Получена: 07 августа 2021 / Принята: 27 января 2022 / Опубликована online: 28 февраля 2022

DOI 10.34689/SH.2022.24.1.019

УДК 618.396+616-084

A MODERN VIEW ON THE ETHIOPATOGENESIS OF PRETERN BIRTH. REVIEW.

Anna S. Nikolaeva[1], https://orcid.org/0000-0002-2642-5141

Guliash A. Tanysheva[1], http://orcid.org/0000-0002-9074-6302

Zhanylsyn A. Ryspaeva[1], http://orcid.org/0000-0002-1063-7908

Zhanar M. Zhumanbayeva[1], http://orcid.org/0000-0001-8941-862X

NJSC «Semey Medical University», [1] Department of Obstetrics and Gynecology, [2] Department of Nursing, Semey city, Republic of Kazakhstan.

Abstract

Introduction: Among all pregnancies worldwide, approximately 5 to 18% end prematurely, a major cause of infant morbidity and mortality. About 70% are spontaneous preterm births and have multiple comorbid causes. Prevention and treatment of preterm birth is an unresolved worldwide problem in modern obstetrics. It is for this reason that studying the pathogenetic mechanisms of preterm birth, which threaten the health and well-being of future generations and represents a major scientific challenge requiring both moral and material investment.

Aim: An analysis of the literature on the role of etiopathogenetic mechanisms of preterm birth.

Search strategy: Sources were searched in PubMed, Medline, Cochrane Library, Web of Science, Embase and Google Scholar, e-Library. The depth of the search was 10 years, from 2011 to 2021. *Inclusion criteria:* full-text articles in Russian and English, reports of cohort and randomized trials describing different etiopathogenetic mechanisms of preterm birth. This review did not include publications describing single cases, abstracts of reports, personal communications and abstracts.

Results: The search retrieved 797 articles. After reviewing titles, abstracts, and full text, 80 sources were selected for detailed review, describing all currently known etio-pathogenetic mechanisms of preterm birth. Among the most significant are the following:

1. activation of the central nervous system (pituitary and hypothalamus) by both the fetus and the mother;
2. preterm birth associated with the development of pregnancy complications, such as: detachment of the normally located placenta, severe pre-eclampsia, acute placental insufficiency, etc.;
3. triggering an inflammatory reaction and involvement of the uterine-placental complex, both with and without the identification of an infective agent.

Conclusions: The analysis of the sources once again demonstrates the polyetiology of the problem. It is clear that preterm birth continues to be an issue for a long time due to the lack of a complete understanding of the pathogenetic mechanisms.

Key words: *preterm birth, etiology, pathogenesis, factors.*

Резюме

СОВРЕМЕННЫЙ ВЗГЛЯД НА ЭТИОПАТОГЕНЕЗ ПРЕЖДЕВРЕМЕННЫХ РОДОВ. ОБЗОР ЛИТЕРАТУРЫ.

Анна С. Николаева[1], https://orcid.org/0000-0002-2642-5141

Гульяш А. Танышева[1], http://orcid.org/0000-0002-9074-6302

Жанылсын А. Рыспаева[1], http://orcid.org/0000-0002-1063-7908

Жанар М. Жуманбаева[1], http://orcid.org/0000-0001-8941-862X

НАО «Медицинский университет Семей», [1] Кафедра акушерства и гинекологии, [2] Кафедра сестринского дела, г. Семей, Республика Казахстан.

Введение: Среди всех беременностей в мире примерно от 5 до 18% заканчиваются преждевременно, что является одной из основных причин младенческой заболеваемости и смертности. Около 70% – спонтанные преждевременные роды, имеют множество сочетанных причин. Профилактика и лечение преждевременных родов – это нерешенная мировая проблема в современном акушерстве. Именно поэтому изучение патогенетических механизмов преждевременных родов, которые ставят под угрозу здоровье и благополучие будущих поколений и представляет собой серьезный научный вызов, требующий как моральных, так и материальных вложений.

Цель: анализ данных литературы о роли этиопатогенетических механизмов преждевременных родов.

Стратегия поиска: поиск источников был проведен в базах PubMed, Medline, Cochrane Library, Web of Science, Embase и Google Scholar, e-Library. Глубина поиска составила 10 лет, с 2011 г. по 2021г. *Критерии включения*: полнотекстовые статьи на русском и английском языках, отчеты о когортных и рандомизированных исследованиях, описывающих различные этиопатогенетические механизмы преждевременных родов. В данный обзор не были включены публикации, описывающие единичные случаи, резюме докладов, личные сообщения и тезисы.

Результаты: В результате поиска было обнаружено 797 статей. После обзора заголовков, выдержек и полного текста было отобрано 80 источников для подробного изучения, в которых были описаны все известные на сегодняшний день этиопатогенетические механизмы преждевременных родов. Среди наиболее значимых можно выделить следующие:

1. активация центральной нервной системы (гипофиза и гипоталамуса) как со стороны плода, так и со стороны матери;
2. преждевременные роды, связанные с развитием осложнений беременности, таких как: отслойка нормально расположенной плаценты, тяжелой преэклампсии, острой плацентарной недостаточности и т.д.;
3. запуск реакции воспаления и вовлечения в нее маточно-плацентарного комплекса, как при идентификации инфекционного агента, так и без.

Выводы: проведенный анализ источников в очередной раз доказывает полиэтиологичность данной проблемы. Становится совершенно ясно, что проблема преждевременных родов продолжает быть актуальной на протяжении длительного времени в виду недостаточно полного представления о патогенетических механизмах.

Ключевые слова: *преждевременные роды, этиология, патогенез, факторы.*

Түйіндеме

МЕРЗІМІНЕН БҰРЫН БОСАНУДЫҢ ЭТИОПАТОГЕНЕЗІНЕ ЗАМАНАУИ КӨЗҚАРАС. ӘДЕБИЕТТІК ШОЛУ.

Анна С. Николаева[1], https://orcid.org/0000-0002-2642-5141

Гульяш А. Танышева[1], http://orcid.org/0000-0002-9074-6302

Жанылсын А. Рыспаева[1], http://orcid.org/0000-0002-1063-7908

Жанар М. Жуманбаева[1], http://orcid.org/0000-0001-8941-862X

КеАҚ «Семей медициналық университеті», [1] Акушерия және гинекология кафедрасы, [2] Мейіргер ісі кафедрасы, Семей қ., Қазақстан Республикасы.

Әлемдегі барлық жүктіліктің шамамен 5 - тен 18% - ы мерзімінен бұрын аяқталады, бұл нәрестелер мен өлім-жітімнің негізгі себептерінің бірі. Шамамен 70% - өздігінен мерзімінен бұрын босану, көптеген біріктірілген себептер бар. Мерзімінен бұрын босанудың алдын алу және емдеу қазіргі заманғы акушериядағы шешілмеген әлемдік проблема болып табылады. Сондықтан болашақ ұрпақтардың денсаулығы мен әл-ауқатына қауіп төндіретін және моральдық және материалдық салымдарды қажет ететін маңызды ғылыми сынақ болып табылатын мерзімінен бұрын босанудың патогенетикалық механизмдерін зерттеу.

Мақсаты: мерзімінен бұрын босанудың этиопатогенетикалық механизмдерінің рөлі туралы әдебиеттер деректерін талдау.

Іздену стратегиясы: деректерді іздеу PubMed, Medline, Cochrane Library, Web of Science, Embase және Google Scholar, e-Library базаларында жүргізілді. Іздеу тереңдігі 2011 жылдан 2021 жылға дейін 10 жылды құрады. *Қосылу критерийлері:* орыс және ағылшын тілдеріндегі толық мәтінді мақалаларды, ерте босанудың әртүрлі этиопатогенетикалық механизмдерін сипаттайтын когорттық және рандомизацияланған зерттеулер туралы есептерді енгіздік. Бұл шолуға оқшауланған жағдайларды сипаттайтын жарияланымдар, баяндамалардың түйіндемелері, жеке хабарламалар мен тезистер енгізілмеген.

Нәтижелер: іздеу нәтижесінде 797 мақала табылды. Тақырыптарды, үзінділерді және толық мәтінді қарап шыққаннан кейін, егжей-тегжейлі зерттеу үшін 80 дереккөз таңдалды, онда мерзімінен бұрын босанудың барлық белгілі этио-патогенетикалық механизмдері сипатталған. Ең маңыздыларының ішінде мыналарды бөлуге болады:

1. орталық жүйке жүйесін (гипофиз және гипоталамус) ұрық жағынан да, ана жағынан да белсендіру;
2. жүктіліктің асқынуының дамуымен байланысты мерзімінен бұрын босану, мысалы: қалыпты орналасқан плацентаның бөлінуі, ауыр преэклампсия, жедел плацентарлы жеткіліксіздік және т. б.;
3. инфекциялық агентті анықтау кезінде де, онсыз да қабыну реакциясын және оған жатыр-плацентарлы кешенді тарту.

Қорытынды: дереккөздерге жасалған талдау осы мәселенің полиэтиленизмін тағы бір рет дәлелдейді. Патогенетикалық механизмдер туралы толық түсінік болмағандықтан, мерзімінен бұрын босану мәселесі ұзақ уақыт бойы өзекті болып қала беретіні анық.

Түйінді сөздер*: мерзімінен бұрын босану, этиология, патогенез, факторлар.*

Библиографическая ссылка:

Nikolaeva A.S., Tanysheva G.A., Ryspaeva Zh.A., Zhumanbayeva Zh.M. A modern view on the ethiopatogenesis of pretern birth. Review // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2022, (Vol.24) 1, pp. 167-177. *doi 10.34689/SH.2022.24.1.019*

Николаева А.С., Танышева Г.А., Рыспаева Ж.А., Жуманбаева Ж.М. Современный взгляд на этиопатогенез преждевременных родов. Обзор литературы // Наука и Здравоохранение. 2022. 1(Т.24). С. 167-177. *doi 10.34689/SH.2022.24.1.019*

Николаева А.С., Танышева Г.А., Рыспаева Ж.А., Жуманбаева Ж.М. Мерзімінен бұрын босанудың этиопатогенезіне заманауи көзқарас. Әдебиеттік шолу // Ғылым және Денсаулық сақтау. 2022. 1 (Т.24). Б. 167-177. *doi 10.34689/SH.2022.24.1.019*

Introduction:

Preterm birth is one of the major problems present in midwifery today, as the number of preterm births has had absolutely no decreasing trend for a long time, but on the contrary continues to increase. The percentage of preterm births ranges from 11% to 18% worldwide [13]. According to data reported by WHO, the countries with the highest percentage of preterm births are as follows: India: 3,519,100 China: 1,172,300 Nigeria: 773,600 Pakistan: 748,100 Indonesia: 675,700 United States of America: 517,400 Bangladesh: 424,100 Philippines: 348,900 Democratic Republic of Congo: 341,400 Brazil: 279,300 [26]. In Kazakhstan, about 100,000 babies are born prematurely every year.

Rather common causes of preterm birth include social, infectious, endocrine, immune, as well as structural abnormalities of the cervix, thrombophilias of various origins and a poor family history. Naturally, the outcome of labour for the foetus depends on gestational age, the most unfavourable being between 22 and 27 weeks. This is because the maturation of all fetal organs and systems is interrupted very early and there is a high risk of mortality among newborns. In preterm birth, there is often a detachment of the normal or low placenta, abnormal fetal position, breech presentation, rapid or rapid delivery, in which the risk of perinatal fetal and neonatal death is increased several times, as well as various complications on the part of the mother [17, 14]. Risk factors include medical factors such as a history of premature birth, spontaneous miscarriage, abortion, inflammatory diseases of the genitals and urinary tract infections, as well as sociodemographic factors such as young age, low social level, unsettled family life, etc. [18, 19]. A major role in the occurrence of preterm birth is played by various diseases that a pregnant woman has had [18, 19]. A special place is occupied by viral infections, including acute respiratory viral infections suffered during pregnancy. There has also been an increase in the number of women in a risk group for the development of preterm birth, such as patients with a uterine scar, severe extragenital diseases, polyhydramnios, multiple pregnancy failure, etc. The widespread use of reproductive technologies contributes to this and is one of the risk factors for preterm birth.

Preterm birth has a number of complications and is the cause of high infant mortality and disability. In order to reduce the number of preterm births and the complications associated with them, the World Health Organization has developed a series of recommendations to improve perinatal outcomes and long-term consequences. This has been made possible by a number of interventions such as

● use of corticosteroids in the antenatal period, which significantly reduces mortality, the rate of cerebral palsy, the duration of artificial ventilation and the risk of severe VTE [61];

● Improvements in neonatal ventilation, in particular the use of cPAP.

● use of a surfactant;

● use of magnesium sulphate, which reduces the risk of cerebral palsy and other musculoskeletal complications.

● use of antibiotics in asymptomatic bacteriuria, in preterm antenatal rupture of amniotic fluid, in order to reduce infectious complications in both the woman and the foetus.

● Kangaroo method (Kangaroo mother care) [77].

In addition, organisations such as WHO and UNICEF have emphasised the need for research to better understand and find new pathogenetic mechanisms of preterm birth. They also emphasise the need for increased financial investment and the formation of specialised working groups to address this issue [26]. For example, the International Federation of Gynaecology and Obstetrics (FIGO) has for a long time had a working group whose main task is: to identify the main risk factors for preterm birth, to develop treatment and diagnostic measures for this obstetric problem, taking into account the pathogenetic features.

Aim: An analysis of the literature on the role of etiopathogenetic mechanisms of preterm birth.

Search strategy: the main sources of information were the following databases: Pub-Med, Medline, Cochrane Library, Web of Science, Embase and Google Scholar, e-Library. Search period: 2011 to 2021.

For the analysis of this problem were selected articles in Russian and English, which were in the public domain with full content. Questionable publications and reports were not included in this analysis.

The search turned up 797 articles. After reviewing the titles, abstracts and full text, 80 sources were selected for detailed study, in which all currently known etiopathogenetic mechanisms of preterm birth were described.

A search for sources is shown in the table below

Database	Found sources on the subject	Met the criteria for inclusion
PubMed	190	36
Medline	113	9
Cochrane Library	98	5
Web of Science	110	6
Embase	76	3
Google Scholar	106	10
e-Library	104	11

Results. During the literature review, the main factors and pathogenetic mechanisms of preterm birth were studied and summarised.

Factors of preterm birth.

The factors of preterm birth include:

- maternal causes ((pregnancy out of wedlock, low socioeconomic status, not following a healthy lifestyle (alcohol, tobacco, drug use), low body mass index (less than 20 kg/m 2), obesity, malnutrition, (deficiency of copper and ascorbic acid obtained with food), anemia,) long-term treatment with steroids, vascular collagen disorders));

- Fetal causes (multiple births, large foetuses, congenital foetal malformations, endocrine disorders and endangered foetal conditions);

- Uteroplacental (uterine abnormalities (cavity septum), premature detachment of the normally located placenta (10-15%), shortening of the cervix in the second trimester to 2.5 cm due to progressive ismicocecal insufficiency, previous cervical conization, uterine overstretch due to polygynous or multiple pregnancy, chorioamnionitis, multiple vaginal bimanual or transvaginal ultrasound examinations).

Pregnant women who undergo invasive diagnostic techniques (amniocentesis, chorionic biopsy) and cervical suturing for ischemic-cesteral insufficiency are at risk of

mechanical iatrogenic injury during diagnostic or therapeutic procedures.

Pathogenetic mechanisms of preterm birth.

The main pathogenetic links studied and proven to date are:

1. Activation of the central nervous system, such as the pituitary gland and hypothalamus, by both the fetal and maternal body;
2. Premature birth associated with the development of pregnancy complications, such as: detachment of the normally located placenta, severe gestosis, acute placental insufficiency, delayed intrauterine development, etc.;
3. Triggering an inflammatory reaction and involvement of the uterine-placental complex, with or without the identification of an infective agent.
4. Premature development of labour for an unclear reason.

1. The central nervous system.

The hypothalamic-pituitary trigger mechanism begins with the occurrence of stressful situations, manifested by feelings of fear, depression, anxiety, to which the production of cortisol increases, both by the mother and the foetus, and the increased production of corticotropin-releasing hormone by the hypothalamus and the placenta (46). This in turn increases the production of corticotropin-releasing hormone in the uterine-placental complex and of prostaglandins E and F2α, and hence activates the onset of labour (31). This pathogenetic mechanism explains the fact that women suffering from depression are twice as likely to develop preterm birth as pregnant women with a more stable psyche.

2. Complications leading to preterm birth.

Preterm birth due to complications of pregnancy or exacerbation of pre-existing chronic diseases of the mother, in which the termination of pregnancy is necessary in order to preserve the life of the mother and the foetus. These situations occur most commonly in severe pre-eclampsia, eclampsia, placental insufficiency, compensatory hemorrhage, etc. Thus, according to a study by E L Davies et al. (2016) the rate of preterm births with pre-eclampsia was almost 4 times higher than in women without the complication. Severe pre-eclampsia increases the risk of extremely early preterm delivery by 5-fold compared with women without pre-eclampsia, and the rate of early preterm delivery in women with severe preeclampsia was, as high as 25% (32).

Chronic diseases such as arterial hypertension, which increases the risk of preterm birth by 2.7-fold [78, 25], chronic kidney disease increases the risk by 5.7-fold [64], diabetes mellitus, according to the study of S.T.Mackin et al. (2018) significantly increases the risk of realisation of preterm birth (with type -1 diabetes increases the risk to 35.3%, type -2 diabetes - 21.8%, while in the control group was only 6.1% ($p < 0.0001$);

3. An infectious factor.

The importance of infection in the pathogenesis of preterm birth is not in doubt, as a huge number of studies over decades have shown a direct link between the presence of an infective agent and preterm birth [16, 2, 62, 77, 33]. In about 20-75% of cases of preterm birth of infectious genesis, there are histological signs of chorioamnionitis; in 30-60% of cases, the causative agent is detected in cultures (45, 7). Although this pathogenetic mechanism has been studied for a long time, various authors show a relationship between preterm birth and various pathogens, the most significant being group B streptococci, Chlamydia trachomatis, Neisseria gonorrhea, Treponema, Trichomonas vaginalis and Haemophilus influenzae [45].

Bacterial vaginosis is also a frequent cause of preterm birth [41, 8].

Recent studies that have investigated the causes of preterm birth have shown that women with bacterial vaginosis (BV) are at higher risk of developing preterm birth spontaneously. Bacterial vaginosis and urogenital candidiasis increase the risk of pregnancy complications such as chorioamnionitis, preterm birth, intrauterine infection of the foetus, polyhydramnios, untimely rupture of amniotic fluid by 2-6 times (52). In pregnancy, BV is found in 15-37 % of women, and it is twice as frequent in the first trimester (24-37 %) than in the second and third trimesters (9-18 %) [41]. The incidence of pregnancy failure in bacterial vaginosis is 21%, of which patients with recurrent failure to conceive account for 52.3%. Bacterial vaginosis is a disorder of the vaginal microbiocenosis that occurs when normal microflora (Lactobacillus sp., producing hydrogen peroxide) are replaced predominantly by anaerobes (Prevotella sp., Mobiluncus sp., Gardnerella vaginalis) and other microorganisms (Mycoplasma hominis), with no clinical signs of vaginal inflammatory changes [41, 8]. As for urogenital candidiasis, a meta-analysis by H.J. Schuster et al. Schuster et al. in 2020, about 30 species of Candida fungi are not responsible for the development of preterm birth [70].

Many researchers describe a correlation between asymptomatic bacteriuria and adverse pregnancy outcomes. Asymptomatic bacteriuria poses a risk to both the pregnant woman and the foetus. According to the World Health Organisation, about 8% of women have asymptomatic bacteriuria, and 15-57% of women with untreated asymptomatic bacteriuria develop symptoms of urogenital tract diseases, such as acute cystitis, pyelonephritis, etc. Therapy of this condition is essential during pregnancy as it reduces the risk of acute urinary tract infections, premature delivery and extremely low birth weight of the newborn.

The diagnosis of asymptomatic bacteriuria is made when 105 CFU/ml of a single bacterial strain or 102 CFU/ml of Escherichia coli uropathogen in 2 urine samples taken >4 h apart and containing >10 leucocytes per field of view in the absence of clinical manifestations of urinary system disease.

It should be remembered that the risk of this pathology is greatest between 9-17 weeks of pregnancy. This is the most appropriate time for the examination. The only reliable method to diagnose asymptomatic bacteriuria is the urine culture method.

International guidelines recommend antimicrobial treatment for asymptomatic bacteriuria as a preventive measure against the risk of preterm birth, low birth weight and perinatal mortality [66, 71]. For example, among patients with asymptomatic bacteriuria, preterm birth is twice as common (13.3% versus 7.6%; $p < 0.001$) [71, 69].

In addition to urogenital tract infections, numerous studies have now focused on periodontal infections (119). To date, there are a number of hypotheses linking periodontal disease and preterm birth [48, 37, 47, 27]. The main flora of periodontal disease are pathogens such as

Tannerella forsythia, Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, Treponema denticola, Fusobacterium nucleatum, which can cause local inflammation or, through inflammatory mediators, activate systemic inflammation.

Thus, the presence of an infectious agent with any localisation in a pregnant woman's body leads to the binding of infectious ligands to toll-like receptors (TLRs) in the decidua, amnion, chorion and cervix and this, in turn, activates the response mechanism of the inflammatory response. Toll-like receptors (TLRs) are receptors for innate immunity and are widely present on various cells in the body. The initial mediators of this response are IL-1β and TNF-α, which enhance prostaglandin production by inducing the expression of cyclooxygenase-2 (COX-2) in the amnion and decidua, while inhibiting the prostaglandin metabolizing enzyme, 15-hydroxyprostaglandin dehydrogenase in the chorion [75,30].

In addition, these mediators enhance the work of matrix metalloproteinases, which contribute to the destruction of the extracellular matrix of the fetal membranes and cervix [72, 36, 57]. This mechanism leads to cervical softening during pregnancy due to a reduction in proteoglycans, which causes collagen bundle breakdown [5]. Cervical maturation is accompanied by an inflammatory response and hence by an increase in pro-inflammatory cytokines and leukocytic infiltration of cervical tissue. I. Osman et al. (2006) determined that the proinflammatory cytokine IL-8 is 11-fold higher in the mature cervix than in the immature cervix [58]. Cytokines contribute to the secretion of different types of metalloproteinases in the cervix, inferior uterine segment, amniotic membranes and amniotic fluid during labour [73, 67]. They, in turn, change the structural composition of the collagen fibres of the cervix, which contributes to its softening, shortening and opening.

Prostaglandins, which are synthesised in the arachidonic acid cycle, under the influence of cyclooxygenase enzymes, are of no small importance in the genesis of preterm birth. Cyclooxygenase-1 (COX-1) is permanently present in the cervix, but cyclooxygenase-2 (COX-2) is triggered by inflammatory mediators. In turn, COX-2 activates the arachidonic acid cycle and this increases the levels of prostaglandins E2 and F2α, which promote cervical 'maturation' and stimulate uterine contractions.

Also, when the inflammatory response is triggered, the number of oxytocin receptors increases dramatically, causing uterine contractions [54, 39].

Thus, preterm birth of infective genesis is realised by activation of the 'cervical maturation' process and uterine contractions through toll-like receptors.

Unfortunately, about 30-50% of cases of unclear genesis are so-called spontaneous preterm births and are of particular interest to researchers, as understanding their pathogenesis will allow the development of preventive measures and generally reduce the percentage of preterm births and complications associated with them;

4. Immunological and molecular genetic aspects of the pathogenesis of spontaneous preterm birth.

To date, the development of the inflammatory process in the absence of an infectious agent of spontaneous preterm birth remains incompletely understood. A significant increase in proinflammatory cytokines in amniotic fluid, uterus, placenta, umbilical cord blood and fetus indicates the initiation of an inflammatory response during spontaneous preterm birth [1, 15, 23, 59].

That is why a large number of scientists are currently paying a lot of attention to the study of the immunological and molecular genetic aspects of the pathogenesis of spontaneous preterm birth it has been proved that the state of the immune system during pregnancy determines its outcome.

For example, an increase in the level of proinflammatory cytokines in the pregnant woman's plasma precedes pregnancy termination [10]. Pregnancy is a very complex process in which a fetus containing paternal antigens is partly a foreign body to the woman's body. It is the mother-placenta-fetus system that contributes to the creation of a unique immunological situation that contributes to prolonged pregnancy. During pregnancy, syncytiotrophoblast, which forms the outer layer of placental villi and is exposed to maternal blood, but does not express class 1 HLA-antigens on its surface and is 'not visible' to the maternal immune system [21]; a number of changes also occur in the trophoblast, such as the production of active substances that activate and stimulate apoptosis of maternal T- lymphocytes (e.g. protein B7H1, IDO) [21, 50, 24]; Trophoblast cells produce regulatory proteins for the complement system (CD46, CD55, CD59) and this helps to protect fetal tissue from cytotoxic maternal antibodies [21, 42]; in utero: a large number of decidual macrophages with anti-inflammatory activity (M2 phenotype) appear, which in turn secrete immunosuppressive factors, reducing inflammatory responses in the mother-placenta-fetal system.

This immunological process is seen not only in preterm birth, but also in pre-eclampsia and placental insufficiency.

Progesterone also has a direct effect on the production of anti-inflammatory cytokines in placental cells (e.g. IL-10); it also helps to suppress the maternal immune response and changes the balance of Th1\Th2-helpers towards the anti-inflammatory state of Th2 and blocks TNF-α synthesis [21, 74].

It should be noted that all these changes are predominantly local in nature and there is no generalised maternal immunosuppression during pregnancy [21]. Many immunologists agree that pregnancy is an anti-inflammatory state. However, when the balance, for one reason or another, shifts to the pro-inflammatory side, there is an increase in the production and concentration of cytokines in the uteroplacental complex, then spontaneous miscarriages and other pregnancy complications occur [6]. For example, increased IL-6, IL-1β and TNF-α in plasma, cervico-vaginal secretion and amniotic fluid are associated with a high risk of premature births [38, 11].

The study of the immunological factor in the development of preterm birth has a long history. Researchers have studied the balance of pro-inflammatory cytokines and anti-inflammatory cytokines in different biological media and in different combinations. Each of the studies has shown the crucial importance in the processes of fetal implantation, placental preparation and pregnancy outcome of certain components of immunity [38, 11]. For example, F. Hertelendy et al. (2002) determined that IL-1β and TNF-α stimulate the release of arachidonic acid and increase the production of prostaglandins in the

myometrium, these processes are similar to the action of oxytocin [40], and a little later J. Dowd et al. (2005) found a significant increase in IL-8 concentration in cervical mucus in women whose pregnancies ended subsequently in preterm birth, R. Romero et al. (2007) found that the increased levels of proinflammatory cytokines (IL-1, IL-6, IL8, TNF-α) in amniotic fluid are directly proportional to the risk of developing preterm birth, and they also found increased concentrations of proinflammatory cytokines in the lungs, intestine, liver and brain of the fetus [63; 34]. Of recent studies in this direction, a significantly increased concentration of IL-1β, IL-6, IL-8, TNF-α, IL-17A, interferon-γ-induced protein-10 in blood, amniotic fluid or cervical-vaginal lavage samples from patients with spontaneous premature birth compared to normal birth was found by J.M. Fettweis et al. (2019).

We would like to elaborate further on the role of tumour necrosis factor (TNF-α) TNF-α during pregnancy. According to the literature, a certain level of TNF-α is necessary for the normal development of pregnancy, as in early gestation it interacts with receptors expressed on the surface of the trophoblast, thereby protecting it from the action of maternal cytotoxic lymphocyte clones.

In the serum of healthy pregnant women, tumour necrosis factor is almost undetectable, but if an infective agent of viral or bacterial nature enters the body, TNF-α concentrations increase tenfold. It is known that high concentrations of this cytokine can increase inflammation and trigger apoptosis of trophoblast cells, thus causing serious complications such as placental detachment and premature delivery [22, 79].

Overproduction of TNF-α can adversely affect the development of pregnancy. A study by V.M. Sidelnikova (2010) found a significant increase in TNF-α levels in the blood of women in the 3rd trimester with threatened fetus compared with a normal pregnancy [15]. There are also studies proving that TNF-α can induce amnion epithelial cell death and hence lead to premature antenatal expulsion of amniotic fluid. Among other things, proinflammatory cytokines are important in the pathogenesis of preterm birth, which in turn cause leukocyte and endothelial cell activation and complement, which correspond to the acute phase of inflammation.

Speaking of proinflammatory cytokines, one cannot but mention anti-inflammatory cytokines, the increased content of which during pregnancy provides maternal immunosuppression in relation to the forming feto-placental complex [1, 68, 20, 28], and can also form highly active oxygen and nitrogen metabolites, enhance differentiation into cytotoxic Th2 cells, activate macrophages, induce proliferation of NK cells [65]. This eventually suppresses the proinflammatory link and ensures the progression of pregnancy to term.

Summarizing the above described mechanisms, there is no doubt about the role of cytokines in the genesis of preterm birth at present.

In the presence of an infectious agent, the mechanism of increased production of proinflammatory cytokines in the uteroplacental complex is quite clear; this cannot be said for preterm birth of a non-infectious genesis, in which the production of proinflammatory cytokines is also increased. One version of this mechanism may be a genetic predisposition as a result of their gene polymorphism [6].

Given that cytokines are polypeptides, their synthesis begins with gene transcription. Currently, there is evidence of a large variation in the polymorphisms of cytokine genes. One of the most studied and significant SNP polymorphisms is the Leiden mutation. This mutation is represented by the substitution of the guanine nucleotide for the adenine nucleotide at position 1691 in chromosome 1 CGA→CAA and as a result, glutamine is synthesised instead of arginine in factor V, which leads to thrombophilia. It is now known that different polymorphisms have been identified for each pro- and anti-inflammatory cytokine [60]. The major gene polymorphisms of a number of cytokine polymorphisms TNF-α -308G/A (rs1800629) -238G/A (rs361525) -863C/A (rs1800630) IL-6 -174G/C - 572G/C - 597G/A -634C/G IL-1β -511C/T (rs16944) 3953 C/T (rs1143634) 3954 C/T (rs1143644) -31 (rs1143627) IL-1Ra VNTR (intron 2) IL-4 VNTR (intron 3) -589 C/T So, the TNF-α -308G/A polymorphism results in a substitution of the guanine (G) nucleotide for adenine (A) in the regulatory region of the gene. Thus there are people in the population with a normal GG genotype as well as heterozygotes (GA) and homozygotes (AA) with a pathological genotype. Pro- and anti-inflammatory cytokine gene polymorphisms have been shown to play a role in many diseases of inflammatory etiology. For example, such diseases as rheumatoid arthritis and chronic periodontitis [43] occur more frequently in patients with TNF-α gene polymorphism. Whereas the presence of TNF-α -308G/A variant increases the risk of developing metabolic syndrome, type 1 diabetes, bronchial asthma, psoriasis, oncological diseases, including cervical cancer in carriers of oncogenic human papilloma virus (HPV). This genotype variant can also be considered as a marker of the efficacy of hormonal therapy for diseases such as Crohn's disease and ulcerative colitis and rheumatoid arthritis (49).

For women with preterm birth, polymorphisms of different cytokine genes are also quite common. For example, a study by E. Moura et al. (2011) found that different polymorphisms of the TNF-α gene are associated with a high percentage of preterm birth, and in a meta-analysis by J. Cui et al. (2015) found an association between IL-1Ra gene polymorphisms and an increased incidence of preterm birth in their carriers [3, 55, 29]. It is also now known that the IL-4 VNTR gene polymorphism (intron 3), particularly the presence of the 2R allele, increases the risk of early termination of pregnancy (6).

However, despite the current knowledge on this issue, there is still interest in identifying different combinations of gene polymorphisms of several cytokines at once and their direct impact on the frequency and duration of pregnancy termination. It is possible that multiple cytokine gene polymorphisms may be combined in one woman and that these combinations may lead to increased production of pro-inflammatory cytokines during pregnancy and hence to the realization of preterm birth.

A brief mention of the role of toll-like receptors in the pathogenesis of preterm birth was made above.

A little history of this type of receptor: they were discovered in 1985 by the German biologist *Christian Nüsslein-Follhard, and years later Jules Hoffmann* was awarded the Nobel Prize in 2011 for the discovery of their gene. TLRs were first discovered in Drosophila Toll, from which they were given their name. They are innate immunity

receptors and are found in large numbers on various cells of the immune system (monocytes, dendritic cells, leukocytes, etc.), as well as on many other cells of the body (fibroblasts, endothelium, epithelium, cardiomyocytes, etc.). They are all similar in chemical structure and are represented by type I transmembrane glycoproteins. Currently, about 13 types of TLRs have been studied in humans, but their properties have not been adequately studied. TLRs have been found to have a specific relationship with the main groups of pathogens with which multicellular organisms - bacteria, viruses, fungi, and protozoa - are in contact [44]. We would like to point out that TLRs recognize not only exogenous structures, but also endogenous molecules that are released or produced during tissue damage and inflammation - damage-associated molecular fragments (DAMPs). These include heat shock proteins, fibronectin, fatty acids, haem, mitochondrial DNA, ATP, uric acid, heparin sulphate and others [44]. These components, once released, interact with toll-like receptors, resulting in the release of cytokines. This inflammatory process is termed "sterile inflammation" due to the lack of identification of the infectious agent [12, 53]. The mechanism of toll-like receptor functioning begins with the recognition of ligands by toll-like receptors, then an activation signal is generated and pro-inflammatory cytokines (TNF-α, interleukins) begin to be produced and the inflammatory process is realized. Different TLRs ligands, interact with their specific receptors and thereby contribute to the production of different cytokines. For this reason, depending on which combination of toll-like receptors is specific to the cell type of a particular tissue, the immune response will differ according to the characteristics of the tissue.

Discussion

Having studied a large number of literature sources, it is evident that the problem of preterm birth is not losing its relevance at present. This can be seen from the statistics that show a fairly high percentage of preterm births in different countries with different levels of socio-economic development [76, 16, 13]. The consequences of early preterm birth affect all areas of national development and cause huge economic losses due to the huge monetary costs of nursing preterm babies and the treatment of chronic diseases that inevitably develop in these newborns in the near future. In addition, preterm birth tends to recur and the literature suggests that about 2.5 million preterm births worldwide are carried out each year. This is why there are a huge number of different programmes and methodologies around the world aimed at reducing preterm birth. In spite of this, there has been no downward trend in the incidence of preterm birth worldwide over the last 20 years, according to WHO data. This is most likely due to delayed preventive measures aimed at treating the complaints rather than the pathogenetic links. Understanding the pathogenetic mechanisms of preterm birth is therefore a particularly important topic for research at this time. Indeed, in 2015, the WHO led recommendations "On measures to improve the outcomes of preterm birth" were adopted to stimulate research into the causes and pathogenetic links of preterm birth, as well as to improve methods for the prevention of preterm birth and reduce the complications associated with it [77]. It has long been known that the inflammatory process is the main cause of the development of preterm birth, as various variations of pro- and anti-inflammatory cytokines are detected in the uteroplacental complex during preterm birth [35, 34]. The interaction of immune complexes on cyclooxygenases (COX-1 and COX-2) results in the activation of prostaglandins, particularly E and F2α, leading to cervical maturation, uterine contractions and the realization of preterm labour. All these mechanisms, where bacterial and viral ligands activate toll-like receptors, resulting in increased production of pro-inflammatory cytokines and triggering the above described mechanism, are well studied and understood.

However, the nature of the occurrence of high concentrations of proinflammatory cytokines in the absence of an infectious factor remains unclear. And since about half of all preterm births are spontaneous, it is the pathogenesis of these spontaneous preterm births that is of great interest to researchers worldwide. Most likely, the realization of spontaneous preterm birth occurs by the same pathogenetic mechanism, through the activation of toll-like receptors. However, in the absence of an infectious agent it is unclear what can activate TLRs. The following hypothesis for the pathogenesis of preterm birth has been proposed by various researchers. One of the trigger mechanisms for spontaneous PR is premature death of placental cells. As a result of their early death, various cellular fragments (DAMPs) are released, which act as a ligand for toll-like receptors. An increased pro-inflammatory cytokine production in the uterine-placental complex may also be due to a genetically determined propensity for increased production due to cytokine gene polymorphism.

Based on the results of the literature review, a certain structure of pathogenetic mechanisms was formed:

➢ one of the significant pathogenetic mechanisms of spontaneous preterm birth is increased production of pro-inflammatory cytokines and is associated with cytokine gene polymorphisms, and their combination most often leads to very early and early preterm birth;

➢ a trigger mechanism for the activation of premature spontaneous labour is premature placental cell death. Dead placenta cell fragments (DAMPs) are ligands of toll-like receptors whose expression is also increased in spontaneous preterm labour. As a result of their activation, and because of the presence of proinflammatory cytokine gene polymorphisms, there is an increased production of the latter in the utero-placental complex - a process of 'sterile' inflammation is realized;

➢ a comprehensive assessment of the key pathogenetic mechanisms of spontaneous preterm birth is required to develop pathogenetically sound algorithms for antenatal preparation, prevention and management of pregnancy in women at risk of preterm birth.

Conclusions: The analysis of the sources once again demonstrates the polyetiology of the problem. It is clear that preterm birth continues to be an issue for a long time due to the lack of a complete understanding of the pathogenetic mechanisms.

Authors' contribution - All authors contributed equally to the writing of this article.

Conflict of interest - No conflicts of interest have been declared. This material has not been previously submitted for publication in other publications and is not under consideration by other publishers.

Funding - There was no third-party funding or medical representatives for this work.

Литература:

1. *Айламазян Э.К.* Дискуссионные вопросы преждевременных родов // Журн. акушерства и женских болезней. 2013. № 4. С. 97-105.

2. *Белоусова В.С., Стрижаков А.Н. и др.* Преждевременные роды: от понимания патогенеза к тактике ведения. Акушерство, гинекология и репродукция. 2018. Т. 12. № 4. С. 47-51.

3. *Белоусова В.С., Свитич О.А., Тимохина Е.В., Стрижаков А.Н., Богомазова И.М.* Полиморфизм генов цитокинов IL-1B, TNF, IL-1RA И IL-4 повышает риск развития преждевременных родов. Биохимия. 2019. Т. 84. № 9. С. 1281- 1288.

4. *Белоусова В.С., Стрижаков А.Н., Свитич О.А. и др.* Преждевременные роды: причины, патогенез, тактика. // Акушерство и гинекология. 2020. № 2. С. 82-87

5. *Брехман Г.И.* Шейка матки: структура шейки и преждевременные роды. // Жіночий лікар, 2012, №3 С. 5-11

6. *Гордеева Л.А., Оскорбина О.С. и др.* Ассоциации полиморфизма генов цитокинов с невынашиванием беременности // Медицинская иммунология, 2017. Т. 19, № 5, стр. 585-596

7. *Кузьмин В.Н.* Влияние неспецифических цервиковагинальных инфекций на перинатальные исходы у женщин с преждевременными родами.// Лечащий врач. 2018. № 12. С. 8.

8. *Кузьмин В.Н.* Перинатальные исходы при преждевременном разрыве плодных оболочек. Лечащий врач. 2018. № 3. С. 34.

9. *Низяева Н.В., Карапетян А.О. и др.* Новые данные о патогенезе преждевременных родов // В сборнике: XIII Международный конгресс по репродуктивной медицине. Материалы конгресса. Под редакцией Г.Т. Сухих и Л.В. Адамян. 2019. С. 112-114.

10. *Павлов А.В.* Особенности продукции дефензинов, протеолитических ферментов и противовоспалительных цитокинов нейтрофилами периферической крови при предевременных родах // Вестн.Уральской мед. академ.науки. 2011. Т.35, №2-1. С.57-58

11. *Пицхелаури Е.Г., Стрижаков А.Н. и др.* Проблемы имплантации и риски осложнений беременности после вспомогательных репродуктивных технологий // Вопросы гинекологии, акушерства и перинатологии. 2017. Т. 16. № 2. С. 34-39.

12. *Потапнев М.П.*, Иммунные механизмы стерильного воспаления // Иммунология, 2015. №5, Т36. С.312-318

13. *Савельева Г.М., Шалина Р.И., Курцер М.А., и др.* Преждевременные роды, как важнейшая проблема современного акушерства // Акушерство и гинекология. 2012. № 8-2. С. 4-10.

14. *Серов В.Н., Сухорукова О.И.* Эффективность профилактики преждевременных родов // Акушерство и гинекология. 2013. №3. С.48-53.

15. Серов В.Н., Сухорукова О.И. Профилактика преждевременных родов // Российский медицинский журнал. 2014. 1. С.3-7.

16. *Сухих Г.Т., Серов В.Н., и др.* Преждевременные роды // Проблемы репродукции. 2018. Т. 24. №6. С. 56-79.

17. *Сухих Г.Т. [и др.]* Преждевременные роды. Клинические рекомендации (протокол). Федеральное государственное учреждение «Научный центр акушерства, гинекологии и перинатологии им. В.И. Кулакова» Минздрава России. - М., 2014.- 35 с.

18. *Фаткуллин И.Ф. [и др.]* Кесарево сечение при недоношенной беременности // Акушерство и гинекология. 2009. №3. С. 46-48.

19. *Ходжаева З.С. [и др.]* Медикаментозная профилактика преждевременных родов. (Результаты международного многоцентрового открытого исследования МИСТЕРИ) // Акушерство и гинекология. 2016. № 8. С.37-43.

20. *Цыбульская О.В., Жаркин Н.А., Бурова Н.А.* Современные аспекты профилактики ранней потери беременности // Лекарственный вестник. 2012. 6(8):3-7.

21. *Abrahams V.M.* Immunology of the maternal-fetal interface. https://www.uptodate.com/contents/immunology-of-the-maternal-fetalinterface?search=Immunology% (Accessed on 10.01.2022)

22. *Alijotas-Reig J., Esteve-Valverde E., Ferrer-Oliveras R., Llurba E., Gris J.M.* Tumor Necrosis Factor-Alpha and Pregnancy: Focus on Biologics. An Updated and Comprehensive Review // Clin Rev Allergy Immunol. 2017 Aug. 53(1):40-53. doi: 10.1007/s12016-016-8596-x. PMID: 28054230.

23. American College of Obstetricians and Gynecologists; Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin no. 127: Management of preterm labor // Obstet Gynecol. 2012 Jun;119 (6):1308-17. doi: 10.1097/AOG.0b013e31825af2f0. PMID: 22617615.

24. *Ban Y., Zhao Y., Liu F., Dong B., Kong B., Qu X.* Effect of Indoleamine 2,3- Dioxygenase Expressed in HTR-8/SVneo Cells on Decidual NK Cell Cytotoxicity // Am J Reprod Immunol. 2016 May 75(5):519-28. doi: 10.1111/aji.12481. Epub 2016 Jan 18. PMID: 26782048.

25. *Battarbee A.N., Sinkey R.G., Harper L.M., Oparil S., Tita A.T.* Chronic hypertension in pregnancy // Am J Obstet Gynecol. 2020 Jun. 222(6):532-541. doi: 10.1016/j.ajog.2019.11.1243. Epub 2019 Nov 9. PMID: 31715148.

26. *Beaino G., Khoshnood B, Kaminski M, et al.* Predictors of the risk of cognitive deficiency in very preterm infants: the EPIPAGE prospective cohort. // Acta Paediatr 2011. 100:370.

27. *Boggess K.A., Moss K, Madianos P, et al.* Fetal immune response to oral pathogens and risk of preterm birth // Am J Obstet Gynecol. 2005. 193:1121.

28. *Casart Y., Tarrazzi K., Camejo M.* Serum levels of interleukin-6, interleukin1β and human chorionic gonadotropin in pre-eclamptic and normal pregnancy // Gynecol. Endocrinol. 2007. 23(5): 300-20. DOI:10.1080/09513590701327638

29. *Cui J., Wang F., Zhang X., Liu L.* Maternal and fetal IL1RN polymorphisms and the risk of preterm delivery: a meta-analysis // J Matern Fetal Neonatal Med. 2015 Jan. 28(1):100-5. doi: 10.3109/14767058.2014.900040. Epub 2014 Apr 9. PMID: 24588341.

30. *Challis J.R., Lye SJ, Gibb W, et al.* Understanding preterm labor // Ann N Y Acad Sci. 2001. 943:225.

31. *Challis J.R., Hooper S.* Birth: outcome of a positive cascade // Baillieres Clin Endocrinol Metab. 1989 Nov. 3(3):781-93. doi: 10.1016/s0950-351x(89)80053-9. PMID: 2698155.

32. *Davies E.L., Bell J.S., Bhattacharya S.* Preeclampsia and preterm delivery: A population-based case-control study // Hypertens Pregnancy. 2016 Nov. 35(4):510- 519.

33. *Di Renzo G.C. Mikhailov A., Papantoniou N., et al.* Preterm Labor and Birth Management: Recommendations from the European Association of Perinatal Medicine // J Matern Fetal Neonatal Med. 2017. T. 30. C. 2011-2030.

34. *Dowd J., Laham N., Rice G., Brennecke S., Permezel M.* Elevated interleukin8 concentrations in cervical secretions are associated with preterm labour // Gynecol Obstet Invest. 2001. 51(3):165-8. doi: 10.1159/000052917. PMID: 11306902.

35. *Fettweis J.M., Serrano M.G., Brooks J.P., et al.* The vaginal microbiome and preterm birth // Nat Med. 2019 Jun. 25(6):1012- 1021. doi: 10.1038/s41591-019-0450-2. Epub 2019 May 29. PMID: 31142849; PMCID: PMC6750801

36. *Fortunato S.J, Menon R., Lombardi S.J..* Role of tumor necrosis factor-alpha in the premature rupture of membranes and preterm labor pathways // Am J Obstet Gynecol. 2002. 187:1159.

37. *Galbraith G.M., Steed R.B., Sanders J.J., Pandey J.P.* Tumor necrosis factor alpha production by oral leukocytes: influence of tumor necrosis factor genotype // J Periodontol. 1998. 69:428.

38. *Gilman-Sachs A., Dambaeva S., Salazar Garcia M.D., Hussein Y., Kwak-Kim J., Beaman K.* Inflammation induced preterm labor and birth // J Reprod Immunol. 2018 Sep. 129:53-58. doi: 10.1016/j.jri.2018.06.029. Epub 2018 Jun 30. PMID: 30025845

39. *Hanna N., Bonifacio L., Reddy P., Hanna I., Weinberger B., Murphy S., Laskin D., Sharma S.* IFN-gamma-mediated inhibition of COX-2 expression in the placenta from term and preterm labor pregnancies // Am J Reprod Immunol. 2004. Apr.51(4):311-8. PMID: 15212685

40. *Hertelendy F., Molnár M., Romero R.* Interferon gamma antagonizes interleukin-1beta-induced cyclooxygenase-2 expression and prostaglandin E(2) production in human myometrial cells // J Soc Gynecol Investig. 2002 Jul-Aug. 9(4):215-9. PMID: 12113880.

41. *Hillier S.L., Nugent R.P., Eschenbach D.A., et al.* Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. The Vaginal Infections and Prematurity Study Group // Engl J Med. 1995.333:1737.

42. *Holmes C.H., Simpson K.L., Okada H., Okada N., et al.* Complement regulatory proteins at the feto-maternal interface during human placental development: distribution of CD59 by comparison with membrane cofactor protein (CD46) and decay accelerating factor (CD55) // Eur J Immunol. 1992 Jun. 22(6):1579-85. doi: 10.1002/eji.1830220635. PMID: 1376264.

43. *Jakovljevic A., Nikolic N., Carkic J., Beljic-Ivanovic K., et al.* Association of polymorphisms in TNF-α, IL-1β, GSTM and GSTT genes with apical periodontitis: is there a link with herpesviral infection? // Int Endod J. 2020 Jul. 53(7):895-904. doi: 10.1111/iej.13298. Epub 2020 Apr 20. PMID: 32216135.

44. *Kaisho T., Akira S.* Toll-like receptor function and signaling // J Allergy Clin Immunol. 2006. 117:979

45. *Klein L.L., Gibbs R.S.* Use of microbial cultures and antibiotics in the prevention of infection-associated preterm birth // Am J Obstet Gynecol. 2004. Jun. 190(6):1493-502. doi: 10.1016/j.ajog.2004.03.014. PMID: 15284720.

46. *Korebrits C., Ramirez M.M., Watson L., Brinkman E., Bocking A.D., Challis J.R.* Maternal corticotropin-releasing hormone is increased with impending preterm birth // J Clin Endocrinol Metab. 1998. May, 83(5):1585-91. doi: 10.1210/jcem.83.5.4804. PMID: 9589660

47. *Kornman K.S., Crane A., Wang H.Y., et al.* The interleukin-1 genotype as a severity factor in adult periodontal disease // J Clin Periodontol. 1997. 24:72.

48. *Kornman K.S., di Giovine F.S.* Genetic variations in cytokine expression: a risk factor for severity of adult periodontitis // Ann Periodontol. 1998. 3:327.

49. *Lanos C., Soto L., Sabugo F., Bastías M.J., et al.* Papel de los polimorfismos -238 y -308 del promotor del factor de necrosis tumoral alfa en la patogenia y respuesta al tratamiento anti-factor de necrosis tumoral alfa en artritis reumatoide [The influence of -238 and -308 TNF alpha polymorphisms on the pathogenesis and response to treatment in rheumatoid 217 arthritis] // Rev Med Chil. 2005 Sep, 133(9):1089-95. Spanish. doi: 10.4067/s0034-98872005000900014. Epub 2005 Nov 9. PMID: 16311703.

50. *Linscheid C., Petroff M.G.* Minor histocompatibility antigens and the maternal immune response to the fetus during pregnancy // Am J Reprod Immunol. 2013. Apr, 69(4):304-14. doi: 10.1111/aji.12075. Epub 2013 Feb 8. PMID: 23398025; PMCID: PMC4048750.

51. *Mackin S.T., Nelson S.M., Kerssens J.J., Wood R, et al.* SDRN Epidemiology Group. Diabetes and pregnancy: national trends over a 15 year period // Diabetologia. 2018 May, 61(5):1081-1088. doi: 10.1007/s00125-017-4529-3. Epub 2018 Jan 11. PMID: 29322220; PMCID: PMC6448996.

52. *Matthews T.J., MacDorman M.F., Thoma M.E.* Infant Mortality Statistics From the 2013 Period Linked Birth/Infant Death Data Set // Natl Vital Stat Rep. 2015. 64(9):1

53. *Mayer C., Adam M., Glashauser L., Dietrich K., et al.* Sterile inflammation as a factor in human male infertility: Involvement of Toll like receptor 2, biglycan and peritubular cells. Sci Rep. 2016 Nov 16. 6:37128. doi: 10.1038/srep37128. PMID: 27849015; PMCID: PMC5111051.

54. *Mittal P., Romero R., Kusanovic J.P.,et al.* CXCL6 (granulocyte chemotactic protein-2): a novel chemokine involved in the innate 213 immune response of the amniotic cavity // Am J Reprod Immunol. 2008. Sep, 60(3):246-57. doi: 10.1111/j.1600-0897.2008.00620.x.PMID: 18782286

55. *Moura E., Mattar R. et al.* Inflammatory cytokine gene polymorphisms and spontaneous preterm birth // J Reprod Immunol. 2009. 80:115- 21.

56. *Nygren P., Fu R., Freeman M., Bougatsos C., Klebanoff M., Guise J.M.;* U.S. Preventive Services Task Force. Evidence on the benefits and harms of screening and treating pregnant women who are asymptomatic for bacterial vaginosis: an update review for the U.S. Preventive Services Task Force // Ann Intern Med. 2008 Feb 5. 148(3):220-33. doi: 10.7326/0003-4819-148-3-200802050-00008. PMID: 18252684.

57. *Oner C., Schatz F., Kizilay G., et al.* Progestin-inflammatory cytokine interactions affect matrix

metalloproteinase-1 and -3 expression in term decidual cells: implications for treatment of chorioamnionitis-induced preterm delivery // J Clin Endocrinol Metab. 2008. 93:252.

58. *Osman I., Young A., Jordan F., Greer I.A., Norman J.E..* Leukocyte density and proinflammatory mediator expression in regional human fetal membranes and decidua before and during labor at term // J Soc Gynecol Investig. 2006. Feb. 13(2):97-103. doi: 10.1016/j.jsgi.2005.12.002. PMID: 16443501.

59. *Protonotariou E., Chrelias C., Kassanos D., et al.* Immune response parameters during labor and early neonatal life // In Vivo. 2010. Jan-Feb. 24(1):117-23

60. *Qin Zhu, Jian Sun, and Ying Chen* Preterm birth and single nucleotide polymorphisms in cytokine genes // Transl Pediatr. 2014. Apr. 3(2): 120–134. doi: 10.3978/j.issn.2224-4336.2014.03.02

61. *Roberts D., Brown J., Medley N., Dalziel S.R.* Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth // Cochrane Database Syst Rev. 2017. Mar. 21. 3(3):CD004454. doi: 10.1002/14651858.CD004454.pub3. PMID: 28321847; PMCID: PMC6464568

62. *Robinson J.N., Norwitz E.R.* Preterm birth: Risk factors, interventions for risk reduction, and maternal prognosis. URL: http://www.uptodate.com/contents/preterm-birth-risk-factors-interventions-forrisk-reduction-and-maternalprognosis? (Accessed on 04.01. 2022).

63. *Romero R., Espinoza J., Gonçalves L.F., Kusanovic J.P., Friel L., Hassan S.* The role of inflammation and infection in preterm birth // Semin Reprod Med. 2007. Jan. 25(1):21-39. doi: 10.1055/s-2006-956773. PMID: 17205421.

64. *Reynolds M.L., Herrera C.A..* Chronic Kidney Disease and Pregnancy // Adv Chronic Kidney Dis. 2020. Nov. 27(6):461-468. doi: 10.1053/j.ackd.2020.04.003. PMID: 33328062

65. *Salamonsen L.A.* Cytokines and chemokinesduring human embrioimplantation: roles in implantation and early placentation // Semin. Reprod. Med. 2007. 25(6):437-44

66. *Schaaf J.M., Hof M.H., et al.* Recurrence risk of preterm birth in subsequent singleton pregnancy after preterm twin delivery // Am J Obstet Gynecol. 2012 Oct. 207(4):279.e1-7. doi: 10.1016/j.ajog.2012.07.026. Epub 2012 Jul 26. PMID: 22917487

67. *Sennström M.B., Brauner A., et al.* Matrix metalloproteinase-8 correlates with the cervical ripening process in humans // Acta Obstet Gynecol Scand. 2003. Oct. 82(10):904-11. doi: 10.1080/j.1600-0412.2003.00249.x. PMID: 12956839

68. *Settin A., Abdel-Hady H., El-Baz R., Saber I. Gene* Polymorphisms of TNF-α− 308, IL-10− 1082, IL-6− 174, and IL-1Ra VNTR Related to Susceptibility and Severity of Rheumatic Heart Disease // Pediatric Cardiology, 2007. Vol. 28, no. 5, pp. 363-371. DOI:10.1007/s00246-006-0002-7

69. *Sheiner E., Mazor-Drey E., Levy A.* Asymptomatic bacteriuria during pregnancy // J Matern Fetal Neonatal Med. 2009. May. 22(5):423-7. doi: 10.1080/14767050802360783. PMID: 19530000

70. *Schuster H.J., de Jonghe B.A. et al.* Asymptomatic vaginal Candida colonization and adverse pregnancy outcomes including preterm birth: a systematic review and meta-analysis // Am J Obstet Gynecol MFM. 2020. 2. 25.

71. *Smaill F.M., Vazquez J.C.* Antibiotics for asymptomatic bacteriuria in pregnancy // Cochrane Database Syst Rev. 2019. Nov. 25. 2019(11):CD000490. doi: 10.1002/14651858.CD000490.pub4. PMID: 31765489; PMCID: PMC6953361. 211

72. *So T., Ito A., Sato T, et al.* Tumor necrosis factor-alpha stimulates the biosynthesis of matrix metalloproteinases and plasminogen activator in cultured human chorionic cells // Biol Reprod. 1992. 46:772. 212.

73. *Stygar D., Wang H., Vladic Y.S., et al.* level of matrix metalloproteinases 2 and 9 in the ripening process of the human cervix // Biol Reprod. 2002. Sep. 67(3):889-94. doi: 10.1095/biolreprod.102.005116. PMID: 12193399.

74. *Szekeres-Bartho J., Halasz M., Palkovics T.* Progesterone in pregnancy; receptor-ligand interaction and signaling pathways // J Reprod Immunol. 2009. Dec. 83(1-2):60-4. doi: 10.1016/j.jri.2009.06.262. Epub 2009 Oct 31. PMID: 19880194.

75. *Van Meir C.A., Sangha R.K., Walton J.C., et al.* Immunoreactive 15- hydroxyprostaglandin dehydrogenase (PGDH) is reduced in fetal membranes from patients at preterm delivery in the presence of infection // Placenta 1996. 17:291.

76. WHO, March of Dimes, Partnership for Maternal, Newborn & Child Health, Save the Children // Born too soon: the global action report on preterm birth. URL: http://www.who.int/maternal_child_adolescent/documents/born_too_soon/en/ (Accessed on 04.01. 2022).

77. WHO recommendations on interventions to improve preterm birth outcomes. URL:https://apps.who.int/iris/bitstream/handle/10665/183037/9789241508988_eng.pdf;jsessionid=2BBC6115AC8D286164CC221FA6550227?sequence=1(Accessed on 04.01. 2022).

78. *Wilmink. A., Reijnierse J. et al.* Research Consortium Neonatology South-West of the Netherlands. Preeclampsia and risk of developing bronchopulmonary dysplasia in very preterm neonates // Pregnancy Hypertens. 2019. Jan. 15:57-63. doi: 10.1016/j.preghy.2018.11.001. Epub 2018 Nov 10. PMID: 30825928.

79. *Zhang C., Deng X., Zhang X., Pan Z., Zhao W. et al.* Association between Serum TNF-α Levels and Recurrent Spontaneous Miscarriage: A Meta-analysis // Am J Reprod Immunol. 2016. Feb. 75(2):86-93. doi: 10.1111/aji.12447. Epub 2015 Nov 20. PMID: 26585408

80. *Zeitlin J., Ancel P.-I.* Interpreting data on the health outcomes of extremely preterm babies // Arch. Dis.Child. Fetal Neonatal Ed. 2011.

References: [1-20]

1. Ailamazyan E.K. Diskussionnye voprosy prezhdevremennykh rodov [Debatable issues of preterm birth]. *Zhurn. akusherstva i zhenskikh boleznei* [Journal of Obstetrics and Women's Diseases]. 2013. № 4.pp. 97-105. [in Russian]

2. Belousova V.S., Strizhakov A.N. et al. Prezhdevremennye rody: ot ponimaniya patogeneza k taktike vedeniya [Preterm birth: from understanding pathogenesis to management tactics]. *Akusherstvo, ginekologiya i reproduktsiya* [Obstetrics, Gynecology and Reproduction]. 2018. T. 12. № 4. pp. 47-51. [in Russian]

3. Belousova V.S., Svitich O.A., Timokhina E.V., Strizhakov A.N., Bogomazova I.M. Polimorfizm genov tsitokinov IL-1B, TNF, IL-1RA I IL-4 povyshaet risk razvitiya prezhdevremennykh rodov [Polymorphisms of the cytokine

genes IL-1B, TNF, IL-1RA and IL-4 increase the risk of preterm birth]. *Biokhimiya*. [Biochemistry]. 2019. T. 84. № 9. pp. 1281- 1288. [in Russian]

4. Belousova V.S., Strizhakov A.N., Svitich O.A., et al. Prezhdevremennye rody: prichiny, patogenez, taktika [Preterm birth: causes, pathogenesis, and tactics]. *Akusherstvo i ginekologiya* [Obstetrics and gynaecology] 2020. № 2. pp. 82-87 [in Russian]

5. Brekhman G.I. Sheika matki: struktura sheiki i prezhdevremennye rody [Cervix: Cervical structure and preterm labour]. *Zhinochii likar* [Personal doctor], 2012, №3 pp. 5-11 [in Russian]

6. Gordeeva L.A., Oskorbina O.S. et al. Assotsiatsii polimorfizma genov tsitokinov s nevynashivaniem beremennosti [Associations of cytokine gene polymorphisms with pregnancy failure]. *Meditsinskaya immunologiya* [Medical Immunology]. 2017. T. 19, № 5, pp. 585-596 [in Russian]

7. Kuz'min V.N. Vliyanie nespetsificheskikh tservikovaginal'nykh infektsii na perinatal'nye iskhody u zhenshchin s prezhdevremennymi rodami [Effect of non-specific cervicovaginal infections on perinatal outcomes in women with preterm birth]. *Lechashchii vrach* [Treating doctor]. 2018. № 12. pp. 8. [in Russian]

8. Kuz'min V.N. Perinatal'nye iskhody pri prezhdevremennom razryve plodnykh obolochek [Perinatal outcomes in premature rupture of membranes*]. Lechashchii vrach* [Treating doctor] 2018. № 3. pp. 34. [in Russian]

9. Nizyaeva N.V., Karapetyan A.O. et al. *Novye dannye o patogeneze prezhdevremennykh rodov* [New data on the pathogenesis of preterm birth]. V sbornike: XIII Mezhdunarodnyi kongress po reproduktivnoi meditsine. Materialy kongressa. Pod redaktsiei G.T. Sukhikh i L.V. Adamyan [In Proceedings: XIII International Congress of Reproductive Medicine. Proceedings of the Congress. Edited by G.T. Sukhikh and L.V. Adamyan]. 2019. pp. 112-114. [in Russian]

10. Pavlov A.V. Osobennosti produktsii defenzinov, proteoliticheskikh fermentov i protivovospalitel'nykh tsitokinov neitrofilami perifericheskoi krovi pri predevremennykh rodakh [Features of production of defensins, proteolytic enzymes and anti-inflammatory cytokines by peripheral blood neutrophils in preterm birth]. *Vestn.Ural'skoi med. akadem.nauki* [Bulletin of the Ural Medical Academy of Sciences]. 2011. T.35, №2-1. pp.57-58. [in Russian]

11. Pitskhelauri E.G., Strizhakov A.N. et al. Problemy implantatsii i riski oslozhnenii beremennosti posle vspomogatel'nykh reproduktivnykh tekhnologii [Implantation problems and risks of pregnancy complications after assisted reproductive technology]. *Voprosy ginekologii, akusherstva i perinatologii* [Problems of Gynecology, Obstetrics and Perinatology]. 2017. T. 16. № 2. pp. 34-39. [in Russian]

12. Potapnev M.P., Immunnye mekhanizmy steril'nogo vospaleniya [Immune mechanisms of sterile inflammation]. *Immunologiya* [Immunology]. 2015. T.36 №5, pp.312-318 [in Russian]

13. Savel'eva G.M., Shalina R.I., Kurtser M.A., et al. Prezhdevremennye rody, kak vazhneishaya problema sovremennogo akusherstva [Preterm birth as a major problem in modern obstetrics]. *Akusherstvo i ginekologiya* [Obstetrics and Gynaecology]. 2012. №8-2. pp. 4-10. [in Russian]

14. Serov V.N., Sukhorukova O.I. Effektivnost' profilaktiki prezhdevremennykh rodov [Effectiveness of prevention of preterm birth]. *Akusherstvo i ginekologiya* [Obstetrics and Gynaecology.]. 2013. №3. pp.48-53. [in Russian]

15. Serov V.N., Sukhorukova O.I. Profilaktika prezhdevremennykh rodov [Prevention of preterm birth]. *Rossiiskii meditsinskii zhurnal* [Russian Medical Journal.] 2014. 1:3-7 [in Russian]

16. Sukhikh G.T., Serov V.N., et al. Prezhdevremennye rody [Preterm birth]. *Problemy reproduktsii* [Reproductive issues]. 2018. T.24. №6. pp. 56-79. [in Russian]

17. Sukhikh G.T. [i dr.] *Prezhdevremennye rody Klinicheskie rekomendatsii (protokol). Federal'noe gosudarstvennoe uchrezhdenie «Nauchnyi tsentr akusherstva, ginekologii i perinatologii im. V.I. Kulakova» Minzdrava Rossii* [Preterm birth. Clinical guidelines (protocol). Federal State Institution Kulakov Scientific Centre for Obstetrics, Gynecology and Perinatology. V.I. Kulakov Ministry of Health of Russia] - M., 2014. 35 p. [in Russian]

18. Fatkullin I.F. [i dr.] Kesarevo sechenie pri nedonoshennoi beremennosti [Caesarean section in a premature pregnancy]. *Akusherstvo i ginekologiya* [Obstetrics and Gynaecology]. 2009. №3. 106. pp.46-48. [in Russian]

19. Khodzhaeva Z.S. [i dr.] Medikamentoznaya profilaktika prezhdevremennykh rodov. (Rezul'taty mezhdunarodnogo mnogotsentrovogo otkrytogo issledovaniya MISTERI) [Drug-assisted prevention of preterm birth. (Results of the international multicentre open-label MISTERI trial*)]. Akusherstvo i ginekologiya* [Obstetrics and Gynaecology]. 2016. № 8. pp.37-43. [in Russian]

20. Tsybul'skaya O.V., Zharkin N.A., Burova N.A. Sovremennye aspekty profilaktiki rannei poteri beremennosti [Current aspects of prevention of early pregnancy loss]. *Lekarstvennyi vestnik* [Medicines Bulletin]. 2012. 6(8):3-7. [in Russian]

Контактная информация:
Николаева Анна Сергеевна, докторант специальности «Медицина», НАО «Медицинский университет Семей», г. Семей, Республика Казахстан.
Почтовый адрес: 071404, Республика Казахстан, г. Семей, ул. Каржаубайулы 249
E-mail: Avealokinanna@mail.ru
Телефон: 87774778212