Comparison of the effects of tibolone and estrogen therapy on hemostasis in surgical menopause: a randomized, double-blind, placebo-controlled study

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Objective: To examine the effects of unopposed estrogen (E) and tibolone therapy on coagulation and natural anticoagulant systems in surgical menopause.
Design: A randomized, double-blind, placebo-controlled study.
Setting: University hospital clinic in Turkey.
Patient(s): Ninety healthy surgically postmenopausal women.
Intervention(s): Ninety surgically postmenopausal women were randomized into three groups: unopposed conjugated ET (0.625 mg/d, group 1), tibolone (2.5 mg/d, group 2), and identical tablets of placebo (group 3).
Main Outcome Measure(s): Effects on parameters in the clotting cascade at baseline and after 24 weeks of treatment.
Result(s): After 6 months, fibrinogen, lipoprotein (a), and factor VIIa were decreased, and activated partial thromboplastin time was increased significantly in the ET group compared with in the placebo group. However, tibolone significantly decreased only the serum levels of factor VIIa and factor IX and prolonged the activated partial thromboplastin time, compared with placebo group. In addition, conjugated ET caused a significantly greater decrease in serum fibrinogen level than did tibolone.
Conclusion(s): Neither E nor tibolone therapy led to activation of coagulation in the surgically menopausal women. Both preparations changed the overall hemostatic balance to a more fibrinolytic state. (Fertil Steril® 2007;87:842–8. ©2007 by American Society for Reproductive Medicine.)

Key Words: Tibolone, estradiol, surgical menopause, hemostasis, coagulation, fibrinolysis.

Cardiovascular disease is the leading cause of death in women (1). The incidence of myocardial infarction in women increases dramatically after the menopause. The increase is at least in part a result of increasing age, but the role of the menopause itself is not so clear (2).

The evaluation of hemostatic differentiation is important during this time period. Many factors contribute to the formation of a thrombus. Mainly, it may result from an overload of local coagulatory activity. Hormone therapy (HT), estrogen (E) therapy (ET), and compounds with tissue-specific hormonal activity, which have been used to relieve vasomotor symptoms of the menopause and to prevent structural abnormalities, affect both coagulation and fibrinolytic activity (3).

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Until recently, only a few epidemiological studies have observed no increased risk of venous thromboembolism (VTE) from E-containing preparations (4–8). However, recent findings from observational (9–12) and randomized controlled studies (13, 14) have indicated a slightly increased risk of VTE in HT users. There is still controversy about the effect of unopposed E on venous and arterial thrombosis because the Women's Health Initiative unopposed E trial found no overall reduction in CHD risk.

In a subgroup analysis of subjects aged 50–59 years, a trend toward a lower risk of CHD was observed with E use vs. placebo (14). Another recent study suggested a lower coronary heart disease risk with conjugated equine E among women 50 to 59 years of age at baseline (15). Thus, the effect of E on CHD risk in younger postmenopausal women still is being debated.

Another alternative in postmenopausal therapy is tibolone, a synthetic steroid with estrogenic, androgenic, and

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progestogenic properties that relieves climacteric symptoms and prevents postmenopausal bone loss. The influence of tibolone on coagulation and fibrinolysis compared with a placebo was assessed in some studies (16), and in others it was compared with continuous combined HT (17, 18). To our knowledge, a comparison with conjugated E in surgically menopausal younger women has not been performed.

The present randomized placebo-controlled double-blind study compares the effects of tibolone and unopposed ET on hemostatic and coagulation variables in surgically menopausal younger women.

MATERIALS AND METHODS

Study Design

A randomized double-blind placebo-controlled study was conducted in Hacettepe University School of Medicine's Department of Obstetrics and Gynecology over 6 months to examine the effects of E and tibolone on extrinsic and intrinsic coagulation cascades and natural anticoagulation systems.

The study was in full compliance with the Declaration of Helsinki plus revisions and with local rules and regulations, and institutional review board approval was obtained. The protocol was approved by the local ethics committees, and all subjects gave written, informed consent before participating.

Ninety postmenopausal women who had undergone hysterectomy and bilateral salpingo-oophorectomy because of benign diseases were randomized prospectively into three groups, and HT was given in the 1st week of the postoperative period. Group 1 (n = 30) received conjugated E (Premarin, 0.625 mg/d oral tablets; Wyeth, Istanbul, Turkey) only, group 2 (n = 30) received tibolone (Livial, 2.5 mg/d oral tablets; Organon, Istanbul, Turkey), and group 3 (n = 30) received placebo, based on computer-generated random numbers. Tibolone and conjugated E tablets are not identical; therefore, a double-dummy method was used for double blinding.

A sample size of 25 subjects in each group was planned to have a power of 80% at an error level of 5% to detect treatment effects or differences in hemostatic parameters (factor VII, fibrinogen, antithrombin III) on the basis of results from a previous study on hemostasis and tibolone (18).

Patient Selection

The patients included were healthy menopausal women 45–50 years of age who had undergone hysterectomy and bilateral salpingo-oophorectomy as a result of benign diseases in the current clinic, and they gave written informed consent.

The exclusion criteria were smoking; history of cerebrovascular, cardiovascular, or thromboembolic events; hypertension (blood pressure: systolic, ≥140 mm Hg or diastolic, ≥90 mm Hg, based on the average of two or more properly measured readings at each of two or more visits after an initial screening); diabetes (fasting plasma glucose of ≥126 mg/dL, with confirmed diagnosis of diabetes on a subsequent day by measurement of fasting plasma glucose criteria); obesity (body mass index of ≥30 kg/m^2); known hereditary hyperlipidemia; use of medications known to alter lipoprotein or coagulation indices, including any hormonal preparations; natural menopause; significant systemic illnesses; and acute or chronic infection. The use of medications that may affect coagulation and/or lipoprotein levels was not allowed.

Study Procedures

Blood levels of modified activated protein C resistance (aPCR), antithrombin III (ATIII), fibrinogen, factor VIIa (FVIIa), factor VIII (FVIII), factor IX (FIX), activated partial thromboplastin time (aPTT), prothrombin time, thrombin time, and lipoprotein (a) were measured just before and after 6 months after the medications were started.

Blood samples were collected in the fasting state between 8:00 and 10:00 AM. Blood was drawn with minimal stasis. All samples for assessment of hemostatic parameters were analyzed at the end of the study by the same laboratory (Hematology Unit, Hacettepe University, Faculty of Medicine Hospital), and assay procedures were followed for preparation and storage.

A modified aPTT-based test (STA-staclot APC-R; Diagnostica Stago, Asnières, France), including steps of factor V–deficient plasma predilution and normalization by plasma, was used for aPCR detection. Antithrombin III activity (STA-Stachrom ATIII) was assayed by the chromogenic substrate method. Prothrombin time, aPTT, TT, FVIII, FIX, and FVIIa levels were determined by clotting assay. Lipoprotein (a) levels were measured by commercially available ELISAs (DAKO, Glostrup, Denmark).

Medical follow-up was repeated at 6-week intervals; compliance was checked by counting returned tablets and by face-to-face questionnaire, and the patients were evaluated clinically.

Two women from the conjugated E group, two from the tibolone group, and three from the control group left the study. Eighty-three women completed the entire study. The average compliance rate for regular drug use among women who completed the entire study protocol was 97%, and that of the least compliant participant was 88%.

Statistical Analysis

Data were expressed as means ± SD. The subjects who dropped out were excluded from the analysis. Within the