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CONDITION OF THE HEMOSTASIS SYSTEM IN FETAL LOSS SYNDROME IN WOMEN WITH THROMBOPHILIA.

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Abstract:

Hemostasis system studied of 54 pregnant complicated women obstetric history and fetal poisoning syndrome. The hemostatic system in pregnant women with thrombophilia is characterized by acivaton of platelet hemostasis by increasing the number of platelets, hypercogulability, as evidenced by an increase in the amount of soluble complexes fibrin monomer thrombinemia witnesses.

Keywords: Letal lose syndrome, fetoplacental complex, hemostatic system, hereditary thrombophilia, heterozygous, hereditary thrombophilia.

Fetal loss syndrome (FLS) is the most significant indicator that determines an unfavorable outcome for the child in terms of both survival and quality of life [2, 5]. The frequency of SPP in different countries ranges from 6 to 12%; in recent years, there has been a tendency for this indicator to increase [2, 3, 5]. The main difficulties associated with studying this problem are due to the polyetiological nature of SPP. This pathology can be caused by chromosomal abnormalities, gene mutations, hereditary predisposition, endocrine and immune disorders, and abnormal development of the uterus [6, 7, 8].In the structure of reproductive losses, the group with unknown etiology, according to many researchers, ranges from 7 to 50%,more than half of patients have a combination of certain causes [4].

It is known that for the hemostasis system during a physiologically occurring pregnancy, the adaptive reaction is to increase the coagulation potential, mainly due to an increase in the concentration of blood coagulation factors and the functional activity of platelets. All these changes are an important physiological reaction necessary to maintain the functioning of the fetoplacental complex and reliably stop bleeding after separation of the placenta. However, these same factors create additional conditions for the development of thrombosis against the background of already existing genetic thrombophilia.

In recent years, much attention has been paid to inherited, and sometimes acquired during life, defects in plasma blood proteins, which cause a predisposition to thrombosis and are an independent risk factor for the development of thrombosis [1].Studying the causes and pathogenesis of SPP allows us to develop basic measures to prevent this syndrome in women of reproductive age, taking into account the identified disorders.

MATERIAL AND RESEARCH METHODS: The hemostatic system was studied in 54 pregnant women with a complicated obstetric history of miscarriage (main group). The control group consisted of 20 conditionally healthy women with uncomplicated pregnancy. The age of the women examined ranged from 20-35 years (on average 27.5±6.8 years).Blood for studying hemostasiological parameters was obtained by puncture of the antecubital vein with a dry needle. A 3.8% solution of trisodium citrate was used as a stabilizer. Evaluation tests of the hemostasis system were used: total activity of coagulation factors - activated recalcification time (AVR); activated partial thromboplastin time; thrombin time (TB), prothrombin index (PTI); determination of fibrinogen concentration, as well as study of the platelet component of hemostasis: determination of the number of platelets in peripheral blood, study of the functional activity of platelets when exposed to various aggregation stimulants.
The molecular genetic stage of the work was carried out in the GENOTEXNOLOGIYA laboratory.

RESEARCH RESULTS:

The average period of miscarriage in patients of the main group was 13.4±1.6 weeks. At the same time, spontaneous miscarriages and non-developing pregnancy occurred in 27.8% of patients (n=15) at a period of up to 9 weeks, in 48.1% (n=72) at a period of 9-16 weeks of pregnancy, and at a period of 17-20 weeks. - in 24.1% (n=13). It follows from this that the vast majority of those examined (48.1%) were 9-16 weeks of gestation at the time of the development of clinical signs of fetal loss.

In 40.7% of 54 women in the main group, hereditary thrombophilia was identified and genetically confirmed. Of these, 19 (86.4%) were diagnosed with a heterozygous form of the MTHFR gene mutation, 1 (4.5%) - a homozygous form of the MTHFR gene

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mutation, 1 (4.5%) - a combined heterozygous form of the factor II gene mutation and MTHFR, 1 (4.5%) had a combined heterozygous form of the mutation of factor V Leiden and MTHFR.

The study of the characteristics of the state of the hemostatic system included an analysis of indicators of the plasma-coagulation and platelet components of hemostasis in pregnant women of the main group with miscarriage and in women with uncomplicated pregnancy in the second trimester showed (Table 1) that in patients of the main group, aPTT, which characterizes the internal coagulation pathway, remained practically unchanged compared to the control (35.9±0.3 and 35.5±0.8 s, respectively; P>0.05). The value of prothrombin time, which characterizes the external mechanism of blood coagulation, corresponded to that of patients in the control group (15.4±0.1 and 14.9±0.2 s, respectively, P>0.05).

In the patients of the main group during the study, there was a slight increase in the level of fibrinogen in the plasma hemostasis, which was within unreliably significant limits from the values of the control group and was 1.2 times higher than the control (respectively 3.8 ± 0.2 g/l and 3 .1±0.1 g/l, P>0.05).

As the gestational age at which women developed clinical signs of miscarriage increased, the amount of soluble fibrin in the plasma also increased. In the main group, this indicator was 1.8 times higher than the control (8.8±0.2 versus 4.9±0.5 μg/100 ml; P<0.01). Moreover, the level of RFMC in plasma correlated with the degree of increase in fibrinogen concentration with an average positive correlation (r = +0.59), which indicated the state of activation of blood coagulation.

The number of platelets in the peripheral blood of these patients was significantly higher than in the control group (235.8±6.6·vs. 203.6±10.8·109/l; Δ%=+13.6; P<0.05), which is obviously associated with activation of the platelet component of hemostasis.

The aggregation activity of platelets in patients of the main group practically did not change, practically no different from the control (97.1±2.0 and 105.3±3.2%, respectively, Δ%=-7.8; P>0.05), which is consistent with the data of many authors on patients with a hereditary predisposition to increased thrombus formation.

Thus, the hemostatic system in women with miscarriage in the second trimester of pregnancy was characterized by activation of platelet hemostasis due to an increase in the number of platelets, increased coagulation potential (hypercoagulation) due to increased procoagulant activity of coagulation factors and a significant expansion of the fibrinogen pool in plasma, resulting in a significant increase in the number soluble fibrin monomer complexes - witnesses of thrombinemia.

To study the characteristics of the laboratory symptom complex in hereditary and acquired thrombophilia, two subgroups A and B were additionally formed from the 54 women studied. Subgroup A included 32 pregnant women with miscarriage without a genetic defect, subgroup B included 19 patients with a diagnosed heterozygous form of the gene mutation MTHFR (Table 2). Thus, according to the results of the analysis, the difference in the average values of platelet parameters and their aggregation in the compared groups turned out to be statistically insignificant (P>0.05).

In patients who are carriers of a heterozygous form of the MTHFR gene mutation (group B), no characteristic changes were detected in the plasma hemostasis during gestation, as evidenced by the values of aPTT (36.5 ± 0.6 and 35.8 ± 0.3 s, respectively; P>0.05) and prothrombin time - PT (15.2±0.2 and 15.5±0.1 s, respectively; P>0.05), which is consistent with the data of L.P. Papayan (2020).

The fibrinogen level in patients of group B was slightly higher than in group A, but the differences did not reach significance (3.7±0.1 and 4.0±0.2 g/l; P>0.05). The same was true for high levels of soluble fibrin in the blood plasma (8.5±0.3 and 9.3±0.4 μg/100 ml; P>0.05). Moreover, in patients of both groups, the level of RFMC correlated with the amount of fibrinogen in plasma with a medium and high degree of positive correlation (rA = +0.55 and gB = +0.74). That is, our data confirm the opinion of experts that markers of increased procoagulant activity reflect the degree of hemostatic potential of the blood, but do not identify thrombophilia.

The results confirm that pregnant women with acquired and hereditary thrombophilia did not show any specific phenotypic laboratory differences. In these patients, high levels of RFMC (8.5-9.3 mcg/100 ml) were an objective indicator of an increased tendency of the blood to thrombogenesis and, therefore, one of the laboratory markers of the risk of miscarriage.

CONCLUSIONS:

1. The state of the hemostatic system in pregnant women with thrombophilia is characterized by activation of platelet hemostasis due to an increase in the number of platelets, increased coagulation potential (hypercoagulation) due to increased procoagulant activity of coagulation factors and a significant expansion of the

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fibrinogen pool in plasma, which is confirmed by an increase in the number of soluble fibrin monomer complexes - witnesses of thrombinemia.

2. High levels of RFMC (>8.8 mcg/100 ml) are a laboratory marker of the risk of miscarriage in women with thrombophilias.

Table 1.
Coagulogram indicators in women with miscarriage in the second trimester

Index	Groups of patients		P
	control (n=20)	main (n=52)	
Platelet count, 109/l	203.6±10.8	235.8±6.6	<0.05
Platelet aggregation, %	105.3±3.2	97.1±2.0	<0.05
APTV, s	35.5±0.8	35.9±0.3	>0.05
PV, s	14.9±0.2	15.4±0.1	<0.05
Fibrinogen, g/l	3.1±0.1	3.8±0.2	<0.01
RFMK, μg/100 ml	6.8±0.5	8.8±0.2	<0.01

Note. * - due to the small sample, 2 cases with a gestational age of 14-15 weeks were excluded from the calculations

Table 2.
Indicators of hemostasis in patients with a hereditary predisposition to increased thrombosis and without a genetic defect in case of miscarriage

Index	Main group		R
	A (n=32)	B (n=19)	
Platelet count, 109/l	240.0±8.2	238.5±9.8	>0.05
Platelet aggregation, %	99.0±3.0	94.9±2.3	>0.05
APTV, s	35.8±0.3	36.5±0.6	>0.05
PV, s	15.5±0.1	15.2±0.2	>0.05
Fibrinogen, g/l	3.7±0.1	4.0±0.2	>0.05
RFMK, μg/100 ml	8.5±0.3	9.3±0.4	>0.05

Note: * - due to the small sample, 3 cases were excluded from the calculations: 1 - combined heterozygous form of mutation of the factor II gene and MTHFR, 1 - combined heterozygous form of mutation of the factor V Leiden gene and MTHFR, 1 - homozygous form of mutation of the MTHFR gene.

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