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MONOGRAPHY

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MONOGRAPHY

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«CLINICAL AND PATHOGENETIC PREDICTORS OF PREMATURE BIRTH, TREATMENT AND PREVENTION»

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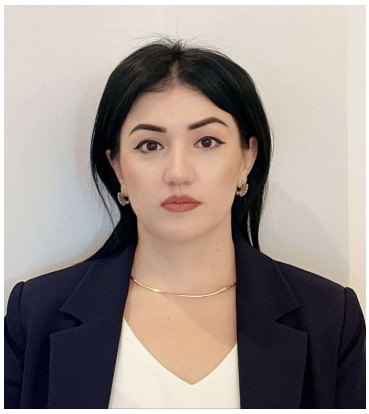

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The book summarizes clinical and laboratory predictors of premature birth. It presents the results of scientific and practical research, as well as our own clinical, instrumental and functional observations conducted on a large contingent of pregnant women at risk of premature birth. The issues of etiology, pathogenesis, anamnesis, complex diagnostics, prognosis and prevention are discussed. The methods of prognosis and prevention in pregnant women at risk of premature birth are summarized and recommended, and a number of diagnostic and clinical examples from our own observations are given.

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

Reviewers

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LIST OF ABBREVIATIONS

AD	-	antioxidant depression
DC	-	diene conjugate
FTN	-	full-term newborns
DEC	-	desquamated endothelial cells
NCh	-	natural childbirth
BMI	-	body mass index
EIA	-	enzyme immunoassay
CO	-	Caesarian operation
MDA	-	malondialdehyde
UA	-	uric acid
PN	-	premature newborns
NO	-	nitric oxide
TCA	-	total albumin concentration
AF	-	amniotic fluid
LPO	-	lipid peroxidation
PB	-	Premature birth
ABR	-	albumin binding reserve
SOD	-	Superoxide dismutase
UL	-	urgent labor
RPS	-	reactive protein status
TBA	-	(thiobarbituric acid) active products
Threatened PB	-	Threatening premature birth
ECA	-	effective albumin concentration
IL	-	Interleukin
TF	-	tissue cell factor
TNFa	-	tumor necrosis factor

Introduction

Today, premature births (PB) are not only a medical problem, but also a socially significant one. The relevance of the topic of premature births is beyond doubt among scientists around the world, primarily due to its significant contribution to perinatal morbidity and mortality rates. According to the World Health Organization, «…the incidence of premature births varies from 5 to 18% and has not shown a downward trend over the past 20 years… PBs increase perinatal mortality by 4 times, neonatal morbidity by 3 times, and are the cause of neonatal death in 40-70% of cases…»[1]. In this regard, the study of the features of early diagnosis of threatening premature birth (PB), the development of methods of prevention, treatment and management of pregnant women at various stages of the pathology that has arisen in order to reduce complications are among the tasks that require solutions in medicine.

In world practice, multicenter scientific research continues aimed at revealing various aspects of this problem, especially identifying new pathogenetic causes and additional diagnostic criteria for the development of premature births. Despite numerous studies, the mechanism of development of premature births has not yet been fully studied. At the same time, determining the pathogenesis of the onset of premature births is a necessary condition for developing effective prognostic and preventive measures taking into account social and ethical norms.

In our country, large-scale measures are being taken for the early diagnosis and prevention of somatic diseases among the population. Along with this, there are a

[1] GBD 2019: Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019.

number of unresolved problems in the healthcare system, among which the most important are the prognosis and prevention of premature births. In this regard, comprehensive measures to radically improve the healthcare system include: "... expanding opportunities for high-quality medical care for mothers and children, providing specialized and high-tech medical care and reducing infant and child mortality." Based on this, at present, it is important to study the causes of premature births in women[2]. In this regard, conducting research aimed at improving the quality of life and reducing perinatal outcomes has served as a reason for searching for additional, new pathogenetic causes of premature birth, for developing principles of early prognosis and prevention of this pathology in order to reduce perinatal mortality and childhood disability.

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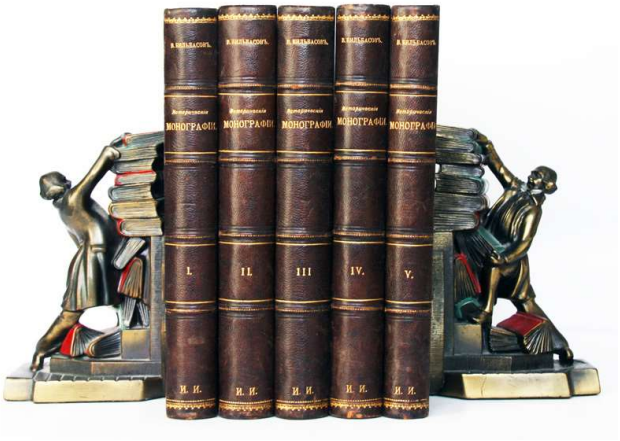


MODERN CONCEPT OF ETIOPATHOGENESIS, DIAGNOSIS AND TACTICS OF MANAGEMENT OF PREMATURE LABOR (LITERATURE REVIEW)

In obstetric practice, premature birth is considered a medical, economic and social issue. This is due to the high prevalence of premature babies, exceeding full-term babies by 35-40 times [15, p. 24-28; 29, p. 56-61; 48, p. 194; 189, p. 791].

The frequency of consequences directly associated with prematurity is proportional to the gestational age of the premature birth. At present, two main tasks are noted - the manifestation of threatening premature births to prevent inappropriate interventions, and safe management of the fetus to premature birth [45, p. 33; 79, p. 33].

Despite significant developments in clinical care in recent decades and the widespread use of adrenomimetics as tocolytic drugs, the prevalence of PB remained the same, amounting to 5-10%. It is noteworthy that the introduction of assisted reproductive technologies into practice has increased the frequency of multiple pregnancies, which also progresses pregnancy and causes its premature termination. [17, p.32].

In the case of premature birth, the outcome of pregnancy depends on the amount of medical care, medical qualifications, and the choice of the correct management tactics [96, p.218-221; 170, p.2852-2861].

Medical and social aspects of premature birth

According to WHO, premature termination of pregnancy is defined as birth occurring between 154 and 259 days of gestation or between 22 and 37 weeks of pregnancy from the first day of the last menstrual period [89, p. 37].

It is noted that premature births are one of the most important indicators of reproductive health of the population [18, p.48]. According to WHO data, it has been demonstrated that by gestational age, premature births (PB) are divided into very early - 22-27 weeks, early - 28-33 weeks and premature - 34-37 weeks. This is due to the choice of obstetric tactics, the course of pregnancy and the outcome of childbirth [105, p.4; 154, p.120]

The data of the scientific work noted that 7% of cases of premature births occur before 28 weeks of pregnancy, 15% - at 28-31 weeks, 22% - at 32-33 weeks, 70% - at 34-37 weeks [2, p.74].

According to the Cochrane Handbook, the incidence of preterm birth has not changed over the past 50 years, despite advances in medical care, including the widespread use of beta-adrenergic agonists as tocolytic agents since the 1970s [35, p.35; 160, p.265].

The conclusion of international literature shows that the prevalence of preterm birth (PB) is approximately 7-11%, while 11% in the USA, 8% in England, 5% in Europe, 7% in France, 9% in Germany, 10% in Hungary, 7% in Norway, 4.3% in Russia, 18% in Africa [6, p.27-29; 18, p.39-48; 153, p.l869; 158, p.437; 178, p.1670; 195, p.128;].

Preterm birth rates are associated with ethnic groups. Afro-Caribbean and African American women have an 18% preterm birth rate compared to 9% white women [140, p.489; 181, p.60].

Prematurity rates in Spain and East Asia are low compared to India and South Asia, which are high [122, p.975; 145, p.59].

K. O'Donoghue et al. (2008, USA) showed in their study that 25% of pregnant women who smoked had a risk of premature birth [173, p.1-6].

It is reported that PB affects 11% of all births, i.e. babies, each year, of which two thirds are spontaneous [139, p.1227].

Literature data indicate that 85% of women who give birth prematurely do not have certain risk factors [200, p.1030].

15-20% of pregnant women with unexpected manifestation of premature labor, and even against the background of the use of hormonal and tocolytic therapy, labor occurs before 34 weeks [141, p.121; 193, p.33-38].

In Russia, the registration of PB occurs every year in the Russian Ministry of Health No. 32 from 28 weeks of pregnancy, while in economically developed countries - from 22 weeks. Therefore, the indicators of perinatal losses were not comparable [89, p.37; 148, p.194; 154, p.120; 156, p.649].

At the moment, premature births are divided into 2 types: spontaneous and induced [100, p.52-55; 187, p.254].

An analysis of scientific publications has shown that many premature births are spontaneous in nature and develop as a result of detachment of an abnormally located placenta or premature rupture of the amniotic sac. A small number of premature births are formed as a result of a violation of the mother's condition, such as preeclampsia [123, p.1768; 200, p.1036].

The key factor in preterm birth may be genetic. It has been found that a woman's history of PB often increases the risk of miscarriage [84, p.71; 123, p.1768; 154, p.120].

The results of the study convincingly prove that molimorphisms of the interleukin-1, interleukin-6 receptor antagonist gene increase the risk of premature babies by 1.6-2 times [175, p.296].

The genetic contribution of the mother to the development of preterm birth has been described by a number of researchers [104, p.591; 133, p.56-71]. Single nucleotide changes (SNPs) in different genes affect gene expression and function [106, p.37-42; 148, p.357-366].

Genetic variability of binding protein-2 and interleukin-10 is a factor in the formation of chorioamnionitis, causing stress to the fetus by imbalance of the

hypothalamic-pituitary-adrenal system, release of cortisol, release of prostaglandins, contributing to damage to the fetal membranes [196, p.359-364].

Intrauterine infections can also cause preterm birth, accounting for 30% of spontaneous PB [79, p.124]. It is noted that intrauterine infections are caused by bacterial colonization, inflammatory process, formation of toxins, intensification of cytokine reaction, production of prostaglandins in chorioamniotic membranes and placenta. Hypo- and hyperreactivity of immunity leads to pathological changes in the mother's body, which leads to increased metalloproteases, depression of chorioamniotic membranes and shortening of the cervix [124, p.21; 189, p.791].

There are publications that prostaglandins can increase contraction of the myometrium, damaging the fetal membranes and causing PB [110, p.12504; 133, p.1388-1395].

Literature data indicate that placental abruption and preeclampsia, which cause disruption of placental blood flow, are often medical indications for induction of labor [97, p.127-134]. According to literature, preeclampsia occurs in 3-5% of pregnant women, and placental abruption occurs in approximately 1% [98, p.50-54; 133, p.1395; 139, p.1227-1233].

An analysis of scientific publications has shown that 75% of cases of PB are due to neonatal morbidity and 70% of neonatal mortality, including consequences leading to complications, cerebral palsy, bronchopulmonary dysplasia, intellectual disabilities, etc. [129, p.934-946; 163, p.181].

A history of PB can often be a factor in premature birth, pregnancy loss, cervical surgery, etc. A history of PB increases the risk of PB by 4-6 times. [146, p. 318-324; 164, p.30495; 171, p.758-70].

Premature birth can be predicted and diagnosed by a series of criteria [161, p. 106-116].

The presence of nagging pain in the lower abdomen is not a sufficient symptom for diagnosing PB [111, p.246].

Regular uterine contractions, characterized by dilation of the cervix and shortening of the cervix, seem to be a traditional clinical sign [128, p.72-77].

The above mentioned signs are considered to have low specificity and sensitivity [61, p.14].

It should be noted that anamnestic features such as nutrition, obstetric history, ethnicity, age, psychological, economic and social status of the mother, bad habits, are used by some clinicians as an indicator of the likelihood of premature birth [79, p.29-33; 137, p.132- 134].

According to modern concepts, it has been shown that the age of over 35 years and up to 20 years reliably increases premature births, especially early and spontaneous types. [110, p.12504].

Other studies have found that single women are 2.5 times more likely to have spontaneous preterm birth than married women [110, p.12504].

It is noted that the level of education, bad habits (smoking, drinking alcohol during pregnancy), physical activity, business employment during pregnancy do not affect PB [11, p.32-34; 106, p.37-42; 131, p.56-71].

Another important indicator of PB is uterine activity, which manifests itself in the form of increased uterine tone and nagging pain in the lower abdomen. However, it is difficult to assess the therapeutic tactics of a pregnant woman based on these data, since they are individual and subjective. Therefore, home monitoring of uterine activity is considered one of the methods for early diagnosis of PB. A.A. Popov and M.S. Minnaard (2017) [64, p.895-899; 158, p.E56-E63] showed in their works that the uterine activity monitor can be used with high accuracy in determining labor activity, high risk of preterm labor and improving neonatal mortality and perinatal outcomes.

An important indicator of preterm labor is the length of the cervix. Bishop (1964) developed a subjective indicator of labor activity and assessment of preterm labor based on dynamic changes in the state of the cervix during vaginal examination [183, p.103-111].

The use of transvaginal ultrasound is considered a universal and objective method for determining the condition of the cervix.

The absence of muscle tone of the uterus during normal pregnancy, its cervix remains closed, long, dense. It can shorten and soften only under the influence of the hormonal system, prostaglandins, before childbirth [123, p.1768; 141, p.121-127]. According to transvaginal ultrasound, the length of the cervix is determined only after 16-20 weeks, since by this period the length of the cervix fluctuates greatly, on the one hand, and it is difficult to distinguish the border with the lower uterine segment, on the other [12, p.62; 131, p.71]. The data of the prospective study of the cervical length by transvaginal ultrasound in 2915 pregnant women showed that the length of the cervix varies with the risk of PB. An increased probability of PB was revealed with a cervical length shorter than the tenth percentile for a given gestational age (26 mm), however, the sensitivity was 37%. It was noted that with a cervical length less than the 25th, 50th and 75th percentile for a given gestational age (30, 35 and 40 mm, respectively), a high risk of PB was recorded compared with a cervical length greater than the 75th percentile. At 24 weeks, the risk of PB was 3.79, 2.35 and 1.98, respectively, and at 28 weeks - 5.39, 3.52 and 2.8, respectively [40, p.86-91].

Hasegawaetal [152, p.203] found that cervical shortening was associated with the risk of PB only in primigravidas [136, p.45].

Another factor of PB is infectious and inflammatory. It has been found that 30% of all cases of PB are accompanied by infection [43, p.10]. Many authors have tried to identify the connection between local infection and this disease. [24, p.21].

Bacterial vaginosis (BV) is considered a non-inflammatory process of bacterial genesis caused by dysbiosis of the vaginal biotope and is accompanied by a decrease in lactobacilli and an increase in obligate and facultative anaerobic microorganisms [138, p.337; 151, p.806].

It is important to note that changes in the vaginal microbiocenosis may be the result of inflammation of the genitourinary system, changes in hormonal activity, and the use of antibacterial therapy [100, p.55].

Pathogenesis links of premature birth

The pathogenesis of premature births is also not fully understood, but it is known that they occur as a result of pathological processes or idiopathic early activation of labor [59, p. 444].

Interestingly, inflammation is also a key trigger in the physiological process of labor [81, p.56].

Feto-maternal immune tolerance results from the production of parental antigens on fetal tissues. The maternal immune system recognizes and responds to these fetal antigens first during intercourse, when the reproductive tract comes into contact with seminal fluid, followed by continuous contact with the paternal antigen throughout pregnancy through the invasion of fetal trophoblast cells into the endometrium. The implantation process is considered inflammatory, during which cytokines, chemokines, and prostaglandins are produced and leukocytes infiltrate the uterus [94, p.508-514]. Around the time of implantation, inflammation is inhibited and a tolerogenic environment is created. Multiple mechanisms are involved in the induction of such an environment, including the release of anti-inflammatory molecules such as TGFβ [98, p.54] and the induction of specialized anti-inflammatory T-cells known as CD4+FOXP3+ regulatory T-cells (Treg), which moderate fetal anti-inflammatory immune responses [132, p.30614-3]. Tolerogenic dendritic cells (DCs), uniquely present in the decidum, cross-present fetal antigens to maternal CD4+ T-cells, thereby also activating the generation of Treg cells [123, p.1768]. Treg cells interact with DCs and macrophages, altering their phenotypic states to be proto-tolerogenic [82, p.51]. Importantly, Treg cells reduce the extent of anti-fetal immune responses, limit the influence of T-effector-cells (Teff), and maintain anergy in the T-cell population (Tcon) that would otherwise differentiate into Teff [139, p.1233]. Placental cells also contribute to the creation of a tolerogenic environment, with the help of colony stimulating factor (CSF)1 secreted from trophoblasts and interleukin (IL)10, which induces decidual macrophages with the regulatory phenotype “M2”, expands functionally suppressive CD4+FOXP3+ Treg

cells, and limits the activation of T-helper (Th) 1-, Th17- and Th2-cytokine-producing Teff cells [130, p.150].

In normal pregnancy, there is significant crosstalk between the maternal and fetal systems due to the shared circulatory system through the placenta. Nutrients and waste products are transferred from mother to fetus, along with cells, signaling molecules, extracellular vesicles (ECVs), and nucleic acids. The exchange of cells results in microchimerism in either mother or fetus, with maternal cells transferred to the fetus being called maternal microchimerism (MMC). Reciprocally, fetal cells transferred to the mother are called fetal microchimerism (FMC). Both MMC and FMC can persist for decades after pregnancy in various tissues of the body, including the brain, skin, heart, lungs, bone marrow, spleen, and lymph nodes [124, p. 21; 137, p. 134; 142, p. 946].

Experimentally, MMC cells have been shown to increase tolerance to maternal antigens in fetal immune cells during pregnancy by inducing non-inherited maternal antigen (NIMA)-specific CD4+FOXP3+ Treg cells [130, p.150]. They can also increase the reproductive fitness of the next generation by inducing sustained tolerance to NIMA [20, p.304-305; 120, p.27].

Microvesicles, exosomes, and cell-free (cf) proteins and nucleic acids such as cfRNA and cfDNA cross the placenta. The concentration of cfRNA, cfDNA transcripts, and RNA in the maternal circulation increases during pregnancy [139, p.1233; 142, p.946]. Immunosuppressive CD71+ fetal erythroid cells are an abundant source of fetal DNA in the maternal circulation [137, p.134]. cfDNA and RNA transcripts can be transferred passively or via exosomes (ECVS) released by exocytosis into the extracellular environment. The placenta releases exosomes into the maternal circulation during pregnancy [145, p.66]. The functional significance of the various ECVs during pregnancy is largely unknown, but they are thought to mediate communication between the fetus and mother at key stages of pregnancy, including implantation and parturition [96, p. 221; 143, p. 1046]. Trophoblasts and villi secrete exosomes containing placenta-specific microRNAs into the maternal circulation, which play a key role in regulating immune signaling [134, p.110287].

Maternally derived exosomes are also enriched during pregnancy, and the transfer of exosomes between the fetus and mother is bidirectional [149, p.198842].

Experimentally and clinically, the authors have found that inflammation is associated with the pathogenesis of idiopathic PB [115, p.249]. In addition, it is believed that PB occurs in the early stages of pregnancy, before the development of the placenta. Thus, PB is a disorder that occurs as a result of defective placentation [116, p.982; 125, p.640], similar to preeclampsia.

Since maternal immune adaptation is involved in processes that support pregnancy throughout gestation, disruption of immune adaptation early in pregnancy and failure to establish immune tolerance or attenuate excessive inflammation may be responsible for PB. This theory raises the possibility that early immune disruptions may have long-lasting effects on pregnancy [117, p.31].

Early immune disturbances caused by maternal stress, infection, and diet may lead to depressed immune tolerance and increased inflammation [114, p.126; 137, p.134]. In addition, the composition of the vaginal microbiota may play a role in PB, as differential vaginal microbial composition has been associated with increased risk of PB in women of African descent [69, p.69; 87, p.10].

Problems that arise later in pregnancy, such as maternal infection, endocrine dysfunction, and metabolic dysregulation, can also aggravate the inflammatory response and lead to preterm delivery [79, p. 33; 110, p. 12504; 146, p. 324].

The role of immune factors in the pathogenesis of premature birth

Given the role of inflammation in the onset of labor at term or preterm, it is important to emphasize that there are multiple pathways that contribute to preterm labor, including immune, hormonal, and environmental factors. Immunomodulatory agents activate or exacerbate physiologically occurring inflammatory pathways involved in labor induction and recapitulate the clinical manifestations of labor associated with infection and/or inflammation.

Using mouse models of PB, macrophages have been identified as major contributors to the induction of preterm labor. Depletion of macrophages by anti-F4/80 prior to experimental LPS-induced PB abolishes susceptibility to PTL [125, p. 640]. Macrophages are involved in the pathogenesis of PB through the secretion of inflammatory cytokines such as tumor necrosis factor (TNF)α, IL1, IL6, and IL8, as well as uterine contractility genes such as matrix metalloproteinases (MMPs) [90, p. 40]. In particular, IL1 is known to be an activator of the inflammatory response, therefore, it is believed that the introduction of IL1 induces PB, and inhibition of its receptor prevents them [112, p. 489], probably through the activation of NF-κb signaling pathways [104, p. 593]. Similarly, IL6, which is another cytokine important in determining the timing of parturition and pathogenesis of PB, as IL6-deficient mice have delayed parturition and are also resistant to LPS-induced PB [65, p.70].

Complement activation plays an important role in the development of PB, which is observed in infectious PB, where women had elevated concentrations of complement products C3a, C4a, and C5a [121]. Mice deficient in the complement receptor C5aR did not have preterm labor. This study noted increased complement deposition in the cervical epithelium of mice with preterm labor [117, p.31].

The innate immune system plays a crucial role in modulating RVP and the adaptive immune response. It is suggested that PB results from impaired maternal tolerance to fetal antigens [7, p.136]. Indeed, Treg and Teff cells show distinct changes in frequency and phenotype in PTB. It is reported that Treg cells in the peripheral blood of women with PB have differential activation and reduced suppressive capacity compared to controls [117, p.31; 139, p.1233]. In normal conditions, there is a decrease in Treg cell activity and a reciprocal intensification of Teff cells, which are usually controlled by Treg cells [92].

A decrease in the number and/or function of Treg cells in pregnancy pathologies is usually associated with an increase in Tcon/Teff activation. This is normal during labor, since T cells increase in the chorionic membranes (fetal membranes) of women with preterm labor [96, p.221]. The number of effector CD4+

and CD8+ T cells is also increased in the decidua of PB relative to those of normal birth, suggesting that the inflammatory potential of these cells is higher in women with preterm birth [73]. CD4+ and CD8+ T cells expressing “exhausted” (PD-1+TIM−3+CTLA4-LAG−3-) and “senescent” (KLRG-1+CD57+) phenotypes have been identified in the decidua of women with full-term and preterm birth [141, pp.121-127]. The number of exhausted CD4+ T cells increased in the parietal decidua with increasing gestational age but decreased in the basal decidua in women who had PB with placental inflammation. Since TNFα and interferon (IFN)γ secretion can be induced ex vivo in exhausted T cells, these cells may restore their effector function in placental inflammation [136, p.45].

Rag1−/− T- and B-cell-deficient mice exhibit increased susceptibility to LPS-induced preterm labor as a result of macrophage activation. However, adoptive transfer of CD4+ T cells in mid-gestation conferred resistance to LPS-induced preterm labor because these cells are able to rapidly differentiate into Treg cells [136, p.45]. Conversely, activation of Teff cells using anti-CD3 induces preterm labor by enhancing local and systemic proinflammatory responses such as IL6 and IFNy [113, pp.168-175]. Interestingly, intrauterine transfer of CD4+ and CD8+ Teff cells induces late fetal resorption dependent on TNFα and IFNy. These cytokines also induce uterine contractility in vitro. However, it is unclear whether these Teff cells induce PB upon subsequent administration or systemically [54, pp.55–62].

Taken together, these studies suggest that activated T cells and Teff cells may be involved in mediating inflammation at normal term. In this case, Tregs may minimize the inflammatory potential or premature activation of exhausted Teff and memory cells. One potential pathway for preterm labor is IL10, which is produced by Tregs. IL10 has been shown to prevent preterm labor, as IL10 deficiency or administration of IL10-neutralizing antibodies increases susceptibility to preterm labor in mice [97, pp.127-134]. Since IL10 deficiency resulted in decreased inflammatory cytokine gene expression in the uterus and placenta, IL10 may regulate inflammatory responses associated with parturition. Recent work demonstrates that TLR4 signaling in decidual endothelial cells at term can induce

IL10 in perivascular stromal cells via activation of NF-κb IL6 and STAT3. This may be a mechanism to maintain homeostatic immune balance during inflammation, which may be disrupted in PB [84, p. 71].

New clinical and experimental data indicate that the fetal environment in RVP is characterized by inflammation, along with priming of fetal T-cells against maternal antigens [54, pp.55-62].

NKT cells, an innately related T cell with specialized functions, are also involved in the development of PB. Maternal NKT cells recognize CD1-restricted lipid antigens that are expressed by fetal trophoblast cells and are thought to play an immunoregulatory role during pregnancy [94, p.508-516]. Interestingly, depletion of invariant NKT cells reduces the incidence of LPS-induced PB in mice, and administration of an NKT cell-specific antibody (α-GalCer) late in pregnancy induces PTB via activation of CD4+ T cells, macrophages, neutrophils, and DCs in the myometrium/decidua [74, p.86; 95, p.129]. A critical component of inflammatory immune responses is the engagement of toll-like receptors (TLRs), which trigger signaling pathways and the activation of cytokines and chemokines by innate immune cells. TLRs are an evolutionarily conserved class of recognition receptors (PRRs) that recognize pathogen-associated molecular patterns (PAMPS) derived from microorganisms and damage-associated molecular patterns (DAMPS) released by immune cells as well as stressed and dying cells. TLR activation is an important initiating component of the inflammatory pathway that can induce normal or preterm labor.

Many studies on the role of TLR in PB have shown that TLR4 is able to bind to PAMP and DAMP ligands, including bacterial LPS. In mice, it was found that TLR4 is activated in the uterus both normally and during PB and is necessary for timely delivery in mice, controlling activation [70, p.5]. Pregnant TLR4−/− mice give birth on average 13 hours later than controls. At the same time, their offspring live shorter lives [127, p.376]. Furthermore, inhibition of TLR4 signaling by the TLR4 antagonist (+)-naloxone after intrauterine administration of E. coli suppressed the inflammatory cascade and effectively prevented the development of PB [78,

p.164]. Recently, it has been established that TLR4 expression by decidual endothelial cells, rather than immune cells, is key to the initiation of this response, as mice with endothelial-specific deletion of TLR4 are resistant to LPS-induced PB [88, p.37]. In humans, maternal single nucleotide polymorphisms (SNPs) in the TLR4 gene are associated with early preterm birth before 32 weeks of gestation [96, p.218-221]. MyD88-dependent and -independent (TRIF-dependent) signaling pathways control the expression of a specific inflammatory gene. In mice with PB, MyD88 plays a role, since MyD88−/− mice are completely protected from PB induced by E. coli [132].

TLR activation subsequently leads to inflammasome activation and the persistence of additional production of cytokines and chemokines in the placenta and decidua, such as IL8, CCL2, IL1β and IL6 [100, p.55]. TLR activation also initiates a number of immune cells, the production of prostaglandins and MMPs, which leads to the activation of cervical ripening and uterine contractions. Furthermore, the influx of immune cells such as macrophages into the amniotic cavity is critical for the onset of labor as it induces the secretion of inflammatory mediators such as NF-κb. NF-κb is a key mediator of the inflammatory cascade leading to labor as it directly binds to the promoters of genes inducing uterine contractility such as PTGFR (prostaglandin F2a receptor), GJA1 (connexin 43), OXTR (oxytocin receptor) and PTGS2 (cyclooxygenase 2, c. COX-2), as well as genes encoding the proinflammatory cytokines TNFα, IL1β, IL6 and IL8 [90, p.40].

DAMPs and PAMPs that are able to bind to PRRs play an important role as "messengers" initiating the inflammatory cascade leading to preterm labor. TLRs are activated during pregnancy during sterile inflammation and in the absence of active infection via DAMPs [101, p. 65]. The most studied dampening factors in preterm labor are high mobility group block 1 (HMGB1), fetal cfDNA, and platelet-activating factor (PAF). Oxidative stress and cellular senescence of the fetal amnion and chorion may trigger labor in humans through the release of DAMPs. In senescent cells, DAMPs are translocated from the nucleus to the cytosol, where they can be secreted as alarmins and trigger the inflammatory labor cascade [102, p.88]. Intra-

amniotic administration of HMGB1, an alarmin, induces preterm labor in mice [76, p.60] and is elevated in the amniotic fluid of women undergoing PTL, regardless of intra-amniotic infection status [103; pp.54-62]. HMGB1 has been found to be primarily expressed by amnion epithelial cells, myofibroblasts, neutrophils, and macrophages [111, p.246], and incubation of chorioamniotic membranes with HMGB1 results in the release of proinflammatory IL1β and IL6 [124, p.21]. cfDNA, a common activator of TLRs, released during cell death has been shown to induce TLR signaling in the placenta [105, p.1]. The inflammatory phospholipid PAF is another factor critical for parturition. It is elevated in the amniotic fluid of women who deliver preterm, and its administration induces PTB in mice via TLR signaling in macrophages [88, p.37; 118, p.48; 129, pp.934-946]. Alarmins released from cells during tissue stress can bind to PRRs. In fact, the levels of the alarmins IL1a and the S11 family proteins calgranulin A and calgranulin C were increased in amniotic fluid during sterile intra-amniotic inflammation [110, p.12504]. Other PRRs, such as NRLP3 and NOD2, activate inflammasomes, which likely play a role in the initiation of PB, since activation of components of this pathway induces the secretion of IL1β in chorioamniotic membranes during normal term labor [100, p.55]. PRR expression in the placenta mediates their functions as a key barrier capable of recognizing and responding to microbes and stress.

Modern approaches to diagnostics and prognosis of premature birth

At present, the main parameters indicating the threat of PB include signs of pressure in the vagina, pulling pains in the lower abdomen, bloody discharge from the genital tract, and shortening of the cervical region of the uterus [16, p. 547].

It is noted that other indicators of PB are considered to be complaints of the pregnant woman, the condition of the cervix and the contractile state of the uterus. Often, according to vaginal examination, the cervix is preserved, but the external os may be closed. A characteristic feature of the course of premature labor is the

presence of a monotonous rhythm of contractions, with no increase in the number of contractions and their duration in the active phase of the first period of labor [12, pp. 60-64].

Classification of PB according to gestational age:

- extremely early PB is at 22-27 weeks 6 days inclusive. This form is characterized by deeply premature newborns, extremely low birth weight (up to 1000 g), severe immaturity of the respiratory system, and an extremely unfavorable prognosis;
- very early PB is 28–30 weeks 6 days. It is accompanied by very low birth weight (up to 1500 g), severe prematurity, immature lungs, and a more favorable outcome;
- premature birth - 31–33 weeks 6 days – premature birth. The newborn has moderate prematurity.
- late PB is 34–36 weeks 6 days, at which time the fetal lungs are mature) [13, p.79].

Depending on the course, PB can be threatening or incipient [6, p.27-29].

Threatening PB are characterized by increased tone and impaired contractility of the uterus, pain syndrome in the lower abdomen, minor bloody discharge from the genital tract, shortening and opening of the cervix.

The onset of PB is accompanied by the discharge of amniotic fluid, rupture of the membranes, dilation of the cervix more than 2 cm, and bloody discharge from the genital tract.

In European countries, a different classification of the distribution of premature babies is used depending on the gestational age: 34–36 weeks – late or borderline prematurity (latepreterm/borderlinepreterm), 32–33 weeks – moderate prematurity (moderateprematurity), 28–31 weeks – deep or very low prematurity (severeprematurity), less than 28 weeks – extremely low prematurity (extremelypreterm).

According to birth weight, newborns are distributed as follows: less than 2500 g – low weight, less than 1500 g – very low, less than 1000 g – extremely low [12, p.64; 13, p.175].

Over the past 40 years, the incidence of premature births in all countries has changed little and amounts to about 10% of all children born, despite the widespread introduction of preventive measures against miscarriage [14, p.23].

According to the US, the rate of prematurity over the past 10 years has averaged 10.1%, in the UK – 7.8%, in France – 7.2%, in Germany – 9–10%, in Norway – 7.9%, in Hungary and Russia – 10% [15, p.249; 16, p.982].

The number of both early and very early premature births (22–28 weeks) also remains constant. In the general population, this figure is about 1%, accounting for approximately half of all perinatal losses [14, p.54].

However, against the background of improving nursing tactics, the survival rate of premature babies is increasing every year. Currently, in developed countries that switched to the WHO criteria for live births more than 30 years ago, among children weighing up to 500.0 g, 10-12% survive, from 500.0 g to 749.0 g - 50%, from 750.0 g to 1000.0 g - about 80-85% [3, p. 9; 5, p. 24].

Diagnosis of premature birth presents certain difficulties due to the lack of specific symptoms and symptoms resembling the onset of premature birth are often encountered during the normal course of pregnancy.

Diagnosis is also complicated by the fact that when amniotic fluid leaks in small amounts or intermittently, and ultrasound scans show a slight decrease in the amniotic fluid index, noninvasive laboratory tests can help diagnose premature rupture of membranes.

Several biophysical and biochemical markers have been proposed to diagnose preterm labor, both asymptomatic and accompanied by cramping pain. There is compelling evidence that cervical ultrasound is superior to digital vaginal examination in determining the risk of preterm labor before 34 weeks. The shorter the cervix, the higher the risk of preterm labor, and vice versa [21, p.59].

When studying the data on the course of pregnancy, various factors leading to the threat of premature birth were identified in all groups of pregnant women. Genital infection was noted in 35 (87.5%) of those examined, one or more abortions in the anamnesis were in 20 (50%), and habitual miscarriage in the anamnesis was in 10 (25%). According to the vaginal examination data, shortening and softening of the cervix, which is not typical for the gestational age, was observed in 15 (37.5%) [12, p.64].

According to S.G. Babson and A.I. Khazanov, the duration of premature labor is usually longer than that of term labor, however, with isthmic-cervical insufficiency, the first stage of labor is shortened. Premature rupture of the membranes occurs in approximately 30-38% of cases. The third stage of premature labor, in contrast to the same period in term labor, is characterized by more frequent bleeding due to uterine hypotension or retention of parts of the placenta. Due to the protracted course of premature labor and premature rupture of membranes, the incidence of postpartum septic diseases increases [75, p. 177; 89, p. 37; 167, pp. 184-190].

Two indicators are important for diagnosing active preterm labor: regular contractions (at least 4 in 20 minutes of observation) and dynamic changes in the cervix (shortening and smoothing), since changes in the cervix are a more objective indicator than the assessment of labor activity. The degree of cervical dilation is an important diagnostic criterion and prognosis for the effectiveness of tocolysis. In the case of threatened or incipient labor, therapy aimed at preserving the pregnancy can be administered, but if the os dilates more than 3 cm (a sign of the active phase of the first period), tocolysis will most likely be ineffective [28, p.37; 92].

Another important diagnostic method is the assessment of uterine contractile activity based on cardiotocography data and the determination of biochemical markers of premature birth (hCG, elastase, protease, phospholipase, α-fetoprotein (α-FP) in the mother's blood serum). The study of biological markers has allowed us to better understand the pathological mechanisms leading to spontaneous premature birth, but the clinical significance of most of them is small [9, p.29]. The

concentration of a number of substances in biological fluids can predict premature birth only 24 hours before its onset, which excludes the possibility of prevention, and other substances serve as markers of premature birth in the late stages of pregnancy, when the incidence among newborns is relatively low. Currently, the greatest clinical significance is fetal fibronectin, a glycoprotein, the detection of which in cervical-vaginal secretions indicates rupture of the fetal membranes [18, p. 48].

The diagnosis of the onset of premature labor can also be clarified using transvaginal ultrasound with measurement of the length of the cervix or determination of fetal fibronectin in cervical-vaginal secretions [10, p. 22].

In the absence of fibronectin in vaginal secretions, the probability that a woman will give birth within a week is about 1% [30, p. 21; 66, p. 136].

Pathogenetic and clinical significance of placental apoptosis as a trigger mechanism for premature birth. Apoptosis and its regulation

Apoptosis is a natural form of programmed cell death (PCD), along with autophagy, oncosis, mitotic catastrophe, etc. [56, p.78-84]. In relation to reproductive issues, this phenomenon has been studied fragmentarily. Nevertheless, at present there is every reason to speak about the participation of PCD processes in all stages of placenta development, starting with implantation and ending with rejection.

The role of apoptosis inducers is assigned to ligands from the tumor necrosis factor superfamily (TNFa, Fas-L, TRAIL, TWEAK, LTa, LTp, 4-1BBL, LIGHT) [12, p. 64], expressed in the human placenta [69, pp. 55-64]. Fas-L-containing cells are capable of inducing apoptosis of cells on the surface of which there is a corresponding receptor, Fas. Fas-L is also present on the surface of the trophoblast [23, pp. 52-53]. Initiation of apoptosis of T-lymphocytes sensitized to the fetus through the FasL-Fas interaction protects it from aggression from the mother's

immune system. Fas is also expressed in small quantities on the surface of the trophoblast itself, but this pathway of apoptosis activation is blocked in it [20, pp. 304-305]. This block is not absolute: in the presence of IFN and TNFα, the sensitivity of the trophoblast to the initiation of apoptosis through the FasL-Fas system increases [24, p. 21].

Trophoblastic expression of Fas-L decreases during labor, which may be evidence of the involvement of apoptotic processes in placental rejection [57, p. 28-35]. It is possible that the FasL-Fas mechanism is involved in the disruption of placental formation in gestosis, since excessive expression of Fas-L and Fas in the decidual tissue has been detected in this pathology [55, p. 30-35].

Unlike Fas, TNFa-induced apoptosis in villous trophoblast is not blocked [20, p.304-305]. The biological purpose of this phenomenon is unclear. It is possible that apoptosis in trophoblast is limited through other regulatory systems.

A study of cytokine regulation of apoptosis showed that TNFα and γ-interferon (IFNγ) synergistically induce apoptosis in trophoblast culture, and the level of Bcl-2 protein expression in the cytotrophoblast modulates the degree of apoptosis. TNFα is involved in the activation of placental apoptosis in intrauterine fetal growth retardation [25, p.320]. It has been shown that spontaneous abortions are accompanied by an increase in the expression of Fas-L in decidual lymphocytes and Fas in the extravillous trophoblast [5, pp.22-24].

Overexpression of Nodal, a member of the transforming growth factor-ß superfamily, activates apoptosis and inhibits trophoblast proliferative activity via the p27-cyclin E/Cdk2 mechanism [65, p. 70].

Studies on another cytokine, placental growth factor (PlGF), which was first isolated in 1991, have shown that PlGF protects trophoblast from apoptosis caused by growth factor deficiency, but does not have a similar protective effect against TNF-α-induced apoptosis. In contrast, epidermal growth factor blocks TNF-α-induced apoptosis, prevents alcohol-induced apoptosis in the placenta [28, p. 37], but does not protect trophoblast in the presence of growth factor deficiency [64, pp. 895-899].

Apoptosis in the placenta is affected by the level of glucocorticoids. 11ß-hydroxysteroid dehydrogenase-2 is localized in the placenta, the expression of which increases with increasing gestational age in parallel with the growth of apoptosis indices in the placenta [38, p.26].

Hepatocyte growth factor suppresses trophoblast apoptosis by phosphorylating serine-threonine protein kinase (Akt), which leads to inhibition of glycogen synthase kinase (GSK-3beta). This, in turn, causes activation of the transcription factor ß-catenin and inducible NO; intase [83, p.187].

It has been established that leptin, a polypeptide hormone with features of a long-chain cytokine (similar to IL-2, IL-12), is synthesized in the placenta, as evidenced by the high homology of its receptor with representatives of class I cytokine receptors [59, p. 444; 71, p. 1040]. A stimulating effect of this cytokine on the proliferation of trophoblast cells has been revealed, as evidenced by the activation of 3H-thymidine incorporation, cell advancement to the G2/M phase of the cell cycle, and increased expression of cyclin D1. In addition, leptin suppresses apoptosis processes in the trophoblast [60, p. 73].

In the extravillous trophoblast, progesterone significantly reduces apoptotic activity by decreasing the number of TUNEL-positive cells, the expression of Fas, Fas-L, caspases 3, 8, and PARP (poly(ADP)ribose polymerase), and increasing the expression of Bcl-2 [79, p.33]. Endothelin-1 also suppresses apoptosis in the trophoblast, which probably suggests its protective role in trophoblast injury [27, p.83].

The myeloid cell leukemoid factor-1 (Mcl-1) system plays an important role in the regulation of placental PCD. This system is represented by the apoptosis-inhibitory factor Mcl-1L and the pro-apoptotic component Mcl-1S, as well as Mtd-L and Mtd-P, isoforms of Mtd/Bok (Matador/Bcl-2-related ovarian killer), a representative of the Bcl-2 family, which induce the development of mitochondria-dependent apoptotic mechanisms [4, p. 163]. The pro-apoptotic activity of the Mcl-1S and Mtd-L molecules is neutralized by its binding to Mcl-1L, which also blocks

the apoptogenic protein BIM and other representatives of the Bak family [21, p. 59; 73, p. 47].

Oxygen is a potential regulator of apoptotic cell death. Some members of the Bcl-2 family, including the BH3 ligands Nix and Nip, as well as Mcl-1 and Mtd, are directly regulated by oxygen via the transcription factor HIF-1 [63, p. 41]. Mcl-1L expression is activated by decreased oxygenation, indicating an activating regulatory effect of HIF-1 [41, p. 144]. In addition, the level of proapoptotic Mcl-1c and Mcl-1S in the placenta increases at 10-13 weeks, when pO2 increases significantly.

Nitric oxide in the placenta not only affects vascular tone, but also acts as a factor influencing cell apoptosis. It also regulates blastocyst implantation [35, p. 35], trophoblast differentiation [36, p. 44], its motility and invasion [17, p. 32]. The dominant effect of nitric oxide during pregnancy is the modulation of the formation of new vessels in the placental villi [72, p. 40; 162, pp. 30-36]. It is assumed that nitric oxide, by increasing the sensitivity of decidual membrane cells to proliferative stimuli, affects the processes of decidualization [76, p. 60].

In vitro studies have shown that extravillous trophoblast cells are more susceptible to apoptosis when cultured, and the addition of NO donors to the medium reduces the sensitivity of extravillous trophoblast cells to apoptogenic stimuli in preeclampsia, but activates the NO-induced apoptotic pathway in normal cells [86, pp. 56-60].

In trophoblast cells, the genes APG9L1 and APG9L2 were found, which carry out post-transcriptional regulation of endothelial NO; intase and are necessary for the formation of such a phenomenon as autophagy - one of the types of programmed cell death - an intracellular system for the degradation of most proteins and some cell organelles [26, p. 77].

An analogue of nitric oxide is carbon monoxide, formed in the process of the heme oxygenase reaction, which is also involved in the regulation of PCG. Carbon monoxide protects trophoblast from apoptosis induced by episodes of hypoxia/reoxygenation. This probably explains the paradoxical fact of the lower prevalence of preeclampsia in smoking pregnant women [16, p.547].

Activation of apoptosis of trophoblastic cells can be caused by increased production of free radicals, accompanying disruption of blood supply to the placenta [74, p. 86]. With inadequate restructuring of the spiral uteroplacental arteries, blood flow in them is variable, since they continue to respond to vasoconstrictor effects. As a result, alternating episodes of hypoxia and hyperoxia occur, which leads to excessive production of free radicals. Activation of apoptosis in the placenta during hypoxia-reoxygenation is carried out through the RT-kB system, p38, stress-activated PC, mitogen-activated PC [66, p. 136], accompanied by an increase in the level of TUNEL-positive nuclei, 4-hydroxynonenal, nitrosylation products, activation of caspase-3 and polyADP-ribose polymerase and is prevented by vitamins C and E [66, p. 136;., 81, p. 56], deferroxamine and superoxide dismutase [17, p. 461; 42, pp. 73-81] and low concentrations of glycerol trinitrate [39, p. 26].

It has been established that hypoxia in the placenta causes caspase-dependent modification of myeloid cell leukemoid factor-1 (Mcl-1). In particular, preeclampsia is accompanied by cleavage of the apoptosis-inhibitory factor McI-1 by caspases-3 and -7 and inclusion of the apoptogenic McI-1. Episodes of hypoxia-reoxygenation in preeclampsia are not only accompanied by cleavage of McI-1, but also activate its expression, along with Mtd-L and Mtd-P. Under conditions of chronic hypoxia, both normal and preeclamptic placentas decrease expression of syncytin, a specific protein marker of syncytial fusion of trophoblastic cells, indicating a decrease in the rate of trophoblast differentiation [4, p. 163; 43, p. 10].

Caspase-14 [52, p. 70] is found in the placenta; it is characteristic of the epidermis and plays an important role in the keratinization process. The peculiarities of caspase functioning in the placenta are a poorly studied issue. Initiator caspases-8 and -10 are activated in the part of the differentiated cytotrophoblast that is intended for syncytial fusion [6]. Effector caspases are expressed in the cytotrophoblast only in an inactive form [13, p. 79].

An increase in the content of caspase cleavage products was revealed in hydatidiform mole, which is difficult to explain at this stage, since in other tissues tumor growth is usually associated with suppression of apoptosis [9, p. 29].

The cytotrophoblast, preparing for syncytialization, initiates the cellular program of apoptosis and, at the same time, produces a significant number of apoptosis inhibitors, including proteins of the Bcl-2 family [49, p. 194]. Bcl-2 is a family of proteins that control the process of programmed cell death. They participate in the mitochondrial regulation of apoptosis.

In the placenta, bcl-2 is expressed in the villous and extravillous trophoblast, villous mesenchyme, and placental macrophages. Maximum expression was detected in trophoblast cells in the first trimester of pregnancy [67, p.70]. The degree of expression significantly decreases in the placenta after 32 weeks of gestation, which occurs simultaneously with the slowdown in placental growth. This may be one of the mechanisms of the so-called "aging" of the placenta [68, p.872]. During labor, bcl-2 expression does not change [80, p.47].

Regulation of a number of caspases is carried out by the flice-like inhibitory protein (Flip). Flip is expressed in the placenta and competes with caspase-8 for binding to death receptors such as TNF-R and Fas [24, p.21], thereby reducing the destructive activity of caspase-8 in the villous cytotrophoblast.

At early stages, apoptosis of underlying endometrial cells frees up space for the growing ovum [7, p. 34; 58]. It has been established that endometrial stromal cells (ESCs) express Fas, while implanting trophoblast cells secrete Fas-L. However, it has been shown that, regardless of hormonal differentiation, ESCs are primarily resistant to Fas-dependent apoptosis. At the same time, γ-interferon and TNF-α are able to unblock this pathway, which is accompanied by activation of caspases-3, -8 and -9 [44, p. 15].

Later, the extravillous trophoblast migrating through the blood vessels of the endo- and myometrium attaches to the vascular wall, causing its transformation. Fibrinoid changes in the wall of the spiral uteroplacental arteries lead to the expansion of these vessels, providing sufficient blood flow to the placenta, regardless of the influence of vasoconstrictor factors [1, p. 404]. Trophoblast cells, participating in this extremely complex dosed invasive process, demonstrate some functional similarity with malignant cells [50, p. 136].

There is a hypothesis suggesting activation of smooth muscle cell (SMC) apoptosis during invasion of extravillous trophoblast into the muscular layer of uterine spiral arteries, which is a fundamental process in their gestational transformation. The key role in this process is assigned to apoptotic cytokines of the TNF family, in particular, the Fas-Fas-L system, TRAIL and metalloproteinases, in particular MPP-12 [11, p. 246; 48, p. 17; 85, pp. 16-19]. This is evidenced by TRAIL production by both villous and extravillous trophoblast [61], expression of TRAIL-R1 and -R2 receptors on SMC of spiral arteries, the ability of TRAIL to induce SMC apoptosis, and induction of SMC apoptosis by trophoblast via a TRAIL-dependent mechanism. At the same time, by activating the Akt-, ERK-dependent pathway, TRAIL promotes the proliferation and viability of endothelial cells [82, p.51].

Also involved in the apoptotic transformation of spiral arteries is uIFN, which increases the sensitivity of SMC to Fas-induced apoptosis [46, p. 102]. A similar permissive effect of uIFN is also observed in the case of stromal cells of the endometrium, trophoblast, etc. It has been established that uIFN, one of the main sources of which in the trophoblast are natural killers (NK), stimulates apoptosis and reduces the secretion of metalloproteinases (MMP2) [45, p. 33], which leads to the suppression of the invasion of extravillous trophoblast [54, p. 62].

Thus, apoptosis is both a mechanism for the transformation of spiral arteries and a mechanism that limits and localizes this process. If, for one reason or another, the process is not localized by apoptosis of the invading trophoblast cells, then, depending on the degree of the disorder, a hydatidiform mole or choriocarcinoma occurs [9, p.29].

On the contrary, early spontaneous abortion, gestosis and fetal growth retardation syndrome have common pathogenetic factors associated with insufficient trophoblast invasion [2, p. 968]. Incomplete restructuring of the uterine spiral arteries causes compensatory reactions in the form of increased apoptosis in the placenta, leading to increased permeability of the fetoplacental barrier to improve fetal nutrition [108, p. 30293-3; 50, p. 130-136].

Apoptosis of the invading trophoblast may be associated with factors causing its premature differentiation [47, p.158-162]. It has been shown that excessive macrophage infiltration of the decidua is observed in gestosis. It has been suggested that macrophages may influence trophoblast invasion, possibly initiating apoptosis of the latter. The specific mechanisms of this process are still unclear, but they are apparently central to the pathogenesis of gestosis [62, p.22].

Apoptosis is of great importance in the formation of fetomaternal tolerance. The participation of HLA-G, Fas-FasL, and TRAIL-TRAIL-R in the apoptosis of maternal leukocytes during pregnancy has been shown [18, p. 48; 50, p. 136]. The ability of syncytiotrophoblast and placental macrophages to secrete a soluble form of Fas-L, which participates in the formation of tolerance, has been discovered [19, p. 80]. Also, the ligand of programmed cell death (PDL1) is expressed in syncytiotrophoblast and cytotrophoblast [67, p. 70], which, by activating T-cell apoptosis, limits the expansion of T-lymphocytes, suppresses the production of IFNγ and promotes the formation of T-cell tolerance [3, p. 9].

It was found that the granzyme inhibitor B-P1-9 is synthesized in the extravillous and villous trophoblast, the maximum expression level of which is registered in the second trimester. It is believed that this protein allows the trophoblast to block the aggression of natural killers of the mother's body [14, p.45].

Thus, apoptosis is involved in the process of formation of fetomaternal tolerance. Cytokines produced by the placenta cause apoptosis in immunocompetent cells of the mother and block their apoptosis-mediated cytotoxicity in relation to trophoblast cells.

A significant amount of research allows us to speak with confidence about the important role of the process of programmed cell death in the decisive periods of placenta development. During the implantation process, apoptosis frees up space for the blastocyst penetrating the endometrium. During the invasion of the extravillous trophoblast, apoptosis plays a leading role in the gestational reorganization of the spiral arteries and the localization of the invasion. The processes of programmed cell death participate in the formation of an immunological partnership between the

immune systems of the mother and the fetus, which is necessary for carrying a pregnancy.

Management of pregnancy and childbirth in women with a history of premature birth

The goal of treatment is to prevent premature birth, prolong pregnancy in case of threat of termination and premature rupture of membranes using drugs that help suppress contractile activity of the uterus, improve the condition of the fetus in preparation for childbirth in order to improve clinical outcomes in newborns, which are better the longer the gestation period [15, p. 28].

In our country, threatened premature birth is recognized as an indication for hospitalization [2, p.74; 6], with bed rest, with the patient preferably lying on the left side (non-drug treatment). According to foreign studies, prolonged bed rest, used as the only treatment method, does not produce positive results. The bedrest regimen is recommended (alternating periods of active rest with periods of complete rest 3 times a day) [12, p.64].

The tactics of management and treatment of the threat of premature birth take into account the possible causes of premature birth and are determined by: the gestational age, the condition of the mother and fetus, the presence of an intact amniotic sac, the nature of the contractile activity of the uterus, the degree of changes in the cervix, the presence of bleeding and its severity [12, p.62].

Inhibition of uterine contractions is indicated in cases where the pregnancy period does not exceed 37 weeks and the cervix is dilated less than 4 cm.

To treat the threat of premature birth, various tocolytic drugs are used - a group of drugs with different mechanisms of action that suppress the contractile activity of the uterus, which are given primary importance in prolonging pregnancy, since their tocolytic effect is due to stimulation of β2 receptors of the uterus [4, p. 163].

Currently, the well-known and actively used tocolytic drug β-adrenergic agonist (Hexoprenaline sulfate) has a fairly wide range of contraindications and undesirable side effects on the body of the mother and fetus [8, p.61].

The need to reduce the dosage and duration of use of β-mimetics has led to the search for new alternative drugs for the treatment of the threat of premature birth. Abroad, calcium channel blockers (Nifedipine) currently occupy a leading place in tocolysis [11, p.246]. Due to the fact that it has less pronounced side effects on the part of the mother and fetus and obvious tocolytic effects [8, p.61].

General contraindications to tocolysis: obstetric contraindications (chorioamnionitis, detachment of a normally or low-lying placenta (risk of developing a kuvelaire uterus), conditions when prolongation of pregnancy is inappropriate (eclampsia, preeclampsia, severe extragenital pathology of the mother), contraindications from the fetus (malformations incompatible with life, antenatal death of the fetus).

Currently, the most popular tocolytics are selective β2-adrenergic agonists, oxytocin receptor blockers and calcium channel blockers [12, p.64].

Selective β2-adrenergic agonists are the most studied in terms of maternal and perinatal effects. Their representatives in our country are Hexoprenaline sulfate and Fenoterol. When using these drugs, myometrium relaxation is achieved by binding them to β2-adrenergic receptors and suppresses the contractile activity of the myometrium [8, p.61].

The recommended hexoprenaline sulfate should be started with a bolus administration of 10 mcg (1 ampoule of 2 ml) of the drug diluted in 10 ml of isotonic solution for 5-10 minutes, followed by infusion at a rate of 0.3 mcg/min [8, p.61].

When performing long-term tocolysis, the recommended dose of Hexoprenaline sulfate is 0.075 mcg/min. The maximum daily dose is 430 mcg. When preparing a solution for administration using intravenous systems, the infusion concentrate is diluted with 500 ml of isotonic sodium chloride solution. The prepared solution is administered intravenously by drip. The calculation of a dose of

0.3 mcg/min corresponds to: 1 ampoule (25 mcg) - 120 drops per minute, 2 ampoules (50 mcg) - 60 drops per minute, etc. [5, p. 24].

When using infusion pumps: 75 mcg of infusion concentrate (3 ampoules) is diluted in 50 ml of isotonic sodium chloride solution, the rate of administration is 0.075 mcg/min.

Fenoterol (fenoterol hydrobromide). When preparing a solution for administration using intravenous systems, the concentrate for infusions is 2 ampoules of 0.5 mg (1 ml - 2.5 mcg) diluted in 500 ml of isotonic sodium chloride solution. Infusion is started at a rate of 0.5 mcg/min (5 drops per minute), increasing the dose if necessary every 15 minutes until the effect is achieved. Most often, the effective dose is 1.5-2 mcg/min (15-20 drops per minute).

Contraindications for the use of β-adrenergic agonists are maternal cardiovascular diseases (aortic stenosis, myocarditis, tachyarrhythmia, congenital and acquired heart defects, cardiac arrhythmias), hyperthyroidism, closed-angle glaucoma, insulin-dependent diabetes mellitus, fetal RDS not associated with uterine hypertonicity.

When using β2-adrenergic agonists, it is necessary to: monitor the mother's heart rate every 15 minutes, monitor the mother's blood pressure every 15 minutes, monitor the blood glucose level every 4 hours, monitor the volume of administered fluid and diuresis, auscultate the lungs every 4 hours, monitor the condition of the fetus and uterine contractility.

I/V tocolysis is performed with the woman lying on her left side under cardiac monitoring.

Side effects: from the mother: nausea, vomiting, headaches, hypokalemia, increased blood glucose levels, nervousness, anxiety, tremor, tachycardia, shortness of breath, chest pain, pulmonary edema; from the fetus: tachycardia, hyperbilirubinemia, hypocalcemia.

It is important to remember that the frequency of side effects depends on the dose of β-adrenomimetics. If tachycardia or hypotension occurs, the rate of

administration of the drug should be reduced, and if chest pain occurs, the administration of the drug should be stopped.

Oxytocin receptor blockers. Oxytocin receptor antagonists are a fundamentally new class of tocolytic drugs, they block oxytocin receptors, help reduce myometrial tone and reduce uterine contractility. This group includes the drug Atosiban.

Atosiban is administered intravenously in 3 consecutive stages: first, 1 vial of 0.9 ml of the drug is administered without dilution over 1 minute (initial dose 6.75 mg), immediately after that, the drug is infused at a dose of 300 mcg/min for 3 hours (infusion rate 24 ml/hour or 8 drops/min), after which a long-term (up to 45 hours) infusion of Atosiban is administered at a dose of 100 mcg/min (infusion rate 8 ml/hour or 3 drops/min). The total duration of treatment should not exceed 48 hours. The maximum dose for the entire course should not exceed 330 mg.

If there is a need for repeated use of Atosiban, it should also be started with stage 1, followed by infusion of the drug (stages 2 and 3). Repeated use can be started at any time after the first use of the drug, it can be repeated up to 3 cycles [3, p.9].

The main contraindications to the use of oxytocin receptor blockers are: gestational age < 24 weeks and > 33 completed weeks, premature rupture of membranes in pregnancies > 30 weeks, growth restriction and/or signs of fetal RDS, uterine bleeding, severe preeclampsia, intrauterine fetal death, suspected intrauterine infection, with placenta previa or premature detachment of a normally located placenta, any other conditions that affect both the mother and the fetus, in which maintaining the pregnancy is dangerous.

Calcium channel blockers. Today, calcium channel blockers are promising drugs for tocolytic therapy due to the lower severity of side effects on the part of the pregnant woman. Nifedipine is used more often, since its advantages compared to other tocolytic drugs have been proven: lower frequency of side effects, increased prolongation of pregnancy, reduction of neonatal complications.

Nifedipine and Atosiban have comparable efficacy in prolonging pregnancy to 7 days. Compared with selective β2-adrenergic agonists, Nifedipine has been

shown to improve neonatal outcomes, although long-term results have not yet been studied. No comparative randomized studies have been conducted on the use of Atosiban and Nifedipine.

A systematic review found a trend towards a greater than 48-hour delay in delivery with Nifedipine.

Schemes for the use of Nifedipine: 20 mg orally, then - if uterine contractions persist - 20 mg again after 30 minutes, then 20 mg every 3-8 hours for 48 hours as indicated. The maximum dose is 160 mg/day. Or 10 mg sublingually, then, if necessary, 10 mg every 20 minutes (maximum dose during the first hour is 40 mg), then 20 mg every 4 hours for up to 48 hours.

Side effects (only on the mother's side): hypotension (extremely rare in patients with normotension), tachycardia, headaches, dizziness, nausea.

Recommended monitoring during tocolysis with Nifedipine: continuous monitoring of fetal heart rate while there are uterine contractions, measuring pulse, blood pressure every 30 minutes during the first hour, then every hour during the first 24 hours, then every 4 hours.

Tocolysis is performed for 48 hours in order to prevent RDS in the fetus and transfer the pregnant woman to a perinatal center.

Nitroglycerin can induce relaxation of the smooth muscles of the myometrium. When using nitroglycerin, a decrease in the frequency of births was noted before 37 weeks, but no effect of therapy on the frequency of births before 32-34 weeks of pregnancy was noted [3, p. 9]. Drugs of this group have not yet found application as tocolytic therapy.

Magnesium sulfate remains one of the most popular means to reduce the contractile activity of the myometrium to this day. Despite this, magnesium sulfate does not have a clear tocolytic effect and its use as a tocolytic is not recommended [3, p.9].

Prevention of premature birth is an extremely complex and difficult task. Therefore, for a more favorable outcome, active management of the prenatal period is recommended for pregnant women with a burdened social history, although its

effectiveness in terms of reducing the number of premature births has not been proven. Prevention of prematurity consists of proper management of women from the very beginning of pregnancy, determining markers that indicate a threatening premature birth [12, p.64].

The new policy challenge is to understand how a 'primary prevention' approach (identifying and treating risk factors in all women planning pregnancy to prevent miscarriage) can reduce the incidence of preterm birth, thereby improving the effectiveness of practical tocolytic therapy with oxytocin analogues or other drugs. Secondary prevention is given to women at risk, with multiple aggravating factors (e.g. prophylactic suturing in miscarriage and multiple pregnancies). Tertiary prevention is given after the onset of labour to delay delivery and improve the prognosis for the newborn.

The outcomes of birth for premature babies are determined by the gestational age, as well as the characteristics of the course of premature birth. Most complications, both in the mother and the fetus, are caused by a violation of the contractile activity of the uterus.

In the first half of the last century it became known that increased activity of endogenous progesterone is a necessary condition for the development and maintenance of pregnancy. A decrease in progesterone is associated with the onset of timely and premature labor [18, p.48].

Since then, progesterone and its synthetic analogues, 17-α-hydroxyprogesterone caproate (17-OPC), have been tested in clinical trials to prevent premature birth. The drugs were administered daily as vaginal injections of 8% gel or 100–400 mg of micronized progesterone [14, p. 45].

Most of the women included in the studies had a history of premature birth. In women with a short cervix (15 mm or less) without signs of threatening premature birth (contractions, etc.), the use of progesterone (200 mg vaginally daily) from the middle of the second and in the third trimesters was effective [14, p. 45]. At the same time, the effectiveness of prescribing 17-OPC in women with a short cervix and sutures on the cervix was not noted.

However, if the same women do not have cervical sutures, 17-OPC reduces perinatal mortality. Neither progesterone nor 17-OPC have been studied as prophylactic agents in women with a positive fibronectin test. Both drugs have proven effective in tertiary prevention of preterm birth after tocolysis [21, p.59].

Synthetic 17-OPC and micronized progesterone differ in chemical structure and have different effects on the woman's body, including the myometrium. Micronized progesterone can slow down uterine contractions, while 17-OPC does not affect the contractility of the uterus. In multiple pregnancies, neither micronized progesterone nor 17-OPC can prevent premature birth [14, p.45].

Chapter conclusions.

Currently, there are no specific pathogenetic studies of the cause of the risk of developing preterm labor in pregnant women with a complicated somatic and obstetric-gynecological history; preclinical diagnostic markers of the risk of development.

Analysis of literary sources showed that premature birth is the result of the impact on the body of a pregnant woman and the fetus of a complex of unfavorable medical and biological, social and other factors. Instability of the socio-economic conditions of life of women of reproductive age, the growth of somatic pathology and sexually transmitted diseases, changes in their reproductive behavior - the birth of the first child at a later age (25-35 years), systematization and identification of the most significant risk factors for the prognosis of premature birth, the impact on termination of pregnancy is not specific and refers to the number of multifactorial pathological conditions. Therefore, determining the significance of groups of factors and each factor separately makes it possible to more accurately predict the development of this pathology using modern laboratory studies when setting which can predict PB. Such an approach to determining the tactics of managing pregnant women will allow targeted prevention of premature birth, which will help reduce perinatal pathology and mortality of newborns.

In this regard, the issue of more accurate forecasting and prevention of the risk of developing PB, based on accessible and objective indicators, remains relevant. All of the above determines the need and relevance of this scientific study.

The review on the topic: "CLINICAL AND PATHOGENETIC PREDICTORS OF PREMATURE BIRTH, OPTIMIZATION OF THE SYSTEM OF TREATMENT AND PREVENTIVE MEASURES" was prepared based on the databases: EBSCOhost, Springer NATURE, Scopus, PubMed, Google Scholar, eLibrary for the period from 2012-2022.

MATERIALS AND METHODS OF RESEARCH.

Study design

This work was carried out in the period from 2020 to 2023.

The study was conducted at the branch of the Republican Specialized Scientific and Practical Center for Pregnancy and Maternity Protection center in Samarkand (chief physician - Khamraeva L.K., Samarkand).

The analysis, processing and calculation of data were carried out in the department of pathology of pregnant women of the branch of the center of the Republican Specialized Scientific and Practical Center for Pregnancy and Maternity Protection in Samarkand (head of the department – Akhmedov Sh.A.).

The study included a prospective comparative analysis (Fig. 2.1).

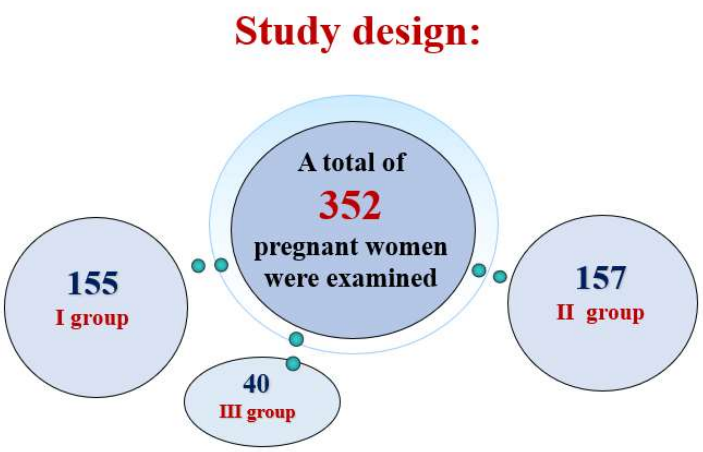


Figure 2.1. Study design

This monograph is the result of a clinical study approved by the local ethics committee of the university and carried out in accordance with ethical standards (Good Clinical Practice).

As a result of the conducted prospective study, the following data were analyzed: initial clinical characteristics, features of the course of pregnancy, as well as its outcomes in 352 pregnant women with threatened premature birth.

The patients were included in the study as they applied. According to the data of both clinical, laboratory and functional examination methods, as well as the diagnosis, as well as in accordance with the developed criteria for inclusion in the study, all pregnant women were divided into 3 groups.

The first (I, n=155) is the main group of pregnant women with threatened PB

The second (II, n=157) is the comparison group of pregnant women with threatened PB

The third group (control, n=40) included 40 pregnant women with a physiological course of pregnancy and childbirth, who delivered on time.

The inclusion criteria were:

1. Singleton pregnancy that occurred in a natural cycle;
2. Age of pregnant women from 18 to 36 years;
3. Repeatedly pregnant women with a gestation period from 22 to 34 weeks;
4. Threat of termination of pregnancy;
5. Women with a history of premature birth who gave birth through the natural birth canal;
6. Informed consent to participate in the study;
7. History of medical abortion (1 or more abortions in the history).

Exclusion criteria:

1. Uterine scar;
2. Pregnant women with severe extragenital pathology;
3. Severe obstetric pathology requiring elective early delivery;
4. Decompensated placental insufficiency;
5. Congenital malformations of the fetus;
6. Multiple pregnancy;
7. Chronic and acute kidney diseases;
8. HIV-infected pregnant women.

All patients included in the study underwent a standard set of examinations in accordance with the order of the Ministry of Health of the Republic of Uzbekistan dated November 19, 2017 №123n “On approval of the Procedure for the provision of medical care in the field of obstetrics and gynecology”.

Each woman was informed about the purpose and methods of the study,

all patients signed a voluntary informed consent for their participation in the scientific study.

In accordance with the set objectives, the following biological material was collected: whole blood (blood serum), secretions from the posterior vaginal fornix, urine.

Treatment of patients with the threat of premature birth, aimed at prolonging pregnancy, was carried out in accordance with the clinical recommendations of the Ministry of Health of the Republic of Uzbekistan "Preterm birth" ICD-10.

The tactics of management and delivery of pregnant women were determined based on a combination of clinical and functional data, as well as the effectiveness of treatment in each specific case.

Research methods

Laboratory examination included determination of endogenous intoxication, antioxidant protection, proinflammatory cytokines, reactive proteins, determination of ceruloplasmin, determination of S-100 protein content, nitric oxide, endothelial dysfunction, uric acid study, morphological study of the placenta, statistical analysis.

All studies were conducted at the laboratories of maternity hospitals and the private medical centers MedSI and INNOVA EXPERT.

Blood for the study of all parameters was collected from the cubital vein into a siliconized tube containing 3.8% sodium citrate, centrifuged at 3000-4000 rpm (1200 g) for 15 minutes, resulting in platelet-poor plasma, which was transferred to another tube, where it was stored until the study. Frozen plasma samples were stored at a temperature of -20 to -16°C.

Methods of studying endogenous intoxication

Hydrophobic toxic products were determined by the characteristics of the physicochemical properties of albumin. For this purpose, the effective (ECA) and total (TCA) concentrations of albumin in the blood serum were studied using the fluorescence method on a specialized analyzer AKL-01 "Zond". A set of reagents

"Zond-Albumin" (Moscow) was used in accordance with the attached instructions. The following were calculated: the albumin binding reserve (ABR), which reflects the proportion of albumin centers in the serum, binding to which is not blocked by metabolites or toxins, was determined by the formula: PCA = ECA / TAR; the plasma toxicity index (IT), reflecting the degree of filling of tissue centers with various toxic substances, was determined by the formula: IT = TAR / ECA-1 (Gryzunov Yu. A., Dobretsov G. E., 1994).

Methods for studying antioxidant protection

Determination of superoxide dismutase (SOD) activity was studied by a biochemical method using the reagents “Reagent for quality control of superoxide dismutase SD 126 “Randox Laboratories (Great Britain)”. 3 ml of phosphate buffer (pH 7.4) were added to the washed erythrocytes and homogenized until a homogeneous suspension appeared. After centrifugation at 5000 rpm for 15 minutes, 0.5 ml of supernatant was collected and added to a centrifuge tube containing 1 ml of a chloroform-alcohol mixture (2:1, by volume). The resulting mixture was cooled, thoroughly mixed and centrifuged. The aqueous-alcohol layer containing the enzyme was collected and several drops of a saturated solution of KH2PO4 were added. The enzyme preparation was obtained by diluting the obtained phase 20 times. The reaction medium contained nitroblue tetrazolium (57 μmol), NADH (98.5 μmol), phenazine metasulfate (16 μmol) and 0.2 ml of the enzyme preparation. Nitroblue tetrazolium is used as an indicator capable of accepting electrons and being reduced to formazan, which has an absorption maximum at 560 nm. The reduced form of biformazan is colored from blue to black. The reaction proceeded for 10 minutes in 0.5 mol phosphate buffer (pH 8.3) with EDTA (0.1 mmol) at 250 C under aerobic conditions (Gurevich V.S. et al., 1990). The enzyme preparation was not added to the control sample.

Quantitative determination of catalase was determined by enzyme immunoassay using reagent “Cat. SEC418Hu” from Cloud-Clone Corp.

Methods for studying lipid peroxidation

Diene conjugates were determined by spectrophotometric method (Ganston F. D., 1986), malondialdehyde (MDA) with thiobarbituric acid test, TBA active products with reagent kit "TBK AGAT" Russia, Moscow. Lipids from erythrocytes were extracted with chloroform-methanol mixture. Total lipid preparation was dried to dryness on rotary vacuum evaporator, lipid residue was dissolved in hexane. Absorption spectrum was recorded at wavelengths of 190-275 nm on SF-46 spectrophotometer (Russia). Lipid oxidation was estimated by oxidation index values calculated per 1 mg of lipids by determination of ratio A 232/A 215 and A 275/A 215 (A is optical density at specified wavelengths). The content was expressed in conventional units/mg lipids.

A = T % / (100% - T%),

where A is the enzyme activity in arbitrary units, calculated per 1 mg of protein, T% is the percentage of inhibition of the nitroblue tetrazolium reduction reaction in the sample per minute.

Determination of malondialdehyde (MDA) was carried out using a thiobarbituric acid test, and diene conjugates were determined spectrophotometrically at 233 nm.

Study of proinflammatory cytokines

The level of cytokines in the blood serum (interleukins 1, 2, 4, 6, 8, 10, tumor necrosis factor) was determined by the enzyme immunoassay method using the appropriate reagents from Vector-Best CJSC according to the manufacturer's protocol.

The primary monoclonal antibodies to the corresponding cytokine were adsorbed onto polystyrene plates (COSTAR, France) at 50 µl per well at a concentration of 10 µg/ml in a 0.1 M sorption carbonate buffer, pH 9.0, for an hour at room temperature on a shaker. The plates were washed twice with a 0.05 M phosphate buffer, pH 7.2, containing 0.1% NP-40 detergent (SIGMA, USA). For this purpose, 100 µl of the washing phosphate buffer was added to each well using a 12-channel automatic pipette (COSTAR, France), after which the added buffer was

aspirated with a pipette. After washing, blocking was performed by adding 100 µl of 0.05 M phosphate buffer with 1% BSA to each well, followed by double washing as described above. Then, the studied samples were added in a volume of 50 µl per well, making 2-3 two-fold dilutions, the studies were performed in 3 parallels. The dilutions of the samples were carried out in a washing phosphate buffer. Simultaneously with the samples, a standard cytokine sample in different concentrations was added to one of the rows of the plate. The plate with the samples was incubated for 1 hour on a shaker at room temperature or at +4-C overnight. After incubation, a double wash was performed as described above. Then, the second polyclonal rabbit antibodies to the corresponding cytokines were added to the plate at 50 µl per well at a concentration of 1 µg/ml. Incubation with the second antibodies was carried out for 1 hour under the same conditions as in the previous stages, followed by a double wash. At the last stage, goat anti-rabbit antibodies labeled with 88 horseradish peroxidase ("SIGMA", USA) were added to the plate and incubated for an hour under the same conditions. The concentration of these conjugates is selected empirically for each specific cytokine. After the end of the last stage, a four-fold wash was performed. Staining was carried out in phosphate-citrate buffer 0.1 M pH 5.0 with added orthophenylenediamine dye at a concentration of 0.5 mg / ml and 0.06% hydrogen peroxide as a substrate. The plates were kept in the dark at room temperature for 15-20 min. until the colored product of the enzymatic reaction completely appeared. The reaction was stopped by adding an equal volume of 1 M HSO to the wells. The reaction results were recorded at a wavelength of 495 nm using a 3550 plate spectrophotometer (Bio-Rad, USA).

Determination of reactive blood proteins

C-protein is a glycoprotein produced by the liver and related to acute phase inflammation proteins. Under the influence of proinflammatory cytokines (interleukin-1, tumor necrosis factor-alpha and especially interleukin-6), its synthesis increases after 6 hours, and the concentration in the blood increases 10-

100 times within 24-48 hours after the onset of inflammation.

C-reactive protein was determined by the method of Immunoturbidimetry mg/l. Increased content of basic concentrations of which in the blood indicates an inflammatory process in the vascular wall, leading to the development of various complications.

Before taking the test, pregnant women were asked not to eat for 12 hours before the test and to avoid physical and emotional stress 30 minutes before the test.

Determination of blood ceruloplasmins

The modified Revin method is based on the participation of ceruloplasmin (CP) in the oxidation of p-phenylenediamine [58]. Determination of ceruloplasmin in the blood was carried out by a biochemical method using the reagents "CER", a reagent for determination on the IMMAGE 800 analyzer.

Reagents: 1. 0.4 M acetate buffer (pH 5.5) prepared by mixing solutions 1 and 2 (in a ratio of 9:1): 1st solution - 54.44 g sodium acetate was placed in a 1 L volumetric flask and brought to the mark with distilled water, and 2nd solution - 22.6 ml glacial acetic acid was dissolved and brought to the mark with 1 L distilled water. 2. 3. 1.3% sodium fluoride solution. 0.5% solution of p-phenylenediamine hydrochloride.

Procedure. 8 ml of acetate buffer and 0.1 ml of plasma were added to the test tubes one by one. 2 ml of sodium fluoride solution were added to the control samples (in order to inactivate the enzymatic activity of ceruloplasmin), the experimental samples were left unchanged. The next step was to add 1 ml of p-phenylenediamine hydrochloride solution to both test tubes. The test tubes were shaken, placed in a thermostat and incubated for an hour at a temperature of 37 ° C. At the end of this time, 2 ml of sodium fluoride solution were added to all test tubes (except the control). The contents of the test tubes were mixed again and sent to the refrigerator for 30 min. Colorimetry of the samples was performed against the control with a pale pink color in cuvettes with a layer thickness of 1.0 cm at a wavelength of 530 nm.

The calculation of the concentration of CP in mg/l was made by multiplying the optical density value by the conversion factor 875:

CP (mg/l) = D. 875, where:

D is the optical density of the analyzed sample.

Determination of protein content S-100

The S-100 protein content was determined by a solid-phase enzyme immunoassay using reagents from CanAg (Sweden). The resulting serum in a volume of 0.5 ml was frozen and stored at a temperature of -20°C for no more than 2 months. Standards and patient samples are incubated together with biotinylated anti-S-100 monoclonal antibodies (obtained from mice) in streptavidin-coated microplate wells. During incubation, the S-100 protein contained in the standards or patient samples is adsorbed on streptavidin-coated microplate wells with biotinylated anti-S-100 monoclonal antibodies. The strips are then washed and incubated with horseradish peroxidase-labeled anti-S-100 monoclonal antibodies. After washing, buffer substrate is added to each well and the enzymatic reaction is carried out. During the reaction, a blue color develops if the antigen is present. The intensity of the color is proportional to the amount of S-100 antigen present in the sample. The color intensity is measured on a microplate reader at 405 nm after adding the stop solution. Standard curves are plotted for each assay as optical density versus concentration for each standard. The concentration of S-100 in patient samples is calculated from the calibration curve.

Methods of studying nitric oxide.

The production of nitric oxide was assessed based on the content of stable metabolites (NOx) in the blood plasma, which were determined by recording the final stable metabolites of nitric oxide – nitrates/nitrites [I.L. Emchenko et al., 1994] – with the reagent “Nitric Oxide (NO)”, 192 (detection – 540 nm), cat. number KGE001 Russia, Moscow.

The concentration of nitrites was determined using the calibration graph and then calculated using the formula:

X (mg/l) = C1 · V1 · 1.016, where:

C1 is the concentration of nitrite ion found using the calibration graph; V1 is the volume of protein-free extract; 1.016 is the ratio of the total volume of the photometric solution (ml) to the volumes of the sample taken for analysis (ml) and the protein-free extract taken for further analysis (ml). Recalculation into μmol/l was performed using the formula:

$$X1 = \frac{X\ (мг/л)}{0{,}054}$$

where 0.054 is the average mass of nitrite/nitrates 0.01 μM.

Methods of studying endothelial dysfunction

- D-dimer is a protein, a product of the destruction of the fibrin molecule. D-dimer was determined by latex agglutination immunoassay using reagents from Renam (Russia).

- Von Willebrand factor (vWf) is a glycoprotein synthesized by endothelial cells. The level of von Willebrand factor indicates the state of the rheological properties of the blood. An increase in the concentration of vWf in the blood plasma is detected during stimulation or damage to endothelial cells, platelet aggregation, etc. [12]. The study of von Willebrand factor was carried out using the TECHOZYM vWF ELISA test system ("Technoclone") by the ELISA method.

Thrombomodulin was determined using the ELISA method with reagents produced by “BCM-diagnostics”.

Uric acid test

Uric acid in the blood serum of the mother and the newborn was determined using an enzymatic colorimetric test using a reaction with uricase (HUMAN, Germany). The blood sample was collected in a simple vial and incubated at 37 ° C for 30 minutes, after incubation the clot was removed and the remaining sample was taken into a centrifuge tube, the test sample was centrifuged at 3000 rpm for 10-20 minutes. The supernatant was collected in a clean and dry serum tube for uric acid analysis.

In case the patient was taking medications affecting MK metabolism (diuretics, aspirin, losartan), they were cancelled for 3-4 days. Also, pregnant women and the control group were prescribed a diet with purine restriction for 3 days before collecting samples. Hydrogen peroxide formed during the reaction reacts in the presence of peroxidase with sodium salt of N-ethyl-N-(2-hydroxy-3-sulfopropyl)-3-trimethylaniline (TOOS) and 4-aminophenazone (PAP) with the appearance of red-violet quinone imine.

Reaction scheme:

Uricase

Uric acid + O2 + H2O <----------> allantoin + CO2 + H2O2

Peroxidase

2H2O2 + DCGBS + PAP <----------> quinoneimine + HCl + 4H2O

After opening the vials, the reagents were stored at a temperature of 2-8°C and were used within 2 weeks. Before the start of the determination, the urine was diluted in a ratio of 1+10 with distilled water. The samples were incubated for 10 minutes at 20-25°C or for 5 minutes at a temperature of 37°C. The calculation of uric acid in the blood serum was performed using the formulas:

Serum:

$$C = 476 \times \frac{\text{A samples}}{\text{A standard}} \text{ [µmol/l];}$$

The test is linear up to a uric acid concentration of 20 mg/dL or 1190 µmol/L. If the uric acid content in the sample exceeded 1190 µmol/L, the sample was additionally diluted with saline in a ratio of 1 + 1 and the test was repeated. The obtained result was multiplied by 2 (dilution factor). The reference limits of UA in blood serum are 200-420 mmol/L. To convert the UA concentration in blood serum from µmol/L to mg/dL, a coefficient of 59.48 was used, by which the value was divided.

Amniotic fluid examination: Anterior amniotic fluid was collected in the first stage of labor during spontaneous rupture of the amniotic sac or amniotomy. Amniotic fluid was collected during examination of the woman from the lower spoon with a syringe in the amount of 5-10 ml. Biochemical examination was performed on the automatic biochemical analyzer "Hitachi-912". Amniotic fluid was pre-centrifuged at 2700 rpm for 5 minutes to separate it from cervical mucus, cheesy lubricant, meconium, epidermal scales and vellus hair of the fetus, then the quantity was determined.

Study of the hemostasis system

To determine the state of the blood coagulation system, its individual links and the overall coagulation capacity of the blood were examined:

spontaneous blood clotting time according to the Lee-White method (1913),

blood plasma recalcification time according to Bergerhof-Rock (1954),

blood plasma tolerance to heparin according to Poller as modified by V. P. Baluda (1954),

kaolin time of blood according to Hattersley (1966),

prothrombin time of blood according to the Quick method (1966),

thrombin time of blood according to Biggs-McFarlane (1962),

antithrombin III concentration according to Hansen as modified by K.M. Bishevsky (1963),

fibrinogen and fibrin degradation products (FDP) in plasma were determined according to the Nanniga Guest method (1967),

fibrin-monomer complexes (paracoagulation products) according to Godal as modified by V.G. Lychev (1975),

natural lysis of a blood clot according to M.A. Kotovshchikova and B.I. Kuznik (1962),

euglobulin method for determining the fibrinolytic activity of blood according to Kovarzhik-Bullock (1954).

In order to determine the coagulation-lytic state of liver tissue structures during the above tests, liver extract obtained according to the method of V.P. Skipetrov (1969) was added to the reaction mixture.

Morphological and histological research methods.

Morphological research methods were carried out in the 1st Clinic of the SamMU at the Department of Pathological Anatomy with a course of sectional biopsy under the guidance of the head of the department, Associate Professor Khamidova F.M.

All placentas were subjected to morphological and histological analysis after delivery. All samples in the amount of 317 were collected immediately after delivery, regardless of the delivery tactics.

Placental tissue was transported in RPMI-1640 medium with glutamine (PanEco) with the addition of 100 μg/ml gentamicin for 1 hour at a temperature of 0 to +4°C. Then, the tissue was homogenized with a small addition of a lysing solution on particles, strictly in accordance with the protocol.

For staining we used methylene blue ×400, ×600, hematoxylin and eosin ×10, ×100, ×200, ×400.

Electron micrographs were taken (×4800, ×5600).

Circulating endothelial cells were determined in the Goryaev chamber.

Macroscopic signs were assessed: - small size and weight of the placenta;

- various pathologies of the umbilical cord.

Microscopic signs: - acute chorioamnionitis and other signs of intrauterine infection; - various disorders of villous differentiation in the form of delayed or accelerated maturation; - signs of maternal and fetal malperfusion; - desquamated endotheliocytes; - the effect of hyperuricemia on placental destruction.

Cytological diagnostics - the number of circulating desquamated endothelial cells in the peripheral blood was assessed using microscopy methods. Using the traditional method, we performed a morphometric study of the functional state of the endothelium in pregnant women. In the work, a modified method for counting desquamated endotheliocytes was used (Ovsyanik D.M., Fomin A.V., 2014) [62],

which included staining the cytological preparation with a 0.1% methylene blue solution, staining the cytoplasm of the cells blue, and nuclear fragments dark blue for optimal color contrast and image clarity during CMM. For each patient, the number of endotheliocytes was counted in 10 samples of the Goryaev chamber, and the average value of the number of circulating DEC was determined. At the same time, the preparation was photographed from the microscope tube with a camera, the image was transferred and saved using a file conversion program. In automatic mode, the image tone correction was performed to minimize the level of errors associated with coloring and lighting. The image of bioobjects was isolated (segmented) under the control of the operator and the average morphometric parameters of desquamated endotheliocytes were determined.

Statistical analysis

Statistical processing of the material was carried out on a personal computer.

All the data obtained were ordered, coded and entered into tables. These data included information on parity, age, gestational age at the time of the ultrasound, data on previous illnesses and data outcomes.

For statistical analysis of the data, the original software package Statistica 12.0, IBM SPSS Statistics 28.0.1.0 and Microsoft Excel 2013 were used.

The mathematical processing of the material was based on nonparametric methods of mathematical statistics.

When analyzing quantitative parameters (variation series), the data were presented as medians of the parameters Me and quartiles of distributions: lower – Q1 and upper – Q2, in the format Me (Q1; Q2), the spread (minimum and maximum values) was also used. Comparison of observation groups with each other of quantitative parameters was made using the Mann-Whitney and Smirnov criteria.

When analyzing frequency tables (contingency tables), the nonparametric criterion 2 (Chi-square) was used.

The differences in distributions were presented as P values; when interpreting the results of statistical analysis, the significance level of P=0.05 was taken as critical;

the differences were considered statistically significant at a parameter value of $P<0.05$; for values close to zero, $P<0.001$ was indicated.

CHARACTERISTICS OF THE EXAMINED PREGNANT WOMEN (PROSPECTIVE STUDY)

Results of a prospective study

To determine one of the links in the pathogenesis of PB, we observed 352 pregnant women with threatened PB at a gestational age of 22-34 weeks. Patients were included in the study as they sought help and were hospitalized in the pregnancy pathology department of the branch of the Republican Specialized Scientific and Practical Medical Center for Maternal and Child Health in Samarkand in the period from 2020-2023.

The following data were analyzed: initial clinical characteristics, features of the pregnancy course, clinical and laboratory examination methods. In accordance with the developed inclusion criteria for the study, all pregnant women were divided into 3 groups (Fig. 3.1).

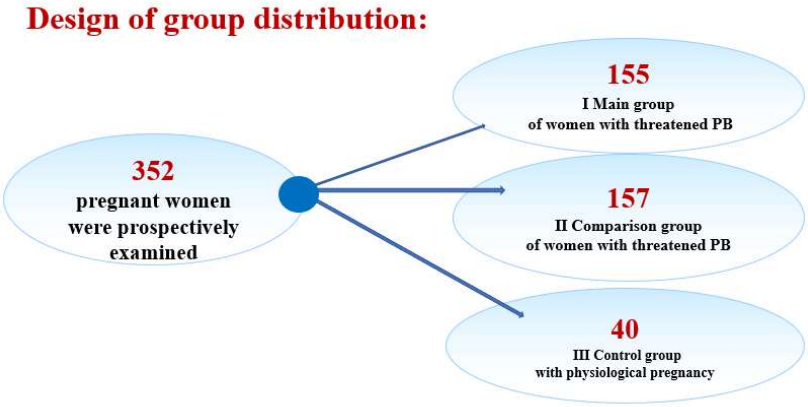


Figure 3.1. Group distribution design

The age of women varied from 19 to 38 years. The youngest age at the onset of premature birth was 18 years, and the later age was 38 years, on average, 27+2.9 years in all groups (Fig. 3.2.).

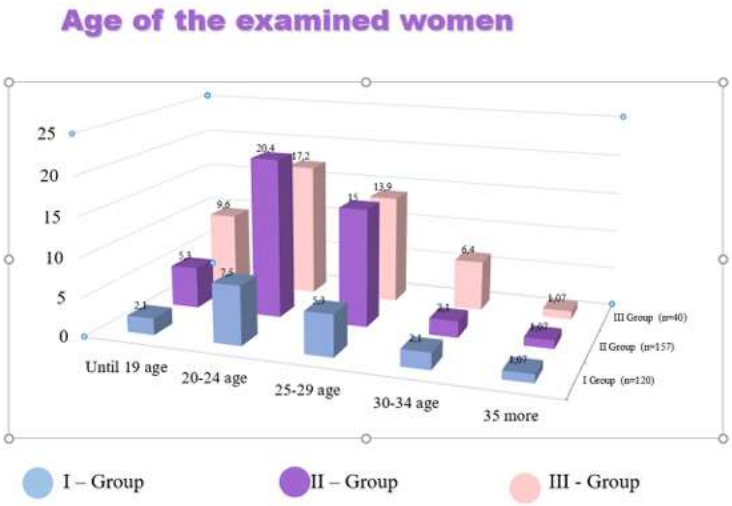


Figure 3.2. Distribution of examined women by age

In group I, the average age was 27 ± 1.7 years, in group II 28 ± 1.0 years, in the control group the average age was 26.5 ± 2.1 years (Table 3.1.).

Table 3.1.

Anthropometric data

Indicator	Groups, n (%)			P value
	1 (n=155)	2 (n=157)	3 (n=40)	
Age	27 (25;33)	29 (26;36)	26,5 (19;29)	p^1=0,52* p^2=0,02*
Height, cm	164,5±6,8	165,4±5,9	167,2±7,6	p^1=0,15 * p^2=0,14*
Body weight, kg	71,2±11,5	68,8±10,2	63,4±5,8	p^1=0,11* p^2=0,14*
BMI, kg/m2	26,8±3,98	25,1±6,2	22,6±2,98	p^1=0,35* p^2=0,45*

Note: p1 – comparison of groups 1 and 3, p2 – comparison of groups 2 and 3.

- significance of differences P <0.05

The average height was 164.5±6.8 cm in group I, 165.4±5.9 cm in group II, and 167.2±7.6 cm in the control group.

Body weight – in group I 71.2±11.5 kg, in group II 68.8±10.2 kg and in the control group was 63.4±5.8 kg. Body mass index – in group I 26.8±3.98 kg/m2, in group II 25.1±6.2 kg/m2 and in the control group was 22.6±2.98 kg/m2.

When analyzing the place of residence, urban residents predominated. By social status among those surveyed: students made up 18.2%, workers – 40.3%, housewives – 41.5%. (Fig. 3.3.)

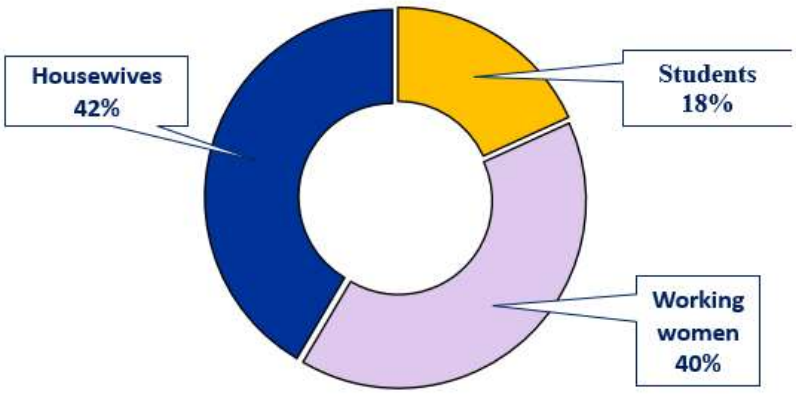


Figure 3.3. Social status of the examined women

The place of residence of the patients is presented in (Table 4.2.)

Table 3.2.

Place of residence of patients

Indicator	Groups, n (%)			P
	1 (n=155)	2 (n=157)	3 (n=40)	
City	92 (59,3 %)	90 (57,3 %)	20 (50 %)	P1=0,358 P2=0,405
Rural area	63 (40,6 %)	67 (42,6 %)	20 (50 %)	P1=0,358 P2=0,405

Note: p1 – comparison of groups 1 and 3, p2 – comparison of groups 2 and 3.

- significance of differences P <0.05

To identify the risk group based on the anamnesis, we used the "Prognostic matrix for identifying risk factors" (computer program: 03/13/2022 (Agency for Intellectual Property under the Ministry of Justice of the Republic of Uzbekistan No. DGU 2022 1122)) (Fig. 3.4.)

Факторы риска		Есть 1 бал /Нет 0 бала	НИП %
Стресс	Есть/нет	1/0	
Вредные привычки	Есть/нет	1/0	
Проф. вредности	Есть/нет	1/0	
Возраст до18 пос 30	Есть/нет	1/0	
Аборты в анамнезе	Есть/нет	1/0	
Неразвивающая беременность в анамнезе	Есть/нет	1/0	
Кровянистые выделения из половых путей I триместре II триместре III триместре	Есть/нет	1/0 1/0 1/0	
Угроза прерывания берем I триместре II триместре III триместре	Есть/нет	1/0 1/0 1/0	
Рубец на матке	Есть/нет	1/0	
Гинекологические заболевания в анамнезе	Есть/нет	1/0	
Угроза прерывания	Есть/нет	1/0	
Гипертензивные нарушения	Есть/нет	1/0	
Тяжелая преэклампсия, Эклампсия	Есть/нет	1/0	
ПИОВ	Есть/нет	1/0	
ПРПО	Есть/нет	1/0	
Отслойка НРП	Есть/нет	1/0	
Кровянистые выделения из п/п.	Есть/нет	1/0	
ПИОВ до 36 недель	Есть/нет	1/0	
Резус отр. кровь не иммунизированная	Есть/нет	1/0	
СС заболевания	Есть/нет	1/0	
Заболевания почек и печени	Есть/нет	1/0	
Тяжелая анемия	Есть/нет	1/0	

Figure 3.4. Prognostic matrix for identifying risk factors

Based on the matrix results, pregnant women can be divided into 3 groups

- ✓ Group 1 – low probability of developing PB (up to 5 points);
- ✓ Group 2 – average, probability of developing PB (from 6 to 20 points);
- ✓ Group 3 – high probability of developing PB (more than 20 points).

In our study, we selected a group of women with medium and high probability of developing PB with hyperuricemia.

Figure 3.5. Uric acid content in the blood of pregnant women

Changes in the content of uric acid in the blood of pregnant women occur due to: a protective antioxidant mechanism at the onset of pregnancy, active placental function, metabolic disorders, perfusion load and inflammatory processes in the kidneys, asymptomatic hyperuricemia of unknown etiology, congenital enzymopathy.

It is known that the reproductive and somatic health of women depends on the normal functioning of the menstrual cycle. A comparative analysis of the nature of the menstrual function did not reveal statistically significant differences in the period of formation, duration of menstruation, and duration of the menstrual cycle between the groups studied. The data characterizing the menstrual function of the examined women are presented in Table 3.3.

Table 3.3.

Characteristics of menstrual function (n, %)

Indicator		Groups, n (%)			P value
		1 (n=155)	2 (n=157)	3 (n=40)	
Age of menarche, years	<11 y.o.	38 (24,5)	24 (15,2)	10 (25)	p^1=0,061 p^2=0,084
	12-14 y.o.	80 (51,6)	105 (67)*	20 (50)	p^1=0,060 p^2=0,030*
	≥ 15 y.o.	37 (23,8)	28 (17,8)	10(25)	p^1=0,15
Duration of menstruation, days	<4	19 (12,2)*	29 (18,4)	10 (25)	p^1=0,045* p^2=1,240
	5-7	125 (80,6)	120 (76,4)	30 (75)	p^1=0,7856 p^2=0,6032
	8-25	11 (7,1)	8 (5)		p^1=0,2022
The nature of menstrual flow	Moderate	81 (52,2)*	116 (73,8)*	40 (100)	p^1=0,021* p^2=0,013*
	Abundant	57 (36,8)	41 (26,2)		
	Scarce	17 (10,9)	0 (0)		
Nature of the cycle	Regular	107 (89,2)	144 (91,7)	40 (100)	p^1=0,081 p^2=0,193
	Irregular	13 (10,8)	13 (8,2)		

Note: p1 – comparison of groups 1 and 3, p2 – comparison of groups 2 and 3.

- significance of differences P <0.05

However, it should be noted that for women who gave birth on time, moderate menstrual bleeding was statistically more common, while for groups 1 and 2, heavy

menstrual bleeding was statistically more common.

When studying the features of the gynecological anamnesis, it turned out that all nosologies were distributed with approximately equal frequency in all groups without statistically significant differences between the studied groups. It is worth noting that gynecological diseases prevailed in the 2nd group (Table 3.4.).

Table 3.4.

Gynecological diseases

Indicator	Groups, n (%)		P value
	1 (n=155)	2 (n=157)	
Uterine myoma	5 (3,2)	12 (7,6)	p=0,232
Cervical ectopia	15 (9,7)	24 (15,2)	p=0,509
Chronic endometritis	40 (25,8)	76 (48,4)	p=0,012*
Chronic salpingo-oophoritis	20 (12,9)	44 (28,0)	p=0,026*

Note: p – comparison of groups 1 and 2 *- significance of differences P <0.05*

It is important to note that inflammatory diseases such as salpingo-oophoritis occurred in 12.9% in the first and 28% in the second group, endometritis in 25.8% and 48.4% in the second group.

In the parity study, according to the inclusion criteria, all women were mainly multiparous.

Table 3.5.

Results of the reproductive history of the study groups.

Indicator	**Study groups, n (%)**			**p**
	I (n=120)	**II (n=157)**	**III (n=40)**	
Type of birth				
Spontaneous	79 (70)	80 (51)	3 (7,5)	P1=0,028* P2<0,001*
Induced	21 (20)	77 (49)	5 (12,5)	P1=0,286 P2<0,001*
Other parameters				
primigravida	20 (12,9)	-	33 (82,5)	P1<0,001*
repeatedly pregnant	135 (87,0)*	157 (100)*	7 (17,5)	P1<0,001* P2<0,001*
Primiparous	18 (11,6)*	-	33 (82,5)	P1<0,001*
Multiparous	137 (88,3)*	157 (100)*	7 (17,5)*	P1<0,001* P2<0,001*
Miscarriage	34 (21,9)	43 (27,3)	0	-

History of Preterm Birth	58 (37,4)	69 (43,9)	0	-
Medical Abortion	67 (43,2)	109 (50,4)	0	P1<0,786
Non-viable pregnancies	32 (20,6)	45 (41,2)	0	P1<0,060
Spontaneous miscarriage	35 (22,5)	64 (58,7)	0	P1<0,057
Hypertensive conditions	51 (32,9)	69 (43,9)	0	P1<0,076
Intrauterine manipulations	16 (10,)	28 (17,8)	3 (7,5)	P1<0,089 P2<0,121

Note: p1 – comparison of groups 1 and 3, p2 – comparison of groups 2 and 3.

- significance of differences P <0.05

The frequency of induced labor was 20% in the first group, 49% in the second and 12.5% in the third group, spontaneous labor was 70% in the first, 51% in the second and 7.5%, respectively.

In the first group, primiparous women accounted for 12.9%, repeatedly pregnant women accounted for 87%, multiparous women accounted for 88.3% in the first group and 100% in the second group.

A study of the gynecological anamnesis showed that miscarriage accounted for 21.9% and 27.3% of cases, respectively.

A history of preterm birth was present in 37.4% of the first and 43.9% of the second group.

The number of abortions in the first group was observed up to 43.2%, in the second 50.4% of cases, of which non-developing pregnancy - 20.6% and 41.2%, spontaneous miscarriage 22.5% and 58.7% of cases.

Hypertensive conditions - 51 (32.9%) and 69 (43.9%), intrauterine manipulations 10% and 17.8%, respectively.

Thus, it is noted that the factors of high risk of threat of termination of pregnancy and premature birth are the first pregnancy, first birth, history of miscarriage, various types of termination of pregnancy (spontaneous, medical), inflammatory diseases. They can negatively affect the course of pregnancy.

When analyzing concomitant diseases, it was found that iron deficiency anemia (IDA), myopia, and varicose veins of the lower extremities were significantly more often diagnosed in women in the study groups.

The analysis of concomitant diseases is presented in (Table 3.6.).

Table 3.6.

Results of somatic diseases

Indicator	Groups, n (%)		P value
	1 (n=155)	2 (n=157)	
Anemia	46 (29,6)	48 (30,6)	p^1=0,12
Cardiovascular disease	2 (1,3)	5 (3,18)	p^1=0,12
Myopia	22 (14,1)	28 (17,8)	p^1=0,12
Hypothyroidism	10 (6,5)	12 (7,6)	p^1=0,39
Chronic cystitis	5 (3,2)	40 (25,4) *	P^1=0,04*
Chronic pyelonephritis	12 (7,7)	32 (20,38)	p^1=0,024*
Varicose veins of the lower extremities	15(9,6)	24 (15,2)	p^1=0,15
Disruption of fat metabolism	6 (3,8)	4 (2,5)	p^1=0,42

Note: p1 – comparison of groups 1 and 2.

- significance of differences P <0.05

It is known that the infectious factor is one of the main reasons for the implementation of premature birth, in connection with which the frequency of infectious and inflammatory diseases was analyzed in the work and the spectrum of possible pathogens was determined. The study of vaginal microflora was performed in all women of the studied groups.

Bacterial vaginosis and vulvovaginal candidiasis were more common in group 2.

In accordance with the Order of the Ministry of Health of the Republic of Uzbekistan №123n dated 19.11.2017, patients with premature births before 34 weeks should be transported to a third-level hospital, and this rule was not violated. At the same time, delivery after 34 weeks is possible in level 2 institutions, and in case of full-term pregnancy - at levels 2 and 1 (depending on the presence or absence of pregnancy complications, extragenital diseases). Thus, the routing of pregnant women and women in labor was observed, and early births in our cohort were equally common among city and rural residents.

Considering that patients with the threat of premature birth often have a complication in the form of premature rupture of membranes, we determined the duration of the anhydrous interval. In the 1st and 2nd groups, the anhydrous interval fluctuated from 17 hours 17 minutes in the first and 12 hours 27 minutes in the second group, the average anhydrous interval was 14 hours 43 ± 29 minutes, 12 hours 33 ± 17 minutes, respectively.

One of the most important issues that concerns obstetricians all over the world is the optimal tactics of delivery in premature births. Taking into account that at present there is no unified concept of management of premature births.

All 352 pregnant women with threatened PB were prescribed traditional pregnancy-preserving therapy, which included:

Drugs for tocolysis: 1. **Nifedipine** - 10 mg orally every 30 minutes (maximum single dose 40 mg). Then - 10 mg every 4-8 hours orally for no more than 48 hours from the start of therapy; or • 20 mg orally, then, if uterine contractions persist after 30 minutes, 20 mg again, then 20 mg every 4-8 hours for no more than 48 hours from the start of therapy.

Indomethacin is an NSAID that blocks the synthesis of prostaglandin synthetase and partially blocks the development of the inflammatory response.

Features of use:

• Use for no more than 48 hours and for gestational ages less than 32 weeks.

• Tocolysis regimen: starting with 50-100 mg rectally or orally, then 25 mg every 6 hours.

Ginipral is a beta2-adrenergic agonist hexoprinaline sulfate. Ginipral doses: 25–50 mcg (1 ampoule of 2.0 ml of 10 mcg) in 500.0 ml of 0.9% sodium chloride solution intravenously by drip at 10 drops per minute. The infusion rate can be increased by 10 drops per minute every 30 minutes until contractions stop or until the maternal pulse exceeds 120 beats per minute. The maximum rate of administration with a dilution of 25 mcg (1 ampoule) is 120 drops per minute, with a dilution of 50 mcg (2 ampoules) — 60 drops per minute.

• Upon completion of intravenous administration - 1 tablet of ginipral (500

mcg) every 4-6 hours.

• Combine tocolysis with ginipral with oral administration of isoptin or phenoptin 40 mg 4 times a day or 80 mg 3 times a day.

Magnesium sulfate - No obvious tocolytic effect and use as a tocolytic is not recommended.

• Used for fetal neuroprotection according to protocol.

Atosiban - oxytocin receptor blocker

A drug that inhibits labor, an oxytocin receptor blocker.

It is administered intravenously in three stages:

1) initially, 6.75 mg is administered over 1 minute;

2) immediately after that, an infusion of 300 mcg/min is administered over 3 hours (infusion rate 24 ml/h, atosiban dose 18 mg/h);

3) after that, a continuous (up to 45 hours) infusion of atosiban is administered at a dose of 100 mcg/min (infusion rate 8 ml/h, atosiban dose 6 mg/h).

The total duration of treatment should not exceed 48 hours. The maximum dose of atosiban for the entire course is 330 mg.

Nitroglycerin - For emergencies.

If necessary, **Progesterone** 200 mg 2 times a day until 36 weeks of pregnancy. Additional to traditional complex therapy, only pregnant women in the main group were prescribed (Chapter 6).

According to the results of the analysis of timely and premature births, it was revealed that among the studied groups (n=352), PB were more often observed in women who received traditional therapy in the second group (33.1% of cases). All births ended more often through the natural birth canal (Chapter 6).

Results of ultrasound examination

The following parameters were analyzed from the ultrasound data as part of the study during abdominal echography: uterine tone, amount of amniotic fluid, placenta condition, cervical length (CL) in mm, and fetal condition.

For the analysis, 352 pregnant women were divided into 2 groups. The first main group (n = 312) of pregnant women with threatened PB and the second control group of 40 pregnant women with a physiological course of pregnancy.

To detect changes in the cervix using ultrasound, it is necessary to take into account its norm (Table 3.7.).

Table 3.7.

Length of the cervix in the norm and with its shortening depending on the gestational age (n = 312)

Gestation period	Cervical length (in mm)	Cervical length (in mm) normal
22-27 weeks	40.3-36.4 mm	48.6-50.0 mm
28-30 weeks	37.2-30.5 mm	36.15-40.2 mm
31-33 weeks	28.5 -2.0 mm	34.6-40.4 mm
34-36 weeks	18 mm and less	40 mm and less

Ultrasound examinations were performed in all study groups. As can be seen from Table 3.7. shortening of the cervix in the main group was observed at 22-27 weeks of gestation - in 18.2% of cases, 28-30 weeks - in 10.29%, 31-33 weeks - in 42.6%, 34-36 weeks - in 10.5% of cases. In 18.41% of pregnant women, shortening of the cervix was not observed.

As can be seen from Table 3.8, in the main group, fetal growth restriction syndrome was observed in 27.8%, an increase in the thickness of the placenta - 26.2%, an expansion of the intervillous space - in 84.9% and early aging of the placenta - in 58.0% of cases, which is directly informative for diagnosis, preventive measures and treatment tactics.

Table 3.8.

Results of Doppler ultrasound in pregnant women from a prospective study group with hyperuricemia.

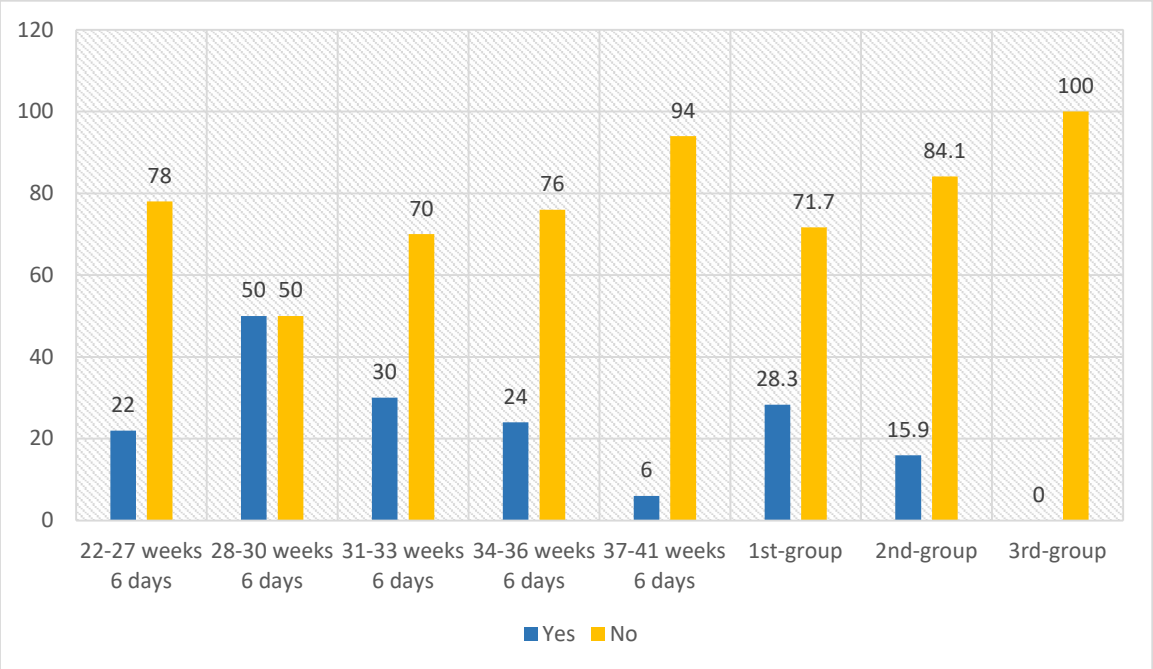
Results	**Main group n= 312**		**Control group n= 40**		**P**
	Abs.	**%**	**Abs.**	**%**	
Hypertonicity of the	**309**	**99,0**	**2**	**5**	**<0,05***

uterus					
Changes in the quantity and composition of amniotic fluid	**210**	**67,3**	**1**	**2,5**	**<0,05***
Fetal growth restriction syndrome stages 1,2,3	**87**	**27,8**	**1**	**2,5**	**<0,05***
Increased thickness of the placenta	**82**	**26,2**	**2**	**5**	**<0,05***
Enlargement of the intervillous space	**265**	**84,9**	**2**	**5**	**<0,05***
Premature aging of the placenta	**181**	**58,0**	**1**	**2,5**	**<0,05***

Note: p1 – comparison of groups 1 and 3, p2 – comparison of groups 2 and 3.

- significance of differences P <0.05

The results of a prospective study showed the presence of a violation of uteroplacental hemodynamics in the examined women with threatened PB and the control group (Fig. 3.6.).



Distribution of the presence of uteroplacental hemodynamic disorders among groups.

With regard to fetoplacental hemodynamic disorders, comparison of groups also demonstrated the existence of statistically significant differences between individuals from 22-27 weeks 6 days and 28-30 weeks 6 days (p=0.037), as well as between 22-27 weeks 6 days and 37-41 weeks 6 (p=0.019).

It follows from this that induction of labor during PB was determined not only by indications from the mother, but also by indications from the fetus in the form of disturbances in fetoplacental hemodynamics.

Table 3.9.

Results of the analysis of blood circulation in the "mother-placenta-fetus" system in groups.

Degree of violations	**Main group n= 312**		**Control group n= 40**		**P**
	Abs.	**%**	**Abs.**	**%**	
No	**47**	**15,0**	**35**	**87,5**	**<0,05***
I A	**73**	**23,3**	**3**	**7,5**	**<0,05***
I Б	**134**	**42,9**	**1**	**2,5**	**<0,05***
II	**58**	**18,5**	**1**	**2,5**	**<0,05***

Note: p1 – comparison of groups 1 and 3, p2 – comparison of groups 2 and 3.

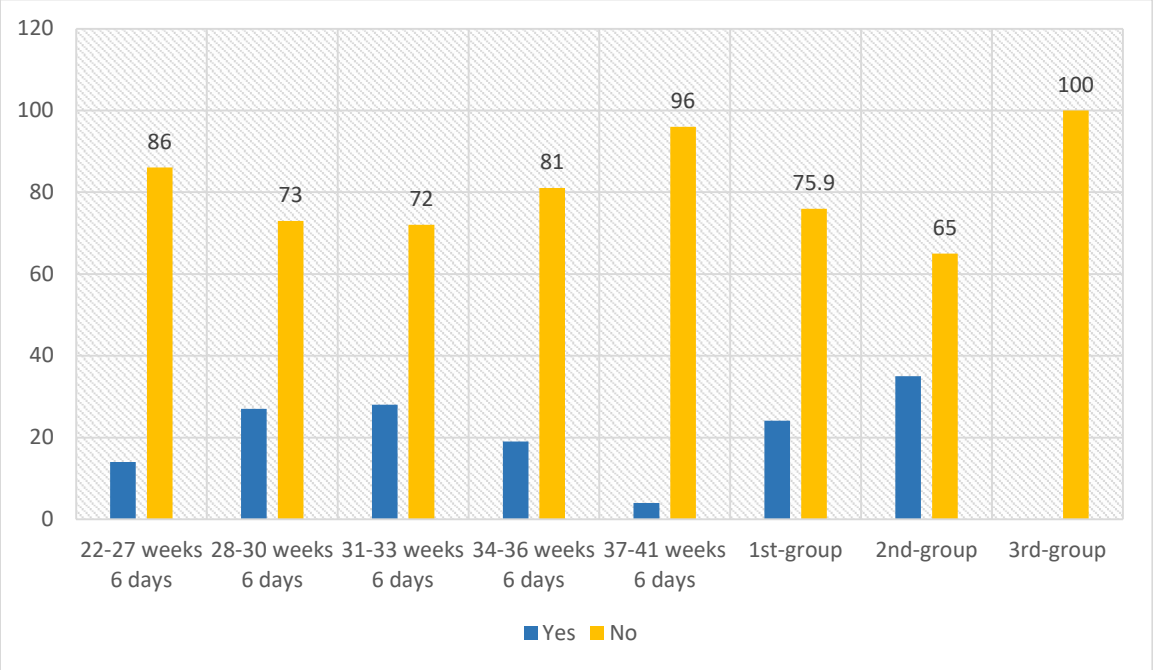
- significance of differences P <0.05

As the results of the study showed, circulatory disorders in the "mother-placenta-fetus" system in the groups were high. In the main group, stage I B occurred in up to 42.9%, stage I A - in 23.3% of cases, stage II - in 18.5% of cases.

Circulatory disorders in the mother-placenta-fetus system, determined by Doppler ultrasound, ultimately lead to FGRS.

Considering that Dopplerometry was performed on all pregnant women, we decided to compare the data from both groups.

The figure shows the presence of significant differences in pregnant women with threatened PB in the 2 study groups compared to the control group (p< 0.028) (Fig. 3.7).



Distribution according to the presence of FGRS fetal and uteroplacental hemodynamic disorder in the first and second groups.

After delivery, all placentas were subjected to pathomorphological examination. In order to identify placental features, we performed statistical analysis of the results by prospective groups.

Among the morphological properties, we compared the disruption of villus maturation, circulatory disorders in the placenta, the presence and severity of compensatory-adaptive reactions.

Among the variants of pathological immaturity of the villi, dissociated villous maturation disorder was more common, obliterative angiopathy was somewhat less common, and chorangiomatosis was noted only in patients with PB (Fig. 3.8).

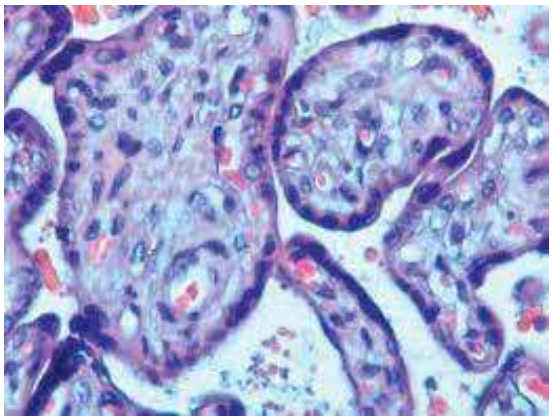


Figure 3.8. Dissociated villous maturation disorder. Hematoxylin and eosin staining. x80 (Umrzokova Bakhora i\b 3516 Pregnancy III 29.7 weeks P III)

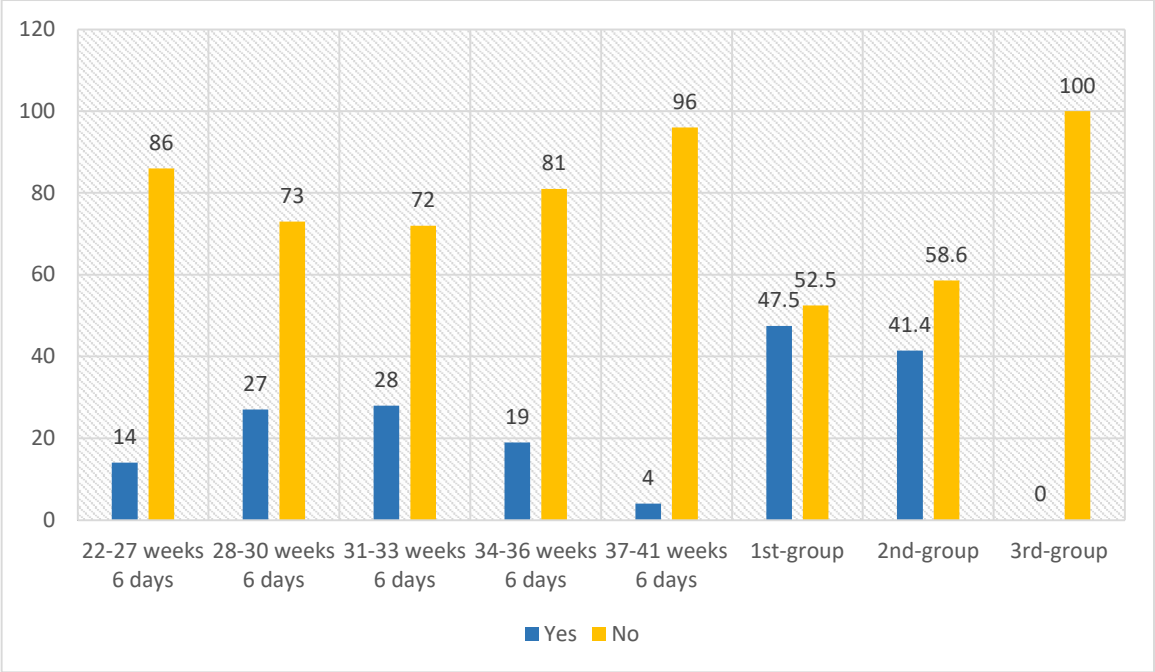


Figure 3.9. Distribution by the presence of dissociated villous maturation in the study groups

The data in Figure 3.9 clearly demonstrate the statistical significance of the differences between pregnancies with preterm and term pregnancies ($p< 0.001$). Thus, disruption of placental villus maturation may contribute to very early preterm birth. In our study, its detection increases the risk of preterm birth compared to term birth by 35.4-48.5 times.

Obliterative angiopathy is a morphological sign of PB when the placenta is infected in the early stages of pregnancy; its existence leads to a disruption of

capillary blood flow in the placenta.

Figure 3.10 shows that obliterative angiopathy is significantly more common in premature births than in term births (p<0.001).

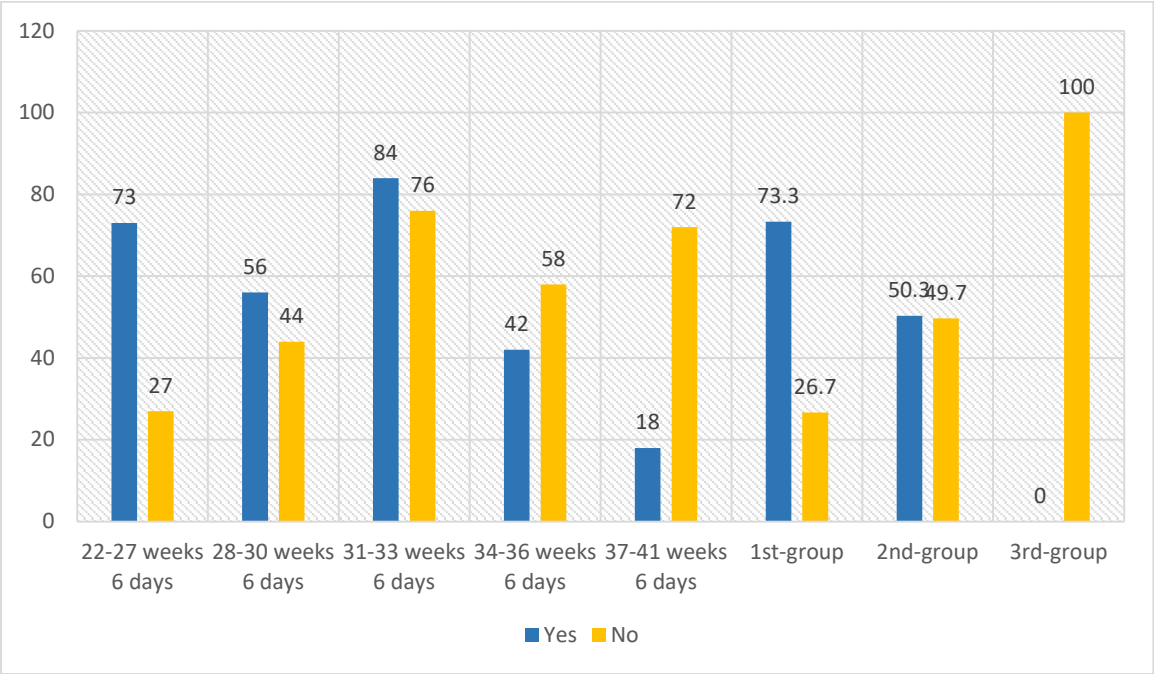


Figure 3.10. Distribution by the presence of obliterative angiopathy in the study groups.

Circulatory disorders in the placenta are represented by ischemia, thrombosis of the intervillous spaces, and infarctions. These changes may be the result of infectious lesions, immunological conflict, vascular spasm in hypertensive conditions, and bleeding in premature placental abruption.

When comparing data by groups, statistically significant differences were found only between preterm and term pregnancies (p<0.001). Circulatory disorders in the placenta are a consequence of pregnancy complications: preeclampsia, infectious damage, immunological conflict. The longer the pregnancy period at the time of delivery, the fewer the number of complications, as has already been shown above.

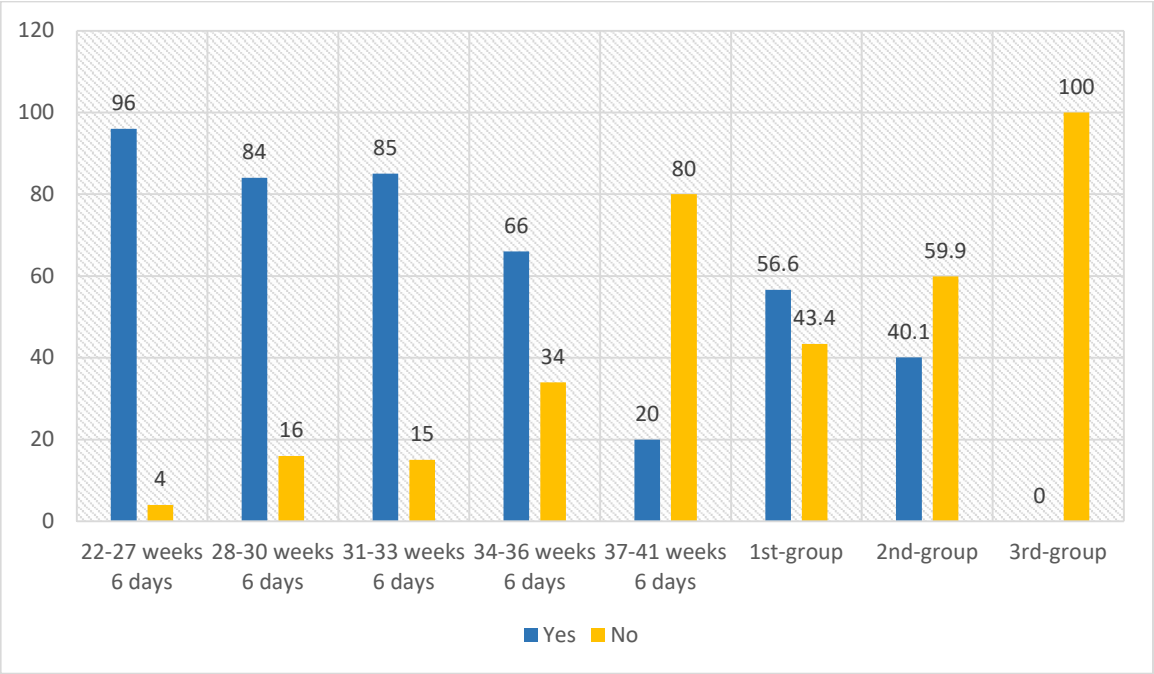


Figure 3.11. Distribution by the presence of placental circulation disorder in the study groups

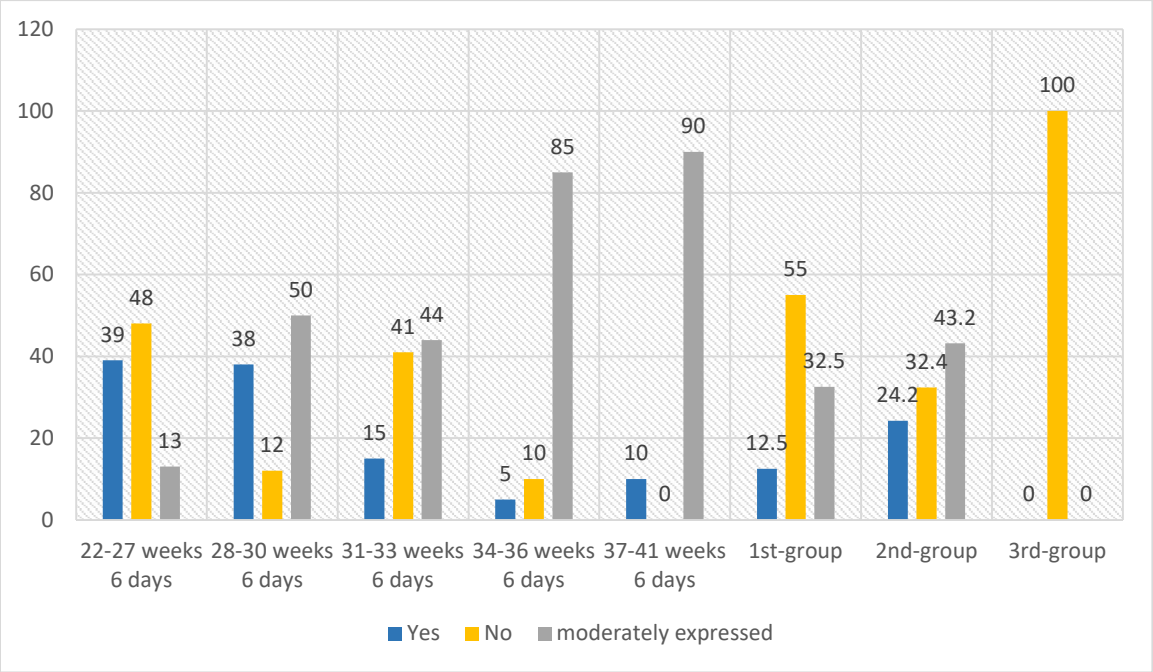


Figure 3.12. Distribution by the presence of compensatory-adaptive reactions in the placenta in the study groups

Of greatest interest are the results of comparison of groups by the presence and severity of compensatory-adaptive reactions in the placenta (Fig. 3.12). It has been shown that statistically very highly significant differences were found in patients with PB ($p<0.001$). This means that the worse the compensatory-adaptive

reactions are expressed (up to their absence), the earlier the pregnancy will be terminated.

Much attention in domestic and foreign literature is paid to the influence of the infectious factor on the course and outcome of pregnancy. Infection of the fetoplacental complex can occur by ascending or hematogenous route, which is confirmed by examination of the placenta after childbirth.

Figure 3.13 shows the prevalence of histological chorioamnionitis by delivery time.

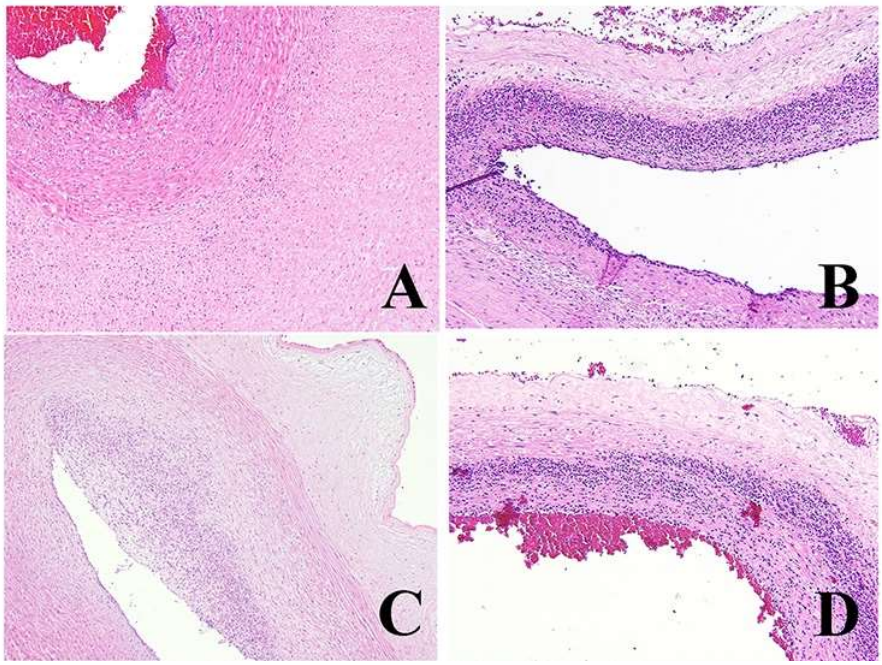


Figure 3.13. Panel of stages (anatomical) and degrees (intensities) of the inflammatory reaction of the fetus in acute chorioamnositis A) Stage 1 degree 1; B) Stage 1 degree 2; C) Stage 2 degree 1; D) Stage 2 degree 2 Hematoxylin and eosin staining. x80 ([A] Karomatullaeva Gulbahor i\b 6799, Pregnancy II 32.4 weeks R I; [C]Abdumanova Ikbol i\b 7280, Pregnancy III 30.1 weeks P III)

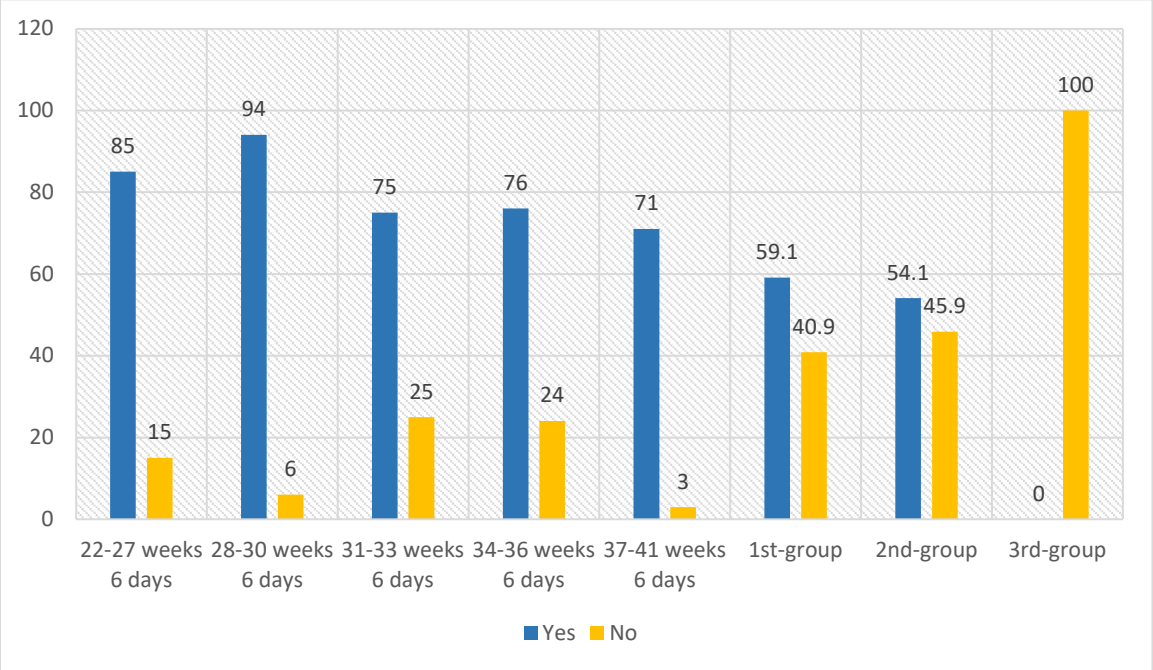


Figure 3.14. Distribution by the presence of histological chorioamnionitis in the study groups

A very high prevalence of chorioamnionitis was shown in all pregnant women. This can be explained by the existing differences between histological and clinical chorioamnionitis. In the absence of clinical manifestations, serous chorioamnionitis is a consequence of the physiological process of separation of the placenta. No significant differences were found between the groups, which suggests the absence of an infectious and inflammatory process in the chorionic plate and membranes in most observations (Fig. 3.14).

The decidua is in direct contact with the amnion (Fig. 3.15).

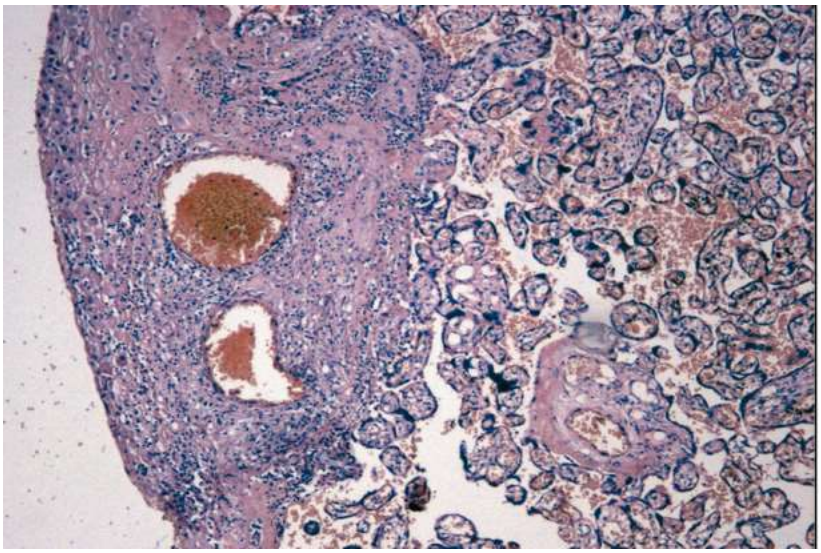


Figure 3.15. Basal deciduitis – pronounced lymphoplasmacytic infiltration of the basal decidual plate. Hematoxylin and eosin staining. x80 (Zakirova Mohira i/b 8594, Pregnancy IV 33.4 weeks P III:)

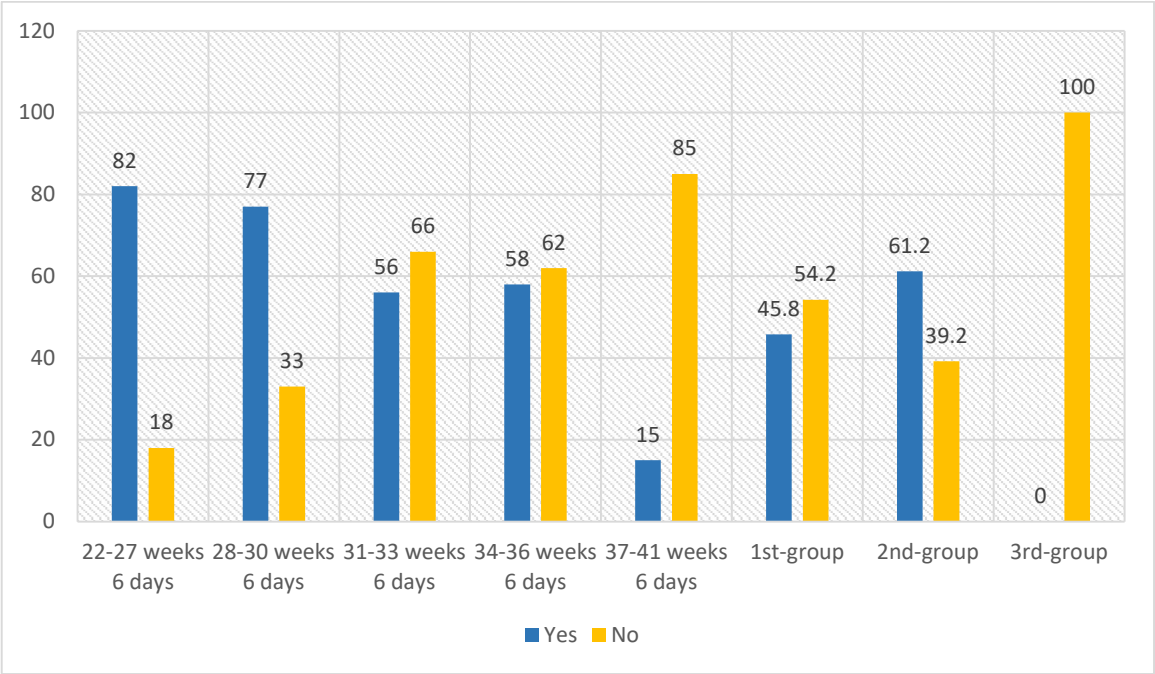


Figure 3.16. Distribution by the presence of deciduitis in the study groups

Statistically significant differences were found between preterm and normal births (p=0.015). In our opinion, firstly, this proves the absence of clinical chorioamnionitis in most observations, since leukocyte infiltration of the chorionic plate and amnion is carried out by maternal neutrophils from the decidua, and secondly, it indicates the participation of an infectious and inflammatory factor in the genesis of preterm birth (Fig. 3.16).

In case of ascending infection, the next localization of the inflammatory process is the intervillous space.

From this, we can conclude that ascending infection contributes to premature birth.

Intevillusitis is a placentitis of the intervillous space, a focal lesion of part of the villi with migration of inflammatory cells.

In ascending infection, the next localization of the inflammatory process is the intervillous space. Figure 3.17 presents the data from our study on the prevalence of intervillousitis.

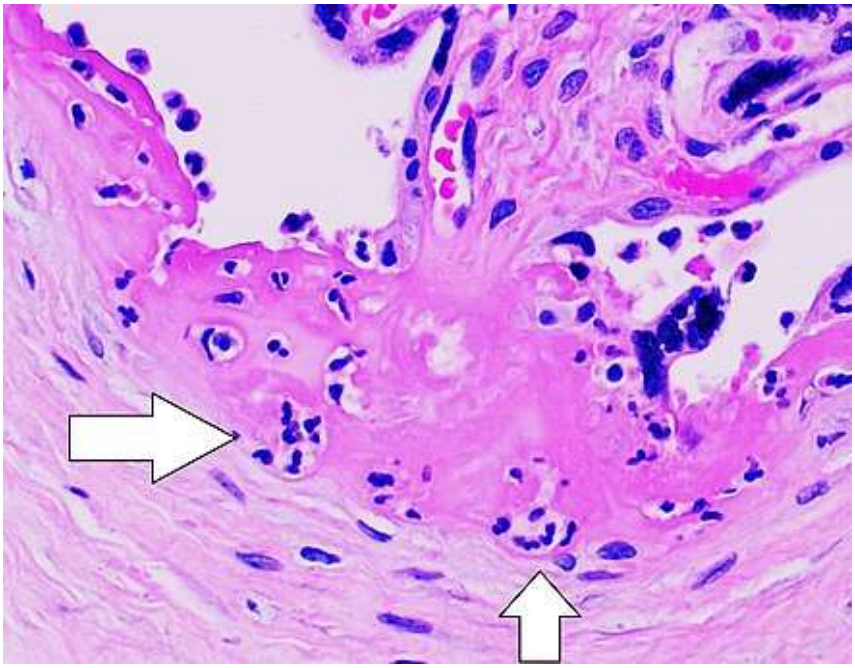


Figure 3.17. Histology of intervilliositis with neutrophils in the fibrinoid layer (on the surface of the fetus, at the base of the chorionic villus, seen at the top right) Hematoxylin and eosin staining. x80

(Salomova Shakhlo i\b 0215, Pregnancy I 31.3 weeks P I)

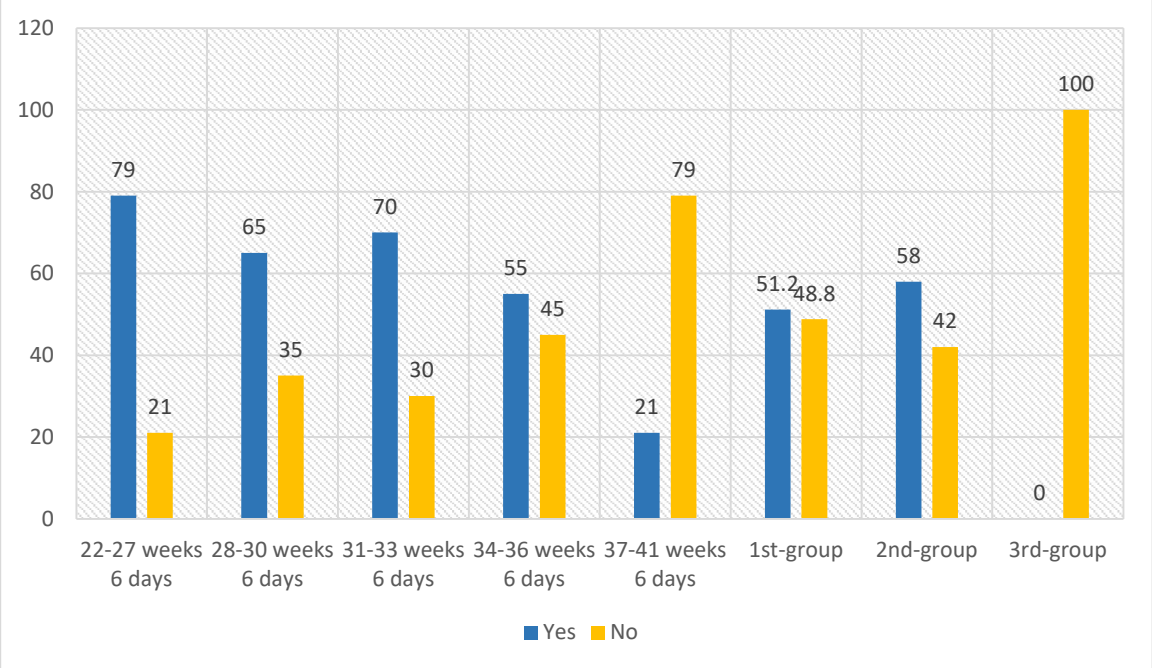


Figure 3.18. Distribution by the presence of intervilsitis in the study groups. Hematoxylin and eosin staining. x80

Statistically significant differences were found between threatened PB and normal births (p=0.0013). This suggests that ascending infection contributes to preterm birth (Fig. 3.18).

However, in addition to the ascending route of infection, there is also a hematogenous route. In this case, the inflammatory process is localized in the villi.

Villusitis is an inflammation of the chorionic villi, which can be terminal or stem, depending on the type of damaged structures (Fig. 3.19).

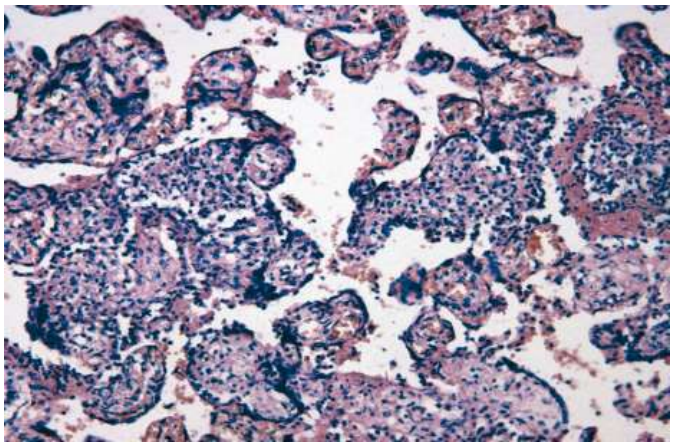


Figure 3.19. Villusitis. Hematoxylin and eosin staining. x125

(Rashidova Mamlakat Khusenovna i\b 1834, Pregnancy IV 34.1 weeks P II:)

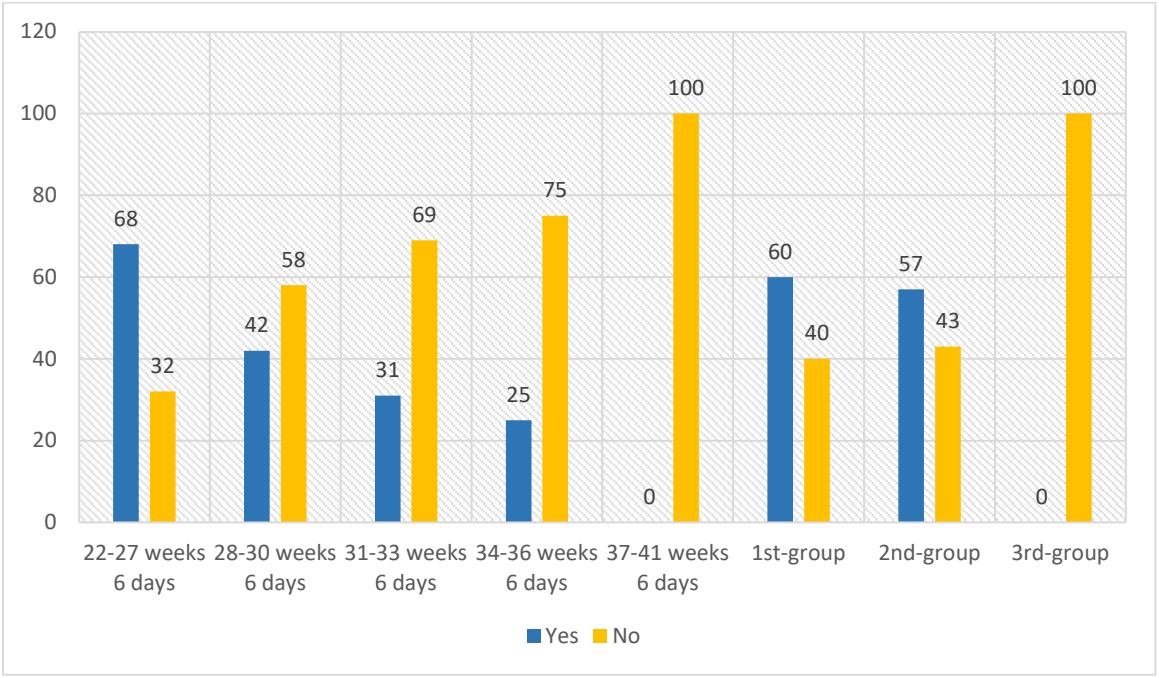


Figure 3.20. Distribution by the presence of villusitis in the placenta in the study groups.

The data in Figure 3.20 clearly show statistically very highly significant differences between PB and normal births. Consequently, hematogenous infection contributes to an earlier termination of pregnancy.

The high frequency of occurrence of umbilical cord phlebitis in preterm births is noteworthy, however, significant differences were found only in term births ($p<0.05$) (Fig. 3.21.).

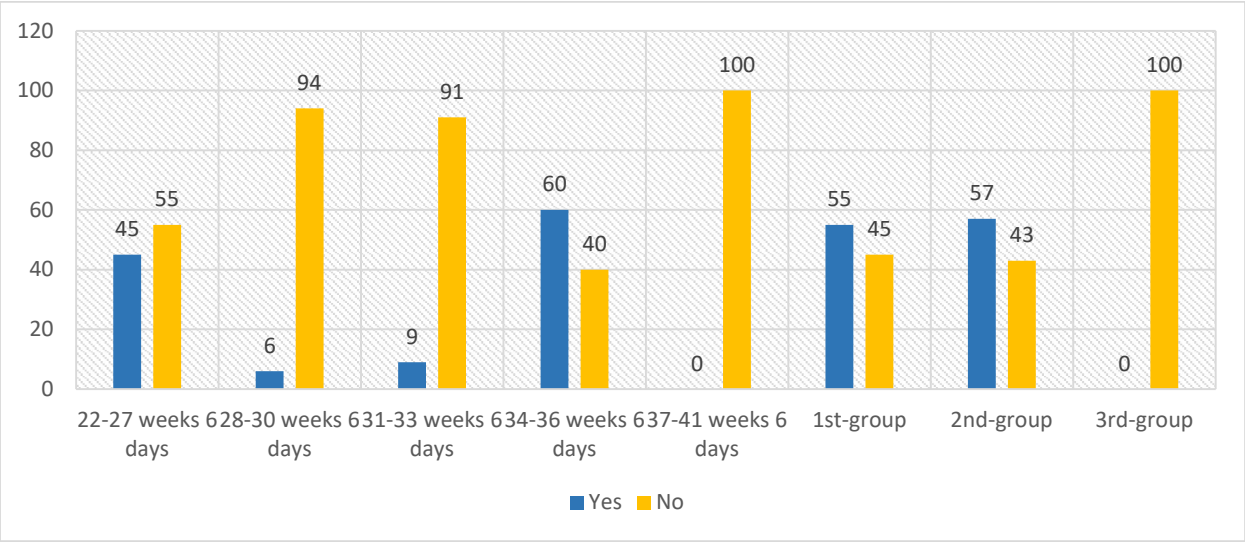


Figure 3.21. Distribution by the presence of umbilical cord phlebitis in the study groups

The umbilical vein is affected first, and the next stage of hematogenous spread of infection is arteritis. The detection of umbilical arteritis indicates a high risk of an unfavorable perinatal outcome (Fig. 3.22).

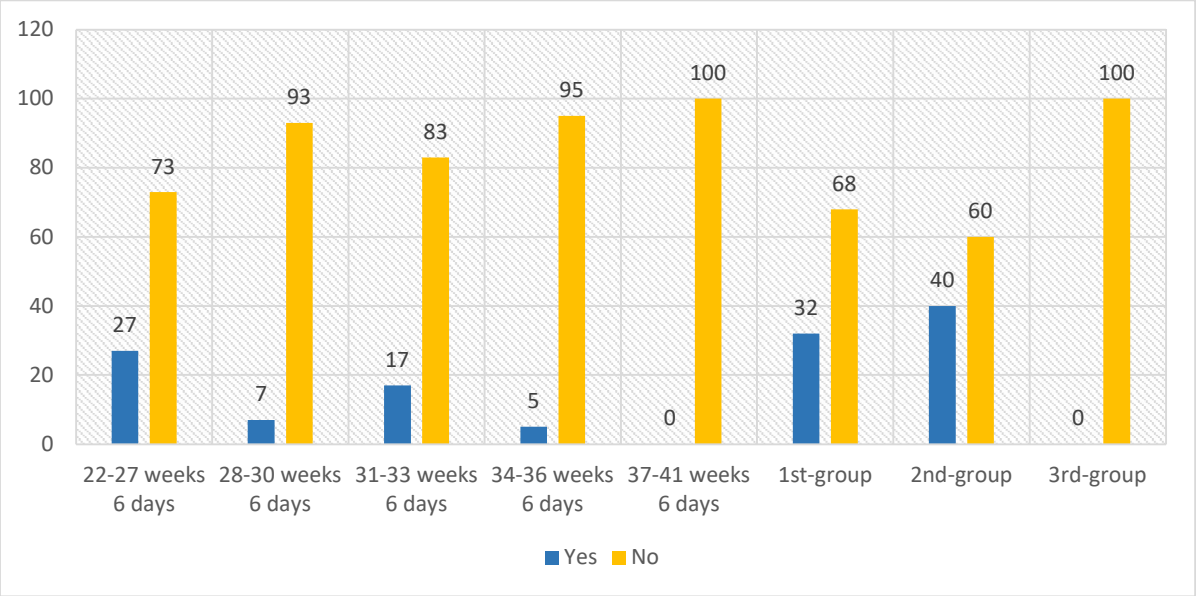


Figure 3.22. Distribution by the presence of umbilical cord arteritis in the study groups

Statistically significant differences were found between PB and normal births ($p<0.05$). This fact may explain the high frequency of intrauterine infection in

children with extremely low body weight, leading to an unfavorable outcome.

Chapter conclusions:

Thus, it is noted that high risk factors for the threat of termination of pregnancy and premature birth are miscarriage, various types of abortions (spontaneous, medical), and CPPT. They can negatively affect the course of pregnancy.

All this suggests a combined effect of factors on the outcome of preterm labor. An increase in the anhydrous interval increases the risk of purulent-septic complications, as well as acute fetal distress due to compression of the umbilical cord. Circulatory disorders in the "mother-placenta-fetus" system, determined by Doppler ultrasound, ultimately lead to fetal growth retardation, which can also be a cause of preterm labor.

Dissociated violation of villous maturation, circulatory disorders in the placenta, the presence and severity of compensatory-adaptive reactions, obliterative angiopathy, chorangiomatosis, phlebitis and arteritis can contribute to very early and early premature birth.

ASSESSMENT OF THE SIGNIFICANCE OF BIOCHEMICAL AND IMMUNOLOGICAL INDICATORS IN PREGNANT WOMEN WITH THREATENED PREMATURE BIRTH

Among the most pressing problems in obstetrics are premature births, which are directly related to the incidence of neonatal and perinatal morbidity and mortality. Currently, the problem is timely diagnosis and subsequent prevention of premature births. The reason for this is that premature births are a complex problem, both medical and socio-economic, associated with solving the problems of improving the quality of subsequent life of children born prematurely, and associated with material and economic costs. It should be noted that in premature births, all measures are aimed at improving the survival rates and health of premature babies. But even these efforts do not reduce the incidence of premature births. In half of the cases, the cause of premature births remains completely unknown. Regardless of the availability of various clinical and laboratory methods for diagnosing threatening premature births, the issue of predicting the outcome of pregnancy for both the mother and the fetus cannot be considered finally resolved. Therefore, the implementation of premature births is a multifactorial problem. Among the risk factors, one can single out medical factors, such as a history of premature births, spontaneous miscarriages, abortions, inflammatory diseases of the genitals and urinary tract infections, as well as socio-demographic factors, including young age, low social status, unsettled family life, etc.

Various diseases suffered by the pregnant woman play a major role in the occurrence of premature birth. A special place is occupied by viral infections, including acute respiratory viral infections suffered during pregnancy. The body's response to infectious agents leads to the occurrence of systemic inflammatory response syndrome. As is known, the activation of the inflammatory response occurs due to cytokines. The participation of which has been indirectly proven in many

studies, and the periodic nature of the fluctuation in the level of cytokines in the amniotic fluid, cervical mucus and peripheral blood of women with the threat of premature birth has been studied.

One of the key stages in the development of premature birth is oxidative stress, described in modern literature, its role is reduced to the activation of a systemic inflammatory response, in which metabolic disorders develop in the body of a pregnant woman.

The balance of oxidative/antioxidant status is a process that begins before birth, and preterm infants are particularly susceptible to oxidative stress. Most complications of prematurity, such as bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, intraventricular hemorrhage, periventricular leukomalacia, and white matter punctate lesions, appear to be related to oxidative stress, mainly due to a mismatch between free radical production and the body's antioxidant capacity. In addition, antioxidant defense mechanisms are underdeveloped or deficient in preterm infants. Preterm infants have decreased antioxidant defense mechanisms, including decreased levels of vitamin E, β-carotene, melatonin, ceruloplasmin, transferrin, and erythrocyte superoxide dismutase (SOD). The combination of hyperoxia, which increases the production of reactive oxygen species, and low antioxidant levels induces oxidative stress, inflammation, and even apoptosis, thereby increasing mortality and morbidity. In line with the mechanisms of oxidative stress and the lack of research in this area, in this prospective study we aimed to compare the serum prooxidant-antioxidant balance levels in pregnant women with preterm labor.

The survey was conducted with a total of 118 pregnant women with threatened PB; of these, Group I (n=41), Group II (n=42), Group III (n=35) were controls with a physiological course of pregnancy and childbirth, and delivery was completed on time.

Assessment of the degree of endogenous intoxication

Premature birth is the result of the combined action of unfavorable endogenous factors.

It has been found that the condition of endotoxicosis aggravates the course of pregnancy, especially in case of gestosis. Until now, there is no single point of view regarding the significance of endotoxicosis in pregnancy pathology.

Taking these facts into account, it becomes appropriate to identify new pathogenetic processes of this condition.

When studying the data of the biochemical study, it was revealed that the effective and total albumin concentration (EAC, TAC) were reduced relative to the control group (Fig. 4.1).

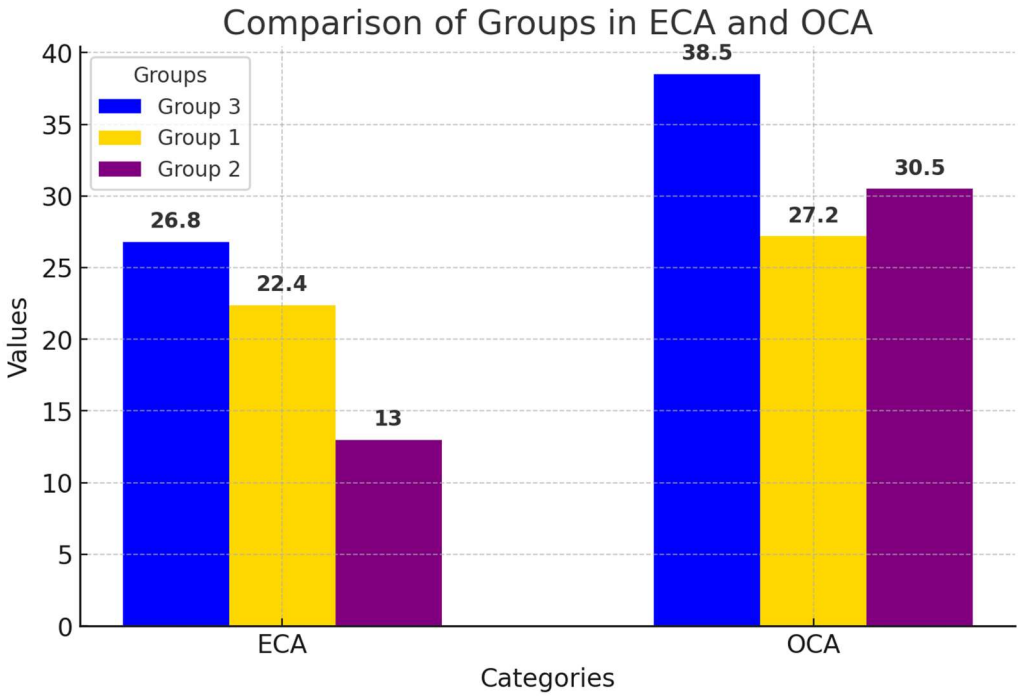


Figure 4.1. EAC and TCA intoxication indices in pregnant women. Note: here and below. EAC is the effective albumin concentration, TCA is the total albumin concentration.

- significance of differences P <0.05

The effective albumin concentration (EAC) was 18.1±0.9 IU/ml, which is ↓1.5 times less in the first group and 22.4 ± 1.02 IU/ml in the second group, which is ↓1.2 times less relative to the control group.

The total albumin concentration (TCA) was reduced by ↓1.4 times in the first group (27.2 ± 1.2 IU/ml) and ↓ 1.3 times (30.5 ± 1.1 IU/ml) in the second group, less than in the control group.

The ABR index was reduced to 0.71 ± 0.002 (%), which is ↓1.2 times less in women of the second group compared to the control group. (Fig. 4.2).

The plasma toxicity index among women of the main group exceeded the control group by 21.1% ($p < 0.05$).

Thus, the development of premature birth is accompanied by the formation of endogenous intoxication in pregnant women.

Status of the pro and antioxidant system

According to the literature, the development of endogenous intoxication is accompanied by activation of lipid peroxidation processes [5, 89].

Taking into account these facts from the literature, it seemed appropriate to find out whether only local activation of lipid peroxidation processes occurs in the "mother-placenta-fetus" system, or with the risk of preterm labor against the background of systemic activation of free-radical oxidation processes.

To partially resolve this issue, a comparative assessment of the state of lipid peroxidation processes (DC, MDA) in the venous blood of pregnant women was carried out.

It was found that the content of diene conjugates (DC) in the blood plasma of women with threatened premature birth was 31.2 ± 1.7 μmol/l, which is 1.5 times higher than 33.1 ± 1.6 μmol/l, which is 1.6 times higher than in the control groups (Fig. 4.3).

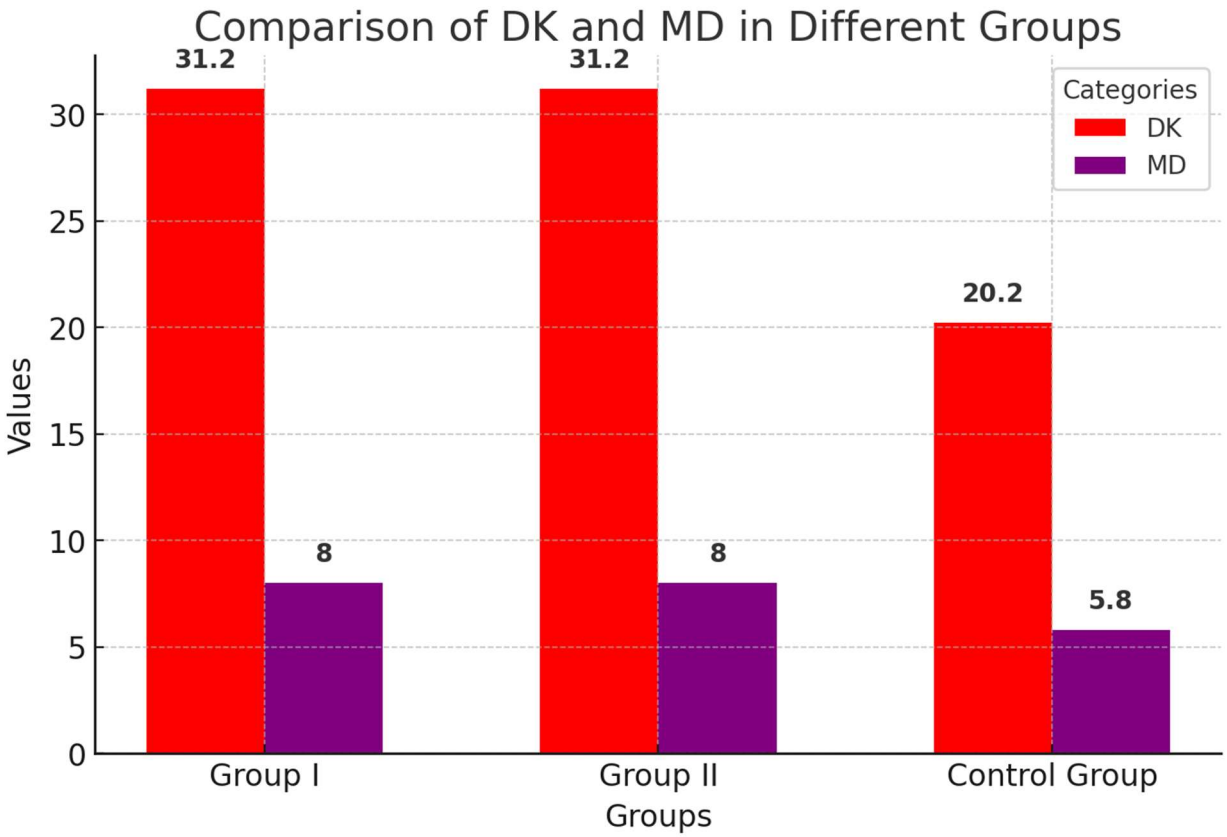


Figure 5.3. Indicators of lipid peroxidation processes in pregnant women with threatened PB

- reliability of differences P <0.05

The content of malondialdehyde (MDA) in blood plasma during threatened PB was highest in the first group at 7.73±0.35 μmol/l (↑1.5), in the second group 7.59±0.28 μmol/l (1.3), and in the control group - 5.8±2.1 (μmol/l), ($p<0.05$).

In recent years, an important role in the pathogenesis of preterm labor has been given to systemic inflammatory response syndrome (SIRS) and oxidative stress. The development of oxidative stress is caused by an imbalance between the generation and elimination of reactive oxygen species (ROS). Our research results, presented in Table 5.1, showed that the content of lipid peroxidation products in the blood plasma of pregnant women in the control group was 41.54±3.67 μmol/l. It was noted that with the progression of the pathology, the content of TBA significantly increases: it was 67.23±5.78 μmol/l in the first, 78.14±6.89 μmol/l in the second, and 41.54±3.67 μmol/l in the control group ($p<0.05$).

An increase in the level of toxic lipid peroxidation products in the blood of pregnant women with threatened PB is certainly 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, and disturbances in the coagulation potential of the blood, which naturally accompany miscarriage of various etiologies.

Simultaneously with the activation of oxidative processes, there is an increase in the activity of blood catalase in pregnant women of group I to 13.57±1.56 kat/l, which is ↑1.7 times, and in group II to 11.32±1.27 kat/l, which is increased by ↑1.4 times compared to the control group, which indicates an increase in the antioxidant activity of the blood.

Increased blood catalase activity in patients of group II indicates depletion of the antioxidant defense system, which is indirectly confirmed by a decrease in SOD and the content of TBA-active products in this group, compared to the control. A decrease in SOD activity in group I by 45%, in group II by 64% compared to healthy pregnant women is noted. There are also suggestions that it is the consequences of decompensation of antioxidant defense that contribute to the accumulation of LPO products.

These changes can be explained by the fact that in healthy pregnant women, activation of LPO processes leads to activation of the antioxidant defense system, but these processes are in balance with each other and are not accompanied by clinically significant damage. It is known that even normal pregnancy initiates some degree of oxidative stress. In the case of premature birth, an imbalance is observed between prooxidant and antioxidant forces towards the predominance of prooxidants, leading to damage to cells, tissues, and primarily the endothelium (Ailamazyan, Mostovaya, 2008).

Table 4.1.

Analysis of LPO-AOS indices in pregnant women with preterm labor

Indicators	I group (n=41)	II group (n=42)	III group (n=35)
TBA-active products, µmol/l	67,23±5,78*	78,14±6,89*	41,54±3,67
Catalase activity cat/l	13,57±1,56*	11,32±1,27*	7,98±0,81
SOD activity IU/1 mg protein	3,46±0,29*	2,31±0,21*	6,34±0,58

Note: p1 – comparison of groups 1 and 3, p2 – comparison of groups 2 and 3.

- significance of differences P <0.05

As is known, catalase begins to work at high concentrations of H2O2, which is not observed during normal pregnancy. These disorders lead to an imbalance between oxidative and reductive processes in the peripheral blood and tissues, accumulation of lipid peroxidation products, products of covalent modification of proteins, a decrease in the efficiency of energy-converting mitochondrial membranes and an increase in the number of damages to nuclear and mitochondrial DNA.

Thus, one of the pathogenetic factors of PB is the activation of free-radical destabilization processes of biological membranes, accompanied by an excessive increase in the content of peroxide compounds in the blood, as well as malonic dialdehyde, diene conjugates and catalase with a pronounced universal cytopathogenic effect and a decrease in the amount of SOD.

Assessment of the state of the cytokine system

The physiological course of pregnancy is accompanied by a certain restructuring of the immune system, ensuring the tolerance of the mother's body to the antigens of the fertilized egg and the bearing of the pregnancy. It has now become obvious that the protection of the fetus from the damaging maternal immune response is based on a complex mechanism and that communication between the different steps in the cascade of events is carried out by cytokines.

In the last decade, active scientific research has been conducted to study the role of cytokines in the development of premature birth (PB). Being biologically active factors, cytokines primarily regulate the development of local protective reactions in tissues with the participation of various types of blood cells, endothelium, connective tissue and epithelium.

Cytokines are responsible for all successive stages of the development of an adequate response to the introduction of a pathogen, ensuring its localization and removal, and then restoring the damaged tissue structure, wherever the inflammatory reaction develops. The main role is assigned to the cytokine network, the functioning of which determines the direction of the immune response during inflammation. The importance of cytokines for the vital activity of the organism can hardly be overestimated. Their participation in the regulation of immunogenesis, where they are necessary at all stages of the immune response, has been studied most thoroughly. Cytokines determine the differentiation of T-helpers into Th-1 and Th 2 types, which differ in the profile of the cytokines they synthesize in response to various inducers [Khaitov R.M., Pinegin B.V., 2000]. Th -1 produce proinflammatory cytokines interleukins: IL-1, IL-3, IL-8; interferons (IFN β and γ), tumor necrosis factor (TNFα), which play an important role in the regulation of inflammatory reactions in the endometrium, limit trophoblast invasion, disrupting its formation [El-Ziben M.Y., 2001]. Th-2 produces - interleukins: IL-4, IL-5, IL-6, IL-10, colony-stimulating factor, etc. - anti-inflammatory cytokines, and IL-10 is also called "suppressor". It is known that Th-1 determines the development of the immune response by the cellular type, and Th-2 - by the humoral type. Physiologically proceeding pregnancy develops with the participation of the Th-2 type of immune response, while there is a certain balance of interaction between Th-1 and Th-2. To date, the main reasons leading to significant shifts in the immune system have not been fully studied. At the same time, the study of the state of the immune system in pathological pregnancy can contribute to the pathogenetic substantiation of rational ways of ante- and intranatal protection of the fetus and the prevention of complications during childbirth.

We examined 35 women in the II and III trimesters of the gestation period with physiologically progressing pregnancy - the control group. It was found that in women of the control group, the level of cytokine IL-1β in the blood serum was 2.15±0.18 pg / ml, IL-2 - 11.14±0.91 pg / ml, IL-4 - 3.58±0.19 pg / ml, IL-6 2.38±0.19 pg / ml, IL-8 - 5.42±0.51 pg / ml, IL-10, - 22.48±1.96 pg / ml, and the level of TNF-α was within 1.76±0.14 pg / ml.

As is known, the main cells producing cytokines are monocytes, macrophages, endothelium and other cells. High values of IL-1 in the blood serum indicate the possibility of occurrence of undesirable immunopathological processes, since IL-1 is characterized by the ability to stimulate the production of prostaglandins. Maintaining this cytokine at a low level is one of the factors contributing to the preservation of pregnancy. In pregnant women at risk of premature birth, the level of IL-8 was increased by 1.5 times in group I patients and by 2 times in patients of group II relative to the indicators of the control group. High level of spontaneous IL-8 production may indicate significant activation of mononuclear phagocytes - producers of proinflammatory cytokines, which play an important role in the development of immunopathological processes. The obtained data on the increase in IL-1β and IL-8 reflect the activity of the inflammatory process. An increase in the concentration of proinflammatory cytokines indicates that in this contingent of pregnant women, the inflammatory reaction has systemic manifestations. At the same time, IL-1 stimulates the release of band leukocytes from the bone marrow, increases the formation and release of collagenase by them, causes the expression of endothelial-leukocyte adhesive molecules (ELAM) on the surface of endothelial cells and leukocytes, promotes the marginal standing of leukocytes and stimulates the process of their emigration.

As our research results show, pregnant women at risk of premature birth have a 1.5-fold increase in the IL-6 serum in the first group and a 2-fold increase in the second group compared to the control group. Due to the disruption of the placental barrier, a large amount of antigenic material of fetal origin enters the mother's circulation. This leads to the induction of an inflammatory response from the

maternal immune system with the production of a large amount of IL-6 and TNF-α, which causes a high level of trophoblast apoptosis. In addition, IL-6 stimulates the production of reactive proteins, which leads to remodeling of the cervix and the development of labor.

According to our data, in pregnant women with risk of preterm delivery, serum TNF-α level increases by 1.5 times in the first group and by 1.7 times in the second group compared to control data. As is known, TNF-α is formed by tissue macrophages, monocytes and lymphocytes in the area of acute inflammation, enhances the main functions of leukocytes, stimulates the release of histamine by basophils and mast cells, causes activation of fibroblasts, smooth myocytes and vascular endothelium in the inflammation focus, induces the synthesis of acute phase proteins. Hypersecretion of TNF-α leads to a significant increase in the number of apoptotic trophoblast cells, which can be one of the factors contributing to miscarriage.

It was found that during normal pregnancy, the cytokine status shifts towards immunosuppressive cytokines (IL-4, IL-10, TGF-β), inhibiting cellular immune responses and stimulating the production of blocking antibodies. In our study, the level of anti-inflammatory cytokines IL-4 and IL-10, respectively, was significantly lower by 1.5 and 2.4 times in the first group, and 0.6 and 3 times in the second group compared to similar indicators in the control group. In this situation, the most informative were the IL-10 indicators, low values of which can serve as a marker of the risk of developing preterm labor.

Table 4.2.

Cytokine status indicators in pregnant women with threatened preterm labor

Indicators	I group (n=41)	II group (n=42)	III-group (n=35)
IL-1 в, пг/мл	**3,31± 0,27***	**4,35± 0,38 ***	**2,15±0,18**
IL-2, пг/мл	**9,53± 0,84***	**7,54± 0,64***	**11,14±0,91**
IL-6, пг/мл	**3,78±0,35***	**4,83±0,39***	**2,38±0,19**
IL-8, пг/мл	**8,51± 0,79***	**10,98± 1,03***	**5,42± 0,51**
TNF-a, пг/мл	**2,68± 0,27***	**3,14± 0,23***	**1,76± 0,14**
IL-4, пг/мл	**2,24± 0,17***	**2,15± 0,13***	**3,58± 0,19**
IL-10, пг/мл	**9,01±0,82***	**7,36±0,62***	**22,48± 1,96**

Note: p1 – comparison of groups 1 and 3, p2 – comparison of groups 2 and 3.

- significance of differences P <0.05

Therefore, in pregnant women at risk of preterm birth, significant disturbances occur in the cytokine system, which may be accompanied by the penetration of proinflammatory cytokines into the systemic circulation, which, in our opinion, contributes to understanding the pathogenesis of preterm birth.

In addition, an increase in TNF-α and cytokines can serve as markers of inflammation of the uterine vascular endothelium, and also indicate high permeability of the membranes of the fetal membranes, which, in our opinion, is one of the reasons for the mechanisms of premature birth and rupture of amniotic fluid. Thus, the results of our study on the activation of proinflammatory cytokines (IL-1 in group I by 1.5 in group II 2 times, IL-2 in group I by 0.8 in group II 0.6 times more, IL-4 in group I was decreased by 1.5, in group II 0.6 times, IL-6 in group I was increased by 1.5 in group II 2 times, IL-8 in group I was increased by 1.5 in group II 2 times, IL-10 was decreased in group I by 2.4 in group II 3 times, TNF-α was 1.5 in group I and 1.7 in group II compared to the control group) allow us to assert that the study of cytokine balance is significant for assessing the direction of the immune response, as well as the outcome of pregnancy for the mother and fetus in case of threat of preterm labor.

The state of the body's reactive proteins

A significant increase in the concentration of C-reactive protein may be associated with various complications of pregnancy, such as stress on the immune system, intrauterine infection, development of hypertension, and threatened premature birth.

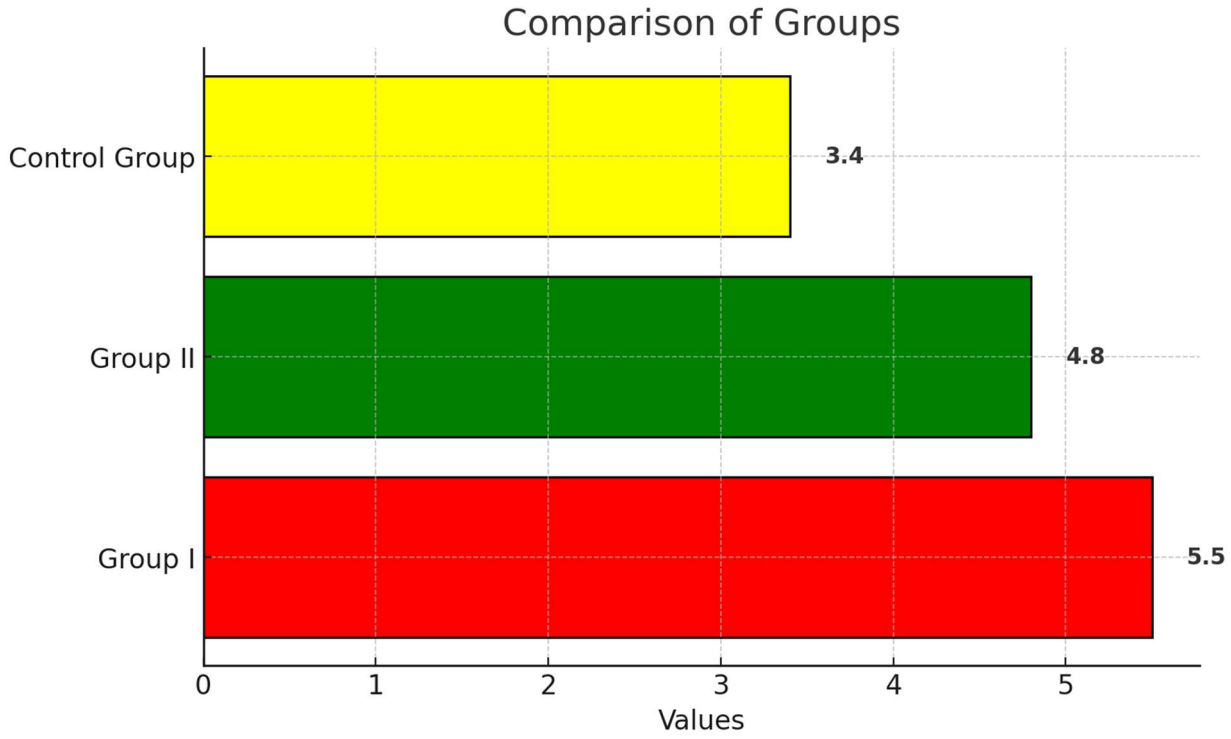


Figure 4.4 Activity of the SRP in women with threatened PB

- reliability of differences P <0.05

The development of threatening premature birth with changes in the immune system was accompanied by an increase in the content of state reactive proteins (SRP) in the first group to 5.87±0.19 mg/l (↑1.7), in the second group to 5.15±0.16 (↑1.5) mg/l, compared to the control group in women with threatened PB.

When studying nitric oxide, it was noted that in women with threatened PB in the main group, nitric oxide levels exceeded the values in the control group.

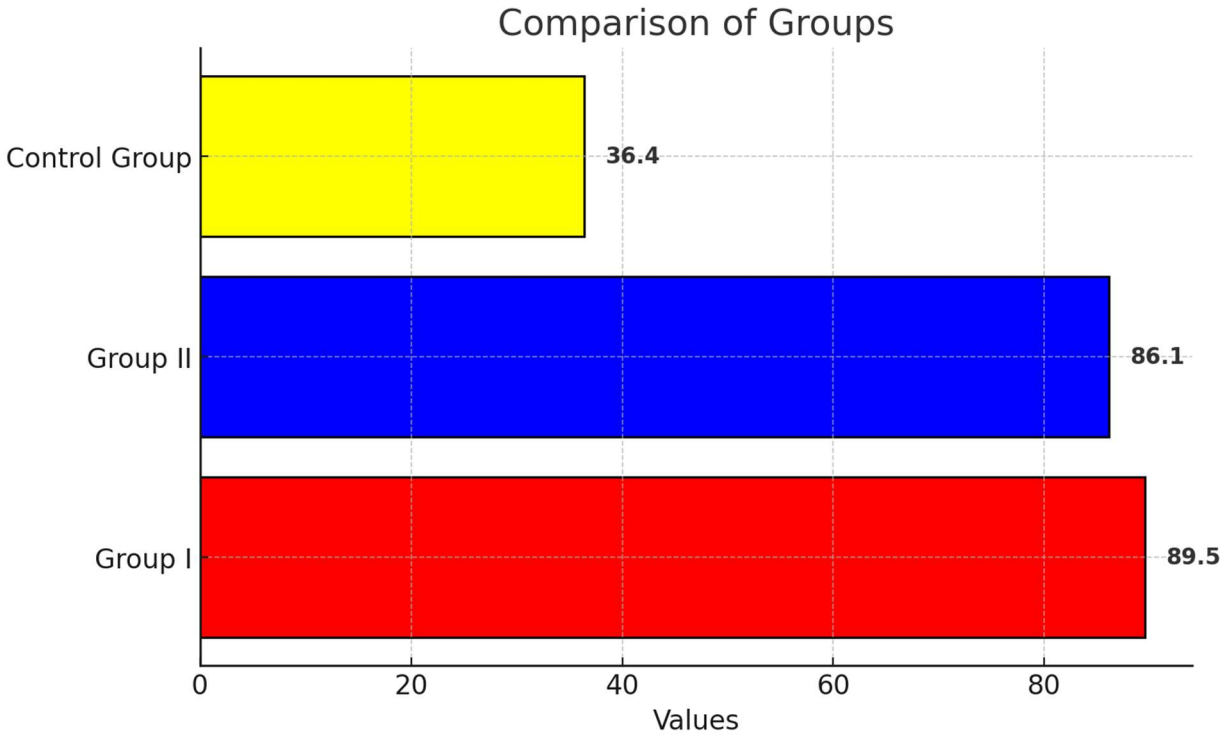


Figure 4.5. Nitric oxide activity in the study groups.

- significance of differences P <0.05

In the first 86.1±3.4 ppb; in the second 89.5±3.1 ppb compared to the control group (Fig. 4.5).

Increased nitric oxide accompanied by cytokine activity can be considered one of the predictors of PB.

It is known that in addition to the copper-binding function, ceruloplasmin has significant antioxidant activity and is involved in the neutralization of peroxides.

We studied the amount of ceruloplasmin as a predictor of PB.

As the results of our study showed, in the first group the level of ceruloplasmin was reduced to 12.6±0.4 mg/dl, which is ↓ 1.6 times less, and in the second group it was reduced to 10.4±0.31 mg/dl, which is ↓ 1.9 times less compared to the control group (Fig. 5.6), which indicates a decrease in the antioxidant system and may be the cause of PB.

It is currently known that S100 is a calcium-binding protein and is involved in the processes of cell division, differentiation and death. A comparative analysis of the S100 protein level in the serum of pregnant women showed a tendency for it

to decrease in groups I and II compared to patients in the control group. The average content of S100 protein in the blood serum of women in the control group was 40.9±5.08 ng/ml, while in the first group it was reduced to — 8.80±0.41 ng/ml, in the second group 7.90±0.21 ng/ml (>0.05) (Fig. 4.6.)

Serum S100 levels equal to or less than 32.55 ng/ml are also a new prognostic criterion for PB and increase the risk of their occurrence after a threatened miscarriage at 22–34 weeks by 4.6 times.

The nature of the violations of the hemostasis system parameters

Numerous studies have shown that elevated levels of oxidized lipoproteins during oxidative stress lead to endothelial damage. Increased levels of lipid peroxides have been noted in platelet and erythrocyte membranes. Lipid peroxides and free radicals inhibit prostacyclin synthesis, which worsens endothelial dysfunction. Lipid peroxides damage capillary permeability for proteins and can thus be involved in the formation of edema and proteinuria. Lipid peroxides promote increased thrombus formation by increasing the thrombin content and endothelial release of plasminogen activator inhibitor 1, while decreasing the antithrombin content and endothelial release of tissue plasminogen activator. Thus, endothelial damage under the influence of LPO products promotes increased vascular permeability and their sensitivity to vasoactive substances, loss of their thromboresistant properties with the formation of hypercoagulation, creating conditions for generalized vasospasm. Generalized vasospasm leads to ischemic and hypoxic changes in vital organs with impairment of their function. In this situation, one of the indicators of intravascular platelet activation is the presence of active forms of platelets and the number of aggregated ones. As can be seen from the obtained research results presented in (Table 5.4), pregnant women with a risk of premature birth have an increase in the sum of active forms of platelets relative to the control values by 24%. An increase in the sum of active forms of platelets in pregnant women of the main group was combined with an increase in the number of platelets involved in aggregates by 1.6 times. The damaging effect of the detected

disorders in the risk of termination of pregnancy on the vascular wall with the development of a thrombophilic state cannot be ruled out. Meanwhile, the determination of factors of vascular wall damage in the blood is an indirect method for assessing the severity of endothelial dysfunction. Such factors include: von Willebrand factor, fibrinogen, thrombomodulin.

Table 4.3.

Dynamics of hemostasis system parameters in pregnant women at risk of premature birth

Indicators	I group (n=41)	II group (n=42)	III group (n=35)	P1	P2
Total active platelet count (%)	30,12±2,56	34,63±3,12	24,32±1,41	>0,05	<0,01
Number of platelets involved in aggregates (%)	14,67±2,01	18,91±2,34	9,44±0,92	<0,05	<0,001
Von Willebrand factor (ng/ml)	127,38±8,01	139,41±8,54	96,58±7,69	<0,01	<0,001
Thrombomodulin, (ng/ml)	9,83±0,76	11,24±0,84	6,34±0,57	<0,001	<0,001
Thrombin time (sec)	17,01±0,24	15,43±0,24	20,57±1,38	<0,05	<0,001
Antithrombin III, (%)	68,51±5,12	60,84±5,47	80,24±6,47	>0,1	<0,05
D-dimer µg/ml	4,23±0,27	2,1±0,11	0,89±0,07	<0,001	<0,001

Note: p1 – comparison of groups 1 and 3, p2 – comparison of groups 2 and 3.

When studying the content of the most significant factors of endothelial damage (von Willebrand factor and fibrinogen), a reliable increase in the latter was noted when compared with the control group, respectively, the von Willebrand factor by 1.3 times. The identified changes in the dynamics of adhesive proteins play an important role in increasing the adhesive-aggregation properties of platelets. Of particular interest is the study of the von Willebrand factor (VWF) as a marker of endothelial damage in premature birth. It is known that at full-term physiological

pregnancy, a moderate increase in the content of the von Willebrand factor occurs, indicating an increase in the thrombogenic potential of the vascular wall. In case of risk of premature birth, the content of von Willebrand factor increases significantly and correlates with the severity of the disease. D-dimer was increased by ↑ 4.7 and ↑ 2.4 times. Thus, in pregnant women with risk of premature birth, we observe an increase in the anticoagulant activity factor against the background of endothelial cell dysfunction. This condition apparently leads to depletion of the level of natural anticoagulant antithrombin III in the blood and is one of the causes of thrombophilic state and thrombotic complications in premature birth.

It is extremely important to study the content of anticoagulant potential indicators in the blood of pregnant women at risk of preterm birth.

When studying the hemostasis system, it was found that premature birth is characterized by changes in coagulation and fibrinolytic activity in the form of hypercoagulation and hypofibrinolysis.

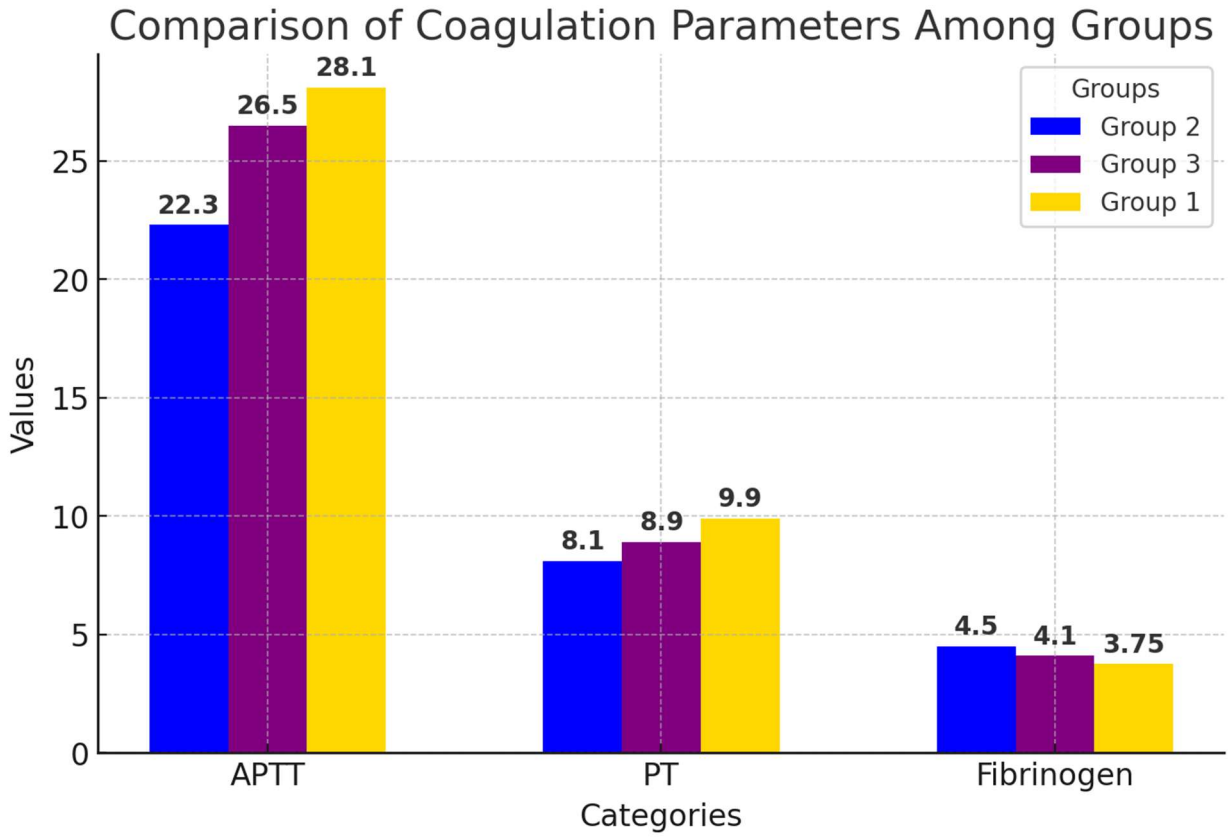


Figure 4.7. Dynamics of hemostasis system parameters in the examined subjects

- reliability of differences P <0.05

In women of the main first group, a shortening of the APTT and PT time by 33.3 and 31.2% ($p<0.05$) was noted relative to the control group; in the second group, the APTT and PT were lower than the control group by 20.1 and 25.4% ($p<0.05$) (Fig. 4.7).

When studying the process of fibrinolysis in premature births, it was found that the amount of fibrinogen increased in groups 1 and 2 by 51.8, 39.4 and 26.9% ($p<0.05$) when compared with the control group (Fig. 4.7).

Recently, vascular and hemodynamic disorders in pregnant women, which are observed in various somatic diseases, have traditionally been considered risk factors for preterm labor. Generalized endothelial dysfunction underlies hemodynamic and microcirculation disorders, including those in the uteroplacental basin, developing in various somatic pathologies. There are several hypotheses explaining the development of endothelial dysfunction in threatened preterm labor.

These changes are associated with the intensification of intravascular blood coagulation processes, 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.

These factors are interconnected and interdependent; their violations often lead to termination of pregnancy at different times, which makes timely diagnosis of intravascular thrombus formation and its therapy with the use of specific and non-specific methods that affect individual links in pathogenesis relevant.

Thus, analyzing the results of the studies, we can conclude that in PB, there is a pronounced intensification of lipid peroxidation processes, hemostasis system disorders, cytokine intensification and immune system, reactive proteins in the blood plasma. It should be noted that the maximum changes in the homeostasis system were found in pregnant women with a high risk of premature birth and with the threat of termination, to a lesser extent - in pregnant women with a high risk of PB who

gave birth prematurely, and minimally - in pregnant women with a high risk of PB who gave birth on time.

Evaluation of the content of purine metabolism product

As is known, uric acid is the end product of purine metabolism in the human body. The last two reactions of its formation, catalyzing the conversion of hypoxanthine to xanthine, and the latter to uric acid, are catalyzed by the enzyme xanthine oxidoreductase, which can achieve two interconvertible forms, namely xanthine dehydrogenase or xanthine oxidase. The latter uses molecular oxygen as an electron acceptor and generates superoxide anion and other products of active oxygen. As noted above, during pregnancy, the activity of oxidative stress increases, which contributes to endothelial damage. Increased serum uric acid concentrations occur as a physiological response to increased oxidative stress during pregnancy, providing a counter-regulatory boost to antioxidant defenses. Uric acid is the end product of purine catabolism, which acts as an antioxidant and reduces DNA damage at physiological concentrations. However, high uric acid concentrations can promote inflammation and endothelial dysfunction. High levels of maternal uric acid can diffuse to the placenta, enter the fetal circulation, cause placental inflammation and dysfunction, and ultimately impair fetal development. Elevated uric acid levels can also inhibit placental amino acid uptake, trophoblast invasion, and trophoblast incorporation into endothelial monolayers, leading to placental hypoperfusion.

The literature indicates that hyperuricemia develops as early as the 10th week of pregnancy in women who subsequently experience premature labor. At this time, invasive trophoblast cells actively remodel the uterine spiral arterioles, integrating and finally replacing the endothelial lining of the vessels. Uric acid caused a concentration-dependent attenuation of trophoblast invasion and integration into the endothelial cell monolayer of the uterine microvessels. Weakened trophoblast integration appears to be the result of decreased trophoblast-induced endothelial cell apoptosis, probably due to the intracellular antioxidant effect of uric acid. In addition, uric acid can initiate inflammatory cascades by increasing the production of monocyte chemoattractant protein-1, IL-1β, IL-6, and tumor necrosis factor

(TNF)-α. Elevated uric acid concentrations can alter endothelial function, health, and repair.

Several studies indicate that uric acid impairs nitric oxide (NO) production in vascular endothelial cells, a key pathogenic event preceding the development of cardiovascular disease. While uric acid has long been identified as an antioxidant, the ability of uric acid to act as a prooxidant capable of initiating intracellular redox signaling and inactivating NO has been described in the context of compromised antioxidant status. Of direct relevance to the current study, uric acid may interfere with key processes involved in normal vascular remodeling, particularly the proliferation and migration of endothelial cells and vascular smooth muscle cells. Also, in late pregnancy, uric acid crystals activate the nodular receptor protein-3 (NLRP3) inflammatory pathway via the IL-1-dependent pathway, causing inflammation at the placental interface and affecting fetal development. According to some researchers, uric acid concentrations change dynamically during normal pregnancy. Uric acid concentrations decrease significantly at 8 weeks of gestation, and these decreased levels remain stable until approximately 24 weeks of gestation, after which maternal uric acid levels rapidly increase to pre-pregnancy levels. These findings highlight the importance of paying attention to uric acid concentrations throughout pregnancy. It should be noted that uric acid, due to its antioxidant properties, may have potentially important and beneficial effects on various body systems. The antioxidant properties of uric acid have long been recognized and, as a result of its relatively high serum concentrations, it is the most abundant free radical scavenger in humans. The effect of uric acid was significantly greater than that of vitamin C. Collectively, these data support the hypothesis that elevated circulating uric acid levels in women at risk for preterm birth contribute to the pathogenesis of the disorder. It should be noted that uric acid levels are influenced by various factors, such as altered renal function, as well as enzymatic defects in purine metabolism. During pregnancy, uric acid levels in early gestation (8-10 weeks) were reduced by numerous factors, such as estrogen exposure and increased glomerular filtration rate. However, from 22 weeks of gestation onwards, they

gradually increased and are one of the causes of the risk for preterm birth.

As we have stated previously, uric acid is a well-known marker of tissue damage, oxidative stress. Based on the above, high uric acid values in the blood are observed in women at risk for preterm birth. If so, uric acid should be increased before the syndrome becomes clinically evident. Hyperuricemia is one of the earliest and generally consistent observations noted in women at risk for preterm birth. Although elevated circulating uric acid concentrations are not always observed in every woman at risk for preterm birth, they appear to identify a subset of women with preterm birth who are at greater risk for maternal and fetal morbidity.

This study was planned to compare serum uric acid values in pregnant women at risk for preterm birth with a control group to identify new pathogenetic links.

To study this issue, we decided to investigate the level of uric acid in various substrates in pregnant women at risk of premature birth at 22-34 weeks of gestation in the entire study group.

The present examination was conducted with a total of 352 pregnant women; of these, Group I (n=155), Group II (n=157), Group III (control, n=40) – 40 pregnant women with a physiological course of pregnancy and delivery, delivered on time were examined. Selection criteria: arterial hypertension, no history of urinary tract infection. Absence of any other medical complications (cardiovascular diseases, renal diseases, collagen vascular diseases) associated with preeclampsia.

ELEKTRON HISOBLASH MASHINALARI UCHUN YARATILGAN
DASTURNING RASMIY RO'YXATDAN O'TKAZILGANLIGI TO'G'RISIDAGI

GUVOHNOMA

O'ZBEKISTON RESPUBLIKASI ADLIYA VAZIRLIGI
№ DGU 24637

Ushbu guvohnoma O'zbekiston Respublikasining «Elektron hisoblash mashinalari uchun yaratilgan dasturlar va ma'lumotlar bazalarining huquqiy himoyasi to'g'risida»gi Qonuniga asosan quyidagi elektron hisoblash mashinalari uchun yaratilgan dasturga berildi:

МОЧЕВАЯ КИСЛОТА КАК ТРИГГЕРНЫЙ МЕХАНИЗМ ПРЕЖДЕВРЕМЕННЫХ РОДОВ.

Talabnoma kelib tushgan sana: 06.04.2023 Talabnoma raqami: DGU 2023 2915

Huquq egasi(lari): ШАВАЗИ НАРГИЗ НУРАЛИЕВНА UZ; Султанов Саидазим Насырович UZ; Ходжиметов Абдугафур Ахатович UZ

Dastur muallifi(lari): ШАВАЗИ НАРГИЗ НУРАЛИЕВНА UZ; Султанов Саидазим Насырович UZ; Ходжиметов Абдугафур Ахатович UZ

O'zbekiston Respublikasining Dasturiy mahsulotlar davlat reyestrida 06.05.2023 y. ro'yxatdan o'tkazilgan.

We have developed a computer program "Uric acid as a trigger mechanism for premature birth" (computer program: (Intellectual Property Agency under the Ministry of Justice of the Republic of Uzbekistan No. DGU 2023 2915 06.05.2023)) (Fig. 4.8).

Figure 4.8. Certificate for the Computer Program.

The analysis of the obtained results of the study, presented in Table 4.5, shows a general increase in the level of uric acid in the first and second groups of examined patients. Uric acid has antioxidant properties and also helps absorb free radicals in human blood serum. An increase in the level of uric acid may occur due to a protective reaction that limits the unsafe effects of free radicals and oxidative stress.

Table 4.4.

Determination of uric acid in the blood serum of pregnant women at 22-34 weeks of gestation with threatened PB (before treatment)

	I group (n=155)		II group (n=157)		III group (n=40)		P
	M	m	M	m	M	m	
22-27 weeks of gestation	436,43	26,1	442,28	31,16	332,87	13,68	p1<0,001* p2<0,001*
28-34 weeks of gestation	441,43	31,1	449,28	33,2	332,87	13,68	p1<0,001* p2<0,001*

Note: p1 – comparison of groups 1 and 3, p2 – comparison of groups 2 and 3. *- significance of differences P <0.05*

As can be seen from the table, the uric acid content upon admission to the hospital in the first group was increased by 1.3 times (on average to 438.5±28.6)

compared to the control group, in the second group by 1.3 times (on average 445.78±32.18 μmol/l) compared to the control group.

After the proposed therapy (Chapter 6), there was a significant improvement in these indicators.

Table 4.5.

Determination of uric acid in the blood serum of pregnant women at 22-34 weeks of gestation with threatened PB (after treatment)

		after treatment on the 1st day		after treatment on the 4th day		after treatment on the 10th day		
22-27 weeks of gestation	I group	436,43	26,1	353,17	21,75	315,55	20,9	p1<0,001* p2<0,001*
28-34 weeks of gestation		451,43	31,1	359,28	33,2	311,80	13,68	p1<0,001* p2<0,001*
22-27 weeks of gestation	II group	442,28	21,16	439,33	27,22	440,18	27,04	p1<0,091 p2<0,087
28-34 weeks of gestation		452,29	33,2	454,31	27,24	451,28	27,04	p1<0,089 p2<0,078

Note: p1 – comparison of groups 1 and 3, p2 – comparison of groups 2 and 3. *- significance of differences P <0.05*

In the first group, the average improvement in the endotoxicosis index was 115.24 μmol/l, in the second group it remained unchanged, which is of no small importance for the prognosis and prevention of this pathology.

Amniotic fluid is a unique biological environment that reflects the functioning of the fetoplacental complex. At the end of gestation, its formation involves the mother's plasma, fetal membranes, placenta, alveolar contents and urine of the fetus. Amniotic fluid ensures fetal homeostasis, protects it from physical, chemical and infectious effects, participates in the metabolism of proteins, lipids, carbohydrates, in the metabolism of hormones, and allows the fetus to develop freely. Complete exchange of amniotic fluid occurs within 3 hours. The possibility of determining the condition of the fetus based on the biochemical study of amniotic fluid is described by many authors. However, most studies devoted to this problem study only individual indicators, and the values of the latter often differ.

The next objective of the study was to examine the level of uric acid in the amniotic fluid.

We were faced with a question! What changes does the biochemical profile of amniotic fluid undergo when uric acid in the mother's blood increases and is there a connection between them?

To address this issue, the biochemical profile of the amniotic fluid composition was examined in women with endotoxicosis who had PROM upon admission, during labor, and in the control group.

The anterior amniotic fluid was collected from pregnant women at risk of premature birth in cases of PRROM, in the first stage of labor in case of spontaneous rupture of the amniotic sac or amniotomy. The posterior amniotic fluid was collected at the end of the second stage of labor, immediately after the birth of the fetus. The amniotic fluid was collected during the examination of the woman in the mirrors from the lower spoon with a syringe in the amount of 5-10 ml. The content of uric acid in the amniotic fluid increases during gestation due to the increase in excretion in the urine of the fetus as it matures.

As can be seen from the presented research results (Table 4.7), the content of uric acid in amniotic fluid has its own dynamics and concentration.

Table 4.6.

Determination of uric acid in the amniotic fluid of pregnant women among groups I and II

Uric acid in amniotic fluid (μmol/l)	I group (n=155)		II group (n=157)		Control group (n=40)		P
	M	m	M	m	M	m	
	364,53	24,3	427,95	9,93	340,92	13,95	p1<0,001 p2<0,001*

Note: p1 – comparison of groups 1 and 3, p2 – comparison of groups 2 and 3. *- significance of differences P <0.05*

As the results of the biochemical profile showed, the content of uric acid in the amniotic fluid in women of the 1st group was increased by a small amount compared to the second group (1.2 times).

The increase in uric acid levels in the amniotic fluid of pregnant women who did not receive the complex that we found may be due to a disruption of metabolic processes during the breakdown of cellular elements.

Our findings of a significant association between maternal serum uric acid levels in the second group, supported by studies demonstrating free transfer of uric acid across the placenta in pathologies, suggest that elevated uric acid levels may be the real etiology of these adverse outcomes.

According to the tasks set, we were faced with a survey on how uric acid affects the fetus? Does uric acid pass through the feto-placental barrier?

To address this issue, we examined the level of uric acid in amniotic fluid and in cord blood serum in all groups, in the early postpartum period in pregnant women with premature and full-term births.

Table 4.7.

Determination of uric acid in umbilical cord blood serum.

Uric acid in the umbilical cord blood of a newborn (μmol/l)	I group (n=155)		II group (n=157)		Control group (n=40)		P
	M	m	M	M	M	m	
	432,86	24,1	425,92	8,66	327,15	13,14	p1<0,001* p2<0,001*

Note: p1 – comparison of groups 1 and 3, p2 – comparison of groups 2 and 3. *- significance of differences P <0.05*

As can be seen from Table 4.8, we observed more pronounced changes in the content of uric acid in the cord blood in pregnant women of the study groups, not significantly in the first group and 1.3 times more in the second group compared to the control group. Apparently, the identified changes in the level of uric acid in various substrates, in our opinion, are due to metabolic disorders in the body of the examined pregnant women and there is a significant relationship between the levels of uric acid in the mother, in the serum of umbilical cord blood and amniotic fluid, which most likely leads to deep endotoxicosis and causes premature birth.

Chapter conclusions:

Thus, analyzing the results of the studies, we can conclude that with threatening PB, in the blood plasma of women there is a pronounced intensification

of endogenous intoxication processes in the form of lipid peroxidation, hemostasis system disorders, cytokine intensification, immune system and reactive proteins. It should be noted that the maximum changes in the homeostasis system and hyperuricemia in various substrates were found in pregnant women with a high risk of preterm labor and with threatening PB, the cause of which is deep endotoxicosis.

RESULTS OF THE STUDY OF PLACENTAL APOPTOSIS

Results of morphological studies

After delivery, the placentas of all patients in the prospective stage of the study were subjected to morphological and histological analysis.

During the histological examination of the placentas in the control group, it was established that the villous tree has a normal structure: stem, mature intermediate and terminal villi are determined. A distinctive feature is the presence of compensatory angiomatosis of the terminal villi. The fetal membranes are without pathological changes (Fig. 5.1).

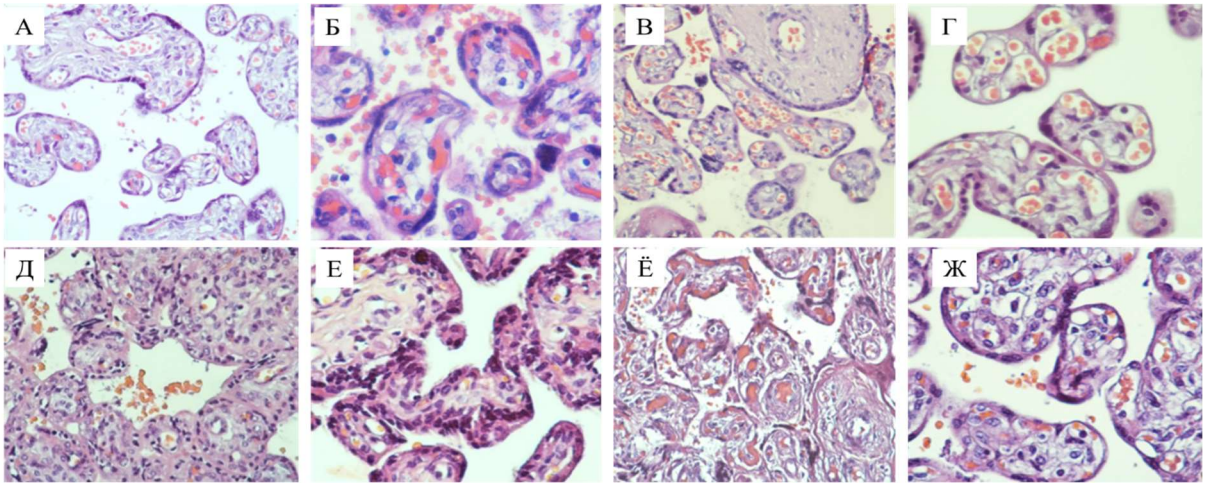


Figure 5.1. Morphological structure of the placenta of the control group

Hematoxylin and eosin staining x10, x100, x200, x400

(a and b – intermediate villi, c and d – stem, intermediate and terminal villi) and the first and second groups (d and e – stromal fibrosis and fibrinoids, d – high degree of apoptosis of structural components with the presence of Hofbauer cells located inside the stromal channels, g – stem villi are not fully formed and stromal channels with circulating macrophages (Hofbauer cells) are present in the villi).

(A.Mardonova, Part №1256, Pregnancy I, 31.3 weeks, Childbirth I; B. Primova, G. №6789, Pregnancy II, 30.3 weeks, Childbirth II; V. Abdullaeva, M. №5678, Pregnancy IV, 29.3 weeks, Childbirth II; G. Kosimova, I. №127, Pregnancy III, 32.3 weeks, Childbirth III; D. Kabilova, I. №2389, Pregnancy I, 31.5.3 weeks, Childbirth

I; E. Mukhtarova, A. №567, Pregnancy III, 32.3 weeks, Childbirth III; E. Ibratova, G. №6543; Zh. Alieva, S. №98, Pregnancy II, 27.5 weeks, Childbirth II.)

When studying the morphology of the villous stroma of the control group, the following was noted: immature intermediate villi, capillaries located on the periphery, stromal channels - in the center, stromal channels formed by the processes (telopodia) of several telocytes (average cell diameter 2.85 ± 0.6 μm), located in the center of the immature intermediate villus, several thin long telopodia (average diameter 0.23 ± 0.08 μm) that do not contain organelles, contacting each other and forming a network of stromal channels in the lumen, where macrophages are located (Hofbauer cells (Hb). It is shown that white blood cells migrate from adjacent blood vessels into the connective tissue to perform their functions as macrophages. A small number of granular cisterns of the endoplasmic reticulum were found only in the expansions of the telopodium. In the mature stroma of the intermediate villi, collagen deposits are found. Stromal channels are absent, and blood vessels are formed. In the stroma of the mature intermediate villus with collagen deposits, there are stellate telocytes (average diameter 2.96 ± 0.8 μm) with 3-4 telopodiums (average diameter 0.23 ± 0.1 μm) forming a network around the blood vessels. The expansion of the telopodiums reaches more than 1.16 μm. The processes of the telocytes are marked by grooves. Erythrocytes are located in the lumen of the vessel. (In the mature intermediate stroma of the villi, under the basement membrane of the cytotrophoblast, there are spindle-shaped telocytes (average diameter 2.65 ± 0.9 μm) with elongated nuclei and usually 2 thin telopodiums (average diameter 0.29 ± 0.1 μm). The elongated processes of these telocytes form a chain under the basement membrane. Smooth and granular endoplasmic reticulum (SER) and mitochondria are mainly located in the extensions of the telopodium. In some areas, in the stroma of mature intermediate villi, telocytes are observed under the basement membrane of the trophoblasts. Spindle/stellate cells are formed and more than 2 processes make contact with stellate telocytes located deeper. Cisterns of granular endoplasmic reticulum, single mitochondria and glycogen granules located in the perinuclear zone and in the extensions of the telopodium. Mature intermediate stroma of the

villi. In the stroma of the trunk villi, myofibroblasts (mean diameter 2.98 ± 1.1 μm) with 2 extensions (mean diameter 0.23-1.16 μm) in the arterial adventitia form a network in the smooth muscle wall of blood vessels. Cisterns of well-developed granular endoplasmic reticulum are located near the nucleus and in the processes; a small number of myofibrils are found on the periphery of the cell, together with dense bodies (characteristic of both fibroblasts and smooth muscle cells).

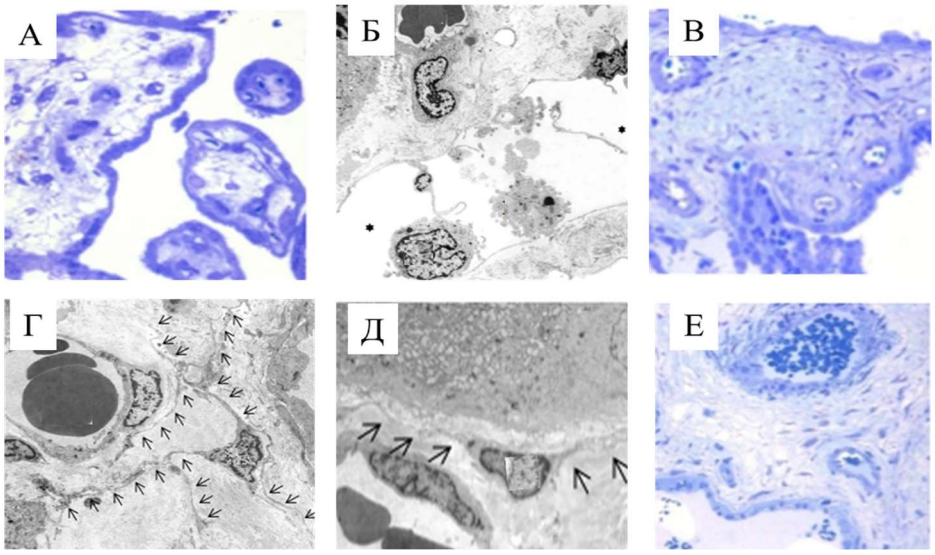


Figure 5.2. Morphology of villous stroma (a-e). Methylene blue staining (×400). Electron micrograph (×4800, ×5600)

(A-B Ziyanova S. i\b, №3214, Pregnancy II, 30.3 weeks, Childbirth II.; B, G, D. - Fikratova A. i\b, №7811 Pregnancy III, 30.2 weeks, Childbirth III,)

Morphological analysis of the placentas of the first and second groups revealed that the villous tree contains supporting, intermediate immature and intermediate differentiated villi. The supporting villi are represented by a loose collagen body, in places with preserved stromal channels with single Kashchenko-Hofbauer cells. Among the intermediate villi, the generation of immature forms predominated up to 80% in the first group and up to 50% in the second with typical stromal channels and the presence of placental macrophages. The epithelial lining is represented by syncytiotrophoblast with separate areas of cytotrophoblast, mainly with light eosinophilic cytoplasm (Fig. 5.1).

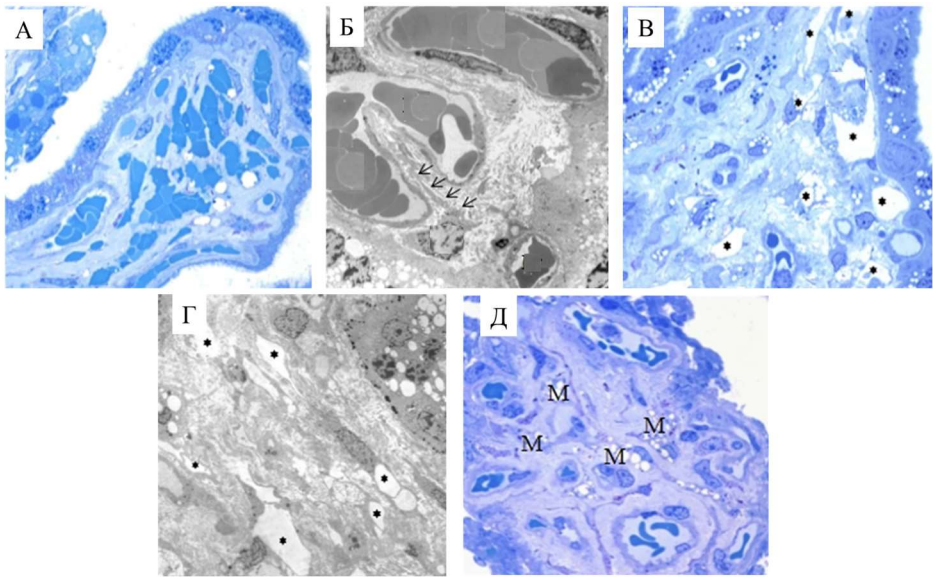


Figure 5.3. Morphological changes in the placenta of the first and second groups (a-d). Methylene blue staining (×400). Electron micrograph (×4800, ×5600). (A-B Primova A. i\b №5783, Pregnancy III, 33.1 weeks, Delivery I; B, G, D. - Zakirova K. №3861, Pregnancy I, 29.1 weeks, Delivery I.)

The capillary bed of intermediate immature villi is represented by a small number of them, centrally located, with their virtual absence in the subepithelial zones. Intermediate differentiated villi were found in 15-20% of the first group and 30-40% of the second with a more densely cellular stroma, single stromal channels and topographically prevailed in the paracentral and central zones of the placental disk.

In all cases of the first and second groups, there were morphological signs of ascending infection with the presence of parietal deciduitis, parietal chorioamnionitis, serous-purulent choriodeciduitis, membranitis, subchorial and subbasal intervillisitis, and placental chorioamnionitis.

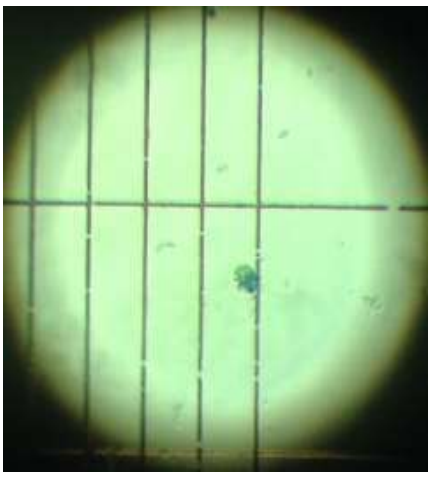
When studying the morphology of the villous stroma of intermediate villi in PR, the following was noted: accumulation of erythrocytes in the lumen of the vessel, stellate telocyte-like cells are located near the blood vessels. The stroma contains collagen fibers, and multiple vacuoles are visible in the syncytiotrophoblasts. Areas of telocyte-like cells form pseudostromal channels in mature intermediate villi. Telocyte-like cells (average diameter 3.25 ± 0.6 μm) are visible in the stroma of fibrous villi due to their processes (average diameter 0.28 ±

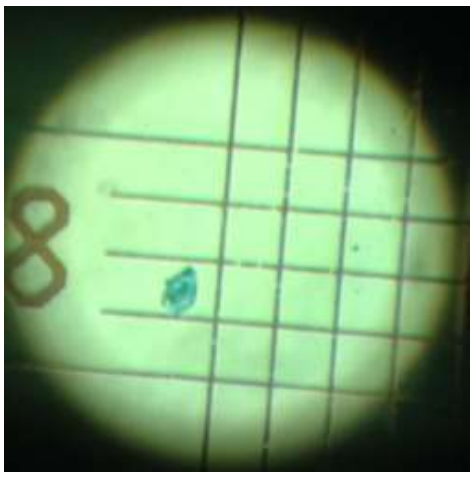
0.1 μm), which limit pseudostromal channels. Macrophages with multilobed nuclei and multiple vacuoles are present.

Evaluation of markers of endothelial dysfunction in placental apoptosis

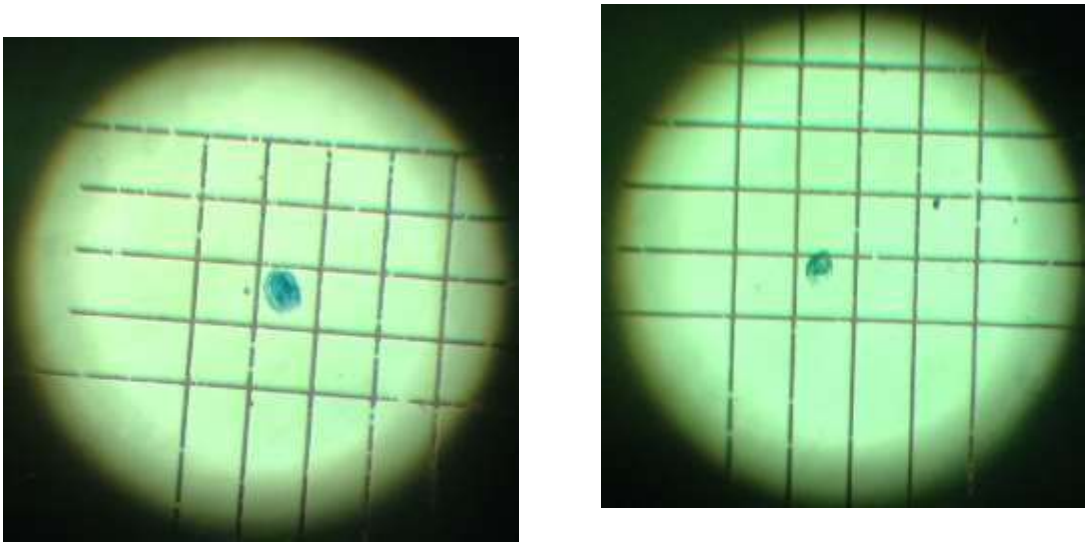
The aim of the morphological stage of the study was to unify the indices of endothelial function using morphometry of DEC. This stage was necessary to accumulate a sufficient volume of cell sample preparations in order to assess physiological variants of quantitative and qualitative features of placental apoptosis and endothelial dysfunction in the peripheral blood of a woman during pregnancy. Due to the volume of processed information, a new information technology for objectifying vascular system damage in pregnant women using vital computer morphometry of desquamated endotheliocytes was created empirically.

Using a traditional method, we carried out a morphometric study of the functional state of the endothelium in pregnant women. In the work, a modified method for counting desquamated endothelial cells was used (Ovsyanik D.M., Fomin A.V., 2014) [62], which included staining the cytological preparation with a 0.1% methylene blue solution (Figures 5.4. (4a-4d))





a) b)



c) d)

Figures 5.4. (4a-4d) – DEC in Goryaev's chamber. Methylene blue staining. Magnification 400×.

(A-Karimova U., No. I\b 1489 Pregnancy II, 32.4 weeks, Childbirth II; B-Azizova A., No. I\b 8975 Pregnancy I, 33.2 weeks, Childbirth I; B- Akilova S., No. I\b 3247 Pregnancy I, 29.3 weeks, Childbirth I, G- Fozilova A., No. I\b 7781 Pregnancy III, 34.3 weeks, Childbirth III.)

The staining with 0.1% methylene blue solution used in the work stained the cytoplasm of cells in blue, and fragments of the nucleus in dark blue for optimal color contrast and image clarity during CMM. For each patient, the number of endotheliocytes was counted in 10 samples of the Goryaev chamber, and the average value of the number of circulating DEC was determined. Simultaneously, the preparation was photographed from the microscope tube with a camera, the image was transferred and saved using a file conversion program. In automatic mode, the image tone correction was performed to minimize the level of errors associated with coloring and lighting. The image of bioobjects was isolated (segmented) under the operator's control and the average morphometric parameters of desquamated endotheliocytes were determined.

When determining the average number of desquamated endothelial cells in the study groups, an almost twofold increase was noted in the group of pregnant women with preterm labor: 12.1±1.54 x104 cells/100 ml in the first group, 7.87±0.58 x104 cells/100 ml in the second, 5.9±0.25 x104 cells/100 ml in the third group ($p \leq 0.001$; $t=3.98$, $p \leq 0.001$; $t=4.24$).

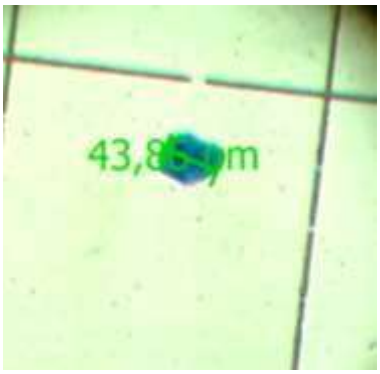


Figure 5.5. – Desquamated endotheliocyte, control group.

Morphometric study in Leica Application Suite LAZ EZ Version 2.1.0. Methylene blue staining. Magnification 600×.

(Kilicheva P. No. 459. Pregnancy II, 34.3 weeks, Labor II)

Figure 5.6. Desquamated endotheliocyte, main group.

Morphometric study in Leica Application Suite LAZ EZ Version 2.1.0. Methylene blue staining. Magnification 600×.

(Abbosova N. No. 189 Pregnancy III, 33.3 weeks, Labor II)

During the damage process, the cell goes through the stages of compression, chromatin condensation and formation of apoptotic bodies. At the same time, the geometry of the affected cell changes. With a pronounced degree of endothelial dysfunction, most of the desquamated endothelial cells are recorded in the

cytomorphometry in the stage of blebbing and apoptotic bodies, which is reflected in the decrease in the geometric parameters of the altered cells (Fig. 4.3).

The following results were obtained in the study groups during the cytometric study of desquamated endotheliocytes of peripheral blood: diameter is the distance between the most distant points (pixels) of the image on the plane. The average diameter of desquamated endotheliocytes of the control group was 44.1±3.88 μm, which is 1.5 and 1 times higher than this indicator of the first group 30.1±6.1 μm and the second - 38.7.1±6.1 μm ($p \leq 0.001$, $t=6.23$, $p \leq 0.01$, $t=5.89$).

During apoptosis, the cell shape changes, going through the stages of compression, fragmentation and formation of apoptotic bodies. The characteristic of the cell perimeter change can be an additional cytometric indicator of endothelial cell apoptosis activity. The average perimeter of desquamated endothelial cells in the control group was 140.5±8.5 μm, in the first group - 92.7±11.4 μm ($p \leq 0.03$, $t=3.47$) and in the second - 115.4±10.6 μm ($p \leq 0.01$, $t=3.24$).

The number of pixels that do not go beyond the object boundary is taken into account. The parameter value is affected by the actual cell size and the ability to form outgrowths. The average area of the desquamated endothelial cell was 1600.5±58.9 μm² in the control group, 850.5±36.5 μm² and 1255.7±34.8 μm2 in the main group ($p \leq 0.001$, $t=4.64$, $p \leq 0.001$, $t=4.64$).

The shape factor is a characteristic of the irregularity of the perimeter of an optical object, a dimensionless value representing a combination of the characteristics of the size and shape of a particle or structural component, representing the ratio of the length to the width or the square of the perimeter to the plane. This indicator of a cytometric study shows the approximation of the shape of an object to the shape of a circle. The shape factor of desquamated endotheliocytes of peripheral blood was 14.1±0.15 in the control group, 9.7±0.23 in the first ($p>0.03$, $t=3.11$), 11.5±0.26 ($p>0.02$, $t=3.54$) in the second.

Polarization is the degree of ellipticity of the object. This parameter varies from 0 to 2. Change in the shape of the desquamated endothelial cell is associated with the loss of the rounded shape of the cell. The polarization index can be used as

an additional parameter of the cytometric characteristic of the desquamated endothelial cell. Polarization of desquamated endothelial cells: 0.075±0.015 in the control group, 0.18±0.024 in the first group (p≤0.003, t=6.23), in the second 0.010±0.019 (p≤0.002, t=6.14). Thus, most of the cytometric indices of desquamated endothelial cells of the peripheral blood differed in the studied groups. The results are presented in Table 5.1.

Table 5.1.

Parameters of desquamated endothelial cells of peripheral blood

Indicator	Study groups			P1	P2
	I group	II group	III group		
Quantity, x10⁴	12,1±1,54	7,87±0,58	5,9±0,25	<0,001	<0,01
Average diameter, µm	30,1±6,1	38,7±6,1	44,1±3,88	>0,05	>0,2
Perimeter, µm	92,7±11,4	115,4±10,6	140,5±8,5	<0,01	>0,05
Area	850,5±36,5	1255,7±34,8	1600,5±58,9	<0,001	<0,001
Form factor	9,7±0,23	11,5±0,26	14,1±0,15	<0,001	<0,001

Note: p1 – comparison of groups 1 and 3, p2 – comparison of groups 2 and 3.

Thus, during the morphological study of desquamated endothelial cells of peripheral blood, in addition to the classical traditional parameter of the amount of DEC, we obtained a digital portrait of the cell, which served as the basis for confirming the possibility of a connection between the onset of oxidative processes in the peripheral blood due to an increase in uric acid, which possibly leads to the onset of PR due to apathosis of placental cells.

The histogram of the distribution of the values of the indicator “Number of DECs” (Figure 5.7) clearly shows the differences between the groups.

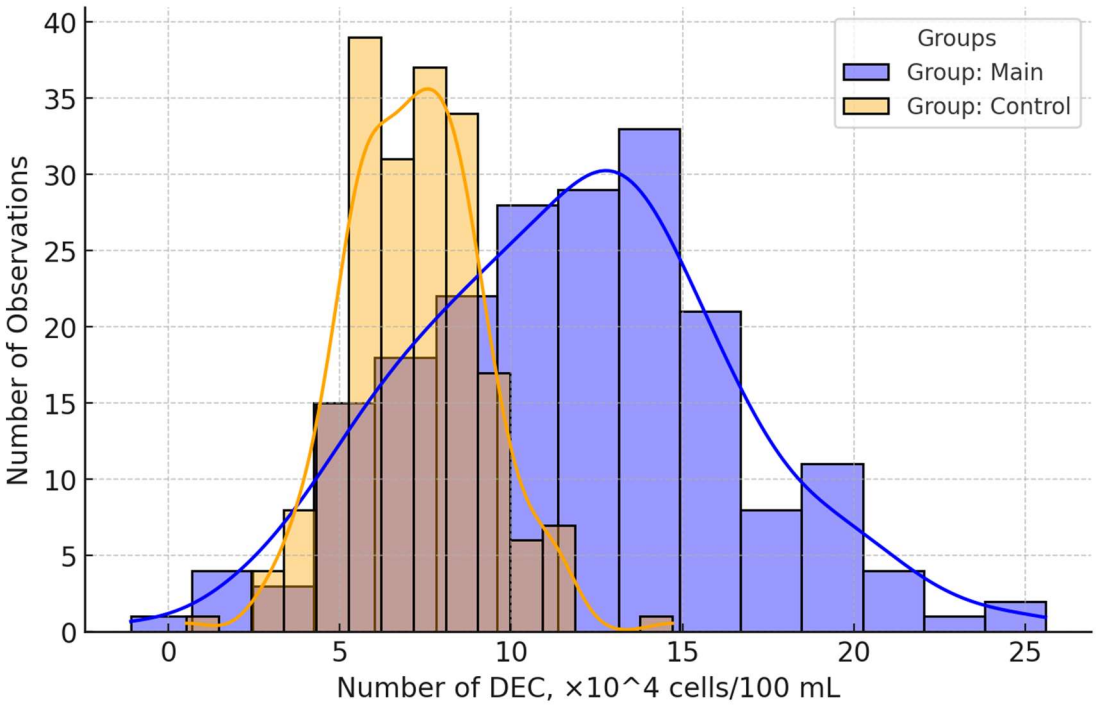


Figure 5.7. – Graph of distribution of the amount of DEC in pregnant women in the study groups.

Note: DEC – dexquamated endothelial cells.

When conducting a comparative analysis of the results of measuring circulating endothelial cells, a statistically significant difference was found in the groups of participants.

The study revealed that the average value of the perimeter of the DEC in women from the control group was significantly higher than in those in the main study group. This indicates that the control group had a more pronounced morphological structure compared to the main group. A similar indicator for the main group was 93.8 μm, which is also statistically significant.

Thus, the results of the study indicate that women from the control group had a higher average area of endothelial cells and a more homogeneous distribution of this morphometric parameter than women from the main study group, which indicates the absence of oxidative processes.

A correlation analysis of the dependence of the number of desquamated endotheliocytes and the average diameter of desquamated endotheliocytes was performed. A model of a two-dimensional normally distributed general population

was constructed. The scatter diagram of the parameters of the cytometric parameters of desquamated endotheliocytes of peripheral blood is shown in Fig. 5.8.

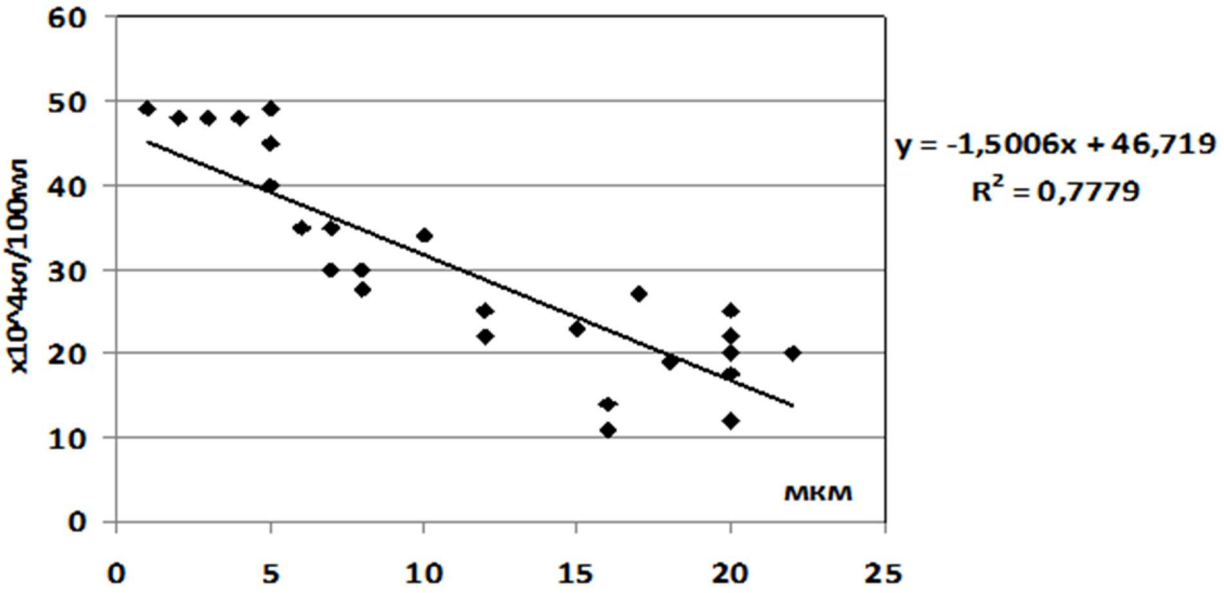


Figure 5.8. Linear correlation diagram of the number and average diameter of desquamated endothelial cells.

We found that the changes in the morphometric parameters of desquamated endothelial cells in gestation disorders are statistically significant and can be used as informative markers of vascular disorders that are the cause of elevated uric acid that led to PB. This means that our results can help in the diagnosis of endothelial dysfunction in pregnant women and improve the prediction of the risk of PB. It is important to note that we used the geometric parameters of desquamated endothelial cells in peripheral blood as a diagnostic criterion for endothelial damage in humans for the first time. This approach can form the basis for future research in this area and help in the development of new diagnostic methods and therapeutic strategies.

Morphometry of placental vessels.

We examined the material obtained after delivery of the placenta and the contents of the uterine cavity in women with PB and physiological course. This material is tissue fragments of placental elements of various colors, having an elastic or spongy consistency, which we studied at the microscopic level. In the

morphometric analysis, the thickness of the capillary wall was determined by the thickness of the cells of apoptosis. In the course of the study, we studied 180 histological preparations of placental villi in patients.

Our study included only those vessels in which pericytes were absent, which allowed us to standardize the research method.

This study analyzed various characteristics of the vessels that are located in the villous space of the placenta (these look like small branches that provide nutrition to the fetus). Several parameters were studied:

1. Average vessel wall thickness.
2. Average diameter of the lumen (empty space inside) of the vessel.
3. Average area of the internal space of the vessel.
4. Kernoghan index is the ratio of the vessel wall thickness to its diameter.
5. Endothelial cell apoptosis index is an indicator that indicates the number of cells showing signs of apoptosis (programmed death) in relation to the total number of cells examined.

To detect apoptosis in endothelial cells, a special technique called nuclear segmentation by indirect immunofluorescence microscopy was used.

In our study, we analyzed the condition of the placental tissue in patients in the group of women with PB. We found that the frequency of villous tissue necrosis in the preparations was 6.7% (6 patients). In addition, 25 patients (27.8%) had hemorrhages in the stroma of tertiary villi, and leukocyte infiltration of the villi was found in 4 patients (4.4%). Placental villous dystrophy was diagnosed in 7 people (7.8%), while placental villous stromal edema was detected in 12 pregnant women (13.3%). These data can help to better understand the condition of the placental villous tissue in patients and identify risk groups for subsequent monitoring and treatment. Thus, we can conduct more effective treatment and reduce the risks of possible complications in pregnant women.

In this study, computer morphometry of the placental villus vessels was performed in each woman.

The obtained results indicate that in the main 1 group the most common vessel

wall thickness is 0.7 μm, with the range of fluctuations of this indicator from 0.48 to 0.99 μm, and the standard deviation was ±0.12 μm. The average value of the vessel lumen diameter was 6.73 μm, and the range of fluctuations of this indicator was from 5.76 to 6.42 μm, with a standard deviation of ±0.38 μm.

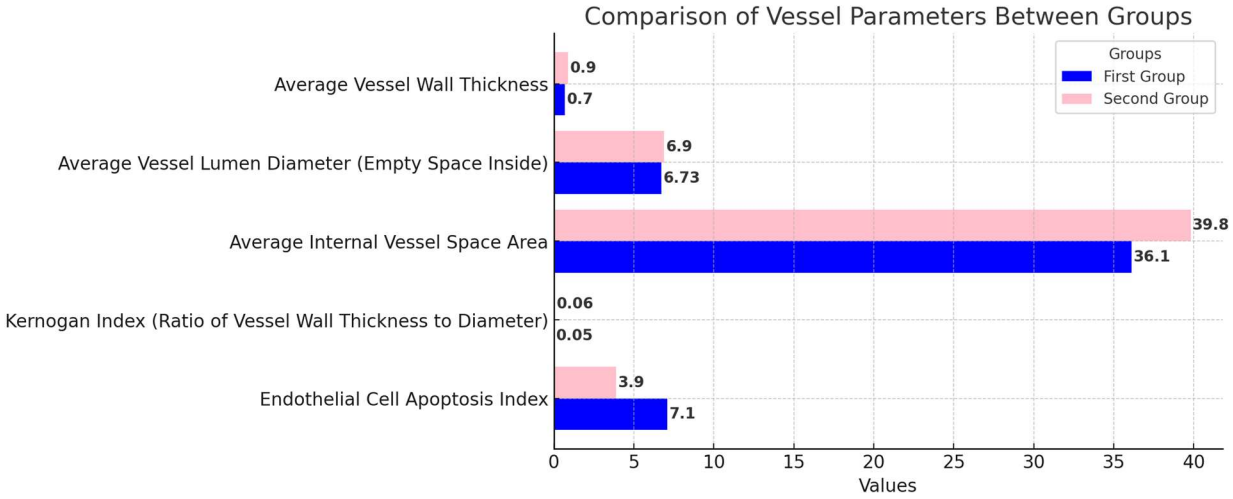


Figure 5.9 Results of morphometry of placental vessels

The average value of the vessel lumen area was 36.1 μm² in the main group, with a range of 22.97 to 51.68 μm² and a standard deviation of ±4.62 μm². The Kerogan index of placental vessels in the main group was 0.05, with a range of 0.036 to 0.073 and a standard deviation of ±0.008, and the endothelial cell apoptosis index in the wall of placental villi vessels was 7.1%, with a range of 2.5 to 11.4% and a standard deviation of ±2.49%.

We found that the average vessel wall thickness in the second group with PB was 0.9 μm, and the range of variations of this parameter was from 1.25 to 0.67 μm. The standard deviation for this indicator was ±0.12 μm, indicating high accuracy of the obtained data. These results will help to better understand the structure of the chorionic vessels and identify any abnormalities.

In the second group of women with preterm labor, we found that the mean lumen diameter of the vessels was 6.9 μm, and the range was from 4.53 to 8.92 μm. The standard deviation of this indicator was ±0.93 μm. The mean lumen area of the primary placental capillaries was 39.8 μm², and the range was from 16.59 to 63.84 μm². The standard deviation of this indicator was ±10.96 μm².

The Kernoghan index in the control group was 0.06, and its range of variation was from 0.044 to 0.117. The standard deviation of this indicator was ±0.017.

The endothelial cell apoptosis index was 3.9%, and the range of fluctuations of this indicator was from 2 to 5.7%. The standard deviation of this indicator was ±1.49%.

A study was conducted to examine microscopic preparations of placental villi, which revealed important differences in the studied features between the groups. As a result of the study, necrotic changes in placental villi were detected with a frequency that significantly exceeded the value of the control group ($p<0.0001$; $t=8.76$).

In addition, placental villous dystrophy was also more common in the main group, where hyperuricemia prevailed and was the cause of preterm birth ($p<0.0001$; $t=7.24$). Other studied parameters were also higher in the group where premature birth occurred. These results may indicate a relationship between the observed changes in microscopic preparations and the risk of premature birth and indirectly confirm the role of hyperuricemia in the process of cell apoptosis, which is largely the cause of preterm birth.

Chapter conclusions:

Thus, morphological studies have shown that the development of premature birth is accompanied by a violation of the maturation of the placental villi, angiopathy, the presence of ischemia, thrombosis of the intervillous spaces, signs of deciduitis, chorioamnionitis, intervillousitis, villitis, phlebitis and arteritis of the umbilical cord.

FEATURE OF OPTIMIZATION OF THE SYSTEM OF TREATMENT AND PREVENTIVE MEASURES IN PREGNANT WOMEN WITH THREATENED PREMATURE BIRTH

Development and implementation of methods for predicting and preventing complications in premature births

When studying the data of a prospective study, it was established that the first pregnancy, repeated births, miscarriage, history of non-developing pregnancy, medical abortion, inflammatory diseases of the reproductive system, etc. are risks of premature birth. When hospitalizing patients with a risk of threat and premature birth, significant changes in the homeostasis system, disturbance of uteroplacental and fetoplacental hemodynamics were noted.

However, to identify the real risk factors for PB, the activities of the most important components of the homeostasis system were determined, such as the presence of endotoxicosis, activation of lipid peroxidation, antioxidant protection, cytokine intensification, the state of the body's reactive proteins, the content of purine metabolism products, and the stability of the hemostasis system.

To demonstrate the pathogenetic mechanism of PB development, we have developed an algorithm that can be used in scientific research and theoretical classes of educational institutions for students.

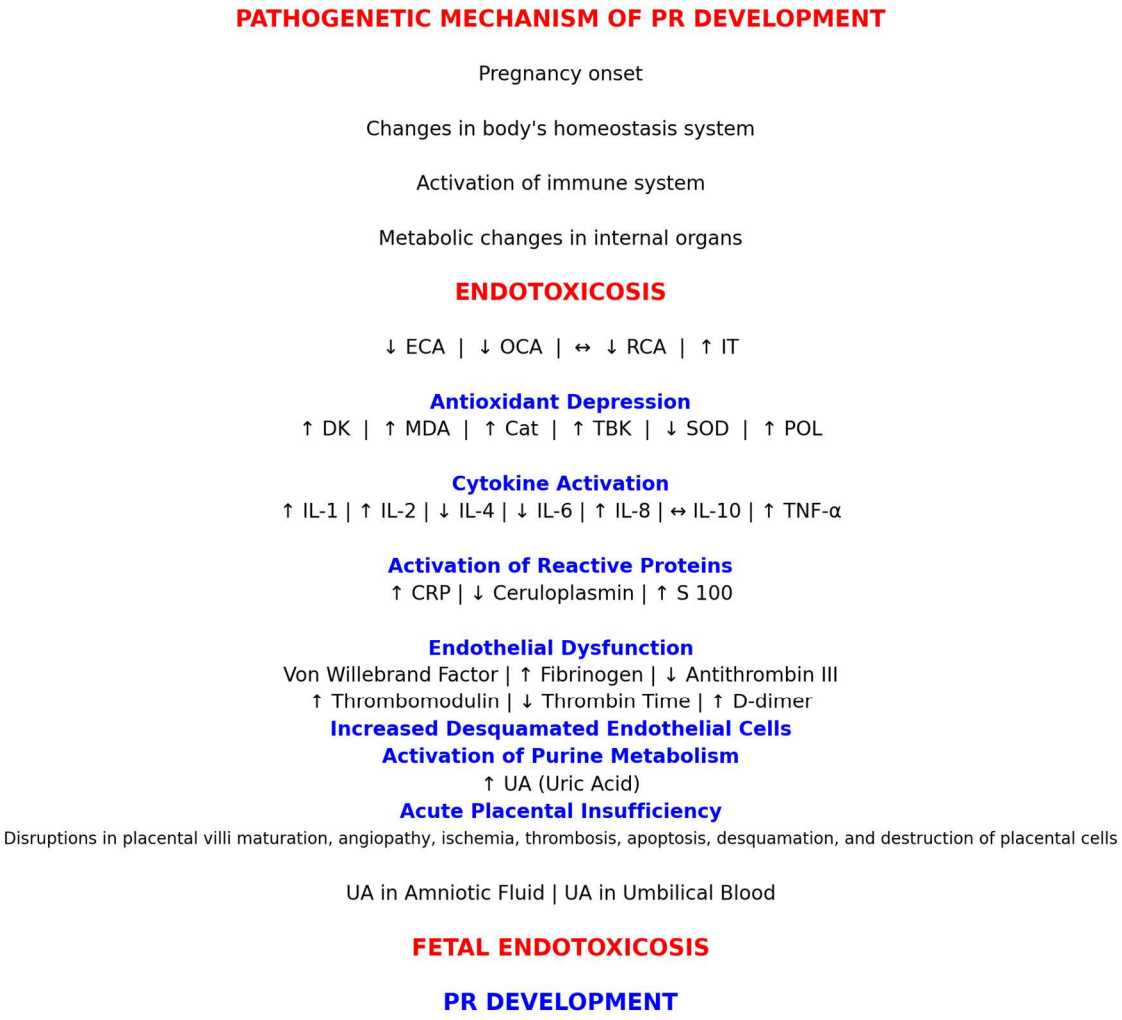


Figure 6.1. Proposed pathogenetic mechanism of PB

As can be seen from Figure 6.1, it has been pathogenetically revealed: after the onset of pregnancy, changes in the body's homeostasis system appear, the immune system is activated, metabolic changes in the internal organs appear, which leads to endotoxicosis of the pregnant woman, this process is accompanied by antioxidant depression causing cytokine activity, reactive proteins of the body are activated leading to endothelial dysfunction, which in turn leads to desquamation of endothelial cells activating purine metabolism leading to placental insufficiency (impaired maturation of placental villi, angiopathy, ischemia, thrombosis of the intervillous spaces, apoptosis, desquamation and destruction of placental cells), and an increase in UA in the amniotic fluid and umbilical cord blood, which leads to fetal endotoxicosis and preterm labor (Fig. 6.1).

As the results of our study showed, changes in the content of uric acid in the blood of pregnant women (without signs of preeclampsia and hypertension) occur due to,

- protective antioxidant mechanism of the body during pregnancy;
- active functioning of the placenta (the placenta is a source of purines - due to its functioning, uric acid is formed, trophoblast microparticles released into the bloodstream damage the placenta leads to dysfunction of the placental vessels, which in turn leads to NMPC, FPN, inflammatory genesis of the placental bed activates cytokines;
- due to metabolic disorders (excess body weight);
- due to perfusion load and inflammatory processes in the kidneys;
- congenital enzymopathies;
- asymptomatic form of hyperuricemia of unclear etiology.

The authors believe that since the intrauterine growth rate of the fetus slows down to 1 mm/day by 20 weeks, it is possible that elevated levels of uric acid in the mother's blood play an important role in this process. This leads to suppression of growth rates, an increase in the level of uric acid in the fetus, a decrease in the amount of nitric oxide in endothelial cells, which is accompanied by "endothelial dysfunction", and, consequently, to the threat of termination of pregnancy.

According to the literature, the pathogenesis of PB cannot be considered only as an isolated lesion of an organ, such as the placenta, without closely linking the nature of local changes with the general disorders that arise in the body [54, 89, 125, 147].

Currently, there are two prevailing points of view on the relationship between the etiology and pathogenesis of PB. According to one of them, PB is a monopathogenetic but polyetiological disease. According to the other, each etiological factor has a pathogenetic mechanism characteristic only of it [12, 79, 148].

Being a polyetiological disease, PB is pathogenetically caused by the influence of metabolic, vascular, neurotrophic, toxic-allergic, and traumatic factors that lead to damage to internal organs [104, 178].

According to modern concepts of the pathogenesis of PB, the causes of the development of this pathology are two closely interconnected groups of damaging factors: 1) neurohumoral (impaired innervation and metabolic functions of internal organs); 2) toxic (the presence of exogenous and endogenous toxic metabolites of various natures) [88, 97, 113, 141].

Activation of the homeostasis system in pregnant women is accompanied by an intoxication syndrome, which contributes to decompensation of the body's detoxification systems and causes frequent cell death. Endotoxicosis is characterized by a complex of metabolic disorders leading to dysfunction of the main life support systems and underlies the development of multiple organ failure. The severity of endogenous intoxication is determined by the content of the total and effective albumin concentration in the blood plasma and by the content of medium-molecular peptides. An increase in the formation of medium-weight molecules has a negative effect on the functioning of various organs and systems and homeostasis as a whole, being one of the most important reasons for the formation of multiple organ failure syndrome [73, 97, 125, 146].

At this time, against the background of increased blood circulation, the process of activation of lipolytic enzymes - phospholipase A and lipase - accelerates. Lipid-water exchange is considered one of the triggers of membrane-destabilizing processes in PB [35, 104, 133].

Recently, the role of interleukins (IL) in the pathogenesis of PB has been widely discussed in the scientific literature. They are bioregulators of the inflammatory-necrotic process and cause the main pathological reactions that occur in the early stages of the disease. Considering that IL-1 intensifies LPO processes, an assumption has been made about the role of this compound in increasing the risk of developing multiple organ failure syndrome and determining the severity of RVP [44, 69, 117, 123].

In RVP, microcirculatory changes occur at the earliest stages of the disease, are generalized in nature, and have a certain staging [59, 101, 134].

Disturbances in macro- and microhemodynamics in PB occur as a “circulatory shock”, are accompanied by significant changes in the rheological properties of the blood and persist at all stages of the pathological process. As a result, foci of local ischemia arise and the process of cellular autolysis is initiated [26, 77, 109, 147].

The results of the prospective study showed that the above changes were registered not only in pregnant women, but also in fetuses.

In the early stages of premature labor, pregnant women experience endogenous intoxication (decrease in TCA, ECA, ABR, and increase in IT), pronounced intensification of lipid peroxidation processes (increase in DC, MDA), and decrease in antioxidant protection (decrease in SOD, Kat). These processes contribute to the progression of pregnancy and lead to intensification of the cytokine system (increase in IL-1,2,4,6,8,10, TNF-a, systematization of the inflammatory process (increase in RPS, nitric oxide, S-100, decrease in ceruloplasmin), activation of purine metabolism (increase in uric acid). At the same time, disturbances in the activity of the coagulation system (decrease in APTT), fibrinolysis (increase in fibrinogen) are recorded.

Moreover, changes in the homeostasis system were associated with the duration of PB.

It can be said with confidence that UA is the final and final parameter of the pathogenetic mechanism of PB, which can be used as a predictor for prognostication and prevention of complications in this pathology. This is confirmed by the value of correlation analysis (Table 6.1).

Table 6.1.

Correlation dependence of UA with indicators of the homeostasis system during PB in pregnant women

Indicators	UA		
	I – group (n = 41)	II – group (n = 42)	III – group (n = 35)
TCA	**-0,955***	**-0,969***	**-0,799***
IT	**0,942***	**0,949***	**0,692***
ДС	**0,926***	**0,939***	**0,753***
MDA	**0,938***	**0,955***	0,311*
SOD	**-0,957***	**-0,981***	**-0,544***
IL1	**0,880***	**0,909***	**0,772***
IL 2	**0,990***	**0,999***	0,159*
IL 4	**0,925***	**0,912***	**0,643***
IL 6	**-0,909***	**-0,898***	**-0,681***
IL 8	**-0,881***	**-0,933***	**-0,697***
IL 10	**-0,681***	**-0,943***	**-0,797***
SRP	**0,731***	**0,790***	0,322*
Nitric oxide	**0,862***	**0,895***	**0,862***
APTT	**-0,951***	**-0,871***	**-0,651***
Fibrinogen	**0,933***	**0,833***	**0,571***

- significance of differences P <0.05

As can be seen from Table 6.1, correlation analysis confirms the relationship between UA and homeostasis system indicators, proinflammatory cytokines, and reactive proteins.

Thus, according to the prospective study data, it has been proven that the UA marker is a specific indicator of the development of PB, which can be used to predict and prevent complications of this pathology (Fig. 6.2).

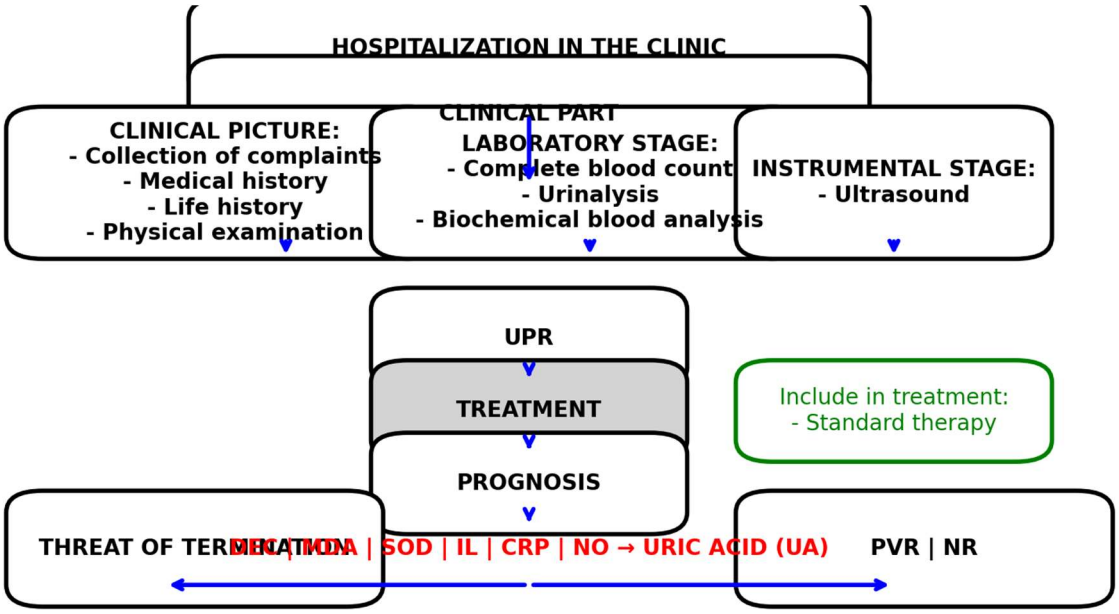


Figure 6.2. Improved algorithm for diagnostics, treatment, and prevention of PB

Development of tactics for the management and treatment of premature births

Currently, many schemes of complex treatment of threatened PB have been proposed. But to date, there are no proposed complex treatment schemes for threatened PB with progressive intoxication and hyperuricemia.

In this regard, we propose a new method for correcting intoxication, homeostasis disorders and hyperuricemia in threatened PB, the spectrum of which, as noted above, is extremely wide, taking into account its ability to correct disorders in various organs and systems.

After a complete clinical and laboratory examination, pregnant women with threatened PB of the second group were prescribed traditional pregnancy-preserving therapy. Pregnant women of the first group (the main one) were recommended to use the proposed course of treatment in addition to traditional therapy + **drugs with an antioxidant effect and containing rosmarinic acid**, which reduces uric acid within 12 hours after taking 1 tablet 3 times a day (in our study, we used Canephron H50) + **Glucurono-2-amino-2-deoxyglucoglucan sulfate**, 1 tablet 2 times a day (in

our study, we used Sulodoxide 250 LE (lipoprotein lipase units)) (according to the coagulogram indicators) and (suppresses the proliferation of smooth muscles of the vascular wall, promotes the restoration of the structure and function of vascular endothelial cells, normalizes the rheological properties of the blood), and **L-Arginine L-Aspartate** 5-10 ml x 3 times a day (has antihypoxic, membrane-stabilizing, cytoprotective, antioxidant, detoxifying effect, has an acid-forming effect and helps correct acid-base balance) if there is FPN.

A diet (plenty of fluids), iodine preparations 200 mg, iron preparations, ascorbic acid 0.1 g 3 times a day for 20 days, progesterone 200 mg 2 times a day until 36 weeks of pregnancy, nifedipine 10 mg orally every 30 minutes (maximum single dose 40 mg) were prescribed. Then - 10 mg every 8 hours orally for no more than 48 hours from the start of therapy under the control of blood pressure, indomethacin 100 mg 1 sv. x 1 time per day for 10 days.

The analysis of the results of the therapy was assessed on the 1st, 4th, 10th day of hospitalization using laboratory research methods. Clinical improvement in the condition was noted by an average of 76% of women in both groups.

However, it was revealed that against the background of the use of a traditional therapeutic course in the second group (1st, 4th, 10th day of hospitalization), homeostasis parameters remained abnormal.

On the contrary, the use of complex therapy in pregnant women of the first group with threatened PB in addition to traditional therapy made it possible in the early stages to: reduce the severity of endogenous intoxication, the activity of lipid peroxidation, improve the state of immune activity, restore blood hemostasis, the fibrinotic system and hyperuricemia (Table 6.2).

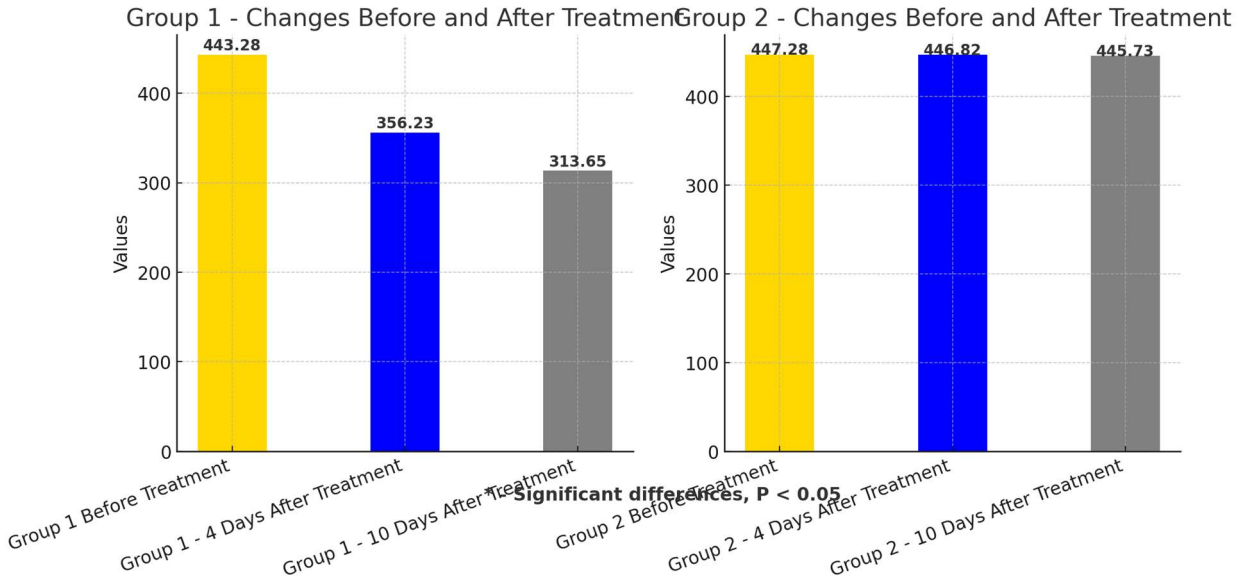


Figure 6.3. Dynamics of the decrease in the amount of uric acid in the groups before and after the therapy

As can be seen from Figure 6.3, after the complex therapy, a significant decrease in uric acid in the blood plasma was noted on the 4th and 10th days.

Table 6.2.

Comparative characteristics of the main biochemical parameters depending on the day of treatment of PB

Indicator	Study groups	Observation period, days			P1	P2
		1-days	4-days	10-days		
IT (%)	I	0,54±0,012	0,49±0,09	0,45±0,05	>0,5	<0,05
	II	0,5±0,011	0,51±0,07	0,52±0,04	>0,5	>0,2
	III	0,39±0,06				
TCA, IU/ml	I	27,2±6,2	35,4±5,8	37,1±4,9	>0,2	>0,2
	II	30,5 ±5,4	31,1±3,8	29,5±3,2	>0,2	>0,1
	III	38,5±5,3				
DC µmol/l	I	31,2±0,012	28,1±0,09	22,53±0,04	<0,05	<0,001
	II	33,1±0,011	33,55±0,08	34,47±0,03	<0,01	<0,001
	III	20,2±0,09				
SOD, IU/1 mg protein	I	3,46±0,33	4,4±0,41	5,1±0,45	<0,05	<0,001
	II	3,31±0,26	3,7±0,34	3,1±0,42	<0,001	<0,001

	III	6,34±0,58				
IL1, pg/ml	I	3,31±0,23	2,8±0,19	2,6±0,15	<0,001	<0,001
	II	4,45±0,17	4,5±0,14	4,6±0,11	<0,001	<0,001
	III	2,15±0,18				
UA, μmol/l	I	443,93±28,6	356,23±27,4	313,26±17,29	<0,05	<0,001
	II	447,28±27,18	446,82±27,3	445,73±27,4	<0,001	<0,001
	III	332±13,				
RPS, mg/l	I	5, 87±0,54	4,5±0,4	3,8±0,36	>0,5	>0,1
	II	5,15±0,41	5,31±0,39	5,61±0,22	>0,05	<0,001
	III	3,4±0,23				
Nitric oxide, ppb	I	89,5±9,6	70,4±8,8	61,7±7,4	>0,5	>0,1
	II	86,1±8,7	85,9±10,9	89,4±8,7	>0,1	<0,05
	III	36,4±5,3				
APTT, sec	I	28,1±1,45	24,1±1,68	25,4±1,95	>0,2	<0,05
	II	32,3±1,74	30,8±1,93	31,1±2,03	>0,05	<0,01
	III	26,5±1,94				
Fibrinogen, g/l	I	4,59±0,53	4,1±0,41	3,32±0,36	>0,5	>0,5
	II	4,48±0,44	4,62±0,21	4,78±0,12	>0,2	>0,1
	III	3,64±0,11				
S -100 protein mg/dl	I	8,8±0,53	15,5±0,64	31,6±0,71	<0,01	<0,001
	II	7,9±0,47	7,5±0,87	8,4±0,91	<0,01	<0,001
	III	40,9±2,04				

Note: P1 – reliability of differences on days 4 and 1, P2 – reliability of differences on days 10 and 1

The complex of therapeutic measures for threatened PB in the main group allowed to significantly reduce the intensity of endotoxicosis indicators in the blood plasma after the start of therapy, as evidenced by the indicators given in Table 6.2. IT on the 4th day after the start of therapy improved by 13.2%, on the 10th day by

20%. TCA on the 4th day was improved by 23.2% and on the 10th day by 26.7% ($p<0.05$).

On the 4th day of dynamic observation, a decrease in the amount of diene conjugates by 11.03% was noted, and by the 10th day by 38.5% from the initial value ($p<0.05$).

The use of complex therapy quickly restored the activity of the system's antioxidants. The concentration of SOD was increased on the 4th and 10th knocks by 27.17 and 47.4% ($p<0.05$). By the last day, SOD corresponded to the control group.

It is important to note that complex therapy of pregnant women with PB allowed to restore the activity of the immune system. A significant improvement in IL1 was observed by 18.21% on the 4th day and 27.31% on the 10th day ($p<0.05$).

The use of complex therapy in pregnant women and threatened PB made it possible to reliably reduce the intensity of lipid peroxidation processes in blood plasma despite the duration of the pathology.

When studying the indicators of metabolic processes, it was revealed that complex therapy reduced their disturbances by the 10th day of the study.

Uric acid was reduced by 24.6% on the 4th day and 37.3% on the 10th day.

RPS and nitric oxide improved on day 4 by 30.4% and 27.1% and on day 10 by 54.5% and 45.1% ($p<0.05$), respectively.

Evaluation of hemostasis parameters in PB against the background of complex therapy revealed that in the first four days of observation, increased coagulation activity and suppression of the fibrinolytic component of the hemostasis system were recorded. The fibrinogen content on the 4th day decreased by 12.0% and on the 10th day by 38.3%.

The use of complex therapy in PB led to the restoration of the state of intrauterine hypoxia of the fetus. At the same time, the result of S-100 protein against the background of complex treatment increased on the 4th day by 43% and on the 10th day by 72.2% compared to the comparison group that received traditional therapy ($p<0.05$).

At the same time, in the group with a complex type of therapy, the number of complications such as fetal hypoxia at birth, postpartum complications, etc. were less common than in the second group.

It should be noted that the inclusion of complex therapy in the early stages of threatened PB allows suppressing intoxication and the activity of lipid peroxidation, restoring antioxidant protection, immunity, and stabilizing metabolic processes.

Pregnancy and childbirth outcomes among the surveyed groups

Analysis of the outcome of births among the study groups: all births in the study groups, regardless of the type of delivery, proceeded without any special features. After conducting complex and traditional therapy, we conducted a comparative analysis, identified and compared the incidence of preterm labor among the 2 groups.

Table 6.3.

Results of birth outcomes among the surveyed groups.

	I group (n=155)	**II group (n=157)**
Premature birth	21,2% (33)	33,1% (52)
Extremely early PB (22-27 weeks 6 days)	3% (1)	9,6 % (5)
Very early PB (28-30 weeks 6 days)	15,1% (5)	17,3% (9)
Early PB (31-33 weeks 6 days)	33,3% (11)	32,6% (17)
Late PB (34-36 weeks 6 days)	48,4 (16)	40,3 (21)
Urgent labor	122 (78,7%)	105 (66,9%)
Childbirth through the natural birth canal	139 (89,7%)	132 (84%)
Childbirth by cesarean section	16 (10,3%)	25 (16%)

- significance of differences P <0.05

According to the results of the analysis of timely and PB, it was revealed that among the studied groups, PB were more often observed in the second group in

women who received traditional therapy in 33.1% of cases, while in the main group PB were observed in 21.2% of cases, which proves the effectiveness of complex therapy and shows a decrease in the number of PB by 11.9%.

In group I, urgent deliveries accounted for 78.7% (122) of cases, and in group II - 66.9% (105).

Based on the results of the analyses of timely and PB, it was revealed that among all the studied groups, births ended more often through the natural birth canal in 89.7% in the first group and 84% in the second.

According to the results of the analysis of timely and PB, it was revealed that among all the studied groups, births ended more often through the natural birth canal in 89.7% in the first group and 84% in the second. By means of cesarean section, 10.3% of the first group and 16% of the second group cases were delivered.

In the PB groups complicated by PRROM, a higher frequency of episiotomy was noted, but no statistically significant differences were found compared to SR. Complications of the third stage of labor were more common in the PR group (Table 6.4).

Table 6.4.

Peculiarities of the birth act in the examined patients (n, %)

Nosological form	Group 1 **(n=139)**	Group 2 **(n=132)**	Group 3 **(n=40)**	p value
Episiotomy	18,6%	23,4%	11,5%	p1=0,0643 p2=0,1811
Manual examination of the uterine cavity	9,3%	6,3%	3,8%	p1=0,5881 p2=0,0507
Blood loss during childbirth (ml)	201 ± 88,4	196 ± 76,2	187 ± 28,2	p1=0,1921 p2=0,6272
Birth injuries (rupture of the cervix, vagina, perineum)	12,8%	15%	2%	p1=0,1881 * p2=0,1507 *

Note: p1 – comparison of groups 1 and 3, p2 – comparison of groups 2 and 3.

- significance of differences P <0.05

Thus, manual examination of the uterine cavity walls and removal of placental

tissue remnants due to placental defects was performed in the first group in 9.3%, in the second 6.3% by groups, respectively. The volume of blood loss did not statistically significantly differ among women in all groups and was: in group 1 201±88 ml, in group 2 – 196±76 ml, in group 3 – 187±28.2 ml.

There were no cases of pathological blood loss or postpartum hemorrhage. When analyzing the postpartum period, anemia was significantly more common among the study groups. Endometritis was diagnosed in only 2.3% of group 1 and 2.1% of group 2. Considering that one of the exclusion criteria for the study was delivery by cesarean section, many women in the study were delivered vaginally. Caesarean section was performed only in emergency conditions of the mother and fetus in 10.3% and 16% of cases (Fig. 6.4.).

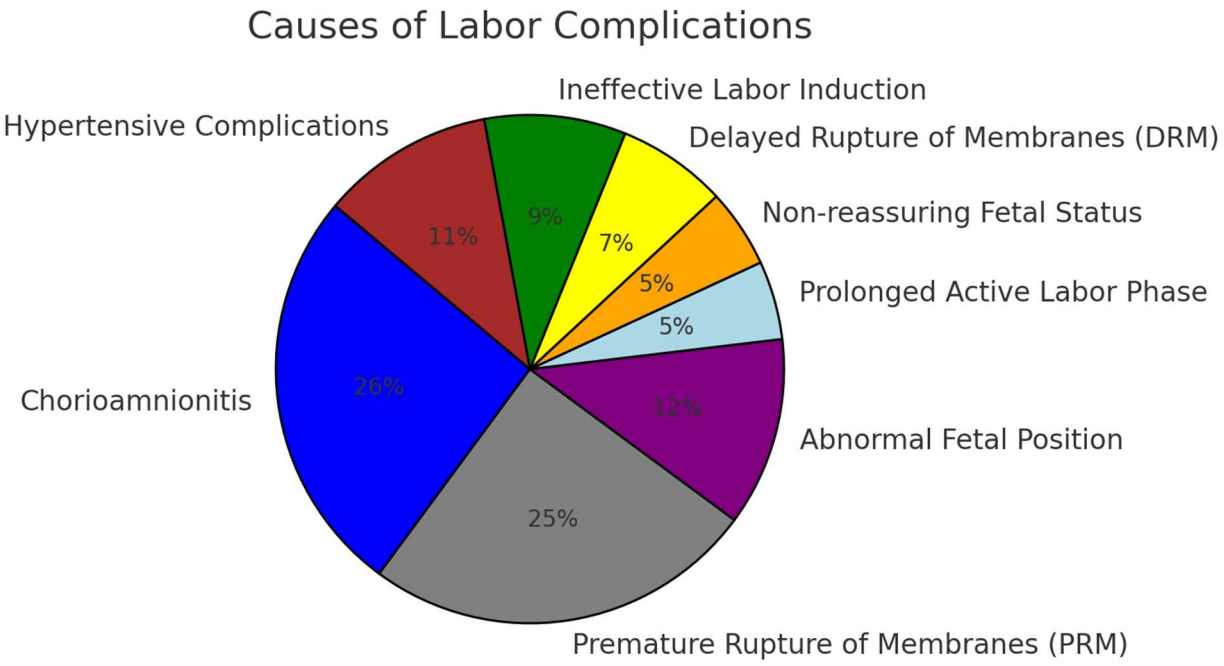


Figure 6.4. Indications for cesarean section

The indications for the operation were: inconclusive condition of the fetus, placental insufficiency, chorioamnionitis, etc. All operations proceeded without any particular complications. After the operation, everyone received traditional preventive therapy.

Perinatal outcomes of preterm birth.

Analysis of the duration of labor through the natural birth canal showed that, in the study, there were rapid births of up to 2 hours.

Newborns were examined after birth and resuscitated when necessary.

Of the 352 newborns born, 85 were premature. Of these, 21.2% of premature newborns were from the first group and 33.1% from the second group (out of 352 mothers in labor).

Of the number of PB (n=85) in the first group (n=33) 38.8%, in the second group (n=52) 61.17% of cases.

Immediately after birth, the condition of premature newborns was assessed using the Silverman scale. The analysis of the assessment of the condition of premature newborns at birth in the 1st and 2nd groups was 5±2.1 and 5±1.5 points at the 1st minute and 6±1.8, / 6±2.9 points at the 5th minute, respectively, while among newborns born on time, the assessment according to the Apgar scale was: at the first minute 7.8±0.20 points, and at the fifth minute - 8.8±0.9 points (Fig. 6.5).

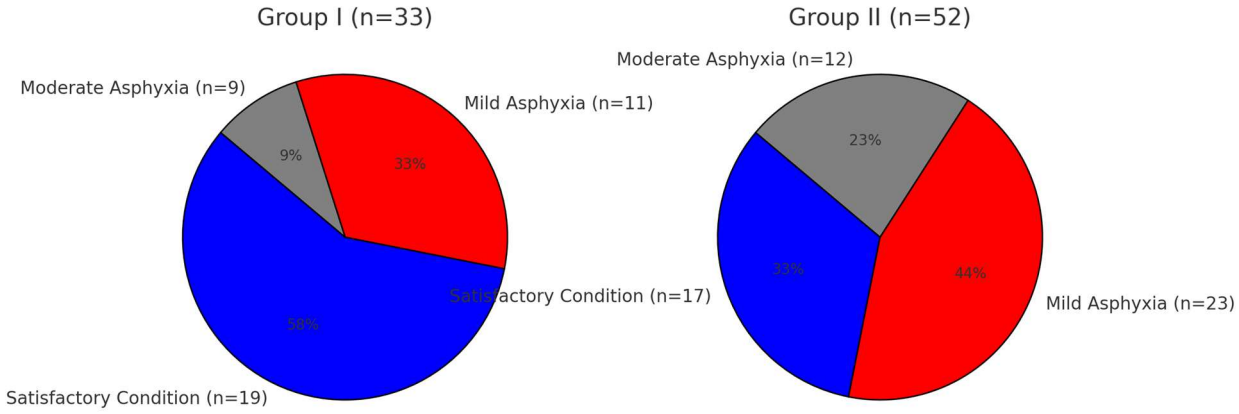


Figure 6.5. Perinatal outcomes of preterm birth

In satisfactory condition were born 57.6% of premature newborns in group I, and 32.6% in group II, in a state of asphyxia of mild severity - 33.3% in group I and 44.2% in group II, respectively, in asphyxia of moderate severity 9% in the first group and 23% of cases in the second group. Newborns born with varying degrees of hypotrophy corresponded to the expected echographic degree of FGRS.

When studying the weight and height indicators of newborns, it was found that the body weight of premature newborns varied from 500 g to 2500 g and was 1861±737 g in group 1 and 1811±693 g in group 2. In group 3, all newborns had an average weight of 3367±351 g. The average length of newborns was 41.0±5.0 cm in the first group, 40.0±6.0 cm in the second group, and 52±2.3 cm in the group of women with a physiological pregnancy.

Transfer to the second stage of nursing was required for 6 newborns from mothers with hyperuricemia, while 100% of newborns from mothers with normal uric acid levels were discharged home in satisfactory condition.

In the study, neonatal mortality was observed in 2.7% (2) of the total number of PBs in the second group, the cause of which was generalized intrauterine infections, neonatal sepsis and acute hypoxia.

Blood was taken from all newborns immediately after birth (from the maternal part of the umbilical cord) to determine the amount of UA and S-100 protein. The results of the study showed a reliable increase in UA and S-100 protein in the umbilical cord blood and in the amniotic fluid in PN more often than in the second group.

Thus, hyperuricemia and decreased S-100 protein are prognostically valuable predictors of the development of preterm labor, fetoplacental insufficiency, FGRS, and fetal hypoxia.

Development of an algorithm for diagnosis, prognosis and management of pregnancy and childbirth in women at risk of premature birth

Based on the data obtained during the study, an algorithm was developed for the diagnosis, prognosis and management of pregnancy and childbirth in women at risk of premature birth (Fig. 6.6).

When a pregnant woman with a risk of premature birth is admitted, it is necessary to conduct a set of clinical, laboratory and instrumental research methods. However, taking into account clinical data remains insufficient for

diagnosis, prognosis and determination of pregnancy and childbirth management tactics in women at risk of premature birth.

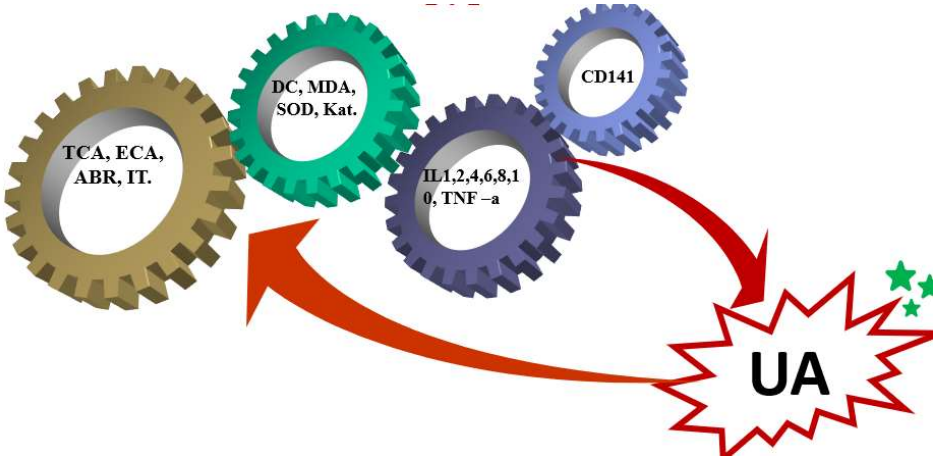
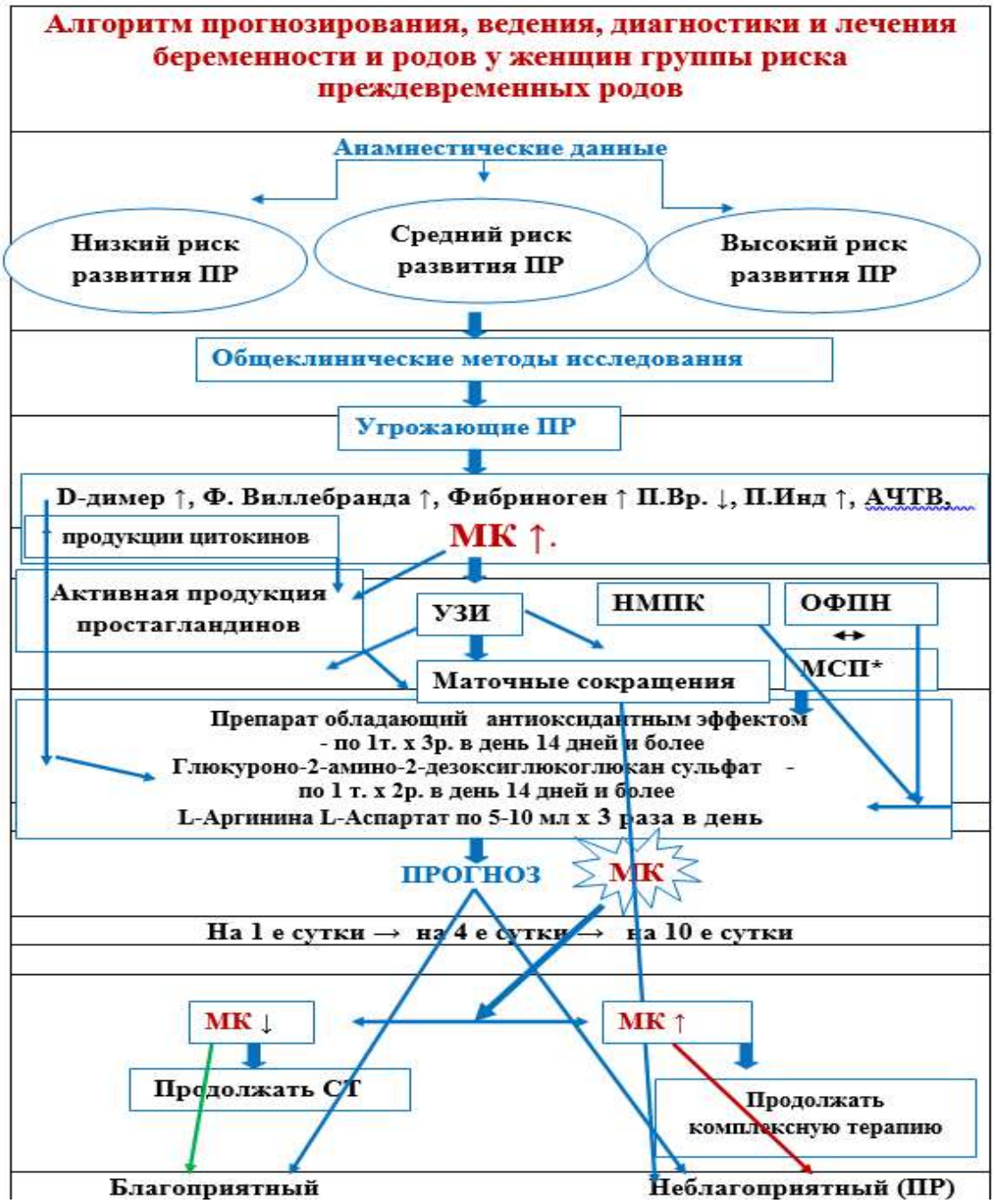


Figure 6.6. Pathogenetic components of PB in hyperuricemia.

At the same time, the results of the studies have shown that the determination of pathogenetic parameters such as TCA, ECA, ABR, IT, DC, MDA, SOD, Kat, IL, CD141, D-dimer can be reliably used in the diagnosis and prediction of the risk of premature birth. However, these parameters have a number of features: technical complexity, high cost, duration of implementation.

We propose to use uric acid as a predictor of diagnosis and prognosis of pregnancy and childbirth in women at risk of premature birth, since it is one of the main links in the pathogenesis of preterm labor.

Regardless of the pregnancy prognosis, additional drugs with antioxidant effect and containing rosmarinic acid, Glucurono-2-amino-2-deoxyglucoglucan sulfate and L-Arginine L-Aspartate, which affect various components of the homeostasis system and antioxidant system, must be included in the therapy.



- The algorithm we propose will help obstetricians and gynecologists to predict, diagnose and correctly treat women with threatened PB accompanied by hyperuricemia.
- After the diagnosis of threatened PB is made, the doctor will be able to determine the degree of risk of developing PB using anamnestic data. After that, it is necessary to conduct general clinical research methods, paying attention to hyperuricemia and the coagulation system.

- The next stage of the algorithm is laboratory and instrumental.
- If hyperuricemia, activation of the coagulation system, fetoplacental insufficiency and uterine hypertonicity caused by activation of prostaglandin production due to cytokine activity are detected, it is proposed to supplement traditional therapy by prescribing drugs with an antioxidant effect, Glucurono-2-amino-2-deoxyglucoglucan sulfate and L-arginine aspartate.
- After the course of therapy we propose, it is necessary to re-evaluate the state of endotoxicosis using uric acid testing, coagulation system activity and ultrasound diagnostics. If the uric acid level is within the normal range, the therapy can be stopped and the prognosis assessed as favorable. If the indicators remain high, it is necessary to continue therapy under the control of a coagulogram, assessing the prognosis as unfavorable.
- To assess fetal endotoxicosis after birth, it is necessary to determine the amount of uric acid in the amniotic fluid and in the umbilical cord blood. If uric acid is within normal limits, then the newborn should be treated according to tradition. If uric acid is increased in the amniotic fluid and umbilical cord blood, then the level of S-100 protein in the blood should be determined. If S-100 protein is decreased, then this condition should be considered as fetal endotoxicosis and traditional therapy should be supplemented with detoxification therapy.

The detection of endotoxicosis in premature babies will allow the development and implementation of methods of treatment and preventive measures in the future.

Chapter conclusions:

Timely hospitalization, identification of risk factors, assessment of the condition of the pregnant woman, timely diagnosis and assessment of laboratory parameters, correctly prescribed therapy, can undoubtedly affect the outcome of pregnancy for both the mother and the fetus, reducing complications that can arise not only during childbirth but also in the early and late neonatal period.

The proposed therapy, which affects various components of the homeostasis system and hyperuricemia, has reduced the incidence of premature birth by 11.9% of cases.

CONCLUSION.

Premature birth is not only a medical problem, but also a socially significant one. The relevance of the problem of premature birth is not in doubt among scientists around the world, primarily due to its significant contribution to perinatal morbidity and mortality rates.

According to the World Health Organization (2018), the incidence of premature births varies from country to country, ranging from 5 to 18%. The risk factors for this complication are varied; genetic, socio-demographic, anamnestic, and the influence of unfavorable environmental factors during pregnancy have been described in the literature [24, 36, 157]. However, it should be noted that for each individual country, its own specific risk factors are of the greatest importance. Thus, for the countries of Southeast Asia and Sub-Saharan Africa, where about 60% of premature births from the global total occur, common infectious diseases against the background of malnutrition and underweight, and the young age of pregnant women are significant. In high-income countries (Northern Europe, Australia, Great Britain), where the rates of premature births are the lowest in the world, extragenital diseases come first, which is associated with the increasing age of women implementing the reproductive function. In addition, in economically developed countries, the contribution of assisted reproductive technologies is significant. That is, a high level of state income does not always lead to low rates of premature births, a striking example of this is the United States of America, they are among the "top ten" countries with the highest rate of premature births.

Thus, the search for the most significant risk factors is a necessary task for each country individually [123, 142, 176]. It is also quite possible that these data will be different for each region of the country [89, 126, 166].

According to the World Health Organization, PB increases perinatal mortality by 4 times, neonatal morbidity by 3 times, and in 40-70% of cases is the cause of death of newborns.

The results of studies conducted to date on a global scale have shown that preterm labor remains the most important problem in obstetrics and gynecology.

Scientists pay much attention to studying the pathogenesis of preterm labor, on the basis of which it would be possible to carry out preventive measures more effectively and successfully (Bolotskikh V.M., 2019)

The American College of Obstetricians and Gynecologists (ACOG, 2020) points out the following risk factors leading to this complication of gestation: previous pregnancy(s) that ended prematurely with premature rupture of membranes; inflammatory diseases of the maternal genital tract and intra-amniotic infection; isthmic-cervical insufficiency; instrumental medical intervention; bad habits and diseases of the mother; abnormalities in the development of the uterus and multiple pregnancies; certain diseases of the mother; injuries.

An important aspect in solving the problem of PB and their prevention is the identification of non-specific regular reactions of the body that initiate termination of pregnancy. The leading pathogenetic factor of various pathological processes in the body is the increased generation of reactive oxygen species (ROS) as a result of the imbalance of pro- and antioxidant systems and the development of oxidative stress [11, 77, 80].

Endogenous intoxication syndrome (EIS) develops in all pathological conditions associated with the blockade of the body's detoxification systems [2,5]. The most informative marker of EI is considered to be the content of substances of average molecular weight (SMW), which include products of nucleotide catabolism, proteins, oligosaccharides, derivatives of glucuronic acids, and oligopeptides (OP), the molecular weight of which does not exceed 10 kD [6]. The accumulation of SMW substances is not only a marker of endointoxication, but, in the future, they aggravate the course of the pathological process due to high biological activity. It is believed that SMW substances have a direct toxic effect on the fetus, causing multiple organ disorders of various natures. An important pathophysiological mechanism for the development of endotoxicosis is the activation of lipid peroxidation processes LPO [1]. In the literature, we have not found data on the relationship between lipid peroxidation processes in the placenta of women whose

pregnancy ended in premature birth and the formation of endogenous intoxication syndrome in it.

According to the literature, about 40% of cases of preterm labor are caused by infectious factors [7,8,10]. The leading pathogenetic mechanism in such cases is the development of a non-specific systemic inflammatory response (SIR) of the body to infectious agents. In the case of SIR syndrome, local tissue damage in the pathogen inoculation zone causes a set of systemic reactions. This process is associated with dysfunction of innate and acquired immunity and is manifested by a violation of the ratio of anti-inflammatory cytokines. Currently, the role of cytokines in the development of preterm labor is being actively studied [11]. Thus, there is evidence that an increase in the level of pro-inflammatory cytokines in the contents of the cervical canal indicates a possible risk of preterm labor [12]. Data on the state of the local immune status make it possible to clarify the molecular biological aspects of the development of various variants of preterm labor.

Pathogenetic causes of PB development are also studied quite deeply, but despite this, the problem of PB remains a social problem of the whole world. In this regard, the issue of more accurate additional pathogenetic mechanisms of premature birth development based on accessible and objective indicators remains relevant. All of the above determines the necessity and relevance of this scientific study.

The problem of the term of premature birth should be discussed separately. There is no doubt that the shorter the gestation period, the worse the prognosis for the newborn. That is why early premature births are singled out as a special group. Identifying risk factors that contribute to termination of pregnancy at 22-27.6 weeks is important for their prediction, and therefore, reducing mortality and disability in children.

In our study, we attempted to identify not only the predictors of preterm birth, but also the circumstances on which its outcome depends.

Now let's move on to the results of our study.

The work was carried out between 2020 and 2023.

The study was conducted at the branch of the center of the Republican Specialized

Scientific and Practical Center for Pregnancy and Maternity Protection in Samarkand.

The analysis, processing and calculation of data were carried out in the department of pathology of pregnant women in the branch of the center of the Republican Specialized Scientific and Practical Center for Pregnancy and Maternity Protection.

The aim of our study was to improve the treatment results for threatened premature birth by developing new methods for predicting and optimizing treatment and preventive measures.

To achieve the set objectives, we conducted a one-stage study.

A prospective study was conducted. It involved 352 women who were divided into 3 groups. I (n=155) is the main group of pregnant women with threatened PB, II (n=157) is the control group of pregnant women with threatened PB, Group III (n=40) is women with normal physiological course of pregnancy and childbirth, delivered on time. In the main 2 groups, all women had hyperuricemia.

Laboratory examination included determination of endogenous intoxication, antioxidant protection, proinflammatory cytokines, reactive proteins, determination of ceruloplasmin, determination of S-100 protein content, nitric oxide, endothelial dysfunction, uric acid study, morphological study of the placenta, statistical analysis.

Prospective study:

To determine one of the causes of the pathogenesis links of PB, we studied 352 pregnant women with threatening PB at the gestational age of 22-34 weeks. Patients were included in the study as they sought help and were hospitalized in the department of pathology of pregnant women.

The following data were analyzed: initial clinical characteristics, features of the pregnancy course, clinical and laboratory examination methods. In accordance with the developed criteria for inclusion in the study.

The age of women varied from 19 to 38 years. The youngest age at the onset of premature birth was 18 years, and the latest was 38 years, averaging 27±2.9 in all groups.

The average height was 164.5±6.8 cm in group I, 165.4±5.9 cm in group II, and 167.2±7.6 cm in the control group.

Body weight – in group I 71.2±11.5 kg, in group II 68.8±10.2 kg and in the control group was 63.4±5.8 kg. Body mass index – in group I 26.8±3.98 kg/m2, in group II 25.1±6.2 kg/m2 and in the control group was 22.6±2.98 kg/m2.

When analyzing the place of residence, urban residents predominated. Social status of the surveyed: students - 18.2%, workers - 40.3%, housewives - 41.5%.

We collected the anamnesis using the developed "Prognostic Matrix for Identifying Risk Factors" (computer program: 03/13/2022 (Agency for Intellectual Property under the Ministry of Justice of the Republic of Uzbekistan No. DGU 2022 1122)) (Fig. 4.3).

It is known that the reproductive and somatic health of women depends on the normal functioning of the menstrual cycle. A comparative analysis of the nature of the menstrual function did not reveal statistically significant differences in the period of formation, duration of menstruation, and duration of the menstrual cycle between the groups studied.

However, it should be noted that for women who gave birth on time, moderate menstrual bleeding was statistically more common, while for groups 1 and 2, heavy menstrual bleeding was statistically more common.

When studying the features of the gynecological anamnesis, it turned out that all nosologies are distributed with approximately equal frequency in all groups without statistically significant differences between the studied groups: salpingo-oophoritis occurred in 12.9% in the first and 28% in the second group, endometritis in 25.8% and 48.4% in the second group. Ectopy of the cervix in 9.7% in the first and 15.2% in the second group.

When studying parity according to inclusion criteria, all women were mostly multigravidas.

The frequency of premature births on average in the first group was 25.9%, and in the second group 26.8% of cases.

The frequency of induced labor was 20% in the first group, 49% in the second

and 12.5% in the third group, spontaneous labor was 70% in the first, 51% in the second and 7.5%, respectively.

In the first group, primiparous women accounted for 12.9%, multigravidas women accounted for 87%, multiparous women accounted for 88.3% in the first group and 100% in the second group.

A study of the gynecological anamnesis showed that miscarriage accounted for 21.9% and 27.3% of observations, respectively. Premature birth in the anamnesis was present in 37.4% of the first and 43.9% of the second group.

The number of abortions in the first group was observed up to 43.2%, in the second 50.4% of cases, of which non-developing pregnancy - 20.6% and 41.2%, spontaneous miscarriage 22.5% and 58.7% of cases.

Hypertensive conditions - 51 (32.9%) and 69 (43.9%), intrauterine manipulations 10% and 17.8%, respectively.

Thus, it is noted that the factors of high risk of threat of termination of pregnancy and premature birth are the first pregnancy, first birth, history of miscarriage, various types of termination of pregnancy (spontaneous, medical), inflammatory diseases. They can negatively affect the course of pregnancy.

When analyzing concomitant diseases, it was found that iron deficiency anemia (IDA), myopia, and varicose veins of the lower extremities were significantly more often diagnosed in women in the study groups.

From the ultrasound data, the following parameters were analyzed in the study during abdominal echography: uterine tone, amount of amniotic fluid, placenta condition, cervical length (CL) in mm, and fetal condition.

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

From the ultrasound data, parameters such as uterine tone, amount of amniotic fluid, condition of the placenta, hemodynamics and condition of the fetus were analyzed during abdominal echography.

For the analysis, 352 pregnant women were divided into 2 groups. The first

main group included 312 pregnant women with threatened PB and the second control group included 40 pregnant women with a physiological course of pregnancy.

In the main group, uterine tone was observed in 99%, FGRS was observed in 27.8%, increased placental thickness – 26.2%, widening of the intervillous space – in 84.9% and early aging of the placenta – in 58.0% of cases, which is directly informative for diagnosis, preventive measures and treatment tactics.

Circulatory disorders in the "mother-placenta-fetus" system in the groups were high. In the main group, stage I B occurred in up to 42.9% of cases, stage I A - in 23.3% of cases, stage II - in 18.5% of cases.

Circulatory disorders in the mother-placenta-fetus system, determined by Doppler ultrasound, ultimately lead to FGRS.

With regard to fetoplacental hemodynamic disorders, comparison of the groups also demonstrated the existence of statistically significant differences between patients at 22-27 weeks 6 days and 28-30 weeks 6 days ($p=0.037^*$), as well as between 22-27 weeks 6 days and 37-41 weeks 6 ($p=0.019^*$).

Placental development occurs in stages. With insufficient uteroplacental blood circulation, in response to moderate hypoxia, excessive proliferation of vessels is observed in the placenta, i.e. compensatory angiomatosis is formed, which helps compensate for placental insufficiency. With severe hypoxia, the development of the villous tree is disrupted in the placenta, and fetoplacental insufficiency develops following uteroplacental insufficiency [98, 142]. Beginning in the second trimester, Doppler ultrasound can detect fetoplacental hemodynamic disorders. Critical fetoplacental hemodynamic disorders are considered as indications for labor induction. In our study, the highest incidence of these disorders was noted in the group of early premature births. This is natural, since the highest incidence of uteroplacental hemodynamic disorders was found in this group, and the described Doppler ultrasound features are successive stages of placental insufficiency development.

The most severe form of fetoplacental insufficiency, indicating the depletion of the compensatory capabilities of the placenta, is fetal growth retardation [33, 92,

173]. This condition may serve as an indication for induction of labor to prevent intrauterine fetal death. According to our data, statistically significant differences in patients with premature birth.

In studying the role of the placenta in the implementation of premature birth, the results of pathomorphological studies of placentas in the studied cohort were considered. Among the morphological changes, pathological immaturity of the villi and circulatory disorders were identified. Villous tree maturation disorder occurs as a result of hypoxia and is characterized by a decrease in the diffusion surface of the villi, i.e. the structure of the placenta does not meet the needs of the fetoplacental complex. In our study, pathological immaturity was represented by dissociated villous maturation disorder, obliterative angiopathy, and chorangiomatosis. Dissociated villous maturation disorder was observed in all groups of premature births with the highest frequency of occurrence in the groups of very early and early births. Obliterative angiopathy was recorded in more than 50% of cases of premature births up to 34 weeks. As for chorangiomatosis, it was noted only in very early births. All the described conditions are morphological reflections of placental insufficiency [15, 49, 66].

Signs of circulatory disorders in the placenta were found in more than half of all cases of premature births, in early births they accounted for 95%, the differences from term births were statistically significant P (<0.05*). It can be assumed that the depletion of the placenta's ability to meet the needs of the fetus leads to premature delivery.

Our study noted a high frequency of histologically confirmed chorioamnionitis in the group with PB. Probably, leukocyte infiltration is associated not with the influence of infection, but with the release of proinflammatory cytokines (IL-6), stress hormones necessary for the normal course of the placental and early postpartum period - separation of the placenta, protection of the placental site from the introduction of microorganisms [13, 59, 164].

When assessing the frequency of deciduitis in the study groups, it turned out that it was statistically significantly more often detected in the group of early PB (81.7%) compared to the groups of late births.

When studying the signs of hematogenous infection, it is necessary to dwell on the inflammation of the placental villi. According to our study, villusitis occurred only in premature births. The highest frequency was found in the PB group (above 50.0%).

Hematogenous damage to the umbilical vessels deserves special attention, since it is often accompanied by fetal infection. The vein is damaged first due to its thinner wall. According to our data, umbilical cord phlebitis was most often detected in very early births (26.8%), was absent in term births, and was detected in the remaining groups of premature births only occasionally, but statistically significant differences were found only between the groups of early and late premature births. The umbilical artery is damaged secondarily in hematogenous infection, so in our study the incidence of arteritis was lower than that of phlebitis. According to our data, arteritis was detected mainly in the group of premature births.

Thus, our results are consistent with literature data [47, 86, 129] on the significance of the infectious factor in the development of premature birth.

In general, the analysis of the results of pathomorphological studies of placentas allowed us to conclude that the duration of pregnancy is determined by the compensatory and adaptive capabilities of the placenta. Premature delivery is facilitated by morphological manifestations of placental insufficiency formed in the 1st and 2nd trimesters of pregnancy under the influence of unfavorable environmental factors.

Thus, dissociated disruption of villous maturation, circulatory disorders in the placenta, the presence and severity of compensatory-adaptive reactions, obliterative angiopathy, chorangiomatosis, phlebitis and arteritis can contribute to very early and early premature births.

We have shown that against the background of the development of PB, significant disturbances in the homeostasis system are recorded, which coincides

with the literature data [73, 97, 125, 146]. It has been revealed that pregnant women experience the development of intoxication, decompensation of detoxification systems, activation of lipolytic enzymes, lipid peroxidation, systematization of the inflammatory response, leading to metabolic disturbances of internal organs, such as hemostasis, etc.

A number of indicators were considered as a biochemical marker, with uric acid being an “acute phase” protein, meaning that its synthesis rapidly increases under the influence of metabolic processes during pregnancy.

Premature birth is the result of the combined action of unfavorable endogenous factors.

It has been found that the state of endotoxicosis aggravates the course of pregnancy, especially in case of gestosis. Until now, there is no single point of view regarding the significance of endotoxicosis in pregnancy pathology.

Taking these facts into account, it became appropriate to identify new pathogenetic processes of this condition.

When studying the data of the biochemical study, it was revealed that the effective and total albumin concentration (EAC, TCA) were reduced relative to the control group. In the control group, ECA was 26.8 IU/ml, in the main first group it was reduced to 18.1 IU/ml, and in the second group 22.4 IU/ml. In the control group, TCA was 38.5, and in the main first group it was reduced by 27.2 IU/ml, in the second group it was reduced to 30.5 IU/ml.

TheABR indicator was also reduced by 0.71; 0.87 g/l in women of the first group compared to the control group ($p<0.05$).

The plasma toxicity index among women in the main group exceeded that in the control group by 21.1% ($p<0.05$).

Thus, the development of premature birth is accompanied by the formation of endogenous intoxication in pregnant women. With a high risk of preterm labor and the threat of interruption, the intensity of toxemia was recorded to the greatest extent relative to other women who gave birth prematurely and on time.

Studying the state of the pro- and antioxidant systems, it was found that,

according to literature, the development of endogenous intoxication is accompanied by the activation of lipid peroxidation processes [5, 89].

Taking these facts into account, it seemed appropriate to find out whether local activation of lipid peroxidation processes in the "mother-placenta-fetus" system occurs in women at risk of preterm pregnancy against the background of systemic activation of free radical oxidation processes.

To partially resolve this issue, a comparative assessment of the lipid peroxidation process (DC, MDA) indicators in the venous blood of pregnant women was conducted. It was noted that the content of diene conjugates (DC) in the blood plasma of women with threatening premature birth was increased. Thus, in the main two groups, the concentration of DC was the highest - higher than in the control group ($p < 0.05$).

It was found that the content of malondialdehyde (MDA) in the blood plasma during threatened PB was highest in the first group 7.73 (μmol/l), in the second group 7.59 (μmol/l), in the control group 5.8 (μmol/l), ($p<0.05$).

In recent years, an important role in the pathogenesis of PR development has been given to systemic inflammatory response syndrome (SIRS) and oxidative stress. The development of oxidative stress is caused by an imbalance between the generation and elimination of reactive oxygen species (ROS). Our research results showed that the content of lipid peroxidation products in the blood plasma of pregnant women in the control group was 41.54±3.67 μmol/l. It was noted that with disease progression, the content of TBA-active products significantly increases, 78.14±6.89 μmol/l in pregnant women of group II versus 41.54±3.67 μmol/l in healthy pregnant women ($p<0.05$).

An increase in the level of toxic lipid peroxidation products in the blood of pregnant women with threatened PB is certainly 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, and disturbances in the coagulation potential of the blood, which naturally accompany miscarriage of various etiologies.

Simultaneously with the activation of oxidative processes, there is an increase in the activity of blood catalase in pregnant women of group I to 13.57±1.56 kat/l, in group II to values of -11.32±1.27 kat/l, against 7.98±0.81 kat/l in the control group, which indicates an increase in the antioxidant activity of the blood ($p<0.05$). An increase in the activity of blood catalase in patients of group II indicates the depletion of the antioxidant defense system, which is indirectly confirmed by the activity of SOD and the content of TBA-active products in this group, compared with the control. A decrease in SOD activity in group I by 45%, in group II by 64% is noted compared with healthy pregnant women. There are also suggestions that it is the consequences of decompensation of antioxidant defense that contribute to the accumulation of lipid peroxidation products ($p<0.05$).

These changes can be explained by the fact that in healthy pregnant women, activation of LPO processes leads to activation of the antioxidant defense system, but these processes are in balance with each other and are not accompanied by clinically significant damage. It is known that even normal pregnancy initiates some degree of oxidative stress. In the case of premature birth, an imbalance is observed between prooxidant and antioxidant forces towards the predominance of prooxidants, leading to damage to cells, tissues, and primarily the endothelium (Ailamazyan, Mostovaya, 2008).

As is known, catalase begins to work at high concentrations of H2O2, which is not observed during normal pregnancy. Since these disorders lead to an imbalance between oxidative and reductive processes in the peripheral blood and tissues, accumulation of lipid peroxidation products, products of covalent modification of proteins, a decrease in the efficiency of energy-converting mitochondrial membranes and an increase in the number of damages to nuclear and mitochondrial DNA.

Thus, one of the pathogenetic factors of PR is the activation of free-radical destabilization processes of biological membranes, accompanied by an excessive increase in the content of peroxide compounds in the blood, as well as malonic dialdehyde, diene conjugates and catalase with a pronounced universal cytopathogenic effect and a decrease in the amount of SOD.

Assessment of the state of the cytokine system.

In the last decade, active scientific research has been conducted to study the role of cytokines in the development of premature birth (PB). Being biologically active factors, cytokines primarily regulate the development of local protective reactions in tissues with the participation of various types of blood cells, endothelium, connective tissue and epithelium.

We examined 35 women in the II and III trimesters of the gestation period with physiologically progressing pregnancy - the control group. It was found that in women of the control group, the level of cytokine IL-1β in the blood serum was 2.15±0.18 pg / ml, IL-2 - 11.14±0.91 pg / ml, IL-4 - 3.58±0.19 pg / ml, IL-6 2.38±0.19 pg / ml, IL-8 - 5.42±0.51 pg / ml, IL-10, - 22.48±1.96 pg / ml, and the level of TNF-α was within 1.76±0.14 pg / ml.

In pregnant women at risk of premature birth, the IL-8 level was increased by 1.5 times in Group I patients and by 2 times in Group II patients relative to the control group ($p<0.05$). A high level of spontaneous IL-8 production may indicate significant activation of mononuclear phagocytes, producers of proinflammatory cytokines, which play an important role in the development of immunopathological processes. The obtained data on the increase in IL-1β and IL-8 reflect the activity of the inflammatory process. An increase in the concentration of proinflammatory cytokines indicates that in this contingent of pregnant women, the inflammatory reaction has systemic manifestations. At the same time, IL-1 stimulates the release of band neutrophils from the bone marrow, increases the formation and release of collagenase, causes the expression of endothelial-leukocyte adhesion molecules (ELAM) on the surface of endothelial cells and leukocytes, promotes the marginal position of leukocytes and stimulates the process of their emigration.

As our research results have shown, pregnant women at risk of premature birth have an increase in the IL-6 serum content by 1.5 times in the first and 2 times in the second compared to healthy pregnant women. Due to the violation of the placental barrier, a large amount of antigenic material of fetal origin enters the mother's circulation. This leads to the induction of an inflammatory response from the maternal immune system with the production of a large amount of IL-6 and TNF-α, which causes a high level of trophoblast apoptosis. In addition, IL-6 stimulates the production of reactive proteins, which leads to remodeling of the cervix and the development of labor.

According to our data, in pregnant women with risk of preterm delivery, serum TNF-α level increases by 1.5 times in the first and 1.7 times in the second compared to control data ($p<0.05$). As is known, TNF-α is formed by tissue macrophages, monocytes and lymphocytes in the area of acute inflammation, enhances the main functions of leukocytes, stimulates the release of histamine by basophils and mast cells, causes activation of fibroblasts, smooth myocytes and vascular endothelium in the inflammation focus, induces the synthesis of acute phase proteins. Hypersecretion of TNF-α leads to a significant increase in the number of apoptotic trophoblast cells, which can be one of the factors contributing to miscarriage. It has been established that during normal pregnancy, the cytokine status shifts towards immunosuppressive cytokines (IL-4, IL-10, TGF-β), which inhibit cellular immune responses and stimulate the production of blocking antibodies.

It has been established that during normal pregnancy, the cytokine status shifts towards immunosuppressive cytokines (IL-4, IL-10, TGF-β), inhibiting cellular immune responses and stimulating the production of blocking antibodies. In our study, the level of anti-inflammatory cytokines IL-4 and IL-10, respectively, was significantly lower by 1.5 and 2.4 times in the first group and 0.6 and 3 times in the second group. In this situation, the most informative were the IL-10 indicators, low values of which can serve as a marker of the risk of developing preterm labor.

Therefore, pregnant women at risk of premature birth experience significant disturbances in the cytokine system, which may be accompanied by the penetration of proinflammatory cytokines into the systemic circulation, which in our opinion contributes to the pathogenesis of premature birth. In addition, an increase in TNF-α and cytokines can serve as markers of inflammation of the uterine vascular endothelium, and also indicate high permeability of the membranes of the fetal membranes, which in our opinion is one of the causes of the mechanisms of premature birth and rupture of amniotic fluid.

Thus, the results of our study allow us to state that the study of cytokine balance is significant for assessing the direction of the immune response, as well as the outcome of pregnancy for the mother and fetus.

The state of the reactive proteins of the body.

The development of threatening premature birth with changes in the immune system was accompanied by an increase in the content of state reactive proteins (SRP) in the first group to 5.87±0.19 mg/l (↑1.7), in the second group to 5.15±0.16 (↑1.5) mg/l, compared to the control group in women with threatened PB ($p<0.05$).

When studying nitric oxide, it was noted that in women with threatened PB in the main group, the value of nitric oxide exceeded the control group. In the first 86.1±3.4 ppb; in the second 89.5±3.1 ppb compared to the control group.

Increased nitric oxide accompanied by cytokine activity can be considered one of the predictors of PB.

It is known that in addition to its copper-binding function, ceruloplasmin has significant antioxidant activity and is involved in the neutralization of peroxides.

As the results of our study showed, in the first group the level of ceruloplasmin was reduced to 12.6±0.4 mg/dl, which is ↓ 1.6 times less, and in the second group it was reduced to 10.4±0.31 mg/dl, which is ↓ 1.9 times less compared to the control group (Fig. 5.6), which indicates a decrease in the antioxidant system and may be the cause of PB.

It is currently known that S-100 is a calcium-binding protein and is involved in the processes of cell division, differentiation and death. A comparative analysis

of the S-100 protein level in the serum of pregnant women showed a tendency for it to decrease in groups I and II compared to patients in the control group. The average content of S-100 protein in the blood serum of women in the control group was 40.9±5.08 ng/ml, while in the first group it was reduced to — 8.80±0.41 ng/ml, in the second group 7.90±0.21 ng/ml (>0.05).

Serum S-100 levels equal to or less than 32.55 ng/ml are also a new prognostic criterion for PTB and increase the risk of their occurrence after a threatened miscarriage at 22–34 weeks by 4.6 times.

The nature of the violations of the hemostasis system parameters.

Numerous studies have shown that elevated levels of oxidized lipoproteins during oxidative stress lead to endothelial damage.

As can be seen from the obtained research results, pregnant women with the risk of premature birth have an increase in the sum of active forms of platelets relative to the control values by 24% ($p<0.05$). The increase in the sum of active forms of platelets in pregnant women of the main group was combined with an increase in the number of platelets involved in aggregates by 1.6 times. It is possible that the damaging effect of the detected disorders in the risk of termination of pregnancy on the damage of the vascular wall and the development of a thrombophilic state. Meanwhile, the determination of vascular wall damage factors in the blood is an indirect method for assessing the severity of endothelial dysfunction. Such factors include: von Willebrand factor, fibronectin, thrombomodulin.

When studying the content of the most significant factors of endothelial damage (von Willebrand factor and fibrinogen), a reliable increase in the latter was noted when compared with the control group, respectively, von Willebrand factor by 1.3 times, and fibrinogen by 1.4 times. The identified changes in the dynamics of adhesive proteins play an important role in increasing the adhesive-aggregation properties of platelets.

Thus, in pregnant women at risk of premature birth, we observe, against the background of dysfunction of endothelial cells, an increase in the anticoagulant

activity factor. This condition apparently leads to depletion of the level of natural anticoagulant, antithrombin III, in the blood and is one of the reasons for the development of thrombophilic state and thrombotic complications in premature birth.

It is extremely important to study the content of anticoagulant potential indicators in the blood of pregnant women at risk of preterm birth.

The study of the hemostasis system demonstrated that premature birth is characterized by changes in the coagulation and fibrinolytic activity of the blood in the form of hypercoagulation and hypofibrinolysis.

In women in the first main group, a shortening of the APTT and PT time by 33.3 and 31.2% ($p<0.05$) was noted relative to the control group; in the second group, the APTT and PT were lower than the control group by 20.1 and 25.4% ($p<0.05$).

When studying the process of fibrinolysis in PB, it was revealed that the amount of fibrinogen was exceeded in groups 1 and 2 by 51.8, 39.4 and 26.9% ($p<0.05$) when compared with the control group.

Our findings of a significant association between maternal serum uric acid levels, supported by studies demonstrating free transfer of uric acid across the placenta in pathologies [6], suggest that elevated uric acid levels may be the real etiology of these adverse outcomes.

These changes are associated with the intensification of intravascular blood coagulation processes, including in the uteroplacental blood flow.

Evaluation of the content of purine metabolism product.

Increased serum uric acid concentrations occur as a physiological response to increased oxidative stress during pregnancy, providing a counter-regulatory boost to antioxidant defenses. Uric acid is the end product of purine catabolism, which acts as an antioxidant and reduces DNA damage at physiological concentrations. However, high uric acid concentrations may promote inflammation and endothelial dysfunction. High levels of maternal uric acid can diffuse to the placenta, enter the fetal circulation, cause placental inflammation and dysfunction, and ultimately

impair fetal development. Furthermore, uric acid can initiate inflammatory cascades by increasing the production of monocyte chemoattractant protein-1, IL-1β, IL-6, and tumor necrosis factor TNF-α. Elevated uric acid concentrations can alter endothelial function, health, and repair. Several studies show that uric acid impairs nitric oxide (NO) production in vascular endothelial cells, a key pathogenic event preceding the development of cardiovascular disease. Also, in late pregnancy, uric acid crystals activate the nodular receptor protein-3 (NLRP3) inflammatory pathway via the IL-1-dependent pathway, causing inflammation at the placental interface and affecting fetal development.

As we stated earlier, uric acid is a well-known marker of tissue damage, oxidative stress. Based on the above, high values of serum uric acid are observed in pregnant women at risk for preterm birth. If so, uric acid should be increased before the syndrome becomes clinically evident. Hyperuricemia is one of the earliest and generally consistent observations noted in preterm birth risk. Although elevated circulating uric acid concentrations are not always observed in every woman at risk for preterm birth, they appear to identify a subset of women with preterm birth who are at greater risk of maternal and fetal morbidity. This study was designed to compare serum uric acid values in pregnant women at risk for preterm birth and normal pregnant women and its relationship with several vital maternal and fetal outcomes.

To study this issue, we decided to investigate the level of uric acid in various substrates in pregnant women at risk of premature birth at 22-34 weeks of gestation in the entire study group.

The present examination was conducted with a total of 352 pregnant women; of these, Group I (n=155), Group II (n=157), Group III (control, n=40) – 40 pregnant women with a physiological course of pregnancy and delivery, delivered on time were examined. Selection criteria: arterial hypertension, no history of urinary tract infection. Absence of any other medical complications (cardiovascular diseases, renal diseases, collagen vascular diseases) associated with preeclampsia.

To study this issue, we decided to investigate the level of uric acid in various

substrates in pregnant women at risk for premature birth at 22-34 weeks of gestation in all study groups.

We have created a computer program “Uric acid as a trigger mechanism for premature birth” (computer program: (Intellectual Property Agency under the Ministry of Justice of the Republic of Uzbekistan No. DGU 2023 2915 06.05.2023)).

Elevated uric acid levels may occur as a protective response to limit the harmful effects of free radicals and oxidative stress.

Determination of uric acid in the blood serum of pregnant women at 22-34 weeks of gestation with threatened PB (before treatment) showed that the uric acid content upon admission to the hospital in the first group was increased by 1.3 times compared to the control group, in the second group by 1.3 times compared to the control group ($P < 0.05^*$).

After the proposed therapy, there was a significant improvement in these indicators.

In the first group, the average improvement in the endotoxicosis index was 115.24 μmol/l, in the second group it remained unchanged, which is of no small importance for the prognosis and prevention of this pathology.

The next objective of the study was to examine the level of uric acid in the amniotic fluid.

The question we were faced with was: What changes does the biochemical profile of amniotic fluid undergo when uric acid in the mother's blood increases, and is there a connection between them?

To address this issue, the biochemical profile of the amniotic fluid composition was examined in women with endotoxicosis who had PROM upon admission, during labor, and among the control group in whom labor occurred on time.

As can be seen from the presented research results, the content of uric acid in amniotic fluid has its own dynamics and concentration.

As the results of the biochemical profile showed, the content of uric acid in the amniotic fluid in women of the 1st group was increased by a small amount compared to the second group (1.2 times).

According to the tasks set, we were faced with a survey on how uric acid affects the fetus? Does uric acid pass through the feto-placental barrier?

To address this issue, we examined the level of uric acid in amniotic fluid and in cord blood serum in all groups, in the early postpartum period in pregnant women with premature and full-term births.

We observed significant changes in the content of uric acid in the cord blood in pregnant women of the study groups insignificantly in the first and 1.3 times more in the second group compared to the control group. Apparently, the identified changes in the level of uric acid in various substrates, in our opinion, are due to metabolic disorders in the body of the examined pregnant women and there is a significant relationship between the levels of uric acid in the mother, in the serum of umbilical cord blood and amniotic fluid, which most likely leads to deep endotoxicosis and causes premature birth.

Thus, analyzing the results of the studies, we can conclude that with UPR, in the blood plasma of women, there is a pronounced intensification of endogenous intoxication processes in the form of lipid peroxidation, hemostasis system disorders, cytokine intensification, immune system and reactive proteins. It should be noted that the maximum changes in the homeostasis system and hyperuricemia in various substrates were found in pregnant women with a high risk of PB and with threatened PB, the cause of which is deep endotoxicosis.

When studying the data of a prospective study, it was established that the first pregnancy, repeated births, miscarriage, history of non-developing pregnancy, medical abortion, inflammatory diseases of the reproductive system, etc. are risks of premature birth. When hospitalizing patients with a risk of threat and premature birth, significant changes in the homeostasis system, disturbance of uteroplacental and fetoplacental hemodynamics were noted.

However, to identify the real risk factors for PB, the activities of the most important components of the homeostasis system were determined, such as the presence of endotoxicosis, activation of lipid peroxidation, antioxidant protection, cytokine intensification, the state of the body's reactive proteins, the content of purine metabolism products, and the stability of the hemostasis system.

The results of the prospective study showed that the above changes were registered not only in pregnant women, but also in fetuses.

In the early stages of premature labor, pregnant women experience endogenous intoxication (decrease in TCA, ECA, RSA, and increase in IT), pronounced intensification of lipid peroxidation processes (increase in DC, MDA), and decrease in antioxidant protection (decrease in SOD, Kat). These processes contribute to the progression of pregnancy and lead to intensification of the cytokine system (increase in IL-1,2,4,6,8,10, TNF-a, systematization of the inflammatory process (increase in RPS, nitric oxide, S-100, decrease in ceruloplasmin), activation of purine metabolism (increase in uric acid). At the same time, disturbances in the activity of the coagulation system (decrease in APTT), fibrinolysis (increase in fibrinogen) are recorded.

Moreover, changes in the homeostasis system were associated with the duration of PB.

It is safe to say that UA is the final and final parameter of the pathogenetic mechanism of PR, which can be used as a predictor of prognosis and prevention of complications in this pathology. This is confirmed by the value of correlation analysis.

Currently, many schemes of complex treatment of threatened PB have been proposed. But to date, there are no proposed complex treatment schemes for threatened PB with progressive intoxication and hyperuricemia.

In this regard, we propose a new method for correcting intoxication, homeostasis disorders and hyperuricemia in threatened PB, the spectrum of which, as noted above, is extremely wide, taking into account its ability to correct disorders in various organs and systems.

After a complete clinical and laboratory examination, pregnant women with UPR of the second group were prescribed traditional pregnancy-preserving therapy. Pregnant women of the first group (the main one) were recommended to use the proposed course of treatment in addition to traditional therapy + drugs **with an antioxidant effect and containing rosmarinic acid**, which reduces uric acid within 12 hours after taking 1 tablet 3 times a day (in our study, we used Canephron H50) + **Glucurono-2-amino-2-deoxyglucoglucan sulfate**, 1 tablet 2 times a day (in our study, we used Sulodoxide 250 LE (lipoprotein lipase units)) (according to the coagulogram indicators) and (suppresses the proliferation of smooth muscles of the vascular wall, promotes the restoration of the structure and function of vascular endothelial cells, normalizes the rheological properties of the blood), and **L-Arginine L-Aspartate** 5-10 ml x 3 times a day (has antihypoxic, membrane-stabilizing, cytoprotective, antioxidant, detoxifying effect, has an acid-forming effect and helps correct acid-base balance) if there is FI.

A diet (plenty of fluids), iodine preparations 200 mg, iron preparations, ascorbic acid 0.1 g 3 times a day for 20 days, progesterone 200 mg 2 times a day until 36 weeks of pregnancy, nifedipine 10 mg orally every 30 minutes (maximum single dose 40 mg) were prescribed. Then - 10 mg every 8 hours orally for no more than 48 hours from the start of therapy under the control of blood pressure, indomethacin 100 mg 1 supp. x 1 time per day for 10 days.

The analysis of the results of the therapy was assessed on the 1st, 4th, and 10th days of hospitalization using laboratory research methods.

On average, 76% of women in both groups noted clinical improvement.

However, it was revealed that against the background of the use of a traditional therapeutic course in the second group (1st, 4th, 10th day of hospitalization), homeostasis parameters remained abnormal.

On the contrary, the use of complex therapy in pregnant women of the first group with threatened PB in addition to traditional therapy allowed in the early stages to: reduce the severity of endogenous intoxication, the activity of lipid

peroxidation, improve the state of immune activity, restore blood hemostasis, the fibrinotic system and hyperuricemia.

The complex of therapeutic measures for threatened PB in the main group allowed to significantly reduce the intensity of endotoxicosis indicators in the blood plasma after the start of therapy, as evidenced by the indicators given in Table 6.2. IT on the 4th day after the start of therapy improved by 13.2%, on the 10th day by 20%. TCA on the 4th day was improved by 23.2% and on the 10th day by 26.7% ($p<0.05$).

On the 4th day of dynamic observation, a decrease in the amount of diene conjugates by 11.03% was noted, and by the 10th day by 38.5% from the initial value ($p<0.05$).

The use of complex therapy quickly restored the activity of the system's antioxidants. The concentration of SOD was increased on the 4th and 10th knocks by 27.17 and 47.4% ($p<0.05$). By the last day, SOD corresponded to the control group.

It is important to note that complex therapy of pregnant women with PB allowed to restore the activity of the immune system. A significant improvement in IL1 was observed by 18.21% on the 4th day and 27.31% on the 10th day ($p<0.05$).

The use of complex therapy in pregnant women with threatened PB made it possible to reliably reduce the intensity of lipid peroxidation processes in blood plasma despite the duration of the pathology.

When studying the indicators of metabolic processes, it was revealed that complex therapy reduced their disturbances by the 10th day of the study.

Uric acid was reduced by 24.6% on day 4 and 37.3% on day 10.

RPS and nitric oxide improved by 30.4% and 27.1% on day 4 and by 54.5% and 45.1% on day 10 ($p<0.05$), respectively.

Evaluation of hemostasis parameters in PB against the background of complex therapy revealed that in the first four days of observation, increased coagulation activity and suppression of the fibrinolytic component of the hemostasis system were

recorded. The fibrinogen content on the 4th day decreased by 12.0% and on the 10th day by 38.3%.

The use of complex therapy in PB led to the restoration of the state of intrauterine hypoxia of the fetus. At the same time, the result of S-100 protein against the background of complex treatment increased on the 4th day by 43% and on the 10th day by 72.2% compared to the comparison group that received traditional therapy ($p<0.05$).

At the same time, in the group with a complex type of therapy, the number of complications such as fetal hypoxia at birth, postpartum complications, etc. were less common than in the second group.

It should be noted that the inclusion of complex therapy in the early stages of threatened PB allows suppressing intoxication and the activity of lipid peroxidation, restoring antioxidant protection, immunity, and stabilizing metabolic processes.

Analysis of the outcome of births among the study groups: all births in the study groups, regardless of the type of delivery, proceeded without any special features.

After conducting complex and traditional therapy, we conducted a comparative analysis, identified and compared the incidence of preterm labor among the 2 groups.

According to the results of the analysis of timely and PB, it was revealed that among the studied groups, PB were more often observed in the second group in women who received traditional therapy in 33.1% of cases, while in the main group PR were observed in 21.2% of cases, which proves the effectiveness of complex therapy and shows a decrease in the number of PB by 11.9%.

In group I, urgent deliveries accounted for 78.7% (122) of cases, and in group II 66.9% (105).

Based on the results of the analyses of timely and PB, it was revealed that among all the studied groups, births ended more often through the natural birth canal in 89.7% in the first group and 84% in the second.

In the PR groups complicated by PRROM, a higher incidence of episiotomy

was noted, but no statistically significant differences were found compared to SR. Complications of the third stage of labor were more common in the PR group.

Caesarean section was performed only in emergency conditions of the mother and fetus in 10.3% and 16% of cases.

Indications for cesarean section were: inconclusive condition of the fetus, placental insufficiency, chorioamnionitis, etc. All operations proceeded without any particular complications. After the operation, everyone received traditional preventive therapy.

Perinatal outcomes of preterm birth.

Analysis of the duration of labor through the natural birth canal showed that, in the study, there were rapid births of up to 2 hours.

The newborns were examined after birth and resuscitated if necessary.

Of the 352 newborns born, 85 were premature. Of these, 21.2% of premature newborns were from the first group and 33.1% from the second group.

Immediately after birth, the condition of premature infants was assessed using the Silverman scale. The analysis of the assessment of the condition of premature infants at birth in groups 1 and 2 was 5±2.1 and 5±1.5 points at the 1st minute and 6±1.8, / 6±2.9 points at the 5th minute, respectively, while among newborns born on time, the assessment according to the Apgar scale was: at the first minute 7.8±0.20 points, and at the fifth minute - 8.8±0.9 points.

When assessing the degree of asphyxia, it was found that asphyxia was more common in the second group.

In satisfactory condition were born 57.6% of premature newborns in group I, and 32.6% in group II, in a state of asphyxia of mild severity - 33.3% in group I and 44.2% in group II, respectively, in asphyxia of moderate severity 9% in the first group and 23% of cases in the second group. Newborns born with varying degrees of hypotrophy corresponded to the expected echographic degree of FGRS.

When studying the weight and height indicators of newborns, it was found that the body weight of premature newborns varied from 500 g to 2500 g and was 1861±737 g in group 1 and 1811±693 g in group 2. In group 3, all newborns had an

average weight of 3367±351 g. The average length of newborns was 41.0±5.0 cm in the first group, 40.0±6.0 cm in the second group, and 52±2.3 cm in the group of women with a physiological pregnancy.

Transfer to the second stage of nursing was required for 6 newborns from mothers with hyperuricemia, while 100% of newborns from mothers with normal uric acid levels were discharged home in satisfactory condition.

In the study, neonatal mortality was observed in 2.7% (2) of the total number of PBs in the second group, the cause of which was generalized intrauterine infections, neonatal sepsis and acute hypoxia.

Blood was taken from all newborns immediately after birth (from the maternal part of the umbilical cord) to determine the amount of UA and S-100 protein. The results of the study showed a reliable increase in UA and S-100 protein in the umbilical cord blood and in the amniotic fluid in PN more often than in the second group.

Thus, hyperuricemia and decreased S-100 protein are prognostically valuable predictors of the development of preterm labor, fetoplacental insufficiency, FGRS and fetal hypoxia.

Development of an algorithm: based on the data obtained during the study, an algorithm was developed for the diagnosis, prognosis and management of pregnancy and childbirth in women at risk of premature birth.

When a pregnant woman with a risk of premature birth is admitted, it is necessary to conduct a set of clinical, laboratory and instrumental research methods. However, taking into account clinical data remains insufficient for diagnosis, prognosis and determination of pregnancy and childbirth management tactics in women at risk of premature birth.

At the same time, the results of the studies have shown that the determination of pathogenetic parameters such as TCA, ECA, RSA, IT, DC, MDA, SOD, Kat, IL, CD141, D-dimer can be reliably used in the diagnosis and prediction of the risk of premature birth. However, these parameters have a number of features: technical complexity, high cost, duration of implementation.

We propose to use uric acid as a predictor of diagnosis and prognosis of pregnancy and childbirth in women at risk of premature birth, since it is one of the main links in the pathogenesis of preterm labor.

Regardless of the pregnancy prognosis, additional drugs with antioxidant effect and containing rosmarinic acid, Glucurono-2-amino-2-deoxyglucoglucan sulfate and L-Arginine L-Aspartate, which affect various components of the homeostasis system and antioxidant system, must be included in the therapy.

Timely hospitalization, identification of risk factors, assessment of the pregnant woman's condition, timely diagnosis and assessment of laboratory parameters, and correctly prescribed therapy can undoubtedly affect the outcome of pregnancy for both the mother and the fetus, reducing complications that may arise not only during childbirth but also in the early and late neonatal period.

The proposed therapy, which affects various components of the homeostasis system and hyperuricemia, has reduced the incidence of premature birth by 11.9% of cases.

CONCLUSIONS

1. In our studies, the risk of premature birth was observed significantly more often in pregnant women with a gestation period of 28-34 weeks than in the group with a gestation period of 22-27 weeks and amounted to 82.5% and 17.6% of cases, respectively. When analyzing the outcome of labor, it was found that the number of premature births was 9.4% in 22-27 weeks and 90.5% in 28-34 weeks of gestation.
2. A pronounced imbalance in the levels of endogenous intoxication in pregnant women with threatened PB in the form of a reliable decrease in ECA, TCA, RSA, SOD ($P < 0.01$) and a reliable increase in Catalase, IT, DC, MDA, KTB ($P < 0.01$) contribute to the activation of lipid peroxidation processes, depression of antioxidant protection, an imbalance in the activity of the immune system, the formation of reactive proteins in the body and increased metabolism of purine bases.
3. In women with threatened and premature labor, a new pathogenetic relationship was established between hyperuricemia and a significant increase in proinflammatory cytokines IL-1, IL-2, IL-6, IL-8, TNF-α ($P < 0.01$) and a decrease in IL-4, IL-10 ($P < 0.01$) in the study groups, the balance of which is significant for assessing the direction of the immune response, as well as the outcome of pregnancy for the mother and fetus.
4. New prognostic predictors of PB are a decrease in the activity of S-100 protein by an average of 4.6 times ($P < 0.01$) and ceruloplasmin by 1.6 times ($P < 0.01$), which, by suppressing endogenous intoxication, lead to decompensation of antioxidant protection, promoting the accumulation of lipid peroxidation products, which in turn leads to fetoplacental insufficiency and fetal hypoxia.
5. Pathogenetic predictors of the development of PB are endothelial dysfunction in the form of a reliable increase in the level of nitric oxide and a disorder of the hemostasis system: an increase in von Willebrand factor, fibrinogen, thrombomodulin, D-dimer and a reliable decrease in antithrombin III.
6. Uric acid is the final metabolite of the pathogenetic mechanism of preterm labor,

the determination of which is better used as a predictor of diagnosis, prognosis and treatment in women at high risk of preterm labor. Uric acid is significantly increased in blood plasma, amniotic fluid by 34% and umbilical cord blood by 27%.

7. In women with threatened premature birth, a vasoconstrictive effect of uric acid in the placenta has been established, which is confirmed by Doppler and pathomorphological changes in the placenta in the form of decreased placental perfusion, ischemia, impaired maturation of placental villi, angiopathy, thrombosis of the intervillous spaces, signs of deciduitis, chorioamnionitis and apoptosis of the placenta and, accordingly, placental insufficiency, which threatens the course of pregnancy and provokes premature birth.
8. Based on the identified significance of hyperuricemia in threatened PB, a pathogenetic and therapeutic-diagnostic algorithm for pregnancy management was developed depending on the gestational age.
9. Based on a comprehensive study of the pathogenesis links of threatened preterm labor caused by hyperuricemia, regardless of the pregnancy prognosis, it is necessary to include in traditional therapy drugs with an antioxidant effect, restoring endothelial function and purine metabolism, which have a beneficial effect on the outcome of labor for both the mother and the fetus in preterm labor. The comprehensive treatment method in the main group made it possible to reduce the incidence of premature birth by 8.5% of cases at 22-27 weeks of gestation and 8.6% of cases at 28-34 weeks of gestation, which is a prognostically significant indicator for preventive measures.

PRACTICAL RECOMMENDATIONS

1. When pregnant women are admitted to the clinic, it is important to form the degree of risk of developing premature birth using the proposed prognostic matrix. When diagnosing, it is necessary to take into account the role of **metabolic disorders** in threatening premature birth, which can play a major role in the development of PB.
2. For early prognosis, diagnosis and treatment of threatened premature birth, it is necessary to determine the parameters of endotoxicosis, activation of lipid peroxidation, antioxidant protection, cytokine activity, reactive proteins, endothelial dysfunction and purine metabolism products.
3. Determination of the amount of uric acid can be used as a predictor for prognosis, diagnosis, and treatment of threatened premature birth.
4. Regardless of the prognosis of pregnancy with hyperuricemia, additional drugs with an antioxidant effect must be included in traditional therapy.
5. In case of endothelial dysfunction, it is necessary to use the drug Glucurono-2-amino-2-deoxyglucoglucan sulfate, which suppresses the proliferation of smooth muscles of the vascular wall, promotes the restoration of the structure and function of vascular endothelial cells, and normalizes the rheological properties of the blood.
6. If a violation of uteroplacental and fetoplacental hemodynamics is detected in threatened PB, a drug containing L-Arginine L-Aspartate, which affects various components of the homeostasis system, must be added to traditional therapy.
7. Accept the proposed algorithm in predicting, diagnosing, treating and preventing threatened PB and PB.

LIST OF REFERENCES

1. Агабабян Л. Р., Азимова Ш. Т. Акушерские кровотечения как ведущая причина материнской смертности в трудах академика из закирова //Журнал Репродуктивного Здоровья и Уро-Нефрологических Исследований. – 2021. – Т. 2. – №. 1.
2. Акушерство: национ. рук-во / под ред. Г.М. Савельевой, Г.Т. Сухих, В.Н. Серова, В.Е. Радзинского. – 2-е изд., перераб. и доп. – М.: ГЭОТАР-Медиа, 2018. – 1088 с.
3. Алексеенко, Л.А. Выхаживание новорождённых от сверхранних преждевре- менных родов в перинатальном центре Окружной клинической больницы: резуль- таты и перспективы / Л.А. Алексеенко, И.В. Колмаков, Е.Н. Шинкаренко [и др.] // Здравоохранение Югры: опыт и инновации. – 2017. – № 3 (12). – С. 4-9.
4. Алексеенко, Н.Ю. Основные проблемы и перспективы выхаживания детей с очень низкой и экстремально низкой массой тела при рождении (литературный об- зор) / Н.Ю. Алексеенко // Международный научный журнал «Символ науки». – 2017. – № 01-2. – С.158-163.
5. Ан А.В., Пахомова Ж.Е. Критические состояния при акушерских кровотечениях // Вопросы гинекологии, акушерства и перинатологии. 2010. Т. 9. № 4. С. 33-37.
6. Ан А.В., Пахомова Ж.Е. Экстрагенитальная патология у беременных в регионе с высокой рождаемостью // Здравоохранение Российской Федерации. 2010. № 4. С. 45-48.
7. Ан А.В., Пахомова Ж.Е. Материнская летальность после кесарева сечения // Проблемы репродукции. 2010. Т. 16. № 3. С. 83-86.
8. Ахмедов Ф. К., Курбонова З. Ш. Мочевая кислота-маркер развития преэклампсия //Новости дерматологии и репродуктивного здоровья. – 2017. – №. 3-4. – С. 27-29.
9. Ахметгалиев, А.Р. Алгоритм идентификации угрозы преждевременных

ро- дов. / А.Р. Ахметгалиев, И.Ф. Фаткуллин, А.А. Мунавирова, Ф.И. Фаткуллин // Ка- занский медицинский журнал. – 2017. – Т. 98, № 1. – С. 132-136.

10. Бабажанова Ш.Д., Любчич А.С., Пахомова Ж.Е. Факторы риска тромбоэмболии легочной артерии по данным конфиденциального анализа случаев материнской смерти // Акушерство и гинекология Санкт-Петербурга. 2019. № 2. С. 19-19.1.

11. Батырева, Н.В. Факторы риска очень ранних преждевременных родов / Н.В. Батырева, С.С. Синицына, Е.Н. Кравченко [и др.] // Мать и дитя в Кузбассе. – 2018. – № 1. – С. 57-61.

12. Белинина А.А., Баринов С.В., Кадцина Т.В., Колядо О.В., Молчанова И.В. Роль акушерского пессария и микронизированного прогестерона в снижении частоты ранних преждевременных родов у беременных с многоплодием // Acta Biomedica Scientifica (East Siberian Biomedical Journal). 2022. Т. 7. № 3. С. 22-29.

13. Борзова Н.Ю., Раджабова Н.Р., Сотникова Н.Ю., Кудряшова А.В., Малышкина А.И. Новый прогностический критерий исхода беременности у женщин с угрожающими преждевременными родами // Клиническая лабораторная диагностика. 2022. Т. 67. № 2. С. 97-100.

14. Буданов, П.В. Современная структура и распространенность осложнений абдоминального родоразрешения / П.В. Буданов, С.В. Регул // Здоровье и образо- вание в XXI веке. – 2018. – Т. 20, № 3. – С. 32-34.

15. Вагинальный микробиом и преждевременные роды. Эффективная фармакотерапия. 2022. Т. 18. № 7. С. 60-64.

16. Волкова, А.С. Тромбофилии в клинической практике акушера-гинеколога / А.С. Волкова, Е.А. Круглова, А.А. Кузьмин [и др.] // Journal of Siberian Medical Sciences. – 2014. – № 3. – С. 79.

17. Волокитина Е.И. Причины, прогнозирование и доклинические методы диагностики сверхранних преждевременных родов // Диссертация на соискание ученой степени кандидата медицинских наук / Ростовский

государственный медицинский университет. Ростов-на-Дону, 2022.

18. Гаврилова, А.А. Сверхранние и ранние преждевременные роды: спорные вопросы / А.А. Гаврилова, А.Н. Парыгина // Здоровье и образование в 21 веке: жур- нал. – 2018. – Т. 20, № 1. – С. 24-28.

19. Гинекология / под ред. Г.М. Савельевой, Г.Т. Сухих, В.Н. Серова, В.Е. Рад- зинского, И.Б. Манухина. – М.: ГЭОТАР-Медиа, 2017. – 1008 с.

20. Гондаренко, А.С. Исходы сверхранних преждевременных родов. / А.С. Гондаренко, Т.В. Галина, Н.М. Маркарян [и др.] // Вестник Российского университета дружбы народов. Серия: Медицина. – 2016. – № 2. – С. 28-32.

21. Горина К.А., Ходжаева З.С., Чаговец В.В., Стародубцева Н.Л., Франкевич В.Е., Припутневич Т.В. Особенности профиля органических кислот амниотической и цервико-вагинальной жидкостей беременных высокого риска преждевременных родов // Акушерство и гинекология. 2022. № 3. С. 39-48.

22. Горюнова, А.Г. Синдром задержки роста плода и адаптация плаценты / А.Г. Горюнова, М.С. Симонова, А.В. Мурашко // Архив акушерства и гинекологии им. В.Ф. Снегирева. – 2016. – Т. 3, №2. – С. 76-80.

23. Джаббарова Л. А., Рузиева Н. Х. ИСПОЛЬЗОВАНИЕ МЕЖДУНАРОДНЫХ ПОДХОДОВ ДЛЯ ОПРЕДЕЛЕНИЯ ПРИЧИН И ПУТЕЙ СНИЖЕНИЯ КОЛИЧЕСТВА ПРЕЖДЕВРЕМЕННЫХ РОДОВ //VOLGAMEDSCIENCE. – 2021. – С. 304-305.

24. Джаббарова Ю.К., Пахомова Ж.Е. Достижения акушерско-гинекологической науки в узбекистане (2018-2021 гг.) // Журнал теоретической и клинической медицины. 2021. № 6-1. С. 47-50.

25. Доброхотова, Ю.Э. Результаты исследования цервико-вагинальной микро- биоты методом ПЦР в реальном времени у беременных с угрожающими прежде- временными родами / Ю.Э. Доброхотова, К.Р. Бондаренко, А.Е. Гущин [и др.] // Акушерство и гинекология. – 2018. – № 11. – С. 50-59.

26. Доброхотова, Ю.Э. Угроза прерывания беременности в различные сроки

гестации / Ю.Э. Доброхотова, П.В. Козлов, Ж.А. Мандрыкина, А.В. Степанян. – М.: ГЭОТАР-Медиа, 2016. – 144 с.

27. Закурина, А.Н. Новые подходы к ультразвуковой диагностике хронической плацентарной недостаточности / А.Н. Закурина, Н.Г. Павлова // Журнал акушер- ства и женских болезней. – 2014. – Т. 63, № 1. – С. 52-53.

28. Игнатко, И.В. Прогностические маркеры синдрома задержки роста плода / И.В. Игнатко, М.М. Мирющенко // Здоровье и образование в XXI веке. – 2016. – Т. 18, № 1. – С. 1-4.

29. Инфекционно-воспалительные заболевания в акушерстве и гинекологии: рук-во для врачей / под ред. Э.К. Айламазяна. – М.: ГЭОТАР-Медиа, 2016. – 320 с.

30. Иуси Е.С., Шарипова М.С., Каспарова А.Э., Гилёва С.Л., Чёрная Е.Е. Влияние курения различных сигарет на риск реализации преждевременных родов // Научный медицинский вестник Югры. 2022. Т. 32. № 2. С. 75-77.

31. Ищенко Л.С., Воропаева Е.Е., Казачкова Э.А., Хайдукова Ю.В., Казачков Е.Л., Шамаева Т.Н., Воропаев Д.Д., Воропаева А.И., Ищенко Ю.С. Частота и исходы экстремально ранних преждевременных родов у беременных женщин с новой коронавирусной инфекцией covid-19 // Якутский медицинский журнал. 2023. № 1 (81). С. 80-83.

32. Казачков Е.Л., Семёнов Ю.А., Веряскина Ю.А., Казачкова Э.А., Чижовская А.В. Профиль экспрессии ряда микрорнк в плаценте при своевременных и преждевременных родах // Journal of Siberian Medical Sciences. 2022. Т. 6. № 1. С. 22-37.

33. Камилова М.С., Пахомова Ж.Е. Оценка маточно-плацентарно-плодового кровотока и морфологических особенностей плаценты при преждевременной отслойке нормально расположенной плаценты // Акушерство и гинекология. 2015. № 5. С. 30-35.

34. Комилова М.С., Разикова К.Х., Искандаров Ж.М., Пахомова Ж.Е. Цитокино-эндокринный профиль организма при физиологической и прерывающейся беременности и морфологические особенности плаценты //

Молодежный инновационный вестник. 2016. Т. 5. № 1. С. 203-205.

35. Комилова М.С., Пахомова Ж.Е. Значение эндотелия в развитии осложнений гестационного периода // Российский вестник акушера-гинеколога. 2015. Т. 15. № 1. С. 18-23.

36. Каримов З.Д., Жаббаров У.У., Хусанходжаева М.Т., Абдикулов Б.С., Пахомова Ж.Е. Последствия тяжелой контузии матки у беременных // Акушерство и гинекология. 2012. № 6. С. 63-68.

37. Кан Н.Е., Салпагарова З.Х., Тютюнник В.Л., Щипицына В.С., Красный А.М. Содержание про- и антиоксидантов в капиллярной крови при преждевременных родах // Акушерство и гинекология. 2022. № 1. С. 56-61.

38. Каплан, Ю.Д. Причины невынашивания беременности у женщин с корре- гированной шейкой матки / Ю.Д. Каплан, Т.Н. Захаренкова // Проблемы здоровья и экологии. – 2017. – № 4 (54). – С. 17-21.

39. Каптильный, В.А. Нарушения маточно-плацентарной перфузии как предиктор инфекционного осложнения беременности / В.А. Каптильный, М.В. Бери- швили, И.М. Красильщиков // Интерактивная наука. – 2016. – № 1. – С. 33-41.

40. Капустин Р.В., Алексеенкова Е.Н., Аржанова О.Н. Преждевременные роды у женщин с сахарным диабетом // В книге: Беременность и сахарный диабет. Абашова Е.И., Алексеенкова Е.Н., Аржанова О.Н., Беспалова О.Н., Боровик Н.В., Евсюкова И.И., Капустин Р.В., Коган И.Ю., Коптеева Е.В., Мишарина Е.В., Тиселько А.В., Толибова Г.Х., Траль Т.Г., Цыбук Е.М., Шелаева Е.В., Шенгелия М.О., Шенгелия Н.Д., Шилова Е.С., Хачатурян А.Р., Ярмолинская М.И. и др. руководство для врачей. Москва, 2023. С. 87-99.

41. Квардина М.М., Орлова Т.Ю., Благодарева М.С. Применение телемедицинских технологий при оказании медицинской помощи беременным с факторами риска преждевременных родов // Научные известия. 2022. № 27. С. 71-73.

42. Керчелаева, С.Б. Анализ перинатальных исходов при преждевременных родах / С.Б. Керчелаева, О.В. Кузнецова, А.В. Тягунова [и др.] // Лечащий врач.

– 2017. – №7. – С. 56.

43. Клинические рекомендации (протокол лечения). Истмико-цервикальная недостаточность / МЗ РФ. – М., 2021. – 44 с.

44. Клинические рекомендации (протокол). Преждевременные роды / Г.Т. Су- хих, В.Н. Серов, Л.В. Адамян [и др.] – М., 2020. – 66 с.

45. Клинические рекомендации. Акушерство и гинекология / под ред. В.Н. Се- рова, Г.Т. Сухих. – М.: ГЭОТАР-Медиа, 2015. – 1023 с.

46. Колобов, А.В. Оценка морфофункционального состояния плаценты при перинатальной передаче ВИЧ / А.В. Колобов, Е.В. Мусатова, В.Е. Карев [и др.] // Архив патологии. – 2014. – № 1. – С. 22-26.

47. Корытко, А.А. Влияние избыточной массы тела и ожирения на фертильность и вынашивание беременности / А.А. Корытко // МЭЖ. – 2016. – №7 (79). – С. 22-26.

48. Красный, А.М. Прогнозирование преждевременных родов путем комбини- рованного определения цитокинов и внеклеточной ДНК / А.М. Красный, Н.Е. Кан, В.Л. Тютюнник [и др.] // Акушерство и гинекология. – 2019. – № 1. – С. 86-91.

49. Кузибаева, Р.К. Опыт прегравидарной подготовки в профилактике прежде- временных родов / Р.К. Кузибаева, Н.Н. Гранатович // Вестник новых медицинских технологий. – 2016. – Т. 10, № 4. – С. 140-144.

50. Құдайберген Б.Т., Едельбаева А.С., Тасыбай А.Қ., Турдыбекова Я.Г., Амирбекова Ж.Т. Сравнительный анализ частоты преждевременных родов среди женщин, заразившихся коронавирусной инфекцией // Наукосфера. 2022. № 8-1. С. 73-81.

51. Лазарева, Г.А. Современный взгляд на проблему фетоплацентарной недо- статочности / Г.А. Лазарева, А.Б. Хурасева, О.И. Клычева // Научные ведомости Белгородского государственного университета. Серия: Медицина. Фармация. – 2014. – Т. 27, №. 18 (189). – С. 5-10.

52. Ланг, Т. Основы описания статистического анализа в статьях, публикуемых в биомедицинских журналах. Руководство «Статистический анализ и

методы в публикуемой литературе (САМПЛ)» / Т. Ланг, Д. Альтман Д.; пер. с англ. О.Ю. Ребровой, Е.А. Ракиной // Медицинские технологии. Оценка и выбор. –2014.– № 1. – С. 10-15.

53. Лебедева, А.В. Особенности течения беременности и состояния плодов у рожениц со сверхранними преждевременными родами / А.В. Лебедева, О.А. Зо- това, В.И. Черняева // Фундаментальная и клиническая медицина. – 2017. – Т. 2, № 4. – С. 27-33.

54. Лосева, О.И. Современные подходы к ведению беременных женщин с ист- мико-цервикальной недостаточностью / О.И. Лосева, Т.И. Прохорович, С.Н. Гай- дуков // Здоровье и образование в XXI веке. – 2018. – Т. 20, № 1. – С. 99-102.

55. Магзумова Н. М. и др. Микробиологические изменения в плаценте у беременных с дородовым излитием околоплодных вод //Инфекция, иммунитет и фармакология. – 2019. – №. 5. – С. 158-162.

56. Мамадалиева Г.И., Рузиева Н.Х., Абдуразакова Г.А. Целесообразность применения cin-diag в диагностике доброкачественных заболеваний шейки матки // Журнал теоретической и клинической медицины. 2021. № 6-2. С. 99-102.

57. Марат А. Структура и факторы риска преждевременных родов / А. Марат, Т. Укыбасова // Клиническая медицина Казахстана. – 2017. – № 3 (45). – С. 14-17.

58. Матвеева Е.А., Малышкина А.И., Филькина О.М., Харламова Н.В. Состояние здоровья детей, родившихся от экстремально ранних преждевременных родов с синдромом задержки развития плода // Российский педиатрический журнал. 2022. Т. 3. № 1. С. 194.

59. Матейкович Е.А., Чернова А.Л., Шевлюкова Т.П., Суханов А.А. Исходы беременности и заболевания щитовидной железы: оценка риска преждевременных родов // Медицинский совет. 2022. Т. 16. № 6. С. 130-136.

60. Мельникова, Т.А. Анализ течения беременности у женщин, инфицирован- ных Ur. Urealyticum, в зависимости от степени колонизации

генитального тракта. / Т.А. Мельникова, М.М. Падруль, Э.С. Горовиц, Г.И. Работникова // Пермский ме- дицинский журнал. – 2017. – Т. 34, № 2. – С. 26-30.

61. Муратова Н.Д., Эшонходжаева Д.Д., Бабаджанова Г.С. Эффективность микронизированного прогестерона в профилактике преждевременных родов // Журнал теоретической и клинической медицины. 2023. № 2. С. 68-70.

62. Намжилова, Л.С. Новые возможности прогнозирования очень ранних преждевременных родов / Л.С. Намжилова, И.Б. Фаткуллина, С.В. Коротова, А.В. Ли-Ван-Хай // Сибирский медицинский журнал. – 2015. – Т. 134, № 3. – С. 60- 63.

63. Нефёдова, Н.А. Маркеры ангиогенеза при опухолевом росте / Н.А. Нефё- дова, О.А. Харлова, Н.В. Данилова [и др.] // Архив патологии. – 2016. – № 2. – С. 55-62.

64. Новикова С.В., Зароченцева Н.В., Дальниковская Л.А., Климова И.В. Истмико-цервикальная недостаточность - предиктор преждевременных родов // Вопросы практической кольпоскопии. Генитальные инфекции. 2022. № 2. С. 30-36.

65. Новикова, В.А. Оценка рисков кровотечения при преждевременных родах исходя из его причин / В.А. Новикова, Г.В. Каменских, А.С. Оленев [и др.] // Акушерство и гинекология. – 2019. – №2. – С. 78-84.

66. Носенко, Е.Н. Проблемные вопросы больших акушерских синдромов / Е.Н. Носенко, С.И. Жук, А.В. Рутинская // Журнал «Жіночий лікар». – 2017. – № 2 (70). – С. 28-35.

67. Норбаева Х.К., Пахомова Ж.Е. Совершенствование клинико-диагностических мероприятий у беременных с бессимптомной бактериурией// Врач-аспирант. 2011. Т. 49. № 6.2. С. 349-353.

68. Обидова В.Л. Изучение компенсаторно-приспособительных особенностей фетоплацентарной системы при преждевременных родах // Экономика и социум. 2023. № 4-1 (107). С. 431-437.

69. Обидова В.Л. Особенности фетоплацентарной системы при

преждевременных родах (литературный обзор) // Экономика и социум. 2023. № 4-1 (107). С. 438-444.

70. Островская, О.В. Морфометрическая характеристика терминальных вор- син плаценты при недоношенности / О.В. Островская, О.В. Кожарская, С.В. Су- прун [и др.] // Бюллетень физиологии и патологии дыхания. – 2018. – №70. – С. 68- 73.

71. Пахомова Ж.Е., Комилова М.С. Оценка дисфункции эндотелия фетоплацентарного комплекса при преждевременной отслойке нормально расположенной плаценты // Вестник современной клинической медицины. 2016. №1. URL: https://cyberleninka.ru/article/n/otsenka-disfunktsii-endoteliya-fetoplatsentarnogo-kompleksa-pri-prezhdevremennoy-otsloyke-normalno-raspolozhennoy-platsenty (дата обращения: 12.07.2023).

72. Пахомова Ж.Е., Абдурахманов О.Р., Абдуразакова Г.А. Особенности течения хронического цервицита у женщин с герпетической инфекцией // Российский вестник акушера-гинеколога. 2013. Т. 13. № 1. С. 51-54

73. Пахомова Ж.Е., Комилова М.С. Основные звенья механизма патогенеза преждевременной отслойки нормально расположенной плаценты // Вопросы гинекологии, акушерства и перинатологии. 2015. Т. 14. № 6. С. 46-53.

74. Погорелова, Т.Н. Протеомные маркеры прогнозирования преждевремен- ных родов / Т.Н. Погорелова, В.О. Гунько, В.А. Линде // Российский вестник аку- шера-гинеколога. – 2016. – № 2. – С. 18-22.

75. Польской В.С., Миненок В.А. Факторы риска преждевременных родов // Интегративные тенденции в медицине и образовании. 2022. Т. 2. С. 117-122.

76. Попов, А.А. Внутриматочные синехии: век спустя / А.А. Попов, Т.Н. Мананникова, А.С. Алиева [и др.] // РМЖ. Мать и дитя. – 2017. – №12. – С. 895-899.

77. Пустотина, О.А. Прегравидарная подготовка / О.А. Пустотина // Медицин- ский совет. – 2017. – №13. – С. 64-70.

78. Пустотина, О.А. Прегравидарная подготовка женщин с невынашиванием беременности в анамнезе / О.А. Пустотина, А.Э. Ахмедова

// Медицинский совет. – 2016. – № 4. – С. 130-136.

79. Раджабова Н.Р., Таланова Ия.Е., Борзова Н.Ю., Сотникова Н.Ю., Малышкина А.И. Патогенетическое обоснование прогнозирования преждевременных родов // Женское здоровье и репродукция. 2022. № 2 (53). С. 56-70.

80. Радзинский, В.Е. Акушерская агрессия.V 2.0 / В.Е. Радзинский. – М.: Изд- во журнала StatusPraesens, 2017. – 872 с.

81. Радзинский, В.Е. Преждевременные роды – нерешенная мировая проблема. / В.Е. Радзинский, И.Н. Костин, А.С. Оленев [и др.] // Акушерство и гинеко- логия: Новости. Мнения. Обучения. – 2018. – Прил. 3 (21). – С. 55-64.

82. Радынова, С.Б. Осложнения беременности и родов у женщин с ожирением / С.Б. Радынова, Е.А. Иванова // Современные проблемы науки и образования. – 2018. – № 5. – URL: https://www.science-education.ru/ru/article/view?id=28042.

83. Рахимов Х.П., Пахомова Ж.Е. Тактика родоразрешения и объем оперативного вмешательства у беременных с миомой матки // Врач-аспирант. 2011. Т. 48. № 5.2. С. 296-301.

84. Рациональная антимикробная терапия: руководство для практикующих врачей / под ред. С.В. Яковлева. – 2-е изд., перераб. и доп. – М.: Литтерра, 2015. – 1040 с.

85. Рузиева Н. Х. Роль оксидантного стресса в развитие преждевременных родов //МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ УЗБЕКИСТАН РЕСПУБЛИКАНСКИЙ СПЕЦИАЛИЗИРОВАННЫЙ НАУЧНО-ПРАКТИЧЕСКИЙ МЕДИЦИНСКИЙ ЦЕНТР АКУШЕРСТВА И ГИНЕКОЛОГИИ АССОЦИАЦИЯ ВРАЧЕЙ ЧАСТНОЙ ПРАКТИКИ УЗБЕКИСТАНА КЛИНИКА «MAHLIYO-SHIFO» & V «MAHLIYO-SHIFO» & V. – 2019. – С. 40.

86. Рузиева Н.Х. Доклиническая диагностика преждевременных родов // Медицинские новости. 2019. № 7 (298). С. 74-75.

87. Рузиева Н.Х. Применение активных методов - элемент повышения

эффективности обучения // Достижения науки и образования. 2018. № 15 (37). С. 85-87.

88. Рузиева Н.Х., Джаббарова Л.А., Джаббарова Ю.К. Причины и пути снижения преждевременных родов с использованием международных подходов // Re-Health Journal. 2021. № 1 (9). С. 14-18.

89. Рузиева Н.Х., Исмаилова И.Р. Магне-в6 в профилактике и лечении анемии у беременных сборнике: ГЛОБАЛИЗАЦИЯ НАУКИ: ПРОБЛЕМЫ И ПЕРСПЕКТИВЫ. Сборник статей Международной научно-практической конференции. Ответственный редактор: А.А. Сукиасян. 2014. С. 148-154.

90.

91. Рузиева Н.Х. Системная воспалительная реакция в патогенезе развитии преждевременных родов // Журнал теоретической и клинической медицины. 2018. № 4. С. 103-105.

92. Рузиева Н.Х., Джаббарова Л.А., Джаббарова Ю.К. ПРИЧИНЫ И ПУТИ СНИЖЕНИЯ ПРЕЖДЕВРЕМЕННЫХ РОДОВ С ИСПОЛЬЗОВАНИЕМ МЕЖДУНАРОДНЫХ ПОДХОДОВ // Re-health journal. 2021. №1 (9). URL: https://cyberleninka.ru/article/n/prichiny-i-puti-snizheniya-prezhdevremennyh-rodov-c-ispolzovaniem-mezhdunarodnyh-podhodov.

93. Садыкова Г.К., Олина А.А. Оценка влияния микроэлементов на экспрессию факторов ангиогенеза при преждевременных родах // Женское здоровье и репродукция. 2022. № 2 (53). С. 71-86.

94. Самешимы Х. Преждевременные роды и досрочное родоразрешение. пер. с англ. под ред. И. В. Игнатко. — Москва : ГЭОТАР-Медиа, 2023. — 312 с.

95. Саргсян Г.С., Беспалова О.Н. Оценка риска спонтанных преждевременных родов у беременных с акушерским пессарием // Журнал акушерства и женских болезней. 2022. Т. 71. № 2. С. 49-60.

96. Саргсян Г.С., Пачулия О.В., Беспалова О.Н. Эффективность акушерского пессария dr. Arabin в профилактике очень ранних и ранних преждевременных родов при двойнях // Журнал акушерства и женских

болезней. 2022. Т. 71. № 3. С. 31-42.

97. Свиридова А.В., Константинова О.Д. К вопросу о преждевременных родах на фоне коронавирусной инфекции // Репродуктивное здоровье. Восточная Европа. 2023. Т. 13. № 2. С. 157-164.

98. Семенов, Ю.А. Факторы риска преждевременных родов / Ю.А. Семенов, В.С. Чулков, М.Г. Москвичёва, В.В. Сахарова // Сибирский медицинский журнал.– 2015. – № 6. – С. 29-33.

99. Серебренникова, Е.С. Сравнительная характеристика факторов риска де- тей, родившихся с очень низкой массой тела и экстремально низкой массой тела / Е.С. Серебренникова, Д.П. Безбородов, Л.Г. Баженова [и др.] // Мать и дитя в Куз- бассе. – 2015. – № 1. – С. 43-47.

100. Симанов, И.В. Сроки появления основных клинических симптомов пре-эклампсии на современном этапе / И.В. Симанов // Научные результаты биомеди- цинских исследований. – 2017. – Т. 3, №3 (13). – С. 51-56.

101. Соснина, А.К. Функциональная морфология виллезного дерева плацент при доношенной одноплодной беременности, достигнутой методами вспомогательных репродуктивных технологий / А.К. Соснина, Т.Г. Траль, Ю.С. Крылова // Журнал акушерства и женских болезней. – 2016. – Т. 65, № 3. – С. 43-51.

102. Стяжкина, С.Н. Перестройка иммунной системы во время беременности / С.Н. Стяжкина, М.Л. Черненкова, Т.А. Повышева, Е.А. Тулынина // Наука, техника и образование. – 2015. – № 4 (10). – С. 185-187.

103. Тетелютина, Ф.К. Особенности родовой деятельности у женщин с хрони- ческим пиелонефритом / Ф.К. Тетелютина, М.Л. Черненкова // Практическая меди- цина. – 2017. – № 7 (108). – С. 67-71.

104. Тошева И. И., Ихтиярова Г. А. Исходы беременности при преждевременном разрыве плодных оболочек //РМЖ. Мать и дитя. – 2020. – Т. 3. – №. 1. – С. 16-19.

105. Тошева И. И., Ихтиярова Г. А. Патоморфология последов, осложнения беременности, родов и исходы новорожденных с дородовым излитием

околоплодных вод //Opinion leader. – 2020. – №. 2. – С. 56-60.
106. Ушакова, С.В. Современные методики коррекции истмико-цервикальной недостаточности / С.В. Ушакова, Н.В. Зароченцева, А.А. Попов [и др.] // Российский вестник акушера-гинеколога. – 2015. – №5. – С. 117-123.
107. Фомичев В.А., Октябрьская Е.В. Влияние вариантов анестезии на сократительную способность миометрия и состояние плода в условиях преждевременных родов // Интерактивная наука. 2022. № 7 (72). С. 30-33.
108. Фомичев В.А., Октябрьская Е.В. Показатели общей гемодинамики и родовой травматизм в условиях преждевременных родов при различных вариантах анестезиологического обеспечения // Интерактивная наука. 2022. № 7 (72). С. 33-37.
109. Фомичев В.А., Октябрьская Е.В. Эффективность обезболивания преждевременных родов при различных вариантах анестезиологического обеспечения // Интерактивная наука. 2022. № 7 (72). С. 37-40.
110. Халитова Р.Ш., Зиганшин А.М., Мухаметдинова И.Г., Мудров В.А. Преждевременные роды: влияние факторов риска на исходы беременности // Журнал акушерства и женских болезней. 2022. Т. 71. № 3. С. 43-52.
111. Хамидова Нигора Рустамовна, Туксанова Дилбар Исматовна, Негматуллаева Мастура Нуруллаевна, Ахмедов Фарход Кахрамонович Современный подход к профилактике ранних послеродовых кровотечений // Биология и интегративная медицина. 2020. №3 (43). URL: https://cyberleninka.ru/article/n/sovremennyy-podhod-k-profilaktike-rannih-poslerodovyh-krovotecheniy
112. Хикматова Н.И., Гариб В.Ф., Пахомова Ж.Е., Гариб Ф.Ю. Определение антиспермальных ige антител у женщин с бесплодием, страдающих хроническими воспалительными заболеваниями органов малого таза // Клиническая лабораторная диагностика. 2020. Т. 65. № 7. С. 435-438.
113. Чудук Н.В., Конашук Д.Р. Факторы риска развития преждевременных родов в гродненской области республики беларусь // Международный студенческий научный вестник. 2023. № 1. С. 16.

114. Чухловина, М.Л. Роль артериальной гипертензии в развитии цереброваскулярных заболеваний при беременности / М.Л. Чухловина, С.Е. Медведев // Арте- риальная гипертензия. – 2018. – Т. 24, № 5. – С. 508-514.

115. Шодиева Х.Т., Пахомова Ж.Е., Назарова Д.Э., Сидикходжаева М.А., Ахмедова Г.А., Парвизи Н.И. Факторы риска преждевременных родов при многоплодной беременности // Журнал теоретической и клинической медицины. 2023. № 2. С. 127-129.

116. Шостак Д.П., Пашов А.И., Волкова Л.В., Степанцова М.Г. Результаты гистологического исследования плацент при преждевременных родах у жительниц калининградской области с наследственной дезадаптацией гемостаза // Бюллетень науки и практики. 2023. Т. 9. № 3. С. 218-221.

117. Щербаков В.И., Поздняков И.М., Ширинская А.В., Волков М.В. Стерильное воспаление при преэклампсии и угрозе преждевременных родов // Патологическая физиология и экспериментальная терапия. 2022. Т. 66. № 1. С. 127-134.

118. Щербаков, В.И. Уровень интерлейкина-6, растворимых рецепторов интерлейкина-6, сосудисто-эндотелиального фактора роста при срочных родах, угрозе преждевременных родов и преэклампсии / В.И. Щербаков, И.М. Поздняков, А.В. Ширинская, М.В. Волков // Акушерство и гинекология. – 2017. – №3. – С. 50- 54.

119. Щербатюк, Е.С. Особенности состояния здоровья и проблемы реабилита- ции детей раннего возраста, родившихся с экстремально низкой и очень низкой массой тела (обзор) / Е.С. Щербатюк, С.А. Хмилевская, Н.И. Зрячкин // Саратов- ский научно-медицинский журнал. – 2017. – Т. 13, № 2. – С. 245-251.

120. Яковлева, О.В. Сравнительная эффективность предикторов преждевременных родов / О.В. Яковлева, Т.Н. Глухова // Лечащий врач. – 2019. – №3. – С. 52- 55.

121. Aboulghar M, Aboulghar M. Singleton birth weight and premature birth after in vitro fertilization: Do we have evidence? Fertil Steril. 2021;116(1):64-65. doi:

10.1016/j.fertnstert.2021.04.010. Epub 2021 May 8. PMID: 33972082.

122. Adams, M. Association between perinatal interventional activity and 2-year outcome of Swiss extremely preterm born infants: a population-based cohort study. /M. Adams, T.M. Berger, C. Borradori-Tolsa [et al.] // BMJ Open. – 2019. – Vol. 9, N 3.– P.e024560.

123. Agarwal, S. Fetal adrenal gland biometry and cervical elastography as predictors of preterm birth: a comparative study / S. Agarwal, A. Agarwal, P. Joon [et al.] // Ultrasound. – 2018. – Vol. 26, N 1. – P. 54-62.

124. Anderson PJ, Zeitlin J. Prognosis after very preterm birth: Insights for the future. Paediatr Perinat Epidemiol. 2022 Sep;36(5):591-593. doi: 10.1111/ppe.12921. Epub 2022 Aug 11. PMID: 35950681.

125. Australian Government Department of Health. Pregnancy Care Guidelines. 23 Risk of preterm birth // Australian Government Department of Health: site. – Common- wealth of Australia, 2018. URL: https://beta. health.gov.au/resources/pregnancy-care- guidelines/part-d-clinical-assessments/risk-of-preterm-birth (23.12.2018).

126. Baer, R.J. High risk of spontaneous preterm birth among infants with gastroschisis. / R.J. Baer, C.D. Chambers, K.K. Ryckman [et al.] // Am. J. Med. Genet. A. – 2019. – Vol. 179, N 1. – P. 37-42.

127. Baer, R.J. Previous Adverse Outcome of Term Pregnancy and Risk of Preterm Birth in Subsequent Pregnancy / R.J. Baer, V. Berghella, L.J. Muglia [et al.] // Matern. Child Health J. – 2019. – Vol. 23, N 4. – P. 443-450.

128. Berry, M.J. Outcomes of infants born at 23 and 24 weeks' gestation with gut perforation / M.J. Berry, L.J. Port, C. Gately, M.D. Stringer // J Pediatr Surg. – 2019. – Apr 17. – P. pii: S0022-3468(19) 30293-3. [Epub ahead of print].

129. Bonuccelli GA, Negrini R, da Silva Ferreira RD. Premature Birth in Women with Endometriosis: a Systematic Review and Meta-analysis. Reprod Sci. 2022 Jan;29(1):250-259. doi: 10.1007/s43032-021-00712-1. Epub 2021 Aug 23. PMID: 34426947.

130. Cannavò L, Perrone S, Viola V, Marseglia L, Di Rosa G, Gitto E. Oxidative

Stress and Respiratory Diseases in Preterm Newborns. Int J Mol Sci. 2021 Nov 19;22(22):12504. doi: 10.3390/ijms222212504. PMID: 34830385; PMCID: PMC8625766.

131. Çekmez, Y. Use of cervicovaginal PAMG-1 protein as a predictor of delivery within seven days in pregnancies at risk of premature birth / Y. Çekmez, G. Kiran, E.T. Haberal [et al.] // BMC Pregnancy Childbirth. – 2017. – Vol. 17, N 1. – P. 246.

132. Chen MJ, Kair LR, Schwarz EB, Creinin MD, Chang JC. Future Pregnancy Considerations after Premature Birth of an Infant Requiring Intensive Care: A Qualitative Study. Womens Health Issues. 2022 Sep-Oct;32(5):484-489. doi: 10.1016/j.whi.2022.03.004. Epub 2022 Apr 28. PMID: 35491347; PMCID: PMC9532354.

133. Chien, H.C. Neurodevelopmental outcomes of infants with very low birth weights are associated with the severity of their extra-uterine growth retardation / H.C. Chien, C.H. Chen, T.M. Wang [et al.] // Pediatr Neonatol. – 2018. – Vol. 59, N 2.– P. 168-175.

134. Cobo T, Kacerovsky M, Jacobsson B. Risk factors for spontaneous preterm delivery. Int J Gynaecol Obstet. 2020 Jul;150(1):17-23. doi: 10.1002/ijgo.13184. PMID: 32524595.

135. Cobo, T. Noninvasive Sampling of the Intrauterine Environment in Women with Preterm Labor and Intact Membranes / T. Cobo, M. Kacerovsky, B. Jacobsson // Fetal Diagn Ther. – 2018. – Vol. 43, N 4. – P. 241-249.

136. Commentaries on Viewpoint: Premature birth: a neglected consideration for altitude adaptation. J Appl Physiol (1985). 2022 Oct 1;133(4):979-982. doi: 10.1152/japplphysiol.00476.2022. PMID: 36216407.

137. Conde-Agudelo A, Romero R. Does vaginal progesterone prevent recurrent preterm birth in women with a singleton gestation and a history of spontaneous preterm birth? Evidence from a systematic review and meta-analysis. Am J Obstet Gynecol. 2022 Sep;227(3):440-461.e2. doi: 10.1016/j.ajog.2022.04.023. Epub 2022 Apr 20. PMID: 35460628; PMCID: PMC9420758.

138. Couceiro J, Matos I, Mendes JJ, Baptista PV, Fernandes AR, Quintas A.

Inflammatory factors, genetic variants, and predisposition for preterm birth. Clin Genet. 2021 Oct;100(4):357-367. doi: 10.1111/cge.14001. Epub 2021 May 28. PMID: 34013526.

139. da Fonseca EB, Damião R, Moreira DA. Preterm birth prevention. Best Pract Res Clin Obstet Gynaecol. 2020 Nov;69:40-49. doi: 10.1016/j.bpobgyn.2020.09.003. Epub 2020 Sep 22. PMID: 33039310.

140. Daalderop, L.A. Periodontal Disease and Pregnancy Outcomes: Overview of Systematic Reviews / L.A. Daalderop, B.V. Wieland, K. Tomsin [et al.] // JDR Clin Trans Res. – 2018. – Vol. 3, N 1. – P. 10-27.

141. Debevec T, Narang BJ, Manferdelli G, Millet GP. Last Word on Viewpoint: Premature birth: a neglected consideration for altitude adaptation. J Appl Physiol (1985). 2022 Oct 1;133(4):983-984. doi: 10.1152/japplphysiol.00503.2022. PMID: 36216408.

142. Debevec T, Narang BJ, Manferdelli G, Millet GP. Premature birth: a neglected consideration for altitude adaptation. J Appl Physiol (1985). 2022 Oct 1;133(4):975-978. doi: 10.1152/japplphysiol.00201.2022. Epub 2022 Jun 16. PMID: 35708701.

143. Deng, W. Endothelial Cells in the Decidual Bed Are Potential Therapeutic Tar- gets for Preterm Birth Prevention / W. Deng, J. Yuan, J. Cha [et al.] // Cell Rep. – 2019. – Vol. 27, N 6. – P. 1755-1768.

144. Desplanches, T. Cost-effectiveness of diagnostic tests for threatened preterm labor in singleton pregnancy in France / T. Desplanches, C. Lejeune, J. Cottenet [et al.] // Cost Eff Resour Alloc. – 2018. – Vol. 16. – P. 21.

145. Di Fabrizio, L. New methods for preterm birth prediction: the PAMG-1 test /L. Di Fabrizio, I. Giardina, I. Cetin [et al.] // Minerva Ginecol. – 2018. – Vol. 70, N 5. – P. 635–640.

146. Di Simone N, Santamaria Ortiz A, Specchia M, Tersigni C, Villa P, Gasbarrini A, Scambia G, D'Ippolito S. Recent Insights on the Maternal Microbiota: Impact on Pregnancy Outcomes. Front Immunol. 2020 Oct 23;11:528202. doi: 10.3389/fimmu.2020.528202. PMID: 33193302; PMCID: PMC7645041.

147. Diemert A, Arck PC. Preterm birth: pathogenesis and clinical consequences revisited. Semin Immunopathol. 2020 Aug;42(4):375-376. doi: 10.1007/s00281-020-00809-w. PMID: 32960305; PMCID: PMC7508730.

148. Dom AM, Mather A, Seligman NS. Prevention of preterm birth in multiples. Curr Opin Obstet Gynecol. 2021 Apr 1;33(2):72-77. doi: 10.1097/GCO.0000000000000686. PMID: 33427762.

149. Dubois, J. The dynamics of cortical folding waves and prematurity-related deviations revealed by spatial and spectral analysis of gyrification / J. Dubois, J. Lefèvre, H. Angleys [et al.] // Neuroimage. – 2019. – Vol. 185. – P. 934-946.

150. Evmenenko A.O. The emotional state of women with preterm delivery experience: a review of russian and foreign publications // Психология. Историко-критические обзоры и современные исследования. 2023. Т. 12. № 1-1. С. 145-150.

151. Ferguson, K.K. Environmental chemicals and preterm birth: Biological mecha- nisms and the state of the science / K.K. Ferguson, H.B. Chin // Curr Epidemiol Rep. – 2017. – Vol. 4, N 1. – P. 56-71.

152. Fischer, L.A. Placental colonization with periodontal pathogens: the potential missing link / L.A. Fischer, E. Demerath, P. Bittner-Eddy [et al.] // Am. J. Obstet. Gyne- col. – 2019. – Apr 30. – P. pii: S0002-9378(19)30614-3 [Epub ahead of print].

153. Fritz ,T. Outcome of extremely preterm infants after iatrogenic or spontaneous birth / T. Fritz, K. Källén, K. Maršál, B. Jacobsson // Acta Obstet Gynecol Scand. – 2018. – Vol. 97, N 11. – P. 1388-1395.

154. Gardener H, Sun Q, Grandjean P. PFAS concentration during pregnancy in relation to cardiometabolic health and birth outcomes. Environ Res. 2021 Jan;192:110287. doi: 10.1016/j.envres.2020.110287. Epub 2020 Oct 8. PMID: 33038367; PMCID: PMC7736328.

155. Goldstein, R.F. Association of gestational weight gain with maternal and infant outcomes: a systematic review and meta-analysis / R.F. Goldstein, S.K. Abell, S. Rana- sinha [et al.] // JAMA. – 2017. – Vol. 317, N 21. – P. 2207–2225.

156. Gomez-Lopez N, Galaz J, Miller D, Farias-Jofre M, Liu Z, Arenas-Hernandez

M, Garcia-Flores V, Shaffer Z, Greenberg JM, Theis KR, Romero R. The immunobiology of preterm labor and birth: intra-amniotic inflammation or breakdown of maternal-fetal homeostasis. Reproduction. 2022 Jun 20;164(2):R11-R45. doi: 10.1530/REP-22-0046. PMID: 35559791; PMCID: PMC9233101.

157. Grgic, G. C-reactive protein as a biochemical marker of idiopathic preterm de- livery / G. Grgic, F. Skokic, G. Bogdanovic // Med. Arh. – 2010. – Vol. 64, N 3. – P. 132- 134.

158. Griggs KM, Hrelic DA, Williams N, McEwen-Campbell M, Cypher R. Preterm Labor and Birth: A Clinical Review. MCN Am J Matern Child Nurs. 2020 Nov/Dec;45(6):328-337. doi: 10.1097/NMC.0000000000000656. PMID: 33074911.

159. Helmo, F.R. Intrauterine infection, immune system and premature birth /F.R. Helmo, E.A.R. Alves, R.A.A. Moreira [et al.] // J. Matern Fetal Neonatal Med. – 2018. – Vol. 31, N 9. – P. 1227-1233.

160. Hernandez-Andrade, E. A soft cervix, categorized by shear-wave elastography, in women with short or with normal cervical length at 18–24 weeks is associated with a higher prevalence of spontaneous preterm delivery / E. Hernandez-Andrade, E. Maymon, S. Luewan [et al.] // J. Perinat. Med. – 2018. – Vol. 46, N 5. – P. 489-501.

161. Hesselman, S. Maternal complications in settings where two-thirds of extremely preterm births are delivered by cesarean section / S. Hesselman, M. Jonsson,E.B. Råssjö [et al.] // J. Perinat. Med. – 2017. – Vol. 45, N 1. – P. 121-127.

162. Hoffman MK. Prediction and Prevention of Spontaneous Preterm Birth: ACOG Practice Bulletin, Number 234. Obstet Gynecol. 2021 Dec 1;138(6):945-946. doi: 10.1097/AOG.0000000000004612. PMID: 34794160; PMCID: PMC8607754.

163. Jacob, J. Cost effects of preterm birth: a comparison of health care costs associated with early preterm, late preterm, and full-term birth in the first 3 years after birth /J. Jacob, M. Lehne, A. Mischker [et al.] // Eur. J. Health. Econ. – 2017. – Vol. 18, N 8. – P. 1041-1046.

164. Jiang, M. A case control study of risk factors and neonatal outcomes of

preterm birth / M. Jiang, M.M. Mishu, D. Lu, X. Yin // Taiwan J. Obstet. Gynecol. – 2018. – Vol. 57, N 6. – P. 814-818.

165. Kaempf JW, Dirksen KM. The Birth of Tragedy? Extremely Premature Births and Shared Decision-Making. Am J Bioeth. 2022 Nov;22(11):59-66. doi: 10.1080/15265161.2022.2123981. PMID: 36332042.

166. Kamilova I.A., Pakhomova J.E., Nadjmutdinova D.K. Analysis of the role of 1g / 2g polymorphism in the mmp1 gene in the development and clinical course of cervical intraepithelial neoplasia// European Journal of Molecular and Clinical Medicine. 2020. T. 7. № 2. C. 850-859.

167. Komilova M.S., Pakhomova Zh.E. The value of the factors of endothelial dysfunction in the development of abruption placentae // European Science Review. 2015. № 7-8. C. 47-48

168. Komilova M.S., Pakhomova Zh.E. The reaction of systemic inflammatory response in premature detachment of normally situated placenta // European Science Review. 2015. № 7-8. C. 49-51..

169. Kim J.I. Multiple factors in the second trimester of pregnancy on preterm labor symptoms and preterm birth / J.I. Kim, M.O. Cho, G.Y. Choi // J. Korean. Acad. Nurs. – 2017. – Vol. 47, N 3. – P. 357-366.

170. Kook, S.Y. Vitamin D-binding protein in cervicovaginal fluid as a non-invasive predictor of intra-amniotic infection and impending preterm delivery in women with pre- term labor or preterm premature rupture of membranes / S.Y. Kook, K.H. Park, J.A. Jang [et al.] // PLoS One. – 2018. – Vol. 13, N 6. – 0198842.

171. Kosinska-Kaczynska, K. Rapid cervical phIGFBP-1 test in asymptomatic twin pregnancies is inefficient in predicting preterm delivery prior to 34 gestational weeks /K. Kosinska-Kaczynska, I. Szymusik, D. Bomba-Opon [et al.] // Ginekol Pol. – 2018. – Vol. 89, N 6. – P. 321-325.

172. Lee WL, Chang WH, Wang PH. Risk factors associated with preterm premature rupture of membranes (PPROM). Taiwan J Obstet Gynecol. 2021 Sep;60(5):805-806. doi: 10.1016/j.tjog.2021.07.004. PMID: 34507652.

173. Linehan, L.A. Subsequent pregnancy outcomes following second trimester

mis- carriage-A prospective cohort study / L.A. Linehan, A.G. Morris, S. Meaney, K. O'Dono- ghue // Eur J Obstet Gynecol Reprod Biol. – 2019. – Vol. 237. – P. 198-203.

174. Magnus, M.C. Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study / M.C. Magnus, A.J. Wilcox, N.H. Morken [et al.]// BMJ. – 2019. – Vol. 364. – P. l869.

175. Masho, S.W. Pre-pregnancy BMI and weight gain: where is the tipping point for preterm birth? / S.W. Masho, D.L. Bishop, M. Munn // BMC Pregnancy Childbirth. – 2013. – Vol. 13. – P. 120.

176. Mastrolia, S.A. Bicornuate uterus is an independent risk factor for cervical os insufficiency: A retrospective population based cohort study / S.A. Mastrolia,Y. Baumfeld, R. Hershkovitz [et al.] // J. Matern. Fetal. Neonatal Med. – 2017. – Vol. 30, N 22. – P. 2705-2710.

177. Melchor, J. C. Predictive performance of PAMG-1 vs fFN test for risk of spon- taneous preterm birth in symptomatic women attending an emergency obstetric unit: ret- rospective cohort study / J.C. Melchor, H. Navas, M. Marcos [et al.] // Ultrasound Obstet. Gynecol. – 2018. – Vol. 51, N 5. – P. 644-649.

178. Melchor, J.C. Prediction of preterm delivery in symptomatic women using PAMG-1, fetal fibronectin and phIGFBP-1 tests: systematic review and meta-analysis /J.C. Melchor, A. Khalil, D. Wing [et al.] // Ultrasound Obstet Gynecol. – 2018. – Vol. 52, N 4. – P. 442-451.

179. Minnaard, M.C. The added value of C-reactive protein measurement in diagnosing pneumonia in primary care: a meta-analysis of individual patient data / M.C. Min- naard, J.A.H. de Groot, R.M. Hopstaken [et al.] // CMAJ. – 2017. – Vol. 189, N 2. – P. E56-E63.

180. Mojahed B.S., Shahraki Z., Fallahi D. Association of maternal serum levels of pregnancy-associated plasma protein a in 11-14 weeks pregnant women with developing abortion and preterm labor // Russian Bulletin of Obstetrician-Gynecologist. 2022. T. 22. № 2. C. 13-17.

181. Morris, R.K. Association of serum PAPP-A levels in first trimester with small

for gestational age and adverse pregnancy outcomes: systematic review and meta-analy- sis / R.K. Morris, A. Bilagi, P. Devani, M.D. Kilby // Prenat. Diagn. – 2017. – Vol. 37, N 3. – P. 253-265.

182. Murray, S.R. Geographical differences in preterm delivery rates in Sweden: A population-based cohort study / S.R. Murray, J. Juodakis, J. Bacelis [et al.] // Acta Obstet. Gynecol. Scand. – 2019. – Vol. 98, N 1. – P. 106-116.

183. Nazarova D. E. et al. THE ROLE OF OXIDANT STRESS IN THE DEVELOPMENT OF PREMATURE CHILDBIRTH //Central Asian Journal of Pediatrics. – 2021. – Т. 2021. – №. 1. – С. 30-36.

184. Nogueira da Gama SG, Martinelli KG, Soares Dias BA, Pereira-Esteves AP, do Carmo Leal M, Dos Santos-Neto ET. A population-based study of the relationship between advanced maternal age and premature/early-term birth in Brazil. Int J Gynaecol Obstet. 2022 Oct;159(1):173-181. doi: 10.1002/ijgo.14057. Epub 2021 Dec 20. PMID: 34860423.

185. Oh, K.J. Evidence that antibiotic administration is effective in the treatment ofa subset of patients with intra-amniotic infection/inflammation presenting with cervical insufficiency / K.J. Oh, R. Romero, J.Y. Park [et al.] // Am. J. Obstet. Gynecol. – 2019.– Vol. 27. – pii: S0002-9378(19) 30495-8. [Epub ahead of print]

186. Oskovi Kaplan, Z.A. Prediction of preterm birth: maternal characteristics, ultrasound markers, and biomarkers: an updated overview / Z.A. Oskovi Kaplan,A.S. Ozgu-Erdinc // J. Pregnancy. – 2018. – Vol. 2018. – P. 8367571.

187. Ottolini KM, Andescavage N, Keller S, Limperopoulos C. Nutrition and the developing brain: the road to optimizing early neurodevelopment: a systematic review. Pediatr Res. 2020 Jan;87(2):194-201. doi: 10.1038/s41390-019-0508-3. Epub 2019 Jul 26. PMID: 31349359; PMCID: PMC7374795.

188. Palacio, M. Uterine cervical length measurement to reduce length of stay in patients admitted for threatened preterm labor: a randomized trial / M. Palacio, J. Carad- eux, M. Sánchez [et al.] // Fetal. Diagn. Ther. – 2018. – Vol. 43, N 3. – P. 184-190.

189. Park, H. Plasma inflammatory and immune proteins as predictors of intra-am-

niotic infection and spontaneous preterm delivery in women with preterm labor: a retro- spective study / H. Park, K.H. Park, Y.M. Kim [et al.] // BMC Pregnancy Childbirth. – 2018. – Vol. 18, N 1. – P. 146.

190. Petel, D. Use of C-reactive protein to tailor antibiotic use: a systematic review and meta-analysis / D. Petel, N. Winters, G.C. Gore [et al.] // BMJ Open. – 2018. – Vol. 8, N 12. – P. e022133.

191. Radochova, V. Periodontal disease and intra-amniotic complications in women with preterm prelabor rupture of membranes / V. Radochova, I. Kacerovska Musilova,M. Stepan [et al.] // J. Matern Fetal Neonatal Med. – 2018. – Vol. 31, N 21. – P. 2852- 2861.

192. Rahman MM, Abe SK, Kanda M, Narita S, Rahman MS, Bilano V, Ota E, Gilmour S, Shibuya K. Maternal body mass index and risk of birth and maternal health outcomes in low- and middle-income countries: a systematic review and meta-analysis. Obes Rev. 2015;16(9):758-70. doi: 10.1111/obr.12293. Epub 2015 Jun 11. PMID: 26094567.

193. Rahmati, S. The relationship between maternal anemia during pregnancy with preterm birth: a systematic review and meta-analysis / S. Rahmati, MiladAzami,N. Parizad, K. Sayehmiri // J. Matern. Fetal. Neonatal Med. – 2018. – Vol. 6. – P. 1-151.

194. Ravi, M. Evaluation of the quantitative fetal fibronectin test and PAMG-1 test for the prediction of spontaneous preterm birth in patients with signs and symptoms sug- gestive of preterm labor / M. Ravi, M. Beljorie, K. Masry // J. Matern. Fetal. Neonatal. Med. – 2018. – May 28. – P. 1-6. [Epub ahead of print].

195. Roman A, Ramirez A, Fox NS. Prevention of preterm birth in twin pregnancies. Am J Obstet Gynecol MFM. 2022 Mar;4(2S):100551. doi: 10.1016/j.ajogmf.2021.100551. Epub 2021 Dec 8. PMID: 34896357.

196. Ronzoni S, Cobo T, D'Souza R, Asztalos E, O'Rinn SE, Cao X, Herranz A, Melamed N, Ferrero S, Barrett J, Aldecoa V, Palacio M. Individualized treatment of preterm premature rupture of membranes to prolong the latency period, reduce the rate of preterm birth, and improve neonatal outcomes. Am J Obstet Gynecol. 2022

Aug;227(2):296.e1-296.e18. doi: 10.1016/j.ajog.2022.02.037. Epub 2022 Mar 5. PMID: 35257664.

197. Rydze RT, Wang S, Schoyer KD. Preterm birth: is it the patient or the process? Fertil Steril. 2021 Mar;115(3):583-584. doi: 10.1016/j.fertnstert.2021.01.021. PMID: 33712102.

198. Santipap, M. Combination of three-dimensional ultrasound measurement of foetal adrenal gland enlargement and placental alpha microglobulin-1 for the prediction of the timing of delivery within seven days in women with threatened preterm labour and preterm labour / M. Santipap, V. Phupong // J. Obstet. Gynaecol. – 2018. – Vol. 38, N 8.– P. 1054-1059.

199. Schummers, L. Association of Short Interpregnancy Interval With Pregnancy Outcomes According to Maternal Age / L. Schummers, J.A. Hutcheon, S. Hernandez- Diaz [et al.] // JAMA Intern Med. – 2018. – Vol. 178, N 12. – P. 1661-1670.

200. Seidmann, L. Immaturity for gestational age of microvasculature and placental barrier in term placentas with high weight / L. Seidmann, Y. Kamyshanskiy, S.Z. Martin [et al.] // Eur. J. Obstet. Gynecol. Reprod Biol. – 2017. – Vol. 215. – P. 134-140.

201. Sethumadhavan, S.P. Cervical length measurement by transvaginal sonography in predicting preterm labour in low risk women / Sandeep Sethumadhavan P., Raju Agarwal, Jayamol M. Anilkumar, Anup Ramchandran Pillai // Int. J. Reprod. Contracept. Obstet. Gynecol. – 2017. – Vol. 6, N 12. – P. 5563-5567.

202. Sharma N, Watkins OC, Chu AHY, Cutfield W, Godfrey KM, Yong HEJ, Chan SY. Myo-inositol: a potential prophylaxis against premature onset of labour and preterm birth. Nutr Res Rev. 2023 Jun;36(1):60-68. doi: 10.1017/S0954422421000299. Epub 2021 Sep 16. PMID: 34526164; PMCID: PMC7614523.

203. Silva TV, Bento SF, Katz L, Pacagnella RC. "Preterm birth risk, me?" Women risk perception about premature delivery - a qualitative analysis. BMC Pregnancy

Childbirth. 2021 Sep 18;21(1):633. doi: 10.1186/s12884-021-04068-x. PMID: 34537000; PMCID: PMC8449432.

204. Šimják, P. Proactive approach at the limits of viability improves the short-term outcome of neonates born after 23 weeks' gestation / P. Šimják, J. Smíšek, M. Koucký [et al.] // J. Perinat. Med. – 2018. – Vol. 46, N 1. – P. 103-111.

205. Smith, C.J. Maternal dyslipidemia and risk for preterm birth. / Smith C.J., Baer R.J., Oltman S.P. [et al.] // PLoS One. 2018 Dec 21;13(12):e0209579.

206. Son, M. Predicting preterm birth: Cervical length and fetal fibronectin / M. Son,E.S. Miller // Semin Perinatol. – 2017. – Vol. 41, N 8. – P. 445-451.

207. Sundrani, D. Investigating the expression of MMPs and TIMPs in preterm pla- centa and role of CpG methylation in regulating MMP-9 expression / D. Sundrani,A. Narang, S. Mehendale [et al.] // IUBMB Life. – 2017. – Vol. 69, N 12. – P. 985-993.

208. Swiatkowska-Freund, M. Cervical elastography during pregnancy: clinical per- spectives / M. Swiatkowska-Freund, K. Preis // Int. J. Womens Health. – 2017. – Vol. 21, N 9. – P. 245-254.

209. Troncoso, F. Gestational diabetes mellitus is associated with increased pro-mi- gratory activation of vascular endothelial growth factor receptor 2 and reduced expression of vascular endothelial growth factor receptor 1 / F. Troncoso, J. Acurio, K. Herlitz [et al.] // PLoS One. – 2017. – Vol. 12, N 8. – P. e0182509.

210. Tsikouras, P. Comparative Evaluation of Arabin Pessary and Cervical Cerclage for the Prevention of Preterm Labor in Asymptomatic Women with High Risk Factors /P. Tsikouras, G. Anastasopoulos, V. Maroulis [et al.] // Int. J. Environ. Res. Public. Health. – 2018. – Vol. 15(4). – P. pii: E791.

211. Varley-Campbell, J. Three biomarker tests to help diagnose preterm labour: a systematic review and economic evaluation / J. Varley-Campbell, R. Mújica-Mota,H. Coelho [et al.] // Health Technol Assess. – 2019. – Vol. 23, N 13. – P. 1-226.

212. Vaz, S.A. Diagnosis and Management of Congenital Uterine Anomalies in Pregnancy / S.A. Vaz, S.K. Dotters-Katz, J.A. Kuller // Obstet. Gynecol. Surv. –

2017. – Vol. 72, N 3. – P. 194-201.

213. Victora, J.D. Collaborators: Pelotas Cohorts Study Group. Prevalence, mortality and risk factors associated with very low birth weight preterm infants: an analysis of 33 years / J.D. Victora, M.F.D. Silveira, C.T. Tonial [et al.] // J. Pediatr. (Rio J). – 2018.– Dec 12. – P. pii: S0021-7557(18) 30631-4 [Epub ahead of print].

214. Vieira VS, Feiten TDS, Ferrari RS, Dalcin PTR, Ziegler B. Predictive factors for premature birth and respiratory exacerbation in pregnancies of women with cystic fibrosis. J Pediatr (Rio J). 2022 Jan-Feb;98(1):33-38. doi: 10.1016/j.jped.2021.02.009. Epub 2021 Jun 8. PMID: 34115976; PMCID: PMC9432334.

215. Vitti, F.P. Association between Caffeine Consumption in Pregnancy and Low Birth Weight and Preterm Birth in the birth Cohort of Ribeirão Preto / F.P. Vitti,C. Grandi, R.C. Cavalli [et al.] // Rev. Bras. Ginecol Obstet. – 2018. – Vol. 40, N 12. – P. 749-756.

216. Walani SR. Global burden of preterm birth. Int J Gynaecol Obstet. 2020 Jul;150(1):31-33. doi: 10.1002/ijgo.13195. PMID: 32524596.

217. Yamaguchi, A. Risk of preterm birth, low birthweight and small-for-gestational-age infants in pregnancies with adenomyosis: A cohort study of the Japan Envi- ronment and Children's Study / A. Yamaguchi, H. Kyozuka, K. Fujimori [et al.] // Acta Obstet Gynecol Scand. – 2019. – Vol. 98, N 3. – P. 359-364

218. Yue, H. Gestational exposure to PM(2.5) impairs vascularization of the placenta / H. Yue, X. Ji, Y. Zhang [et al.] // Sci Total Environ. – 2019. – Vol. 665. – P. 153-161.

219. Zhang, G. Genetic Associations with Gestational Duration and Spontaneous Preterm Birth / G. Zhang, B. Feenstra, J. Bacelis [et al.] // N Engl J Med. – 2017. – Vol. 377, N 12. – P. 1156-1167.

220. Zhang, Y. Maternal haemoglobin concentration and risk of preterm birth in a Chinese population / Y. Zhang, Z. Li, H. Li [et al.] // J. Obstet. Gynaecol. – 2018. – Vol. 38, N 1. – P. 32-37.

221. Zhou Y, Li H, Zhang Y, Zhang L, Liu J, Liu J. Association of Maternal

Obesity in Early Pregnancy with Adverse Pregnancy Outcomes: A Chinese Prospective Cohort Analysis. Obesity (Silver Spring). 2019 Jun;27(6):1030-1036. doi: 10.1002/oby.22478. Epub 2019 May 8. PMID: 31070002.