



Changes of Hemostasis Indicators in Women in Accuracy Practice

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ABSTRACT

Objectives: To study changes in the parameters of thromboelastometry and the plasma link of the hemostasis system in women with uncomplicated pregnancy and with manifestations of thrombophilia in the perinatal period.

Methods: The analysis of indices of thromboelastometry and coagulogram in 408 women was conducted. The study was conducted from 8.09.2016 for 13.09.2016. The subjects were conventionally divided into groups: A - women without pathology of hemostasis (n = 152), B - women with clinical manifestations of thrombophilia (n = 256). The examination was carried out in the third trimester of pregnancy, on days 1 and 5 after delivery.

Results: In patients with thrombophilia, significant changes in coagulation potentials, characterized by hypercoagulation, thrombinemia and a decrease in the reserve of natural anticoagulants, and a decrease in fibrinolysis activity were noted. Changes were observed in the prenatal period, increased in the first day after childbirth.

Conclusion: The studied parameters of hemostasis can be used in assessing the risk of thrombotic complications and the rationale for antithrombotic therapy.

The hemostatic system is one of the fundamental systems of the human body, which ensures the functioning of all organs. During pregnancy are hemostatic changes which are intended at maintaining normal functioning of the fetoplacental complex and stop bleeding from the vessels of the placental bed after the separation of the placenta. Moreover, in the course of gestation, the conditions for the development of a hypercoagulable state and complications of pregnancy.

Keywords: Pregnant Women, Thromboelastometry, Plasma Haemostasis, Thrombophilia, Hypercoagulation

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INTRODUCTION

Most authors think that a prothrombotic status may reason the development of obstetric complications such as placental insufficiency, plus the syndrome of intrauterine development of the fetus, miscarriages, moderate and severe forms of preeclampsia, premature detachment of normally location placenta. Fault of these complications are mediated hypercoagulation defects of implantation of the ovum, invasions of the trophoblast in early pregnancy and circulatory disorders in the system mother-

placenta-fetus at late terms of gestation [1-4]. In addition to the physiological changes in hemostasis during pregnancy, a special role in the increased risk of thrombosis have congenital and acquired defects of the hemostatic system, which potentiate a status of hypercoagulability with a tendency to develop thrombosis. Disorders that can generate clinical symptoms of thrombosis determine the condition of thrombophilia [2,5]. Purpose of research is to evaluate changes in parameters of hemostasis of women with uncomplicated pregnancy and the manifestations of thrombophilia in the third trimester of pregnancy, in the 1st and 5th day of the neonatal period.

MATERIALS AND METHODS

The study of hemostasis was performed in 408 women in the period of delivery in the maternity ward of City hospital of Stavropol from 8.09.2016 for 13.09.2016. Age of mothers is 20-35 years, averaging 25.2 +0.6 years. The taking of blood was carried out with the consent of the attending doctor, subject to the rules of the pre-analytical phase of the study [6]. Surveyed was divided into groups: A – group of healthy pregnant women (n=152), B – patient with thrombophilia (n=256). The study was conducted according to the protocols of examination of patients with obstetric pathologies, approved by the Ministry of health of the Russian Federation.

The inclusion criteria in the study were: personal and family history indicating the various symptoms of thrombophilia complications in patients and their cognates, the fetal loss syndrome, severe gestosis during the previous pregnancies. Laboratory criteria for the selection were the research data of hemostasis, which indicate hypercoagulability and thrombophilic disorders.

To confirm the hypercoagulability status in patients of group B used the method of rotating thromboelastometry ROTEM, which is based on the graphic registration of changes of viscosity and flexible-elastic properties of blood in the course of formation of the fibrin clot and, that way, reflects the kinetics of all stages of clot formation, stability and density, and the activity of fibrinolysis. It assessed the following parameters of thromboelastometry: CT - the start time of clot formation; CFT - the time for clot formation, the angle «A» the kinetics of the clot formation; MCA - the maximum density of the clot; LI 30, LI 45 - the degree of cell lysis of the clot at different periods of the research.

For the study of plasma hemostatic parameters were used samples of venous blood. Blood sampling from patients was performed in the morning on an empty stomach a needle puncture of the cubital vein before the onset of labour, first and the fifth day after birth. To prevent clot formation used vacutainer containing a 3.8% solution translesanas sodium citrate. The study was conducted in platelet-poor plasma blood. For this purpose, the blood sample was centrifuged at 3000 rpm in for 20 min [6]. Blood samples with signs of hemolysis and hilesi not been investigated. Study all of the indicators of hemostasis held not later than 2 hours after blood sampling in female patients.

Plasma hemostatic parameters were studied on the automatic coagulopathies the ACL 7000 analyzer by the company – «Instrumentation Laboratory», (USA). Research methods the

plasma coagulation hemostasis included the following tests: activated partial thromboplastin time (APTT) in Caen, prothrombin index (PTI) and prothrombin time (PT) to Quick with thromboplastin; INR – international normalized rati, the concentration of fibrinogen in plasma by Clauss, determination of soluble fibrin-Monomeric complexes (SFMC) ortofenantrolinom method quantitatively, XIIa – dependent lysis of euglobulin for Eremin G. F. and Arkhipov A. G. (XII-DF). For laboratory evaluation level of natural inhibitors of blood coagulation using next methods: determination of the activity of antithrombin III (AT III) and protein C by the method of chromogenic substrate.

RESULTS AND DISCUSSION

The analysis of the parameters of thromboelastometry pregnant patients with thrombophilia received compelling data enhances the coagulation activity of blood in relation to healthy pregnant patients.

Table 1. The changes of plasma hemostatic parameters in patient groups ($X \pm m$)

Parameter	A group (n=152)	B group (n=256)
CT,c	488±0,9	783±0,82*
CFT,c	81±0,82	156±0,65*
Angle α ,o	74±0,71	41±0,63*
MCF,MM	76±0,62	58±0,74*
LI 30,%	91±1,02	96±1,05*
LI 45,%	75±0,87	81±0,99*

*differences are authentic compared with the A group ($p \leq 0.001$).

So we observed a statistically significant ($p \leq 0.001$) shortening of the time of formation of the first fibrin in the sample, characterizing the enzymatic portion of coagulation cascade, shortened the time for clot formation to achieve a fixed level of strength to 81 c, reflecting the kinetics of increasing the density of the clot. The increase in the angle «A» of 80%, in comparison with the index in healthy pregnant women shows an increase in the rate of growth of the fibrin network, enhancement of fibrin polymerization and increase the strength of the clot. The increase in MCF to 76 mm characterizes the maximum dynamic properties of a compound of fibrin and platelets and represents the maximum clot endurance. An indicator of the quality of the clot depends on platelet aggregation and the quality of the formed fibrin. Estimation of the area under the curve of thromboelastometry over the next 30 and 45 minutes after reaching the maximum amplitude show a decrease fibrinoliticscuu

activity of blood in women with thrombophilia. Indicators of clot lysis at 30 and 45 minute was 96 and 81%, whereas in healthy women, 91 and 75%, respectively ($p \leq 0.001$).

Comparative analysis of indicators of plasma hemostasis in the perinatal period in healthy pregnant women the increase of fibrinogen concentration in plasma before the birth and in first days after birth 80% and a gradual decrease by the fifth day (table 2). There was slight shortening of the PV and the increase in PTI before the birth, in the first and fifth day after birth in comparison with the indicators in the third trimester of pregnancy, indicating activation of the external path of blood clotting during childbirth. Parallel to the increase in the concentration of fibrinogen and activity of the external path coagulation increases the activity of the internal mechanism of blood clotting, which is reflected in the shortening of the APTT. By the fifth day after birth, these figures are lengthened. The activity of AT III and protein C were within the reference frame borders, but after the birth observed decrease in at III activity by 10%, and protein 20%. The level of D-dimer has not changed much before the birth and in the postpartum period. There was a trend to decrease HSV in late pregnancy and during delivery, on the fifth day fibrinolytic activity returned to normal.

Table 2. The changes of plasma hemostatic parameters in patient groups ($\bar{X} \pm m$)

	Parameter	A group (n=152)	B group (n=256)
before childbirth	Fibrinogen, g/l	2,8±0,21	5,8±0,14*
	APTT, sec.	27,9±0,69	23,9±0,24*
	PTI, %	99,8±0,65	109,4±0,98*
	PT, sec.	11,3±0,32	9,5±0,23*
	INR	0,92±0,02	0,93±0,01
	SFMC µg/ml	4,2±0,026	6,3±0,28*
	D-dimer, mg/DL	0,44±0,08	0,65±0,09
	AT III,%	95,3±0,71	78,4±0,81*
	Protein C,%	112,7±0,74	85,2±0,76*
	XII-DF, min	10,1±2,16	18,2±3,21***
1 day	Fibrinogen, g/l	5,0±0,29	6,51±0,13*
	APTT, sec.	25,2±0,39	22,1±0,21*
	PTI, %	106,8±0,68	126,5±0,9*
	PT, sec.	10,4±0,25	8,7±0,25*
	INR	0,91±0,02	0,92±0,01
	SFMC µg/ml	4,5±0,21	6,5±0,22*
	D-dimer, mg/DL	0,43±0,08	0,91±0,09*
	AT III,%	86,7±0,72	75,6±0,85*
	Protein C,%	91,5±0,65	73,5±0,66*
	XII-DF, min	9,7±2,12	19,7±4,15***

5 days	Fibrinogen, g/l	4,2±0,18	5,5±0,13*
	APTT, sec.	26,7±0,52	23,6±0,34*
	PTI, %	104,5±0,79	119,2±0,72*
	PT, sec.	10,8±0,27	8,9±0,26*
	INR	0,92±0,01	0,91±0,01
	SFMC µg/ml	3,0±0,4	4,2±0,15**
	D-dimer, mg/DL	0,47±0,08	0,83±0,09**
	AT III,%	85,6±0,65	76,5±0,79*
	Protein C,%	92,2±0,66	75,4±0,64*
	XII-DF, min	7,5±2,11	18,7±3,17**

*differences are authentic compared with the A group ($p \leq 0,001$);

**differences are authentic compared with the A group ($p \leq 0,01$);

***differences are authentic compared with the A group ($p \leq 0,05$).

The result of the comparison of plasma hemostasis in women with clinical manifestations of thrombophilia revealed a 2-fold increase in the concentration of fibrinogen in the plasma before birth compared to healthy women. In the first days after birth, the concentration of fibrinogen was increased to 6.51 g/l and by the fifth day saw a decline of this indicator to the level corresponding to the antenatal period. Fibrinogen is the main substrate of thrombus, so hyperfibrinogenemia in group B should be considered as a high risk factor of thrombosis in childbirth and the postpartum period.

It is noted a significant increase in PTI and shortening of the PV ($p \leq 0.001$) at all stages of medical examination in patients of group B. In the third trimester of pregnancy in women with thrombophilia index, PTI was higher by 9.6% and the PV shortened by 16% compared to healthy women. On the first day after birth, these figures differed by 18% and 16%, respectively, while on day 5 - PTI was higher by 14% and PV shortened by 18%. The changes of PTI and PT indicate the upregulation of factors in the external way of coagulation.

The activity factors of the intrinsic pathway of coagulation were evaluated by the APTT level. The indicators were within reference limits, but in women of group B noted their significant shortening ($p \leq 0.001$), indicating hypercoagulability shear and is regarded as a risk factor for thrombosis. By the fifth day after birth, these figures are slightly lengthened, but did not reach values as in the group of women without pathology of hemostasis.

In the group of women with thrombophilia discovered increase the concentration of SFMC prior to delivery by 50% relative to the norm, in the first days after birth on 44%, on the fifth day, the figure was closer to normal, but in comparison with a group A was increased by 40%. SFMC is fibrin-monomers and oligomers, and their complexes with degradation products

of fibrin, which reflect the activity of thrombin in vivo. Because of quantitative expression of the results, the test allows for dynamic control over the content of SFMC in plasma and monitoring the efficacy of therapeutic interventions.

The level of D-dimer indicates the intensity of the processes of thrombogenesis and fibrinolysis. In the group of women with thrombophilia in the third trimester of pregnancy was an increase in D-dimer to 0.65 mg/dl ($p > 0.05$) on the first day after birth there was a significant increase of this indicator to 0.91 mg/dl ($p \leq 0.001$), on the fifth day the figure was slightly lower – 0,83 mg/dl ($p \leq 0.01$). In patients with thrombophilia along with hypercoagulability had significantly reduced reserve of natural anticoagulants ($p \leq 0.001$): activity of at III before birth was reduced by 17% compared with healthy women, the activity of the protein by 27%. The survey in the first days after birth showed that the deficiency of at III and protein C was 11% and 18%, respectively, and on the fifth day after childbirth and 9% and 17%, respectively. In patients of group B there is no clear dynamics of change HSF, but showed a significant inhibition at all stages of the survey ($p \leq 0.01$, $p \leq 0.05$).

CONCLUSION

Data analysis coagulation in healthy women indicates the activation of the external and internal path of blood clotting before the birth and in the postpartum period. Perhaps this is due to consumption for the inactivation of activated factors of the coagulation system of blood in childbirth. Also, a slight inhibition of fibrinolysis in the 3rd trimester of pregnancy and during childbirth, which is the main reason for the shift of hemostatic balance towards the hypercoagulable state. The revealed changes of hemostatic parameters are compensatory-adaptive character, promoting the general mechanisms of adaptation to childbirth, and consistent with a number of national and foreign authors [1,7]. In women with thrombophilia observed significant changes in the indices of coagulation potential, characterized by hypercoagulation, thrombinemia and reduced reserve of natural anticoagulants, as well as decreased activity of fibrinolysis. The changes observed in the prenatal period, intensified in the first days after birth. Data analysis of thromboelastometry confirms strengthening of all the basic processes of hemostasis – coagulation, formation of fibrin clot and fibrinolysis in patients with thrombophilia. In some studies the interrelation between the parameters of thromboelastometry, and the risk of developing venous tromboamboliceski

complications in patients with different pathologies [8], that can be used to develop principles of prevention and risk assessment of complications in obstetric practice. The use of the method of thromboelastometry in an obstetric hospital will identify the prothrombotic status (hypercoagulability alertness) patients and timely initiation of preventive measures. Investigated parameters of coagulation and thromboelastometry we can use to evaluate the risk of thrombotic complications, rationale targeting protivodiabeticheskikh drugs and anticoagulants. Since the results of these studies of hemostasis systems in patients has prognostic significance and confirm the clinical picture of thrombophilia.

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