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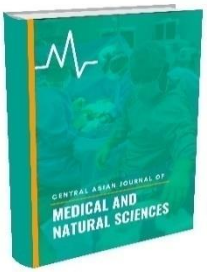

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Evaluation of Clinical and Instrumental Results of Patients with a Risk of Development of Recurrent Mission

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Abstract: PNP is one of the most urgent problems of modern medicine. Despite a long study of the problem of miscarriage, the etiological factors, pathogenetic mechanisms of spontaneous miscarriage have not yet been fully disclosed. The main difficulty in determining the immediate cause of abortion is due to the fact that miscarriage is a multifactorial process in which some factors may be of paramount importance, while others will be the background. In practice, in a particular clinical case, it can be quite difficult to separate them. Obviously, the causes of miscarriage must be considered in the light of the causes of deterioration in reproductive health in general.

Actuality. One of the promising areas that contribute to solving the problem of miscarriage is the selection of risk groups among pregnant women and their monitoring. This allows for new approaches to the management of pregnancy, to take into account and use all possible preventive and therapeutic measures, to ensure an interdisciplinary approach [3,4,10]. Many researchers paid attention to finding out the causes and studying the pathogenesis of this pregnancy complication. Scientists have identified a group of acquired defects in hemostasis - thrombophilia, leading to pregnancy loss [1,2,12].

The high frequency of this complication of pregnancy indicates the difficulties encountered in the management of women with miscarriage. On the one hand, they are due to the multifactorial nature of the etiology and pathogenetic mechanisms of the disease, on the other hand, the imperfection of the methods used and the lack of markers for prognosis and early diagnosis and, accordingly, the lack of an adequate approach to preventive therapy [5,6,7,9]. According to different authors, in 25-50% of observations, the genesis of spontaneous miscarriage remains unidentified. That is why they have an unfavorable outcome of childbirth, which leads to a high level of premature or early birth and a high level of perinatal losses [8,11,14]

Violation of the hemostasis system is a common cause of NB. Even with the physiological course of gestation, pronounced changes occur in this system, especially in the 1st trimester. Morphological and functional disturbance of the placenta is the main cause of NB, however, to date, reliable methods for their early prediction and their correlation features by the hemostasis system and the lipid spectrum have been little studied. The proposed methods are devoid of a comprehensive pathogenetically substantiated approach for choosing an adequate prevention of recurrent pregnancy loss. In this regard,

the search for new methods of timely prediction and preclinical detection of the threat of habitual abortion continues to be one of the priority areas of obstetrics [13].

Materials and research methods. 116 women with risk factors for the development of miscarriage for the period 2020-2022. The first group consisted of 30 pregnant women with a physiological course of previous and current pregnancies (group I), 40 pregnant women with OAA due to pregnancy loss, women registered for pregnancy in the early stages of gestation 4-9 weeks (group II) and 46 patients consisting registered at a later date of 9-14 weeks (group III). The women included in the study were examined and received treatment in the antenatal clinics of the city of Bukhara and the gynecological department of the FRCSENPBO. Statistical analysis of the results was performed using Student's t-test, Fisher's exact method, X^2 (Pearson), correlation analysis was performed using the Stat Graf software package and Microsoft excel.

Research results. It should be noted that the age of women in the groups ranged from 18 to 35 years and averaged 29.5 years in the main group and 26.7 years in the control group ($p> 0.05$). The duration of the menstrual cycle ranged from 25 to 32 days, averaging 28-30 days in the main group and 26-27 days in the control group (>0.05). The duration of bloody discharge did not have significant differences in the groups - 4.2 ± 0.5 days, and blood loss in all was regarded as average.

In women of the studied groups, we studied the types of gynecological diseases. At the same time, in women of the main group, the incidence of gynecological diseases compared with the control group.Isthmic-cervical insufficiency in the main group occurred by 1.7% more than in the comparative group, and follicular cyst by 4.5%, endometrial cyst by 7.9%, menstrual disorders by 15.4%, TORCH infection by 13.5 % and chronic cystitis by 18.2%. It should be noted that the somatic pathology occurring during pregnancy directly affects the condition of the fetus, because of this it is important to determine the anamnestic information and the results of physical examinations.

Diseases of the thyroid gland in the first group was 21 (52.5%), in the second group 18 (39%), and in the control 12 (40%). Chronic arterial hypertension occurred only in the second group and amounted to 4.3%. Obesity occurred in this group by 3.9 times, and in the first by 2.3 times compared with the control group.

In the study groups, when analyzing the obstetric anamnesis, the following was determined. There were 95 live births, 120 first trimester miscarriages, 62 second trimester miscarriages and 53 third trimester miscarriages. In total, habitual miscarriages were 158 cases, most of which occurred in the first trimester. There were 67 live births in the control group.

All pregnant women of the main group at the time of the examination had a risk of abortion, some of them had some clinical signs of a threatened abortion - pain in the lower abdomen and lower back, slight bloody discharge from the genital tract, general weakness. At the same time, threatening miscarriage was diagnosed in the second group of 37 patients (92.5%) of 40 women, incipient miscarriage - in 2 (5%) and incomplete miscarriage in 1 (2.5%). In the third group, we found 31 cases (67.4%) of threatened miscarriage, incipient miscarriage 12 cases (26%), incomplete miscarriage 3 cases (6.5%) out of 46 studied patients of this group. Detachment of the ovum with the formation of retrochorial hematoma according to ultrasound was determined in the second and third groups 17 (42.5%) and 12 (26%), respectively.

In addition, in this study, the thickness of the chorion and the yolk sac are important. Data concerning these parameters are given in table 1

№	index	Control group (n=30)	Main group (n=86)	
			II-group (n=40) 4-9 weeks	III-group (n=46) 9-12 weeks
1	Chorionic thickness	8,32±0,16	5,46±0,16	5,18±0,08
2	Yolk sac	2,14±0,01	3,03±0,12	2,68±0,16

In the main group -II, in addition to the effect on the central nervous system, the corpus luteum hypofunction, hemostasiological and metabolic disorders were corrected. BMI from 25 to 29.9 was interpreted as overweight and its treatment was started with non-drug methods. The package of interventions included exercise and diet and therapeutic lifestyle modification.

When anemia was detected, the patients received iron in the amount necessary to normalize the hemoglobin level of more than 110 g/l. For treatment and prevention, oral preparations of iron salts were used. Endocrine disorders, which are characterized by a decrease in the synthesis of progesterone in the yolk sac, were prescribed microdosed progesterone orally or intravaginally at a dose of 200-400 mg / day intravaginally or 200-600 mg / day orally until 22 weeks of gestation.

In order to correct hemostatic disorders, pregnant women with hyperaggregation syndrome received antiaggregants and aticoagulants - clexane and chimes in average daily doses. Against the background of therapy, the indicators studied by us were monitored and their effectiveness was evaluated. In order to evaluate the effectiveness of pathogenetic differentiated treatment of recurrent miscarriage, we carried out a comparative characteristic of the course of pregnancy in patients with early recurrent miscarriage, depending on the inclusion of correction of hormonal, hemostasiological and metabolic disorders in the treatment complex.

Studies have shown that 27 out of 30 women with physiological pregnancy noted mild anemia.In women of the 2nd and 3rd groups in the analysis of peripheral blood in 13 patients (15.12%) with miscarriage, anemia of the 2nd degree was determined. They were diagnosed with bleeding and all of them had a miscarriage. The rest of the women were noted to have mild anemia. In women who had a miscarriage, there was a statistically significant decrease in hemoglobin.

It is known that hemostasis has an important place in coagulation hemostasis, because it involves stepwise reactions of plasma factors. There are 3 stages of coagulation hemostasis, we studied each of them separately. The main indicator of the first link is VSK (blood clotting time) and APTT (active partial thromboplastin time); the second link is determined by prothrombin time (PTT), prothrombin index (PTI) and international normative ratio (INR); and the level of fibrinogen determines the 3rd link. We studied the indicators of women who applied during a threatened miscarriage and did not receive treatment (Group 3) and patients who applied during a threatened miscarriage who received treatment (Group 2) and women with physiological pregnancy (Group 1).

We did not state a shortening of the VSC in women with a threatened miscarriage (see table 2). In patients of the 3rd and 2nd groups, the onset of VSC was 98.59±1.99 and 97.95±1.20 seconds, the end of coagulation was 255.35±2.47 and 264.95±1.25 seconds. In pregnant women of the first group, these indicators were in the following values: beginning 108.13±5.00 seconds, end 253.4±4.38 seconds. Compared with the physiological pregnant women of the main groups, there was an elongation of the VSC, which, in our opinion, led to bloody discharge from the genital tract. When analyzing the indicators, we determined that there were no obvious differences between the groups in the nosologies of FFP. The results obtained show that the APTT practically did not differ from the normal parameters relative to the control group, and this is suitable for the VSC indicators. In the control group, VSC was 27.37±0.13 seconds, while in the second and third groups this indicator was 26.31±0.29 and 26.12±0.35 seconds. A shortening of the VSC was noted in the III-group / Step-by-step preventive

measures carried out in the second group led to a statistically significant lengthening of the APTT (up to 39.77±0.96 sec., P<0.05).

Table 2. Assessment of the first stage of coagulation in women at risk of miscarriage, M±m

Groups	Blood clotting time, sec		APTT, sec.
	Begin	End	
1st group, n=30	108,13±5,00	253,4±4,38	27,37±0,13
2nd group, n=40	97,95±1,20	264,95±1,25	26,12±0,35 29,01±0,57 б,в
3 rd group, n= 46	98,59±1,99	255,35±2,47	26,31±0,29

Note: a - the reliability of the studied parameters in patients with physiological and pathological pregnancy (P <0.05); b - reliability of comparative indicators between treated and untreated patients (P <0.05); a significant difference in indicators between the 2nd and 3rd groups (P <0.05).

It is known that to determine the second stage of hemostasis of plasma coagulation, it is necessary to determine the prothrombin time, prothrombin index and INR. PTT provides information about phases I and II of plasma hemostasis and shows the activity of the prothrombin complex. In our study, PTT did not differ significantly in patients of the second and third groups (see Table 3.2.5.). Women of the 3rd group had a significant lengthening of this indicator up to 19.50±0.72 seconds (in the control group 16.06±0.36 seconds). Especially this lengthening occurred in the group who took prophylactic anticoagulant therapy during pregnancy (up to 24.00±1.00 seconds, P<0.05). And this showed their commitment to hypocoagulation.

Table 3. Assessment of the second stage of coagulation in women at risk of miscarriage, M±m

Groups	**PTV, sec**	**PTI, %**	**BY**	**INR**
1st group, n=29	16,06±0,36	78,8±1,01	1,10±0,01	1,03±0,03
2nd group, n= 40	16,88±0,29 17,24±0,4	81,18±0,81 86,18±1,49	1,12±0,01 1,15±0,03	1,09±0,03 1,11±0,04
3 rd group, n= 46	16,67±0,3	79,65±1,32	1,05±0,03	0,99±0,05

Note: a - the reliability of the studied parameters in patients with physiological and pathological pregnancy (P <0.05); b - reliability of comparative indicators between treated and untreated patients (P <0.05); a significant difference in indicators between the 2nd and 3rd groups (P <0.05).

The study of the second link of coagulation in pregnant women with the threat of miscarriage and the use of anticoagulant therapy in them affects coagulation hemostasis, therefore, hemostasis indicators should be controlled to prevent hypocoagulation. It should be noted that, for assessing the third link, the level of fibrinogen in plasma, plasma tolerance to heparin, thrombotest and thrombin time are important. For this reason, we studied fibrinogen and D-dimer (see table 4).

Fibrinogen is the first factor that is synthesized in the liver. The study of the level of fibrinogen showed that its concentration has increased significantly, which confirms that a strong hypercoagulable shift is taking place. In the 2nd and 3rd groups, the fibrinogen level was at the level of 3033.6±54.12 and 3211.0±85.78 mg/l (P<0.001), while in the 1st group it showed 2672.14 ±105.2 mg/l. Summarizing, we can say that the study of indicators of hemostasis of the third link in women with a risk of threatened miscarriage showed hypercoagulability.

Table 4. Fibrinogen and D-dimer levels in women at risk of recurrent miscarriage, M±m

Группы	**Fibrinogen, mg/l**	**D-dimer, ng/ml**
1st group, n=29	2672,2±105,2	63,26±3,81
2nd group, n= 40	3211,0±85,78 а	209,24±31,75 а,в

	3159,1±96,82 [а]	122,2±15,63 [а,б,в]
3 [rd] group, n= 46	3033,6±54,12 [а]	332,28±27,64 [а]

Note: a - the reliability of the studied parameters in patients with physiological and pathological pregnancy (P <0.05); b - reliability of comparative indicators between treated and untreated patients (P <0.05); a significant difference in indicators between the 2nd and 3rd groups (P <0.05).

In a prospective analysis of the amount of fibrinogen, we determined that in women taking adequate maintenance therapy, its level was 2981.5±108.06 and 3225.87±99.74 mg/l (P<0.05), and in patients who did not receive timely therapy with the beginning of the first trimester of gestation by 3233.3±190.2 (P<0.05) and 3517.5±85.39 mg/l (P<0.05), in women -6 from group 2 and 13 from the 3rd group who had a miscarriage at 3994.5±176.7 (P<0.01) and 4480.0±80.00 mg/l (P<0.01) level, which meant obvious hypercoagulability in who had a miscarriage. After carrying out treatment and preventive measures in the remaining 67 women and in patients with FGR, this indicator decreased to 3031.32±84.21 and 2777.0±230.35 mg/l.

To date, the level of D-dimer in the blood is the main marker of hemostasis activity. This substance appears as a result of the breakdown of fibrin fibers. Its amount is determined by specific antibodies using enzyme immunoassay and shows how active fibrinolysis is. The level of D-dimer is important for determining fibrin and its breakdown, which is especially active in thrombosis and DIC. The appearance of D-dimer in the blood begins with the onset of pregnancy and by its end it is 3-4 times higher than normal. Especially, this is clearly manifested in hypertensive conditions during pregnancy and preeclampsia. The conducted studies in the 2nd and 3rd groups show that its level was higher than the norm by 3.31 (P<0.001) and 3.99 (P<0.001) times than in the first group, amounted to 209.24±31.75 and 332.28+-27.64 ng/ml. In the first group, it showed 63.26±3.81 ng/ml. In the second and third groups, in women receiving adequate therapy, this indicator was at the level of 197.6 ± 25.62 and 117.02 ± 10.23 ng / ml, while it statistically significantly differed from the indicators of the first group by 3.13 (P <0.001) and exceeded its level by 1.85 times (P<0.01). In pregnant women of the 3rd group, the amount of D-dimer was 676.53±104.02 ng/ml, it exceeded the values of the 1st group by 10.69 (P<0.001) times. In patients who had a miscarriage, its amount was at the level of 586.64±46.04 and 488.28±8.81 ng/ml, it exceeded the indicators of the first group by 9.27 (P<0.001) and 7.72 (P <0.001) times. These indicators differed statistically from the indicators of the second group and turned out to be 1.59 (P<0.01) and 1.69 (P<0.01) times less. After preventive treatment in the third group, the level of D-dimer was statistically significantly lower by 1.71 (P<0.001) times and amounted to 122.2±15.63 ng/ml. But it was 1.93 (P<0.001) times higher than in the first group. It should be noted that these positive changes in this group also occurred in women of the 2nd group. The D-dimer index statistically significantly decreased by 1.57 (P<0.01) and 4.04 (P<0.001) times and amounted to 75.92±5.63 and 167.33±16.97 ng/ml after the therapy. These indicators were higher than in the 1st group by 1.2 (P<0.05) and 2.64 (P<0.001) times. These changes, in our opinion, were the result of heparin-like substances or indirect anticoagulants.

It is known that the amount of D-dimer increases during infectious and inflammatory processes. The marker of inflammation is C-reactive protein (CRP). Its synthesis is increased in the liver as a result of IL-6 and cytokines. The main function of CRP is the binding of T-lymphocytes and the activity of leukocytes in the blood. Calcium ions bind to ligands of polysaccharides of microorganisms and ensure its elimination. Therefore, its amount increases during infectious and inflammatory processes. CRP determines the level of the inflammatory process. Given the above, we have identified CRP in the blood of pregnant patients with threatened miscarriage. During the study, in women of the 2nd and 3rd groups, the amount of CRP exceeded its level by 2.05 (P<0.001) and 2.76 (P<0.001) times compared with the first and amounted to 11.79±1.51 and 15.88±1.81 IU/l

In a prospective study, it was determined that CRP remained within the limits of the norm in women who took timely pregestational and in the early stages of maintaining etiopathogenetic therapy, and in patients receiving treatment at the end of the first trimester of pregnancy, it was high. This was clearly manifested in women of the 3rd group (it exceeded by 3.89 times (P<0.001)) and indicates an inflammatory process. It corresponds to an increase in the level of D-dimer in the blood. The highest rates were detected in the second and third groups and increased the standard level by 3.66 (P<0.001) and 5.6 (P<0.001) times compared with the first group, it was 21.10±2.82 and 32, 23±5.25 IU/l.

Conclusion. Despite the high risk of developing primary placental insufficiency, the correction of hormonal, hemostatic and metabolic disorders in the complex treatment of threatened miscarriage in women with recurrent miscarriage in the early stages of the first trimester of gestation significantly reduces preterm birth by -11%, improves the intrauterine state of the fetus 38.9 %, reduces the birth of low birth weight newborns by 27.4% and reproductive losses by 35.6%.

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