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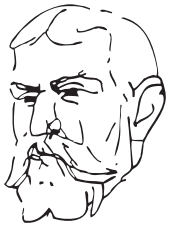

Memory of
dr Władysław
Biegański

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ORIGINAL ARTICLE

INFLAMMATORY RESPONSE STATUS IN INFANTS WITH INTRAUTERINE INFECTION FROM MOTHERS WITH IDENTIFIED TORCH INFECTION

DOI: 10.36740/WLek20220420110

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ABSTRACT

The aim: To investigate the status and possibilities of markers of the inflammatory response of organism in infants with identified IUI born to mothers diagnosed with TORCH infection.

Materials and methods: The study group included: infants diagnosed with IUI (n = 40), born to mothers (age 31.31 ± 2.08 years) with the diagnosis of TORCH infection and a control group (n = 25 infants). Childbirth in all newborns was physiological. The average weight of newborns was 1877.69 ± 981.78 g (min – 600 g; max – 4000 g). Gestational age: 32.25 ± 5.15 weeks. Observation and treatment of newborns lasted up to 7 days (included stay in the emergency department of the Uzhhorod maternity hospital in the Zakarpattia region). Cytokine profile, γ-IFN, TNF-α, Pg E2, serum neopterin and procalcitonin levels were studied.

Results: The values of the parameters of the cytokine profile (IL-1, IL-6, IL-8, IL-10) varied within the reference values, but with significant differences with the values of the control group, which was 1,2; 4; 10; 6 times, respectively. The levels of inflammatory mediators (γ-IFN Procalcitonin Neopterin TNF-α Pg E2) differed significantly from the data of the control group of infants and exceeded the upper limit of the reference values by 1,3; 3; 25; 4 times, respectively. According to the correlation analysis, there are positive correlations of medium level: IL 1 and procalcitonin (r = 0.33); IL 6 and IL10 (r = 0.44); IL 10 and prostaglandin E2 (r = 0.44); neopterin and prostaglandin E2 (r = 0.39), which indicates synergism in the performance of biologically active processes. Negative correlations of moderate degree were observed between the following parameters: IL 1 and gestational age of infants (r = -0.36); IL 6 and IL 8 (r = -0.34); γ-IFN and TNF-α (r = -0.43), which indicates the diversity of interactions between participants in the inflammatory response of the organism.

Conclusions: Various infectious agents can act as «primary affect» of sepsis as a complex pathological process involving the organism, and each of the infections has its own characteristics of the pathological process, therefore curent changes in infectious circumstances make new demands on research. It has been proven that intrauterine infection has a negative effect on the homeostatic parameters of infants, in particular, on the indicators of the inflammatory response of the child's organism. Symptomatic inflammatory biomarkers can be used to identify the pathological condition of the infant, in addition to routine laboratory tests, for early correction of VUI. This delay in identifying affected infants can lead to long and unnecessary therapy, the emergence of resistant strains of microorganisms, increased treatment costs and, in particular, a higher risk of complications such as cerebral palsy or intraventricular hemorrhage.

KEY WORDS: intrauterine infection, inflammatory response, cytokine profile, newborns

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INTRODUCTION

One of the biggest problems that doctors face is deciding when to diagnose an intrauterine infection and what correction to prescribe. Intrauterine infections (IUI) and neonatal sepsis are the most relevant and controversial issues of modern neonatology, given that infectious pathology determines a high level of morbidity and mortality in newborns [1, 2]. In recent years, the problem of IUI has become particularly relevant, as the achievements of modern resuscitation allow to ensure the survival of newborns who have suffered severe IUI [3, 4]. The results of studies conducted in obstetrics and gynecology and neonatal clinics have shown that a variety of opportunistic pathogens not only cause acute and chronic inflammatory processes of the pelvis of the pregnant woman, but also lead to severe of the IUI fetus and newborn, and can form pathology directly not associated with the development of the inflammatory process [5, 6]. IUI is an established fact of intrauterine penetration of microorganisms into the fetus, in which there are pathophysiological changes characteristic of infectious pathology, manifested prenatally or shortly after birth, while intrauterine infection of the fetus and newborn is the pathological condition formed under the influence of infectious pathology of the mother. associated infection of amniotic fluid, placenta, umbilical cord, fetus on the background of changes in the immunological reactivity of the newborn without signs of infectious disease [7, 6]. The frequency of IUI has not been definitively established, however, according to resources, the prevalence of IUI can reach 10-15% of all pregnancies, and intrauterine infection ranges from 6 to 55%, reaching 80% among premature infants. In the structure of IUI viral and / or virus-associated infections are the most dangerous

Table I. Parameters of the inflammatory response in infants

Laboratory indicators	M ± m (n=40)	min	max	Reference values	Control group (n=25)
IL-1, pg/ml	0,83 ± 0,73•	0,00	3.39	0-11pg/ml 1,6 pg/ml	0,65 ± 0,06
IL-6, pg/ml	10,79 ± 5,24•	1,23	19,30	0-10 pg/ml 2,0 pg/ml	0,77 ± 0,04
IL-8, pg/ml	4,56 ± 3,72•	1,00	25,20	0-10 pg/ml 2,0 pg/ml	0,48±0,056
IL-10, pg/ml	7,78 ± 6,65•	0,50	28,30	0-20 pg/ml 5,0 pg/ml	1,2 ± 0,25
γ-IFN, pg/ml	20,14 ± 25,56•	0,10	102,80	no more than 15,0 pg/ml	5,8±0,3
Procalcitonin, ng/ml	1,67 ± 1,09•	0,15	4,23	no more than 0,5 ng/ml	7,6 ± 1,5
Neopterin, nmol/l	32,32 ± 18,50•	0,50	77,40	no more than 10 nmol/l	0,12±0,022
TNF-α, pg/ml	157,21 ± 21,05•	102,30	196,30	till 6 pg/ml 0,5 pg/ml	8,4 ± 0,32
Pg E2, pg/ml	1671,38 ± 1555,16•	956,80	11190,20	200-400 pg/ml	390,21± 31,19

Significance of values: P <0,001 •

and difficult to predict. Viral infections during pregnancy lead to a number of consequences for the mother and fetus, ranging from asymptomatic disease to critical conditions that cause severe maternal morbidity, stillbirth, premature birth, birth defects and congenital anomalies that become apparent at birth or later [5, 8]. The highest risk of infection of the fetus is observed in the case of primary infection of the pregnant woman [9]. Thus, IUI, especially viral, remain almost uncontrollable causes of reproductive loss, childhood morbidity and disability. Pathological effects of microorganisms on the fetus during pregnancy lead to various disorders, including abortion, organ defects, the development of severe infectious inflammation or latent process with elements of persistence in the postnatal period. IUI infection is often accompanied by the development of life-threatening conditions in newborns, which determining the medical and social significance of the problem and requires further in-depth research.

THE AIM

To investigate the status and possibilities of markers of the inflammatory response of organism in infants with identified IUI born to mothers diagnosed with TORCH infection.

MATERIALS AND METHODS

The study group included: infants diagnosed with IUI (n = 40), born to mothers (age 31.31 ± 2.08 years) with the diagnosis of TORCH infection and a control group (n = 25 infants). Childbirth in all newborns was physiological. The average weight of newborns was 1877.69 ± 981.78 g (min – 600 g; max – 4000 g). Gestational age: 32.25 ± 5.15 weeks. Observation and treatment of newborns lasted up to 7 days (included stay in the emergency department of the Uzhhorod maternity hospital in the Zakarpattia region). Cytokine profile, γ-IFN, TNF-α, Pg E2, serum neopterin and procalcitonin levels were studied.

RESULTS

The examination revealed pathological changes in the levels of immunological parameters and inflammatory response factors of the organism, their interactions and relationships (table I.).

According to table I, there is a significant increase in the level of IL-1 (0.83 ± 0.73 pg / ml) compared to the control group (0.65 ± 0.06 pg / ml), but within the reference values; significant increase in IL-6 levels by 14-fold (10.79 ± 5.24 pg / ml) compared to controls group of infants (0.77 ± 0.04 pg / ml) and within the upper limit of reference. The level of IL-8 in the studied contingent (4.56 ± 3.72 pg / ml) also differs significantly from the data of the control group (0.48 ± 0.056 pg / ml), almost 10 times, but the variation occurs within the reference. There is also a significant, difference between the values of IL-10 (7.78 ± 6.65 pg / ml) from the values of the control group (1.2 ± 0.25 pg / ml).

Consequently, the values of the cytokine profile varied within the reference values, but with significant differences

Table II. Statistically significant correlations between the studied laboratory parameters

Laboratory indicators	Pearson's correlation coefficient, r	Statistical signifacance, p
IL-1 Procalcitonin	0,33	0,04
IL-1 Gestational age	0,36	0,02
IL-6 IL-8	0,34	0,03
IL-6 IL-10	0,44	0,005
γ-IFN TNF-α	-0,43	0,006
Pg E IL-10	0,44	0,006
Pg E2 Neopterin	0,39	0,02

with the values of the control group, which was 1,2;14;10; 6 times, respectively.

The level of γ-IFN (20.14 ± 25.56 pg / ml) also differed significantly (in 4 times) from the data of the control group (5.8 ± 0.3 pg / ml) and exceeded the reference values by 1.3 times. The value of procalcitonin (1.67 ± 1.09 ng / ml) differed significantly from the control group (7.6 ± 1.5 ng / ml) and exceeded the upper limit of reference by 3 times. The level of Neopterin (32.32 ± 18.50 nmol / l) differed significantly (267 times) from the data of the control group (0.12 ± 0.022 nmol / l) and was 3 times higher than the upper limit of the reference. The value of TNF-α (157.21 ± 21.05 pg / ml) in the study group differed significantly from the data of the control group (8.4 ± 0.32 pg / ml) and was 25 times higher than the upper limit of reference. The Pg E2 study also presented a significant difference in levels (1671.38 ± 1555.16 pg / ml compared to 390.21 ± 31.19 pg / ml), which was a significant difference in data and exceeded the upper limit of reference by 4 times.

Therefore, the values of γ-IFN Procalcitonin Neopterin TNF-α Pg E2 differed significantly from the data of the control group of infants and exceeded the upper limit of the reference values by 1,3; 3; 25; 4 times, respectively.

A correlation analysis of the relationships between the studied parameters was performed, and reliable correlation coefficients of different degrees were identified (Table II.).

According to table II, there is a correlation between the average level of IL-6-IL-10 (r = 0.44) and IL-6 -IL-8 (r = -0.34), which corresponds to the physiological patterns of interactions between interleukins. IL-1, 6 – make up the group of pro-inflammatory interleukins, while IL-10 belongs to the anti-inflammatory group. IL-10 suppresses the production of almost all proinflammatory cytokines and prevents the adhesion of leukocytes to the endothelium, inhibits the secretion of superoxide radicals and cytokines (IL6, IL8, TNFα) [8]. According to leading scientists, IL-10 has been shown to inhibit the effect of interferon-γ and neopterin synthesis by monocytes / macrophages.

A complete immune response is provided only by active interaction between cytokines. The biological effect of one cytokine is usually realized together with the action of others. The main correlograms of relationships between the participants in the inflammatory response are as follows.

Consider the correlogram of the relationship between the level of γ-IFN and TNF-α in the blood of examined newborns (Fig. 1.)

It is known that cytokines have a wide range of biological properties – interact with each other, form a universal network that triggers and regulates the cascade of inflammatory, immune, metabolic processes – both local and systemic, aimed at neutralizing and eliminating pathogens. In addition to cytokines, interferons also belong to inflammatory mediators involved in the development of the inflammatory response. The main proinflammatory mediators are TNF-α and IL-1. The role of TNF-α in the development of sepsis is associated with: increasing the procoagulant properties of the endothelium, activation of neutrophil adhesion, induction of other proinflammatory cytokines, stimulation of catabolism, fever, synthesis of acute phase proteins.

The importance of IFNγ in the immune system is ascribed to its ability to directly inhibit viral replication, as well as its ability to act as immunostimulator and immunomodulator. According to our data, the multidirectional correlation between the levels of γ-IFN and TNF-α in the blood of the examined newborns is r = -0.43, which is due to the characterological data of the considered indicators.

Consider the correlogram of the relationship between the levels of IL-6 and IL-10 in the blood of examined newborns (Fig. 2.)

Interleukins are cytokines responsible for the transfer of information between leukocytes. When used, one group of leukocytes may affect another. Interleukin 6 (IL 6) is multidirectional. It is produced by monocytes and macrophages. IL 6 directly and effectively stimulates inflammatory processes. However, high concentrations of this substance can limit the development of inflammation. This is because interleukin 6 blocks the synthesis of inflammatory cytokines through a feedback inhibition mechanism. IL-6 is a proinflammatory

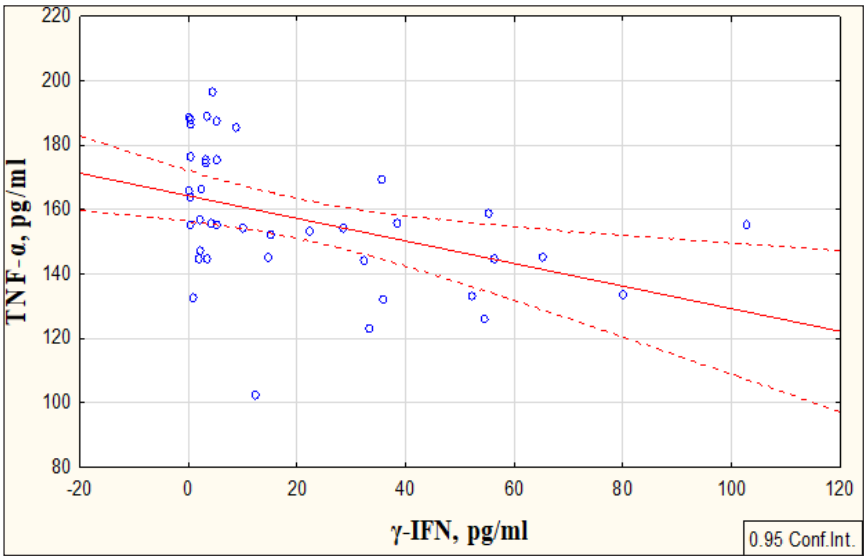

Fig. 1. Correlation between γ-IFN and TNF-α levels in the blood of examined newborns.

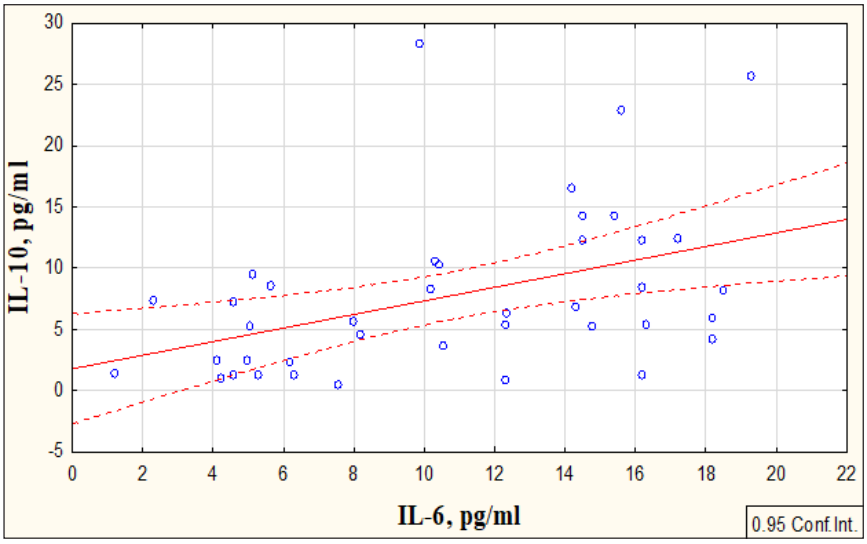

Fig. 2. Correlation between IL-6 and IL-10 levels in the blood of examined newborns

cytokine with two directions of action. On the one hand, it inhibits the production of proinflammatory cytokines by macrophages, on the other hand, it induces the production of acute phase proteins, promotes the activation of T lymphocytes by antigen-presenting cells, enhances B cell proliferation and induces the formation of immunoglobulins, stimulates hematopoiesis and platelet formation, is synthesized by activated macrophages and T cells [10,11]. Increase in the level of the anti-inflammatory cytokine IL10 can be explained by increase in secretion in response to the elevated content of pro-inflammatory cytokines in the serum. IL10 suppresses the production of almost all proinflammatory cytokines, inhibits leukocyte adhesion to the endothelium and inhibits the secretion of superoxide radicals and cytokines (IL6, IL8, TNFα). The positive correlation coefficient between interleukins 6 and 10 (r = 0.44) demonstrated compliance with the classical rules.

Consider the correlogram of the relationship between Procalcitonin and Interleukin 1 (Fig. 3.)

Interleukin 1 (IL 1) defines a whole group of cytokines that are crucial in the inflammatory process, are the main trigger mechanism for initiating the production of other proinflammatory cytokines. As a result, the biochemical and functional cascade of inflammatory pathobiochemical processes is developing. It is produced in response to a variety of antigens.

The Procalcitonin test also has a high diagnostic potential, which can be traced in our studies and allows to diagnose the disease, determine the severity, course and subsequent prognosis. Synergism of interactions and a positive correlation with the proinflammatory cytokine Interleukin-1 (r = 0.33) is observed.

An important milestone in research is the gestational age of infants, which has significant effects on the development of the disease and the nature of the inflammatory process. Here is a correlogram of relationships (Fig. 4.).

When analyzing the correlogram (Fig. 4) attention should be payed to the features of nonspecific resistance in

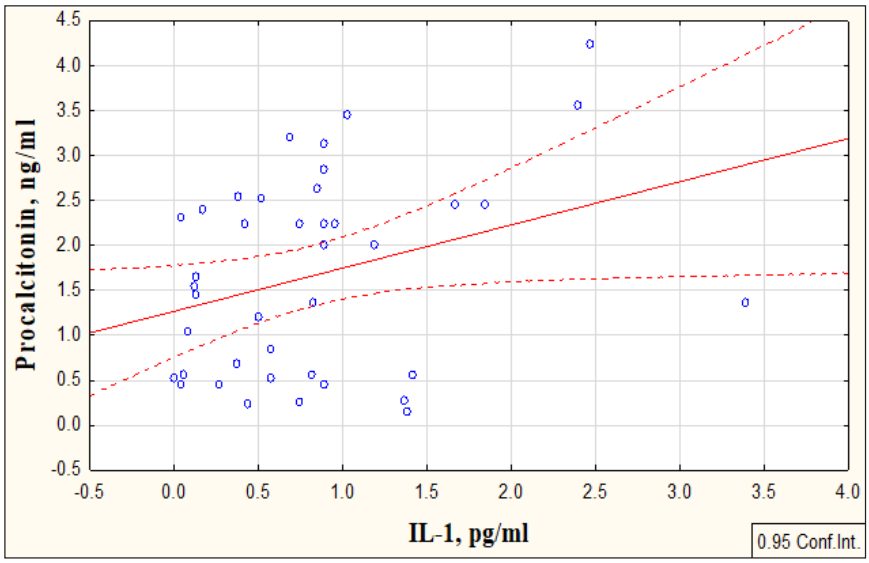

Fig.3. Correlation between Procalcitonin and IL-1 levels in the blood of examined newborns

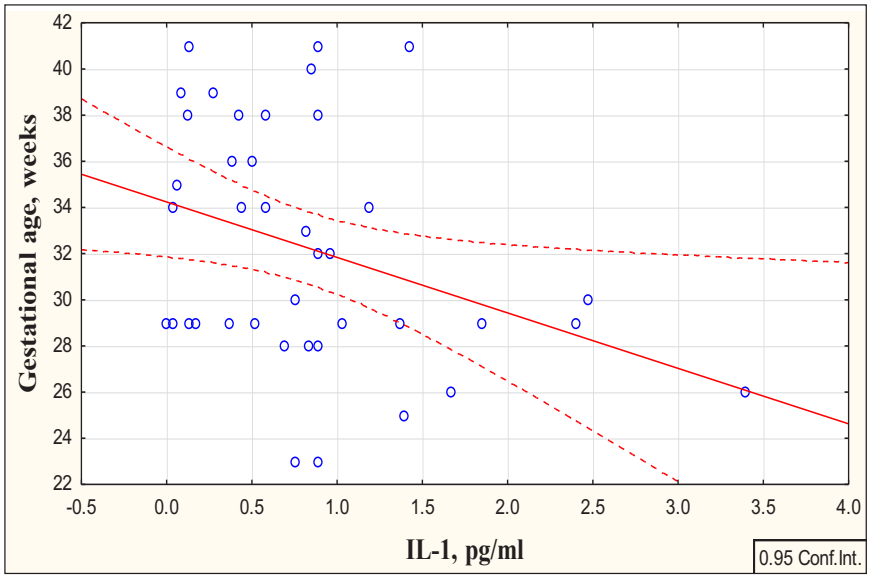

Fig. 4. Correlation between IL-1 level and Gestational age in the blood of examined newborns

the fetus and newborn. Intrauterine capacity of phagocytic cells is relatively insignificant. After birth, the phagocytic ability of leukocytes increases. At the same time, both neutrophils and monocytes in the first 6 months of life do not cope with the final phase of phagocytosis – the destruction of the ligand, which is especially evident in relation to pathogenic microorganisms. At this age, the child's phagocytes are unable to fight pneumococci, which explains the frequent occurrence of pneumonia and relatively high mortality in infants. In the newborn, along with the imperfection of phagocytosis, there is a low ability to synthesize interferons [1,8]. In this regard, the newborn has a tendency to generalized bacterial inflammation and sepsis. These patterns are observed in our studies. The IL-1 relationship and gestational age have a mid-inverse correlation (r = -0.36). This fact can be interpreted as follows: the smaller the gestational age, the greater the production of IL-1 due to physiological age characteristics.

Consider the correlogram of the relationship between the levels of IL-6 and IL-8 in the blood of examined newborns (Fig. 5.)

The action of IL-6 is realized after interaction with two components of a specific heterodimeric receptor (gp130 and IL-6R). IL-6 is a proinflammatory cytokine with two directions of action. On the one hand, it inhibits the production of pro-inflammatory cytokines by macrophages, on the other hand, it induces the production of acute phase proteins (which activate corticosteroid synthesis), promotes the activation of T-lymphocytes by antigen-presenting cells, enhances B-cell proliferation and induces the formation of immunoglobulins, stimulates hematopoiesis and platelet formation. IL-8 is one of the main proinflammatory chemokines formed by macrophages, epithelial and endothelial cells. Interleukin 8 (IL 8) is a cytokine that stimulates the migration of immune cells throughout the body. This means that it stimulates the movement and

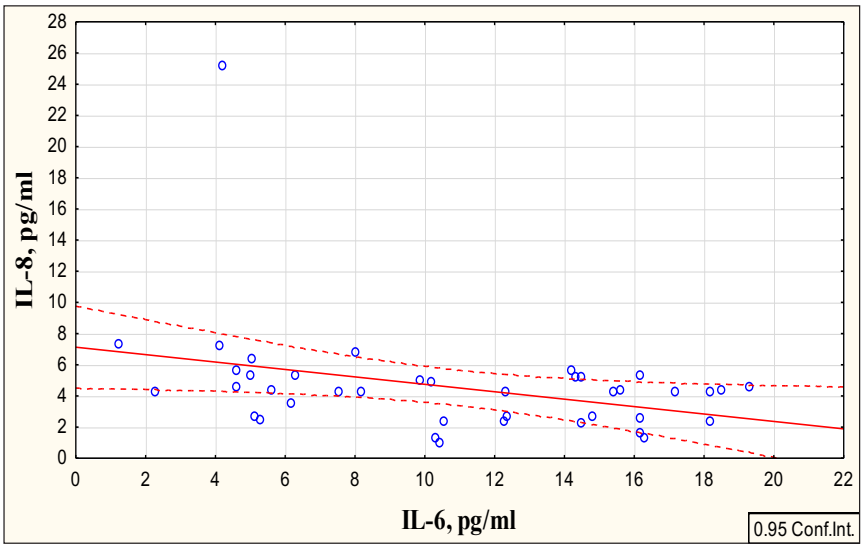

Fig. 5. Correlation between IL-6 and IL-8 levels in the blood of examined newborns

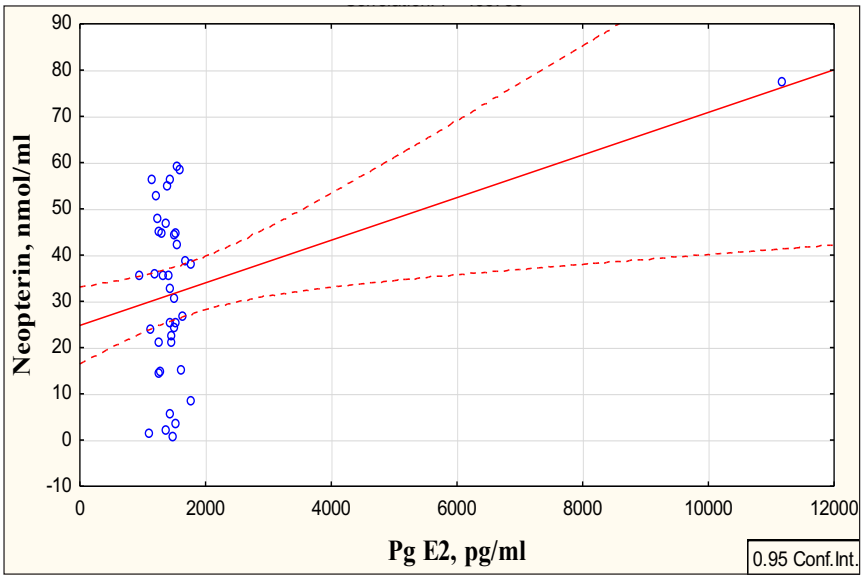

Fig. 6. Correlation between Neopterin and Prostaglandin E2 levels in the blood of examined newborns

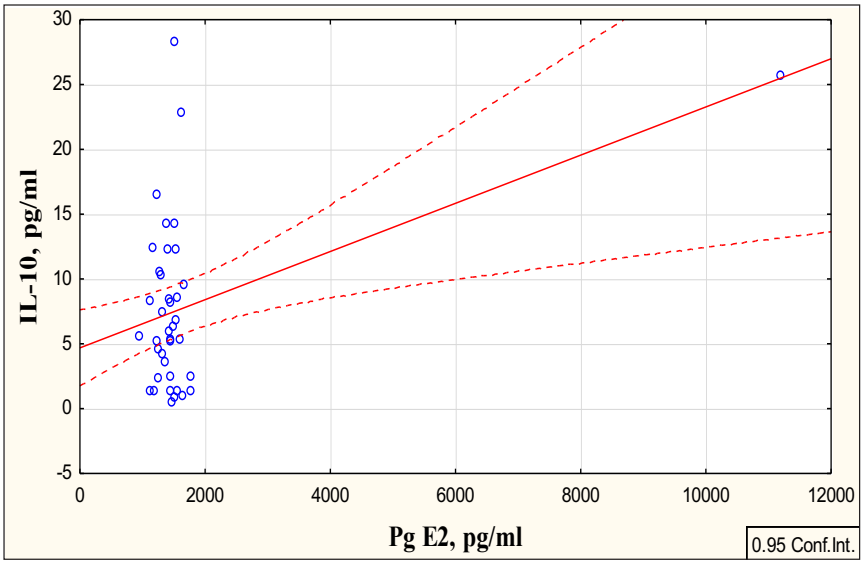

Fig. 7. Correlation between IL-10 and Prostaglandin E2 levels in the blood of examined newborns

distribution of T lymphocytes, neutrophils and monocytes. This action is defensive in nature. [8]. According to our data (Fig. 5). , there is a correlation relationship of the middle level (r = 0.44), which presents the unidirectionality of the interaction of biologically active substrates.

Consider the correlogram of the relationship between the levels of Neopterin and Prostaglandin E2 in the blood of examined newborns (Fig. 6.).

In the inflammatory process, an important role belongs to the mediators of inflammation – cytokines. However, the concentration of separate cytokines reflects only a limited view of the interaction between them and immunocompetent cells. Therefore, it is best to measure the level of Neopterin. Neopterin is a substance that is synthesized by monocytes and macrophages under the influence of interferon γ and to a lesser extent by activated vascular endothelial cells. Neopterin plays a role in the mechanism of cytotoxic action of activated macrophages. Its concentration reflects the combined effect of different cytokines on the population of monocytes / macrophages. Prostaglandins have an extremely wide range of physiological effects, are among the most active biological substances, which perform three main functions in the body: supportive, molecular, mediatory. The participation of prostaglandins in the inflammatory process has been proven. They are able to change the activity of enzymes, affect the synthesis of hormones and adjust their action on various organs and tissues. Imbalance in synthesis leads to the development of various diseases[8]. Thus, prostaglandins F2 and E2 are formed in the tissues of the respiratory tract, in particular E is synthesized in the lung tissue in the bronchi and can cause contraction of the bronchial muscles. Prostaglandins can be attributed to intracellular low molecular weight regulators, but they are also active in the extracellular space. Correlation analysis (Fig. 6.).of the obtained results showed positive dependences of the average level of Neopterin concentration on PgE2 (r = 0.39, p = 0.02).

Consider the correlogram of the relationship between the levels of IL-10 and Prostaglandin E2 in the blood of examined newborns (Fig. 7).

According to our data(Fig. 7)., there are significant correlations between the levels of IL-10 and Prostaglandin E2. In inflammation, PgE2 is involved in all processes that lead to the classic signs of inflammation: redness, swelling, pain. It also has immunomodulatory properties and effects on growth, bone structure, which is especially important for infants. IL10 suppresses the production of almost all proinflammatory cytokines, inhibits the adhesion of leukocytes to the endothelium and inhibits the secretion of superoxide radicals and cytokines, inhibits the effect of interferon on the synthesis of neopterin by monocytes / macrophages. The increase in the level of the anti-inflammatory cytokine IL10 can be explained by the increase in the secretion of this cytokine in response to the increased content of pro-inflammatory cytokines in the serum [8,12].

According to the results of correlation analysis, a positive moderate relationship between Pg E2 and IL-10 (r = 0.44, p = 0.006) was presented.

DISCUSSION

Modern research shows that the most common intrauterine infection of the fetus is caused by viral infections of the mother. The range of viruses that cause congenital pathology is constantly expanding. In addition to rubella, HSV, CMVand some others. Pathogens of infectious diseases of the mother during pregnancy are especially dangerous for the fetus, because the fetus lacks both active and passive immunity to microorganisms, which determines the development of the infectious process. Because most of the diseases of pregnant women that leading to IUI occur in subclinical, latent form with activation of the process in any violation of homeostasis, it complicates the clinical diagnosis. Thus, diagnostics based on clinical manifestations only, without involvement of specific microbiological studies, leads to diagnostic errors in 90-95% of cases. It is known that cytokines have a wide range of biological properties – interact with each other, form a universal network that triggers and regulates the cascade of inflammatory, immune-metabolic processes – both local and systemic, aimed at neutralizing and eliminating pathogens. Markers of inflammatory response in newborns diagnosed IUI present changes at all levels, The values of the cytokine profile parameters are within the reference values but have significant differences from the data of the control group according to our data. The levels of other inflammatory mediators (γ-IFN Procalcitonin Neopterin TNF-α, Pg E2) exceeded the upper limit of the reference values in 1,3,3, 25, 4 times, respectively, and significantly differed from the data of the infants control group. Immunological immaturity of the newborn can lead to a violation of the response to infectious agents. Various infectious agents can act as «primary affect» of sepsis as a complex pathological process involving the organism, and each of the infections has its own characteristics of the pathological process, therefore curent changes in infectious circumstances make new demands on research. It has been proven that intrauterine infection has a negative effect on the homeostatic parameters of infants[6], in particular, on the indicators of the inflammatory response of the child's organism. Symptomatic inflammatory biomarkers can be used to identify the pathological condition of the infant, in addition to routine laboratory tests, for early correction of VUI. This delay in identifying affected infants can lead to long and unnecessary therapy, the emergence of resistant strains of microorganisms, increased treatment costs and, in particular, a higher risk of complications such as cerebral palsy or intraventricular hemorrhage.

CONCLUSIONS

1. The values of the parameters of the cytokine profile (IL-1, IL-6, IL-8, IL-10) varied within the reference values, but with significant differences with the values of the control group, which was 1,2; 4; 10; 6 times, respectively.
2. The levels of inflammatory mediators (γ-IFN Procalcitonin Neopterin TNF-α Pg E2) differed significantly from the data of the control group of infants and exceeded the upper limit of the reference values by 1,3; 3; 25; 4 times, respectively.

3. According to the correlation analysis, there are positive correlations of medium level: IL 1 and procalcitonin (r = 0.33); IL 6 and IL10 (r = 0.44); IL 10 and prostaglandin E2 (r = 0.44); neopterin and prostaglandin E2 (r = 0.39), which indicates synergism in the performance of biologically active processes.
4. Negative correlations of moderate degree were observed between the following parameters: IL 1 and gestational age of infants (r = -0.36); IL 6 and IL 8 (r = -0.34); γ-IFN and TNF-α (r = -0.43), which indicates the diversity of interactions between participants in the inflammatory response of the organism.

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