

PLACENTA AS AN IMPORTANT COMPONENT OF THE «MOTHER-PLACENTA-FETUS» MEDICAL-BIOLOGICAL SYSTEM: A LITERATURE REVIEW

*M.M. Tussupbekova¹, L.M. Stabayeva¹, I. Muhammad¹, M.C. Useeva²,
K.N. Sharafutdinova³, T.B. Bisimbayev³*

¹«Medical University of Karaganda» NCJSC, Karaganda, the Republic of Kazakhstan;

²«University Medical Center» Corporate Fund, JSC «NSCMCh», Astana, the Republic of Kazakhstan;

³«Regional Clinical Children's Hospital» MSE, Karaganda, the Republic of Kazakhstan

ABSTRACT

Relevance: To date, there is no single approach between clinicians and morphologists in assessing the role of placental insufficiency in the development of fetal and maternal pathology. This situation is due, firstly, to the complexity of the histological assessment of the degree of compensatory reaction of placental tissue, and secondly, to the assessment of the degree of its maturity and the level of circulatory disorders that affect the features of intrauterine development of the child.

The study aimed to review the placenta examination as an essential component of objective diagnostics to identify prenatal risks for the baby.

Materials and Methods: A comprehensive search was performed in the databases e-Library, Pubmed, Web of Science, Scopus, and Embase to identify relevant articles on the topic published over the past decade. A total of 78 publications were analyzed, of which 47 articles corresponded to the purpose of the study.

Results: By the nature of the structural state of the placenta, it is possible to diagnose vascular and dystrophic changes and verify inflammatory processes of nonspecific and specific genesis. Since the placenta serves as a mirror image of the infectious pathology of the mother, their children are at risk of infection.

Conclusion: Thus, the assessment of the nature of morphological changes in the placenta, both in the relatively physiological course of pregnancy and the presence of pathology of pregnancy and childbirth, with somatic or infectious pathology of the mother, makes it possible to make a prognosis about the condition of the child, both during intrauterine development, and to give a prognostic assessment during the newborn and postnatal period.

Keywords: *Placenta, antenatal death, placental insufficiency, fetal hypoxia, pregnancy, immaturity of villi, fetal programming*

«АНА-ПЛАЦЕНТА-ҰРЫҚ» МЕДИЦИНАЛЫҚ-БИОЛОГИЯЛЫҚ ЖҮЙЕСІНІҢ МАҢЫЗДЫ ҚҰРАМДАС БӨЛІГІ РЕТІНДЕ ПЛАЦЕНТА: ӘДЕБИЕТКЕ ШОЛУ

*M.M. Тусупбекова¹, Л.М. Стабаева¹, И. Мухаммад¹, М.С. Усеева²,
К.Н. Шарафутдинова³, Т.Б. Бисимбаев³*

¹«Қарағанды медицина университеті» КЕАҚ, Қарағанды, Қазақстан Республикасы;

²«University Medical Center» КҚ, АҰ «ҰҒАБДО», Астана, Қазақстан Республикасы;

³«Облыстық балалар клиникалық ауруханасы» КМК, Қарағанды, Қазақстан Республикасы

АНДАТПА

Өзектілігі: Бүгінгі күні ұрық пен ана патологиясының дамуындағы плацентарлы жеткіліксіздіктің рөлін бағалауда дәрігерлер мен морфологтар арасында бірыңғай тәсіл жоқ. Бұл жағдай, біріншіден, плацентарлы тіннің компенсаторлық реакциясының дәрежесін гистологиялық бағалаудың күрделілігіне, екіншіден, оның жетілу дәрежесін және баланың жатыршілік даму ерекшеліктеріне әсер ететін қан айналымының бұзылу деңгейін бағалауға байланысты. Плацентаның құрылымдық-функционалдық бұзылыстарына және олардың ұрыққа да, жатырдан тыс өмірдегі баланың бейімделу процесіне де әсер етуіне байланысты ана патологиясы мен босану белсенділігінің асқынуы арасындағы байланыс мәселесі де өзекті болып қала береді.

Зерттеудің мақсаты – бала өмірінің пренатальды кезеңінде қауіп факторларын анықтау үшін объективті диагностиканың маңызды құрамдас бөлігі ретінде плацентаны зерттеуге жан-жақты шолу жасаңыз

Материалдар мен әдістері: Соңғы 10 жыл ішінде жарияланған тақырып бойынша тиісті мақалаларды анықтау үшін eLibrary, Pubmed, Web of Science, Scopus және Embase дерекқорларында жан-жақты іздеу жүргізілді. Барлығы 78 ба-сылым талданды, оның ішінде зерттеу мақсаттары 47 мақалаға сәйкес келді.

Нәтижелері: Плацентаның құрылымдық күйінің сипаты бойынша тамырлы және дистрофиялық өзгерістерді ғана емес, сонымен қатар спецификалық емес және спецификалық генездің қабыну процесін тексеруге болады. Сонымен, туберкулез, мерез, АИТВ-инфекциясы және басқа вирустық-бактериялық инфекциялармен байланысты плацентиттерді тек гистологиялық зерттеу арқылы тексеруге болады. Бұл ереже плацента ананың жұқпалы патологиясының айна бей-несі ретінде қызмет етеді, ал олардың балалары инфекцияны жүзеге асыру үшін қауіп тобына кіреді.

Қорытынды: Осылайша, плацентадағы морфологиялық өзгерістердің сипатын бағалау жүктіліктің салыстырмалы физиологиялық ағымында да, жүктілік, босану патологиясы болған кезде де, ананың соматикалық немесе инфекциялық патологиясында да баланың жағдайы туралы болжам жасауға мүмкіндік береді. жатыршілік даму кезеңінде де, жана туған және босанғаннан кейінгі кезеңде де болжамды бағалау

Түйінді сөздер: плацента, антенатальды өлім, плацентарлы жеткіліксіздік, ұрықтың гипоксиясы, жүктілік, вилланың жетілмегендігі, «ұрықтың бағдарламалануы».

ПЛАЦЕНТА КАК ВАЖНЫЙ КОМПОНЕНТ МЕДИКО-БИОЛОГИЧЕСКОЙ СИСТЕМЫ «МАТЬ-ПЛАЦЕНТА-ПЛОД»: ОБЗОР ЛИТЕРАТУРЫ

*М.М. Тусунбекова¹, Л.М. Стабаева¹, И. Мухаммад¹, М.С. Усеева²,
К.Н. Шарафутдинова³, Т.Б. Бисимбаев³*

¹НАО «Медицинский университет Караганды», Караганда, Республика Казахстан;

²КФ «University Medical Center», АО «ННЦМД», Астана, Республика Казахстан;

³КГП «Областная детская клиническая больница», Караганда, Республика Казахстан.

АННОТАЦИЯ

Актуальность: На сегодняшний день нет единого подхода между клиницистами и морфологами в оценке роли плацентарной недостаточности в развитии патологии плода и матери. Такое положение обусловлено, во-первых, сложностью гистологической оценки степени компенсаторной реакции плацентарной ткани, во-вторых – оценкой степени её зрелости и уровня нарушения кровообращения, оказывающее влияние на особенности внутриутробного развития ребенка. Остается также актуальным вопрос взаимосвязи патологии матери и осложнением родовой деятельности, обусловленные структурно-функциональными нарушениями плаценты и их влиянием, как на плод, так и на процессы адаптации ребенка во внеутробном периоде жизни.

Цель исследования – дать всесторонний обзор по исследованию плаценты, как важнейшего компонента объективной диагностики по выявлению факторов риска в пренатальном периоде жизни ребенка.

Материалы и методы: Всесторонний поиск был произведен в базах данных e-Library, Pubmed, Web of Science, Scopus и Embase, чтобы выявить соответствующие статьи по теме, опубликованные в течении последних 10 лет. Всего было проанализировано 78 публикаций, из них цели исследования соответствовали 47 статей.

Результаты: По характеру структурного состояния плаценты можно диагностировать не только сосудистые и дистрофические изменения, но и верифицировать воспалительные процессы неспецифической и специфического генеза. Так, плацентиты, ассоциированные с туберкулезом, сифилисом, ВИЧ-инфекцией и другими вирусно-бактериальными инфекциями, можно верифицировать только при гистологическом исследовании. Данное положение говорит о том, что плацента служит зеркальным отражением инфекционной патологии матери, а их дети входят в группу риска по реализации инфекции.

Заключение: Таким образом, оценка характера морфологических изменений в плаценте, как при относительно физиологическом течении беременности, так и при наличии патологии беременности, родов, при соматической или же инфекционной патологии матери позволяют сделать возможным прогноз о состоянии ребенка, как в период внутриутробного развития, так и дать прогностическую оценку в период новорожденности и постнатальном периоде.

Ключевые слова: плацента, антенатальная смерть, плацентарная недостаточность, гипоксия плода, беременность, незрелость ворсинок, «фетальное программирование».

Introduction: The placenta is an important component of the «mother-placenta-fetus» complex medical-biological system, which supports the relationship between the mother's body and the fetus. The degree of maturity of the structural elements of the placenta and its vascular component is of great importance in delivering the necessary nutrients and oxygen to the fetus, which is reflected in all stages of the anatomical and physiological formation of the child's organs and systems. It is well known that the state of health of the mother and the characteristics of the course of pregnancy affect the morphofunctional maturation of the placenta, which affects the development of the fetus and its adaptation in the postnatal period [1-4].

Placental insufficiency is one of the most common pregnancy complications, accompanied by fetal hypoxia. According to the time and mechanism of occurrence, primary placental

insufficiency is distinguished, which occurs before 16 weeks of pregnancy, and secondary, which develops after this period under the influence of various factors on the formed placenta. Primary placental dysfunction is caused by changes in the histological structure, location, attachment of the placenta, disruption of the maturation of the chorionic villi, and the formation of the placenta. Among the causes of primary placental insufficiency may be genetic factors, enzymatic disorders that interfere with the normal development of the ovum, viral-bacterial factors, or other infectious agents. Secondary placental insufficiency, as a rule, develops against the background of pregnancy complications as a threat of interruption, preeclampsia, or the presence of various diseases of the cardiovascular system, kidneys, lungs, diseases of the blood system, diabetes mellitus, and thyroid dysfunction in a woman. Placental dysfunction can have an acute and chronic

course. Acute - develops against the background of extensive structural changes and premature detachment of a normal or low-lying placenta, which, if untimely medical care, can lead to intrauterine fetal death. Chronic placental insufficiency develops because of a breakdown of compensatory-adaptive mechanisms in the placental system and a violation of the relationship in the "mother-placenta-fetus" system due to structural changes in the placenta [5, 6]. Each of the stages of placental growth and maturation of chorionic villi during pregnancy are important factors determining the function of the placenta at the end of pregnancy. Placental dysfunction triggers antenatal and neonatal mortality and increased postnatal morbidity [7].

The study aimed to review the placenta examination as an essential component of objective diagnostics to identify prenatal risks for the baby.

Materials and Methods: The search was made in the e-Library, PubMed, Web of Science, Scopus, and Embase databases and involved articles published over the past decade. The search queries included a combination of the following keywords: «placenta,» «antenatal death,» «placental insufficiency,» «fetal hypoxia,» «pregnancy,» «immaturity of villi,» and «fetal programming.» Out of 78 analyzed publications, 47 corresponded to the purpose of the study.

Results: There are five known stages of the placenta formation or histological development: (1) the lacunar, or pre-villous stage; (2) the formation of secondary and tertiary villi; (3) the formation of cotyledon; (4) the fertilization stage, and (5) the formation of a mature placenta [8, 9].

The first lacunar, or pre-villous, stage begins from Day 6-7 after fertilization when the blastocyst is implanted in the endometrium, and a layer of cytotrophoblast with high lytic capacity proliferates at the site of contact. On Days 8-9, the foci of endometrial melting are combined into communicating cavities (lacunae), which serve as a prototype of the intervillous space. Subsequently, trabeculae from the primary cytotrophoblast or primary villi are formed between the lacunae. Gradually, the narrow maternal capillaries of the endometrium are transformed into sinusoids, which are aroused. Instead of the existing histotrophic, a chemotrophic type of nutrition is formed, corresponding to the period of uteroplacental blood circulation, and by about Day 12, the implantation phase is completed [10, 11].

The second stage is the stage of formation of secondary and tertiary villi from Days 12-13 when the extraembryonic mesenchyme from the wall of the fetal sac grows into the primary villi simultaneously with the differentiation of the villous cytotrophoblast and syncytiotrophoblast. By Days 14-15, branching secondary or final villi are formed, covered with bilayer epithelium with a stroma consisting exclusively of mesenchymal cells, so they are better called secondary or mesenchymal villi [12, 13]. An important stage in the placenta formation occurs on Days 21-22 when autochthonous angiogenesis occurs in the mesenchyme of the stroma of the villi, which become tertiary or vascularized. On Day 32, the allantoic vessels are connected to the capillaries of the villi, and fetoplacental blood circulation begins. From Day 32 to 50 of gestation, the tertiary villi differentiate towards the supporting villi or grow in length, giving numerous branches. In their stroma, capillaries intensively arise and connect, and young and mature fibroblasts are formed, the processes of which border special stromal canals with free-lying Hofbauer cells [14, 15]. By the period of embryogenesis - villi from Day 22 to 56 of gestation are designated embryonic, and it is necessary to distinguish them from mesenchymal.

The third is the stage of formation of cotyledons. It is indicated that the development of the placenta and its morphofunctional units, "cotyledons," occurs through a complex interaction of the villous tree, allantoic vessels, two waves of migration of the extravillous cytotrophoblast with an

erosion of the spiral arteries, as well as conjugate histogenesis of the epithelium, stroma and capillary bed of the villi, which is a structural prerequisite for possible disorders of placental maturation. The stage of cotyledon formation lasts from Day 51 till the end of the first trimester. From Week 9, the first intermediate immature branches are formed [16-18], in which stromal channels with Hofbauer cells and numerous capillaries are preserved. From Week 4 to 10, the first wave of cytotrophoblast migration into the endometrial segments of the spiral arteries and their sequential opening occurs, which leads to a sharp increase in uteroplacental blood flow. Gradually, 35-50 cotyledons are formed, and by Week 12, the placentation phase is completed [19, 20].

The fourth stage, fertilization, lasts throughout the entire second trimester until Week 35 of the third trimester. During this period, the entire intervillous space is filled with an extensive system of intermediate immature villi. The maximum falls on Week 16. During Weeks 16-18, the increase in uterine blood flow is provided by the second wave of migration of the cytotrophoblast into the walls of those segments of the spiral arteries that are located above the endometrium in the adjacent part of the myometrium [21]. These hemodynamic processes stimulate further growth of the villous tree. From Weeks 19-20, the placenta is constructed using ultrasound examination, and until Week 28 corresponds to stage 0 according to the gradation of P. Grannum [22]. According to Milovanov A.P. [23], it is advisable to divide this segment of gestation into 2 phases: weeks 21-25, when an approximately equal number of intermediate immature and differentiated villi is histologically determined, and at weeks 26-28 with the dominance of densely packed intermediate differentiated villi and the beginning of the growth of terminal branches. According to the number of terminal villi and the total mass, the placenta grows up to 35-36 weeks. The echography image of the placenta at 30-32 weeks corresponds to stage I and at 33-36 weeks – stage II by P. Grannum [22].

The fifth stage is the stage of formation of a mature placenta, characteristic of the last month of pregnancy, when the continued weight gain of the fetus is not due to the formation of new villi but mainly through the transformation of narrow capillaries of terminal villi into wide sinusoids and the formation of scientia capillary membranes, i.e., functional specialization of small villi, which helps to reduce the diffusion distance through the placental barrier. Such villi are called terminal specialized forms. Scanning electron microscopy reveals a dichotomous type of branching of terminal villi with characteristic terminal extensions that correspond to specialized villi. From Week 37, according to ultrasound data, stage III of placental maturity is recorded [24, 25]. At the same time, involutivity changes occur in the mature placenta in the form of fibrinoid deposition and calcification.

Even with a thorough morphological examination, it is not always possible to establish the alleged cause of antenatal fetal death. At the same time, the study of damage to the placenta in cases of sudden fetal death, which is about 30% in the structure of antenatal mortality, is particularly important. Among all stillborn children, antenatal fetal death reaches 77.9% and remains an important clinical and socially significant problem. The antenatal stillbirth rate in Russia in 2010 was 4.05‰, with a minimum level of 0.87‰ in Kabardino-Balkaria and a maximum of 7.14‰ in the Chechen Republic. The low level of antenatal stillbirth corresponds to the range of 0.87-2.96‰, the average level is 2.97-5.05‰, and the high level is 5.06-7.14‰.

In most cases, antenatal fetal death occurs at Weeks 22-36 of gestation - 60.3%, with full-term pregnancy - 34.8%, with prolongation of pregnancy for more than 40 weeks - 4.9%. The stillbirth rate in different countries ranges from 5 per 1000 births in developed countries and up to 32 per 1000 births in South Asia and Africa. In Kazakhstan, the antenatal stillbirth rate was 9.2‰ in 2011, 9.6‰ in 2012, and 9.1‰ in 2013 [26].

The most common risk factors for antenatal fetal death are chronic fetal hypoxia against the background of severe anemia, preeclampsia, fetal growth retardation syndrome, and somatic and viral-bacterial diseases in the mother. The difference in stillbirth rates between developing and developed countries is because the main causes of perinatal mortality are manageable, and many causes are preventable, while the organization of antenatal care is important. However, antenatal fetal death may be accompanied by a clinically latent course due to damage to the placenta. Chronic placental insufficiency with antenatal hypoxia/asphyxia of the fetus in 63% of cases correlates with the morphological picture of pathological immaturity of the placenta [27].

Pathological immaturity of the villi of the placenta is often associated with post-term pregnancies, multiple pregnancies, and pregnancies of women suffering from obesity, hereditary or acquired thrombophilia, intrauterine, in particular viral infection, latent or manifest forms of diabetes mellitus, autoimmune diseases, chronic fetal anemia or chronic fetal transfusion syndrome. In 50%, we are talking about an "idiopathic form of placental immaturity" when the cause and pathophysiological mechanisms of delayed chorionic villi's delayed maturation are unknown. It was noted that in cases of pathological immaturity of the placenta, the risk of development and recurrence of fetal hypoxia significantly increases. Available clinical and epidemiological data and experimental studies have shown an association between an unfavorable intrauterine environment during fetal development, the occurrence of diseases in the postpartum period, and the development of diseases in adulthood [28-30].

Even with a clinically physiological pregnancy, hypoxia of the fetus can develop suddenly and lead to the antenatal death of the fetus. The criteria for assessing antenatal fetal death are gestational age, often more than 36 weeks of pregnancy, and the absence of obvious risk factors despite regular and professional observations during pregnancy. It is possible to establish and explain the pathogenesis of the cause of fetal hypoxia after a morphological study of the postpartum placenta, and the information obtained is essential in developing methods of prenatal prophylaxis [31, 32]. The study of the morpho-functional state of the placenta in conditions of chronic placental distress can help in the early stratification of the heterogeneous population of newborns with the determination of the individual risk of diseases in the postnatal period. The close relationship in the mother-placenta-fetus system is indicated by studies indicating that an increase in placental weight is associated with fetal macrosomia, gestational diabetes mellitus, a decrease in the growth potential of the placenta occurs in preeclampsia, HELLP syndrome, and is associated with intrauterine growth retardation. Chronic placental insufficiency with antenatal asphyxia of the fetus in 63% correlates with the morphological picture of pathological immaturity of the placenta [33, 34].

It has been noted that disruption of placental maturation processes is observed in gestational diabetes mellitus, idiopathic fetal macrosomia, congenital and/or chromosomal abnormalities of fetal development, chronic willies of unknown etiology, in the placenta of the donor fetus in monochorionic twin pregnancies with chronic fetal transfusion syndrome, chronic anemia of pregnant women [35, 36]. By the nature of the structural state of the placenta, it is possible to diagnose vascular and dystrophic changes and verify inflammatory processes of nonspecific and specific genesis. Thus, placentitis associated with tuberculosis, syphilis, HIV infection, and other viral and bacterial infections can be verified only by histological examination. This provision suggests that the placenta mirrors the mother's infectious pathology, and their children are at risk for the infection.

Assessment of the nature of morphological changes in the placenta, both in the relatively physiological course of pregnancy and in the presence of pathology of pregnancy and childbirth, with somatic or infectious pathology of the mother,

make it possible to predict the condition of the child both during fetal development and to give a prognostic assessment during the neonatal period and the postnatal period. The study of the morphofunctional state of the placenta is becoming relevant, especially in complicated pregnancy and obstetric history. It must be remembered that antenatal hypoxia is not always the main disease of the fetus, but most often serves as a direct cause of death in other nosological forms. The cause of intrauterine asphyxia of the fetus and newborn is often due to the mother's pathology, the peculiarities of the course of pregnancy, labor, the gestational maturity of the fetus, or the presence of structural pathology of the placenta or its anomalies. The main cause of fetal death can be objectively identified in a comprehensive assessment through clinical and morphological comparisons of maternal, placental, and fetal factors. It is also possible to obtain prognostic information for a favorable outcome of subsequent pregnancy or correction of monitoring of the child in the postpartum period.

Perinatal losses are one of the main indicators reflecting the quality of medical care for pregnant women, infants, and newborns. According to the conclusion of the United Nations Interdepartmental Mortality Assessment Group, Kazakhstan has made significant progress since the end of 2000 in reducing infant mortality rates by 64% and infant mortality rates by 65%. There is a downward trend in stillbirths, amounting to 10.7‰ in 2008 and 9.3‰ in 2015. At the same time, in 2015, in the structure of perinatal death, the stillbirth rate increased, and its ratio to early neonatal death was 3:1. In the structure of perinatal losses in 2015-2016, fetuses and newborns with a normal body weight of 2500g were in the lead in weight categories and account for about 30% [37]. According to Medinform official data, the causes of early neonatal mortality in the weight category of 2500 g or more in 2016 were congenital malformations (37%), asphyxia (15%), pneumonia (13), other causes (11%), aspiration syndromes (5%), sepsis (4%), respiratory distress syndrome (3%), intraventricular hemorrhages (3%), 1% each were such nosological forms as hemolytic disease of the newborn, hemorrhagic disease of the newborn and necrotizing enterocolitis. The most common causes of stillbirth in the category of antenatal losses were intrauterine growth retardation (11%), polyhydramnios (11%), hypertensive conditions of the mother (5%), premature detachment of the normally located placenta (9%), placental insufficiency (31%) [38]. Such causes of antenatal losses as chronic infection of the mother were identified by experts in 7%, placental insufficiency in 31% of cases based on ELISA and retrospective histological examination of the placenta, and requires clarification regarding the diagnosis legitimacy. In each case, etiological verification of the PCR factor in dynamics is needed to exclude an infection that affects the characteristics of the course of pregnancy. When analyzing intranatal losses, it is necessary to assess maternal and fetal risk factors, such as severe preeclampsia, uterine scar, prenatal rupture of amniotic fluid, and labor induction. There is epidemiological evidence of the influence of adverse conditions in the antenatal period, which increases the risk of developing diseases in the postnatal period and adulthood [39].

Evidence in the literature indicates a relationship between maternal health and fetal development in preeclampsia and low birth weight with type 2 diabetes mellitus and cardiovascular diseases, referred to as "fetal programming." This should be reflected in the public health strategy for maternal and child health. The placenta study is among the important components of objective diagnostics to identify prenatal risks for the baby [40, 41].

In world statistics, the difference in the incidence of preeclampsia is mainly due to the criteria used to diagnose it. Thus, in economically developed countries, it is detected in 3-5% of all pregnant women; in developing countries, this figure reaches 17%. Children born from pregnancies with preeclampsia are twice as likely to be at risk of developing cerebrovascular diseases and diabetes in adulthood, more often

in this group of pre-escalation and childbirth high body mass index compared to those born in the normal course of pregnancy. To date, the etiological and Pathogenetic mechanisms of the development of preeclampsia are still insufficiently studied. It is known that a genetically determined decrease in the expression of the syncytin-2 gene, an imbalance of endothelial growth factors and factors inhibiting angiogenesis, causes superoxide distress of organs and tissues, which, according to most researchers, leads to impaired placentation with insufficient remodeling of the spiral arteries of the uterus and placental malperfusion [42-44]. It has been established that the identified abnormalities at the level of "uterus-placenta-fetus" affect the normal angiogenesis and structural maturation of the villi of the placenta and, therefore, affect the respiratory and metabolic potentials of the placenta, which certainly affects the features of intrauterine development. The ratio of compensatory-adaptive and pathological processes determines the severity of the mother's disease and the development of complications in the fetus and newborn.

There is evidence that the development of preeclampsia in full-term pregnancy (Weeks 37-42 of pregnancy) is more closely related to cardiac and metabolic dysfunction in the mother rather than to placentation pathology and angiopathy of decidual tissue. It has been suggested that preeclampsia in full-term pregnancy is a completely different pregnancy complication compared to very early and early preeclampsia [45, 46].

The diversity of views on the pathogenesis and clinical forms of preeclampsia determines the need for further study of the features of the histopathological manifestations of the placenta, which will allow a new attitude to the principles of identifying risk groups and optimize the tactics of treatment and prevention of an unfavorable outcome of pregnancy.

In recent years, thanks to a bilateral international scientific agreement between researchers from the Institute of Pathology of the Johannes Gutenberg University Hospital, Mainz (Germany) and the Department of Pathological Anatomy of the Medical University of Karaganda (Kazakhstan), as well as with the "maternity ward of the Regional Clinical Hospital (Karaganda, Kazakhstan), a prospective blind immunohistochemical study of 593 placentas in physiological and pathological Pregnancy [47]. The study aimed to assess the diagnostic significance of CD15-immunophenotyping of the placenta in diagnosing chronic antenatal hypoxia of the fetus in the third trimester of pregnancy due to placental insufficiency. During the study, a comparative morphological analysis was carried out by CD15 immunophenotyping of the placenta during the physiological and pathological course of pregnancy. The diagnostic significance of endothelial CD15 expression as a marker of the immaturity of the fetoplacental unit in antenatal fetal death, gestational diabetes mellitus, large fetal for gestational age, idiopathic intrauterine growth retardation, preeclampsia, HELLP syndrome, and premature placental abruption was evaluated.

The results of a retrospective study of normal and pathological placentas of different gestational ages using a new method made it possible to identify manifest and latent forms of chronic placental insufficiency, which is based on postnatal immunophenotyping of placental tissue with antibodies against CD15 antigen with the determination of its degree. It is indicated that the severity of pathological CD15 expression in placenta macro- and micro vessels reflects the placenta's pathological immaturity [47]. It was revealed that placentas from pregnancies with antenatal fetal death with chronic placental insufficiency are accompanied by a significant increase in CD15+ expression in the macro- and microvasculature, significantly distinguishable from other pathological pregnancies and placentas during physiological pregnancy, regardless of the histological phenotype and weight of the placenta. At the same time, in placentas with antenatal fetal death in acute placental insufficiency associated with premature detachment of the normally located placenta,

there was no statistically significant difference in endothelial expression CD15+ compared with placentas during physiological pregnancy.

In placentas with increased weight in the physiological and pathological course of pregnancy with a heterogeneous histological phenotype associated with gestational diabetes mellitus, high fetal weight for gestational age, idiopathic intrauterine growth retardation of the fetus, and preeclampsia, there was an increase in the expression of CD15+ endothelial cells with a statistically significant increase in the relative amount of CD15+ micro vessels and capillaries of the placental barrier. In placentas with a mature histological phenotype associated with HELLP syndrome, with normal or reduced weight, a statistically significant decrease in CD15+ endothelial cells in micro vessels were noted, which may indicate the pathogenetic specificity of this syndrome.

At the same time, in placentas with a mature histological phenotype with normal and low weight, associated with a small fetus for gestational age, preeclampsia, a large fetus for gestational age, intrauterine growth retardation of the fetus without clinical signs of placental insufficiency, there was no significant difference in CD15 expression in the macro- and microvascular bed from the placentas during physiological pregnancy. At the same time, with clinical signs of antenatal placental insufficiency with fetal hypoxia, there was a statistically significant increase in CD15 expression in the macro- and microvascular bed, in contrast to the placentas in physiological pregnancy, but significantly less than in placentas with antenatal fetal death in chronic placental insufficiency.

Discussion: The results obtained showed that the effect of stressful situations on the placental complex caused by latent chronic placental insufficiency is accompanied by adaptive processes and growth of the placental vasculature associated with the reactivation of immature CD15+ endothelial cells and, thereby, compensatory remodeling of the vascular bed of the placenta with prolongation of growth potential. The heterogeneity of placental weight, associated with both physiological and pathological pregnancy, reflects the different gestational periods of the onset of the disease and the stage of development of the adaptive capabilities of the placenta. It should be emphasized that CD15+ endothelial cells mark the vascular zones of adaptation and growth of the placental vasculature and also reflect the mechanism of prenatal adaptation and remodeling of the vascular bed to changes in fetal hemostasis in conditions of reduced respiratory diffusion and perfusion potentials of the placenta, which indicates the possibility of providing new therapeutic approaches in chronic placental insufficiency.

The study showed that the new method of CD15 immunophenotyping of the placenta makes it possible to postnatally determine latent clinical forms of placental insufficiency, which indicates the possibility of identifying risk groups in the neonatal period. This provision indicates the importance of histological examination of the placenta and that when stratifying the risk of morbidity, it is necessary to develop individual therapy for such newborns, and when diagnosing the inflammatory process in the placenta, it is a fact of the possibility of intrauterine infection and that newborns and their mothers should be at risk for the implementation of infectious pathology in the postpartum period.

Conclusion: Thus, a multidisciplinary approach is needed to study the morpho-functional maturity of the placenta in complicated pregnancy, taking into account the diagnostic significance of CD15 and their expression in the macro- and micro vessels of the placenta in antenatal asphyxia of the fetus in order to objectively assess the degree of morphological maturity of the placenta, which is of practical importance not only for pathologists but also for obstetrician-gynecologists and neonatologists to develop methodological recommendations to protect the health of the child in different periods of development and to substantiate the pathogenetic mechanisms of fetal and placental disorders.

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Данные авторов:

Тусупбекова Майда Масхаповна – профессор, доктор медицинских наук, профессор кафедры патологии, НАО «Медицинский университет Караганды», г. Караганда, Республика Казахстан, тел.: 87754590630; e-mail: M.Tusupbekova@qmu.kz, ORCID ID: <https://orcid.org/0000-0003-3105-4450>;

Стабаева Лейла Медеубаевна (автор для корреспонденции) – PhD, ассоциированный профессор кафедры патологии НАО «Медицинский университет Караганды», г. Караганда, Республика Казахстан, тел.: 87013277033; e-mail: Stabaeva@qmu.kz, ORCID ID: <https://orcid.org/0000-0001-8598-1829>;

Ирфан Мухаммад – магистр медицины, ассистент кафедры патологии НАО «Медицинский университет Караганды», г. Караганда, Республика Казахстан, тел.: 87013277033, e-mail: MuhammadI@qmu.kz, ORCID ID: <https://orcid.org/0000-0002-2825-5983>;

Усеева Мария Садвокасовна – врач-патологоанатом отделения патологической анатомии КФ «УМС», Астана, Республика Казахстан, тел.: 87013277033, e-mail: mary@mail.ru; ORCID ID: <http://orcid.org/0009-0000-0796-1726>;

Карина Наильевна Шарафутдинова – клинический наставник кафедры патологии НАО «Медицинский университет Караганды», г. Караганда, Республика Казахстан, тел.: 87017088859, e-mail: karina_shara@mail.ru, ORCID ID: <http://orcid.org/0009-0009-3101-8911>;

Тарас Булатович Бисимбаев – заведующий патоморфологическим отделением КГП «Областная детская клиническая больница», Караганда, Республика Казахстан, тел.: 87053007915, e-mail: tasbulat-84@mail.ru, ORCID ID: <http://orcid.org/0009-0002-1992-2892>.

Адрес для корреспонденции: Стабаева Лейла Медеубаевна, НАО «Медицинский университет Караганды», ул. Гоголя 40, г. Караганда 1000008, Республика Казахстан.

Вклады авторов:

вклад в концепцию – **Тусупбекова М.М., Стабаева Л.М.**

научный дизайн – **Мухаммад И., Шарафутдинова К.Н.**

исполнение заявленного научного исследования – **Усеева М.С., Шарафутдинова К.Н.**

интерпретация заявленного научного исследования – **Бисимбаев Т.Б., Мухаммад И.**

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