ЦИТОКИНОВАЯ ДИАГНОСТИКА В ПРОГНОЗЕ КРИТИЧЕСКИХ СОСТОЯНИЙ У НОВОРОЖДЕННЫХ, РОДИВШИХСЯ ОТ МАТЕРЕЙ, ИНФИЦИРОВАННЫХ COVID-19

Наврузова Ш.И., Баратов С.С., Набиева З.Т.

Бухарский государственный медицинский институт, г. Бухара, Республика Узбекистан

Резюме. Статья посвящена разработке способа цитокиновой диагностики для прогнозирования развития критических состояний у новорожденных, родившихся от матерей с COVID-19, что имеет большое значение для органов здравоохранения при организации специализированной неонатологической и педиатрической службы.

Цель – разработать метод неинвазивной цитокинодиагностики для прогнозирования развития критических состояний у новорожденных, рожденных от матери с COVID-19. Предложенный способ позволяет ранней диагностики и профилактики развития критических состояний у новорожденных, что имеет важное практическое значение. Контроль цитокинов мочи в динамике определяет прогноз развития критических состояний, как в ранний, так и в поздний период адаптации новорожденных. Являясь маркером воспалительного процесса и ключевым цитокином костной резорбции, IL-17A играет сложную роль в процессе адаптации новорожденных, родившихся от матери с COVID-19. Новорожденные, рожденные от матери с COVID-19, имеют повышение IFNγ и IFNα в крови в первый день жизни на фоне повышения IL-17A в 1,48 раза, что свидетельствует о риске развития как инфекции, так и нарушений остеогенеза. Установлена активация интерферонового статуса к 7-му дню жизни у новорожденных на фоне повышения ключевого цитокина костной резорбции (IL-17A). У новорожденных детей, рожденных от матери, инфицированной COVID-19, обнаружено снижение в моче молекулярных маркеров повреждения эндотелия сосудов – MSR-1 в 4,25 раза. Было обнаружено снижение VEGF в моче новорожденных как при заражении COVID-19 у матери, так и при его отсутствии. Неинвазивная уроцитокинодиагностика позволяет достичь экономической эффективности за счет сокращения больничных коек, а также эффективности лечения за счет минимальной травматизации новорожденных.

Ключевые слова: новорожденные, цитокины, COVID-19, критические состояния, прогноз, дети

Адрес для переписки:

Наврузова Шакар Истамовна
Бухарский государственный медицинский институт
200100, Республика Узбекистан, г. Бухара,
ул. А. Навои, 1.
Тел.: +998 93 383-44-45.
E-mail: shakar.navruzova@gmail.com

Address for correspondence:

Shakar I. Navruzova
Bukhara State Medical Institute
1 A. Navoi St
Bukhara
200100 Republic of Uzbekistan
Phone: +998 93 383-44-45.
E-mail: shakar.navruzova@gmail.com

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CYTOKINE DIAGNOSTICS IN THE PROGNOSIS OF CRITICAL CONDITIONS IN NEWBORNS BORN TO MOTHERS INFECTED WITH COVID-19

Navruzova Sh.I., Baratov S.S., Nabieva Z.T.

Bukhara State Medical Institute, Bukhara, Republic of Uzbekistan

Abstract. The article is devoted to the development of a cytokine diagnostic method for predicting the development of critical conditions in newborns born to mothers with COVID-19, which is of great importance for health authorities when organizing specialized neonatology and pediatric services.

Objective: to develop a method of noninvasive cytokine diagnostics for predicting the development of critical conditions in newborns born from a mother with COVID-19.

The proposed method allows early diagnosis and prevention of the development of critical conditions in newborns, which is of great practical importance. The control of urine cytokines in dynamics determines the prognosis of the development of critical conditions, both in the early and late period of adaptation of newborns. As a marker of the inflammatory process and a key cytokine of bone resorption, IL-17A plays a complex role in the adaptation process of newborns born from a mother with COVID-19. Newborns born from a mother with COVID-19 have an increase in IFNγ and IFNα in the blood on the first day of life against the background of an increase in IL-17A by 1.48 times, which shows the risk of developing both infection and osteogenesis disorders. Activation of interferon status by the 7th day of life in newborns was established against the background of an increase in the key cytokine of bone resorption (IL-17A). A decrease in the urine of molecular markers of vascular endothelial damage – MSR-1 by 4.25 times was found in newborn children born from a mother infected with COVID-19. A decrease in VEGF in the urine of newborns was found, both with COVID-19 infection in the mother and in its absence. Non-invasive urine cytokine diagnostics allows achieving economic efficiency by reducing hospital beds, as well as medical efficiency due to minimal traumatization of newborns.

Keywords: newborns, cytokines, COVID-19, critical conditions, prognosis, children

Introduction

In modern perinatology, extensive data have been accumulated explaining the processes occurring in the mother – placenta – intrauterine child system both during the physiological course of pregnancy and childbirth, and in the case of pathological changes in the gestational period [1]. Rendering assistance to newborn children in critical condition at the stage of inter-hospital transportation is one of the most acute problems of modern neonatology and neonatal resuscitation.

Newborns in critical condition, delivered to the ICU of a level III hospital three days after birth, had a more severe course of the pathological process with a high probability of developing multiple organ failure syndrome [1]. Proinflammatory cytokines (TNFα, IFNγ and IL-6) differentially increase in newborns with sepsis depending on gestational age. As expected, these cytokine values were high for newborns ≥ 32 weeks during sepsis; however, they were insignificant for newborns born < 32 weeks [2].

Limited data are available on COVID-19 during pregnancy, but studies published to date do not show an increased risk of developing severe diseases in late pregnancy or a significant risk for the newborn. Neither a congenital infection nor a virus was detected in the materials of the afterbirth, which confirms the relevance of this area of scientific research [4].

Objective: to develop a method of noninvasive cytokine diagnostics for predicting the development of critical conditions in newborns born from a mother with COVID-19.

Materials and methods

The medical histories of 37 full-term and 22 premature newborns born to a mother with COVID-19 and hospitalized in inpatient treatment at the Department of Neonatology of the Bukhara Children's Multidisciplinary Medical Center in the periods from 2020 to May 2022 were retrospectively studied. During their stay in the hospital, all patients were subjected to general clinical, laboratory, functional, biochemical, radiographic studies.

Among all (59) newborns born to a mother with COVID-19 and who died in the first months of life, there were 22 premature newborns (37.3%), 37 full-term (62.7%). For the convenience of comparing the main indicators of the severity of newborns, they were divided into 2 groups depending on the gestation period:

Group 1: premature newborns – 22;

Group 2: full-term newborns – 37.

The minimum gestation period of group 1 newborns was 26 weeks; the maximum period was 37 weeks, which averaged 33.55±0.66 weeks. At the same time, the minimum weight of newborns in this group was 1090 g, and the maximum weight was 2880 g, which averaged 2023.23±114.64 g.

The analysis of the days of life lived by newborns showed that the minimum day of life was 1.0 days, the maximum lived up to 93 days, that on average the days of life of premature newborns born from a mother with COVID-19 is 23.09±5.37 days.

The maximum gestation period of full-term infants was 42 weeks. The average gestation period was 38.61±0.57 weeks. At the same time, the weight of full-term children was a maximum of 4,400 grams. On average, newborns were born weighing 2819.12±151.55 grams.

Results and discussion

The structure of the morbidity of premature newborns showed a predominance of congenital malformations-13 (59.1%), in particular, patients with congenital heart defects-5 (22.7%), with anomalies of the kidneys and urinary tract-3 (13.6%), with malformations of the gastrointestinal tract-5 (22.7%). The second place in the structure of morbidity is occupied by intrauterine infections (TORCH infection) with the development of neonatal sepsis-8 (36.4%). The third place is occupied by perinatal lesions of the central nervous system of hypoxic genesis-1 (4.5%) (Figure 1).

To determine the indications for antibacterial therapy and evaluate its effectiveness in systemic inflammatory reaction syndrome in newborns, a study was conducted to determine the level of PCTs in the blood. A fluctuation in the concentration of MPC was detected in the range from 0.1 to 11.8 pg/mL, which on average is 2.49 = 0.5 pg/mL. Consequently, the results of general laboratory and biochemical blood parameters in newborns with critical conditions indicate the beginning of the development of a systemic inflammatory reaction syndrome.

For a comparative assessment of the significance of cytokine status indicators in the prognosis of the development of critical conditions of newborns, a clinical and laboratory examination of 94 newborns was carried out: 33 newborns born from a mother with COVID-19 (group 1), 30 newborns with perinatal central nervous system lesion (PPCNS), born from a mother with somatic diseases (group 2) and 31 healthy newborns born from a healthy mother.

As a result of the analysis of the cytokine content in the blood of newborns on the 2nd day of life, it was found that the concentrations of IL-17A in group 1 exceed the upper limit of the concentration range of these indicators in the group of healthy newborns (Table 1).

The interferon status of newborns of Group 1 and 2 is characterized by a significant increase in IFNγ to 23.64±0.81 and 29.20±1.28 pg/mL, respectively, against the indicators of the control group-20.96±0.66 pg/mL ($p < 0.05$).

At the same time, IFNα has a statistically significant tendency to increase in newborns of the 1st group – 33.71±1.22 pg/mL ($p < 0.05$), in relation to the indicators of the control group – 26.49±1.20 pg/mL.

And in newborns of the 2nd group, its value was at the level of the control indicators.

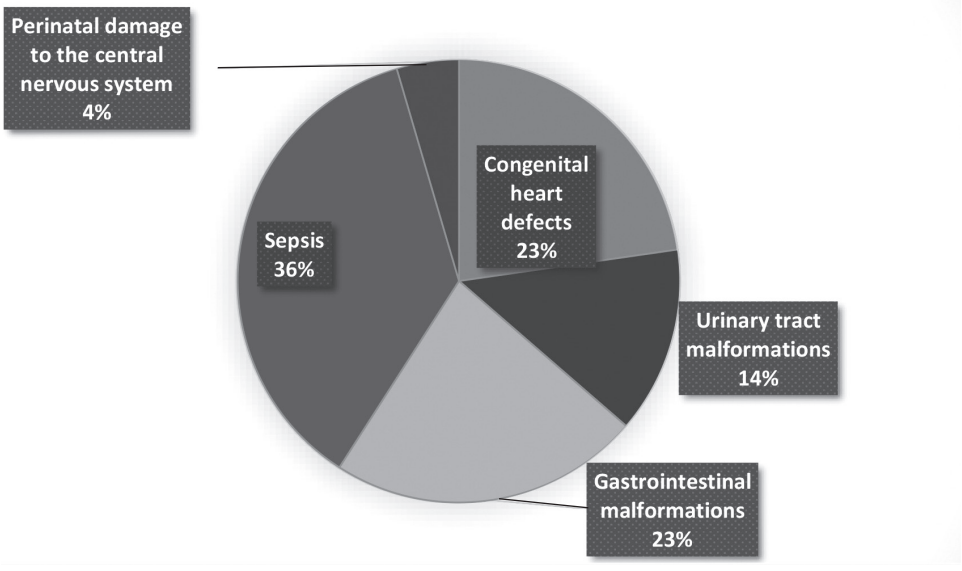

Figure 1. Nosological structure of newborns with critical conditions born from a mother with COVID-19

TABLE 1. CONTENT OF CYTOKINES IN THE BLOOD OF NEWBORNS

Cytokines in pg/mL	Healthy newborns		1st group		2nd group	
	min-max	average	min-max	average	min-max	average
IFNγ	14.48-27.35	20.96±0.66	15.27-32.25	23.64±0.81*	17.05-39.63	29.20±1.28*
IFNα	15.83-38.21	26.49±1.20	21.79-47.37	33.71±1.22*	15.83-38.21	24.43±1.36
IL-17A	29.93-64.97	46.99±1.70	55.34-92.06	69.68±1.70*	24.22-56.17	38.74±2.07*
MCP-1	98.29-305.71	196.69±9.92	422.15-1058.15	765.66±33.07**	98.29-305.71	116.47±7.86*
VEGF	19.21-59.93	38.47±2.23	25.17-54.67	40.05±1.49	19.21-59.93	42.15±1.82

Note.*, significantly relative to the healthy group (*, $p < 0.05$; * $p < 0.01$).

TABLE 2. CONTENT OF CYTOKINES IN THE URINE OF NEWBORNS

Cytokines in pg/mL	Healthy newborns		1st group		2nd group	
	min-max	average	min-max	average	min-max	average
IFNγ	4.25-8.75	5.94±0.23	10.08-24.11	16.84±0.66***	6.94-15.42	10.21±0.41*
IFNα	3.68-8.06	5.78±0.23	4.33-11.87	7.60±0.39*	5.48-14.33	9.49±0.43*
IL-17A	20.05-38.48	30.75±0.93	41.15-92.50	65.48±2.30**	23.55-54.67	37.07±1.43*
MCP-1	74.51-130.20	99.25±2.63	16.72-33.10	23.36±0.75***	39.45-71.27	54.75±1.80**
VEGF	18.36-34.97	26.99±0.87	10.26-30.15	19.79±1.02*	14.48-33.05	22.72±0.96*

Note.*, significantly relative to the healthy group (*, $p < 0.05$; * $p < 0.01$).

In our studies, IL-17A in group 1 newborns was increased to 69.68±1.70 pg/mL, compared to the control group – 46.99±1.70 pg/mL ($p < 0.05$), and in group 2 it has a significant tendency to decrease to 38.74±2.07 pg/mL ($p < 0.05$), against the control values of -46.99±1.70 pg/mL.

MCP-1 is produced by many types of cells, including mononuclear cells, mast cells, T cells, osteoblasts, fibroblasts, endothelial cells, bone marrow cells, epithelial cells, astrocytes. The synthesis of MSR-1 is induced by IL-1β, TNFα, IFNγ, IL-6, IL-4. Under the influence of MCP-1, proliferation of vascular smooth muscle cells also occurs with their secretion of proinflammatory cytokines that contribute to the progression of the disease due to vascular damage [1].

As a result, a 3.89-fold increase in MSR-1 was found in group 1 newborns – 765.66±33.07 pg/mL, against the control – 196.69±9.92 pg/mL. In group 2 newborns, a statistically significant decrease in MSR-1 was found to 116.47±7.86 pg/mL, against the control – 196.69±9.92 pg/mL.

The study of another vascular endothelial growth factor, VEGF, showed that there was no connection between its synthesis and the development of critical conditions in newborns on the first day of life.

The results of the studies showed a significant increase in the synthesis of IFNγ in the first day of life in newborns, regardless of the presence of somatic and infectious diseases of the mother. At the same time, IL-17A protects the mother's body from extracellular bacterial and fungal infections, thereby resorption of bone. On the other hand, osteoporosis is promoted by the use and use of anticoagulant drugs in the treatment of COVID-19.

Consequently, an increase in the concentration of IL-17A by 1.48 times in the blood of newborns born from a mother with COVID-19 shows the risk of developing both infection and osteogenesis disorders.

In order to assess the dynamics of cytokine synthesis, the above cytokines were studied in the urine of newborns of the examined groups on the 7th day of life.

As a result, an increase in IFNγ was found to be 2.84 times in group 1 newborns, 1.72 times in

group 2 newborns ($p < 0.001$), against the control – 5.94±0.23 pg/mL ($p < 0.05$). With respect to IFNα, an increase to 7.60±0.39 pg/mL was also detected in urine. in newborns of the 1st group, up to 9.49±0.43 pg/mL in newborns of the 2nd group, the indicators of the control group were 5.78±0.23 pg/mL, the results obtained were reliable in the range of $p < 0.05$.

At the same time, there is an increase in the level of IL-17A in the urine of group 1 newborns by 2.2 times (65.48±2.3 pg/mL), up to 37.07±1.43 pg/mL in group 2 newborns against the control values of -30.75±0.93 pg/mL ($p < 0.05$).

In contrast to the indicators VEGF in blood, in urine studies VEGF compared to control -26.99±0.87 pg/mL, was reduced to 19.79±1.02 pg/mL and 22.72±0.96 pg/mL in newborns of the 1st and 2nd groups, respectively ($p < 0.05$). All the obtained results of the study of cytokines in the urine of newborns had statistical significance in the ranges from $p < 0.05$ to $p < 0.0001$.

Thus, the obtained results of the study of cytokines in urine show activation of interferon status by the 7th day of life against the background of an increase in the key cytokine of bone resorption (IL-17A).

At the same time, there is a decrease in urine of the leading molecular markers of vascular endothelial damage – MSR-1 by 4.25 times and by 1.82 times at the birth of children from mothers infected with COVID-19 (group 1) and with other somatic diseases (group 2), respectively. And VEGF also decreases significantly in newborns, both with COVID-19 infection in the mother and in her absence.

When comparing the results of the cytokine status with clinical and biochemical data, symptoms of systemic inflammation are noted in parallel on day 7 in patients with group 1 newborns: an increase in body temperature, leukocytosis, tachycardia, an increase in reactive protein and a change in the prothrombin index.

Some differences in the values of this indicator in the blood and urine of group 2 newborns have been established. Thus, with an increase in IL-17A and MCP-1 in the blood on the first day of life, VEGF tends to increase to 42.15±1.82 pg/mL, which shows the risk of developing a systemic inflammatory response syndrome at the level of blood vessels with endothelial damage. On the 7th day of life, there was a tendency to increase IL-17A in urine to 37.07±1.43 pg/mL, than in the healthy group – 30.75±0.93 pg/mL $p < 0.05$.

The obtained results of the study show the accumulation of cytokines in the focus of inflammation and indicate the activity of the inflammatory process, requiring correct anti-inflammatory therapy. Thus, the advantages of noninvasive immunodiagnostics in neonatology have been established by the determination of cytokines in the urine of newborns. The control of urine cytokines in dynamics determines the prognosis of the development of critical conditions in newborns both early and in the late period of adaptation.

Consequently, IFNγ in urine acts as an indicator of the severity of the condition and the development of critical conditions in premature newborns at birth prematurely from a mother with COVID-19.

Thus, the clinical and laboratory assessment of the condition of newborns shows the importance of taking into account the state of cytokine synthesis. To reduce invasive procedures and preserve the blood volume of premature newborns, it is recommended to study cytokines, in particular IFNγ in urine, which allows early prediction of the development of critical conditions in newborns.

Based on the conducted scientific studies, it was found that newborns born from a mother with COVID-19 in the first day of life have an increase in IFNγ and IFNα in the blood against the background of an increase in IL-17A by 1.48 times, which shows the risk of developing both infection and osteogenesis disorders. At the same time, in response to the synthesis of IL-17A, activation of interferon status is noted by the 7th day of life in premature newborns.

Consequently, the study of interferons in urine reduces the risk of sepsis from invasive procedures and predicts the development of critical conditions. In this case, the threshold concentration is IFNγ in urine < 10.1 pg/mL and IFNγ in blood < 15.3 pg/mL. A decrease in IFNγ below the indicated concentrations in blood and urine shows the risk of developing severe critical conditions with the development of coagulopathy, hemorrhagic syndrome.

Conclusions

1. Newborns born from a mother with COVID-19 have an increase in IFNγ and IFNα in the blood on the first day of life against the background of an increase in IL-17A by 1.48 times, which shows the risk of developing both infection and osteogenesis disorders.
2. Activation of interferon status by the 7th day of life in newborns was established against the background of an increase in the key cytokine of bone resorption (IL-17A).
3. A decrease in the urine of molecular markers of vascular endothelial damage – MSR-1 by 4.25 times was found in newborn children born from a mother infected with COVID-19.
4. A decrease in VEGF in the urine of newborns was found, both with COVID-19 infection in the mother and in its absence.
5. Non-invasive urine cytokine diagnostics allows achieving economic efficiency by reducing hospital beds, as well as medical efficiency due to minimal traumatization of newborns.

References

1. Alexandrovich Yu.S., Pshenisnov K.V., Vardanyan R., Ignatov V., Hienas V., Alexandrovich I.V., Nezabudkin S.N. Modeling of the influence of the position of the newborn's body on the stress of carbon dioxide in an oxygen tent. *Bulletin of Anesthesiology and Resuscitation, 2021, Vol. 18, no. 5, pp. 57-61.* (In Russ.)
2. Segura-Cervantes E., Mancilla-Ramírez J., González-Canudas J., Alba E., Santillán-Ballesteros R., Morales-Barquet D., Sandoval-Plata G., Galindo-Sevilla N. Inflammatory response in preterm and very preterm newborns with sepsis. *Mediators Inflamm., 2016, Vol. 2016, 6740827.* doi: 10.1155/2016/6740827.
3. Senkevich O.A., Popova K.E., Kozharskaya O.V., Musatov D.V. Morphofunctional features of the placenta of newborns in critical conditions that occurred at birth: the results of a retrospective cohort study. *Pediatric Pharmacology, 2017, Vol. 14, no. 3, pp. 179-185.* (In Russ.)
4. World Health Organization. Q&A on COVID-19, pregnancy, childbirth and breastfeeding. 2020. Available at: https://www.who.int/news-room/q-a-detail/qa-on-covid-19- pregnancy-childbirth-and-breastfeeding.

Авторы:

Наврузова Ш.И. *– д.м.н., профессор, заведующая кафедрой педиатрии, Бухарский государственный медицинский институт, г. Бухара, Республика Узбекистан*

Баратов С.С. *– самостоятельный соискатель Бухарского государственного медицинского института, г. Бухара, Республика Узбекистан*

Набиева З.Т. *– ассистент кафедры педиатрии, Бухарский государственный медицинский институт, г. Бухара, Республика Узбекистан*

Authors:

Navruzova Sh.I., *PhD, MD (Medicine), Professor, Head, Department of Pediatrics, Bukhara State Medical Institute, Bukhara, Republic of Uzbekistan*

Baratov S.S., *Independent Applicant, Bukhara State Medical Institute, Bukhara, Republic of Uzbekistan*

Nabieva Z.T., *Assistant Professor, Department of Pediatrics, Bukhara State Medical Institute, Bukhara, Republic of Uzbekistan*

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