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Prediction of Premature Outflow of Amniotic Fluid in Preterm Pregnancy

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Abstract--- *Premature discharge of amniotic fluid is a complication of pregnancy, characterized by a violation of the integrity of the membranes of the fetus and the discharge of amniotic fluid before labor, regardless of gestational age. The aim of the study is to develop optimal methods for predicting the threat of premature outflow of amniotic fluid in pregnant women. A total of 478 pregnant women were examined to assess risk factors for the development of premature amniotic fluid flow. Retrospectively analyzed 350 stories of pregnant women from 2016-2019. Prospectively, under our supervision, there were 128 pregnant women. The main group consisted of 93 pregnant women. The control group consisted of 35 women. All birth histories were studied and risk factors leading to this pathology were identified. Prospective analysis. We identified risk factors such as stress, bad habits, age, abortion, gynecological diseases, the threat of abortion, premature discharge of amniotic fluid. We have developed a prognostic matrix according to the anamnesis and clinical symptoms, using the method of normalizing intensive indicators E.N. Shigan. According to this indicator, the computer program was created on January 25, 2019 (Intellectual Property Agency under the Ministry of Justice of the Republic of Uzbekistan. No. DGU 06117). "A program for identifying risk factors in case of the threat of premature discharge of amniotic fluid." We identified and divided pregnant women into 3 groups: The first group included (n = 17) pregnant women with a low probability of premature discharge of amniotic fluid, group 2 (n = 31), the average probability of an outflow, and group 3 - (n = 45) with a high risk. The results of our studies showed that diene conjugates were 2.2 times higher than normal, and malondialdehydes were 1.4 times higher, which certainly can be one of the pathogenetic factors in the thinning of the amniotic membranes, leading to their failure. Based on the foregoing, we also studied the functional state of the endothelium, a 1.3-fold increase in thrombomodulin content, a 1.5-fold increase in von Willebrand factor, a 2.1-fold increase in fibronectin, a 1.3-fold increase in soluble cell adhesion molecules, and a 1.3-fold increase in vascular cell adhesion molecule 1.1 times. From the cytokine status, a significant increase in the content of proinflammatory cytokines, interleukin was detected 2.9 times, tumor necrosis factor 2.6 times, C-3 1.9 times, and C-4 2.0 times patients at risk of developing premature amniotic fluid outflow in comparison with the control group. An important role in remodeling of the intercellular space of blood vessels is played by matrix metalloproteinases. A significant increase in the content of MMP -1 as the main enzyme was 2.5 times, MMP -3 was 4.9 times, MMP-9 was 1.5 times, and the concentration of TIMP-1 was 0.8 times lower compared to control group. Another indicator may be the indicator of fetal fibronectin determined in the vaginal secretion, which in 66% of cases was positive.*

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Keywords--- *Premature Birth, Prognosis, Premature Discharge of Amniotic Fluid, Normalized Intensive Rate, Threat, and Risk Factors.*

I. RELEVANCE OF THE STUDY

Premature discharge of amniotic fluid and rupture of membranes is a complication of pregnancy that lead to premature birth - today it is one of the most important problems of protecting mother and child, as they determine the level of perinatal morbidity and mortality. According to the literature, it has been studied that, in more than 35-60% of cases of preterm birth, regardless of the characteristics of etiological factors, they begin with premature rupture of the membranes and untimely discharge of amniotic fluid [1,2,3,4,5,6,7]. This is the most common cause of premature birth and severe complications in newborns. According to the World Health Organization, premature discharge of amniotic fluid in premature pregnancy increases perinatal mortality by 4 times, the incidence of newborns by 3 times, and in 40-70% of cases it causes the death of newborns [8,9,10,11,12,13].

In world practice today, multicenter scientific research is ongoing aimed at revealing various aspects of this problem, especially identifying risk factors and additional diagnostic criteria for the development of premature amniotic fluid flow. Despite numerous studies, it is still not clear what the mechanism of premature amniotic fluid flow is. At the same time, determining the risk factors for premature amniotic fluid outflow is a prerequisite for developing effective prognostic measures taking into account social and ethical standards [14,15,16,17,18].

In our country, large-scale measures are being taken for the early diagnosis and prevention of somatic diseases among the population. Along with this, there are a number of unresolved problems in the healthcare system, among which the most important are the prediction of premature amniotic fluid discharge.

The Aim of the Study

Is to develop optimal forecasting tools for the threat of premature amniotic fluid flow in pregnant women.

II. MATERIALS AND RESEARCH METHODS

To achieve the goal of the study and solve the tasks, anamnestic data of the retro and prospective groups of pregnant women were used. A total of 478 pregnant women were examined to assess risk factors for the development of premature amniotic fluid flow. Retrospectively analyzed 350 stories of pregnant women from 2016-2019. Prospectively, under our supervision, there were 128 pregnant women. The main group consisted of 93 pregnant women. The control group consisted of 35 women with a physiological course of pregnancy with a gestational age of 30-34 weeks of pregnancy. General clinical research methods, biochemical research methods were also applied, fetal fibronectin levels were determined and an ultrasound examination was performed (measuring the length of the w / and with a vaginal probe), an enzyme-linked immunosorbent assay for the determination of markers leading to premature discharge of amniotic fluid, based on the INNOVA private clinic.

III. RESULTS OF THE STUDY

An analysis of the retrospective group showed that the distinguishing feature of obstetric history in those examined with preserved pregnancy was such factors as stress (27.9%), bad habits (2.3%), and the age under 18

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after 30 years (8.5 %), history of abortion (37.2%), gynecological diseases (44.9%), threatened abortion (98.4%), early gestosis (100%), premature discharge of amniotic fluid up to 22 weeks (0.77 %), premature discharge of amniotic fluid up to 36 weeks (53.4%), cardiovascular disease (1.5%), hypertensive damage (6.2%).

At the same time, the examined with preterm birth showed an increase in the frequency of risk factors in comparison with women with preserved pregnancy: stress (31.2%), bad habits (3.6%), age under 18 after 30 years (6.33%), history of abortion (44.7%), gynecological diseases (56.5%), threatened abortion (99.5%), early gestosis (100%), PIU up to 22 weeks (0.90%), premature discharge of amniotic fluid waters up to 36 weeks (45.2%), cardiovascular diseases (5.4%), hypertensive disorders (11.3%).

Table 1: Delivery Outcome in 350 Pregnant Women in a Retrospective Group

Amount ofpatients	**Preservedpregnancy**		**Prematurebirth**	
350 – 100 %	129	36,8%	221	63,1%

It can be assumed that many risk factors remained unexplored: the doctor of the admission department did not pay attention to the anamnesis, did not interview the pregnant woman, and thus the assessment of the state of the pregnant woman could be slightly distorted. In our opinion, the causes of premature birth and premature discharge of amniotic fluid are late referral to the hospital, concomitant pathology, and insufficient history, delayed identification of risk factors and lack of prevention of premature birth. Prospective analysis: to identify risk factors for premature birth and premature discharge of amniotic fluid, we examined 93 women with gestational age of 30-34 weeks of pregnancy. The results showed that stress was 38.7%, bad habits up to 25.8%, occupational hazards 30.1%, allergic background 24.7%, stomatitis 12.9%, antibiotic use 26.8%. It can be assumed that the above features of life can lead to premature discharge of amniotic fluid.

Table 2: Assessing the Risk of Developing Premature Amniotic Fluid and Premature Birth by Collecting an Obstetric History (n = 93)

Riskfactors	**Noted**	**%**	**Notnoted**	**%**
Abortion	34	36,5	59	63,4
Gynecologicaldiseases	22	23,6	71	79,5
Vaginal bleeding	53	56,9	40	43,0
I trimester	53	56,9		
II trimester	23	24,7		
III trimester	9	9,6		
The threat of abortion	93	100	-	-
I trimester	93	100	-	-
II trimester	39	41,9	54	58,0
III trimester	9	9,6	84	90,3
Gestosis during pregnancy	93	100	-	-
I trimester	93	100	-	-
II trimester	41	44,0	52	55,9
Preeclampsia	14	15,0	79	84,9
Mild	9	9,6		
Severe	5	5,3		
Eclampsia	1	1,07	92	98,9
Premature discharge of amniotic fluid up to 22 weeks	18	19,3	75	80,6
Premature discharge of amniotic fluid up to 36 weeks	7	7,5	86	92,4
Acuteplacentalabruption	2	2,1	91	97,8
Uterusscar	11	11,8	82	88,1

As can be seen in table 2, a thorough collection and study of the anamnesis has a significant role in determining

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the risk of premature discharge of amniotic fluid and premature birth. The highest numbers rest on the threat of interruption and gestosis in 100% of cases, abortions in history 36.5%, gynecological diseases 23.6%, spotting 56.9%, preeclampsia 15.0%, eclampsia 1.07%, premature discharge amniotic fluid up to 22 weeks 19.3%, up to 36 weeks 7.5%, placental abruption 2.1%, uterine scar 11.8%.

According to table 3, cardiovascular diseases 6.4%, hypertensive disorders 13.9%, kidney diseases 16.2, respiratory diseases 11.8%, liver pathology 21.5%, anemia 60.2%, metabolic disorders 25,8% and Rh negative blood in 2 cases can increase the risk of premature amniotic fluid flow.

Thus, in all the studied groups, women had a history of different outcomes of the previous pregnancy, the main share of which was occupied by the combined outcomes of several pregnancies, which could subsequently cause premature birth. Women who previously had the above factors are at risk for the development of preterm birth and premature discharge of amniotic fluid during pregnancy.

Table 3: Assessing the Risk of Developing Premature Amniotic Fluid Outflow and Preterm Birth by Determining Extra Genital Pathology (n = 93)

Riskfactors	Noted	%	Not noted	%
Cardiovasculardiseases	6	6.4	87	93,5
Hypertensivedisorders -Gestational hypertension -Chronichypertension	13 7 6	13,9 7,5 6,45	80	86,0
Kidney disease -Gestational pyelonephritis -Chronic pyelonephritis	15 11 4	16,2 11,8 4,3	78	83,8
Respiratorydiseases	11	11,8	82	88,1
Pathology of the liver -hepatitis B, C -cholecystitis -hepatosis	20 2 13 5	21,5 2,1 13,9 5,3	73	78,4
Anemia - lightdegree - severe	56 37 9	60,2 39,7 9,6	37	39,7
Metabolicdisorders -I degree -II degree	24 14 10	25,8 15,0 10,5	69	74,1
Rhesus negative blood, not immunized	2	2,1	91	97,8

After collecting the anamnesis, we had the question of what new things could be put into practice to quickly and accurately identify the anamnesis with the result of assessing the general condition of the pregnant woman.

Given that it is important in the prevention of preterm birth and premature discharge of amniotic fluid is the identification of risk factors for development by comparing various prognostic criteria. We have developed a prognostic matrix according to the anamnesis and clinical symptoms, using the method of normalizing intensive indicators E.N. Shigan. According to these indicators, a computer program was created on January 25, 2019. (Intellectual Property Agency under the Ministry of Justice of the Republic of Uzbekistan. No. DGU 06117). "A program for identifying risk factors in case of the threat of premature discharge of amniotic fluid."

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To compile a prognostic table, comparable indicators of the predicted phenomenon were obtained by gradations of the most important factors. The significance of factors and their gradations was determined using the relative risk indicator (R). This indicator is the ratio of the maximum (c) to the minimum (d) intensity level within each individual factor (R = c / d).

If the factor has no effect, then it is equal to unity. The higher (R), the greater the significance of the factor for the occurrence of this type of pathology.

The essence of the method is that instead of the usual intensive indicators, indicators are used that can be calculated by the formula:

$$N = r / M,$$

Where: N is the normalized intensive indicator, r is the intensive indicator TL C C per hundred examined, M is the "normalizing indicator".

In this case, the average frequency of premature discharge of amniotic fluid according to the entire study (per 100 examined) is taken as the normalizing value in this case.

For example, the preterm birth rate (r) was 46.7, and the premature discharge of amniotic fluid was 54.5. The same indicator among all examined was 51.0. This value was taken as a "normalizing" indicator (M). Substituting the corresponding values into the above formula, we obtained the following normalized intensive indicators: for premature discharge of amniotic fluid, normalization of the intensive indicator = 46.7 / 51.0 = 0.934, and premature birth - 2 = 54.5 / 51.0 = 1.069. Relative risk indicator (R) = 1.032 / 0.934 = 1.167.

The normalization of the intensive indicator for all other risk factors was calculated similarly.

The obtained norms of the intensive indicator are the initial standard with which you can give an integrated assessment of the risk of developing premature amniotic fluid outflow, both for a separate factor and for their complex.

As you know, risk factors have different strengths of influence on the development of premature outflow of amniotic fluid. Therefore, we took into account the value of the relative risk indicator for each factor. Knowing that the indicator of the relative risk (R) of the occurrence of the disease and the normalized intensive indicator (N), we can determine the strength of the influence on the development of premature outflow of amniotic fluid of each individual factor, i.e. prognostic factor (X).

This value is defined as follows:

$$X = (R) \times (N),$$

Where X is an integrated indicator of risk from the strength of the influence of a single factor (prognostic coefficient); (N) - rationing of an intensive indicator on the development of premature amniotic fluid outflow; (R) is an indicator of relative risk.

If we take into account that in our example the relative risk indicator (R) was 1, 17, the normalization of the intensive indicator was 1 = 0.916, and the normalization of the intensive indicator was 2 = 1.069, then the integrated

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indicator of the influence power of each individual factor, i.e. prognostic coefficient, amounted to 1.17-0.916 = 1.072, if premature discharge of amniotic fluid 1.17x 1.069 = 1.25.

The prognostic matrix includes all the risk factors identified for prediction of the development of premature amniotic fluid outflow with their gradation and the values of the integrated risk indicator on the strength of the influence of an individual factor (X), the relative risk indicator for each factor (R) and their sum for a complex of factors (RN), and also the normalizing value is the average rate of premature amniotic fluid outflow according to the entire study (N).

Table 4: Predictive Map for a Comprehensive Assessment of the Risk of Premature Birth and Premature Amniotic Fluid Outflow

Riskfactors	Yes / no	%	N	R	X	Xmin	Xmax
Stress	Yes / no	96,8/3,2	1,94/0,06	44,6	1,96/85,93	1,96	85,93
Badhabits	Yes / no	55,8/44,2	1,12/0,89	3,26	1,12/1,41	1,12	1.41
Occupationalhazards	Yes / no	64,5/35,5	1,64/0,36	4,56	1,64/7,47	1,64	7,47
Ageto 18 after 30	Yes / no	24,5/75,5	1,16/0.84	1,38	1,16/1,60	1,16	1,60
Historyofabortion	Yes / no	84,5/15,5	1,49/0,51	5.48	1.29/2,34	1.29	2,34
Historyofgynecologicaldiseases	Yes / no	65,3/34,7	1,46/0,54	3,89	1,40/3,22	1,40	3,22
Historyofthreatenedabortion	Yes / no	76,4/23,6	1,29/0,71	3.24	1,49/4,35	1,49	4,35
Historyofearlygestosis	Yes / no	65.5/34,5	1,40/0,60	2.76	1,34/4,35	1,34	2,72
Historyofpreeclampsia	Yes / no	68,3/31.7	1,49/0,51	3.28	1,46/3.95	1,46	3.95
Historyofeclampsia	Yes / no	75,4/24,5	1,34/0,66	3.89	1.49/4,35	1.49	4,35
Low levels of amniotic fluid	Yes / no	24,8/75,2	1,46\0,54	1.78	1.47/4,08	1.47	4,08
High levels of amniotic fluid	Yes / no	82,5/17,5	1,49/0.51	2.98	1,44/3,65	1,44	3,65
Premature discharge of amniotic fluid up to 22 weeks	Yes / no	78,2/21,8	1,47\0,53	4.22	1.29/2,34	1.29	2,34
Premature discharge of amniotic fluid up to 36 weeks	Yes / no	56,5/43,3	1,44/0,56	1,68	1,40/3,22	1,40	3,22
Acuteplacentalabruption	Yes / no	0,5/0,3	1,34\0,66	1,56	1,49/4,35	1,49	4,35
Vaginal bleeding	Yes / no	6,5/3,3	1,32/0,68	1,08	1,34/2,72	1,34	2,72
Respiratorydiseases	Yes / no	1,5/3,3	1.24/0,76	1,94	1,46/3.95	1,46	3.95
Rhesus negative blood not immunized	Yes / no	1,0/0,2	1,38/0,62	2,38	1.49/4,35	1.49	4,35
Cardiovasculardiseases	Yes / no	56,5/43,3	1,46/0,54	1,56	1.47/4,08	1.47	4,08
Hypertensivedisorders	Yes / no	76,5/43,3	1,44/0.56	1,44	1,44/3,65	1,44	3,65
Pathologyoftheliver	Yes / no	6,5/3,3	1,36/0,64	2.35	1,34/2,72	1,34	2,72
Kidneydisease	Yes / no	1,5/4,3	1,37/0,63	2.12	1,46/3.95	1,46	3.95
Severeanemia	Yes / no	86,5/53,3	1,80/0,20	4.85	1.49/4,35	1.49	4,35
Metabolicdisorders	Yes / no	15/3,3	1,72/0,28	2,32	1.47/4,08	1.47	4,08

In addition to the prognostic table, we determined a possible range of risk values for the complex of factors taken. The possible risk range for premature amniotic fluid outflow was determined as follows. In the prognostic table, we find the minimum values of the prognostic coefficient X for each factor and summarize them. This value is the initial risk value of this pathology. For example, in table 3.11, for an integrated risk assessment for the development of premature amniotic fluid outflow, the minimum values were as follows:

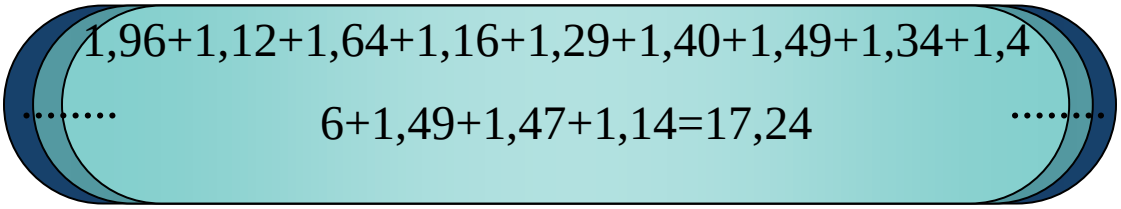

Figure 1

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In this case, the minimum initial risk value is 17.24

Then, in a similar way, we find the sum of the maximum values of prognostic indices for each factor.

85.93 + 1.41 + 7.47 + 1.60 + 2.34 + 3.22 + 4.35 + 2.72 + 3.95 + 4.35 + 4.08 + 3.65 = 124.07

In this case, the risk range is in the range of 17.24 + 124.07.

It follows that the higher the standardization value of the intensive indicator of the risk of premature amniotic fluid outflow, the higher the probability of developing it in this individual and the more reason for his allocation to the group of unfavorable prognosis.

In this regard, we identified a possible range of risk (17.24-124.07), as well as under the ranges. In practice, the entire risk range is better in three intervals: a low probability (17.24-52.85), an average probability (52.86-88.47), and a high (88.48-124.47) risk of developing premature discharge amniotic fluid. With a low probability of risk, the prognosis is favorable, with moderate probability, attention should be paid to the condition of a pregnant woman, and with a high probability, a poor prognosis should be expected and maximum attention should be paid to the condition of the pregnant woman.

Thus, the threshold values of the final prognostic coefficients and risk groups for the occurrence of pathology were determined.

With our results, we identified and divided the pregnant women into 3 groups:

The first group included (n = 17) women with gestational age of 30-34 weeks of pregnancy with a low probability of premature birth and premature outflow of membranes; Group 2 - (n = 31) - medium, the likelihood of premature birth and premature discharge of amniotic fluid and group 3 - (n = 45) with a high risk.

According to the objectives, biochemical and immunological studies were carried out such as lipid peroxidation, endothelial dysfunction, cytokine status and metalloproteinases.

The results of our studies showed that diene conjugates were 2.2 times, and malondialdehydes were 1.4 times higher than normal, which certainly can be one of the pathogenetic factors in the thinning of the amniotic membranes, leading to their failure. We also drew attention to the functional state of the endothelium. A highly specific marker of the functional state of the endothelium is thrombomodulin, von Willebrand factor, fibronectin and cell adhesion molecules.

Table 5: The Content of Markers of Endothelial Dysfunction in the Blood of the Examined

Examined groups	Indicators				
	Тромбомодулин нг/мл	Factor VonWillebrandng / ml	Fibronectinng / ml	sICAM-1 ng / ml	sVCAM-1ng / ml
Controlgroup(n=21)	6,74± 0,20	109,28± 2,59	233,17± 8,14	998,88± 15,0	742,30± 9,86
Main group (n=72)	8,93 ± 0,28*	169,57 ±3,67 *	504,77± 10,31*	1307,11± 26,14 *	798,97± 8,70

Note: * - significance of differences P <0.05

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As can be seen from table 4, the results of the study showed a significant increase in the content of thrombomodulin 1.3 times, von Willebrand factor - 1.5 times, fibronectin 2.1 times, soluble cell adhesion molecules - 1.3 times and vascular cell adhesion molecule 1 , 1 time in pregnant women of the main group in comparison with the control group. The reason for the increase in these markers is damaged trophoblast, which indicates the activation and stimulation of endotheliocytes, and the severity of hemostasis shifts leads to termination of pregnancy at different times.

Further, we screened for abnormalities in the system of protein C, D-dimer, antithrombin III.

Table 6: The Content of Markers of Endothelial Dysfunction in the Examined

Examined groups	Protein C %	D-dimerng / ml	Antithrombin%
Control group (n= 21)	86,61 ± 3,48	179,25 ±4,76	109,45 ±3,90
Main group (n=72)	128,51 ± 5,10*	318,05±5,62*	86,16 ±2,90*

Note: * - significance of differences P <0.05.

A decrease in the content of antithrombin III was detected, against the background of an increase in the level of protein C and D-dimer, which was due to the high values of thrombomodulin, which is diagnostic and prognostically significant in the diagnosis of premature amniotic fluid in pregnant women.

It is known that proinflammatory cytokines activate the blood coagulation process, which made it advisable to find out whether proinflammatory cytokines do not play the role of mediators that ensure the realization of procoagulant effects in case of premature amniotic fluid discharge.

To partially resolve this issue, we investigated the contents of Interleukin -1, Tumor Necrosis Factor, C-3 and C-4 complement fractions and insulin-like growth factor-1.

As the results showed, in pregnant women at risk for PIU, a significant increase in the content of pro-inflammatory cytokines was found.

Table 7: The Content of Cytokine Status in the Examined

Indicators	Main group (n=72)	Control group (n=21)
Interleukin -1 (IL -1) (pg / ml)	4,30 ± 0,18*	1,43 ± 0,07
Tumor Necrosis Factor (TNF-a) (pg / ml)	4,03 ± 0,16*	1,53 ± 0,07
Component of complement C3 (g / l)	2,25 ± 0,09*	1,15 ± 0,07
Component of complement C4 (g / l)	0,57 ± 0,02*	0,27 ± 0,02
Insulin-like FR-1 (ng / ml)	151,29 ± 5,50*	279,92 ± 5,96

Note: * - significance of differences P <0.05

As the results of assessing the cytokine status showed, a significant increase in the content of pro-inflammatory cytokines, interleukin was found to be 2.9 times, tumor necrosis factor - 2.6 times, C-3 - 1.9 times, and C-4 - 2. 0 times in patients at risk of developing premature amniotic fluid outflow in comparison with the control group. A decrease in the level of insulin-like growth factor 0.54 times, with an increase in serum concentration of insulin, reliably predicts conditions that threaten the life of the fetus.

The results of the studies allowed us to conclude that there is a pathogenetic relationship between increased levels of pro-inflammatory cytokines and procoagulant changes in pregnant women with a risk of premature

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amniotic fluid discharge

An important role in remodeling of the intercellular space of blood vessels is played by matrix metalloproteinases, which are involved in the exchange of proteins of connective tissue and are specific markers of collagen breakdown, therefore, to solve this problem, the content of matrix metalloproteinases in the examined was determined.

Table 8: Comparative Characteristics of the Content of Matrix Metalloproteinases in the Examined

Examined group	Indicators			
	MMP-9, ng / ml	MMP-1, ng / ml	MMP-3, ng / ml	TIMP-1, ng/ml
Control group (n=30)	73,97±2,89	4,37±0,27	7,72±0,32	728,34±19,48
Main group (n=72)	117,91±4,51*	11,10±0,57*	38,01±1,58*	597,69±9,46

Note: * - significance of differences P <0.05

In pregnant women with a risk of premature amniotic fluid outflow in the blood serum, a significant increase in the content was noted - MMP -1 as the main enzyme 2.5 times, MMP -3 was 4.9 times, MMP-9 1.5 times, and the concentration TIMP-1 was 0.8 times lower compared to the control group.

Thus, the study made it possible to establish that in the risk of developing premature amniotic fluid outflow, an important role is played by lipid oxidation indicators, endothelial dysfunction markers, proinflammatory cytokine and metalloproteinases, the study of which will predict the development of premature amniotic fluid outflow.

Another indicator of premature discharge of amniotic fluid may be an indicator of fetal fibronectin, determined in vaginal secretion during pregnancy.

As you know, fetal fibronectin is an immunochromatographic test - which can normally be determined at the very beginning of pregnancy, when implantation occurs and a connection is formed between the embryo and the uterine wall, as well as at the very end of pregnancy, before childbirth. We conducted this test in both groups.

Table 9: Fetal Fibronectin Test Results

	Test (+)		**Test (-)**	
	Abs	**%**	**Abs**	**%**
Main group (n=93)	**62**	**66,6**	**31**	**33,4**
Control group (n=35)	**2**	**5,7**	**33**	**94,3**

As can be seen from the table, in 66% of cases the test was positive. The appearance of fetal fibronectin in a separate form leads to the activation of enzymes in the zone where it accumulates and can lead to rupture of the membranes.

The data obtained indicate that the determination of fetal fibronectin in the gestation period from 22 to 36 weeks of pregnancy apparently leads to rupture of the amniotic membrane, thus this method can be attributed to the prognosis and one of the risk factors for the development of premature amniotic fluid outflow.

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At the same time, we analyzed the data of ultrasound examination of the cervix of pregnant women.

In patients with a threat, a pronounced shortening of the cervix was observed - in 3 - up to 20 mm, - in 39 - up to 25 mm and - in the 51st - up to 30 mm.

Thus, ultrasound examinations of the cervix at a gestational age of 30-34 weeks with (shortening of the cervix less than 28 mm) is an informative method in the diagnosis of premature birth, along with laboratory research methods.

IV. CONCLUSIONS

1. A retrospective analysis showed that untimely identification of risk factors contributes to the development of preterm delivery in 63.1% of cases.
2. A prognostic risk matrix for the development of preterm labor and premature outflow of amniotic fluid has been developed according to the method of normalizing intensive indicators E.N. Shigan using a computer program.
3. It has been established that the predictors of the development of premature amniotic fluid outflow and premature birth are an increase in the level of lipid peroxidation, markers of endothelial dysfunction, pro-inflammatory cytokine, metalloproteinases in the blood and the determination of fetal fibronectin.
4. Miscarriage due to premature rupture of the membranes is combined with the formation of metabolic disorders characteristic of the systemic inflammatory response syndrome, the criteria of which are a 1.4-fold increase in malondialdehyde, a 2.2-fold conjugate of diene conjugates with an increase in superoxide dismutase activity.

In premature pregnancy complicated by premature amniotic fluid outflow, hemostatic disorders are observed in the form of an increase in the content of thrombomodulin by 1.3 times, von Willebrand factor by 1.5 times, fibronectin by 2.1 times, intercellular adhesion molecules (sICAM-1) by 1.3 times, vascular adhesion molecule 1.1 times.

An increase in maternal blood levels of pro-inflammatory cytokines (IL-1 β 2.9 times, TNF-α 2.6 times, C-3 1.9 times, C-4 2.0 times) contribute to the rupture of amniotic membranes and premature birth.

The revealed high activity of metalloproteases shows a predominance of synthesis of type III collagen and a violation of the expression of coding proteins of the MMP and TIMP family genes, which determines the multilevel changes in the microarchitecture of the amniotic membranes in pregnant women with a risk of premature discharge of amniotic fluid and is the cause of rupture of the membranes.

A study of the fibronectin test in women with the threat of premature birth and premature discharge of amniotic fluid showed a positive result in 66.6% of cases, which is important in predicting.

5. Ultrasound examination of the cervix at a gestational age of 30-34 weeks (shortening of the cervix less than 28 mm) is an informative method for the diagnosis of preterm labor along with laboratory research methods.

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