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A B S T R A C T

of the dissertation for the degree of Doctor of Philosophy

THE IMMUNOPATHOGENETIC MECHANISM OF RETROCHORIAL HEMATOMA FORMATION AS A PREDICTOR OF PREGNANCY COMPLICATIONS

Speciality:	3215.01 - Obstetrics and gynecology
Field of science:	Medicine
Applicant:	**Nayila Ahmadaga Azizova**

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The dissertation work was conducted at the Scientific Research Institute of Maternal and Child Health and at the Republican Clinical Hospital named after Academician M. Mirqasimov.

Scientific supervisor: Doctor of Medical Sciences, Professor
Jamila Fazil Gurbanova

Official opponents: Doctor of Medical Sciences, Professor
Shayman Hasanali Gadimova

Doctor of Medical Sciences, Professor
Leyla Musa Rzaguliyeva

Doctor of Medical Sciences, ass.prof.
Konul Galib Garayeva

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Saadat Hasan Sultanova

GENERAL CHARACTERISTICS OF THE WORK

The actuality of the subject. One of the most pressing issues in modern obstetrics is early reproductive loss during the early stages of gestation.[1;2;3;4] At this stage, the fetoplacental system forms, laying the foundation for the fetus's tissues and organs, and extraembryonic structures develop. All of these factors contribute to a successful pregnancy. Retrochorial hematoma that occurs in the first trimester can worsen the prognosis of pregnancy, posing a risk of miscarriage.

The risk level of pregnancy loss depends on the gestation period. In our country, investigating the international standards for "live birth" aimed at stimulating the system for protecting mothers and children in the fight against reproductive loss is of current interest. To develop personalized treatment programs for women exhibiting symptoms of retrochorial hematoma, such as abdominal pain and uterine bleeding, it is necessary to study the prognostic characteristics of the risk factors.

Retrochorial hematoma is a specific pathological condition that manifests as bleeding and blood accumulation in the retrochorial space during the first trimester of pregnancy. It accounts for 3.0-22.0% of all pregnancies and is the main cause of bleeding in the first trimester. In 5.2-29.5% of cases, retrochorial hematoma during pregnancy leads to a risk of miscarriage. The frequency of habitual pregnancy loss (or miscarriages) is 3.0-5.0%, with the risk of a desired pregnancy not reaching term increasing as the number of previous failures rises, reaching 35.0-38.0% after two prior miscarriages. It is known that up to 80.0% of previously unexplained causes

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[3]Dimitriadis, E., Menkhorst. E., Saito S. Recurrent pregnancy loss // Nat Rev Dis Primers., - 2020, -6(1), - p. 98.

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of habitual pregnancy loss are related to undetected immunological changes, and the chances of a successful outcome without treatment after three early miscarriages are 30.0%, dropping to 25.0% after four, and 5.0% after five miscarriages.[5;6]

The clinical significance of retrochorial hematoma as a predictor of pregnancy complications is debatable. There is extensive literature suggesting that retrochorial hematoma is a leading factor in the development of perinatal complications, such as spontaneous miscarriages, preterm births, intrauterine growth restriction (IUGR), preeclampsia, premature separation of a normally located placenta, and premature rupture of fetal membranes.[7] Considering this, retro-chorial hematoma can be assessed as a predictor of perinatal compli-cations.

It has recently been recognized that changes in immune hemostasis form the structure of gestational complications. Inflammatory processes activated due to an imbalance between pro-inflammatory and anti-inflammatory cytokines result in pathological conditions during pregnancy. In a physiological pregnancy, the synthesis of Th2-type cytokines activates the immune system, which, in turn, reduces gamma interferon (IFN-γ) and transforming growth factor-beta (TGF-β) while promoting the secretion of anti-inflammatory cytokines such as IL-2, IL-4, and IL-10. These cytokines affect lymphocytes in the decidual tissue, producing CD56+ NK cells and destroying the progesterone-induced blocking factor (PIBF), thus ensuring normal progesterone secretion and having an anti-abortive effect. Furthermore, IL-2 cytokine inactivates the prothrombinase enzyme, preventing hypercoagulation, thereby creating a favorable environment for fetal development.

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[6]Утробин, М.В., Юрьев С.Ю. Иммунологические и генетические изменения как предикторы потери беременности при формировании ретрохориальной гематомы в первом триместре // Acta Biomedica Scientifica (East Siberian Biomedical Journal), - 2018,- Т. 3, -№ 5, -С. 9-15.

[7]Hashem, A., Sarsam,S.D. The Impact of Incidental Ultrasound Finding of Subchorionic and Retroplacental Hematoma in Early Pregnancy // The Journal of Obstetrics and Gynecology of India, - 2019, - № 2, p. - 33-39

Conversely, an increase in Th1-type helper cells leads to the opposite scenario, where the activated pro-inflammatory IL-6 stimulates necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ). This situation results in an increase in the prothrombinase enzyme, which converts inactive prothrombin to active thrombin in endothelial cells. Subsequently, the resulting thrombin enhances the synthesis of the pro-inflammatory cytokine IL-13, leading to the destruction of polymorphonuclear leukocytes (PMNs) in endothelial cells. This cascade of events results in vascular ischemia and rupture.[8;9;10;11]

Overall, a localized and systemic thrombohemorrhagic syndrome emerges, worsening the course of pregnancy. Therefore, it is crucial to study in greater depth the obstetric and perinatal complications caused by chorionic pathology in the early stages of pregnancy. Current literature contains limited information on the immunopathogenesis of retrochorial hematoma during the first trimester. Thus, by understanding the immunopathogenesis of this reproductive loss, we can establish adequate and modern prevention measures. The main goal is to discover early markers of risk factors that complicate the course of pregnancy and develop treatment and preventive algorithms.[12;1314;15]

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[8] Султанова, Н.А., Негматуллаева М.Н. Клиническое значение ретрохо- риальной гематомы у беременных, имеющих факторы риска репродуктивных потерь // Журнал теоретической и клинической медицины, - 2021, - № 6-1, - с. 145-147.

[9]Михайлова, А.М. Генетические факторы тромбофилии в патогенезе структурных нарушений плаценты / А.М. Михайлова, О.Н. Куликова, Т.С. Будыкина, М.А. Чечнева, С.М. Захаров // Российский кардиологический журнал, - 2019, -Т. 24.,-№ 3S1, - С. 14b-15a.

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[12]Логинова, Ю.В., Абрамовских О.С. Анализ субпопуляционного состава Th-лимфоцитов в периферической крови у женщин с невынашиванием беременности // Российский иммунологический журнал, - 2018,- Т. 12, - № 3 (21),- с. 354-357.

The object and subject of the research. The study involved 210 pregnant women. Among them, 100 women with both retrochorial hematoma and signs of threatened miscarriage were included in the main group. In the comparison group, retrochorial hematoma was detected in 80 pregnant women, but no signs of threatened miscarriage were observed. The remaining 30 healthy pregnant women were included in the control group.

The purpose of the research work. The aim of the research is to identify the immunopathogenetic mechanisms involved in the formation of retrochorial hematoma, using clinical and laboratory evidence as a foundation, to develop an individualized approach for the prevention of perinatal complications in pregnant women.

Tasks of the study:

1. To study the clinical features of early reproductive loss and pregnancy complicated by retrochorial hematoma during the early reproductive period.
2. To identify risk factors for pregnancy loss in the early stages based on comprehensive clinical, laboratory, and instrumental examinations.
3. To evaluate the Th1/Th2 ratio by studying cytokine markers associated with retrochorial hematoma in early pregnancy.
4. To establish a treatment algorithm based on the dynamic monitoring of cytokine levels with significant diagnostic and prognostic value during the first trimester of pregnancy.

Research methods:

The following examination methods were applied in the dissertation work: clinical-anamnestic, general clinical, obstetric-gynecological,

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[13]Robertson, S. A. Embryotoxic cytokines-potential roles in embryo loss and fetal programming / S. A. Robertson, P. Y. Chin, J. G. Femia, H. M. J. Brown // Reprod. Immunol., - 2018, -125, - p. 80-88.

[14]Макацария А.Д., Бицадзе В.О., Акиньшина С.В., Андреева М.Д. Патогенез и профилактика осложнений беременности, обусловленных тромботической микроангиопатией // Вопросы гинекологии, акушерства и перинатологии. 2013; 12 (6): - с. 63-73.

[15]Мамедова, С.Н. Последствия факторов высокого риска перинатальной потери на фоне предшествующих искусственных абортов и применения контрацептивных средств // - Bakı: Sağlamlıq. Elmi-praktik jurnal. 2016, №2, - s. 68-73

ultrasound inspection of the small pelvis (USI). Laboratory tests include: peripheral blood indicators, hemostasis system analysis (blood coagulation time, prothrombin index, plasma recalcification time, blood clot retraction, fibrinogen content, thrombotest, hematocrit), cytokine status study (IL-2, IL-6, IL10, IL-13, IL-17).

The main provisions of the thesis defended:

- It is imperative to assess the clinical-anamnestic, hemostasiological and immunological risk factors in the development of retrochorial hematoma during early pregnancy.
- Unsatisfactory prognostic ultrasound signs: appearance of retrochorial hematoma up to the 6th week of pregnancy (11.0%), delay of the umbilical cord measurement (UCM) for 7 days or more (28.0%), hematoma corporal localization (74.0%) and it's large volume (27.0%), impaired uterine blood cir-culation (60.0%).
- In patients with retrochorial hematoma, immunological disturbance of the immune system resulting in the predominance of the Th 1/Th 2 pro-inflammatory fraction cytokine imbalance.
- The prognostic significance of IL-13 > 20.3 pg/ml in the development of retrochorial hematoma and risk of miscarriage during early pregnancy.

Scientific novelty of the research.

- The immunopathogenetic mechanism of retrochorial hematoma formation as a predictor of early reproductive loss was studied.
- Based on the study of Th 1/Th 2 cytokine status, the importance of cytokines in the development of retrochorial hematoma during early pregnancy was studied.
- Pro-inflammatory (IL-6, IL-13, IL-17) and anti-inflammatory (IL-2, IL-10) cytokines were determined in the blood serum of pregnant women with retrochorial hematoma and their inter-system relationship was shown.
- Based on the obtained results, immunozed, an immunostimulating drug, was applied to the complex therapy.

Practical significance of research.

- The clinical and laboratory risk signs for the development of retrochorial hematoma during early pregnancy are: history of retrochorial hematoma, history of antiphospholipid syndrome,

impaired uterine blood circulation and serum IL-13 level higher than 20.3 pg/ml to be

- Creating an algorithm for predicting the development of retrochorial hematoma based on the results of the analysis, thereby developing the principles of an individual approach to high-risk early reproductive losses during pregnancy.

Approval of work. Separate fragments of the dissertation were discussed in the following scientific-practicalmeetings:IX Международная научно-практическая конференция «передовое развитие современной науки: опыт, проблемы, прогнозы» (17 октября 2022 г., Российская Федерация, г.Петрозаводск.); Международный форум «Наука и инновации – современные концепции»тема доклада «особенности эхографических параметров развития эмбриона при формировании ретрохориальной гематомы на ранних сроках беременности» (21 октября 2022г.,г.Москва).

The preliminary discussion of the dissertation was reported at the Scientific Research Institute of Obstetrics and Gynecology on December 16, 2022 at meeting No. 13. At the meeting, "Gynecology", "Obstetrics", "I Obstetrics", "Pathology of pregnancy", "Analytical medical information", "Reproductive health", "Neonatology", "Polyclinic" departments of "ETMGI" PHS Employees of the "Medical Genetics" laboratory, "Obstetrics and Gynecology" of ASATID named after A. Aliyev and I Department of Obstetrics and Gynecology of ATU participated.

The results of the research were also presented at the scientific seminar of the Dissertation Council ED 2.06 (09.02.2024, protocol No9), where they were reported and discussed.

Published scientific works: The main propositions and findings of the dissertation were published in 7 journal articles (including 3 published internationally) and 3 conference abstracts (including 2 presented internationally).

Application of work in practice: The results of the study are utilized in the daily practice of the Scientific Research Institute of Obstetrics and Gynecology, as well as at the Republican Clinical Hospital named after Academician M.Mirgasimov. In addition, the scientific data obtained from ultrasound examinations, as well as

clinical, laboratory, and instrumental studies, are incorporated into the educational process.

The organization where the dissertation work was performed. The dissertation research was conducted at the Scientific Research Institute of Obstetrics and Gynecology and at the Respublican Clinical Hospital named after Academician M. Mirga-simov.

The scope and structure of the dissertation work. The thesis is written on 159 pages printed on a computer, "Table of Contents", "Introduction" (volume: 12482 characters), research results 4 chapters, "Conclusion" (volume: 15251 characters), "Results" (volume: 1594 characters), It consists of "Practical recommendations" (volume: 733 marks) and "Literature list" sections.

The main content of the dissertation is divided into 6 chapters: Chapter I "Literature review. Retrochorial hematoma is a problem of modern obstetrics" (volume: 48023 marks), Chapter II. "Materials and methods" (volume: 7564 marks), Chapter III. "Clinical and anamnestic features of pregnancy with retrochorial hematoma" (volume: 30626 marks), Chapter IV."Characteristics of EXO and clinical-laboratory examinations in pregnant women with risk of miscarriage as a result of retrochorial hematoma during early pregnancy" (volume: 24405 marks), Chapter V. "In pregnant women with retrochorial hematoma during early pregnancy and risk of miscarriage" cytokine indicators" (volume: 13546 characters), chapter VI. "Danger of miscarriage and prediction of reproductive losses in pregnant women with retrochorial hematoma" (volume: 16292 marks).

310 literary sources were used in the writing of the dissertation, 21 of them are in Azerbaijani, 143 Russian and 146 foreign scholars. The dissertation work is documented with 48 tables, 5 diagrams, 6 pictures, 1 scheme.

The total volume of the dissertation with signs (excluding spaces, title page, table of contents, tables, diagrams, bibliography and abbreviated terms) consists of 170516 signs.

MATERIALS AND METHODS OF RESEARCH

This dissertation study was conducted at the base of the Scientific-Research Institute of Obstetrics and Gynecology of the

Ministry of Health ofAzerbaijan Republic, Republican Clinical Hospital named after Academician Mirqasimov.

Forachieving the goal, 210 pregnant women were studied. Clinical, laboratory and instrumental methods are included in complex examinations. The age of the studied women is around 16-42 and corresponds to the reproductive period.

Women were divided into two groups according to the results of the ultrasound examination. 100 pregnant women who were at risk of miscarriage and were diagnosed with retrochorial hematoma by ultrasound were assigned to the main group (n=100). Although 80 pregnant women included in the control group had signs of miscarriage, retrochorial hematoma was not confirmed by ultrasound examination (n=80). The control group consisted of 30 women with a physiological course of pregnancy (n=30).

The main classification criterion is the determination of retrochorial hematoma by ultrasound examination. According to the following criteria, pregnant women were included in the main group:

– pregnancyperiod 6-12 weeks
– riskofmiscarriage
– retroxorial hematomanın olması.

The control group inclusion parameters are as follows:

– pregnancy period 6-12 weeks
– risk of miscarriage
– absenceofretrochorialhematoma.

The control group inclusion parameters are as follows:

– pregnancyperiod 6-12 weeks
– there are no signs of miscarriage
– no retrochorial hematoma.

These criteria were not considered for pregnant women in all groups:

– women becoming pregnant through assisted reproductive technology
– multiple pregnancy
– termination of pregnancy on medical advice
– period of exacerbation of acute and chronic inflammatory processes
– decompensated extragenital pathology.

FMA, bleeding from the uterus, and retrochorial hematoma detected by ultrasound are generally accepted criteria for the reason for referral to a doctor. Obstetric anamnesis is collected from applying women, reproductive function is studied, the presence of extragenital diseases is studied, and the diagnosis is made according to the international classification of diseases (XBT-10). When conducting the research, it is necessary to adhere to the ethnic principles of the World Medical Association Declaration of Helsinki (1964, 2000).

Research methods. Used: clinical, obstetric-gynecological, ultrasound, general, biochemical, hemostasis system, cytokine system research, statistical method.

Clinical research is based on menstruation, reproductive function, somatic and gynecological anamnesis of pregnant women. When collecting an obstetric gynecological anamnesis, it is necessary to pay special attention to the age of menarche, the characteristics of the menstrual function, the age of coitus, the number of sexual partners, methods of contraception, the time of the first pregnancy, gynecological diseases, surgical interventions, postoperative or anesthetic complications. When collecting reproductive anamnesis, the number of pregnancies, termination results, medical abortions, spontaneous abortions, non-developing pregnancies, and their termination should be carefully examined. In addition, the course of pregnancy should be evaluated in term, way, and perinatal outcomes.

Laboratory research refers to: The pregnant women in the study had a general analysis of blood (together with the formative element and leukoformula), coagulogram (prothrombin time, prothrombin index, INR, fibrinogen, coagulation time), vitamin D, HBV, HSV, ureaplasma, mycoplasma, SMV, Rubella, herpes II in the blood. They were involved in laboratory examinations such as type of infection, TSH hormone, general analysis of urine. In all women, blood analysis was taken in the morning, on an empty stomach, in a sitting position, in the amount of 8 ml from the elbow vein in a vacuum test tube. 40 min at room temperature. after exposure, 10 min to collect blood serum. 1 500 cycles/min. Centrifuged. The received serum was frozen in a special cooler - 60 Celsius. Peripheral blood circulation indicators met all clinical and hematological examination requirements. These examinations were carried out with the STAT FAX machine.

Study of hemostasis. 3.8% sodium citrate in blood was taken from the patient in a VACUETTE vacuum tube. Here, the ratio of blood to sodium citrate solution is 9÷1. Blood coagulation time, prothrombin index, plasma recalcification time, blood clot retraction, fibrinogen amount, thrombotest, hematocrit were analyzed by analyzing the blood coagulation system.

10×10/1 000 tests of human thromboplastin were used to study the hemostasis parameter. Ingredients: human placental thromboplastin, calcium chloride, stabilizers; preservatives: 5-chloro-2-methyl-4-isothiazol-3-OH and 2-methyl-4-isothiazol-3-OH (max 20mg/l).

The study of cytokines. The level of IL-2, IL-6, IL-10, IL-13, IL-17 cytokines in blood serum was investigated by immunoenzymatic method in a semi-automatic analyzer.

Medical ultrasound examination. During the first visit, all pregnant women underwent ultrasound examination (VOLUSON E 10, USA). This device with transvaginal and transabdominal sensors works in impulse and color doppler mode. By means of ultrasound examination, chorion rupture, retrochorial hematoma (size and localization), embryo development (the size of the crest-fold, fetal heart rate and its frequency), the diameter of the yolk sac, the amniotic cavity, the cervix in the first trimester the size, condition of the cervical canal and internal sphincter, corpus luteum are studied.

An ultrasound examination sign of retrochorial hematoma is detachment of the chorion from the uterine wall. At this time, the ultrasound examination reveals a hypoechoic (new hematoma) or hyperechoic (stabilization and regression of the hematoma) area on the periphery of the fetal egg between the decidual membrane and the chorion. With this examination, the localization, volume and structure of the hematoma are known.

Statistical examination method. I carried out the statistical work on my personal computer called IBM PC/AT with Statistica 10.0 and IBM SPSS Statistics 23 software.

Clinical and laboratory examination methods were collected using Excel software. Algebraic mean (M) and standard errors (m) were determined. According to Kolmogorova-Smirnova criteria, indicators were analyzed as normal. Non-parametric criteria were also used in these examinations. Mann-Whitney non-parametric test and Kraskell-

Wilson criterion were used for comparison. Statistically significant factors were evaluated by means of X2 Pearson's criterion. At this time, the Yets correction was also used. Correlation analysis was performed using Spearman's method.

Clinical informativeness was calculated with a four-pole 2x2 table. Diagnostic test: sensitivity (Se), specificity (Sp), diagnostic effect test (Acc), positive result prognostic value (PPV), negative result prognostic value (NPV), positive result relative flatness (PLR), negative result relative flatness (NLR), relative diagnostic chance (DOR), Youden's index (J), prognostic arch index (PSI) were investigated. Tables were used to examine relative risk: relative risk (RR) and 95% two-sided confidence interval (CI). Calculations were made according to the formula RR-[A×D]/[B×C]. Here, A and B are the presence of signs, and C and D are their absence. $P<0.05$ is the result of statistical analysis.

CLINIKAL AND ANAMNESTIK CHARACTERISTICS OF PREGNANT WOMEN WITH RETROCHORIAL HEMATOMA

The age of the patients involved in the study varies from 16 to 42 years (mean – 27.7±0.3 years) (95% CI: 27.1 to 28.3 years). Most of the pregnant women live in the city (n=127; 60.5%) and the rest (n=83; 39.5%) live in the village.

Body weight index was 27.4±0.6kg/m2 (95% CI: 26.3 - 28.6kg/m2) in pregnant women who were not diagnosed with retrochorial hematoma and risk of miscarriage. Body mass index in pregnant women diagnosed with miscarriage and retrochorial hematoma was 29.0±0.6 kg/m2 (95% CI: 27.8 - 30.3 kg/m2). In the control group, this figure was 29.4±0.8 kg/m2 (95% CI: 27.7 - 31.1 kg/m2).

The index of somatic diseases was high in all groups, and the largest number was 77 (77.0%) in the main group. This figure is 58 (72.5%) in the control group, 17 (56.7%) in the control group. 97 (97.0%) women from the main group, 79 (98.8%) from the control group, 29 (96.7%) from the control group had a number of infectious diseases in childhood. The incidence of surgical operations is 55.0% (n=55) in the main group, 41.3% (n=33) in the control group, and 50.0% (n=15) in the control group.

When collecting gynecological anamnesis, it is known that the most basic are 35 (35.0%) gynecological diseases in the group. This

type of pathology is 20.0% (n=12) of undiagnosed retrochorial hematoma. 15.0% (n=6) of pregnant women in the control group had gynecological diseases. 81 (81.0%) of the main group, 64 (80.0%) of the control group, and 24 (80.0%) of the patients had no pathology detected in their menstrual function..

During the study, when collecting the family anamnesis of thrombosis, it was found that this pathology was not detected in 30 (100.0%) patients from the control group, 79 (98.8%) from the control group, and 100 (100.0%) from the main group. Also, none of the pregnant women in the study had hereditary thrombophilia. When analyzing venous thromboses from pregnancy, venous thrombosis was detected in 14 (46.7%) women in the control group, 9 (11.3%) in the control group, and 11 (11.0%) in the main group. 7 (23.3%) of the control group, 27 (33.7%) of the control group and 80 (80.0%) of the main group had a history of pregnancy with retrochorial hematoma. 6 (20.0%) of the control group, 19 (23.8%) of the control group, and 65 (65.0%) of the main group suffer from antiphospholipid syndrome.

When collecting obstetric anamnesis, 8 (26.7%) women from the control group, 14 (17.0%) from the control group, and 31 (31.0%) from the main group had a primary pregnancy. Repeat pregnancy is 69 (69.0%) in the main group, 66 (82.5%) in the control group, 22 (73.3%) in the control group. There were 8 (26.7%) women in the control group, 15 (18.8%) women in the control group, and 33 (33.0%) women in the main group. Repeated births occurred in 22 (73.3%) women from the control group, 65 (81.3%) from the control group, and 62 (62.0%) from the main group. A history of abortions was reflected in 8 (26.7%) women in the control group, 18 (22.5%) in the control group, and 62 (62.0%) in the main group. 30 (100.0%) of the control group, 78 (97.5%) of the control group and 100 (100.0%) of the main group did not experience infertility.8 (26.7%) women in the control group, 18 (22.5%) in the control group and 54 (54.0%) in the main group had a preterm pregnancy. Ectopic pregnancy was recorded in only 1 (1.0%) woman from the main group. Anamnesis of early reproductive loss was confirmed in 1 (1.3%) patients from the control group and 6 (6.0%) patients from the main group. In the anamnesis, antenatal death was shown in 1 (1.3%) woman from the control group and 2 (2.0%) women from the main group. In the past, perinatal loss was confirmed in 1

(1.3%) woman from the control group and 1 (1.0%) woman from the main group. When confirming the course of pregnancy in these women, it was found that 2 (6.7%) of the control group, 9 (11.3%) of the control group, and 11 (11.0%) of the main group had premature natural birth with a live fetus. 2 (6.7%) of the control group, 9 (11.2%) of the control group, and 22 (22.0%) of the main group had premature pregnancies with live fetuses.

Thus, during the comparative analysis of somatic and obstetric anamnesis, it was possible to detect potential risk signs in early pregnancy.

Clinical and laboratory characteristics of pregnant women with risk of miscarriage and retrochorial hematoma in the first trimester.

The reasons for admission to the doctor at 3-16 weeks of pregnancy (mean-8.0±0.2 weeks) (95% CI: 7.6-8.4 weeks) were complicated obstetrics, bloody discharge from the uterus, dull pain in the lower abdomen. He went to the doctor with his complaint, and during the examination, a hematoma was detected by ultrasound examination. All examined pregnant women had clinical signs of miscarriage. 85.0% of pregnant women with retrochorial hematoma in the main group suffered from pain syndrome, 71.0% from increased uterine tone, and 42.0% from epizootic bleeding from the uterus.In the control group of pregnant women who are at risk of miscarriage but without retrochorial hematoma, the pain syndrome is 86.3%, increased uterine tone is 77.5%, uterine bleeding is 46.3%. During examination, the shortening of the cervix in the main group of pregnant women is 26 (26.0%) and the expansion of the external cervix is 18 (18.0%). In the control group, 22 (27.5%) had a shortening of the cervix, 15 (18.8%) had an expansion of the external yaw.No special difference was found in the clinical form of the pregnant women in these two groups with a risk of miscarriage in the first trimester (PP>0.05). During the MUS examination, a marker of the risk of miscarriage was detected in both the main group and the control group. Pregnant women in the control group underwent MUS at 4-13 weeks (mean-7.4±0.4 weeks) (95.0% CI: 6.6-8.3 weeks). In the control group, at 4–16 weeks (mean–7.8±0.3 weeks) of hetasia (95.0% CI: 7.1–8.4 weeks). In the main group, at 3–14 weeks of gestation (mean–8.3±0.3 weeks) (95.0% CI: 7.8–8.8 weeks). In the main group, retrochorial hematoma was detected in 13

(13.0%) women before 6 weeks, and in 87 (87.0%) women after 6 weeks.

In the control group, in 80.0% of cases (24 out of 30 pregnant women), the chorion is detected at the bottom of the uterus. In the main group, 55.0% (55 out of 100 pregnant women) and in 75.0% (60 out of 80 pregnant women) of the control group, the chorion is localized at the bottom of the uterus.

From the control group, 6.7% (n=2) chorion is localized in the front wall of the uterus, 10.0% (n=3) chorion is located in the back wall of the uterus, 3.3% (n=1) is located at the level of the chorion including the chorion. In the control group, 10.0% (n=8) anterior, 13.8% (n=11) posterior, 1.3% (n=1) chorion was located at the level of the internal iliac crest. In the main group, the chorion is localized in 8.0% (n=8) of the front wall of the uterus, 31.0% (n=31) in the back wall, and 6.0% (n=6) at the level of the internal gap.

The next echographic feature is the structure of the chorion. None of these pregnant women in the control group underwent structural changes 30 (100.0%). In the control group, chorionic structure was normal in 78 (97.5%) patients, and fragmented in 2 (2.5%) pregnant women. Of the main group, 95 (95.0%) pregnant women had unchanged chorion, while 5 (5.0%) pregnant women had fragmented ($p>0.05$).

Jaundice sac was visualized in 6 (20.0%) of the control group, 19 (23.8%) of the control group, 9 (9.0%) of the main group. In the control group - 28.6±4.0 mm (95.0% CI: 20.4–36.8 mm), in the control group - 27.9±2.9 mm (95.0% CI: 22.1– 33.7 mm), in the main group – 38.9±2.3 mm (95.0% CI: 34.4–43.5 mm) mean internal diameter of the yolk sac.

In all pregnant women in the main group, retro-chorial hematoma of different localization was detected by ultrasound examination. The most frequent corporal variant was 74.0% (in 74 out of 100 pregnant women).

The smallest volume hematoma was found in the main group, 73.0% (73 out of 100 patients). In the main group, 27.0% of pregnant women have a large retrochorial hematoma). By determining the Spearman coefficient, it is possible to distinguish between a routine abortion and the localization of a hematoma correlation is confirmed ($r_s=0.260$; $p=0.009$).Based on the results of the analysis, 22 (33.8%) pregnant women with large volume hematoma also had antiphospho-

lipid syndrome (AFS) (χ^2=4.416; p=0.036). Determination of Spearman's coefficient shows a correct correlation between anti-phospholipid syndrome and large volume hematoma (rs=0.210; p=0.036).

When studying the structural characteristics of retrochorial hematoma, in the main group, 94 (94.0%) patients were identified as an anoxogenic derivative, and 6 (6.0%) patients were identified as non-organizing. In the main group, 75.0% (n=21) of pregnant women have corporal localized hematoma, and 21.0% (n=7) have supracervical localized hematoma. As a result of retardation of intrauterine development of the fetus, 39.3% (n=11) of women have a large hematoma, which shows the reduction of the size of the umbilical cord. 17 (60.7%) women have small hematoma. In 27 (96.4%) women, the decrease in the size of the folds of the nipple is manifested by an organized hematoma, and in 1 (3.6%) woman by an unorganized hematoma. Uterine circulation of all pregnant women in the control group is normal. In the control group, uterine blood circulation was normal in 49 (62.8%) women, and impaired in 29 (37.2%) women. In the main group with retrochorial hematoma, uterine blood circulation was disturbed in 60 (60.0%) women, and not disturbed in 40 (40.0%) women (χ^2=35.541; p=0.000). 28 (48.3%) women have normal uterine blood circulation, 30 (51.7%) have impaired uterine blood circulation due to a reduction in the size of the folds.

If the retrochorial hematoma has a large corporal localization and the reduction in the size of the umbilical cord, which occurs up to the 6th week of pregnancy, is observed with a violation of uterine blood circulation, the outcome of the pregnancy will be more severe.

The clinical-pathogenetic picture obtained during pregnancy pathology corresponds to the laboratory results. Hemo-globin (Hb) (PK/A=0.000), color indicator (PK/A=0.000), leukocyte level (WBC) (PK/A=0.003) in the main group and the control group, ac-cording to EHS (PK/A=0.047) is a statistical difference. When comparing statistically between control and control group, hemo-globin level (PK/N=0.015), erythrocyte (RBC) level (PK/N= 0.002), color index (PK/N=0.000), leukocyte (WBC) level (PK/N =0.002), the EHS indicator is (PK/N=0.020).

Clinical symptoms of the development of retrochorial hematoma in pregnant women in the main group are observed with the following

changes in the hemostasis system. Blood coagulation time is shortened (6.3±0.1 min. vs. (7.4±0.2 min., p=0.000), prothrombin index increases (106.1±1.2% vs. 99.4±1.1 %, p=0.000), increased plasma recalcification time (222.9±5.4s vs. 181.9±5.6s, p=0.000), increased blood clot retraction (0.449±0.011 vs. 0.381± 0.010, p=0.000), increased fibrinogen (4.06±0.09g/l vs. 3.58±0.10g/l, p=0.000), increased hematocrit indicator (62.0±0.5% vs. 60.1±0 .7%, p=0.039). It turned out that in pregnant women with retrochorial hematoma, the coagulogram changes towards blood clotting. An increase in blood coagulation time, an increase in the prothrombin index and fibrinogen against the background of an elevated hematocrit confirm hypercoagulation.

The amount of vitamin D studied in blood concentration ranges from 3.5 to 85.0 ng/ml. The amount of vitamin D in both the control and the main group varies around 21-29 ng/ml. The amount of TSH in the blood was 5.72±0.31mME/l in the main group, 4.67±0.34 mME/l in the control group, and 4.04±0.33mME/l in the control group.

Based on the obtained results, when comparing the control group and the main group: protein in urine (PK/A=0.015), bacteria in urine (PK/A=0.000), mucus in urine (PK/A=0.005), epithelial cells in urine (PK/A=0.023), leukoside in urine (PK/A=0.005). When com-paring the control group with the control group: protein in urine (PK/N=0.042), erythroside in urine (PK/N= 0.014), bacteria in urine (PK/N=0.004), mucus in urine (PK/N=0.000), leukoside in urine (PK/N=0.006). According to statistical indicators, the main group is different from the control group in terms of mucus in urine (PN/A=0.012).

INDICATORS OF CYTOKINE STATUS IN PREGNANT WOMEN WITH HEMATOMA AND RISK OF MISCARRIAGE

The study of pro-inflammatory and anti-inflammatory cytokine ratio is physiological and pathology was studied in pregnant women.

When admitted to the hospital, it was found that unlike pregnant women in the control group, the levels of pro-inflammatory IL-6, IL-13, IL-17 cytokines were higher in pregnant women at risk of miscarriage.

The level of IL-6 in blood serum of pregnant women in the control group was 21.2±0.5 pg/ml (PK/N=0.000). The level of IL-6 in the blood serum of pregnant women in the main group with retro-chorial hematoma was higher than of the control group, 22.0±0.5 pg/ml (PK/A=0.000), but there was no significant difference with the control group (PN/A= 0.142).

The level of IL-13 in the control group was 19.5±0.5 pg/ml (PK/N= 0.000). The level of IL-13 in pregnant women in the main group was higher and was 21.2±0.5 pg/ml (PK/A=0.000) and different from the control group (PN/A=0.008). When studying IL-17 in blood serum, in contrast to the control group, the average amount of cytokine in the control group is 1.458±0.021 pg/ml (PK/N=0.000). The level of IL-17 in pregnant women in the main group was 1,496±0,046 pg/ml and was different from the control group (PK/A=0,000) and did not differ from the control group (PN/A=0,544).

Among the anti-inflammatory cytokines, IL-2 and IL-10 were studied. Although it was 8.20±0.12 pg/ml higher than the control group in the control group, it was not statistically different (PK/N=0.481). In the main group, this indicator was 8.75±0.29 pg/ml (PK/A=0.352). The amount of IL-10 in the supervision group was 1.1 times higher than the control group and was on average 4.30±0.10 pg/ml (PK/N=0.011). IL-10 cytokine in the main group was 1.2 times higher than in the control group and was on average 4.54±0.15 pg/ml (PK/A=0.013).

If a disorder in the cytokine system is detected, beta glucan preparation in a dose of 180 mg was prescribed to the patients in both the main and supervision groups for the purpose of treatment. In addition to the immunostimulating drug, hestogens (duphaston) were prescribed to pregnant women with a risk of miscarriage.In the supervision group, one month after the complex treatment, the laboratory indicators differed significantly from the indicators before the treatment: the amount of IL-6 decreased by 1.6 times (p=0.000), IL-13 decreased by 1.5 times (p=0.000), IL-17- also decreased by 1.6 times. During dynamic treatment, the amount of IL-2 and IL-10 in blood serum practically did not change. Although positive clinical results were obtained during complex treatment in pregnant women in the main

group, the amount of IL-6, IL-13 and IL-17 did not reach the norm.During the comparison, Year-6 decreased by 1.2 times (p=0.000), Year-13 by 1.2 times (p=0.000), and Year-17 by 1.2 times (p=0.000). During the dynamic treatment, the amount of Il-2 in the blood serum practically changed little, while the level of IL-10 remained high. The reduction of the pro-inflammatory cytokine fraction led to the activation of reparative processes. Based on the received treatment results, we can say that the anti-inflammatory IL-2 and IL-10 cytokines increase the amount of Th2, while the amount of pro-inflammatory cytokines IL-6, IL-13 and IL-17 decreases, the amount of Th1 also decreases. When calculating the coefficient of Spearman's correlation, a linear relationship was determined between IL-2 and IL-6 ($rs=0.203$; $p=0.05$), between IL-2 and IL-10 ($rs=0.411$; $p<0.01$), IL- There is a positive correlation between 6 and 13 years ($rs=0.270$; $p<0.01$). There is an inverse relationship between the years 10 and 17 ($rs=0.221$; $p<0.05$) according to the Spearman correlation coefficient.

RISK OF THE MISCARRIAGE AND PREDICTION OF EARLY REPRODUCTIVE LOSS IN PREGNANT WOMEN WITH RETROCHORIAL HEMATOMA

In order to reveal the role of clinical and anamnestic indicators in the formation of the miscarriage risk during early pregnancy, the following indicators were studied in the supervisiongroup: relative risk indicator, reliable border interval, relative risk release, risk difference, specificity and sensitivity.

During the first-stage analysis, a prognostic model was created by collecting 14 clinical and anamnestic symptoms. From the 14 studied characteristics, only two have prognostic value: the presence of retrochorial hematoma in the mother (RR=1.23) and habitual abortions (RR=1.30). During the study, this prognostic model reflected 4 echographic signs. Only one of them has prognostic significance: impaired uterine circulation (RR=1.33). The sign of retrochorial hematoma in the anamnesis has the following high indicators: sensitivity (59.4±3.3), diagnostic efficacy test (61.9± 3.3%), flat rate of positive result (2.55) and diagnostic odds ratio (4 .82±0.07). Habitual abortions in the anamnesis have indicators such as high specificity (100.0±3.3%) and

prognostic assessment of a positive result (100.0±7.8%). High specificity in disturbed uterine cycle (100.0±3.5%), prognostic evaluation of positive result (100.0±7.3%), negative evaluation of result (24.7±1.3%), Youden index (0.490) and the prognostic arch index is (0.247).

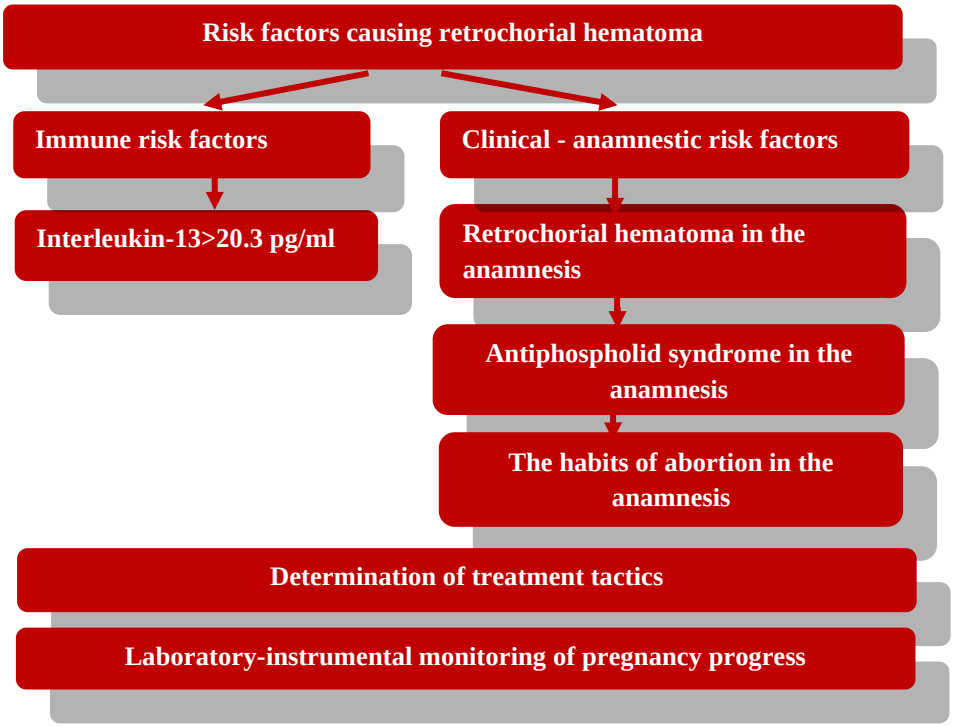
In the second stage, the risk factors of miscarriage in pregnant women with retrochorial hematoma were studied. During this analysis, the symptoms that caused complications in the mother-nez were reviewed again (according to Pearson and Kruskal-Wallis symptoms). Based on the analysis, a prognostic model reflecting 13 clinical and anamnestic symptoms was discovered. Only four of them have great prognostic value:Special attention is paid to retrochorial hematoma, antiphospholipid syndrome, abortion and miscarriage in the anamnesis. There are four echographic signs in the prognostic model we built. The most important of them are the following: disturbed uterine blood circulation (RR=1.50) and localization of the chorion at the level of the internal gap (RR=1.57). The sign of retrochorial hematoma in the anamnesis has the following high indicators: sensitivity (80.0±5.1%), diagnostic efficacy test (73.8±3.8%), prognostic value of a negative result (68.8±3, 2%), Youden's index (0.462) and the relative flattening result of the negative result (0.30).Relative flattening of the positive response in antiphospholipid syndrome in the anamnesis (2,74).

History of routine abortions had the following results: positive response prognostic value (96.7±6.3%), relative diagnostic chance (34.0±9.2%) and prognostic arch index (0.497). Specificity in the localization of the choroid at the level of the internal yawn is (98.8±6.6%) and the relative flatness of the positive response is (5.0). The percentage of hypersensitivity symptoms was as follows: history of retrochorial hematoma (80.0±5.1%), history of antiphospholipid syndrome (65.0±3.7%) and uterine circulatory disorder (60.0±3.6%).

IL-13, which was elevated among the cytokines we studied, has a high statistical significance. When studying the prognostic value of cytokines, it was found that it’s amount was very high in pregnant women in the main group with a risk of miscarriage. The prognosis of development of retrochorial hematoma in pregnant

women at risk of miscarriage depends on IL-13 in blood serum higher than 20.3 pg/ml.

A prognostic algorithm for pregnant women with retrochorial hematoma in the early period was developed by mathematically analyzing the risk factors. These factors include history of retrochorial hematoma, history of antiphospholipid syndrome, history of miscarriage, and interleukin-13 (Picture).



Picture. Prognostic algorithm of risks causing retrochorial hematoma during early pregnancy.

RESULTS

1. In studying the clinical course during the first trimester of pregnancy, retrochorial hematoma was detected in 69.0% of women with previous births, 33.0% of first-time pregnancies, 30.0% of cases with a history of habitual miscarriage, and 54.0% of non-viable pregnancies.

Among these groups, retrochorial hematoma was observed in 80.0% of pregnant women, 65.0% with antiphospholipid syndrome, 77.0% with various somatic diseases, and 35.0% with gynecological pathologies [1,2].

2. Unsatisfactory sonographic markers include retrochorial hematoma occurring before six weeks in 13.0% of cases, with corporal localization in 74.0%, hematoma volume in 27.0%, delayed organization process in 6.0%, delayed fetal growth in 28.0%, and impaired uterine arterial blood flow in 60.0%. In pregnancies with retrochorial hematoma, altered hemostasis indicators included a shortened blood clotting time (6.3±0.1 minutes, p=0.000), increased prothrombin index (106.1± 1.2%, p=0.000), prolonged plasma recalcification time (222.9±5.4 seconds, p=0.000), increased clot retraction (0.449±0.011, p=0.000), and elevated fibrinogen levels (4.06±0.09 g/L, p=0.000) [1,3,4,7].

3. Pregnant women with retrochorial hematoma showed elevated pro-inflammatory cytokines (IL-6=22.0±0.5 pg/ml, IL-13=21.2±0.5 pg/ml, IL-17=1.496±0.046 pg/ml) and reduced anti-inflammatory cytokines (IL-2=8.75±0.29 pg/ml, IL-10=4.54±0.15 pg/ml) in their blood serum. The resulting Th1/Th2 cytokine imbalance complicates the course of pregnancy in 85.0% of cases [6,9].

4. The prescribed treatment for pregnant women with significant prognostic risk factors (history of retrochorial hematoma, antiphospholipid syndrome, habitual miscarriages, or inter-leukin-13 levels above 20.2 pg/ml in the serum) prevented the threat of miscarriage in 97.5% of cases [1,5, 8,10].

PRACTICAL RECOMMENDATIONS

1. If retrochorial hematoma is detected during early pregnancy along with general clinical standard examinations, the blood circulation in the uterine arteries, localization of the hematoma, volume, biometric parameters of the embryo, CRL and heart activity should be studied by USM doppler.

2. In order to predict the development of retrochorial hematoma during early pregnancy, it is necessary to examine IL-13, which is a

predictor of the risk of miscarriage. At this time, it's amount in blood serum should be higher than 20.3 pg/ml.

3. It is necessary to predict the development of retrochorial hematoma during early pregnancy according to the developed algorithm. This algorithm was created by mathematical analysis of clinical-anamnestic and immune factors. By dealing with gestational complications in this way, we effectively prevent early reproductive loss.

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THE LIST OF CONDITIONAL ABBREVIATIONS

WHO	-	World Health Organization
BMI	-	Body mass index
IECS	-	Integral evaluation of the cytokine system
ME	-	Medical ultrasound
CI	-	confidence interval
İgA	-	immunoglobulin A
İgM	-	immunoglobulin M
İgG	-	immunoglobulin G
İL-6	-	interleukin 6
İL-13	-	interleukin 13
İL-17	-	interleukin 17
İL-2	-	interleukin 2
İL-10	-	interleukin 10
Th 1	-	Type 1 T helper
Th 2	-	Type 2 T helper
TSH	-	thyroin stimulating hormone
Se	-	həssaslıq
Sp	-	specificity
RR	-	relative risk
χ^2	-	“x square” criterion

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