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# THE STATE OF PROINFLAMMATORY AND ANTI-INFLAMMATORY CYTOKINES IN BLOOD SERUM OF INFANTS WITH LOW BIRTH WEIGHT IN THE PRSESENCE OF INTRAUTERINE INFECTION

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**Abstract**

The study aimed to compare the content and status of the pro- and anti-inflammatory cytokines in full-term newborns and in newborns having low birth weight with intrauterine infection. This study was carried out using serological and molecular-biological methods, the analyzer MULTISKAN ASCENT using the T-System Chemo. Analysis of results was performed by comparison using the Mann-Whitney criterion, Spearman correlation, and nonparametric statistics. Cytokine imbalance was revealed in infants with congenital infection. The level of proinflammatory cytokines in infants with low birth weight was significantly lower as compared with the same cytokine level in full-term infants.

**Keywords:** Neonatal Prematurity, Infant, Low Birth Weight Infant, Gestational Age.

## Introduction

Perinatal diseases present a serious medical and social problem. The intrauterine infection has always been in the limelight of neonatologists.

Pathogens of intrauterine infections usually cause inflammatory diseases, their clinical signs and symptoms are non-specific, which complicates their diagnosis (1–4). Neonatal sepsis is the most frequent and dangerousconsequence of intrauterine infection for newborns, more specifically, for premature new borns(4–6). The probability of severe sepsis in premature infants is much higher than in the full-term newborns(7). The average number of septic processes in this age group makes 0.1 - 0.2% in full-term newborns and 1 - 1.5% in preterm infants (8).

Despite the use of modern medicinal drugs, sepsis still determines the neonatal mortality statistics. Mortality in case of sepsis is still very high and reaches 30 - 40% in full-term and 75% - in preterm infants (9,10). It increased by 3.4% in children with surgical pathology associated with their congenital malformations as well as extremely low and very

low birth weight (11). Morphological studies indicate that morphological signs of sepsis are observed in 33% of newborns with surgical pathology. At the same time, immaturity of the immune system is the main factor that leads to sepsis(4).

Weak or inaccurate diagnostic tests is among the reasons that cause high mortality rate of newborns with early sepsis(12). Some of these tests demand greater objectivity, speed, sensitivity and specificity (7,12).

Research relevance is also determined by an increase in the number of premature deliveries, which largely cause infant mortality. More than one million children in the world die annually because of preterm birth complications, mainly in the developing countries (6,12,13). At the same time, 25% of premature births are caused by exceptional circumstances, such as infections(6,14).

Topicality of this research problem is highly relevant keeping in mind permanent increase in the number of preterm delivery risks, and other factors leading to the development of immunodeficiency in women of reproductive age, which are considered as a favorable background for the infectious agents (unfavorable living conditions, smoking, poor nutrition, stress, increased extra genital pathologies)(5,14,15).

Today, the role of cytokines(which are directly involved in the inflammatory reactions) in the development of infectious processes is well known. In recent years, the pathogenetic mechanisms of a number of inflammatory diseases were revealed in terms of studying cytokines and the cytokine concept of systemic inflammatory response was presented (16,17). Despite the fact that the pro-inflammatory and anti-inflammatory cytokines are already considered as reliable markers of neonatal infection, their further study presents new opportunities for early diagnosis, choice of treatment tactics and prevention of a number of complications, caused by intrauterine infection.

Given the emerging risk factors related to preterm deliveries, significantly negative life prognosis for premature infants in the presence of intrauterine infection, as well as the lack of an ideal marker providing early diagnosis of neonatal sepsis, one can conclude that development of new diagnostic methods and markers stands among the most important tasks in modern pediatrics (1–4,7,12,18).

Recent years have been marked by an increase in the number of intrauterine infections (3). These infections remain the key factors that lead to the intrauterine infection of the fetus and the newborn (3,4,11,18–23).

Manifestations of infection and its consequences in the fetus and in newborns is largely determined by the stage of the embryo-fetal development during ingress of infection (1,23,24). The ingress of fetus infection in early gestational age is revealed in malformations, anomalies, or intrauterine fetal demise (24). Gestational age and birth weight are

considered among the main factors influencing perinatal mortality (25). In case of fetus survival or in the case of its contamination at the later stages of pregnancy, this infection affects the already formed organs, - mainly the CNS, cardiovascular, respiratory and the digestive system (24–26).

Studies have shown that fetal intrauterine contamination is largely caused by viral infections of the mother (27). Although the range of virus types steadily expands, herpetic viruses remain among the most widespread and dangerous(24). The incidence of congenital forms of these viral infections makes 2.5% (27,28). The detection rate of viral infections in children who died in the early neonatal period and during their first year of life reaches 88 - 92%. The majority of children who died during that period had congenital "chronic" generalized disease of mixed viral etiology (24).

Viral infections may proceed either asymptomatically or severely with fatal consequences(3). Another, important property of infectious matters is their polyorganotrophic feature, which means that they can affect different organs and tissues (26,29). Fetus lesion depends on the intensity of virus replication and on the gestation period, when the infection is developed (30). This process may be characterized by minimal signs and symptoms (asymptomatic, subclinical forms) as well as by severe lesions, such as embryopathy, fetopathy and generalized inflammatory changes (26,29).

Adverse outcomes in case of DNA virus infection caused by herpes simplex virus type I and type II and cytomegalovirus are based on immune mechanisms. These viruses have immunosuppressive properties; they also can inhibit the immune functions (31). The intensiveness of viral infections matters as well. Viruses can inhibit the immune response due to high viral load [1, 34]. Keeping in mind crucial role of the time factor and specific type of pathogen in the development of intrauterine infection, the nature and severity of its consequences for the newborn organism is also determined by its immunological reactivity (32,33). Despite the fact that the immune system of the fetus is formed in embryogenesis and during postnatal period, newborns are characterized by immune deficit during the neonatal period. Immune immaturity facilitates the development of intrauterine infection and its transformation into the infection process (32). The prematurely born infants present a special risk group, determined primarily by the deep failure of their functional immunity (34).

The lack of specific immunity, infection consequences for infants are determined by thee interaction between microorganism and macro organism, primarily by the response of the innate immune system components, including phagocytes, natural killer cells, antigen presenting cells, humoral mediators of inflammation (35) .

Normal functioning of the immune system mechanisms prevents irregular release of cytokines and other inflammatory mediators, providing adequate response to inflammation (16). At the same time, the immune immaturity of newborns can change the immunological response orientation under the impact of infectious agents, thus provoking sepsis (36–38).

Proceeding from the above, it is of particular scientific interest to study the behavior of cellular immunity components, in particular the anti-inflammatory and proinflammatorycytokines in infants with various gestational period, in the simultaneous presence of the viral infection and functional unavailability to resist it.

The study of cytokines is also essential in this aspect in view of the possibility of using research results to carry out prognostic assessment of infectious processes, selecting adequate medical tactics related to children with congenital and acquired abnormalities. Research objective: comparative study of the content and state of proinflammatory(IL-1β) and anti-inflammatory (IL-10) cytokines in full-term and preterm infants with low birth weight in the presence of intrauterine infection.

**Materials and methods**

The study was carried out by permission of the West Kazakhstan Marat Ospanov State Medical University Ethics Committee (protocol No. 1 dated December 25, 2009).

Research was carried out during the period 2013-2015 at the premises of the Department of Neonatal Pathology and departments of neonatal resuscitation and intensive care of RPC (Regional Prenatal Centre) in Aktobe. The authors of this study carried out clinical-laboratory and instrumental examination of 120 newborns, of which 60 newborns were referred to the main group and the same number – to the comparison group.

The children were selected into groups with regard to thorough analysis of their medical history, obstetric history; the clinical intrauterine infection of viral etiology were detected in the neonatal period, as well as with regard to gestational age and birth weight.

The main group consisted of preterm infants weighing less than 2500 grams, who were delivered by women threatened with premature birth and burdened with a history of infectious diseases. This group consisted of 42 (70%) infants who had low birth weight (LBW), 16 (26%) infants had very low body weight (VLBW) and two (4%) infants had extremely low birth weight (ELBW) (see Figure 1). Four infants from this groupof subjects diedin the neonatal period (their body weight was less than 2500grams.).

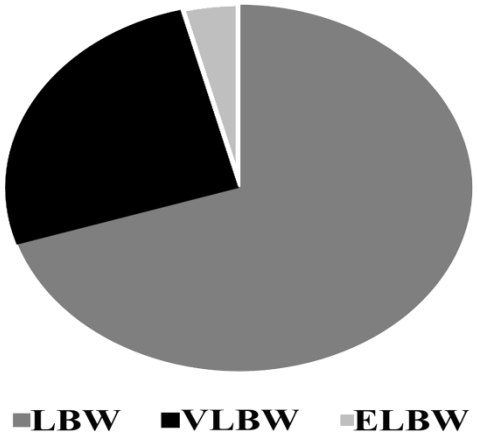


**Figure 1.Distribution of newborns by their birth weight.**

The comparison group consisted of full-term infants delivered by women with a history of infectious diseases weighing more than 2500 grams. The observation of infected children was carried out dynamically, from the first days of their life, along with identification of clinical signs of congenital viral infection and definition of blood hematology and chemistry, including trace elements. The study implied ultrasound examination of their parenchymal organs and the brain.

Laboratory diacrisis of intrauterine infection was carried out in the early observation stages of infants in the neonatal resuscitation and intensive care units as well as in the neonatal pathology unit. Confirmation of the intrauterine infection diacrisis of the fetus was performed through serum diagnostics and molecular-biological methods, defining the level of Ig M and Ig G antibodies to HSV (type 1 and 2), CMV and Chlamydia infection by enzyme-linked immunoassay (ELI) using the analyzer MULTISKAN ASCENT with T-System "Chemo" and DNA virus detection by polymerase chain reaction (PCR) in children (DNA-related system test).

Determination of cytokines IL-1β, IL-10 in the serum was performed by chemiluminescence immunoassay, using Siemens reagents («IMMULITE 1000", Moscow, Russia). Statistical processing of the results was performed using the program «SAS» version 9.2. Analysis of the obtained results was performed by comparing two independent groups by using Mann-Whitney U-test, Spearman correlation, nonparametric statistics. Differences were considered accurate at $p < 0.05$.

**Results**

The clinical-laboratory and instrumental examination of 120 newborns showed the following results.

The serological and molecular biological studies detected intrauterine infection in all newborns. The etiological verification of intrauterine infection identified markers of herpes simplex virus in 7% of full-term newborns and in

4% of preterm infants with low birth weight, markers of cytomegalovirus were identified in 5% and 2%, and the mixed infection (herpes simplex virus and cytomegalovirus) - in 88% and 94% of the examined groups of infants, respectively (see Table 1). Chlamydia infection was not diagnosed in any case.

**Table 1.Verification of pathogens through immunoassay and polymerase chain reaction in both groups of newborns.**

| Typeofagent | Full-term infants | Newborns with low birth weight |
|---|---|---|
| Combined virus infection (cytomegalovirus, herpes simplex virus type I, II) | 53 (88 %) | 57 (94 %) |
| Herpessimplexvirus | 4 (7 %) | 2 (4%) |
| Cytomegalovirus | 3 (5 %) | 1 (2%) |
| Total | 60 | 60 |

It was found that the structure of intrauterine infection in both groups of infants was characterized by predominance of combined virus infections (herpes simplex viruses and cytomegalovirus) - in contrast to the monoinfection cases (cytomegalovirus and herpes virus). Therefore, the incidence of mixed infection in the main group differed from the frequency of diagnosed viral monoinfection cases by 16 times, whereas in the control group (full-term infants) – by 7 times, respectively.

The difference in terms of mixed infection incidence between the studied groups of infantsmade 6% (see Table 1).

Chemiluminescent immunoassay of blood serum in full-term and preterm newborns with low birth weight showed the following results (see Table 2).

**Table 2.Content characteristic of IL-1β and IL-10 in blood serum of infants from both groups.**

| Cytokines | Full-term infants (comparison group) | Preterm infants with low birth weight | p |
|---|---|---|---|
| IL-1β | 154,2 ± 22,5 | 59,2 ± 4,5 | p = 0,001* |
| IL-10 | 19,3 ± 4,8 | 6,17 ± 1,6 | p = 0,002* |

Note: * – significant differences between groups (p< 0,05).

The study of pro-inflammatory (IL-1 β) and anti-inflammatory (IL-10) cytokine content in the blood serum of full-term and preterm newborns with low birth weight, found significant differences between the groups.

Comparative assessment showed that the content of IL-1 β and IL-10 in the blood serum of infants from a comparison group was significantly higher than the relevant content of cytokines in the blood serum of infants from the main group (threefold increase).

The content of pro-inflammatory cytokine (IL-1β) in the blood serum of infants from both groups was significantly higher than the anti-inflammatory cytokine (IL-10) content. Taking into account the fact that the content of IL-1 β amounted to 154,2 ± 22,5 in newborns from the control group and the content of IL-10 - 19,3 ± 4,8, the content of the relevant cytokine made only 59.2 ± 4 5 ± 1.6 and 6.17 in the main group.

The authors traced the difference between the content of proinflammatory cytokine (IL-1β) and the anti-inflammatory cytokine (IL-10) in each group. The content of pro-inflammatory cytokine (IL-1β) exceeded the content of anti-inflammatory cytokine (IL-10) in the main group (premature infants with low birth weight) by 10 times, whereas in comparison group –by eight times.

The clinicopathologic findings provided the possibility to distinguish the following abnormalities in newborns (Figure 2). Thus, the main nosological forms found in the full-term infants included (along with their combinations): perinatal hypoxic-ischemic encephalopathy (HIE), which was observed in 46% of cases, congenital pneumonia (CP) - in 13% of cases, congenital fetal malformations (CFM) - in 18% of cases, respectively. Prolonged hyperbilirubinemia was found in 34% of the examined full-term newborns.

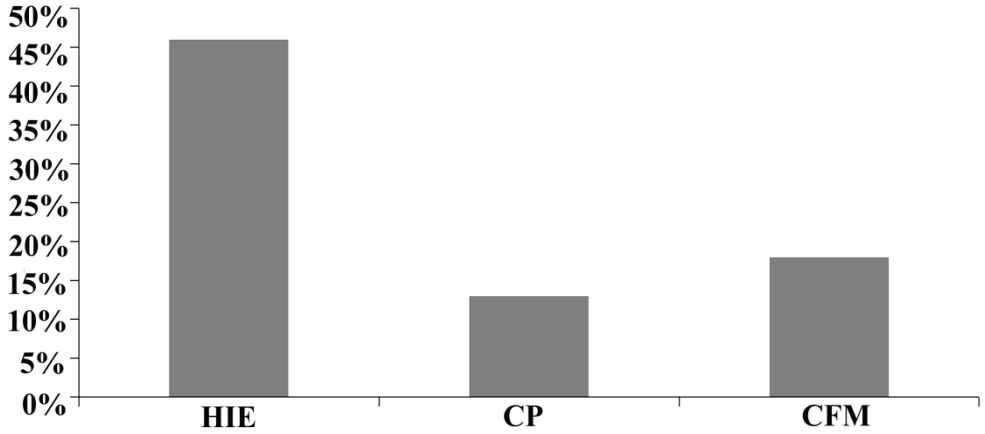


**Figure 2.Basic nosological forms among full-term newborns.**

Premature infants with low birth weight had the following incidence of basic nosological forms (including their combinations): perinatal hypoxic-ischemic encephalopathy (HIE) was diagnosed in 87% of cases, congenital pneumonia (CP) - in 72% of cases, fetal hepatitis (FH) - in 35 % of cases, intracranial hemorrhage (ICH) – in 38.3% of cases and congenital fetal malformations (CFM) - in 32% of cases, respectively (Figure 3).

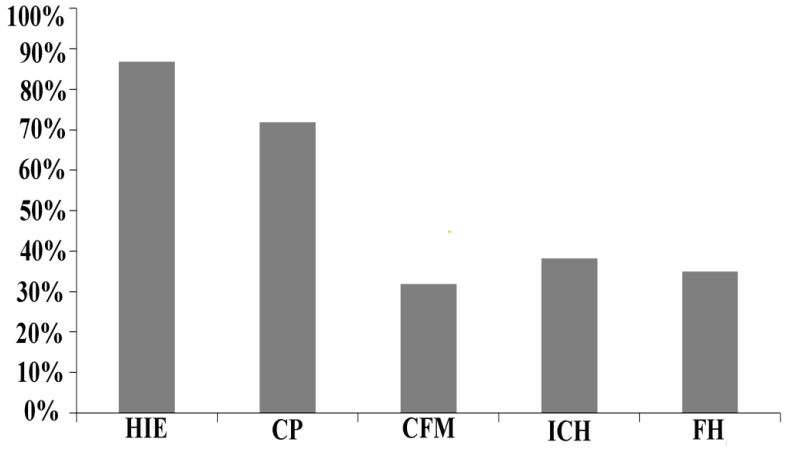


**Figure 3. Basic nosological forms among preterm infants.**

Comparative evaluation of the frequency of major clinical entities identified in the studied children showed the prevalence in the group of premature babies with a low weight in the incidence of perinatal hypoxic-ischemic encephalopathy by 41%, congenital pneumonia by 59%. At the same time, other manifestations of congenital viral infection were diagnosed in preterm newborns with low birth weight, in contrast to the full-term infants, namely, hepatitis and fetal intracranial hemorrhage.

The ultrasound examination of parenchymal organs and brain in newborns found the following congenital malformations: congenital heart defects (CHD), congenital kidney disease (CKD), congenital urinary system defects (CUSD), congenital gastrointestinal tract defects (CGITD), as well as congenital central lesion (CCL). Research results based on the body weight of infants and their gestational age are presented in Table 3.

**Table 3. Structure of congenital malformations in infants, depending on their body weight and gestational age.**

| Congenitalmalformations | Full-term infants n =11 (18% of all infants) | Pre-term infants with low birth weight 19 (32% of all infants) | | | |
|---|---|---|---|---|---|
| | | LBW | VLBW | ELBW | All cases |
| Heartdefects | 3 (27 %) | 4 | 2 | - | 6 (32 %) |
| Kidney and urinary system defects | 4 (37 %) | 4 | 3 | 1 | 8 (42 %) |
| Gastrointestinaltractdefects | 2 (18 %) | - | 1 | - | 1 (5 %) |
| Centrallesion | 2 (18 %) | 2 | 2 | - | 4 (21%) |

The study of congenital malformations in newborns showed the following incidence: CKD and CUSD - 36%, CHD - 27%,CGITD and CCL - 18% each. Meanwhile, as regards newborns with low birth weight, the incidence statistics of

congenital malformations was as follows: CKD and CUSD - 42%, followed by CHD - 32% and CCL - 21%. The difference in the incidence of birth defects detected in preterm infants as compared with the full-term newborns made 6% with respect to the kidneys and urinary system, 5% with respect to heart defects, 3% with respect to central lesion (predominated in the main group), 13%with respect to CGITD (these defects were more frequent in the group of full-term infants). Newborns with low birth weight had various degrees of anemia in the clinical picture. Stage I of iron deficiency anemia (hemoglobin below 110 g / l) was detected in 40% of newborns (24 infants),stage II of iron deficiency anemia(hemoglobin within 100-80 g / l) was detected in 15% (9 infants) and stage III of iron deficiency anemia(hemoglobin below 80 g / l) – in 5% of newborns (3 infants) (Figure 4).

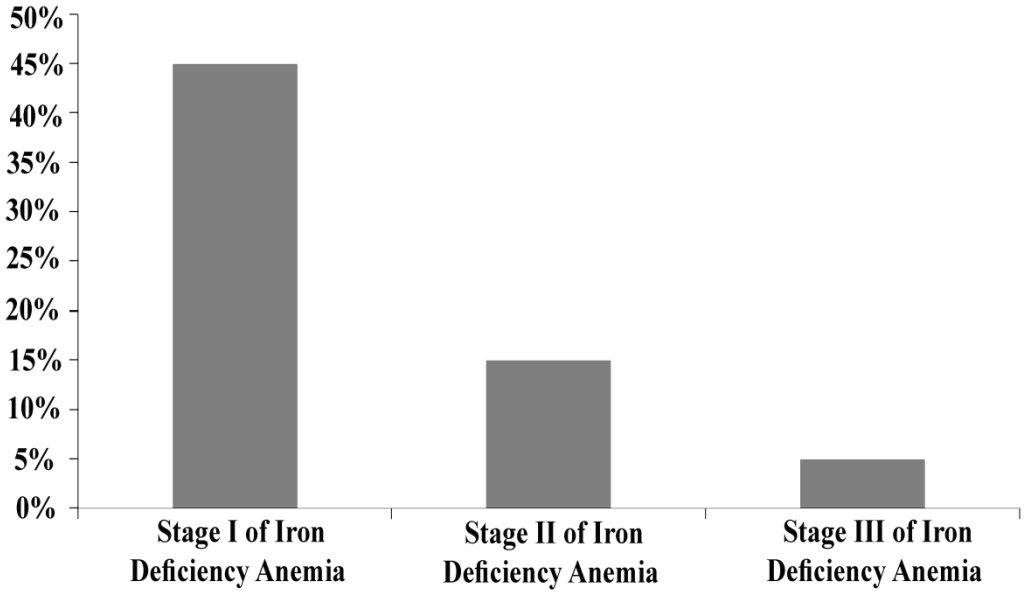


**Figure 4. Anemia of varying severity in preterm newborns with low birth weight.**

**Discussion**

The study showed that the structure of intrauterine infection in newborns from both groups was dominated by the combined virus infection (herpes simplex viruses and cytomegalovirus) - in contrast to the monoinfection cases (cytomegalovirus and herpes virus). Therefore, the incidence of mixed infection in the main group differed from the frequency of diagnosed viral monoinfection cases by 16 times, whereas in the control group (full-term infants) – by seven times, respectively. At the same time in preterm infants with low birth weight,the combined virus infection tends to prevail (6%) as compared with its frequency in full-term newborns.

One can assume that the frequency of revealed virus-associated intrauterine infection is associated with certain gestational age associated with virus infestation. Perhaps lower incidence of mixed infection can be explained by the later period of intrauterine infection. Conversely, higher rate of virus detection in preterm infants is probably

determined by the inability of their immune surveillance system to provide a full immune response, which helps viruses to "avoid" immune surveillance (39).

In this respect, comparative assessment of proinflammatory and anti-inflammatory content of cytokines in infants with congenital infection showed significant difference ($p < 0,05$) in their performance between the two groups. One could notice significantly low levels of IL-1β and IL-10 in the group of preterm infants (these values differed from those revealed in full-term infants by three times).

When interpreting the results, and forming markers for prognostic assessment of infection process in a particular study, one should consider properties of the diagnosed virus: the ability to immunosuppression, as well as their doubled potential associated with high virus load (combined herpes-virus effect). On the other hand, one should take into account physiological characteristics of newborns, their immune characteristics associated with gestational age. It is important to consider the Tx2 orientation of immune response in full-term and preterm infants, as well as the decreased expression of proinflammatory cytokines and increased expression of anti-inflammatory cytokines, in terms of specific humoral arm(35).

Obviously, lower rates of cytokines such as IL-1β, and IL-10 in the blood serum of newborn infants with low birth weight(as compared with full-term infants) can be explained by a more pronounced "small-for-dates" syndrome related to varying degrees of all units immune system components determined by smaller gestational age.

Thus, lower levels of proinflammatory cytokines in preterm infants, as compared with the full-term newborns (by three times), being considered in line with their functional activity indicate low capacity of monocytes and macrophages in preterm infants in terms of their response to virus infections along with greater sensitivity of immature immune systems to succumb to immunosuppressive properties of mixed virus infections.

At the same time, higher levels of proinflammatory cytokines in full-term newborns with intrauterine virus infections (in comparison with relevant values in preterm newborns) demonstrate relevant capacity of the cellular arm to respond (although with low efficiency) to infection starting from the first days of life, despite the aggravating circumstances: Tx2 cytokine polarity, morphofunctionalimmaturity of the immune system, high virus load.

The analysis of research results also revealed insufficiency of pro-inflammatory cytokines in infants from both groups. Hence, the level of IL-10 in preterm infants differed from the same cytokine level in full-term infants (like IL-1β) by three times. Low levels of anti-inflammatory cytokine in preterm infants were noted in other studies [44].

The reduced IL-10 synthesis in preterm infants, as compared with the full-term newborns can be explained by different maturity degree of their immune systems, which corresponds to their gestational age. This is confirmed by other scholars who studied similar cytokine levels in the amniotic fluid of women with preterm and normal delivery, with intrauterine infection and without it (40). The lack of significant differences in the levels of inflammatory cytokines in this and the above experiment can indirectly confirm dependence of IL-10 concentration on gestational age.

The study of newborns also revealed insignificant difference between the levels of pro-inflammatory mediator in comparison with the level of anti-inflammatory cytokine in both groups of infants. Proinflammatory cytokine level exceeded the level of anti-inflammatory cytokine in the main group by 10 times, whereas in the control group –by eight times. Keeping in mind that IL-10 is a suppressant interleukin, which inhibits the function of T-lymphocyte type 1 helpers, one can evaluate the activity of this cytokine by its regulatory function (17).

These results demonstrate that the level of its immunomodulation activity against IL-1β indicates a trend toward its higher activity against inflammatory cytokines in full-term infants. Consequently, it can be assumed that IL-10 more actively inhibits the synthesis of IL-1β with the increase in gestational age. Similar result was observed when comparing the content of IL-10 in preterm infected infants with indicators of premature virus-infected infants presented in another study (40).

Considering the immunoregulatory role of inflammatory cytokines in terms of inflammation, it should be noted that macrophages of newborns could cause a weak immune response to the bacterial infection due to their inability to produce sufficient quantities of inflammatory cytokines like IL-1β and IL-12. Instead of that, they produce more immunosuppressive cytokines, including IL-10. Therefore, one can assumed that the production and the level of functional activity of relevant pro- and anti-inflammatory cytokines, which depend on gestational age, depend on the infection factor. Considering low content of IL-10 in terms of the immune response to the herpes infection, one can assume the following. The lack of specific humoral immunity and low functional activity of cellular immune mechanisms, along with the propensity for Tx2 cytokine polarity, do not allow newborns to restrain intensive multiplication of viruses under these circumstances. Perhaps intentional reduction in anti-inflammatory cytokine defines the development of the immune process towards differentiation Tx0 into Tx1, which is responsible for cell-type reactions. Low content of anti-inflammatory cytokine and high level of the inflammatory one may indicate the modulation of this very immune response against viruses in newborns, which is not only the only possible, but also

the most effective option. Obviously, the decrease in inflammatory cytokine helpsnewborns to protect themselves against viruses that are controlled by cellular immunity, thereby increasing its effectiveness.

Such imbalance of cytokines may be regarded as a specific type of adaptation immunoregulatory mechanism in response to intense virus replication in newborns, which is typical for adults. At the same time, as noted by other research sources, chronic herpes virus infection cause the opposite immune response - towards Tx2 (39). Thus, low levels of inflammatory cytokines in infants from both groups can be regarded as a pathogenetic mechanism mediating development of the infection process, its acute phase.

Considering results obtained in terms of the inflammatory process development, taking into account the ability of IL-1β and IL-10 to the reciprocal suppression, as well as modern views regarding the damaging role of proinflammatory cytokines without their adequate suppression, such values can be interpreted as a possible threat of inflammatory response in infants from both groups(38).

Despite the fact that the level of IL-1β in preterm infants group appears to be much lower (by three times) in comparison with the relevant value in full-term newborns, one should predict higher risk of damage caused by this inflammatory agent in preterm infants. The low functional activity of IL-10 in preterm infants was decisive in the development of a more negative prognosis. Therefore, low levels of anti-inflammatory cytokine will be a key marker, because the level of inflammatory cytokine depends on its immunomodulatory activity.

Today, the main reasons for severe state of newborns with small gestational age and serious birth defects are multiple organ failure, morphofunctional immaturity, as well as the infectious process (viral and / or bacterial infection as well as fungal infection). Contributing factors in the development of their systemic inflammatory response include intrauterine infection, small gestational age, perinatal hypoxia (40).

Comparative analysis of clinical and instrumental diagnosis of birth defects in preterm infants with low birth weight and full-term infants, showed no significant differences in their frequency. At the same time, among congenital malformations in both groups of infants in the first place one could observe defects of kidneys and the urinary system, in the second place - heart defects. In the third place, one could observe central lesion and gastrointestinal tract defects in the group of full-term newborns; at the same time, preterm infants had central nervous system defects. Malformations of the gastrointestinal tract were more common (by 13%) in the group of full-term infants. The study showed that the frequency of clinical and instrumental manifestations of malformations in preterm infants depended on their birth weight: the increase in body weight led to the increased frequency of diagnosed malformations.

The clinical picture of newborns with congenital viral infection was predominantly characterized by lesions of the respiratory system, central nervous system, urinary system, gastrointestinal tract and homeostasis system. The results of clinical and instrumental studies provided the possibility not only to diagnose the prevalence of selected nosological forms in preterm newborns with low birth weight (prevalence in the incidence of perinatal hypoxic-ischemic encephalopathy by 41%, congenital pneumonia - by 59%), as compared with the full-term newborns, but also the presence of another significant pathology - fetal hepatitis, intracranial hemorrhage, anemia.

Differences in the frequency of acquired disease prevalence between the studied groups of infants indicate varying degrees of their lesion. Research studied show that this process depends on the virus replication intensity and on the gestational age when relevant infection is developed(7). According to the clinical picture, the lack of normal resistance to the virus attack in the organism of preterm infants with low birth weight, caused by profound immaturity of their immune systemled to a massive lesion of their body systems, as compared with the full-term newborns.

Despite the number of lesions, the authors of this study will not consider the infection cause as decisive with regard to the general inflammatory process in preterm infants with low birth weight taking into account small difference in virus load frequency between the studied groups of infants. It is rather a predisposing cause in preterm infants with low birth weight because it is determined by functional activity of cellular immune mechanisms, as indicated by cytokine studies. Given more pronounced perinatal hypoxia (frequency of affected organs and systems involved in its occurrence and the organs, which can compensate it - heart, lungs, kidneys, liver, nervous system, hematopoiesis - was higher in preterm infants, as compared with the full-term newborns), we can assume a higher risk of systemic inflammatory reaction in preterm infants. At the same time, another negative factor that influences further prognosis is the diagnosed hemorrhagic brain lesions in a significant number of preterm infants with low birth weight(13).

Speaking about prognostic factors it should be noted that some scientists considered the logical connection between the number of favorable outcomes in infants with extremely low birth weight and the increase in their gestational age. At the same time, they also indicate that their number is less dependent on their body weight. In this study, the weight factor has greater impact on the incidence of diagnosed congenital abnormalities.

Systemic virus infection, diagnosed in newborns, only underscores inability of their immature organisms to provide adequate adaptation and compensatory mechanisms in the development of infection processes. Being regarded as klendusity, the inflammation turns into the damaging mechanism against this background. Moreover, research results show that in the presence of combined lesions of organs and systems that can provide normal mutual functioning as

well as in the extremely stressful situations (immune morphofunctional deficiency immunosuppressive combined virus attack) difficult tasks of newborn organisms are additionally aggravated, which is reflected by their clinical picture and confirmed by the cytokine screening results.

Proceeding from the fact that the purpose of any inflammatory process is to eliminate the pathogenic agent and the related consequences, its performance criteria in terms of viral infection can be regarded as the severity of systemic damages of the infant body systems and their adaptation abilities. Therefore, cytokine screening indicators, namely, reduction in the functional activity of the anti-inflammatory cytokine that regulates the level of pro-inflammatory mediator having proinflammatory function, can act as prognostic markers of virus replication and relevant adaptation abilities of immature organisms.

Considering high levels of pro-inflammatory cytokine IL-1β in terms of underdeveloped specific immunity, morphofunctional deficiency of innate cellular link,Tx2 cytokine pattern, doubled suppressive virus attack, and, most importantly, keeping in mind weak induction of virus interferon, we can assume the existence of other, alternative ways to cope with virus agents in newborns.

In this regard, there is a research interest in conducting a comparative study related to the content of the said and other regulatory cytokines in the blood serum of newborns with different physiological characteristics and capabilities, infected with other viruses.

**Conclusion**

1. In newborns with low birth weight immune response to the infectious process is significantly reduced as compared with full-term infants, due to the immaturity of their cellular-humoral immunity.
2. In newborn infants with congenital infection cytokine deviations were found in the form of cellular immunity imbalance: significantly elevated content of pro-inflammatory cytokine IL-1β associated with a significant decrease in the content of anti-inflammatory cytokine IL-10.
3. Significantly lower (by three times) content of pro-inflammatory cytokine IL-1β and anti-inflammatory cytokine IL-10 in preterm infected infants as compared with the full-term newborns could be explained both by the morphofunctional immaturity of cellular immunity caused by smaller gestational age, and by higher susceptibility of the immature immune system to immunosuppressive properties of Herpesviruses.

4. Despite the fact that the content of IL-1β in preterm infants appears much lower (by three times) as compared with its relevant values in full-term newborns,caused by the lower functional activity of IL-10 in preterm infants, one should predict a high risk of lesion caused by this pro-inflammatory agent in preterm infants.
5. Low content of anti-inflammatory cytokine IL-10 can be considered as a marker in the development of prognostic assessment related to systemic inflammation in infants with different gestational age, as the level of the proinflammatory cytokine IL-1β depends on their reciprocal interaction.
6. Elevated content of pro-inflammatory cytokine IL-1β in full-term newborns with intrauterine virus infection, in comparison with its relevant values in preterm infants, indicate the ability of the cellular arm to provide immune response to infection during the first days of life, albeit with low efficiency, in the presence of the Tx2 cytokine polarity, morphofunctional deficiency and high virus load.
7. The structure of intrauterine infection both in full-term infants and preterm newborns with low birth weight is dominated by the combined virus infection (cytomegalovirus with herpes simplex viruses), in contrast to monoinfection.
8. The clinical picture of newborns with congenital viral infection is predominantly marked by lesions of the respiratory system, central nervous system, urinary system, gastrointestinal tract and homeostasis. Newborns with low birth weight are more frequently b subject to lesions of the internal organs and systems than the full-term newborns. The authors of this research found correlation between the clinical manifestations of congenital viral infection, gestational age of newborns and the content of the immunomodulatory cytokine IL-10.

Thus, immune immaturity is the main risk factor as regards the development of systemic inflammatory response in preterm infants. Clinical manifestations of congenital viral infection depend on gestational age and birth weight; they are characterized by involvement of two or more internal organs and systems in the pathological process, along with primary central lesion, defects of respiratory system, hepatobiliary system and homeostasis. Perinatal hypoxia is a related factor in the development of systemic inflammatory response in preterm infants along with the presence of hemorrhagic brain lesions. In order to provideprecise interpretation of research results, the authors recommend considering the role of modulating cytokine IL-12 in newborns in terms of their ability to resist infectious agents.

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