ISSN 2181-3187

UDC: 618.39-021.3:618.396-085.35

THE SIGNIFICANCE OF ANTIPHOSPHOLIPID SYNDROME IN MARRIAGE AND THEIR RELATIONSHIP WITH HEMOSTASIS INDICATORS

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Summary. According to current estimates, APS is widely used in autoimmune thrombophilia, at high concentrations in the body at higher concentrations than phospholipids and glycoproteins with negatively charged phospholipids. This leads to a decrease in endothelial thrombocytopenia and activation of platelet hemostasis, as well as an imbalance in the coagulation hemostasis system. This leads to the occurrence of local macro- and microthromboses in the microvasculature, impaired placental vascularization and habitual miscarriage due to placental insufficiency. In this article, we conducted our own study in women with miscarriage due to APS.

Relevance. One of the pathogenetic factors of miscarriage are congenital and acquired disorders of the hemostasis system [2,4,8,9,10]. This problem is very multifaceted and relevant. Many questions still remain open, there are no definitive data on the influence of certain factors on recurrent miscarriage, fetal growth retardation syndrome, the development of a formidable complication of preeclampsia, hypertension during pregnancy and miscarriage [1,3,7,11,12]. However, many researchers observe the effects of antiphospholipid syndrome on adverse gestational outcomes. Physiological activation of the blood coagulation system during pregnancy begins from the earliest terms, promotes the introduction of the blastocyst and prevents peri-implantation hemorrhage during endovascular invasion of the trophoblast [5, 6, 8, 13,18]. In practice, these created situations, the growth of extragenital diseases, primarily vascular, caused by antiphospholipid syndrome, lead to systemic changes in hemodynamics, microcirculation, including in the uterus [14,5,16,17].

Excessive deposition of fibrin at the site of implantation and micro thrombosis of the spiral arteries and arterioles disrupt the invasion of the fertilized egg and can lead to both abortion and primary placental insufficiency with the subsequent development of obstetric complications.

Purpose of the study. Study of the role of markers of the hemostasis system and AFA in the early diagnosis of structural and functional disorders of the placenta.

Materials and research methods. The object of the study were 70 pregnant women at risk of miscarriage and 35 women with uncomplicated pregnancy, who were under the supervision of the Bukhara Regional Perinatal Center in 2020-2022. The subject of the study was venous blood and blood serum of patients for hematological

ISSN 2181-3187

and biochemical studies. The study used general clinical, functional, ultrasound, Doppler, biochemical, hematological and statistical methods. Statistical analysis was carried out according to the Fisher-Student method.

Research results. In all women who had a recurrent miscarriage at 9–10 weeks of gestation, the number of VAs was high, and the statistically significant number of repetitions of gestational age was 3.76 (P<0.001). However, in pregnant women, the level of IgM anti-PL and IgG anti-β2 -GP increased 15-fold (P<0.001) and 11.8-fold (P<0.001) compared to the control group. The results showed that women who had recurrent miscarriage at 9-10 weeks of gestation had APS.

Table 1. Indicators for antiphospholipid syndrome in recurrent miscarriage, M ± m

Index	**Physiological pregnancy, 9-10 week, n = 35**	**Misscarriage 9-10 week, n = 35**
VA, conventional unit	0,50±0,04	1,88±0,06***
IgM anti-FL, U/ml	1,17±0,11	23,43±1,00***
IgG anti-β2-GP	1,33±0,14	15,74±1,01***

Note: * - differences between the control group and patients with APS are significant (P<0.05), ** - P<0.01 and * - P<0.001.**

It should be noted that when interpreting the results of the VA indicator, it is necessary to pay attention to the degree of its increase, i.e.: if its value is about 1.2-1.5 conventional units - the average change, if it is 1.5-2.0 conventional units - the formation of blood clots in the veins, if it is above 2.0, then the danger is strong. In our study, VA was 1.88 ± 0.06 units, which is due to the formation of macro- and microthrombosis in the fetal tract, impaired fetoplacental circulation, and the absence of habitual miscarriage.

It is known from the literature that antibodies to APL slow down the synthesis of prostacyclin in endothelial cells by inhibiting phosphorylase A2 and protein S and contribute to the formation of blood clots. The resulting antibodies bind to the phospholipids of cell membranes and lead to conformational and metabolic changes in the membranes. This leads to their dysfunction, slowing down and cessation of blood flow in capillaries and venules, as well as to thrombosis. However, it should be noted that antibodies to APL are also present to some extent in the blood serum of healthy people, and this is associated with cell renewal.

In our study, women who had recurrent miscarriage were 15 (P < 0.001) higher than those in the control group, indicating the presence of APS. Such a sharp increase leads to the connection of platelets and vascular endothelium and, as a result, to their destruction, the development of thrombosis and thromboembolism. At the same

ISSN 2181-3187

time, we observed a 12-fold (P<0.001) increase in serum anti-β2-GP IgG. The oxidized form of the β2-GP protein binds to dendritic cells, the activation of which can accelerate the formation of antibodies.

In turn, they lead to disruption of the complement system, as well as to the activation of the hemostasis system, a complex course of the disease, a sharp increase in thrombosis in the fetoplacental microcirculation system and fetal death. As noted above, long-term circulation of APL antibodies in plasma, free lipid vesicles in plasma, as well as in the endothelium, platelets and other cellular phospholipid compounds. This, in turn, reduces the platelet resistance of endothelial cells, activates platelets and leads to an imbalance in the coagulation hemostasis system. For this reason, we have identified some indicators of hemostasis in women with recurrent miscarriage.

Platelets are involved in primary hemostasis and in the first stage of stagnation. At this stage, platelets become active, and platelets activate platelets by exposing them to plasma factors, which in turn increase platelet aggregation. At the third stage of coagulation, a prothrombinase complex is formed on the surface of active platelets, which, in turn, increases the production of thrombin. Thrombin is involved in the conversion of fibrinogen to fibrin. At the same time, platelets provide thrombus retraction and complete the blood clotting process.

To study the vascular-platelet stage of hemostasis, the number of platelets in the general blood test was counted. Studies have shown that the amount of hemoglobin, erythrocytes and platelets in women who have undergone RPL tends to decrease compared to the group of women who are physiologically pregnant. In particular, the amount of hemoglobin in the main and control groups was 91.93±3.68 and 108.11±1.04 g/l, the number of erythrocytes was 3.17±0.06 and 3.57±0.08x1012/l , leukocytes - 7.31±0.15 and 6.48±. 0.34x109/l, platelet count - 211.70±3.82 and 234.23±4.40x109/l, ECG - 18.23±0.69 and 10.83±0.66 mm/h. In other words, in the group of women who had a normal abortion, there was a partial decrease in the number of platelets and a statistically significant increase in ESR.

Coagulation hemostasis consists of a cascade of reactions involving plasma factors. Coagulation hemostasis was studied at all three stages of coagulation: according to the Morawitz method of clotting time (MAC) and active partial thromboplastin time (APTT) (1 stage of coagulation); prothrombin time (PT), prothrombin index (PTI) and international normalization coefficient (INR) (2 stages of blood coagulation); the amount of fibrinogen (3 stages of blood coagulation).

In the group of women who had recurrent miscarriage, a significant reduction in bleeding time was observed (see Table 3.2). In this group, the start time of blood clotting was 151.00 ± 6.82 seconds, and the end time of blood clotting was 190.54 ± 5.47 seconds. In the control group, these values were as follows: the onset of bleeding 148.69±3.73 sec, the end 205.75±4.48 sec. That is, a 1.5-fold reduction in bleeding

ISSN 2181-3187

time (P<0.01) in the control group of women who had experienced habitual miscarriage indicated a pronounced hypercoagulability in plasma hemostasis.

However, in the group of women who had recurrent miscarriage, plasma APTT increased to 42.8±1.26 (P<0.001) sec. In the control group, APTT was 28.26±0.15 sec. It should be noted that an increase in the APTT level of 1.7 (P<0.001) indicates the presence of LA in women. In fact, our study showed that the VA value was 3.76 times (P < 0.005) higher than normal, indicating a correlation between the two.

Table 2. Assessment of the first stage of blood coagulation coordination in recurrent miscarriage, M ± m

Indicators	**Physiological pregnancy, 9-10 weeks, n = 35**	**Habitual miscarriage, 9-10 weeks, n=35**
Start VSK, sec	148,69±3,73	151,00±6,82
Completion of VSC, sec	205,75±4,48	190,54±5,47
APTT, sec	28,26±0,15	42,8±1,26***

Note: * - differences between the indicators of the studied control group and patients with APS are significant (R < 0.05), ** - R < 0.01 and *** - R < 0.001. It has been shown that significant disturbances in blood clotting time and partial thromboplastin time are associated with hypercoagulability at the first stage of coagulation hemostasis in habitual miscarriage. To characterize the second stage of plasma hemostasis, prothrombin time, prothrombin index and INR were studied. The study of prothrombin time showed that the hemostasis system is significantly shifted towards hypercoagulation in patients in groups of women who experienced RPL in relation to the control group. So, if in the main group PT was 16.49 ± 0.20 s (see Table 3), then in the control group it was 17.69 ± 0.28 s.

Table 3. Assessment of the second stage of blood coagulation by recurrent miscarriage, M±m

Indicators	**Physiological pregnancy, 9-10 weeks, n = 35**	**Habitual miscarriage, 9-10 weeks, n=35**
PV, sec	16,49±0,20	17,69±0,28
PTI, %	84,4±0,40	96,23±1,48*
ON	1,16±0,01	1,20±0,01
MNO	1,05±0,01	1,25±0,05*

ISSN 2181-3187

Note: * - differences between the indicators of the studied control group and patients with APS are significant (R < 0.05), ** - R < 0.01 and *** - R < 0.001.

The prothrombin index was calculated using a special formula and amounted to 96.23 ± 1.48% in the main group and 84.4 ± 0.40% in the control group. This indicated the presence of hypercoagulation in women with recurrent miscarriage (see Table 3). The table shows that the international normalized ratio was 1.25 ± 0.05 in all women who underwent RPL, and 1.05 ± 0.01 in the control group. The study of indicators of the second stage of blood coagulation showed a significant shift of blood towards hypercoagulability in women of the main group.

The level of fibrinogen, plasma tolerance to heparin, thrombotest and thrombin time, which characterize the third stage of blood coagulation, were determined. Fibrinogen is the first coagulation factor synthesized in the liver. The study of the fibrinogen level showed a significant increase in the concentration of fibrinogen, which indicated a strong hypercoagulable shift. The content of fibrinogen in the group of women with RPL was 4334.2±148.7 mg/ml (R<0.001), in the control group this figure was 2677.14±28.91 mg/l. Thus, the study of the third stage of blood coagulation showed the presence of pronounced hypercoagulability relative to the control group in women with RPL.

Currently, one of the main markers of activation of the hemostasis system is an increase in the amount of D-dimer in the blood. The formation of fibrin D-dimer is one of the factors indicating both its breakdown and the development of thrombosis and is important in the diagnosis of DIC. A gradual increase in D-dimer in blood plasma begins in the early stages of pregnancy and ends 3-4 times higher than normal. Such changes are especially observed in preeclampsia.

Table 4. The amount of fibrinogen and D-dimer in women with recurrent miscarriage, M±m

Indicators	Physiological pregnancy, 9-10 weeks, n = 35	Habitual miscarriage 9-10 weeks, n = 35
Fibrinogen, mg/ml	2677,14±28,91	4334,2±148,7***
D-dimer, ng/ml	45,09±2,94	577,74±44,5***

Note: * - differences between the indicators of the studied control group and patients with APS are significant (R < 0.05), ** - R < 0.01 and *** - R < 0.001.

Therefore, we estimated the amount of D-dimer in the blood plasma of women with APS who had RPL. The study showed that the frequency in this group of women was 12.81 (R<0.001) times higher than in the control group, and amounted to 577.74±44.5 ng/ml. In the control group, its content was 45.09±2.94 ng/ml.

ISSN 2181-3187

Conclusion. Thus, based on the results obtained, women with RPL develop hypercoagulable syndrome in the blood at 8-9 weeks of gestation due to the presence of APS. This is due, in our opinion, to the fact that antibodies are formed not only against phospholipids and the b2-GP protein, but also against all proteins associated with negatively charged phospholipids. To date, antibodies to AF have also been shown to be present in prothrombin, thrombin, protein S, protein C, thrombomodulin, annexin II and annexin V. Most of them have procoagulant effects and have thrombogenic effects.

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