

**THE INFLUENCE ON COAGULATION OF TRANSDERMAL
ESTROGEN HORMONE REPLACEMENT THERAPY
AS A PREOPERATIVE PREPARATION OF THE TISSUE
BEFORE VAGINAL HYSTERECTOMY**

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Abstract: In 32 postmenopausal patients who underwent vaginal hysterectomy due to the presence of uterine prolapse at the Department of Urogynaecology and Pelvic Floor Disorders in the Clinic of Gynaecology and Obstetrics, Medical School, Skopje in the period from 1st January 2002 to 1st January 2003, and who were preoperatively treated with transdermal estradiol 50 µg/day during 14 days the following parameters of the coagulating status were estimated: prothrombin time (PT) that is expressed in: absolute value, percentage and INR; activated partial thromboplastin time (aPTT Pathrombin SL); thrombin time and platelets number before and after hormone replacement therapy. After 14-day transdermal estrogen therapy, the parameters: PT, PT%, PT INR, aPTT Pathrombin SL didn't expressed significant changes, the thrombin time expressed significant extension, and the platelets expressed a significant decrease.

According to our results, the transdermal estrogens might not have any influence on the hepatic synthesis of coagulating factors till the step of prothrombin formation. They might have an essential influence on the step of prothrombin transformation into thrombin, as well as on the process of megacariocytes segregation into platelets.

Key words: transdermal estrogen therapy, genital prolapse, prothrombin time, platelets.

Introduction

According to the existing experience regarding contraceptives, it was assumed by analogy that hormone replacement therapy (HRT) might have a negative influence on haemostasis in women. The changes that predispose to vein thrombosis include a decrease of the factors that inhibit coagulation or a decrease of the fibrinolytic promoters. The menopause as a physiology in women's life, leads to changes of the coagulating factors (an increase of the fibrinogen, factor VII and inhibitor of plasminogen-activator) and all these changes increase cardiovascular risk. That HRT leads to an increase of the local prostacyclin production, and it seems that this is due to its positive effects of haemostasis, is well known. Prostacyclin prevents platelet adhesion to the vascular vessel wall, and with this feature it prevents thromb formation. Its production decreases during the menopause, but estrogens are capable of restoring it completely. It seems that estrogens express this effect directly by stimulation of the prostacyclin synthesis and indirectly by increase of the serum HDL-cholesterol, which is a prostacyclin precursor (1). According to Conard (2) HRT results in a minimal increase of the fibrinogen and factor VII, as well as in an increase of the antithrombin III and plasminogen activator. Astedt (3) and Davies (4), in their studies independently of another, found an increase of plasminogen during estrogen therapy, whereas Beller (5) found an increase of alpha1 antitripsin antigen, which takes place in the fibrinolytic process, too. The combined therapy with transdermal estradiol/ medroxyprogesteron acetate leads to a decrease of either the fibrinogen or the factor VII and plaminogen activator-inhibitor (6). Progestagens have little effect on the coagulating factors, but it seems that they can accentuate the estrogen effect on the fibrinolytic system (7). All the above-mentioned to be taken into consideration when we decide to use hormone replacement therapy. It is very important to know whether the patient has had some thromboembolic episodes in her medical history and to know the conditions in which they had occurred. If the incident did not occur during favourable conditions, e.g. long-lasting immobilization, there is no reasonable contraindication for HRT. If the thromboembolism developed during pregnancy or previous hormonal contraceptives usage, HRT might be used only after meticulous investigation of the most coagulating parameters, especially antithrombin III and protein C. Some genetic disorders of coagulating factor production and the metabolic pathways of estrogens, i.e. a presence of idiosyncrasis, might be a satisfactory explanation for these above-mentioned cases.

Material and methods

32 postmenopausal women were included in the study. They were treated at the Department for Urogynaecology and Pelvic Floor Disorders of the

Clinic for Gynaecology and Obstetrics, Medical Faculty in Skopje, during the period from 1st January 2002 to 1st January 2003. An operative treatment for genital prolapse was done during the hospitalization. In the preoperative period, they were treated with transdermal estradiol in a dose of 50 micrograms daily, for 14 days in order to get a satisfactory quality of the vaginal epithelium and thickness of the vaginal endopelvic fascia–Halban. Before and after the treatment with hormone replacement therapy some coagulating parameters, such as: prothrombin time (expressed in absolute values, percentage and INR), activated partial thromboplastin time, thrombin time and number of platelets were estimated. All patients underwent an operative treatment: vaginal hysterectomy accompanied with some corrective procedures of the anterior and posterior vaginal wall. Suburethral plication was done as a preventive procedure for postoperative urinary stress incontinence. In this study all patients of generative age, with chronic liver disease, acute thromboembolic event, blood disturbances and thyroid gland dysfunction were excluded.

Results

The results of the study are represented in the next table.

Table 1 – *Coagulating status in postmenopausal women-users of 14-day transdermal estrogen hormone replacement therapy (n = 32)*

Estimated parameters	Before therapy	After 14-day therapy	P
Protrombin time(min)	10,60 ± 2,04	10,73 ± 2,18	NS
PT%	97,68 ± 17,76	88,23 ± 18,67	NS
PT INR	1,003 ± 0,15	1,06 ± 0,18	NS
aPTT Paththrombin(min)	27,64 ± 2,43	29,09 ± 5,58	NS
Thrombin time(min)	13,06 ± 0,97	15,07 ± 1,26	< 0,0001
Tr	292,64 ± 63,17	248,32 ± 52,14	< 0,002

Regarding the effects of applied therapy for tissue preparation we could emphasise the following:

1. We obtained a satisfactory thickening of the vaginal epithelium accompanied with a solid strength and elasticity of connective tissue, features that are very important for easier surgical tissue preparation and a significant decrease of intraoperative bleeding.

2. We did not register any kind of complication in the early postoperative period. The healing process of the operative wound was in *per primam* mode. Also, there were no postoperative complications, present such as post-

operative bleeding or inflammatory local processes, vaginal leakage, increase in the number of white blood cells, increased values of C-reactive protein and body temperature. The mean time of postoperative hospitalization was pretty short (7.3 days), as a result of quick recovery after the operation. Only one patient had a recurrent cystocele. At the sixth-month postoperative control only 2 recurrent cystoceles grade 1 and one cystocele grade 2 were registered.

3. After the 14-day transdermal estrogen therapy, the parameters: PT, PT%, PT INR, aPTT Pathrombin SL expressed no significant changes, the thrombin time expressed significant increase, and the platelets expressed significant decrease.

Discussion

From Table1, the following conclusion can be drawn:

1. If we take into consideration the results from the first four parameters, which offer a clear picture of the transdermal estrogen therapy effect on the coagulating cascade system till prothrombin formation, we can conclude that there is no significant difference between the serum levels of the parameters before and after therapy. Indirectly this could mean that this therapy has no influence on the liver's production of coagulating factors, which take part in prothrombin formation. This is expectable because of the fact that the transdermal estradiol application offers an avoidance of the first drug passage through the liver, before the drug enters into the circulation. With this process, there is no excessive activation of liver cells for protein synthesis.

2. The fifth parameter – the thrombin time – showed a significant extension after the fourteen-day transdermal estrogen therapy. If we accept the previous conclusion that the prothrombin synthesis is not significantly affected, it seems to be possible that estrogens have a strict role in prothrombin transformation into thrombin, a step of a coagulating cascade where antithrombin III and protein C play a great part, as competitive inhibitors of prothrombin. As activators of protein synthesis, estrogens could lead to increased synthesis of these two factors, which are proteins too.

3. The last investigated parameter – number of trombocytes shows a significant reduction after the 14-day transdermal estrogen therapy, which indirectly means that estrogens have a negative influence on trombocyte segregation from megakaryocytes in the bone marrow.

According to recent available literature regarding the correlation between cerebrovascular insults and HRT, there are many dilemmas about the fact whether HRT is a protector or factor of risk. Thus, Rosental *et al.* (7) consider that there are subgroups of women with prothrombotic and other genetic anomalies of the coagulating system, who could be in risk of HRT, especially in the first year of treatment. Boudoulas *et al.* (8), researching the estrogen effects on trom-

bocyte aggregation induced by standard agonists (epinephrine and adenosine diphosphate), found a significant inhibition of P₁A₂ trombocyte aggregation in physiological estrogen concentration, and that inhibition was strongly dependent on the presence or absence of P₁A₂ polymorphism. The presence of the blocking effects on estrogen influence by estrogen-specific inhibitor ICI suggests that this effect on trombocyte aggregation be expressed by estrogen trombocyte receptor. Falco *et al.* (9), researching the components of the fibrinolytic system, coagulating inhibitors and lipid profile in patients with coronary disease and healthy patients and effects of transdermal HRT with or without progestogens, found that coronary disease was associated with a reduction of fibrinolytic activity, maybe induced by an increased level of PAI-1. When HRT was included in the group of patients with coronary disease, the fibrinolytic activity increase and of PAI-1 and Lp(a) reduction was following. Seed *et al.* (10) noticed a reducing of lipoprotein cholesterol, Lp(a), factor VII and E-selectine, in users of combined cyclic HRT without any dependence of the way of HRT application. About the dilemma whether HRT leads to worsening or improving of coagulating status, we have to note some recent referred studies. Nozaki *et al.* (11), divided 134 postmenopausal women into 3 groups: a group with continuous estrogen therapy, a group with continuous combined HRT, and a placebo group, and estimated some coagulating factors in the first, thirth and sixth month of the treatment. They found that, with the exception of the factor VII growth in the group-user of continuous estrogen HRT, there were no other negative effects of HRT on coagulation and fibrinolysis, but on the contrary, HRT resulted in a significant increase of protein C activity, a reduction of fibrinogen and plasminogen-activator inhibitor 1(PAI-1). Ye *et al.* (12) in 53 postmenopausal women with estrogen HRT, combined estrogen/ progestogen HRT or placebo after 6 months found a significant reduction of the fibrinogen and protein S in groups with HRT. Hoibraaten *et al.* (13) in 140 patients with continued HRT (estradiol/norethysteron acetate) or placebo over 24 months, found that HRT induced: a significant increase of prothrombin fragments 1+2, thrombin-antithrombin complex and D-dimmer, and also a significant reduction of the factor VII, anti-thrombine and protein. C. Vehkavara *et al.* (14) in 27 postmenopausal women with oral estrogen therapy or transdermal estrogen HRT, found that the oral therapy increased the markers of fibrinolysis, reduced soluble E-selectine, and had a positive influence on lipid profile, but at the same time increased markers of coagulation and led to hypercoagulability. Gottsater *et al.* (15) in 51 postmenopausal women treated with 3-month therapy with estradiol valerate, combined in the last 10 days with medroxyprogesteron acetate over 12 months noticed a significant reducing of the fibrinogen, whole protein S, and antithrombine III, and at the same time an increase of the factor VII. Demirool *et al.* (16) in a series of 110 patients treated with combined HRT (conjugated estrogens/medroxyprogesteron acetate) or a placebo over 6 months found a significant reduction of fibrinogen, Lp(a) and activated protein C, but an increase of antithrombin III

and prolonged partial thromboplastin time and prothrombin time in the group with HRT, and with that they tried to explain the cardioprotective effects of HRT. Hoibraten *et al.* (17), in a study of 118 patients with angiographically verified coronary disease with continuous 3-month transdermal estrogen therapy, combined at the end with two-week therapy with medroxyprogesteron acetate, after 12 months therapy, found a significant reduction of the protective: antithrombin III, protein C, but also a reduction of the procoagulating factors protein S and PAI-1.

Conclusion

From all the above-mentioned data we can see that many clinical studies give contradictory results, that is to say that there is a long way for clinical doctors to pass in the future in order to crystallize and put in concordance the scientific attitudes about HRT and its role in coagulation. Until that moment the clinical doctor should not deprive postmenopausal women of this therapy because of his/her own fear and insecurity. In order to clear up the results of this study, we are planning a study on a new material where there would be included research into the parameters: antithrombin III, protein C, thrombocyte aggregation, and some parameters of the fibrinolytic cascade, such as: plasminogen, plasminogen activator and inhibitor of plasminogen activator. We hope that in the near future we will be able to present new facts, which could contribute to clearing up the question about the effects of estrogens and progestogens as a complementary parts of HRT at the postmenopausal age.

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Резиме

**ВЛИЈАНИЕ НА ТРАНСДЕРМАЛНА ЕСТРОГЕНА ХОРМОНСКА
ЗАМЕСТУВАЧКА ТЕРАПИЈА КАКО ПРЕДОПЕРАТИВНА
ПОДГОТОВКА НА ТКИВОТО ПРИ ВАГИНАЛНА
ХИСТЕРЕКТОМИЈА ВРЗ КОАГУЛАЦИЈАТА**

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Кај 32 постменопаузални пациентки, третирано оперативно заради генитален пролапс на Одделението за урогинекологија и тазова статика при Клиниката за гинекологија и акушерство, Медицински факултет, Скопје, во периодот од 1. I 2002 до 1. I 2003 година предоперативно, во период од 14 дена беше администриран трансдермален естрадиол во доза од 50 µг/ден и беа одредувани следниве параметри на коагулациониот статус: протромбинско време(ПТ) изразено во апсолутни вредности, во проценти и во INR, aPTT Pathtrombin SL, тромбинско време и тромбоцити пред и по хормонската заместувачка терапија. По 14-дневна трансдермална естрогенска терапија параметрите: ПТ, ПТ%, INR, aPTT Pathtrombin SL не покажаа сигнификантни промени, тромбинското време покажа сигнификантно продолжување, а тромбоцитите сигнификантен пад. Добиените резултати зборуваат во прилог на можноста трансдермалните да естрогени не влијаат на хепаталната синтеза на коагулационите фактори до стапката на формирање на протромбин, а битно влијаат на стапката на претворање на протромбинот во тромбинот, како и на процесот на сеграгација на мегакариоцитите во тромбоцити.

Клучни зборови: трансдермална естрогенска терапија, генитален пролапс, протромбинско време, тромбинско време, тромбоцити.

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