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FEATURES OF THE CYTOKINE PROFILE AND APOPTOSIS FACTORS IN NEWBORN CHILDREN WITH DELAY OF IN DELAYED INTRAUTERINE DEVELOPMENT

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ABSTRACT

The delay in fetal development of the fetus currently remains an urgent problem of modern perinatology, due to the continuing high incidence of morbidity and mortality.

Objective: to study the features of changes in the concentration of cytokines and apoptosis factors in the blood serum of newborns with intrauterine growth retardation, depending on the clinical variant.

Material and methods: 122 newborns were examined. All newborns were divided into 3 groups: 1 - the main group - 58 children with IUGR, born in asphyxia, 2-comparison group - 45 newborns with IUGR, born without signs of asphyxia, and 3 - control group - 19 practically healthy newborns. The concentration of interleukins and interferons in blood serum was determined by ELISA, CD95 + lymphocyte cells using monoclonal antibodies.

Results: In children with IUGR, born in asphyxia, there is a significant imbalance in the production of pro-inflammatory (IL-1β, IL-8 increase by 2.6; 3.6 times, INF-γ decreases by 1.5 times) and anti-inflammatory (IL -4 decrease 2.3 times) of cytokines. An increase in the production of apoptosis-IL-18 factors (2.5 times), CD95 + cells (1.2 times) was also detected, compared with healthy children. Moreover, in newborns with a symmetric variant of IUGR, the most pronounced changes are revealed.

KEY WORDS: newborn, intrauterine growth retardation, immunity, cytokine, interleukin, interferon, apoptosis factors.

INTRODUCTION

The delay in fetal development of the fetus currently remains an urgent problem of modern perinatology, due to the continuing high incidence of morbidity and mortality, the development of chronic pathology and disability of children in perinatal and infancy [8,11,14].

IUGR syndrome is characterized not only by a decrease in weight, but also by a decrease in other parameters of the fetal physical development, signs of morphofunctional immaturity of a number of organs and systems, significantly reduced immunological reactivity and adaptive reserves [13]. Although intrauterine growth retardation among small children is observed in 20-30% of cases, the total number of newborns has a rather high frequency of occurrence [3]. Studies by Russian scientists have revealed that newborns with IUGR make up 4.5 to 39% of all newborns with low birth weight. In economically developed countries, the birth rate of children with IUGR is 30-40%, in developing countries it reaches 70% against the background of a higher birth rate of children with low body weight [1.8].

Research Zamaleeva R.S. et al. (2016) showed that in obstetric practice IUGR occurs in 5-17.6% of cases of all pregnancies, and among stillborn fetuses 20% have IUGR.

According to foreign literature, IUGR is detected in children of healthy mothers in 5–7% of cases, and in mothers with a history of history up to 25% [9].

Factors leading to deficiency of body weight at birth are able to persistently change the structure of the body, disrupt metabolic stability, reduce the level of adaptive capabilities of the body, realized through the activity of the endocrine, immune, nervous and cardiovascular systems [6].

The frequency of intrauterine growth retardation in newborns does not tend to decrease, due to the unsatisfactory state of health of pregnant women, the widespread introduction of a range of therapeutic measures in the practice of healthcare aimed at

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preserving pregnancy in sick women, the intensive development of reproductive technologies, as well as methods of resuscitation and intensive care of newborns [4].

Studies of domestic and foreign scientists show that a high level of morbidity and mortality in newborns with IUGR is also due to a breakdown in adaptation from the immune system.

The immune system is one of the three integrative systems of the body, which, together with the nervous and endocrine systems, ensures the maintenance of homeostasis under conditions of a constant change in the nature of the influences of factors of the external and internal environment [10].

In the development of intrauterine growth retardation, much attention is paid to the role of the immune system, since the physiological reactions that ensure the development of the fetus are controlled by immune mechanisms.

The formation and development of both immunity and functional systems occurs even in the early stages of gestation, and by the time a full-term baby is born, immunity is already quite mature, although it has a number of features that reflect the conditions of its intrauterine development. This is especially true for children with a low degree of maturity at birth - premature and newborns with intrauterine growth retardation, both full-term and premature. To date, there are few and often conflicting information about the state of the immune system in newborns with IUGR [2].

An important informative indicator of the state of the newborn's immune system during the adaptation period is the level of production of cytokines, which are the link between immunity, hemostasis, hematopoiesis, angiopoiesis and nonspecific resistance of the body, act as regulators of all the main stages of life. Cytokines are universal, regulatory proteins designed to control the proliferation, differentiation, apoptosis and functional activity of cellular elements in the hematopoietic, immune and other body systems [2].

Immunological relationships between mother and fetus are formed within the framework of a single functional system, the fundamental factor of which is the optimal development of the fetus. Violation of normal relationships in this system is the leading link in the pathogenesis of various forms of pathology of both the mother and the fetus, which largely determines the course of the perinatal period and subsequent periods of childhood.

Despite a significant number of studies on this problem, many issues related to the clinical and immunological features of the course of the neonatal period and the health status of newborns with IUGR remain unclear. In this regard, the study of the state of the immune status in the dynamics of the neonatal period is important.

The aim of our study was to study the characteristics of changes in the concentration of cytokines and apoptosis factors in the blood serum of newborns with intrauterine growth retardation, depending on the clinical variant.

MATERIALS AND METHODS

During the work, an immunological examination was carried out in 122 newborns. All newborns were divided into 3 groups: 1-the main group consisted of 58 children with intrauterine growth retardation, born in asphyxia, the 2nd comparison group consisted of 45 infants with intrauterine growth retardation, born without signs of asphyxia and 3-control group consisted of 19 healthy babies. A blood test was performed within 48 hours after collection. Blood was delivered to the laboratory after a maximum of 2 hours, the study was conducted on the same day.

The concentration of interleukins and interferons (IL-1β, γ-IFN, IL-4, IL-8, IL-18) in the blood serum was determined by the method of enzyme-linked immunosorbent assay using test systems LLC "Cytokine" (St. Petersburg, Research Institute of Especially Clean Biological Products) . Quantitative assessment of the results was carried out by constructing a calibration curve or using the commercial computer program "Microplate manager", reflecting the dependence of optical density on concentration for a standard antigen and allowing comparison of the studied samples with it. The sensitivity of the method is 5-30 pg/ml.

To determine CD95 + lymphocyte cells, the following method was used: isolation of lymphocytes from peripheral blood (Boyum, 1968) on a ficoll-verographin gradient; CD95 + lymphocyte cells were determined using monoclonal antibodies (manufactured by Sorbent LLC, Russian Federation, Moscow).

The results of the obtained data were subjected to statistical processing using the programs developed in the EXCEL package, using statistical functions, student criterion (t), with the calculation of the probability of error (P). Correlation analysis with the calculation of the correlation coefficient (r) and its reliability was carried out according to the Pearson method. Differences were considered statistically significant at achieved significance level of $p < 0.05$.

RESULTS AND DISCUSSION

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Immunological mechanisms in the pathogenesis of IUGR are dominant, their pathological development largely characterizes the variety of clinical manifestations in IUGR.

The study of the level of production of pro- and anti-inflammatory cytokines, due to which intercellular regulation of body functions occurs, is essential for assessing the state of immunity, including the cytokine profile in newborns with IUGR.

An important physiological role in the processes of immunoregulation is played by the pro-inflammatory cytokine - IL-1β, which initiates inflammation and is sometimes the main pathogenesis link in many diseases, including immunomediated ones. The disruption of the cytokine balance towards the overproduction of IL-1β can be a central link in the pathogenesis of many known chronic diseases [2,12].

The results of studies by Chistyakova et al (2014) showed that in all newborns who underwent asphyxia at birth, the levels of IL-1β, TNF-α, IL-10 decreased, the content of IFN-γ and IL-6 in cord blood increased, which is a sign of hypoxic changes. Also prognostically significant markers of perinatal pathology of infectious and non-infectious genesis was a significantly high content of IL-8 in the umbilical cord and peripheral blood of newborns during the first week of life.

We conducted a study to determine the level of production of IL-1β as an important mediator, which is one of the most universal regulators of immunity and inflammatory reactions with a wide range of biological effects, including proliferation of T and B lymphocytes, antibody formation, and the synthesis of other cytokines. It was established that in healthy newborn children, individual indicators of IL-1β production ranged from 140 to 260 pg/ml, while the average value of this cytokine was 200.5±6.28 pg/ml. In newborns with IUGR born in asphyxia, the level of pro-inflammatory cytokine IL-1β before treatment in peripheral blood was 514.8±6.05 pg/ml, while remaining significantly high (P <0.001) in relation to control values, and was 1 , 2 times higher than in children with IUGR, born without asphyxiation (Table 1.).

A high level of IL-1β production in newborns with IUGR suggests the presence of a certain dependence of its concentration on the nature of the pathological process, as evidenced by its increase in newborns with IUGR born in asphyxia.

Table 1. The concentration level of cytokines in newborns with IUGR in the observation groups (pg/ml)

Indicators pg/ml	Control (n = 19)	Main group (n = 58)	Comparison group (n = 45)	P
IL-1β	200,5±6,28	514,8±6,05	417,4±4,08	P<0,001
IL -8	188,4±11,30	671,7±10,97	528,6±10,25	P<0,001
IL -4	60,8±1,56	26,7±1,19	27,4±1,07	P<0,001
INF-γ	25,7±1,56	17,0±0,65	16,3±0,62	P<0,001

IL-8, the earliest pro-inflammatory cytokine, is a protein, belongs to chemokines, and is a powerful chemotactic and activating factor for neutrophils. The main function of IL-8 is to act as a chemoattractant for neutrophils, macrophages, lymphocytes, eosinophils.

Our studies showed that in newborn children with IUGR born in asphyxia, the concentration of IL-8 was significantly (3.6 times) increased 671.7±10.97 pg/ml than in children of the control group 188.4±11, 30 pg/ml. A comparative analysis of the production of IL-8 among children of the main group and comparison showed that in children with IUGR born in asphyxia, the concentration of IL-8 was 1.3 times higher (671.7±10.91 pg/ml) than in newborns with IUGR, born without asphyxia (528.6±10.25 pg/ml), (Table 1.).

Currently, some of the main reasons for the development of immunodeficiency states are becoming clear. One of the reasons for this is a violation in the body under the influence of various factors, including asphyxia, immunoregulatory processes carried out using Th1 and Th2 helpers. As is known, the former synthesize cytokines that stimulate cellular immunity (IL-1,2,6,8,12, IFN, etc.), the latter synthesize cytokines that stimulate humoral immunity (IL-4,5,10, TGF-b, etc. .). In a normally functioning organism, there is a certain balance of interaction between Th1 and Th2 helper cells. But a strong change in their activity under the influence of any effect can lead to serious adverse consequences in the functioning of the immune system as a whole. It has been established that hypoxia can cause activation of Th2 helpers and the synthesis of

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cytokines that have a suppressive effect on cellular immunity [16, 18].

One of the important immunoregulatory anti-inflammatory cytokines is IL-4, the biological role of which is to inhibit the production of several T-cell cytokines, including pro-inflammatory and it is called "suppressor."

A study of the concentration of IL-4 in serum in healthy newborns showed that its values range from 40 to 100 pg/ml, and on average are 60.8±1.56 pg/ml. In newborns of the main and comparison groups, IL-4 production was reduced by 2.3 and 2.2 times (26.7±1.19 pg/ml, P <0.001) relative to the control group, which indicates impaired functioning cytokine network. A comparative analysis of the concentration of IL-4 among children of the main group and the comparison group did not have significant differences (Table 1.).

An important role in coordinating the functional conjugation of a multicomponent immune system is played by interferons, which are a group of biologically active proteins or glycoproteins synthesized by a cell in the process of a protective reaction to foreign antigens. It is known that IFN-γ is one of the important mediators for characterizing the state of the immune system of patients, which regulates the intensity of the immune response, increasing the bactericidal activity of phagocytic cells, and has antiviral and immunomodulating activity.

The interferon system is aimed at recognizing and eliminating foreign genetic information. The most important function of IFN-γ is its participation in the implementation of the relationship between lymphocytes and macrophages, as well as in the regulation of cellular and humoral immune responses. In our studies, the level of production of IFN-γ in healthy newborns averaged 25.7±1.56 pg/ml (Table 1.).

For newborns of the main and comparison groups, the presence of reduced production of IFN-γ before treatment was 1.5 times characteristic of the control group, which amounted to 17.0±0.65 pg/ml and 16.3±0.62 pg/ml (P <0.001), this once again reflects the degree of impaired immune system function in IUGR.

The concentration of IFN-γ among children of the main group and the comparison group did not have significant differences. The low ability of newborns to synthesize IFN-γ causes a violation of the immunoregulatory index in the direction of the predominance of suppressor activity of T-lymphocytes and a decrease in killer cell activity.

We also analyzed the state of the cytokine profile in newborns with IUGR in the study groups, depending on the clinical variant (Table 2.).

As can be seen from the presented data, the concentration of the pro-inflammatory cytokine IL-1β (525.5±8.8 pg/ml) was significantly higher (P <0.001) in newborns of the main group with a symmetric variant of IUGR than in infants with an asymmetric IUGR 501.5±6.9 pg/ml).

Table 2. The state of the cytokine profile in newborns with IUGR depending on the clinical variant (pg/ml)

Indicators	Main group		Comparison group	
	symmetric option n-32	asymmetric option n-26	symmetric option n-20	asymmetric option n-25
IL-1β	525,5±8,8*^	501,5±6,9	425,1±7,7	411,3±7,0
IL -8	699,2±13,1*^	637,8±15,7^	566,6±17*	506,2±17,1
IL -4	23,9±1,4*	30,1±1,7	25,1±1,9*	29,2±1,8
INF-γ	17,0±0,9	17,0±0,8	16,1±1,0	16,44±1,1

Note: * - the difference between the IUGR options within the groups P <0.001. ^ - the difference between the IUGR options between the groups P <0.001.

In the comparison group, no significant differences between the options were observed. A significant difference between the IL-1β cytokine indices in newborns with a symmetric variant of the IUGR of the main group (525.5±8.8 pg/ml) and a symmetric version of the comparison group (425.1±7.7 pg/ml) was also revealed. as well as with an asymmetric version of the main group (501.5±6.9 pg/ml) and an asymmetric version of the comparison group (411.3±7.0 pg/ml).

The levels of the pro-inflammatory cytokine IL-8 had significant (P <0.001) differences between the symmetric and asymmetric variants of IUGR 699.2±13.1 pg/ml and 637.8±15.7 pg/ml in the main group and in the comparison group, respectively 566.6±17 pg/ml and 506.2±17.1 pg/ml. It was found

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that the level of IL-8 in newborns with a symmetric variant of IUGR of the main group (699.2±13.1 pg/ml) was significantly higher than in children of the same version of the comparison group (566.6±17.7 pg/ml). In children with an asymmetric variant of the IUGR of the main group, this indicator is significantly higher than in newborns with an asymmetric version of the comparison group.

The concentrations of the anti-inflammatory cytokine IL-4 in children with a symmetric variant were significantly (P <0.001) lower than in children with an asymmetric variant of IUGR, as in the main group (23.9±1.4 pg/ml and 30.1±1, 7 pg/ml) and in the comparison group (25.1±1.9 pg/ml and 29.2±1.8 pg/ml).

Apoptosis, or programmed, physiological cell death, is an energetically active, genetically controlled process that serves to eliminate defective or damaged cells. Apoptosis helps preserve the order and normal functioning of the biological system, cleansing of unclaimed, sick (who have completed their life cycle or resulting from mutations of potentially dangerous) cells and is a fundamental process of maintaining homeostasis: both an increase and a decrease in the level of apoptosis lead to disruption homeostasis and the development of various diseases [7.15].

To identify increased readiness of lymphocytes for apoptosis (a condition preceding programmed death), the level of cells expressing apoptosis receptors is determined. In the process of initiation of programmed cell death involved IL-18 and expressing apoptosis antigen - CD95 + -cells of lymphocytes.

The pro-inflammatory cytokine interleukin-18, a non-glycosylated polypeptide that does not have a classical signal sequence, occupies a special position among immunoregulatory mediators, since it is one of the key cytokines in the formation of an innate and acquired immune response, differentiation and functional activity of macrophages, dendritic cells and T lymphocytes .

IL-18 stimulates the production of IFN-γ, TNF-α, IL-1, IL-2, adhesion molecules and apoptosis factors RaB/Taz, which contributes to the activation of cytotoxic T-lymphocytes, NK cells and the formation of an effective anti-infection immune response. IL-18 itself is induced by stress signals (neurogenic or bacterial in origin). IL-18 not only stimulates the synthesis of IFN-γ, but also modulates its functional activity. It was shown that the expression of the Fas ligand of CD4 + - Th1 and NK cells also occurs under the influence of IL-18.

On the other hand, it was shown that IFN-γ is involved in the activation of expression of Fas itself. Thus, we can conclude that IL-18 alone (FasL) or through IFN-γ (Fas) stimulates the initialization of apoptosis.

In the peripheral blood serum of healthy newborns, the level of IL-18 ranged from 45 to 80 pg/ml, and averaged 64.5±2.15 pg/ml. A study of the production of IL-18 in infants with IUGR born in asphyxia before treatment revealed an increased concentration of 2.5 times (160.5±4.95 pg/ml, P <0.001) compared with the control group (table. 40)

The level of IL-18 in infants with IUGR born without asphyxiation was also 2.1 times higher before treatment than in children of the control group, and compared with newborns of the main group it was reduced by 1.2 times.

Increased production of IL-18 leads to activation of the expression of Fas proteins (CD95 +), the stimulation of which as a result leads to apoptosis processes (Table 3).

Table 3. The concentration of interleukin-18 and the number of CD95 + in newborns with IUGR (PG/ml)

Indicators	Control (n=19)	Main group (n=58)	Comparison group (n=45)	P
IL-18	64,5±2,15	160,5±4,95	138,1±3,93	P<0,001
$CD95^+$	25,1±0,82	29,8±1,16	27,9±1,04	P<0,001

On the surface of activated lymphocytes, binding of soluble and expressed receptors (FasL- and Fas-) occurs, which causes cell apoptosis.

In the peripheral blood of healthy newborns, the number of apoptosis antigen-expressing CD95 + cells expressing an average of 25.1±0.82% with individual fluctuations from 22% to 30%. The content of CD95 + cells in newborns with IUGR born in asphyxia was significantly increased (P <0.001) before treatment compared with those in healthy newborns and averaged 29.8±1.16%. In newborns with IUGR who were born without signs of asphyxia, the concentration

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of CD95 + - cells averaged 27.9±1.04%, which is 1.1 times higher than in newborns in the control group, but there were no significant differences compared with the main group .

With an increase in the expression of apoptosis antigen - CD95 + cells in the peripheral blood, which refers to a membrane or receptor-mediated factor, the development of apoptosis is initiated. The implementation of the apoptogenic signal is activated through the C-terminal intracellular domain of this receptor (the so-called death domain). Detection of CD95 + on the surface of lymphocytes is regarded as their readiness for apoptosis.

We also analyzed the state of apoptosis factors in newborns with IUGR in the study groups depending on the clinical variant (Table 4).

Table 4. The state of apoptosis factors in newborns with IUGR depending on the clinical variant (pg/ml)

Indicators	Main group		Comparison group	
	symmetric option n-32	asymmetric option n-26	symmetric option n-20	asymmetric option n-25
IL-18	166±6,3^	153,8±7,4^	149,1±7,7	129,2±6,2
CD-95$^+$	32±1,4*	27,3±1,7	29,6±2,0	26,6±1,7

Note 8 .: * - the difference between the IUGR options within the groups P <0.001. ^ - the difference between the IUGR options between the groups P <0.001.

The levels of the IL-18 cytokine stimulating apoptosis processes were significantly higher in children of the main group with a symmetric variant of IUGR (166±6.3 pg/ml) than in children with a symmetric version of IUGR in the comparison group (149.1±7.7 pg/ml). Similarly, the content of IL-18 in children of the main group with an asymmetric variant of IUGR (153.8±7.4 pg/ml) was significantly higher than in children with an asymmetric version in the comparison group (129.2±6.2 pg/ml).

Analysis of the indicator of apoptosis factor CD-95$^+$ showed that in the main group in newborns with a symmetric variant of IUGR, its content (32±1.4 pg/ml) was significantly higher (P<0.001) than in children of the same group with an asymmetric variant (27.3±1.7 pg/ml).

CONCLUSION

Thus, our studies have shown that in children with IUGR, especially those born in asphyxia, there is a significant imbalance in the production of pro-inflammatory (IL-1β, IL-8 increase by 2.6; 3.6 times, IFN-γ decreases by 1 5 times) and anti-inflammatory (IL-4 are reduced by 2.3 times) cytokines. It was found that in children with IUGR born in asphyxia, an increase in the production of apoptosis factors occurs in the peripheral blood: the concentration of the IL-18 cytokine increases by 2.5 times, the number of apoptosis expressing antigen - CD95 + cells - by 1.2 times, compared with children of the control group. It was found that the most pronounced changes are detected in newborn children born in asphyxia, with a symmetric variant of IUGR.

REFERENCES

1. Altynbayeva G. B., Bozhbanbayeva N. S., Adilbekova I. M., Zhexengul S. S. Modern ideas about the birth of children with low weight the assessment of their development // Bulletin of KazNMU. 2017; (1): 185 - 187.

2. Bakhmutova L.A., Shtepo M.V., Palkina E.V., Shustova S.S., Lapeko S.V. The clinical significance of cytokine status indicators in assessing the course of postnatal adaptation of children with intrauterine growth retardation // Bulletin of new medical technologies. 2016; 2: 4: 183–187

3. Bliznetsova E.A., Antonova L.K., Kulakova N.I. Features of the course of the neonatal period in premature infants with intrauterine growth retardation // Neonatology: news, opinions, education. 2017; (3): 83–88.

4. Chernenkov Yu.V., Nechaev V.N., Dudukina E.S. Features of newborn children with intrauterine growth retardation // Saratov Journal of Medical Scientific Research. 2017; 13 (1): 62-67.

5. Chistyakova G.N., Remizova I.I., Gazieva I.A., Bychkova S.V., Zanina E.V., Charipova B.T. Pro- and anti-inflammatory mediators in newborns with perinatal pathology // Russian Bulletin of Perinatology and Pediatrics. 2014; 2: 66-70.

ISSN- 2394-5125 VOL 7, ISSUE 04, 2020

6. Deepak Sharma, Sweta Shastri and Pradeep Sharma. Intrauterine Growth Restriction: Antenatal and Postnatal Aspects //Pediatrics.– 2016; (10): 67–83.

7. Khaertinov H.S., Anokhin V.A., Boychuk S.V., Rizvanov A.A. Sepsis and apoptosis // Genes & Cells. 2016; XI: 4: 18-21.

8. Khodjamova N.K., Rakhmonkulova Z.J., York Stein., Fazliddinova S.F. The value of antenatal risk factors in the formation of intrauterine growth retardation // Eurasian Journal of Pediatrics. 2020; 1 (4): 20-28.

9. Levine T.A., Grunau R.E., McAuliffe F.M., Pinnamaneni R. et al. Early childhood neurodevelopment after intrauterine growth restriction: a systematic review // Pediatrics. 2015; 135: 1: 126–141.

10. Levkovich M.A., Plahotya T.G., Berdichevskaya E.M., Tsaturyan L.D. Features of cytokine regulation in chronic placental insufficiency // Modern problems of science and education. 2016; 4: 1-8.

11. Nardozza, L.M.M., Caetano, A.C.R., Zamarian, A.C.P. et al. Fetal growth restriction: current knowledge. Arch Gynecol Obstet. 2017; (295): 1061-1077. https://doi.org/10.1007/s00404-017-4341-9

12. Panova M.S., Panchenko A.S. The role of cytokines and their genetic polymorphism in the development of hypoxic-ischemic encephalopathy in full-term newborns // Pediatric. 2017; 8: 6: 99–104. doi: 10.17816/PED8699-104

13. Rakhmankulova Z.J., Khodjamova N.K., Abdukadirova M.K. The content of certain trace elements in newborns with intrauterine growth retardation // Eurasian Journal of Pediatrics. 2019; 3(3): 230-237.

14. Ryumina I.I., Kirillova E.A., Narogan M.V., Grosheva E.V., Zubkov V.V. Feeding and postnatal growth of preterm infants with intrauterine growth retardation // Neonatology: News, Opinions, Training. 2017; (1): 98–107.

15. Ustinova T.I., Medvedeva N.N., Malinovskaya N.A., Ustinova T.I., Medvedeva N.N., Malinovskaya N.A. The processes of apoptosis and neurogenesis in neurons of the motor nuclei of the spinal cord of young rats after exogenous effects // Modern problems of science and education. 2015; 2-1.

16. Yakornova G.V., Remizova II, Chistyakova G.N., Ustyantseva L.S. Dynamics of pro-inflammatory cytokines in children born to women with complicated pregnancy, depending on the course of the early adaptation period // Russian Bulletin of Perinatology and Pediatrics. 2015; 4: 50-56.

17. Zamaleeva R.S., Maltseva L.I., Cherepanova N.A., Frizina A.V., Lazareva V.K., Yupatov E.Yu., Kogan Ya.E., Fattakhova F.A.. The state of the problem of treatment and prediction of fetal growth retardation // Practical medicine. 2016; 1 (93): 41-44.

18. Zhukova A.S., Vanko L.V., Nikitina I.V., Balashova E.N., Matveeva N.K., Vtorushina V.V., Krechetova L.V., Ionov O.V., Mullabaeva S.M., Degtyarev D.N. The content of cytokines in the blood plasma of premature infants in the early neonatal period. Immunology. 2017; 38 (3): 143-147. DOI: http: //dx.doi. org/10.18821/0206-4952-2017-38-3-143-147