warranted.

**Keywords** • Blood coagulation factors • Hormone therapy • Factor VII • Factor VIII  
Factor IX • Serum fibrinogen

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## Introduction

Epidemiologic studies have demonstrated that hormone replacement therapy (HRT) with estrogen (ERT) or estrogen/medroxyprogesterone can decrease the risk of coronary heart disease.<sup>1</sup>

Estrogen has a potent effect against coronary artery disease (CAD) in postmenopausal women.<sup>2</sup>

Estrogen decreases risk of CAD through decreasing LDL cholesterol, increasing HDL cholesterol,<sup>3</sup> decreasing coronary artery constrictions,<sup>4</sup> decreasing coronary artery endothelial hyperplasia,<sup>5</sup> and affecting coagulation factors.<sup>6</sup>

Increase in coagulation factors is one of the major factors in the development of myocardial infarction (MI).

Given the importance of blood clotting in the induction of acute ischemic heart syndrome, studies

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on factors accelerating or decelerating the induction of vascular thrombus have gained much attention. Factor VII is a vitamin-K-dependent factor that is produced in the liver and acts as a proenzyme.

Factor VIII is a cofactor in the adhesion of platelets and is involved in the activation of the coagulation cascade. Increase in serum level and activity of coagulation factors VII, VIII and IX is associated with induction of coronary heart diseases.<sup>8,13</sup> Serum level of factor VII and its activity increase after menopause independently of aging,<sup>9</sup> but aging is involved in the increase of serum factors VII, VIII and IX.<sup>6</sup> Also, factor VII increases with aging, hormonal changes, pregnancy, menopause and HRT.<sup>10</sup> One study has shown that transdermal application of estradiol 50mg/day with oral medroxyprogesterone 10mg/day for 10 days of each month can decrease serum levels of coagulation factors VII and VIII.<sup>11</sup> Prevention of endometrial cancer is the important reason for prescribing progesterone compound in postmenopausal women, although combined use of these hormones has many side effects.<sup>12</sup>

In view of the importance of coagulation factors and their impact on thrombosis, we evaluated the effect of oral conjugated estrogen with and without medroxyprogesterone on the coagulation factors VII, VIII, IX and fibrinogen.

## Materials and methods

This double-blind clinical trial involved sixty menopausal women aged between 45 and 60 years with history of hysterectomy. The subjects were selected randomly among patients referring to Isfahan Cardiovascular Research Center for HRT.

Informed consent was taken from all patients. Determination of the age of menopause was based on the time of undergoing bilateral oophorectomy and

hysterectomy, or the onset of flushing in patients with history of hysterectomy alone (in 6-month follow-ups), or FSH serum level  $>30\mu$ /lit in patients without a history of flushing.

History of diabetes or fasting blood sugar  $\geq 126$ mg/dl in more than two measurements, known CAD (myocardial infarction, stable or unstable cardiac angina, history of coronary artery angiography) and history of acute thrombophlebitis, acute cholecystitis, warfarin use, breast cancer, and vaginal bleeding were considered as exclusion criteria.

Menopausal women were randomly allocated into groups A and B. Group A (30 patients) was treated with one conjugated estrogen tablet (0.625mg) per night. Group B (30 patients) was treated with one estrogen tablet (0.625mg) and one medroxyprogesterone tablet (2.5mg) per night at bedtime for 3 months.

Serum triglyceride, LDL cholesterol, HDL cholesterol and total cholesterol values were measured before and 3 months after treatment after 12-hour of fasting. "Diagnostica Stago" kit and "Cascade-4" fibrometer were used to measure coagulation factors VII, VIII, IX and serum fibrinogen, respectively.

Collected information, including age, height, weight and results of the laboratory tests before and after hormone therapy were analyzed with SPSS10 using t-test.

## Results

The results showed that activity of coagulation factor VII was increased in group A ( $P=0.000$ ), but there were no changes in coagulation factors VIII, IX and fibrinogen after treatment with estrogen  $\pm$  progesterone.

The results also showed that triglyceride level was mostly increased in group A, but did not change significantly in group B ( $P=0.23$ ).

**TABLE 1.** Comparison of fibrinogen and activity of coagulation factors before and after HRT in groups A and B

Group	Fibrinogen (mg/dl)		Factor VII (%)		Factor VIII (%)		Factor IX (%)	
	before	after	before	after	before	after	before	after
A	243.02 $\pm$ 50.77	241.17 $\pm$ 48.97	120.99 $\pm$ 30.41	136.2 $\pm$ 42.09	129.52 $\pm$ 40.71	127.83 $\pm$ 39.42	94.81 $\pm$ 17.3	95.62 $\pm$ 16.86
B	239.4 $\pm$ 48.8	236.59 $\pm$ 47.53	119.87 $\pm$ 32.56	121.63 $\pm$ 29.98	126.34 $\pm$ 41.3	124.68 $\pm$ 39.75	96.73 $\pm$ 21.2	98.23 $\pm$ 22.32

**TABLE 2.** Comparison of serum lipid values before and after HRT in groups A and B

Group	Triglyceride (mg/dl)		Total cholesterol (mg/dl)		LDL (mg/dl)		HDL (mg/dl)	
	before	after	before	after	before	after	before	after
A	241.5 $\pm$ 72.63	279.46 $\pm$ 69.26	225.17 $\pm$ 40.45	213.21 $\pm$ 39.48	143.17 $\pm$ 35.42	132.45 $\pm$ 32.51	48.06 $\pm$ 5.67	56.23 $\pm$ 4.34
B	256.67 $\pm$ 86.02	257.28 $\pm$ 84.27	228.23 $\pm$ 38.69	221.46 $\pm$ 41.57	145.14 $\pm$ 32.47	136.39 $\pm$ 41.56	49.02 $\pm$ 9.21	53.18 $\pm$ 10.48

Significant decrease in serum cholesterol and LDL-cholesterol, and significant increase in serum HDL-cholesterol were observed in both group A and B ( $P=0.000$ ) (Table 2).

### Discussion

Several studies have shown the effect of HRT (estrogen  $\pm$  progesterone) on blood lipids.<sup>9,14</sup> These studies have suggested that oral HRT (estrogen  $\pm$  progesterone) can significantly decrease cholesterol and LDL-cholesterol, and significantly increase HDL-cholesterol and triglyceride.<sup>14</sup>

In our study, there was a significant decrease of cholesterol and LDL-cholesterol in both groups A and B ( $P=0.000$ ). There was a significant increase in serum HDL-cholesterol in both groups ( $P=0.000$ ), but serum triglyceride level was significantly increased only in group A ( $P=0.000$ ). However, there was no significant change in serum triglyceride in group B ( $P=0.230$ ). Other studies have suggested that estrogen therapy alone significantly increases serum triglyceride level as compared with estrogen progesterone therapy.<sup>14</sup> Different HRT regimens and routes of use (oral or transdermal) have different effects on blood lipids.<sup>3</sup>

It is expected that different hormone therapy doses and regimens have different effects on coagulation factors and fibrinogen. We searched the literature for studies similar to our study of HRT regimens, but found no similar studies. In one study, 28 women with history of hysterectomy were treated with cutaneous 17-beta estradiol (50mg/day) for 16 weeks. Activity of coagulation factor VII was decreased at the end of study.<sup>15</sup>

Transdermal application of estradiol 50mg with medroxy progesterone 10mg for 10 days in each month decreased serum coagulation factors VII and VIII after a 6 month-period.<sup>11</sup> Sixteen and 28 menopause women were treated with micronized estradiol 2mg/day and micronized estradiol 2mg/day with progesterone 14 days/month for 3 months, respectively. At the end of the study, there was no significant change in coagulation factor VII in either group.<sup>12</sup> Different doses of conjugated estrogen 1.25 mg/day, 0.6 mg/day or 0.3 mg/day were used in 12-member homogenous groups of menopausal women for six months. The 0.3 mg/day dose did not increase coagulation factor VII after six months, but doses of 0.6 mg/day or more increased it significantly.<sup>13</sup> In another study, long-term use of estrogen in 45 menopause women increased coagulation factor VII activity but treatment with progesterone did not affect this factor.<sup>16</sup>

Given the results of our study and in light of the fact that HRT can increase coagulation factors and thereby increase the risk of cerebrovascular and cardiac accidents, larger studies with newer estrogen and progesterone compounds are recommended to evaluate the long term effects of treatment and its effects on fibrinolytic systems.

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