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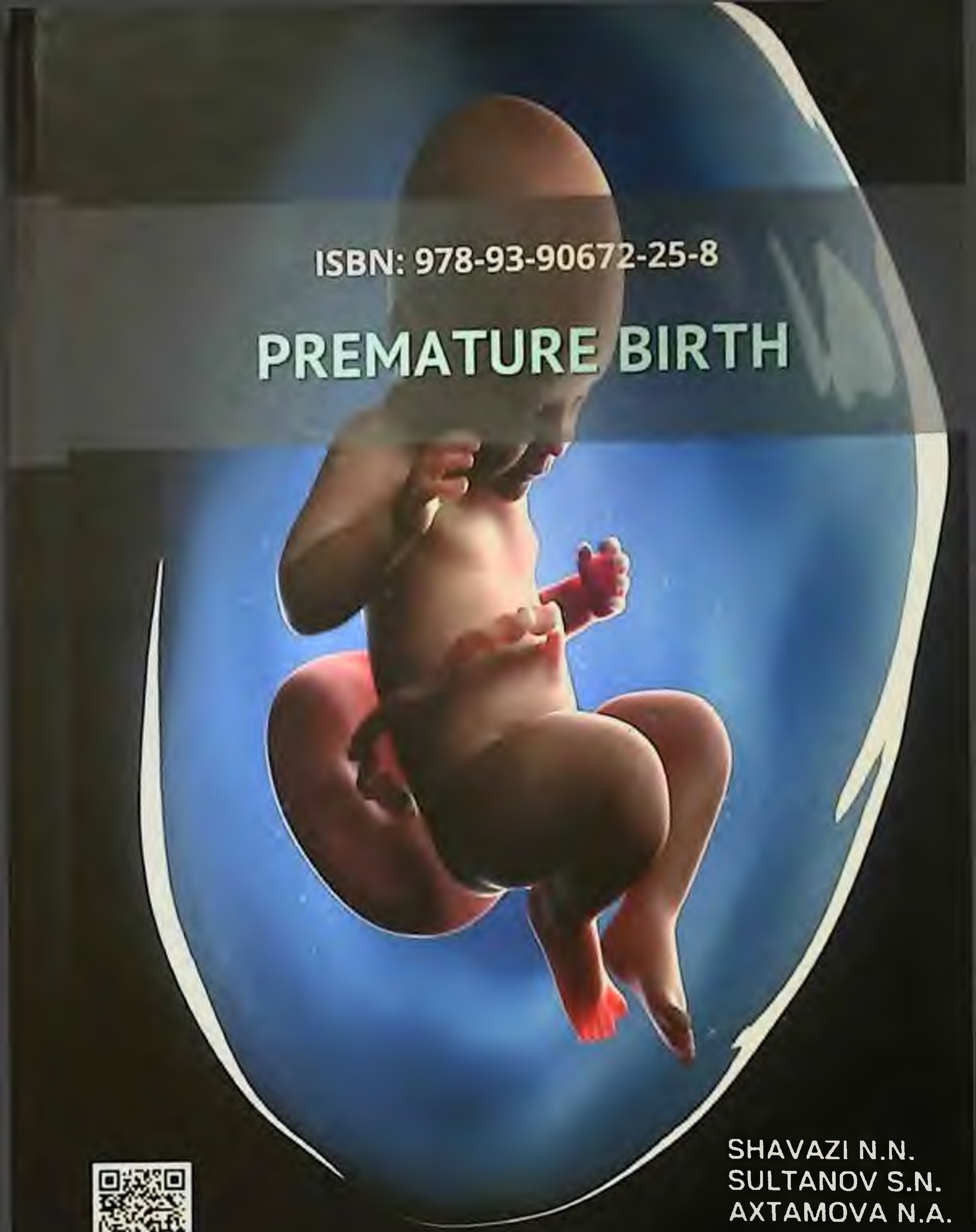
PREMATURE BIRTH



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The book summarizes clinical and laboratory predictors of the development of premature rupture of amniotic fluid. The results of scientific and practical research are presented, as well as our own clinical, instrumental and functional observations performed in a large contingent of pregnant women at risk of premature rupture of amniotic fluid. Issues of etiology, pathogenesis, anamnesis, complex diagnostics, prognosis and prevention are discussed. Methods for prognosis and prevention in pregnant women with the risk of developing premature rupture of amniotic fluid are summarized and recommended, a number of diagnostic and clinical examples from among their own observations are given.

The publication is intended for obstetricians, gynecologists, and doctors of related specialties.

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CONTENT

LIST OF ABBREVIATIONS

PIOV - premature rupture of amniotic fluid

PR - preterm birth

FFn - fetal fibronectin

SMC - smooth muscle cells of the vascular media

MMP - matrix metalloproteinases

TIMP - tissue inhibitors of metalloproteinases

C3 - complement component

LPO - lipid peroxidation

SICAM - soluble cell adhesion molecule

SVCAM - vascular cell adhesion molecule

NIP - rationing of intensive indicators

ELISA - enzyme immunoassay

MDA - malonic dialdehyde

DC - diene conjugate

CVD - cardiovascular disease

Foreword

Foreword

Premature rupture of amniotic fluid (PIOV) is a complication of pregnancy leading to preterm birth (PR), which is the most important problem for the protection of mother and child, as they determine the level of perinatal morbidity and mortality.

In developing countries, maternal mortality and morbidity are primarily caused by postpartum hemorrhage [8]. Approximately 14 million women worldwide experience bleeding after giving birth each year [4]. About 529,000 females each year are die due to complications during or after pregnancy, up to 30% of these deaths occur because of postpartum hemorrhage in the developing countries [9]. Therefore, heavy bleeding is the leading cause of maternal mortality worldwide. Research has been conducted to discover prenatal risk factors for postpartum hemorrhage and the underlying causes of this complication. Obstetrics textbooks often list multiple risk factors without specifying their relative importance or frequency. Several publications [5-7] discuss factors that influence postpartum hemorrhage. Postpartum hemorrhage is more common in vaginal births when certain factors are present, including nulliparasy, multiparasy, prolonged or enhanced labor, hypertension, episiotomy, and multiple pregnancy. In this study we aimed to identify the risk factors for acute postpartum hemorrhage in pregnant women.

More than 35-60% of cases of preterm birth, regardless of the characteristics of etiological factors, begin with premature rupture of the

membranes and untimely discharge of amniotic fluid. The presence of premature rupture of amniotic fluid (PIOV) during premature pregnancy, according to the World Health Organization, increases perinatal mortality by 4 times, the incidence of newborns by 3 times, and in 40-70% of cases is the cause of death of newborns.

In world practice, today, multicenter scientific studies are ongoing, aimed at revealing various aspects of this problem, and it is still unclear what is the mechanism of premature rupture of amniotic fluid. At the same time, the identification of risk factors and diagnostic criteria for the development of premature rupture of amniotic fluid is a prerequisite for the development of effective prognostic and preventive measures, taking into account social and ethical standards.

In recent years, large-scale measures for the early diagnosis and prevention of somatic diseases among the population have been carried out. Along with this, there are a number of unresolved problems in the healthcare system, among which the most important are the prognosis and prevention of premature rupture of amniotic fluid.

Based on this, it is currently important to study the cause of the development of premature rupture of amniotic fluid and preterm labor in women, it is important to conduct research aimed at improving the quality of life and reducing perinatal outcomes, which was the reason for the search for additional early informative biomarkers of premature rupture of amniotic fluid. and development of principles for early prognosis and prevention of this pathology.

The lack of modern monographs on the prediction of premature rupture of amniotic fluid is one of the reasons for the preservation of outdated ideas rooted in practice in the use of modern functional research methods.

The author of the monograph has been dealing with the pathogenesis, diagnosis and prevention of this pathology for a long time, and has set herself the task of highlighting its modern aspects. The book reflects the results of scientific research on the theoretical and practical issues of the development of premature rupture of amniotic fluid, which are compared with the generalized data of special literature, as well as the invaluable experience of the obstetric departments of hospitals in Samarkand, Samarkand State Medical University.

The author does not claim to be exhaustive of the provisions expressed in the book and admit that some of them may turn out to be

controversial, believing that this work will find its reader and will ultimately contribute to a further improvement in the quality of knowledge and skills of medical personnel.

INTRODUCTION

Introduction:

In modern obstetrics, the problem of premature rupture of amniotic fluid (PROM) is the most relevant due to the high risk of perinatal morbidity and mortality. According to the literature, up to 60% of preterm births, regardless of the characteristics of the etiological factors, begin with premature rupture of the membranes and untimely discharge of amniotic fluid.

Despite numerous studies devoted to this pathology, the relevance of the problem still remains in the attention of both domestic and foreign researchers.

The desire to improve maternal and perinatal outcomes has led to the search for additional early informative biomarkers in preterm pregnancy, the development of principles for early prediction and prevention, and this is what this book is devoted to.

CHAPTER I. CURRENT ASPECTS OF DIAGNOSTICS, PREVENTION AND RISK OF PREMATURE ROUTING OF FLUID IN PREGNANT WOMEN (REVIEW OF LITERATURE)

§1.1. Modern aspects of the etiology and pathogenesis of the development of premature rupture of amniotic fluid and premature birth.

Premature birth is a syndrome that can be caused by various factors, such as infection, cervical pathology, uterine overgrowth, progesterone deficiency, vascular changes (uteroplacental ischemia, decidual bleeding), maternal and fetal stress, allograft reaction, allergic phenomena, etc. there may be several other unknown factors. These different etiologies can lead to pathological activation of the common pathway of the decidual/fetal membranes, which causes contractility of the uterus, maturation of the cervix and rupture of the fetal membranes. Moreover, the mechanisms responsible for these processes, which include receptors, chemokines and inflammatory cytokines, have been identified. It is very important to understand the cellular and biochemical pathways responsible for premature birth, for timely detection, treatment and prevention of a negative outcome. Clinicians and researchers play a key role in improving the biochemical knowledge of preterm birth, identifying risk factors and developing interventions aimed at eliminating this complex syndrome.

Preterm birth is associated with approximately 75% of perinatal mortality and increased long-term morbidity. Of particular concern are strong associations with various neurological, mental, cognitive and behavioral consequences, including cerebral palsy, mental and cognitive impairments, sensory impairments, attention deficit hyperactivity disorder, schizophrenia, autism spectrum disorder and

epilepsy.Premature rupture of amniotic fluid (PIOV) is a complication of pregnancy characterized by a violation of the integrity of the membranes of the fetus and the rupture of amniotic fluid before the onset of labor, regardless of the gestational age. According to the literature, more than 35-60% of PR, regardless of the characteristics of etiological factors, begin with premature rupture of the membranes and untimely discharge of amniotic fluid [1, p.110; 2, p.56; 3, p.20; 4, p.26; 5, p.93; 6, p.49; 7, p.123; 8, p.17]. It is the most common cause of premature birth and severe complications in newborns. The presence of PIOV in preterm 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 [9, p.18; 10, p.14; 11, p.41; 12, p.38]. The main problem that determines the difficulties in the timely diagnosis of PIOV is due to the polyetiology of miscarriage [13, p.483; 14, p.57; 15, p. 452; 16, p.81; 17, p.30]. The cause of PIOV can be gene mutations and chromosomal disorders, hereditary predisposition, immune and endocrine disorders, infectious diseases, thrombophilic disorders, anatomical causes: malformations of the uterus, genital infantilism, uterine hypoplasia, isthmic-cervical insufficiency, uterine fibroids, synechia [18, p. .32; 19, p.30; 20, p.17; 21, p.14; 22, p.1; 23, p.137; 24, p.24]. According to the Lancet magazine (2021), miscarriage is usually defined as the loss of pregnancy to viability. It is estimated that 23 million miscarriages occur worldwide every year, resulting in 44 pregnancy losses every minute. The combined risk of miscarriage is 15·3% (95% CI 12·5-18·7 %) of all recognized pregnancies. The prevalence in the population of women who have suffered one miscarriage is 10·8% (10·3-11·4%), two miscarriages – 1·9% (1·8-2·1%), and three or more miscarriages – 0·7% (0·5-0·8%). Risk factors for miscarriage include very young or elderly women (under 20 and over 35), elderly men (over 40), very low or very high body mass index, black ethnicity, previous miscarriages, smoking, alcohol, stress, working night shifts, air pollution and exposure to pesticides. The consequences of miscarriage are both physical, such as bleeding or infection, and psychological. Psychological consequences include an increased risk of anxiety, depression, post-traumatic stress disorder, and suicide.

Miscarriage, and especially repeated miscarriage, is also a marker of the risk of obstetric complications, including premature birth, fetal growth restriction, placental abruption and stillbirth in future pregnancies, as well as a predictor of long-term health problems such as cardiovascular diseases and venous thromboembolism.

According to studies (Harrison MS, Muldrow M, Kirub E.2021), mothers who had prolonged labor had a 5 times higher chance of postpartum bleeding compared to normal delivery times. A similar conclusion was obtained from studies conducted in China, Pakistan and Cameroon. This may be due to the fact that prolonged labor causes uterine atony, which is the leading cause of postpartum hemorrhage. This meta-analysis also showed that the probability of postpartum hemorrhage among mothers who did not have prenatal follow-up was 9 times higher than their counterparts. This may be due to the fact that mothers can receive adequate information about institutional childbirth, as well as about the readiness for childbirth and the reddening of complications during visits (prenatal care) to the ANC, which can reduce the risk of postpartum bleeding.

The problem of premature rupture of amniotic fluid (PROM) is directly related to preterm birth (PR). Premature births are called births that occurred at a gestational age of 22 to 37 (259 days) weeks or births that occurred before 37 weeks [1, p.56; 12, p.38]. Most often (55.3%) preterm birth occurs at 34-37 weeks of pregnancy. The frequency of preterm births from the total number of births ranges from 5% to 12% of cases [8, p.17; 9, p.18; 10, p.14; 12, p.38; 25, p.9; 29, p.37; 35, p.99].

Preterm birth is characterized by multifactorial causes, among which it is conditionally possible to single out the causes associated with the body of the mother, fetus and combined.

Maternal factors: isthmic-cervical insufficiency, malformations of the uterus (one-horned, two-horned, etc.), general and genital infantilism, uterine fibroids, extragenital diseases of the mother (heart defects in the stage of decompensation,

hypertension, neuroendocrine diseases, etc.), infectious diseases of the mother (influenza, SARS, viral hepatitis, toxoplasmosis, listeriosis), amniotic fluid infection, bacterial vaginosis, herpes infection.

Fetal factors include malformations, developmental anomalies and fetal death, genetic diseases.

Combined factors: premature rupture of amniotic fluid, hypertensive disorders, isoserological incompatibility, antiphospholipid syndrome, anomalies of placental attachment, premature detachment of a normally located placenta, abnormal fetal positions, conditions leading to uterine hyperdistension (multiple pregnancy, some fetal malformations accompanied by polyhydramnios), bleeding during pregnancy, sepsis, intrauterine effects on the placenta, malformations and diseases of the cervix or body of the uterus and vagina [7, p.123]. Of all these PR factors, premature rupture of amniotic fluid (PIOV) is considered the most significant. PIOV is a rupture of the membranes before the onset of regular labor. Many authors call this condition "premature rupture of the membranes" (PROM), which corresponds to the term "premature erupture of membranes" adopted in Europe [12, p.38].

To understand the causes and earlier treatment of premature birth, rather than their consequences, the question of introducing markers of premature birth into clinical practice is being urgently raised. It is known that premature birth is accompanied by an imbalance of pro- and anti-angiogenic factors, which is, apparently, the result of the activity of certain alleles. With the progress of molecular biology, it became possible to isolate the DNA of almost any protein from biological fluids (amniotic fluid, urine, cervical mucus, vaginal secretions, serum, plasma, saliva) using a polymerase chain reaction. An attempt is being made to find molecular predictors of premature development of labor activity, which will make it possible to choose a rational etiopatho genetically justified therapy.

Currently, there are no known biomarkers for antenatal screening of coronary artery disease, despite the fact that it is one of the most common congenital birth defects. Clinical strategies for the diagnosis of coronary heart disease mainly depend on fetal echocardiography, which is often limited in resources and offered only to high-risk mothers. According to a multicenter study conducted in China, despite the high specificity of fetal echocardiography at 99·8%, the sensitivity was much lower, only 33· 9%.

According to some authors, the frequency of premature outflow of water before the onset of labor varies widely, reaching 38-51% in preterm birth. PIOT in preterm birth has percentages from 5% to 35%, and does not tend to decrease [87, p.276]. Over 50% of preterm births, regardless of the characteristics of etiological factors, begin with premature rupture of amniotic fluid [149, p.37]. Other authors in their study indicate that PIOV will lead to an increase in complications in the birth process and in the postpartum period, both on the part of the mother, and on the part of the fetus and newborn [147, p.445].

Romagano MP, Fofah O, Apuzzio JJ (2020) the authors' study was aimed at determining whether early preterm birth leads to an increase in maternal morbidity. Women were included if they gave birth between 23 0/7 and 28 6/7 weeks of pregnancy and their newborn was admitted to the neonatal intensive care unit. The prevalence of maternal morbidity was assessed, including blood transfusion, maternal infection, placental abruption, postpartum depression or screening for positive depression, hemorrhage and prolonged postpartum hospitalization of the mother. A composite outcome was developed, including blood transfusion, maternal infectious morbidity, placental abruption and postpartum depression. Outcomes were compared for women who gave birth between 23 0/7 and 25 6/7 weeks of pregnancy (early group) and 26 0/7 and 28 6/7 weeks of pregnancy (late group). A multivariate logistic regression analysis was performed to assess the factors contributing to cumulative morbidity, with confusion control. The data indicate that maternal morbidity is

higher during childbirth at the perivim gestational age. Combined morbidity and maternal infection were more frequent in women who gave birth at less than 26 weeks of pregnancy. Management of women at risk of childbirth in early gestational age should include discussion of the increase in maternal complications.

At the same time, a number of authors Baev O.R., Vasilchenko O.N., Kan N.E., and others believe that premature outflow of water during preterm pregnancy occurs (up to 37 weeks of pregnancy) - from 6 to 32% and do not tend to decrease. At the same time, it should be noted that PIOV has a tendency to re-develop in subsequent births with a frequency of up to 20-32% [7, p.123; 21, p.14].

The American College of Obstetricians and Gynecologists indicates that rupture of amniotic fluid during pregnancy before 37 weeks complicates 2-4% of singleton pregnancies and 7-20% of multiple pregnancies. The frequency of births before 37 weeks is 5-10% of all pregnancies and has not shown a downward trend over the past 30 years. Every year about 13 million premature babies are born in the world [47, p.127; 30, p.35].

Meanwhile, there is still no clear understanding of the diagnosis and treatment of PIOV in women with preterm pregnancy. During the physiological course of pregnancy, simultaneously with the maturation of the cervix, the fetal membranes in the region of the internal os soften: along with the thickening of the connective tissue, the layer of cytotrophoblast and decidua becomes thinner, and the connections between the amnion and the chorion are broken. However, the launch of similar mechanisms can also be caused by pathological processes, for example, local inflammation (intra-amniotic infection), the formation of retro chorial hematoma, placental abruption [26, p.48; 27, p.5; 28, p.79; 29, p.37; 30, p.35].

The rates of premature birth before 34 and 37 weeks of pregnancy were 7.3 and 17%, respectively. Uterine contractions, persistent bleeding, two or more episodes of APHUO, and a history of spontaneous preterm labor were significant risk factors for

preterm labor up to 34 weeks in multivariate logistic regression. Women with one risk factor had a risk factor of 5.5 (95% CI: 3.2-9.6) at preterm birth before 34 weeks compared to women without risk factors, whereas women with any two risk factors had a risk factor of 5.2 (95% CI: 2.1-12.9) compared to women with one factor risk.

APHUO up to 34 weeks of pregnancy is associated with a three- to five-fold increase in the risk of premature birth. Identifying multiple risk factors can also help in predicting early preterm labor and proper triage management. It has been proven that a decrease in the concentration of collagen in PIOV can occur as a result of its destruction by collagenases, enzymes of matrix metalloproteinase (MMP) [2, p.56].

During the histochemical study of fetal membranes, a number of authors found tissue inhibitors of matrix metalloproteinase (MMP) in them, which, by covalent binding with MMP, weaken their enzymatic activity, preventing the destruction of collagen, which prevents PIOV [59, p.1].

MMPs belong to the family of zinc metalloproteinases, the function of which is associated with the metabolism of extracellular matrix proteins [85, p.483].

It was found that during the birth act, the enzymatic activity of MMP-2, MMP-8, MMP-9 in the amniotic fluid and MMP-1 in the maternal blood serum increases. It is known that MMP-1 is capable of hydrolyzing interstitial collagen types I, II, and III, gelatins of various collagens, and connective tissue matrix proteins. MMP-2 promotes the hydrolysis of collagen I, IV, V, VII, XI types, gelatin. MMP-8 promotes the hydrolysis of type I–III collagens. MMP-9 hydrolyzes gelatins, elastins, and collagen types III–V and XIV [85, p.483]. Since the connective tissue of the fetal membranes is mainly represented by collagen types I and III, an increase in the enzymatic activity of these MMPs can lead to rupture of the fetal membranes and PIOV.

The inhibitor of TGF-p metalloproteinases is progesterone, which induces this on endometrial stromal cells. During pregnancy, the diameter of the uterine arteries

increases by about 2 times, accompanied by a slight thickening of the vessel wall. According to a number of authors lumen expansion can also be achieved by hypertrophy of the smooth muscle cells (SMCs) of the media. This was confirmed in rats and guinea pigs: the researchers noted an increase in cell length up to 80% with a uniform increase in its thickness [61, p.30].

It is noted that along with hypertrophy of the media, hyperplasia of endothelial cells also occurs. The biomechanical properties of the uterine vessels also change significantly during pregnancy in the direction of increased extensibility. First of all, this is due to a change in the volume of the intercellular matrix of blood vessels, the composition of collagen, the orientation of the fibers, and the decrease in elastin [77, p.1131; 78, p.135]. An important role in the remodeling of the intercellular space of vessels is played by matrix metalloproteinases (MMPs), which is manifested by increased expression of MMP, which is noted that in some pathological conditions, such as eclampsia, there is a decrease in MMP expression [56, p.145].

An opinion was expressed about the role of the complicated course of early pregnancy in the development of PIOV: in the presence of bleeding in the first trimester of pregnancy, extraplacental deposition of hemosiderin occurs, which provokes the expression of the cellular factor-transmembrane 45 to D-glycoprotein-decidual cells [99, p.516]. Vascular injury activates coagulation, during which plasma factor VII binds to the extracellular domain of perivascular membrane-binding tissue factors (TF). The TF/VII a complex cleaves prothrombin to thrombin [70, p.877]. Thrombin weakens the place in the fruit membrane, previously saturated with blood for metalloproteinases MMP-3 and MMP-9 [33, p.76].

These changes are similar to the physiological changes that occur with rupture of the membranes during term labor, but the key stimuli that provoke rupture of the membranes in preterm and full-term pregnancies are most likely different. The cause of early rupture of the membranes should be considered the influence of the vascular endothelial factor, while local inflammation occurs secondary after PIOV [23, c.48].

Fibronectin (FN) is a high molecular weight glycoprotein found in soluble form in plasma (plasma FN) and insoluble form [151, p.154].

Plasma fibronectin (PFN) is one of the substances with an opsonizing ability, due to which it largely determines, regulates phagocytic activity in normal conditions and stimulates this process during inflammation. By now, it is well known that PFN is able to bind and eliminate products of phagocytosis (particles of tissue detritus, endotoxins of viruses and bacteria), as well as immune complexes through the macrophage system, and it acts as a kind of marker of the acute phase of inflammation.

A decrease in the level of PFN is observed: with hepatitis, sepsis, physical trauma, in the postoperative period. The concentration of PFN increases: during complicated pregnancy (severe preeclampsia, preeclampsia), in violation of the vascular endothelium, inflammation, the development of malignant tumors and their metastasis.

Fibronectin can bind proteoglycans, collagens, fibrin, hyaluronic acid, plasma membrane carbohydrates. FN has binding sites for staphylococcus aureus. Staphylococcus aureus adheres tightly to proteins such as fibronectin and fibrinogen. In contrast, Staphylococcus epidermidis attaches only to fibronectin. Due to its structure, FN can play an integrating role in the organization of the intercellular substance, as well as promote cell adhesion. Both soluble and insoluble forms of FN are involved in a variety of processes: they promote adhesion and spread of epithelial cells, stimulate the proliferation and migration of embryonic and tumor cells, control the differentiation and maintenance of the cell cytoskeleton, perform an important role in the mechanisms of hemostasis, are actively involved in inflammatory and reparative processes.

Since FN performs a large number of diverse functions in the body, its plasma level is influenced by many factors, such as age, gender, trauma, shock, inflammation, administration of various drugs, the presence of malignant tumors, etc.

Fibronectin is known to be an acute phase protein of inflammation. In the acute course of the inflammatory process, FN is able to participate in the elimination and neutralization of viruses, endo and exogenous pathological microparticles, stimulate phagocytosis of various objects, subcellular structures and cells, taking part in the course of the immune response.

The desire to improve perinatal outcomes, in the context of the development of pregnancy complications PIOV, was the reason for the search for additional early informative biomarkers of the pathological course of pregnancy, the development of principles for early prevention and therapy.

Neonatal complications and their frequency depend on the gestational age in which PIOV occurred. In preterm birth, PIOV increases the risk of perinatal mortality by 4 times, the incidence of newborns by 3 times, including fetal RDS, which occurs in 10-40% of cases of PIOV in preterm pregnancy, and in 40-70% of cases is the cause of neonatal death. Among the complications of pregnancy according to [35, p.99; 36, p.1; 147, p.445] has a certain place anomalies of labor, premature detachment of the placenta, chorionamnionitis, fetal hypoxia and asphyxia of the newborn. The most optimal methods for the prediction and prevention of PIOV have not been developed in modern obstetrics at the moment. This is most likely due to insufficient knowledge of the etiology and pathogenesis of PIOV and changes in the body of pregnant women in the third trimester of pregnancy, preceding or determining the development of the above complication.

Causes of BP may include bacterial vaginosis, multiple pregnancies, polyhydramnios, premature contraction of the myometrium, bleeding in the first

trimester of pregnancy, nicotine addiction, preterm birth (PR), or a history of PIOV. PIOV occurs due to a decrease in the resistance of the amnion to pressure.

The American College of Obstetricians and Gynecologists indicates the following risk factors leading to this complication of gestation: the presence in the past of pregnancy (pregnancies) that ended prematurely with PIOV; inflammatory diseases of the genital organs of the mother and intra-amniotic infection; isthmic-cervical insufficiency; instrumental medical intervention; bad habits and diseases of the mother; anomalies in the development of the uterus and multiple pregnancy; some diseases of the mother; injury. [47, p.127].

Many factors are involved in the genesis of prenatal rupture of membranes in preterm pregnancy. Among the risk factors for spontaneous rupture of membranes in preterm pregnancy, 3 groups are conditionally identified: maternal, uteroplacental and fetal [30, p.35]. Maternal factors include out-of-wedlock pregnancy, low socioeconomic status, bad habits (tobacco, drugs), body mass index less than 20 kg/m², dietary deficiency of copper and ascorbic acid, anemia, prolonged steroid treatment, premature birth, violation of the content of vascular collagen. Great importance is attached to premature rupture of the membranes in a history of premature pregnancy. Recurrence risk reaches 16-32% compared with 4% in the group of women with previous uncomplicated timely delivery.

Of the uterine-placental factors, the greatest importance is attached to abnormalities in the development of the uterus (septum in the cavity), premature detachment of a normally located placenta (10-15%), shortening of the cervix in the II trimester to 2.5 cm due to progressive isthmic-cervical insufficiency or previous conization cervix, uterine distension due to polyhydramnios or multiple pregnancies, chorioamnionitis, multiple vaginal bimanual or transvaginal ultrasound research. Fetal risk factors are also associated with multiple pregnancies. Iatrogenic causes of premature rupture of the membranes in preterm pregnancy are rare and mainly in the process of invasive intrauterine interventions [23, c.14].

Until now, there are various concepts regarding the etiology and risk factors for the development of premature rupture of the membranes, according to which the most often initiating mechanisms for the development of these pathologies are intrauterine infection of the fetus, neuroendocrine pathology, autoimmune processes in the mother-placenta-fetus system, various forms of extragenital pathology. mothers, etc. However, as is known, one of the regularities in the development of pathological conditions and diseases of various origins is a dynamic change in cause-and-effect relationships, when, following the triggers for the development of pathology, typical pathological processes and reactions are included that ensure the implementation of efferent links in the development of pathology.

These changes are similar to the physiological changes that occur during rupture of the membranes during timely delivery, however, the stimuli that provoke rupture of the membranes in preterm and full-term pregnancies are most likely different. In addition, the influence of the vascular endothelial factor should be considered the cause of early rupture of the membranes, while local inflammation occurs secondary after PIOV [45, p.18].

The fetal membranes are metabolically active tissue and consist of amniotic epithelium, basement membrane, connective tissue, chorion, and decidua. Microscopically, the amnion consists of 5 layers: epithelium, basement membrane, compact layer, fibroblasts, spongy layer. Connective tissue is built from collagen types I and III, which provide strength to the membranes. The basement membrane is located under the epithelium in the form of a narrow eosinophilic cell-free mass; the compact layer is represented by a homogeneous mass, devoid of cells (indicating the strength of the amniotic membrane). The fibroblast layer is located in a dense network of collagen and reticular fibers and intercellular substance. The spongy layer of the amnion is connected by means of connective tissue fibers and intercellular substance with a smooth chorion. In a smooth chorion, four layers are distinguished: cellular; reticular, containing fibroblasts and a pseudobasal membrane formed by a

layer of trophoblast [80, c.136]. Microscopic studies of the fetal membranes, carried out immediately after childbirth, revealed structural changes associated with the rupture of the amnion, as well as a decrease in the amount of collagen [43, p.245].

A number of researchers believe that the leading pathomorphological causes of PIOV are the structural features of the collagen filaments of the membranes, which change their mechanobiological properties, leading to untimely rupture [43, p.245].

It was found that in patients with PIOV, the total concentration of collagen in the fetal membranes is lower compared to patients with timely discharge of amniotic fluid [105, p.67]. When examining the place of rupture of the membranes, a special zone of morphological changes was revealed, characterized by thinning of the trophoblast layer adjacent to the decidua of the uterus, thickening of the components of the connective tissue of the membranes, and a break in the connection between the amnion and the chorion. The morphologically altered zone is localized near the cervix before the onset of labor, and increased intrauterine pressure during childbirth increases pressure on the weakened area of the fetal membrane and leads to its rupture. Also in this place there is a significant decrease in the density of collagen fibers of types I, III and V and an increased content of tenascin. There is an assumption that the verification of expression and tenascin in the reticular layer may indicate defects in the fetal membrane and a predisposition to PIOV [23, p.137].

When studying the characteristics of the membranes in women with PIOV, degradation of the collagen of the membranes was found. It has been established that the formation of a rupture site is associated with a local change in the collagen cross-link [149, p.7]. It was found that with PIOV there is not only an absolute decrease in the amount of collagen, but also a percentage change in it. fractions. The change in collagen content in patients with PIOV is associated with a decrease in the concentration of type III collagen [149, p.7].

The work showed a change in the biophysical properties of collagen in PIOV, which occurs without violating the integrity of the cell membranes of the surface layer of the membranes [43, p.245]. A possible cause of morphological changes in the membranes are changes in collagen metabolism [43, p.245]. When comparing the histological structure of the fetal membranes in patients with timely and premature outflow of water at full-term pregnancy, a relationship between PIOV was revealed not only with a decrease in the number of collagen fibers, but also with a violation of the usual wavy pattern of these fibers and the deposition of an amorphous substance between these fibers.

It has been proven that a decrease in the concentration of collagen in PIOV can occur as a result of its destruction by collagenases, enzymes of matrix metalloproteinase (MMP) [87, p.276].

During histochemical examination of fetal membranes, a number of authors found tissue inhibitors of matrix metalloproteinase (IMMP) in them, which, by covalent binding with MMP, weaken their enzymatic activity, preventing the destruction of collagen, which prevents PIOV [85, p.483].

MMPs belong to the family of zinc metalloproteinases, the function of which is associated with the metabolism of proteins of the extracellular matrix Kazlovskaya I.A. [86, p.1057].

It was found that during the birth act, the enzymatic activity of MMP-2, MMP-8, MMP-9 in the amniotic fluid and MMP-1 in the maternal blood serum increases. MMP1 is known to be able to hydrolyze interstitial collagen types I, II, and III, gelatins of various collagens, and connective tissue matrix proteins. MMP-2 hydrolyzes collagens I, IV, V, VII, XI types, gelatins. MMP-8 hydrolyzes type I-III collagens. MMP - 9 hydrolyzes gelatins, elastin, collagens III-V and XIV types [83, p.1682]. Since the connective tissue of the fetal membranes is mainly represented by

collagen types I and III, an increase in the enzymatic activity of these MMPs can lead to rupture of the fetal membranes and PIOV.

A number of researchers have proven that PIOV is associated with a significant increase in MMP activity in the amniotic fluid both in full-term and premature pregnancies [85, p.483]. With PIOV, the level of MMP-2, MMP-8 and MMP-9 in the amniotic fluid is significantly higher in women in labor with PIOV than with timely discharge of water. An increase in the concentration of MMP and a decrease in this UTI may be one of the reasons leading to PIOV due to the destruction of collagen in the fetal membranes [87, p.276]. Thus, further study of the change in the level of MMP in order to possibly predict PIOV is very promising. MMP in saliva to identify patients at risk of PIOV [85, p.483]. Saliva samples were collected in the following groups: non-pregnant women, second trimester pregnant women, women in term labor before rupture of amniotic fluid, women with PIOV before preterm labor, and women in the early postpartum period after term labor. As a result of the study, it was found that MMP-9 activity is higher in saliva samples of women with PIOV before preterm birth compared to all other groups. The results of this study highlight MMP-9 as a possible biomarker for PIOV.

They expressed the opinion that the pathogenesis of PIOV is based on inflammation, which can be infectious and aseptic; they believe that PIOV occurs against the background of a chronic inflammatory process, and after the outflow of water, a secondary acute inflammatory process develops, the prevalence and severity of which increases with an increase in the anhydrous gap [74, p.567].

In embryonic membranes, endothelial growth factor is the primary regulator leading ultimately to PIOV regardless of the presence or absence of chorioamnionitis, and inflammation occurs more often after PIOV. There is no unequivocal opinion on this problem, which indicates the need for further study of the relationship between the inflammatory process and PIOV [77, p.1131].

Activins and inhibins are important modulators of inflammation. Studies have shown lower levels of inhibin-A and increased levels of activin-A in PIOV. The authors also confirmed that an increase in the collagenolytic activity of MMPs is important for the occurrence of PIOV even in the absence of infection. Activin-A stimulates the activation of MMP-2 and MMP-9, while inhibin-A inhibits this process. Thus, it was suggested that an increase in the ratio of activin-A to inhibin-A in the amniotic fluid and/or a genetically determined inability to synthesize inhibin-A may contribute to the development of PIOV [105, p.67].

It is known that the activation of free radical oxidation is the leading pathogenetic factor in the development of typical pathological processes and diseases [69, p.250]. A simultaneous increase in the content of intermediate products of lipid peroxidation in the amniotic fluid was found: diene conjugates, malondialdehyde, and the total indicator of oxidative status. The authors also proved that the total antioxidant status of amniotic fluid increases dramatically in pregnant women with PIOV.

Strengthening of lipid peroxidation processes can be activated by microorganisms with the participation of phagocytes and macrophages. Activation of this system leads to the launch of cytokine production processes, and this, in turn, can cause damage to the membranes. He also believes that PIOV is accompanied by a change in the parameters of the lipid peroxidation system in the fetoplacental complex, which is a consequence of a pronounced imbalance of the main microelements and vitamins [124, p.124; 125, p.124]. According to many researchers, oxidative stress and the depletion of antioxidant systems lead to a decrease in the body's ability to activate protease inhibitors and, therefore, may be the cause of collagen destruction. The hypothesis about the relationship of changes in the antioxidant system with the occurrence of PIOV is supported by the results of a double-blind, placebo-controlled study, which found that taking 100 mg of vitamin C

daily from 20 weeks of gestation significantly reduces the incidence of PIOV [68, p.859].

There was no evidence that dietary antioxidants affect the frequency of PIOV. The study of the level of antioxidants in blood plasma in PIOV showed the presence of the only significant dependence of this obstetric pathology on the level of the antioxidant lutein. Moreover, it is the increase in the level of this antioxidant in early pregnancy that increases the frequency of PIOV [104, p.12].

A number of researchers suggested a possible role of the vascular endothelial growth factor in the pathophysiology of PIOV. VEGF is a multifunctional protein that plays an important adaptive role in the body, namely, restoration of disturbed blood supply to tissues in case of any damage [131, p. 828].

Also, PIOV is associated with a lower concentration of VEGFR-1 in the amniotic fluid, regardless of gestational age and the presence or absence of intra-amniotic infection [131, p. 828].

Studies have shown that with PIOV there is a metabolic disturbance in the exchange of plasminogen. Plasminogen, when bound to the cytoplasmic components of damaged cells of the amniotic epithelial cells of the amnion and chorion trophoblast, is activated into plasmin, which leads to thinning of the fetal membranes and their rupture. A number of authors in studies evaluated the effect of thrombin and progestin on the expression of metalloproteinase-3 (MMP-3) in decidual cells in PIOV. According to them, thrombin formed during PIOV contributed to the development of labor by stimulating the destruction the extracellular matrix of the membranes by increasing the expression of MMP-3 by decidual cells, while progesterone suppressed this effect [94, p.121; 103, p.187].

Serine proteases, in particular, leukocyte elastase, capable of destroying components of the extracellular matrix of fetal membranes, were found in the secret of the cervical canal in patients with PIOV during a biochemical study [1, p.10]. It was

found that the addition of erythromycin or clindamycin to the vinocula of microorganisms producing proteases prevented the weakening of the chorioamniotic membrane caused by bacterial proteases [1, p.10].

Many authors point to the important role of micronutrient deficiencies in the occurrence of PIOV. It was reported that patients with PIOV had lower concentrations of copper in maternal and umbilical serum than patients with timely discharge of waters. Based on the data obtained, it was suggested that with copper deficiency, delayed maturation of collagen and elastin occurs [55, p.61]. At the same time, they did not find a significant difference in the level of this microelement in the blood serum of the mother and umbilical cord blood of the fetus with PIOV, determining the level of zinc in the blood serum showed that the concentration of zinc was lower in patients with PIOV with timely delivery than without PIOV [1, p.10; 93, p.121].

To diagnose and predict the development of infectious complications in PIOV, a number of authors suggest using C-reactive protein. In particular, studying the concentration of C-reactive protein in patients with PIOV, it was found that the sensitivity and specificity of this method for predicting chorioamnionitis was 80% [122, p.351]. An increase in the level of C-reactive protein is a rather sensitive sign for the diagnosis of chorioamnionitis and can be used to monitor the effectiveness of treatment with antibacterial drugs [99, p.516]. The method for determining C-reactive protein is diagnostically significant only when highly sensitive methods are used - immunofluorometric and enzyme immunoassay. However, other authors believe that the determination of C-reactive protein is not sensitive enough to confirm the presence of chorioamnionitis.

In their studies, soluble intercellular adhesion molecule-1 (SICAM-1) was used to diagnose and predict chorioamnionitis in patients with PIOV. The authors compared the levels of SICAM-1 and C-reactive protein in patients with PIOV and in patients with timely rupture of water. In patients with PIOV, chorioamnionitis was

confirmed histologically. According to the data obtained, it was concluded that the level of SICAM-1 is more significant for the diagnosis of intra-amniotic infection and chorioamnionitis than the level of C-reactive protein. [151, p.154; 145, p.502]

There are indications in the literature that a more than 2-fold increase in the content of β-fetoprotein (AFP) in the second trimester of pregnancy indicates a possible risk of PIOV, but at the same time it was emphasized that a change in the concentration of AFP in the third trimester of pregnancy has a special effect on the occurrence of PIOV didn't have. A number of researchers assign a significant role in the pathogenesis of PIOV to an increase in the synthesis of prostaglandins E2 and F2a by amniotic epithelial cells. At the same time, several ways of accumulation of prostaglandins are distinguished. The first option is associated with the reproduction of pathogenic microflora in the amniotic fluid. As a result of this process, there is an accumulation of microbial phospholipases that trigger the synthesis of prostaglandins from tissue amnion and chorion phospholipids. Influence of a long anhydrous interval on early neonatal mortality in premature rupture of amniotic fluid and preterm pregnancy.

A number of researchers have noted that often PIOV at preterm occurs against the background of a high content of endotoxin. The second way to increase the content of prostaglandins is associated with their synthesis under the action of cytokines, which are produced by macrophages in the area of the uterine-placental barrier in response to bacterial toxins [99, p.516].

The third variant of increased production of prostaglandins is associated with damage to the amnion, the subsequent development of vascular disorders and aseptic inflammation. Therefore, the pathogenesis of prenatal rupture of the membranes is based on inflammation, which can be infectious and aseptic. However, studies have not found a significant increase in prostaglandin levels in PIOV. Obviously, there are several different views on the biochemical aspects of the pathogenesis of PIOV. Clarification or refutation of some of them will speed up the solution of a number of

obstetric problems related to the management of pregnancy and childbirth in PIOV, as well as develop new methods for predicting a number of complications in this pathology [99, p.516].

Thus, in the modern literature there is no unambiguous opinion regarding the etiology and pathogenesis of PIOV. In order to reduce perinatal morbidity and mortality associated with this pathology, there is a need for further study of the mechanisms of PIOV at the molecular and cellular levels. Of particular interest is the verification of key signaling molecules that ensure the integrity of the membranes and the development on this basis of possible biomarkers that optimize the prediction of PIOV.

Today, modern medicine should be not only accessible, but also safe, especially when it comes to a pregnant woman. The task of obstetricians at present is to provide pre-gestational preparation of couples with a history of pregnancy loss, careful monitoring of pregnancy in terms of preventing infectious and inflammatory complications, the use of evidence-based medicine in the secondary prevention of threatening preterm birth and gentle delivery using new technologies to reduce neonatal morbidity and mortality.

§ 1.2. Evaluation of clinical and laboratory parameters of pregnant women with premature rupture of amniotic fluid

In 60-70% of cases, the diagnosis of PIOV does not cause difficulties. Diagnosis of rupture of amniotic fluid is usually based on the presence of a sudden rush of amniotic fluid from the vagina and then, continuing in very small portions of the discharge. If the watery discharge is not permanent, it must be distinguished from vaginal discharge, urine leakage or cervical mucus thinning preceding the onset of labor [15, p.462; 16, p.81]. With small, so-called subclinical ruptures, when there is only a slight leakage of amniotic fluid, diagnosis can cause significant difficulties. Amniotic fluid can be released drop by drop and mixed with vaginal secretions. A pregnant woman may not notice the moment of water leakage, especially if there was

abundant vaginal discharge against the background of the inflammatory process [4, c.26; 17, p.30; 93, p.144].

Making an accurate diagnosis of PIOV is a key moment for further obstetric tactics. An erroneous diagnosis of PIOV can, on the one hand, lead to unjustified hospitalization and subsequent labor induction, on the other hand, to an unreasonably long expectant position of the obstetrician with a high risk of ascending infection.

In these circumstances, much depends on a carefully collected anamnesis. It is necessary to obtain information on when and how the liquid was released from the vagina, whether this happened before, how much liquid flowed out, what color, smell, consistency it was, and whether there were any other features [3, p.20; 4, p.26; 20, p.17].

Detection of amniotic fluid in the posterior vaginal fornix when examined in sterile specula is the simplest method for diagnosing PIOV. It is also possible to conduct a "cough push test", which consists in the fact that when viewed in mirrors, a woman is asked to cough: leakage of fluid from the cervical canal indicates PIOV [4, p.26]. Confirmation of the diagnosis of PIOV is the absence of a fetal bladder during vaginal examination and increased leakage of water during repulsion of the presenting part [73, p.223]. A certain difficulty is the diagnosis of PIOV with a slight leakage of liquid contents from the genital tract with an "immature" cervix, therefore, in doubtful cases, one has to resort to various laboratory research methods [25, p.9].

In order to clarify the diagnosis of PIOV, a smear obtained from the posterior fornix of the vagina is examined for "arborization" (fern phenomenon). For a better assessment of the results, microscopic examination is best done 10 minutes after the smears have dried [83, p.1682]. However, this method can give a fairly large number of false positive results due to the admixture of sperm elements, the discharge of the cervical canal, and even if there are fingerprints on the glass slide [25, p.9]. You can also carry out a nitrazine test, which consists in determining the pH of the vaginal contents. When amniotic fluid enters the vagina, the acidity of the vaginal contents decreases, which is detected using a nitrazine test strip. It is known that the

information content of these methods decreases as the anhydrous gap increases [83, p.1682]. According to a number of authors, ultrasound imaging of a reduced volume of amniotic fluid can also help confirm the diagnosis of PIOV. Moreover, the control of the amniotic fluid index is necessary to resolve the issue of the possibility and expediency of prolonging pregnancy. In some cases, ultrasonic criteria allow predicting the duration of the latent period. However, to date, the value of the volume of amniotic fluid for the diagnosis of PIOV has not been finally determined. It is believed that other causes of oligohydramnios should be taken into account, such as congenital anomalies of the urogenital tract, intrauterine growth retardation of the fetus. Conversely, a normal amount of amniotic fluid also does not exclude PIOV [148, p.510]. In the case of uterine hypertonicity with PIOV, an ultrasound examination is necessary to exclude premature detachment of the placenta. We have developed a quick method for diagnosing PIOV by determining the activity of diamine oxidase. Product Based Method diaminooxidase by cells of the placenta, its presence in the amniotic fluid and its absence in the vaginal contents [90, p.379].

Proposed to determine the level of prolactin [96, p.363] in the vaginal contents for the diagnosis of PIOV. The sensitivity of this method was 94.5%, and the specificity was 95.4% [56, p.351]. Fetal fibronectin (PFN), a glycoprotein located in the extravillous cytotrophoblast of the placenta, amniotic membranes and amniotic fluid, examining PFN in PIOV at term, reported that the sensitivity of this method was 98.2%, and the specificity was only 26.8% [87 , p.276]. A positive result for PFN reveals a decrease in the extracellular matrix in the mother-fetus system, which precedes the clinical onset of labor more than PIOV. This hypothesis is based on the observation that patients without PIOV but positive for PFN in cervical discharge are more likely to be delivered within 72 hours, in contrast to patients with a negative result for PFN. It is believed that the detection of PFN is not specific for PIOV [112, p.1340]. However, monoclonal antibody PFI was more accurate in diagnosing amniotic fluid than prolactin and more practical than diamino oxidase, with an overall accuracy of 98%. The level of fetal fibronectin in the cervico-vaginal contents,

cervical shortening (<20 mm) as determined by transvaginal sonography, and bacterial vaginitis were found to be the three most significant risk factors for spontaneous preterm birth or preterm rupture of the membranes. According to modern concepts, the main importance in the development of preterm labor is given to three factors - the presence of latent infection, pathological changes in the cervix and hormonal factors [131, p.828; 133, p.6.] There is another method for diagnosing PIOV - amniocentesis with the introduction of indigo carmine dye. This method is usually recommended for very premature pregnancies. The method is quite accurate, but extremely traumatic and can itself lead to rupture of the membranes [99, p.115]. Based on amniocentesis, it is possible to clarify the diagnosis of chorioamnionitis (according to an increased content of leukocytes in the amniotic fluid, a decrease in glucose concentration) or even the final confirmation of intrauterine infection according to bacteriological examination of the amniotic fluid [4, p.26; 25, p.9]. Modern immunological methods for diagnosing PIOV are based on the use of antigen-specific monoclonal antibodies to detect the presence in the vagina of substances that are found in large quantities mainly in the amniotic fluid. The level of protein-1 binding insulin-like growth factor (PSIFR-1) was determined. This method has a sensitivity of 85.4% and a specificity of 92.6%. However, it is less accurate for trace amounts of amniotic fluid and requires qualified medical personnel [87, p.276].

One of the most common methods for diagnosing PIOV is the Amnisure test. The test detects placental b-microglobulin (PAMG-1) in the vaginal contents. PAMG-1 is found in large quantities in amniotic fluid (2000–25000 ng/ml). The sensitivity threshold of the Amnisure test is 5 ng/ml, which provides 99% accuracy in detecting PIOV even in preterm pregnancy [53, p.285; 33, p.76]. Given the wide variety of methods for diagnosing PIOV, it is necessary to determine the most sensitive and specific of them, since the establishment of an accurate diagnosis is the key to the correct tactics of managing pregnancy and childbirth in patients with PIOV.

CHAPTER II. CHARACTERISTICS OF THE CLINICAL MATERIAL AND THE METHODS USED IN PREGNANT WOMEN WITH THE RISK OF PREMATED FLUID ROUTING AND PRETERM LABOR

§2.1. Clinical characteristics of pregnant women

The work was performed in clinic No. 1 of the Samarkand State Medical Institute at the Department of Obstetrics and Gynecology No. 1 and in the Regional Perinatal Center of Samarkand in the Department of Pathology of Pregnant Women.

A total of 478 pregnant women were examined to assess risk factors for the development of AR and PIOV. 350 birth histories for 2016-2019 were retrospectively analyzed. Prospectively analyzed the initial clinical characteristics, as well as the features of the course of pregnancy. We observed 128 pregnant women. Pregnant women were included in the study as they were referred. In accordance with the data obtained from the clinical and laboratory examination, the diagnosis made and the criteria for inclusion in the study developed.

The inclusion criteria were:

1. Pregnant women with a period of 30 -34 weeks
2. Age of pregnant women from 18 to 36 years
3. Informed consent to participate in the study
4. The presence of a medical abortion in history (1 or more abortions in history).
5. Women who had a history of premature birth.
6. Women who had a history of premature rupture of amniotic fluid.
7. Not severe extragenital pathology.

Exclusion Criteria:

1. Gestational age less than 30 weeks.
1. 2. Anomalies and tumors of the uterus and ovaries.
3. Isthmic cervical insufficiency.
4. Multiple pregnancy.
5. Complicated preeclampsia.

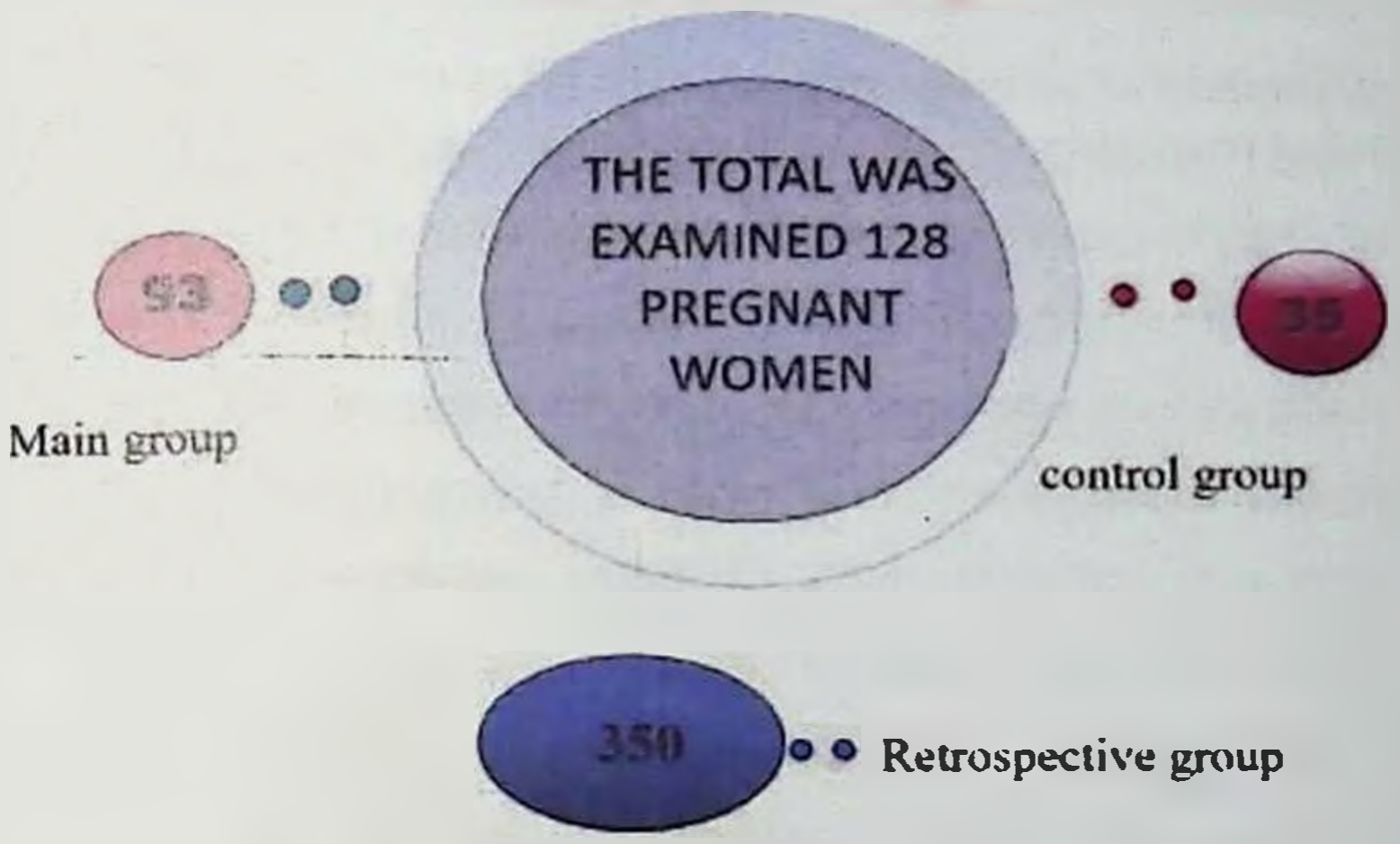
6. Decompensated placental insufficiency.

7. Congenital malformations of the fetus.

8. Severe somatic pathology.

We observed 128 pregnant women. The main group consisted of 93 pregnant women with a gestational age of 30-34 weeks of pregnancy. who were divided into 3 groups according to the history. The control group consisted of 35 pregnant women with a physiological course of pregnancy.

Study design:



Rice. 2.1. Study design

The criteria for identifying risk factors for preterm birth (PR) and premature rupture of amniotic fluid (PROM) based on the materials of the birth histories were the outcomes of the birth of a retrospective group that was collected by us at the Perinatal Center in Samarkand for 2016-2019.

We studied 350 birth histories of pregnant women who had undergone preterm labor and premature discharge of amniotic fluid at a gestational age of 30-34 weeks of gestation. When identifying PR and PIOV, it was found that more often pregnant women complained of the following: frequent stress, bad habits, occupational hazards, age from 18 to 37, a history of a threatened miscarriage, a history of early

gestosis, a history of preeclampsia, a history of eclampsia, oligohydramnios, polyhydramnios, PIOV in history in the short term, and extragenital diseases (EGD). Taking into account all these studied risk factors, a matrix was compiled that included all the data of the anamnesis of pregnant women that were available in the history of childbirth.

To obtain written consent to participate in a scientific study, all pregnant women were familiarized with the purpose and methods of the study. All pregnant women included in the study underwent a standard set of examinations.

In the course of the work, general clinical and special research methods were used: laboratory, instrumental.

§2.2. Methods of research of pregnant women

General clinical research methods: : in all patients included in the study, the data of the somatic and obstetric-gynecological anamnesis were analyzed. Particular attention was paid to past infectious and inflammatory diseases, the conduct or absence of pregravid preparation, the course and outcomes of previous pregnancies. We took into account the presence in the anamnesis of cases of non-developing pregnancies, spontaneous miscarriages, premature births, premature rupture of amniotic fluid, polyhydramnios. An objective examination included a general examination, which assessed the state of the cardiovascular, respiratory, nervous, digestive and urinary systems.

During an external obstetric examination, the position, presentation, position of the fetus, the nature of its motor activity were determined, the heart rate of the fetus, uterine tone, the degree of tension of its walls, and the size of the uterus corresponding to the gestational age were determined. During a gynecological examination, attention was paid to the nature of the discharge, the presence of rashes or papillomas on the skin and mucous membranes of the labia, perineum, vagina, the presence of pathology of the cervix, the length of the cervix, consistency, and the state of the inguinal lymph nodes were assessed. All patients additionally underwent a number of standard studies: determination of the blood group and Rh factor, clinical and biochemical blood tests, hemostasiogram, general urinalysis, vaginal and cervical canal smear analysis for flora.

In the presence of inflammatory diseases of the urinary system, the examination plan additionally included urinalysis according to Nechiporenko, Zimnitsky and Reberg samples, bacteriological examination of urine and vaginal contents, ultrasound of the kidneys.

Laboratory examination was carried out in the laboratory of the INNOVA clinic (head of the lab. Kilichova D.O.). The studies included the determination of parameters of the hemostasis system, endothelial dysfunction, oxidative stress, activity of matrix metalloproteinases and their inhibitor.

To study the parameters of the hemostasis system, blood was taken from the cubital vein into a siliconized tube containing 3.8% sodium citrate, centrifuged at 3000-4000 rpm (1200 g) for 15 minutes, as a result, platelet-poor plasma was obtained, which was transferred to another tube, where they were stored before the study. Frozen plasma samples were stored at -20 to -16°C.

Determination of malondialdehyde (MDA) was carried out by a test with thiobarbituric acid, diene conjugates - spectrophotometrically at 233 nm. Thrombomodulin was determined by ELISA with reagents manufactured by BCM-diagnostics, von Willebrand factor - by ELISA with reagents manufactured by Technoclone, protein C - with Parus-test kits manufactured by Technology-Standard. (Russia), D-dimer - by latex agglutination immunoassay using Renam reagents (Russia). The concentration of soluble cell adhesion molecules sICAM-1 sVCAM-1 - ELISA method reagents manufactured by "Bender Med Systems". The concentration of matrix metalloproteinases MMP1, MMP-3, MMP-9, type and tissue inhibitor - TIMP-1 - ELISA using the Cusabio kits.

For the determination of fibronectin, the IFA-Fn kit manufactured by CJSC NVO Immunoteks (Russia) was used.

Complement components C3 and C4 were determined by ELISA using BCM-diagnostics reagents.

Fetal Fibronectin Test: All examined women, after communication and explanation about the information content, were tested for fibronectin. This test is designed to

determine the level of fFN in vaginal secretion by visually evaluating the color change in the test area. Anti-fFN antibodies were immobilized on the surface of the membrane in the test zone (T). If there is a sufficient amount of fFN in the sample, then a strip will appear in the T zone. The presence of a colored strip indicates a positive result, the absence of a negative one, respectively. The presence of a strip in the control zone (C) serves as an indicator of test performance.

Functional research methods:

Ultrasound procedure. Using ultrasound (cervicometry), the state of the cervix was assessed, as well as the dynamics of changes in the cervix: length and width, the state of the placenta and its blood circulation. In addition, the thickness, degree of maturity, location and structure of the placenta, the presence of amniotic fluid were taken into account. The studies were carried out using the apparatus "Aloka 500" (Japan), "Mindray" (China). In a prospective study, complaints were analyzed at admission, the causes contributing to preterm labor and PIOV, the state of the birth canal, concomitant diseases. In diseases of the kidneys and liver, an additional ultrasound examination was performed to control of the size, structure and condition of the renal-pelvic system, the presence of stones and the structure of the liver, etc.

For the purpose of prevention, an obstetric pessary was inserted into the pregnant women.

In order to prevent PIOV, pregnant women underwent the procedure for installing an obstetric pessary modified by Bayramov S.Zh. with improved drainage function (FAP patent No. 01226 of 03/14/2017). Before the introduction of the pessary, a screening of the cervix was performed, the results of measuring the length of the cervix were used for evaluation before insertion and after to identify changes. Before the installation of the pessary, it is recommended to conduct vaginal microscopy in case of positive pathological results, treatment was carried out according to local protocols by sanitation. The obstetric pessary is coated with an antibacterial cream, gel, or liquid that provides lubrication for ease of insertion. Then the pessary is squeezed between the thumb and the rest of the fingers and inserted longitudinally into the vagina. In the

vagina, the pessary is straightened so that its inner ring is directed upwards towards the cervix. The proximal part of the dome of the pessary is carefully pressed against the upper fornix so that it completely covers the cervix, and then the front part of the pessary is lightly pressed against the sacrum. It is recommended that the patient be asked to stand up after inserting the pessary and walk a few steps to determine how she feels - the woman should not be able to feel the pessary being inserted. Some patients even report a reduction in the sensation of pressure. If the patient complains of discomfort, it is necessary to change the size or position of the pessary. The patient is then clinically and re-examined to ensure that the cervix is completely within the proximal inner ring. For the same purpose, some patients may be shown an examination in the mirrors. Before removal, it is recommended to ensure that the cervix is pushed back out of the inner ring of the pessary dome. If there are signs of cervical edema, the woman should be informed that removal may be painful.

There are several indications for removing and reinserting a pessary. If a woman complains of discomfort or slight bleeding, it is recommended to examine in the mirrors or even take a smear from the cervix to exclude erosion or tears. In this case, it is advisable to remove the pessary, rinse it in running water and reinsert it if nothing suspicious is found. The pessary should always be removed at the onset of labor, and should not be forgotten in women entering labor or caesarean section.

§ 2.3. Statistical processing methods

Statistical processing of the results was carried out on a Pentium-IV personal computer using the Statistica 6.0 software package, with the calculation of the arithmetic mean (M), the error of the arithmetic mean (m), Student's test (t) and the equality of general dispersions (F - Fisher's test). Statistically significant changes were taken as the level of significance $P<0.05$.

Chapter 3

CHAPTER III. RESULTS OF OWN RESEARCH

§3.1. A retrospective analysis of pregnant women with premature rupture of amniotic fluid and preterm labor.

The criteria for identifying risk factors for preterm birth and premature rupture of amniotic fluid based on the materials of the birth histories were the outcomes of the birth of a retrospective group that was collected by us at the Perinatal Center in Samarkand for 2016-2019. We studied 350 birth histories of pregnant women who had undergone preterm labor and premature discharge of amniotic fluid at gestational age 30-34 weeks of gestation. The age of women is shown in the table (3.1)

Table 3.1

Age of women in the retrospective group.

Age	350 pregnant women with R.G.	
	abs.	%
18-20 years old	11	3.1
21-24 years old	127	36.2
25-29 years old	115	32,8
30-33 years old	82	23,4
34-35 years old	15	4,2
Social status		
Housewives	196	56
Employees	103	29,4
Students	51	14,5

The age of women ranged from 18 to 34 years. More common were 20-24 years old 36.2%, as well as 25-29 years old 32.8%, and less common over 35 years old 4.2% and less than 19 years old 3.1%.%. In terms of social status, employees 29.4%, housewives 56.0%, students 14.5% prevailed.

When collecting an anamnesis, it was found that more often pregnant women complained of the following: frequent stress, bad habits, occupational hazards, age under 18 after 30, a history of the threat of interruption, a history of toxicosis, a history of preeclampsia, a history of eclampsia, oligohydramnios, polyhydramnios, PIOV in the anamnesis in small terms, and extragenital pathology. An important role

in the development of complications was played by the presence and frequency of EHD in the examined women. Thus, 61 women had a history of inflammatory diseases in childhood, SARS, diseases of the respiratory system, ear, throat and nose, kidney disease, which could have a negative impact on the state of various organs and systems during the formation of the reproductive function of the future woman. When collecting a gynecological history, the main pathology was identified - inflammatory diseases of the genital tract, among them colpitis (61.4%), inflammatory diseases of the uterus (39.3%), menstrual disorders (16.2%) prevailed. By parity, among the surveyed primiparas there were 32.3% of multiparous 67.7%. Of no small importance for the current pregnancy are the outcomes of previous pregnancies in the examined women. A distinctive feature of the obstetric history in pregnant women with PIOV is the high frequency of spontaneous abortions (29.3%), induced abortions (21.4%), the threat of preterm birth (57.3%), hypertensive disorders (39.7%), preterm birth history (31.3%), postpartum diseases (17.3%). Taking into account all the risk factors, Table 3.2 was compiled.

As can be seen from Table 3.2, many anamnestic criteria for risk factors remained unexplored: the doctor of the admission department did not pay attention to the EG, the anamnesis did not interrogate the pregnant woman and, therefore, may not have assessed her condition.

In our opinion, the reasons for AR and PIOV are late admission to the hospital, comorbidities, insufficiently collected anamnesis, late identification of risk factors and the lack of prevention of preterm birth.

As the results of the study showed, not timely identification of risk factors and prevention of preterm birth lead to preterm birth in 63.1% of cases.

Table 3.2

Prognostic card for a comprehensive assessment of risk factors for 350 women from a retrospective group

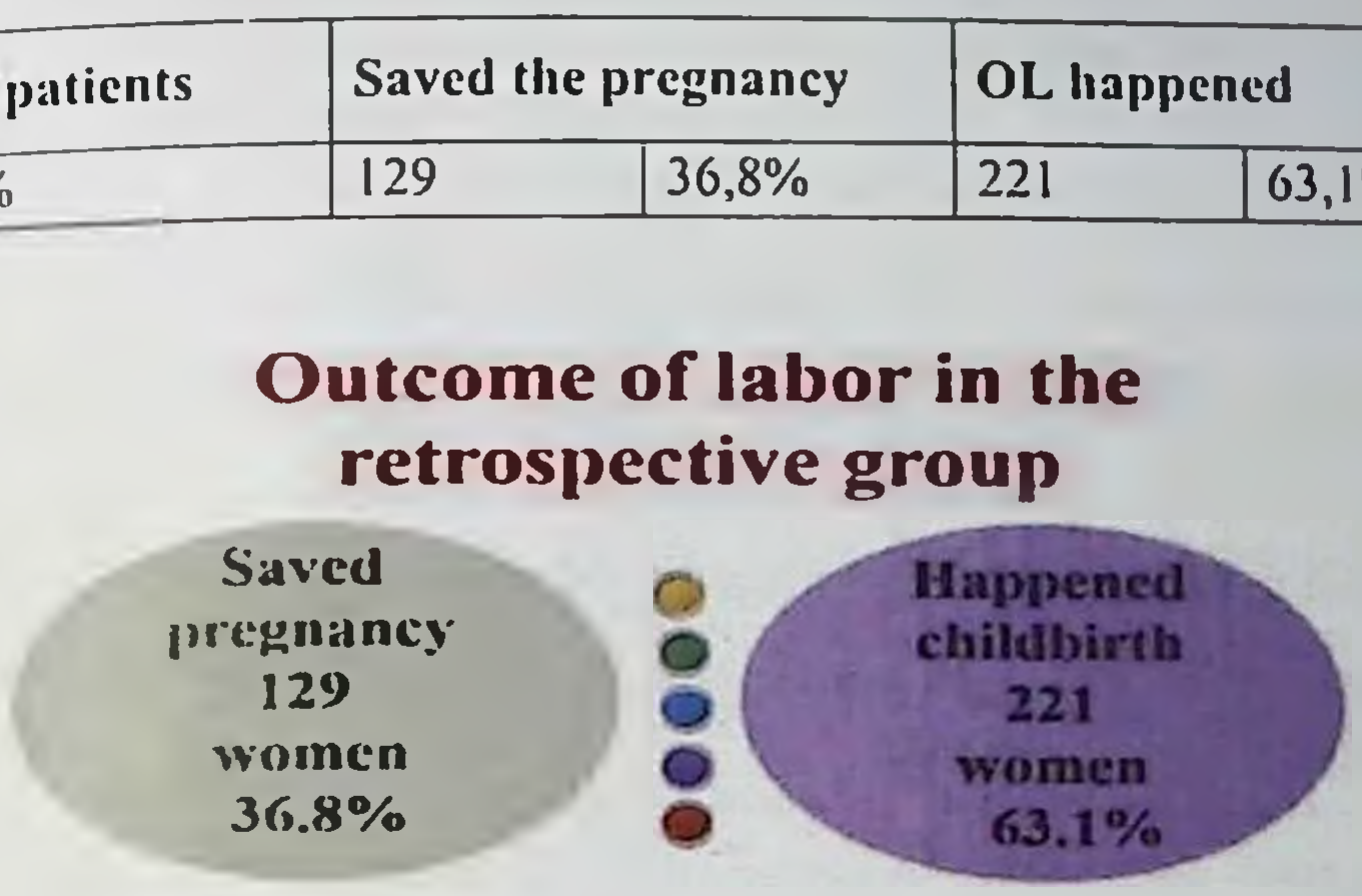
Risk factors	Noted	Doesn't mark	Notes in history	Didn't mark in anam	Total quantity we take
Stress	105	245	Not op	Not op	350
Bad habits	11	339	28	322	350
Prof. harmfulness	98	252	128	222	350
Age under 18 after 30	25	325	36	314	350
Gynecological goiter	340	10	340	0	350
History of abortion	147	203	101	249	350
Threat of interruption	347	3	Not op	Not op	350
Early gestosis	350	0	348	2	350
Preeclampsia ber	45	305	Not op	Not op	350
Eclampsia in temp.ber	8	342	Not op	Not op	350
Ultrasound oligohydramnios	153	197	Not op	Not op	350
Ultrasound Polyhydramnios	29	331	Not op	Not op	350
Ultrasound of FPN and NK	147	203	Not pom	Not pom	350
PIOV up to 22 weeks	3	347	Not op	Not op	350
PIOV up to 36 weeks	169	181	Not op	Not op	350
Acute NRP detachment	5	345	1	349	350
Diseases n.p.	7	343	9	341	350
SS diseases	14	336	Not otm	Not otm	350
Hypertensive drugs	33	327	37	313	350
Kidney pathology	28	332	31	329	350
Anemia	205	145	215	135	350

Taking into account the outcome of 221 pregnancies ended in preterm birth, we decided to re-examine the history of childbirth and identify risk factors and determine methods for maintaining pregnancy in 129 pregnant women whose pregnancy continued (Fig. 3.1). Apparently, 129 pregnant women who survived the pregnancy were hospitalized in a timely manner and received maintenance therapy according to the standards.

Table 3.3

The outcome of childbirth in 350 pregnant women of the retrospective group

Number of patients	Saved the pregnancy		OL happened	
350 – 100 %	129	36,8%	221	63,1%



Rice. 3.1. Birth outcomes in the retrospective group

An analysis of the retrospective group showed that a distinctive feature of the obstetric anamnesis in those examined with a preserved pregnancy was such factors as: stress (27.9%), bad habits (2.3%), age up to 18 after 30 years (8.5%), history of abortion (37.2%), gynecological diseases (44.9%), threatened miscarriage (98.4%), early preeclampsia (100%), PIOV up to 22 weeks (0.77%), PIOV up to 36 weeks (53.4%), cardiovascular diseases (1.5%), hypertensive disorders (6.2%).

At the same time, in those examined with preterm birth, an increase in the frequency of risk factors was observed in comparison with women with a 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 miscarriage

(99.5%), early preeclampsia (100%), PIOV up to 22 weeks (0.90%), PIOV up to 36 weeks (45.2%), cardiovascular diseases (5.4%), hypertensive disorders (11.3%).

Table 3.4

Prognostic chart for assessing risk factors in women who have continued pregnancy and experienced preterm birth in a retrospective group

Risk factors	Save ber (n=129)		before childbirth (n=221)	
	abs	%	abs	%
Stress	36	27,9	69	31,2
Bad habits	3	2,3	8	3,6
Professional Hazards	38	23	60	27,1
Age under 18 after 30	11	8,5	14	6,33
History of abortion	48	37,2	99	44,7
DPR	127	98,4	220	99,5
Early gestosis	129	100	221	100
Preeclampsia c. e.b.	15	11,6	30	13,5
Eclampsia	2	1,5	6	2,7
Ultrasound oligohydramnios	9	6,9	20	9,0
Ultrasound Polyhydramnios	58	44,9	125	56,5
Ultrasound of FPN and NK	49	37,9	98	44,3
PIOV up to 22 weeks	1	0,77	2	0,90
PIOV up to 36 weeks	69	53,4	100	45,2
NRP detachment	0	0	5	2,26
Respiratory diseases	1	0,77	6	2,7
SS diseases	2	1,5	12	5,4
Hypertensive drugs	8	6,2	25	11,3
Anemia	100	77,5	105	47,5
Kidney pathology	12	9,3	16	12,4

We were faced with the following questions: What activities could save the pregnancy? Could the timely hospitalization and ongoing therapy in 129 pregnant women in whom the pregnancy persisted be the reason for the preservation of pregnancy, and what methods of treatment were carried out for them? In our studies, it was found that women received the following therapy: to threaten and eliminate tone, they were prescribed nifedipine tablets 10 mg 3 times a day under the control of blood pressure for 4-5 days, hormone therapy, depending on the threat, indomethacin suppositories 100 mg 2 times per day 4 days rectally, antibiotics were prescribed for the kidneys 2 times a day, tutukon 30 ml 3 times a day, Canephron 1 tablet 3 times a day, kidney tea, panangin, riboxin, tivortin, cocarboxylase were prescribed for the pathology of cardiovascular pathology.

As can be seen from Table 3.5, therapeutic measures were carried out for all pregnant women. but the above treatment measures did not give the expected effect.

Table 3.5

Table of therapy according to ICD standards

D.Z	Was held		Not prov.		The effect of the treatment (+)		effect from treatment (-)	
	350	%	350	%	350	%	350	%
Threatening PR	127	36,2	87	24,8	127	36,5	87	124,8
Preeclampsia	53	15,1	0	0	45	12,8	8	2,28
Hyp. violations	33	9,4	0	0	27	7,1	6	1,7
SS diseases	14	4,0	0	0	11	3,14	3	0,85
Anemia	205	58,5	0	0	185	52,8	20	5,7

Almost all pregnant women were at risk of premature birth, in particular, 87 pregnant women did not receive adequate therapy, due to the fact that these pregnant women went to the hospital too late, often with labor activity already started.

If we pay attention to the fact that many somatic pathologies did not respond to therapy, which probably could also affect the development of PIOV and PR. Fetoplacental disorders were not treated separately, which, in our opinion, could also lead to PIOV and PR.

Other laboratory tests, such as a complete blood count, urine, a smear for flora, blood clotting did not provide accurate diagnostic information.

Thus, a clinical analysis of a retrospective study of preterm birth and premature rupture of amniotic fluid showed that the risk factors for this pathology include a history of preterm birth, threats of spontaneous miscarriage, inflammatory diseases of the uterus, colpitis, abortion, hypertensive disorders.

Lately identified risk factors for the development of AR and PIOV in 63.1% (out of 350) cases ended in AR. At the same time, the question arises why more than half of the women studied still had PIOV and PR.

In our opinion, under such circumstances, biochemical markers of premature rupture of water and preterm labor, which can play a major role in the development of the above conditions, remain unexplored.

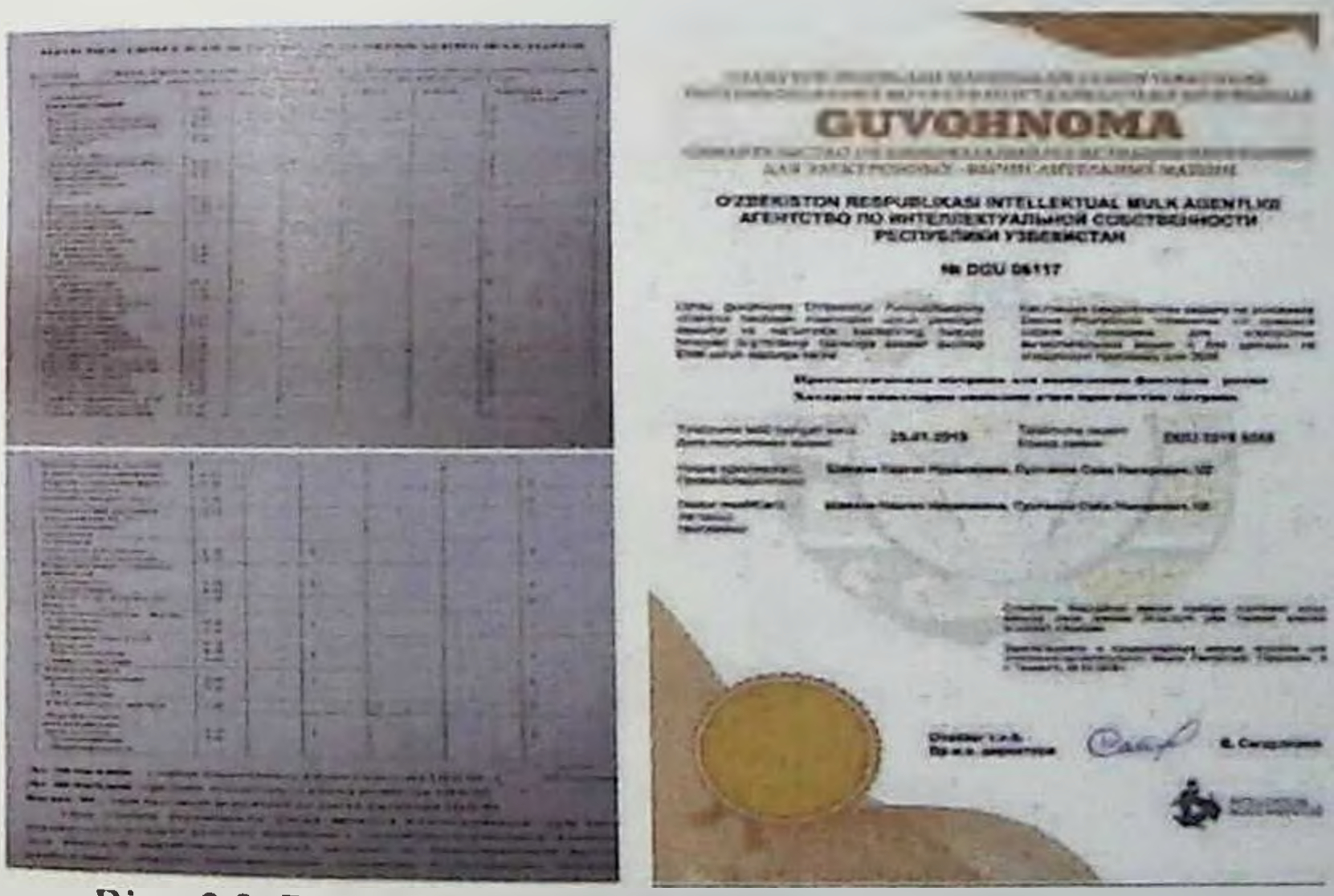
In connection with the data obtained, we decided, on the basis of risk factors, to draw up a prognostic map of the retrospective group, to study the biochemical aspects of the development of PIOV.

§ 3.2. Assessment of the functional state (prospective analysis) of pregnant women at risk for premature rupture of amniotic fluid

To determine the optimization of the management of pregnant women with the threat of preterm birth, we observed 128 women at a gestational age of 30-34 weeks, whose pregnancy was complicated with the threat of preterm birth. All pregnant women who were under our supervision were hospitalized in the department of pathology of pregnant women in the Regional Perinatal Center of Samarkand, as well as in the department of the clinical base of the Department of Obstetrics and Gynecology of SamMI for the period from 2016 to 2019.

All pregnant women included in the study were comparable in age and somatic health.

To collect anamnesis, we used ***"Prognostic matrix for identifying risk factors"*** (according to the computer program created by us (DGU 06117 dated January 25, 2019; Fig. 3.3).



Rice. 3.3. Predictive matrix to identify risk factors.

A prognostic matrix was developed according to the anamnesis and clinical symptoms, using the method of normalization of intensive indicators (NIP) (E.N

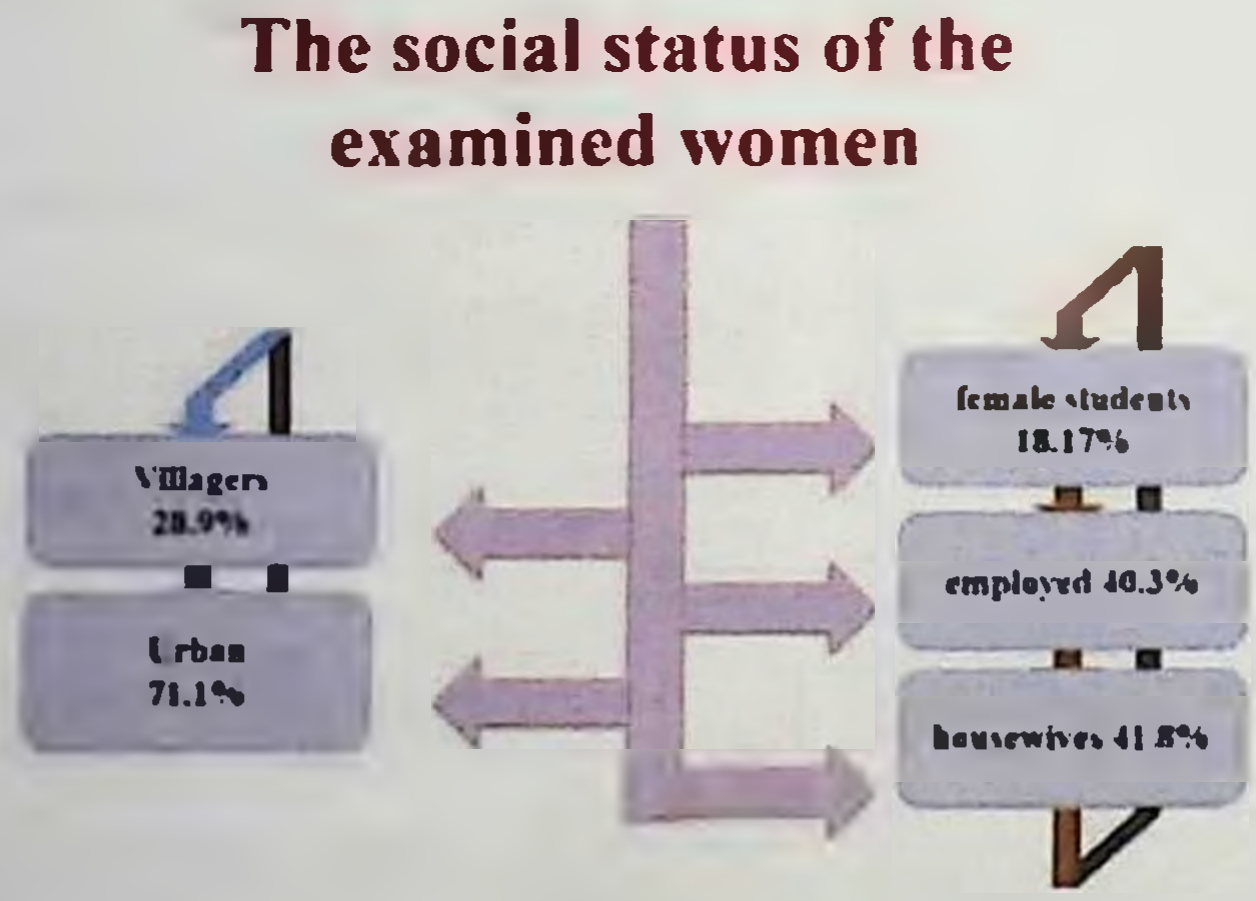
Shigana 2008), which will allow dividing 93 subjects into three groups (the method is described in the fifth chapter).

Women were divided into 3 groups:

- Group 1 – low probability of development of PR;
- Group 2 - medium, probability of development of PR;
- Group 3 - high probability of developing PR and PIOV

The age of women ranged from 19 to 38 years. The youngest age at the onset of preterm birth is 18 years, and the later is 38 years, averaging 27 ± 2.9. The main group consisted of every second woman of reproductive age from 25 to 32 years in all groups. In the high-risk group, every third woman was aged 28-35 years (Table 3.6).

In all 3 groups, women were mostly Uzbeks. Residents of the village - 37 (28.9%); urban - 91 (71.1%). According to the social status of those surveyed (Fig. 3.4): students - 18.17%, working - 40.3%, housewives - 41.8%.



Rice. 3.4. The social status of the examined women

Table 3.6.

The social status of the examined women

Age	Main group PIOV (n=93)		Control group PR and PIOV (n=35)	
	abs.	%	abs.	%
18-20 years old	9	9,6	2	5.7
21-24 years old	29	31.1	15	42.8
25-29 years old	38	40.8	7	20
30-33 years old	11	11.8	8	22.8
34-35 years old	6	6,4	3	8,5
Social status				
Housewives	39	41.8	12	34,3
Employees	37	40.3	14	40,0
Students	17	18.2	9	25,7

An analysis of the weight-height ratios in the examined pregnant women did not reveal any deviations from the population norms. The average body weight was 71.1±2.1, 78.3±2.2, 79.8±2.0 kg, the average height was 166.1±3.2, 165.4±3.9 and 167, 9±4.6 cm in groups 1, 2 and 3, respectively.

Strictly healthy women were included in the control group by selection; if a pathology of the obstetric or EG anamnesis was detected, further observations were stopped.

The onset of menarche varied from 10 to 18 years, the average for the entire group of patients was 13.1±0.3 years.

- Early menarche (before 11 years) was in 4 women
- Belated - older than 16 years in 8 women.

In the general group of examined women, menstrual dysfunction (oligomenorrhea, algomenorrhea) was 15 women (16.1%)

Table 3.7.

Gynecological history of the examined pregnant women

Nosological forms	Main group n=93 (%)
Menstrual disorders	15 (16.1%)
cervicitis	21 (45.7)
Cervical erosion	7 (7.5%)
Chronic endometritis	43 (46.2)
Inflammation of the appendages	36 (38.7%).
uterine fibroids	6 (6.4%).
Infertility I and II	13 (14%)

Of the gynecological diseases, inflammation of the uterus and appendages occurred in history in 36 women out of 93 pregnant women (38.7%).

7 (7.5%) of the 93 women studied had erosion of the cervix.

Uterine fibroids were diagnosed before the onset of this pregnancy in 6 women out of 93 studied (6.4%).

Of the surveyed 93 - pregnant women.

- Primiparous 46 (49.4%)
- multiparous47(50.6%)

As can be seen from Table 3.7, 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 background can also lead to PIOV and PR.

Table 3.8.

Table for assessing the risk of developing PIOV and PR by collecting general data during a given pregnancy (n=93)

Risk factors	Celebrated	%	Not noted	%
Stress	36	38,7	57	61,2
Bad habits	24	25,8	69	74,1
Occupational hazards	28	30,1	65	69,8
Age under 18 after 30	12	12,9	81	87,0
Allergic background	23	24,7	70	75,2
Stomatitis	12	12,9	81	87,0
Use of antibiotics	25	26,8	68	73,1

The obstetric anamnesis was also studied in the main group according to the survey matrix. As can be seen from Table 3.9, the study and identification of anamnesis has a lot of information for determining and identifying PIOV and PR. The highest numbers rest on the threat of interruption and preeclampsia 100% of cases, abortions 36.5%, gynecological diseases 23.6%, spotting 56.9%, preeclampsia 15.0%, eclampsia 1.07%, PIOV up to 22 weeks 19 , 3%, PIOV up to 36 weeks 7.5%, ONRP 2.1%, uterine scar 11.8%.

Table 3.9.

Table for assessing the risk of developing PIOV and PR by collecting an obstetric history during this pregnancy (n=93).

Risk factors	Celebrated	%	Didn't notice	%
abortion	34	36,5	59	63,4
Gynecological diseases	22	23,6	71	79,5
Bloody discharge from the genital tract	53	56,9	40	43,0
	53	56,9		
	23	24,7		
	9	9,6		
I trimester	93	100	-	-
	93	100	-	-
	39	41,9	54	58,0
	9	9,6	84	90,3
II trimester	93	100	-	-
	93	100	-	-
	41	44,0	52	55,9
III trimester	14	15,0	79	84,9
	9	9,6		
	5	5,3		
We take the threat of interruption	1	1,07	92	98,9
I trimester	18	19,3	75	80,6
II trimester	7	7,5	86	92,4
III trimester	2	2,1	91	97,8
Gestosis during pregnancy	11	11,8	82	88,1

The results of Table 3.10 showed that CVD amounted to 6.4%, hypertensive disorders - 13.9%, kidney disease - 16.2%, respiratory diseases 11.8%, liver pathology 21.5%, anemia 60.2% , metabolic disorders 25, 8%, Rh negative blood 2 cases.

Table 3.10.

Table for assessing the risk of developing PIOV and PR by determining extra-genital pathology (n=93)

Risk factors	Celebrated	%	Not noted	%
Cardiovascular diseases	6	6,4	87	93,5
Hypertensive Disorders	13 7 6	13,9 7,5 6,45	80	86,0
-Gestational hypertension	15 11 4	16,2 11,8 4.3	78	83,8
-Chronic hypertension	11	11,8	82	88,1
kidney disease	20 2 13 5	21.5 2,1 13,9 5.3	73	78,4
- Gestational pyelonephritis	56 37 9	60,2 39,7 9,6	37	39,7
-Chronic pyelonephritis	24 14 10	25,8 15,0 10,5	69	74,1

Thus, there was no significant difference in the frequency of gynecological pathology in the examined groups in pregnant women.

Based on the study of the reproductive history, it was found that every second was primiparous. One birth in history was in 46 women (42.78%), 2 births - in 32 (29.76%), 3 births - in 8 (7.44%), and in 7 women (6.51%) before the onset of this pregnancy was 4 births.

In all the studied groups, women had a history of different outcomes of a previous pregnancy, the main share of which is occupied by the combined outcomes of several pregnancies, which could later cause PR. Women who previously had the above factors are at risk for the development of PR and PIOV of pregnancy.

Based on the prospective medical history (according to the matrix), and the identification of the most significant risk factors for PIOV and PR, a prognostic map

was compiled using the method of normalization of intensive indicators (IIP) by E.N. Shigan with the help of which it was planned to divide all the examined (n=93) into 3 groups according to the likelihood of developing PIOV and PR.

§ 3.3. Development of a prognostic risk map for the development of premature rupture of amniotic fluid and preterm birth

At present, computational methods for diagnosing and predicting a number of somatic diseases have been developed (EN Shigan, 2008). Important in the prevention of PR and PIOV is the risk factors for the development of PIOV and PR by comparing various prognostic criteria. We have developed prognostic matrices according to the anamnesis, clinical symptoms, using the method of normalization of intensive indicators (IIP) by E.N. Shigan.

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

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

The essence of the method lies in the fact that instead of the usual intensive indicators, the NIP is used, which can be calculated by the formula: N = r / M, where: N is the normalized intensive indicator (NIP), r is the intensive indicator TL coC per hundred examined, M is "normalizing indicator".

In this case, the average frequency of PIOV according to the data of the entire study (per 100 examined) is taken as a normalizing value.

For example, in PIOV, the incidence of PIOV (r) was 46.7, and NP with PIOV 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 PIOV, NIP = 46.7/51, 0 = 0.934, and for PIOV, NIP 2 =54.5/51, 0 = 1.069. risk (R)= 1.032/0.934= 1.167.

The NIP for all other risk factors was calculated similarly.

The obtained NIP are the initial standard by which it is possible to give an integrated assessment of the risk of developing PIOT, both for a single factor and for their complex.

As is known, risk factors have different strength of influence on the development of PIOV. Therefore, we took into account the value of the relative risk index for each factor. Knowing that the relative risk indicator (R) of the occurrence of the disease and the normalized intensive indicator (N), it is possible to determine the strength of the influence on the development of PIOT of each individual factor, i.e. predictive coefficient (X).

This value is determined as follows: X = (R)x(N), X is an integrated indicator of risk from the strength of the influence of an individual factor (prognostic coefficient); (N) - NIP for the development of IRIP; (R) - relative risk indicator.

If we take into account that in our example, the relative risk indicator (R) was 1.17, NIP 1 = 0.916, NIP 2 = 1.069, then the integrated indicator of the strength of influence of each individual factor, i.e. prognostic coefficient was 1.17-0.916= 1.072 if PIOV 1.17x 1.069=1.25 if PIOV.

The prognostic matrix (Table 3.11) includes all the risk factors for the development of PIOV identified for predicting with their gradation and the values of the integrated risk indicator from the strength of the influence of a single factor (X), the relative risk indicator for each factor (R) and their sum for a complex of factors (RN), as well as a normalizing value - the average frequency of PIOV according to the data of the entire study (N).

In addition to the prognostic table, we determined the possible range of risk values for the complex of factors taken. The possible risk range for PIOV 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 value of the risk of this pathology.

For example, in Table 3.5 for an integrated risk assessment for the development of PIOV, the minimum values were as follows: 1.96+1.12+1.64+1.16+1.29+1, 40+1.49+1, 34+1 .46+1.49+1.47+1.14=17.24

Then, similarly, 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

Table 3.11.

Prognostic map for a comprehensive risk assessment for the development of PIOT and ADR

Risk factors	Yes/No	%	NIP	R	X	X Min	X Max
Stress	Yes/no	96,8/3,2	1,94/0,06	44,6	1,96/85,93	1,96	85,93
Bad habits	Yes/no	55,8/44,2	1,12/0,89	3,26	1.12/1,41	1,12	1.41
professional hazards	Yes/no	64,5/35,5	1,64/0,36	4,56	1.64/7,47	1,64	7,47
Age from 18 to 30	Yes/no	24,5/75,5	1,16/0,84	1,38	1.16/1,60	1,16	1,60
History of abortion	Yes/no	84,5/15,5	1,49/0,51	5,48	1.29/2,34	1,29	2,34
Gynecological diseases in anam.	Yes/no	65,3/34,7	1,46/0,54	3,89	1,40/3,22	1,40	3,22
Threat of interruption	Yes/no	76,4/23,6	1,29/0,71	3,24	1,49/4,35	1,49	4,35
Early gestosis	Yes/no	65,5/34,5	1,40/0,60	2,76	1,34/4,35	1,34	2,72
We take preeclampsia	Yes/no	68,3/31,7	1,49/0,51	3,28	1,46/3,95	1,46	3,95
We take eclampsia.	Yes/no	75,4/24,5	1,34/0,66	3,89	1,49/4,35	1,49	4,35
oligohydramnios	Yes/no	24,8/75,2	1,46\0,54	1,78	1,47/4,08	1,47	4,08
Polyhydramnios	Yes/no	82,5/17,5	1,49/0,51	2,98	1,44/3,65	1,44	3,65
PIOV up to 22 weeks	Yes/no	78,2/21,8	1,47\0,53	4,22	1,29/2,34	1,29	2,34
PIOV up to 36 weeks	Yes/no	56,5/43,3	1,44/0,56	1,68	1,40/3,22	1,40	3,22
NRP detachment	Yes/no	0,5/0,3	1,34\0,66	1,56	1,49/4,35	1,49	4,35
Bloody discharge from p /.p.	Yes/no	6,5/3,3	1,32/0,68	1,08	1,34/2,72	1,34	2,72
Respiratory diseases	Yes/no	1,5/3,3	1,24/0,76	1,94	1,46/3,95	1,46	3,95
Rhesus (-) blood not immunized	Yes/no	1,0/0,2	1,38/0,62	2,38	1,49/4,35	1,49	4,35
SS diseases	Yes/no	56,5/43,3	1,46/0,54	1,56	1,47/4,08	1,47	4,08
Hypertensive drugs	Yes/no	76,5/43,3	1,44/0,56	1,44	1,44/3,65	1,44	3,65
Liver pathology	Yes/no	6,5/3,3	1,36/0,64	2,35	1,34/2,72	1,34	2,72

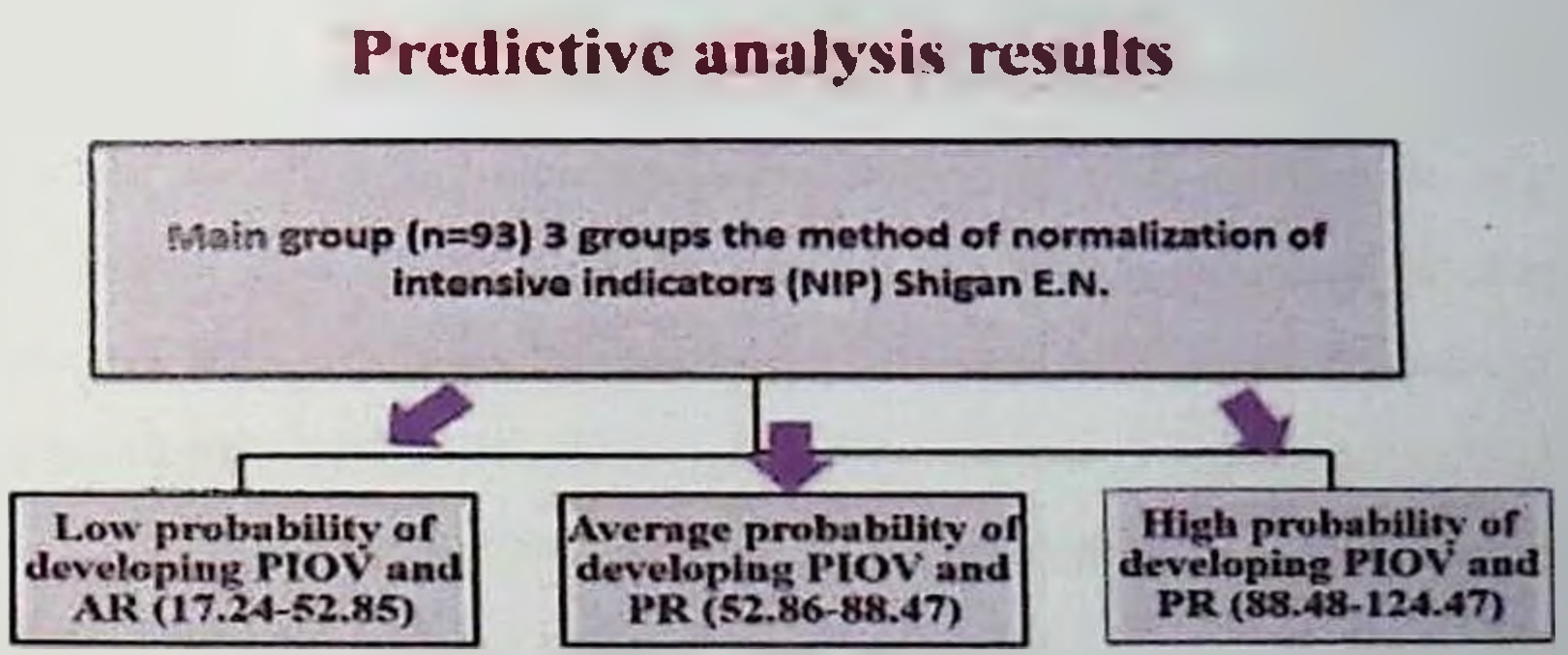
kidney disease	Yes/no	1.5/4.3	1,37/0,63	2.12	1.46/3.95	1.46	3.95
severe anemia	Yes/no	86.5/53.3	1,80/0.20	4.85	1.49/4.35	1.49	4.35
Obesity	Yes/no	15/3.3	1,72/0,28	2,32	1.47/4,08	1 47	4,08

It follows that the higher the NIP value of the risk of developing PIOV, the higher the risk of developing it in a given individual and the more grounds for his allocation to the group of unfavorable prognosis.

Women were divided into 3 groups according to anamnestic risk factors for the development of PIOV (Fig. 3.5):

- group - low probability of development of PR;
- Group 2 - medium, probability of development of PR;
- Group 3 - high probability of development of PR and PIOT;

In this regard, we have identified a possible risk range (17.24-124.07), as well as subranges. In practice, the entire risk range is better by three intervals: a low probability (17.24-52.85), an average probability (52.86-88.47), and a high probability (88.48-124.47) of the risk of developing PIOV.



Rice. 3.6. Predictive analysis results

With a low probability of risk, the prognosis is favorable, with an average probability, attention should be paid to the condition of the pregnant woman, and

with a high probability, an unfavorable 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 for the risk group for the occurrence of pathology were determined, based on the somatic and obstetric anamnesis.

§ 3.4. Evaluation of fetal fibronectin in pregnant women at risk of developing premature rupture of amniotic fluid and preterm birth

Another predictor of PIOV was fetal fibronectin (FFn), measured in vaginal secretions during pregnancy. As a rule, the test for FFn is positive 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. The appearance of FFn in the vaginal secretion indicates a potential risk of activation of proteolytic enzymes and destruction of the membranes in the places of accumulation of FFn, which can lead to PIOV

The detection of FFn in the vaginal secretion in the period from 30 to 34 weeks of pregnancy indicates a violation of the fixation of the fetus to the uterine wall and the threat of abortion. FFn is detected earlier than other signs of preterm labor: changes in the width of the cervix or the appearance of contractions and PIOV.

Significantly more often ($p<0.05$) a positive test result for fetal fibronectin in a vaginal smear was found in women with a high risk of PIOV, relative to patients with low and medium risk, determined by the prognostic map (Table 3.12).

Table 3.12

Fetal fibronectin test results

(n=93)	(n=17)		(n=31)		(n=45)		
	abs	%	abs	%	abs	%	(n=93)
Test (+)	3	3.22	21	22,6	38	40, 8	66, 6%
Test (-)	14	15,7	10	10,1	7	7, 6	33, 4%
Test (-)Test (+)							
	abs		%	abs		%	

K.G.(n=35)	2	5.7	33	94,3

In general, in 66.6% of pregnant women of the main group, the test for FFn was positive, while in the physiological course of pregnancy it was only in 5.7% of cases ($p<0.05$). The data obtained indicate that the increase in FFn in the gestational age of 30-34 weeks of pregnancy, apparently, is associated with rupture of the amniotic membrane.

The dynamics of fetal fibronectin was also studied depending on the timing of women's pregnancy (Table 3.13). According to the data obtained in the main group, out of 93 pregnant women, the test was positive in 62 pregnant women at different gestational ages.

Table 3.13.

Dynamics of the level of fetal fibronectin depending on the duration of pregnancy in women

	30 Week		31 Week		32 Week		33 Week		34 Week		Total Qnty
	abs	%	abs	%	abs	%	abs	%	abs	%	
Test +	9	9,6	6	6,4	11	11,8	17	18,2	19	20,4	(n=62)
Test -	5	5,3	7	7,5	4	4,3	9	9,6	6	6,4	(n=31)
Control group (n=35)											
Test +									2	5.7	(n=2)
Test -	-	-	-	-	-	-	-	-			(n=33)

In 9 (9.6%) pregnant women at 30 weeks of gestation, in 6 (6.4%) - at 31 weeks of gestation, in 11 (11.8%) - at 32 weeks of gestation, in 17 (18.2%) at 33 weeks' gestation and in 19 (20.4%) at 34 weeks' gestation.

In the control group out of 35 pregnant women, it was found only in 2 (5.71%) at a gestational age of 34 weeks. As can be seen from the table, the longer the gestation period, the more often the result is positive. But given the fact that in pregnant women, fetal fibronectin is normally allowed up to 8 weeks of gestation and after 37 weeks of gestation, the data obtained indicate that this method can be attributed to the prognosis and one of the risk factors for the development of PIOV.

Thus: A clinical analysis of a retrospective study of preterm birth and premature rupture of amniotic fluid showed that risk factors for this pathology include a history of premature birth, threats of spontaneous miscarriage, inflammatory diseases of the uterus, colpitis, abortion, hypertensive disorders. Lately identified risk factors for the development of PIOV and AR in 63.1% (out of 350) cases ended in PR.

Based on the study of the reproductive history, it was found that every second was primiparous. One birth in history was in 46 women (42.78%), 2 births - in 32

(29.76%), 3 births - in 8 (7.44%), and in 7 women (6.51%) before the onset of this pregnancy was 4 births.

In all the studied groups, women had a history of different outcomes of a previous pregnancy, the main share of which is occupied by the combined outcomes of several pregnancies, which could later cause PR. Women who previously had the above factors are at risk for the development of PR and PIOV of pregnancy According to the results obtained, in 66.6% of pregnant women of the main group, the test for FFn was positive, while in the physiological course of pregnancy it was only in 5.7% of cases ($p<0.05$). The data obtained indicate that the increase in FFn in the gestational age of 30-34 weeks of pregnancy, apparently, is associated with rupture of the amniotic membrane.

CHAPTER IV. EVALUATION OF THE PROGNOSTIC SIGNIFICANCE OF BIOCHEMICAL INDICATORS IN PREGNANT WOMEN WITH A RISK OF PREMATURE ROUTING OF AMniotic Fluids

§ 4.1. Features of indicators of the hemostasis system in the blood in pregnant women with the risk of developing premature rupture of amniotic fluid

It should be noted that in 50-60% of observations, the manifesting sign of the threat of abortion is prenatal rupture of amniotic fluid.

Free radicals are known to be normal components of metabolic processes in cells, they are formed during redox reactions in mitochondria, the endoplasmic reticulum, and also in the process of phagocytosis. Free radicals are also formed in systems containing cations of variable valence, as well as in the process of auto-oxidation of catecholamines, thiols, hydroquinones. The latter indicates the possibility of excessive formation of free radicals in a wide variety of typical

pathological processes and conditions that complicate the course of gestation [20, p. 41-42].

To partially resolve this issue, a comparative assessment of the same indicators of the state of lipid peroxidation processes (DC, MDA) in the venous blood of pregnant women with the indicated complication of the gestational period was carried out at the same time of pathology development (Table 4.1).

Table 4.1

Blood levels of lipid peroxidation products in pregnant women at risk of PIOV

Indicators	Control group n=21	Main group n=72
Diene conjugates, μm/l	14,05±0,49	31,56±1,51*
Malondialdehyde, μmol/l	5,25±0,20	7,78±0,28*

Note: *- significance of differences between groups P < 0.05

As the results of our studies have shown, PIOV is formed against the background of systemic activation of lipid peroxidation processes, as evidenced by an increase in the blood levels of all the studied parameters.

An increase in the level of toxic products of lipid peroxidation in the blood of pregnant women at the risk of early PIOV is, of course, one of the pathogenetic factors of free-radical modification of lipid and protein components of the blood, degradation of biological membranes of blood cells, endothelial dysfunction, disorders of the coagulation potential of the blood, naturally associated with various miscarriages. etiology.

Thus, one of the pathogenetic factors of membrane failure and the risk of PIOV is the activation of free-radical destabilization of biological membranes, accompanied by an excessive increase in the content of peroxide compounds in the blood, as well

as malondialdehyde and diene conjugates with a pronounced universal cytopathogenic effect.

§4.2. The nature of changes in markers of endothelial dysfunction and hemostasiological parameters in the blood of pregnant women with a risk of premature rupture of amniotic fluid

Recently, vascular and hemodynamic disorders in pregnant women, which are observed in various somatic diseases, have traditionally been considered PIOV risk factors. At the heart of violations of hemodynamics and microcirculation, including in the uteroplacental pool, developing with preeclampsia and various somatic pathologies, is a generalized dysfunction of the endothelium. There are several hypotheses that explain the development of endothelial dysfunction in the pathological course of pregnancy. The theory of placental ischemia received the greatest evidence. Absolute or relative placental ischemia may develop primarily as a result of insufficient invasion of the trophoblast into the spiral arteries of the decidua, or secondarily against the background of diffuse endothelial pathology observed in patients with somatic pathology. As a result of placental ischemia, endothelial-damaging substances enter the bloodstream, an imbalance occurs between vasoconstrictors and vasodilators, between the thrombogenic potential of the vascular wall and its thromboresistance, regional blood flow is disturbed, and progressive disorders of vital organs and placental functions occur. Based on the foregoing, we studied the functional state of the endothelium in women at risk of PIOV. As is known, thrombomodulin, soluble adhesion molecules - ICAM-1 and VCAM-1, as well as von Willebrand factor, which promotes platelet adhesion to damaged endothelium, are highly specific markers of the functional state of the endothelium. Platelets are another source of von Willebrand factor. Fibronectin is a subendothelial extracellular glycoprotein that is also found in platelets and plasma and is an important platelet adhesion factor at the site of vascular injury.

In our studies, presented in the table, it is shown that an increased level of plasma fibronectin in the control group occurs in 13% of cases, while in the

group with a risk of PIOV it is increased in 25% of cases, the content of endothelial dysfunction markers such as thrombomodulin, soluble adhesion molecules , von Willebrand factor and fibronectin, at risk for PIOV had a peculiar dynamics.

The results of our study showed an increase in the content of thrombomodulin, sICAM-1, von Willebrand factor, fibronectin in the maternal circulation in PIOV, which indicates the activation and stimulation of endotheliocytes in this pathology. In women with PIOV, a statistically significant increase in the content of fibronectin in the blood was observed, which, apparently, is associated with damage to the trophoblast. The source of the increase in the content of thrombomodulin in the blood of these women also seems to be the trophoblast. As you know, as the gestational age increases, the degree of thrombinemia increases, which is detected by an increase in the content of soluble fibrin-monomeric complexes (SFMK), fibrinogen degradation products (PDF) and fibrin (D-dimer). These changes are associated with the intensification of intravascular blood coagulation, including in the uteroplacental blood flow. The severity of shifts in the vascular-platelet, coagulation, fibrinolytic and anticoagulant links of hemostasis is determined by the characteristics of the course of pregnancy and the initial state of the coagulation system [99, p.516].

These factors are interrelated and interdependent; their violations often lead to termination of pregnancy at different times, which makes timely diagnosis of intravascular thrombosis and its therapy using specific and non-specific methods that affect individual links of pathogenesis relevant.

It is extremely important to study the blood content of pregnant women at risk of PIOV of indicators of the anticoagulant potential of the blood, in particular, the content of the main anticoagulant - antithrombin III. At the risk of developing PIOV, its amount was 85.15±5.31 mg/l, which is significantly lower than in women with a physiological course of pregnancy, which indicates the important

role of antithrombin III deficiency in the development of these terrible complications of pregnancy (Table 4.2).

Table 4.2

The content of markers of endothelial dysfunction in the blood

Indicators	Group of examined pregnant women	
	Control group,n= 21	Main group., n=72
Thrombomodulin, ng/ml	6,74±0,20	8,93±0,28*
Willebrand factor, ng/ml	109,28±2,59	169,57±3,67*
Fibronectin, ng/ml	233,17±8,14	504,77±10,31*
sICAM-1, ng/ml	998,88±15,0	1307,11±26,14*
sVCAM-1, ng/ml	742,30±9,86	798,97±8,70*

Note: *-significance of differences P <0.05

Taking into account that the coagulation potential according to the APTT, PT and RFMK tests in women at risk of PIOV tended to increase, it can be assumed that the decrease in antithrombin activity in our studies is associated with the depletion of the anticoagulant system and may be the cause of the development of gross shifts in the hemostasis system.

We also screened disorders in the protein C system in pregnant women at risk of PIOV, which revealed a statistically significant increase in the amount of protein C in the blood. Therefore, in pregnant women at risk of PIOV, a decrease in the content of antithrombin III is detected, against the background of an increase in the level of protein C, due to high values of thrombomodulin. In order to identify the activation of intravascular coagulation in women with premature rupture of amniotic fluid, the content of D-dimer in the blood was examined (Table 4.3).

Table 4.3

The content of markers of endothelial dysfunction in the blood

Group	Protein C %	D-dimer ng/ml	Antithrombin %

Examined	86,61±3,48	179,25±4,76	109,45±3,90
Control group, n= 21	128,51±5,10*	318,05±5,62*	86,16±2,90*

Note: *-significance of differences P <0.05

In 49.8% of women at risk of PIOV, an increase in the content of D-dimer in the blood above 300 ng/ml was revealed. This indicates the processes of fibrin cross-polymerization in the process of intravascular blood coagulation observed. Therefore, in PIOV, there is a deficiency of natural anticoagulants (antithrombin III) and activation of intravascular coagulation (an increase in the content of protein C and D-dimer). It is possible that an important pathogenetic risk factor for the development of PIOV can be the presence of congenital defects in the hemostasis system, which create an unfavorable premorbid background and contribute to the manifestation of hypercoagulability in the intervillous space.

Thus, on the basis of the obtained research results, it can be indicated that the detection of an increase in the content of D-dimer, protein C, antithrombin III in the blood has the highest specificity, positive and negative predictive value and diagnostic accuracy, and the highest sensitivity is an increase in the content of thrombomodulin. Therefore, the determination of blood levels of a number of markers of endothelial dysfunction, such as thrombomodulin and fibronectin, as well as a marker of intravascular blood coagulation D-dimer, protein C, is diagnostically and prognostically significant in the diagnosis of PIOV in pregnant women.

The content of C-3 and C-4 fractions of complement was also studied (Table 4.4).

Activation of the complement system was detected, which was confirmed by a significant increase in the content of the complement component C3 in the blood serum of patients - by 1.9 times and the complement component C4 - by 2.0 times compared with similar indicators of healthy pregnant women.

Table 4.4

Indicators of the content of C3, C4 fractions of the complement system in blood serum

Indicators	Main group n=72	Control group n=21
Complement component C3 (g/l)	2,25±0,09*	1,15±0,07
Complement component C4 (g/l)	0,57±0,02*	0,27±0,02

Note: *-significance of differences P <0.05

As is known [4, p. 14], activation of the complement system due to the inclusion of the classical and alternative cascades, closely related to the activation of Hageman factor XII, the kallikrein-kinin system, platelets, the formation of immune complexes and the state of metabolic acidosis, which is accompanied by activation of the C3 fraction and increased blood coagulation by an internal mechanism . At the same time, the expression of IL-1 and TNF-b support the processes of complement activation, providing the release of plasminogen activator inhibitor, tissue factor, from monocytes, macrophages and endothelial cells, which is accompanied by platelet aggregation. Proteolytic enzymes of the complement system stimulate the release of biologically active substances from platelets, micro-, macrophages, mast cells, cause retraction of endothelial cells, which promotes adhesion and aggregation of platelets on the exposed collagen of the vascular wall.

Activated platelets and leukocytes complete a vicious circle, inducing the formation of new portions of active complement fractions, in particular C3a.

The obtained results of the studies allow us to conclude that there is a pathogenetic relationship between an increase in the levels of C3-, C4-complement fractions and procoagulant changes in pregnant women with PIOV.

§4.3. Comparative characteristics of the content of matrix metalloproteinases in the blood serum of pregnant women with a risk of premature rupture of amniotic fluid

As is known, the presence of PIOV in preterm 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. The main problem that determines the difficulties in the timely diagnosis of PIOV is due to the polyetiology of miscarriage. The cause of PIOV can be gene mutations and chromosomal disorders, hereditary predisposition, immune and endocrine disorders, infectious diseases, thrombophilic disorders, anatomical causes (malformations of the uterus, genital infantilism, uterine hypoplasia, isthmic-cervical insufficiency, uterine fibroids, synechia). Meanwhile, a clear understanding of the diagnosis and treatment of PIOV in women with preterm pregnancy still does not exist. During the physiological course of pregnancy, simultaneously with the maturation of the cervix, the fetal membranes in the region of the internal os soften: along with the thickening of the connective tissue, the layer of cytotrophoblast and decidua becomes thinner, and the connections between the amnion and the chorion are broken. This occurs under the influence of phospholipases, eicosanoids (especially prostaglandin E 2), cytokines, proteases (elastase, matrix metalloproteinases). However, the launch of similar mechanisms can also be caused by pathological processes, for example, local inflammation (intra-amniotic infection), the formation of retrochorial hematoma, placental abruption. The biomechanical properties of the uterine vessels also change significantly during pregnancy in the direction of increased extensibility. First of all, this is due to a change in the volume of the intercellular matrix of blood vessels, the composition of collagen, fiber orientation, and a decrease in elastin.

Matrix metalloproteinases types 1 and 9 (MMP-1 and MMP-9), which play a central role in the metabolism of connective tissue proteins and are specific markers of collagen breakdown, were studied in blood serum of pregnant women at risk of PIOV.

Biochemical parameters of blood serum in pregnant women with PIOV are shown in fig. 4.1.

Attention was drawn to a significant increase in the content of MMP-1 in pregnant women with PIOV as the main enzyme that denatures the fibrillar collagen of the extracellular matrix.

Matrix metalloproteinases in the blood of pregnant women

Control group (n=12)	73,97±2.89	4,37±0,27	7,72±0,32	728,34±19,48	0,54
Main group (n=12)	117,91±4,51* (↑1.6)	11,10 ±0,57* (↑2,5)	38,01± 1,58 * (↑4,9)	597, 69±9,46 (↓-0,8)	1,33*

*Note: *- reliability of differences P <0,05*

Rice. 4.1. Comparative characteristics of the content of matrix metalloproteinases in the blood serum of pregnant women at risk of PIOV

Similar changes were revealed in the study of the content of MMP-9, the concentration of which in pregnant women of the main group was 1.6 times higher than in pregnant women of the comparison group, which, according to N.I. Solovieva and O.S. Ryzhakova (2010), may indicate an activation of type IV collagen hydrolysis. The concentration of TIMP-1 in cases of TMJ decreased when compared with the control group.

Increased MMP-9/TIMP-1 coefficients confirm the possibility that the rate of collagen degradation by matrix proteinases exceeds the rate of its synthesis (Fig. 4.2).

Representatives of the MMP groups are also interstitial collagenase MMP-3. which cleave fibrillar collagen of the corresponding types, also into proteoglycans, laminin, fibronectin and amorphous collagens. In our studies, presented in the table .. indicated a significant increase in MMP-3 in pregnant women with PIOV. when compared with the control group.

The revealed imbalance of type I and III collagens due to the high activity of metalloproteases indicates the predominance of the synthesis of type III collagen,

which belongs to embryonic proteins with low strength, which correlates with a systemic decrease in the level of collagen, which determines the integrity of the connective tissue in the amniotic membranes.

A decrease in the synthesis of total collagen and the predominance of its immature fraction with a deficiency of intracellular matrix components that determine the weakening and overstretching of the connective tissue.

Established differences in the quantity, nature of distribution and localization of collagen and elastic fibers, along with a violation of the expression of protein-coding genes, in particular, the MMP and TIMP families, determine the multilevel changes in the microarchitectonics of the amniotic membranes in pregnant women at risk of PIOV.

Thus, in pregnant women at risk of PIOV, there is a change in the activity of matrix metalloproteinases of types 1, 3, 9 in the blood serum, indicating remodeling of the connective tissue, indicating metabolic disorders.

Thus: one of the pathogenetic factors of insolvency of the membranes and the risk of PIOV is the activation of the processes of free-radical destabilization of biological membranes, accompanied by an excessive increase in the content of peroxide compounds in the blood, as well as malondialdehyde and diene conjugates with a pronounced universal cytopathogenic effect.

On the basis of the obtained research results, it can be indicated that the detection of an increase in the content of D-dimer, protein C, antithrombin III in the blood has the highest specificity, positive and negative predictive value and diagnostic accuracy, and the highest sensitivity is an increase in the content of thrombomodulin. Therefore, the determination of blood levels of a number of markers of endothelial dysfunction, such as thrombomodulin and fibronectin, as well as a marker of intravascular blood coagulation D-dimer, protein C, is diagnostically and prognostically significant in the diagnosis of PIOV in pregnant women.

The obtained results of the studies also allow us to conclude that there is a pathogenetic relationship between an increase in the levels of C3-, C4-fractions of complement and procoagulant changes in pregnant women with PIOV.

In pregnant women at risk of PIOV, there is a change in the activity of matrix metalloproteinases of types 1, 3, 9 in the blood serum, indicating remodeling of the connective tissue, indicating metabolic disorders.

CHAPTER V. PREDICTION AND PREVENTION OF THE RISK OF THE DEVELOPMENT OF PREMOTIONAL FLUID

Chapter 5

§ 5.1. Ultrasound results

Ultrasound is the simplest and most informative method of obtaining the necessary information - allowing for constant monitoring of how the process of fetal development is going.

Ultrasound of the cervix is performed using power Doppler mapping, which makes it possible to visualize even the smallest vessels. Thanks to the three-dimensional reconstruction, the image is richer, so pathologically altered areas are detected quite easily and quickly. At the present stage of development of medicine, gynecology and ultrasound are inseparable. Currently, there are no convincing data on the predictive value of the risk of PR [1]. Biophysical screening involves determining the length of the cervix (CCL) using a gynecological examination or transvaginal ultrasound. However, the sensitivity of this method is low (25-30% for gynecological examination and 35-40% for ultrasound), which does not allow using this test as a screening [1, 5]. Biochemical screening includes determination of the levels of fetal fibronectin and phosphorylated protein-1 that binds insulin-like growth factor in the cervico-vaginal secretion in order to determine the risk for PR and PIOV. The disadvantages of the method include the need to use vaginal mirrors and high cost [1, 5, 12].

From the ultrasound data, the study analyzed the amount of amniotic fluid. hypertonicity of the myometrium, with transvaginal echography - the length of the cervix (DSM) in mm, the diameter of the internal cervical os (DVZ), in mm, took into account the presence of varicose veins of the pelvic organs, the condition of the sinuses.

To detect changes in the cervix using ultrasound, it is necessary to take into account its norm (Table 5.1).

An ultrasound study was conducted in both groups to determine the significance of this method in predicting pregnancy and to determine the ways of prevention by observing the identified pathology in dynamics.

Of the 93 pregnant women examined by us with the threat of miscarriage at 30-34 weeks of gestation, we analyzed the data of ultrasound examination (cervicometry) of the cervix.

As can be seen from table 5.2. shortening of the cervix was observed in 42 pregnant women, up to 20 mm in 3, which amounted to 3.2%, in 39 from 20 mm to 28 mm, which amounted to 41.9%. In 51 pregnant women (54.8%) no pathology was observed.

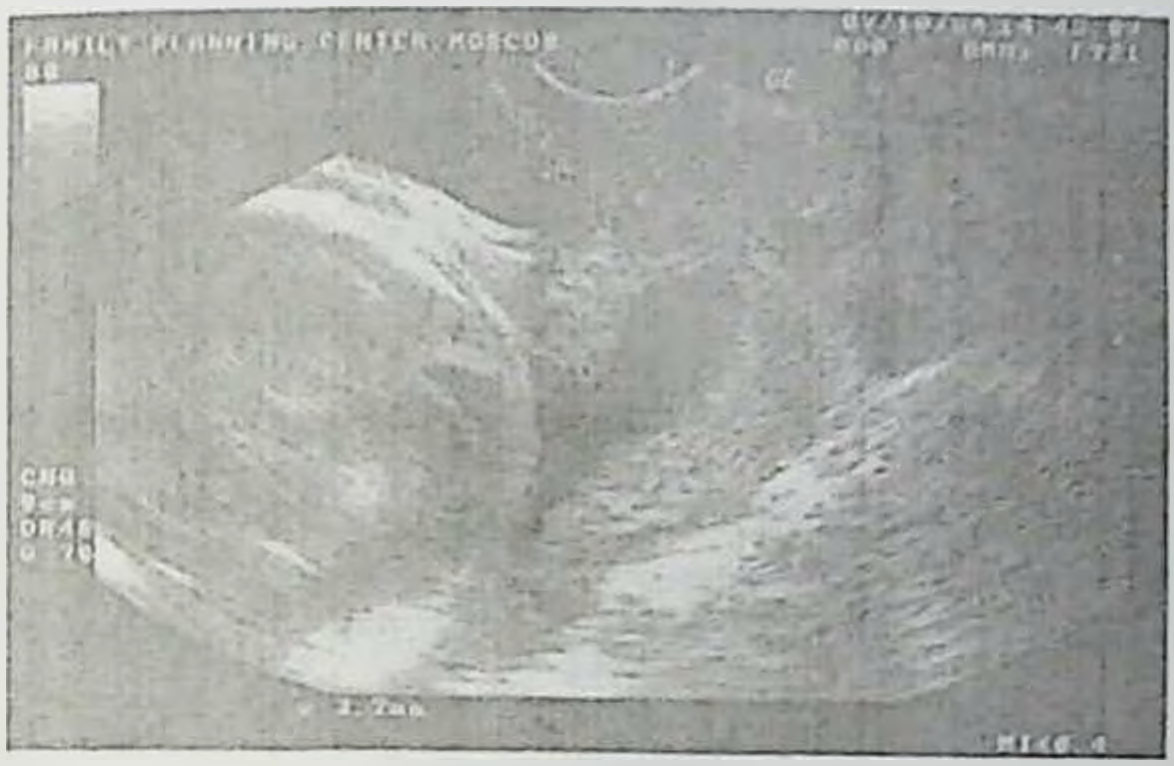
The rate of cervical shortening in patients at 30-34 weeks' gestation appears to be 1.13 mm/week. These indicators were practically identical in the groups of patients who had the threat of PR and PIOV up to 34 weeks.

Table 5.1

The results of the study of ultrasound of the cervix (length in mm)

Length w/m in mm	Number of pregnant women (n=93)	%
From 15-20 mm	3	3,2
From 20-28 mm	39	41, 9
From 28-33 mm	51	54, 8

Also, an ultrasound of the uterus was performed in all pregnant women in the main group, as well as in the control group. As can be seen from the table, almost every pregnant woman has a threat of interruption, a change in the composition of amniotic fluid, a change in the amount of water such as oligohydramnios and polyhydramnios, uterine hypertonicity of both the anterior and posterior walls, impaired placental circulation and varicose veins of the uterus and sinuses.



Rice. 5.1. Echo drawing of the expansion of the internal os and cervical canal

As can be seen from the drawings and tables of the ultrasound of the uterus, the nature of the amniotic fluid was assessed, which was light in 22.5%, and turbid in 77.4%.

Depending on the amount of water, the norm was 20.4%, low water 12.9%, high water 66.6%. The increase in blood circulation reached up to 69%, the threat was observed in almost 55.9%, as well as varicose veins of the uterus and appendages up to 61.2% of cases (Table 5.2).

Table 5.2

The results of the ultrasound of the uterus in both study groups

		Main group (n=93)		Control group (n=35)	
		abs	%	abs	%
Fetal position	Head	87	93,5	34	97,1

	Pelvic	6	6,5	1	2,8
Location of the placenta	front st	59	63,4	23	65,7
	back st	34	36,45	12	34,2
amniotic fluid	Light	21	22,5	33	94,2
	muddy	72	77,44	2	5,7
Number of O.V.	Norm	19	20,4	34	97,1
	oligohydramnios	12	12,9	1	2,8
	Polyhydramnios	62	66,6	0	0
Violation of blood circulation	I degree	65	69,8	1	2,8
	II degree	28	30,1	0	0
Uterine hypertonicity	front wall	52	55,9	2	5,7
	back wall	41	44,0	1	2,8
Threat interruption	Moderate	25	26,8	3	8,5
	Expressed	68	73,1	0	0
Varicose veins of the uterus	Moderate	57	61,2	4	11,4
	Expressed	36	38,7	0	0

It has been established that the changes in hemostasis that were listed above can cause not only the expansion of the uterine veins, but can also lead to rupture of the sinuses of the organ, which can complicate differentiation in the diagnosis and treatment of a practical doctor.

When processing the data of the studied women, it was revealed that kidney pathology in the main group was observed in 49.35% of cases, and in the control group 17%, and liver pathology in the main group 33.74%, in the control group was not observed.

Based on the results obtained, according to the influence of MMP and TIMP on the nature of the distribution and localization of collagen and elastic fibers, it is recommended to prevent the risk of developing PIOV with the inclusion of protease

inhibitors, general strengthening therapy, and vitamin therapy in complex therapy. For clarity, here is a clinical example:

Pregnant K., 24 years old, was admitted to the hospital at 31 weeks of gestation with complaints of minor pain in the lower abdomen and in the lumbar region, the flow of amniotic fluid for 5 hours.

From the anamnesis, the pregnancy proceeded with symptoms of a threatened miscarriage in the I and II trimester with episodes of spotting spotting, for which she was treated on an outpatient basis, the previous II births ended in premature births at 28 and 32 weeks. On admission: the uterus is excitable, there is no regular labor activity. Notes the discharge of the waters of the house once in a small amount, light.

The diagnosis was made: Pregnancy III, weeks 31, Childbirth III.OAA. PRPO. Threatening premature birth.

After collecting an anamnesis, it was revealed that the pregnant woman belongs to a group with a high level of risk factors.

History of risk factors				*Extragenital diseases*			
№	Stress	*Yes*	*No*	*№*	Name	*Yes*	*No*
1	Bad habits	+		*1*	Blood.vyd from p / p	+	
2	Prof. harmfulness	+		*2*	SS diseases		
3	Allergic background	+		*3*	Hypertensive drugs	+	
4	Stomatitis			*4*	Respiratory tract diseases, SARS	+	
5	The use of anti	+		*5*	Pat. Liver: Hepatosis		
6	Age under 18	+		*6*	Vir.hepatitis (B, C)		
7	Age after 30 years	+		*7*	Cholecystitis		
8	History of abortion			*8*	kidney disease	+	
9	Threat of interruption			*9*	Violation of the exchange of things	+	
10	Stress	+		*10*	severe anemia	+	
11	Early gestosis	+		*11*	Diabetes		
12	Preeclampsia			*12*	Pa. shields. Wish.		
13	Eclampsia			*13*	Vision pathology (myopia)		

During this pregnancy

Name	*Yes*	*No*	*Name*	*Yes*	*No*
Early gestosis	+		Hemorrhages	+	
oligohydramnios			SS diseases		
Polyhydramnios	+		Chronic hyp.		
Threat of interruption in the 1st trimester	+		Gestational hip.		
Threat of interruption in the 2nd trimester	+		Pat. Liver: Liver hepatosis, cholecystitis		
Threat of interruption in the 3rd trimester			Hepatitis virus (B, C)		
PIOV up to 22 weeks	+		Obstruction of the airways		
PIOV up to 36 weeks			Pyelonephritis xp		
mild preeclampsia			Pyelonephritis ges	+	
Severe preeclampsia			NEW	+	
Eclampsia			The use of anti	+	
Acute NRP detachment			Allergic background		

In this case, the test performed on pregnant K. gave a positive result. To clarify the state of the birth canal (assessment of the state of the cervix), an ultrasound study was performed: the fetus is in breech presentation, corresponds to the expected gestational age, the placenta is on the anterior wall, amniotic fluid is normal. With transvaginal echography, it was possible to obtain more complete information about the state of the cervix: the cervix is 25 mm long, the external os is closed, and a U-shaped expansion of the internal os up to 16 mm is noted.

A pregnant woman was hospitalized (In the Perinatal Center of Samarkand) to a hospital for pregnancy prolongation. Within 2 weeks, with a complete clinical examination (complete blood count, urine, blood biochemistry, blood clotting test, examination by a therapist), therapy was carried out aimed at maintaining pregnancy: protease inhibitors were prescribed (kontrykal 10,000 units in a physical solution of 200 ml), vitamin E, tocolytics, bed rest. During dynamic observation, negative dynamics from the side of the uterus and cervix were not noted. The patient was discharged home with a progressive pregnancy under the supervision of an obstetrician-gynecologist at the place of residence.

§ 5.2. Preventive measures for premature rupture of amniotic fluid and premature birth

It is recognized that the membranes of the fetus are sensitive to mechanical stress and related damage (such as infection and inflammation), with a degree of sensitivity that depends in part on genetic predisposition [128, c.1444; 129, p.361]. In this regard, the effect of a purely mechanical device in different populations and in individual patients with clinical manifestations of premature maturation of the cervix may vary.

The pessary is also thought to protect the cervical mucosal plug. This can be achieved by fixing the tissue of the remaining cervix with a pessary.

We examined 128 pregnant women who were divided into two groups. The main 93 pregnant women and the control 35 pregnant women with a gestational age of 30-34 weeks who-were hospitalized in the SamMI I-clinic for the period 2019-

2020. All pregnant women underwent cervical screening as the main method for detecting shortening of the cervix and bacteriological examination of the microflora. **Vaginal swab** - A smear analysis for microflora is a laboratory study based on the evaluation of biological material under a light microscope. This is one of the main methods for assessing the presence and nature of the inflammatory process of the genitourinary organs. A vaginal smear is taken for flora during pregnancy 2 times - when registering, as well as for a period of 30 weeks. Also, a smear analysis for flora during pregnancy is taken if a woman has complaints of itching in the genital area, their redness, unusual vaginal discharge.

An analysis taken from a healthy woman shows a high concentration of lactobacilli. They secrete lactic acid, protecting the genitals from the pathogen, maintaining the acidity necessary for the microflora. During pregnancy, the titer decreases, the natural local immunity weakens, and the risk of developing pathogenic microflora increases. The study of the vaginal microflora was carried out in all women with a threat of preterm labor in order to assess and prepare pregnant women for the insertion of an obstetric pessary. The table presents the results of bacteriological studies of follow-up in women at risk of PR.

As a result, the data obtained showed that the morphological changes in the vaginal smear do not carry reliable information in predicting preterm labor, but it is a necessary method before inserting an obstetric pessary to assess the flora of a pregnant woman (Table 5.3). Contraindications for the insertion of an obstetric pessary are purulent discharge, bloody discharge from the genital tract, the onset of labor.

To treat the threat of premature termination of pregnancy, obstetric pessaries are currently used in many obstetric institutions.

Table 5.3

Morphological parameters of a smear from the vagina.

Indicators	I group (n=17)		II group (n=31)		III group (n=45)	
	Абс	%	абс	%	Абс	%

Leukocytes	17	100	19	90, 4	36	80, 0
squamous epithelium	17	100	8	38, 0	11	24, 4
Gonococci	-	-	-	-	-	-
Trichomanas	1	5, 8	2	9, 5	3	6, 6
key cells	2	1, 7	-	-	5	11, 1
cocci	4	23, 5	6	28, 5	12	26, 6
Microflora (Dederlein sticks)	6	35, 9	13	61, 9	18	40, 0
Slime	10	58, 8	17	8, 9	20	44, 4

At the same time, it is considered extremely important to detect shortening of the cervix in a timely manner, before the onset of pain. Of all 128 pregnant women examined, shortening of the cervix was found in 42 pregnant women.

As shown by the results of cervicometry, shortening of the cervix was observed up to 20 mm in 3, which amounted to 3.2%, in 39, from 20 mm to 28 mm, which amounted to 41.9%. In 51 pregnant women (54.8%) no pathology was observed (Table 5.4).

Table 5.4

Results of the cervicometry study

Examined pregnant women (n=93 / 100%)						
	From 15-20 mm		From 20-28 mm		From 28-33 mm	
Length w/m in mm	3	3,2%	39	41,9%	51	54,8%

According to the results of cervicometry, assessing the length of the cervix (<2.5 cm) and after explaining and agreeing to the pregnant woman, preparations were made for the placement of the pessary by taking a smear on the flora and treating the vagina with cicial, after which the obstetric pessary was inserted (modified by the author, according to patent No. FAP 01226 dated 03/14/2017 for the utility model of Bayramov S.D., as well as according to the act of rationalization proposal Shavazi N.N., No. 1911 dated 02/12/2020 "Improved drainage function"), obstetric pessaries were first put into practice in the city of Samarkand.

Table 5.5

Results of cervicometry after insertion of an obstetric pessary

Inserted obstetric pessary (n=37 / 100%)						
Re-screening s/m after 2 weeks	2	5,40%	35	94,5%	-	-

Its main strategy is its availability and the price is 3 times cheaper than those imported from abroad. 37 pregnant women in the gestational age of 30-34 weeks. The manipulation was carried out at the Department of Pathology, the pregnant woman before the beginning of the manipulation was offered 2 tablets of valerian to prevent the emotional state.

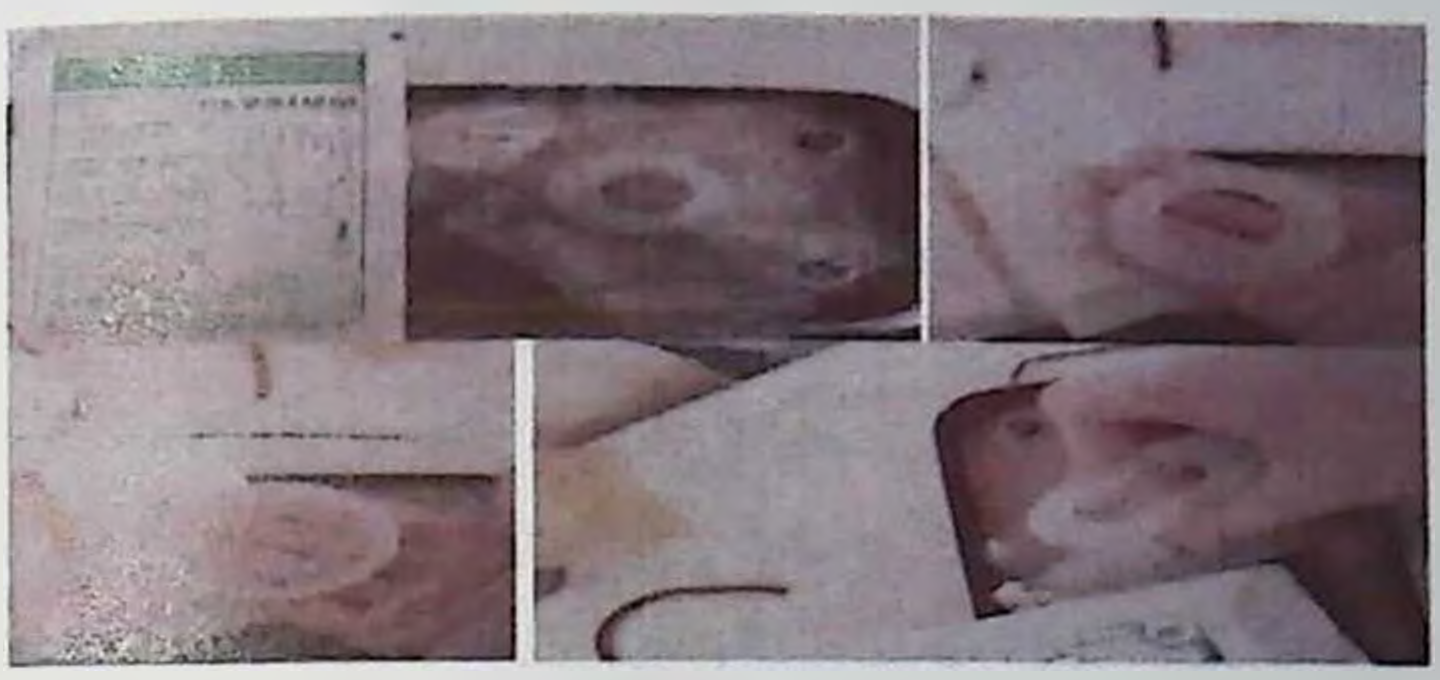
All 37 pregnant women did not complain during the insertion of the pessary.

Complaints about a burning sensation were presented by 3 pregnant women in the first 2 hours, in the following hours, complaints and anxiety were not noted. As a rule, after the insertion of the pessary, the control screening was scheduled after 2 weeks of its insertion.

Pregnant women were recommended moments before discharge, with the slightest feeling of burning, pain, discharge of any nature or a feeling of a foreign body, immediately go to the hospital.

Within 2 weeks there were no complaints from pregnant women. Portability

was in 100% of cases. Upon re-examination of the cervical screening after 2 weeks, it was noted that the cervix did not shorten after the introduction of the PESSARY, thereby reducing the incidence of adverse outcomes and prolonging the pregnancy, while the shortening of the cervix did not progress. It should also be noted that the use of pessaries does not exclude the appointment of progesterone, indomethacin, and sexual activity.



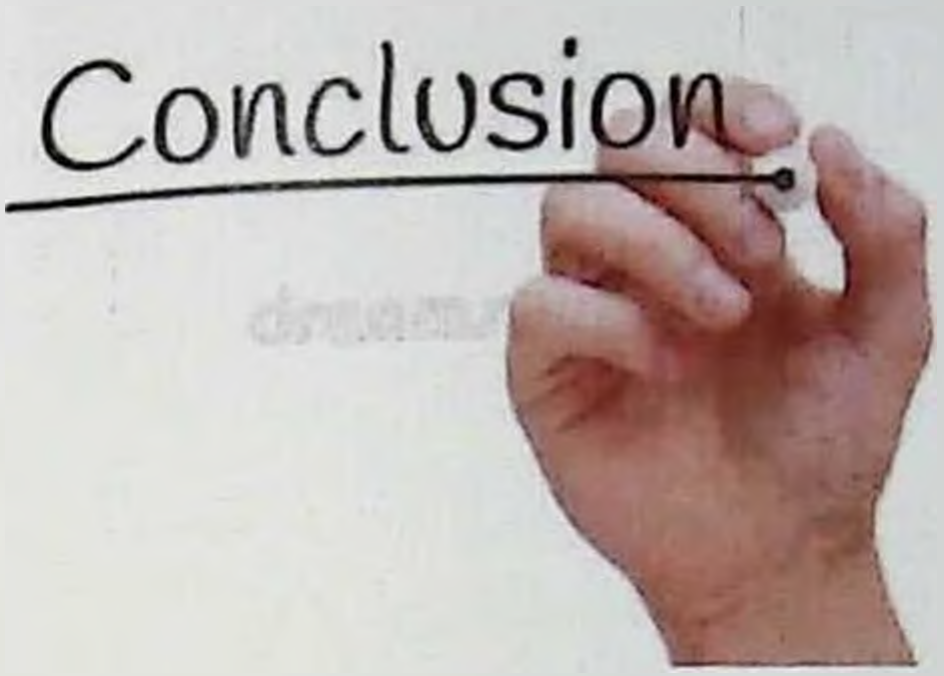
Rice. 5.2. Overview of the Obstetric Pessary

The advantages of obstetric pessaries were their ease of installation ("in one step"), a minimum of side effects, good patient tolerance and relatively low cost compared to currently available alternative methods.

When using a pessary, it is necessary to take a vaginal swab every 2 weeks to prevent colpitis and an ultrasound scan of the cervix every 3-4 weeks. Once every 2 weeks, the vagina and pessary are treated with antiseptic solutions. It is not necessary to remove the pessary. The obstetric pessary was removed at 37-38 weeks, or in case of emergency indications, if labor began.

Thus: according to the results of an ultrasound study, determining the length of the cervix showed its shortening of less than 28 mm in 42 (45.2%) women, which is considered to be risky for PR. The mean value was 23.4±1.2 mm. Considering the fact that pregnant women with a cervical length of less than 25 mm, a positive test for fetal fibronectin in a smear, as well as with an increased level of MMP and components of the hemostasis system, represent a risk group in terms of increased degradation of connective tissue and thrombotic disorders, for the prevention of

PIOV and PR in 37 women with a cervix less than 25mm used an obstetric pessary. We used SD Bayramov's pessary, but we expanded the indications for its use. When re-screening the cervix after 4 weeks, it was found that the cervix did not shorten after the introduction of the pessary (Table 5). Thus, this procedure reduced the incidence of adverse outcomes and ensured the prolongation of pregnancy in 100% of cases.



Conclusion:

In modern obstetrics, the problem of PIOV is the most urgent problem due to the high risk of perinatal morbidity and mortality, the huge costs of premature babies, which constitute a high-risk group in terms of incidence. Premature rupture of amniotic fluid (PIOV) is a complication of pregnancy characterized by a violation of the integrity of the membranes of the fetus and the rupture of amniotic fluid before the onset of labor, regardless of the gestational age. According to the literature, more than 35-60% of preterm births, regardless of the characteristics of the etiological factors, begin with premature rupture of the membranes and untimely discharge of amniotic fluid.

At present, thanks to the efforts of many generations of obstetrician-gynecologists, the problems of prognosis and prevention are generally resolved. This became possible as a result of an intensive search for predictors leading to premature rupture of amniotic fluid, the selection of the most significant clinical and laboratory signs, the development of modern methods for diagnosing this pathology, and finally due to the widespread introduction of non-invasive methods of prevention.

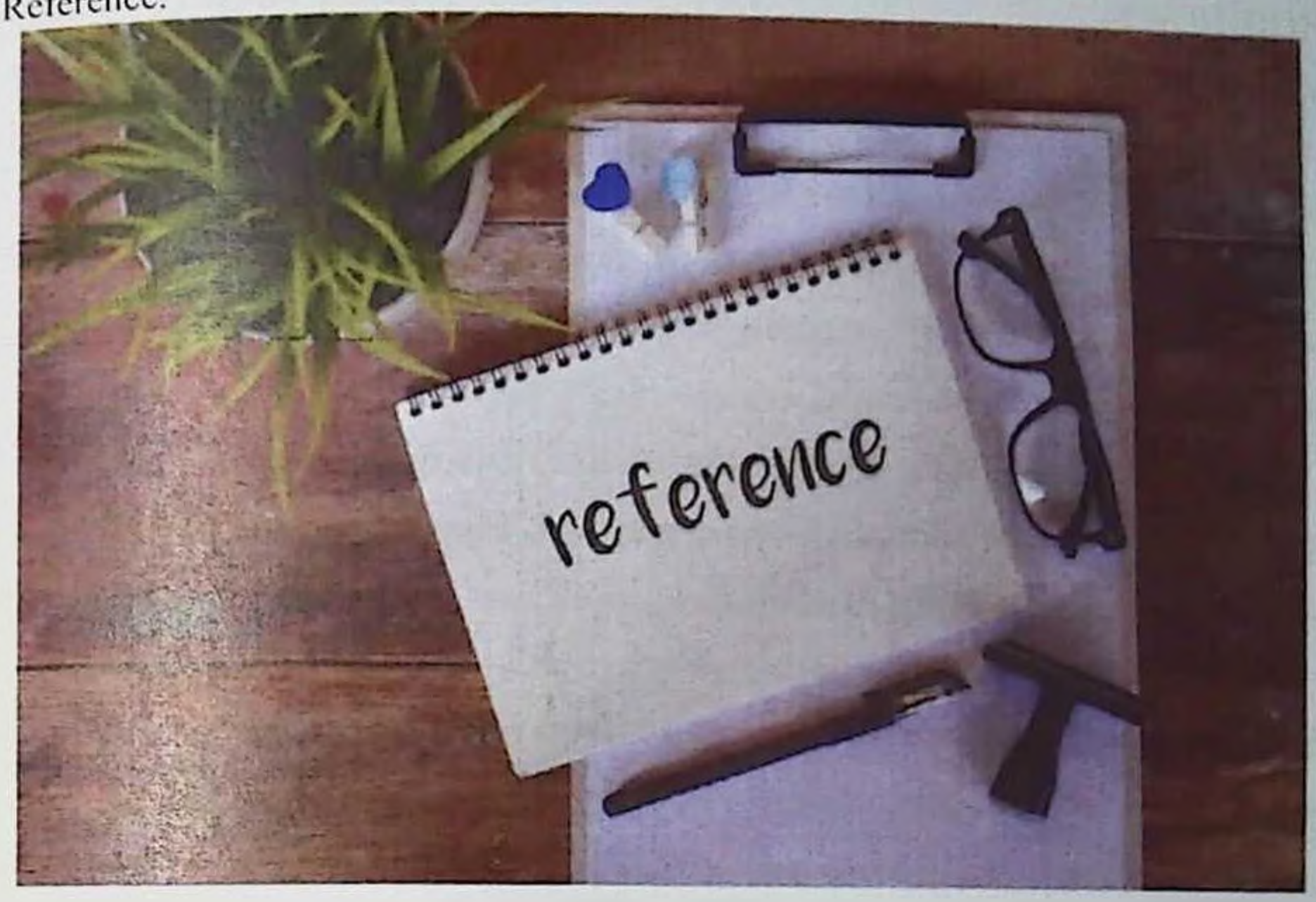
The results of the study in this monograph are as follows: the results of the study should be used in the formation of risk groups according to the likelihood of developing premature rupture of amniotic fluid and preterm birth; developed. substantiated and implemented an algorithm for identifying risk factors for the development of premature rupture of amniotic fluid and preterm birth; on the basis of the conducted studies, the prognostic value of the determination of fetal fibronectin in a smear in establishing the risk of premature rupture of amniotic fluid and preterm birth was established; the significance of determining markers of endothelial dysfunction and activity of matrix metalloproteinases in women with a high risk of premature rupture of amniotic fluid for the timely prevention of preterm labor has

been proven: a prognostic risk matrix for the development of premature rupture of amniotic fluid and preterm labor was developed using the method of normalization of intensive indicators (NIP); proposed a method for assessing the state of the cervix (ultrasound of the cervix at 30-34 weeks' gestation) in the early diagnosis of premature rupture of amniotic fluid and preterm labor; a method for the prophylactic use of an obstetric pessary in case of shortening of the cervix less than 25 mm has been developed and implemented.

The solution to this problem, in our opinion, largely depends on increasing the general level of knowledge about PIOT by doctors of all specialties, on organizational principles aimed at improving diagnostic and preventive methods, as well as on the further search for new safe, adequate methods of disease prevention, more effective complex measures.

Finally, we note that the further solution of the problem of PIOT, regardless of the development of methods for managing pregnant women, still depends on the quality of timely and primary diagnosis. Only in this case it will be possible to achieve the main goals - minimizing the development of PIOT.

Reference:



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