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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

OPTIMISATION OF EARLY DIAGNOSTICS AND MANAGEMENT OF NECROTIZING ENTEROCOLITIS IN FULL-TERM NEONATES

Speciality: 3220.01 - Pediatrics

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GENERAL DESCRIPTION OF WORK

Relevance of the topic. Necrotizing enterocolitis (NEC) remains one of the major life-threatening acquired diseases of the gastrointestinal tract (GIT) in the neonatal period. Morbidity and mortality associated with this disease remain high. Clinical studies conducted by S. Gephart (2014) and D. Watkins (2013) show that the mortality rate from NEC ranges from 15-30%, and if surgery is required, it can reach up to 50%. According to various authors, there is a tendency for an increase in the incidence of NEC not only among premature, but also in full-term newborns. From the work of O. Abbo (2013), we know that the incidence rate among full-term infants is 10-12.5% of the total number of children affected by this disease.

Improving the quality of neonatal and resuscitation services leads to the preservation of children who have undergone hypoxia in utero and during childbirth, and have severe congenital malformations of the gastrointestinal tract, cardiovascular and respiratory systems [1]. M. Ahle (2018) reports that the etiology of NEC is multifactorial and depends on the gestational age of the patient. The fundamental etiological difference between NEC in full-term newborns, compared with preterm infants, is the localization of the pathological process in the intestine, as well as the period of onset of the disease [2]. The high mortality rate in NEC is the reason for the active study of this disease. The upward trend in the incidence of NEC among term infants calls into question the role of prematurity as the main predisposing risk factor in the onset of the disease [3]. The following factors contribute to

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the development of NEC in full-term newborns: hypoxic-ischemic damage to the central nervous system, respiratory distress syndrome, congenital heart defects of the "blue" type, anemia-hemotransfusion[4,5]. The nature of enteral nutrition and intestinal contamination with pathological microflora is of considerable importance[6].

NEC is suspected in patients at risk with a combination of one non-specific systemic sign and one symptom from the gastrointestinal tract. Early and timely diagnosis of NEC remains difficult due to its sudden onset and rapid progression. The absence of specific markers of NEC creates difficulties in diagnosing and determining strategies for preventing and managing patients[7,.8]. Therefore, it is necessary to identify predictive biomarkers for early and more accurate identification of the disease.

The purpose of the study: to study the risk factors for the development of NEC and to identify new biomarkers to improve early diagnosis and management of the disease in full-term newborns.

Research objectives:

1. To identify the etiological significance of perinatal predisposing risk factors for the development of NEC in full-term newborns and to establish a correlation between them and the pathogenesis of the disease.

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[5]Collin LE Intestinal microbiota and blue baby syndrome: probiotic therapy for term neonates with cyanotic congenital heart disease / John C. Rutledge & Mark A. Underwood. Journal "Gut Microbes", - 2010, Volum 1, issue 6, pages 359-366.

[6] Yapıcıoğlu H. Zamanında doğan bebeklerde nekrotizan enterokolit/ Akçalı M., Özlü F. - İstanbul: Çocuk Sağlığı ve Hastalıkları Dergisi., - 2015, 58: 157-160.

[7] Chang-Qing H. Novel biomarkers to determine neonates with necrotizing enterocolitis/ Xiao-ye Wei. - Yulin: Biomedical Research, - 2017. 28 (13): 6002-6006.

[8] Wang K. Recent Potential Noninvasive Biomarkers in Necrotizing Enterocolitis/Tao G., Sun Z., Sylvester KG Gastroenterology Research and Practice, - 2019. V. (5). P 1-9.

2. To study the role of caesarean section as a risk factor for the development of NEC and to establish the influence of the form of delivery on the clinical course of the disease in full-term infants.
3. To determine the significance of biochemical markers of Nitric Oxide (NO), Erythropoietin (EPO), Calcium ions (Ca^{+2}) for early diagnosis of NEC in full-term newborns.
4. To develop a diagnostic algorithm to improve the early diagnosis and management of NEC in term infants.

The scientific novelty of the work.

- Perinatal predisposing risk factors have been studied for the development of NEC and the role of caesarean section was assessed as a risk factor in the formation of the disease in full-term newborns.
- EPO has been used as a biomarker for the early diagnosis of NEC in term newborns.
- EPO, NO and Ca^{+2} in combination were used as new biomarkers, the use of which allows not only early diagnosis, but also to identify severe forms of NEC and the development of septic complications in full-term newborns.
- Algorithms for testing early diagnosis, progression and development of septic complications of NEC in full-term newborns.

The practical significance of the study

The identified new biomarkers can be used not only to improve early diagnosis but also to identify severe forms of NEC.

NO can be used to timely detect septic complications and correct the dynamics of management tactics and treatment of this pathology.

The mathematical model of the testing algorithm will determine the sequence of diagnostic and therapeutic measures in full-term newborns with NEC.

The main provisions of the dissertation work put forward for defense:

- hypoxic damage to the central nervous system is a primary predisposing risk factor for the development of NEC in full-term newborns, and it forms the foundation of the disease's pathogenesis;
- while a Caesarean section is not a risk factor for NEC, it exacerbates the clinical progression of the disease;

- in full-term newborns diagnosed with NEC, there exists a direct correlation between alterations in serum concentrations of EPO, NO, and Ca^{+2}, and the severity of the disease;
- the levels of NO in the serum of patients with NEC are significantly elevated in comparison to those in patients with NEC who also have septic complications;
- the developed mathematical testing algorithm makes it possible to significantly improve the accuracy of early diagnosis, and to identify severe cases and septic complications of NEC in full-term newborns.

Approbation of work. The main provisions of the dissertation were reflected in reports and discussions: scientific and practical conference "CURRENT PROBLEMS OF MEDICINE", dedicated to the 100th anniversary of the Azerbaijan People's Republic (2018), "Medicine: challenges of today", V International Scientific Conference, Russia (2018.), Scientific and Practical International Congress of the Azerbaijan Medical University, dedicated to the 100th anniversary of Tamerlan Aliyev (2021), IX Congress of Pediatricians of Kazakhstan (2021), VI International National Congress "Healthy Children - the Future of the Country", Russia (2022) , 1st International Congress of Pediatrics, Pediatric Surgery and Nursing (2022), XXIV International Congress "CURRENT PROBLEMS OF PEDIATRICS", Russia (2023).

A preliminary discussion of the dissertation work took place on September 29, 2022 at a joint meeting of employees of the Department of Childhood Diseases of the Azerbaijan Medical University and the Scientific Research Institute of Pediatrics named after. K.Y. Farajova (protocol No. 1). The dissertation work was discussed at the meeting of the Scientific Seminar of the Dissertation Council ED 2.27, operating on the basis of AMU on November 21, 2023 (protocol No. 2).

Implementation into practice. The results obtained are put into practice in the departments of the pathology of full-term newborns, intensive care and early childhood surgery of the Research Institute of Pediatrics. K.Y. Farajeva.

Publications. On the topic of the dissertation, 15 scientific papers were published, of which 8 articles (4 - abroad) and 7 theses (4 - abroad) and 1 presentation at an international congress were done.

The structure and scope of the dissertation. The dissertation is presented on 162 (208.342 characters) pages of typewritten text and consists of an introduction (6 pages – 8.314), 6 chapters (60.307 + 15.115 + 25.068 + 16.927 + 34.064 + 18.301 characters), four of which reflect the results of their own research, conclusions (1816 characters), practical recommendations (991 characters), a list of references, and a list of accepted abbreviations. The list of references includes 4 domestic and 131 sources of foreign authors. The work is illustrated with 21 tables, 5 graphs and 15 figures, and extracts from the case histories of newborns.

MATERIALS AND RESEARCH METHODS

The dissertation work was carried out on the basis of the Research Institute of Pediatrics named after K.Y. Farajeva for the period from 2016-2020. The clinical part of the study was carried out in the departments of resuscitation and intensive care, pathology of full-term newborns, pediatric surgery of early age, and the laboratory wing - in the scientific and diagnostic laboratory of the above institute.

The design of scientific work is presented by retrospective and prospective studies. In order to solve the set objectives, 130 full-term newborns were examined. 100 of them were patients with NEC (main group). The main group of newborns was divided into three groups depending on the severity of the clinical course of NEC according to the classification of J. M. Bell. Group I consisted of 53 (53.0%) patients with NEC stage I, who were suspected of this disease (of moderate severity). Group II included 29 (29.0%) patients with stage II NEC (severe form), in which the disease, in the absence of adequate management, is fraught with progression and complications. In group III, 18 (18.0%) newborns with stage III NEC (extremely severe form) were studied, who developed various complications such as perforation, peritonitis, and ascites, that is, emergency conditions

requiring immediate surgical intervention. The control group consisted of 30 conditionally healthy children from maternity hospital No. 7 in Baku, Azerbaijan. In these newborns, born to mothers with uncomplicated pregnancy and childbirth, the ante- and intrapartum periods proceeded relatively well.

Additionally, we conducted a case-control to study a group of patients with a septic complication of NEC.

To identify the etiological role of caesarean section in the development of NEC in full-term newborns, the main and control groups were divided into two subgroups: infants born naturally and surgically. 62 patients with NEC were born by vaginal delivery, and 38 by caesarean section. 16 newborns of the control group were born by natural delivery, and 14 by caesarean section.

In all examined newborns, anamnestic, demographic and anthropometric data were analyzed, the levels of EPO, NO and Ca^{+2} were determined in the blood. The children of the main group underwent radiography, ultrasound examination of internal organs, neurosonography, dopplerography, clinical and biochemical analyzes of blood, urine, feces, bacteriological analysis of blood and feces.

The level of EPO was determined using ELISA instrument. The results of the analysis were evaluated visually by changing the intensity of staining using the ElisysUnoHuman spectrometric machine. The level of Ca^{+2} in blood serum was determined using the BioScreenMS -2000, a photometric test. Colorimetric analysis measured the concentrations of nitrate/nitrite in a simple two-step method using the Griess reagent. The level of NO metabolites was determined by the colorimetric method by the development of color in the reaction of diazotization with nitrite of sulfanilamide, which is part of the Griess reagent. The color intensity was determined on an ELISYSUNOHUMAN instrument by measuring the optical density of the samples in a standard 96-well plate (for enzyme immunoassay) at a wavelength of 540 nm (the principle of operation is vertical photometry). Statistical analysis was performed using Python 3-sklearn 0.22, scipy 1.6.3 and MSExcel 2016. The determination of the statistical difference in averages between populations was performed

using the Mann-Whitney test. To elucidate the etiological significance of predisposing risk factors for NEC, Pearson's Chi-square independence test was used. To include patients with NEC in the risk group, a statistical testing algorithm was prepared. Using ROC (Receiver Operating Characteristic curve) analysis, the correct parameters of the model were determined.

RESULTS AND DISCUSSION

Various antenatal and intranatal risk factors on the part of the mother, fetus and newborn child have a negative impact on the clinical course and outcome of the disease. After analyzing perinatal risk factors, we identified the etiological significance of obstetric and gynecological causes in the development of NEC (Necrotizing Enterocolitis) among the full-term newborns in our study. These babies were born from women with complicated pregnancy and childbirth. It is known from anamnestic data that antenatal and intranatal factors contributing to the formation of NEC include: abortions, miscarriages, early toxicosis, threatened miscarriage, and various gynecological and extragenital diseases of women. The mothers of patients with NEC in most cases (51.8%) had a combination of these pathologies. Subsequently, the above prenatal factors were born children who underwent hypoxia and/or asphyxia in utero and during childbirth. To study the influence of maternal antenatal and intranatal risk factors on the development of NEC in newborns, we analyzed anamnestic data using Pearson's chi-square test with 1 degree of freedom (α=0.05). The anamnestic data of mothers of patients with NEC and apparently healthy infants, as well as patients with a complicated course of the disease (NEC + Sepsis) were compared. "In the control group, occurrences of parity in pregnancy and childbirth, as well as abortions, miscarriages, and early toxicosis, are less frequent among mothers compared to those in the group of mothers with infants diagnosed with NEC. The threat of termination of pregnancy and infection in these women were not observed. Complications of childbirth (31.9%) and extragenital

diseases (3.9%) are more common in mothers of patients with NEC. Based on our data, in the 'case-control' group of mothers, the incidence rates of pregnancy parity (65%), childbirth (53%), gynecological diseases (12%), infectious diseases (29%), anemia (41%), and toxicosis (53%) are higher in percentage terms compared to those in the mothers of the control group. The research results show that in all groups of mothers, the most common pathological condition during pregnancy is early toxicosis (χ^2=13.5; $p < 0.001$). Furthermore, patients with NEC +Sepsis are antenatalally exposed to hypoxic and infectious factors more frequently than other patients.

Clinical characteristics of risk factors in full-term neonates with NEC. A retrospective analysis of medical records showed that among the postnatal risk factors contributing to the development of NEC in our study were the following: hypoxia and/or asphyxia (88%), intrauterine infection (61%), pneumonia (26%), anemia (18%), congenital heart disease (13%), hemolytic disease of the newborn (10%), intrauterine growth retardation (7%), and gastrointestinal anomalies (5%). The risk factors identified by us were divided into hypoxic (67%), infectious (22%) and organic (malformations of the gastrointestinal tract; 11%) groups. Hypoxic factors include: hypoxia and / or asphyxia, congenital heart disease, anemia, hemolytic disease of the newborn; infectious - intrauterine infection, pneumonia. Malformations of the gastrointestinal tract in patients and in the main group under study are as following: anus atresia, anomaly of rotation and fixation of the intestine, anal stenosis, and congenital intestinal obstruction. Hypoxia and/or asphyxia (88 patients) occupies the main place among the NEC risk factors. The presence of hypoxic damage to the central nervous system in most patients confirms the existence of a pathogenetic relationship between it and the development of NEC. Of intrauterine infections (TORCH), 61 children were found to have: cytomegalovirus - 100%, toxoplasmosis - 26%, herpes II virus - 23%.

The frequency of occurrence of these risk factors for the development of NEC were considered depending on the stage of the disease. The hypoxic factor was a more common in patients with a more severe degree of the pathological process.

Table 1

Risk factors in term neonates with NEC by disease stage

Total number of term neonates with NEC (n -100)						
Risk factors	NEC I (n -53)	NEC II (n -29)	NEC III (n -18)	p1	p2	p3
Hypoxia and/or asphyxia	45 (84.9%)	26 (89.6%)	18 (100.0%)	$\chi^2 = 0.070$ p = 0.791	$\chi^2$1.738 p = 0.187	$\chi^2 = 0.635$ p = 0.426
VUI	38 (71.6%)	20 (68.9%)	3 (16.6%)	$\chi^2 = 0.000$ p = 0.995	$\chi^2 = 14.498$ p < 0.001	$\chi^2 = 10.154$ p < 0.001
Pneumo-nia	14 (26%)	9 (3 1.0 %)	3 (1 6.6%)	$\chi^2 = 0.035$ p = 0.851	$\chi^2 = 0.268$ p = 0.605	$\chi^2 = 0.569$ p = 0.451
Anemia	9 (16.9%)	5 (17.2%)	5 (2 7.7 %)	$\chi^2 = 0.000$ p = 1.000	$\chi^2 = 0.425$ p = 0.514	$\chi^2 = 0.241$ p = 0.623
UPU	9 (16.9%)	3 (10.3 %)	1 (5.5 %)	$\chi^2 = 0.236$ p = 0.667	$\chi^2 = 0.659$ p = 0.417	$\chi^2 = 0.001$ p = 0.973
IUGR	3 6%	1 3 %	1 (5.5 %)	$\chi^2 = 0.000$ p = 1.000	$\chi^2 = 0.000$ p = 1.000	$\chi^2 = 0.000$ p = 1.000
HDN	0 00%	3 (10.3 %)	1 (5.5 %)	$\chi^2 = 3.134$ p = 0.077	$\chi^2 = 0.326$ p = 0.568	$\chi^2 = 0.001$ p = 0.973
Anomalies of the gastroin-testinal tract	0 00%	3 (10.3 %)	2 (11.1%)	$\chi^2 = 3.134$ p = 0.077	$\chi^2 = 2.680$ p = 0.102	$\chi^2 = 0.000$ p = 1.000

Note: 1. The table shows the mean value of μ and 95% (p=0.05) confidence interval (lower and upper limits). χ^2- Pearson's chi-square test results. Degree of freedom (df) = 1.

According to Table 1, hypoxia and/or asphyxia and infection are the main and leading risk factors for NEC in term newborns. A relationship was found between hypoxic CNS lesions and the development of NEC in full-term newborns. In addition, an association has been established between intrauterine infections and severe disease in this population of children. In term newborns with IUI, the septic complication of the clinical course of NEC is more common, in contrast to patients with only hypoxic lesions.

When considering hypoxia from a physiological and pathophysiological perspective, it becomes evident that the biggest problem is the regulation of cerebral blood flow. Initially, the existing autoregulatory system tries to compensate for the results of hypoxia. It is known that the cerebral autoregulatory system in various situations can increase or decrease the volume of cerebral circulation. Initially, low oxygen levels in the blood lead to reduced cerebral blood flow, triggering the activation of the autoregulatory system that stabilizes the condition temporarily. In cases where conditions of decreased oxygen levels continue, metabolic acidosis develops. This forms the basis of hypoxia. With developing metabolic acidosis, a drop in blood pressure and failure of the autoregulatory system, centralization of blood circulation occurs due to vasoconstriction and a decrease in peripheral circulation. To improve blood circulation and meet the metabolic needs of the brain, blood flow in the intestines, kidneys, skin, and skeletal muscles decreases. This is accomplished through compensatory vascular vasoconstriction, which is facilitated by an increase in serum EPO levels. As a result of this process, mesenteric ischemia occurs, which is the main link in the pathogenesis of NEC. As a protective reaction, intestinal ischemia provokes vasodilation, which is realized by an increase in NO synthesis. Thus, as we know, overproduction of NO leads to persistent barrier failure of the intestinal mucosa and creates conditions for bacterial invasion, resulting in the clinical picture of NEC. At the same time, under the influence of this increased production of NO, intracellular migration of Ca^{+2} occurs, which explains the decrease in its level in the serum. It is also known that intracellular Ca^{+2} inhibits NO production in

macrophages exposed to bacterial endotoxin. If this process continues and in the absence of measures to prevent it, necrosis of cells and tissue occurs, respectively. For this reason, we expected an increase in the levels of EPO and NO and a decrease in the level of Ca^{+2} ions, which is what we observed.

Influence of the form of delivery on the clinical course of necrotizing enterocolitis in full-term newborns. We prospectively studied the etiological role of caesarean section in the development of NEC in full-term newborns. As a result of the clinical and laboratory study, it was revealed that the main cause of the disease is hypoxia and/or asphyxia, regardless of the form of delivery. From the data, it turns out that there is no statistically significant difference between the levels of the studied biomarkers, as in patients (II NB; II CS), and conditionally healthy newborns (I NB; I CS) born naturally and operatively. "In sick newborns born via vaginal delivery and experiencing NEC, the differences in serum levels of NO ($p=0.636$) and EPO ($p=0.331$) were statistically not significant, with NO levels being high and EPO levels elevated. Similarly, the decrease in calcium levels (Ca^{+2}, $p=0.317$) was also statistically insignificant.

To identify the effect of caesarean section on the clinical course of NEC, we also studied the clinical course of the disease in children in both groups. The number of cases of clinical complications and mortality is higher in newborns born surgically. It is known that this method of delivery is mainly used when there are antenatal and/or intranatal pathologies on the part of the mother and/or child. In this regard, the lives of children exposed to hypoxia and infection in utero, with intrauterine growth retardation, with various malformations of organs and systems, are saved. Studying the clinical course of the disease in both groups, it turns out that seven children (11.3%) who were born naturally, two of whom died (28.6%), needed surgery. Surgical treatment was used in six newborns (15.8%) who were born by caesarean section, of which three died (50.0%). Among children born by caesarean section, cases of surgical treatment are 1.4 times more than in infants of the other group. In group II NB, septic complications are observed in 14.5% of children, and in newborns II

CS - 21.1%. In addition, there are comparatively more deaths among children born operatively than among newborns born vaginally.

Signs of necrotizing enterocolitis in full-term newborns born by caesarean section appear a little later than in the other group. Using the Mann-Whitney test, we arrives to a *p value* of <0.001 and found that there was a statistically significant difference in the time of onset of illness between these groups of newborns. In children born naturally and surgically, the difference in the time of onset of the disease is approximately two days.

According to multiple scientists, the increase in the number of NEC cases among the full-term population may be linked to the increase in the number of births through cesarean section. The main risk factor for developing NEC in these newborns, regardless of the mode of delivery, is hypoxic-ischemic. The number of cases of intrauterine infection, pneumonia, and intrauterine growth retardation among children of group II C-section is also higher than in II natural birth. The differences observed between the two groups studied children born via natural delivery and those born by cesarean section though not statistically significant, imply a potential adverse effect of cesarean delivery on the clinical course of NEC. Among children born by cesarean section, there are more cases of surgical treatment, septic complications of the clinical course of the disease, as well as deaths than in infants of the opposite group. There are no statistically significant changes in serum NO, EPO, and Ca^{+2} levels in full-term newborns with NEC depending on the mode of delivery. However, in patients born by surgery, as the severity of NEC progresses, various clinical complications and extremely high levels of NO are observed more frequently compared to patients of the other group.

Thus, the operative method of delivery does not contribute to the formation of NEC, but can create unfavorable conditions that affect the clinical course and outcome of the disease.

Diagnostic value of EPO, NO and Ca^{+2} in necrotizing enterocolitis in full-term newborns. Our analysis suggests that in full-term newborns, the most significant link in the pathogenesis of NEC (necrotizing enterocolitis) is the combined effect of hypoxic

damage to the central nervous system (CNS) and intestinal ischemic reperfusion, both resulting from hypoxia and/or asphyxia. An imbalance of vasoconstriction and vasodilation contributes to this pathological process. In full-term newborns, the main substrates characterizing NEC are two-fold. Firstly, there's a hemodynamic disturbance in the intestine, resulting from blood circulation centralization due to hypoxic damage to the nervous system. Secondly, an inflammatory reaction, often initiated by infectious contamination and pathological colonization of the intestines, occurs in the early neonatal period. The combined synergistic effects of hypoxia and endotoxin produced by infection promote intestinal ischemic necrosis. In this regard, we studied the role of EPO, NO, and Ca^{+2} - mediators of hypoxia - in the pathological process in necrotizing enterocolitis and investigated the interaction of these biomarkers.

According to our studies, hypoxia and/or asphyxia, being the main predisposing perinatal risk factors for the development of NEC in full-term newborns, cause an interconnected change in the levels of EPO, NO, and Ca^{+2}. EPO, NO and Ca^{+2} as mediators of hypoxia are involved in the modification of the pathological process in NEC. With the contribution of EPO, vasoconstriction of peripheral vessels contributes to the centralization of cerebral circulation during hypoxia. Compensatory vasodilation occurs as a result of vasoconstriction ischemic damage to the intestine, which is realized by an increase in production of NO. Elimination of hemodynamic disorders in the form of a plethora of vessels of the submucosal layer in the intestinal wall is carried out by lowering the serum level of Ca^{+2}. It is known that low values of Ca^{+2} contribute to the slowing down of NO hyperproduction. In patients with NEC, our analysis revealed a statistically significant alteration in certain biochemical markers compared to the control group. Specifically, there was a 95.65% increase in EPO levels, a 218.85% increase in NO levels, and a 62.32% decrease in Ca^{+2} levels. These variations were consistent not only in comparison to the control group's values but also varied depending on the stage of the disease. As the severity of NEC develops, that is, the patient's condition worsens, there was an increasing change in the levels of these

biomarkers. Therefore, the related change in the values of these three markers can be used not only to identify the disease but also to determine its severity. A direct relationship was noted between an increase in the content of EPO and NO and a decrease in the level of Ca^{+2} in the blood of patients on the severity of the pathological process of the disease, which suggests the pathogenetic significance of these biomarkers in the development and progression of NEC.

Table 2

Changes in the levels of NO, EPO and Ca^{+2} depending on the stage of NEC

Indicators	Control group (n=30)	NEC I (n=49)	NEC II (n=26)	NEC III (n=8)	p1	p2	p3	p4	p5	p6
NO (μmol/l)	36.60 [34.53; 38.05]	54.40 [44.60; 82.20]	81.90 [58.79; 98.05]	116.70 [108.60 ;126.75]	p<0. 001	p<0. 001	p<0. 001	p=0. 012	p=0. 002	p=0. 056
EPO (mmol/l)	11.50 [11.30; 11.60]	17.80 [14.90; 19.70]	19.45 [16.03; 21.20]	22.50 [20.63; 25.10]	p<0. 001	p<0. 001	p<0. 001	p=0. 086	p=0. 004	p=0. 042
Ca^{+2} (mmol/l)	2.07 [1.99; 2.19]	1.71 [0.82; 1.90]	0.80 [0.71; 1.24]	0.78 [0.50; 0.85]	p<0. 001	p<0. 001	p<0. 001	p=0. 030	p=0. 004	p=0. 155

Note - Median, lower and upper quartiles of biomarker values for each group. Data were presented in the form: median [1st quartile; 3rd quartile].

In a routine blood test in sick newborns with NEC, in addition to Ca^{+2}, other parameters were also retrospectively studied, such as: potassium, sodium, platelets, erythrocytes, leukocytes, hemoglobin, total bilirubin, sugar, hematocrit. All patients showed changes in the values of blood parameters. When comparing the parameters of these indicators in patients with NEC and NEC +Sepsis, a statistically significant difference was noted in the levels of platelets and total

bilirubin. The lowest platelet count was found in patients with NEC III 65.00 [39.75; 109.75], while its level in the NEC +Sepsis group was 197.00 [61.25; 326.75]. The lowest value of the level of total bilirubin is observed in the case-control group was 176.00 [104.00; 208.00] compared to the neonates with NEC III, which was 244.00 [220.00; 311.20].

The observed difference in total bilirubin levels among patients can be attributed to its known anti-inflammatory and antioxidant properties. Most likely, the low value of total bilirubin in the blood in NEC patients with septic complications is associated with the child's immunodeficiency. It is known that the basis of hemolytic disease of the newborn and transfusion-associated anemia is hemolytic anemia, which is one of the risk factors for the development of NEC in full-term newborns. Increased erythropoiesis and hyperbilirubinemia in newborns with NEC have a causal relationship with the pathogenesis of the disease.

The values of the serum levels of EPO, NO, Ca^{+2} were also used to construct the ROC curve. By calculating the area under the curve, the best cutoff, specificity, sensitivity, positive predictive value, and negative predictive value were obtained. The combination of these three biomarkers achieved the highest area under the curve. To determine the parameters of the studied markers, which can be used for early identification, assessment of the severity and development of a septic complication of the course of NEC, an ROC analysis was performed. The calculated areas under the curves were as follows: NO (AUC=94.78%; CI [90.95%; 98.61%]; p =0.6735); EPO (AUC=97.55%; CI [95.03%; 100.00%]; p =0.7698); Ca^{+2} (AUC=96.87%; CI [93.83%; 99.92%]; p =0.5151); EPO, NO , Ca^{+2} (AUC =98.90%; CI [97.15%; 100.00%]; p =0.6416).

To compare the diagnostic values of biomarkers and their combinations, Table 3 was compiled. As can be seen from the table, the highest value of area under the curve was obtained by the combination of these three biomarkers.

Table 3.
Comparison of diagnostic values of biomarkers and their combinations between patients with NEC and the control group

Biomar-kers	AUC	Sensitivi-ty	Specifici-ty	TPR	FPR	p
NO	94.78%	89.16%	100.00%	100.00%	75.00%	0.673
EPO	97.55%	91.57%	100.00%	100.00%	76.92%	0.770
Ca^{+2}	96.87%	98.63%	83.33%	93.42%	92.59%	0.515
NO, EPO	97.39%	92.77%	100.00%	100.00%	81.08%	0.661
NO, Ca^{+2}	97.44%	94.52%	100.00%	100.00%	85.71%	0.572
EPO, Ca^{+2}	99.68%	95.89%	100.00%	100.00%	88.24%	0.431
NO, EPO, Ca^{+2}	99.90%	97.26%	100.00%	100.00%	90.91%	0.642

Note: AUC - area under the curve; PPV, positive predictive value; NPV, negative predictive value; p-section.

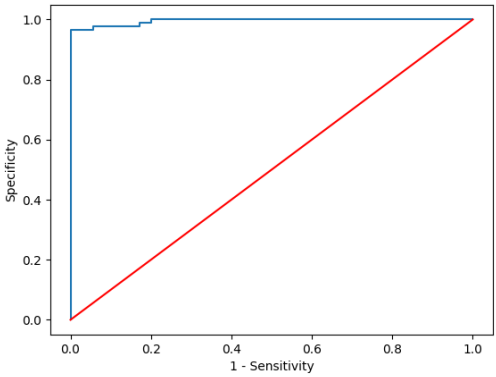

Figure 1. ROC curve of the combination of EPO, NO, Ca^{+2} in sick children and the control group

To identify the diagnostic value of biomarkers, we studied them not only in combination but also separately. However, as mentioned

above, the best results of the study were obtained when using three markers at the same time. This proves the existence of a pathogenetic interconnectedness among them.

Table 4

Comparison of diagnostic values of biomarkers and their combinations between patients with NEC I and NEC II, NEC III

Biomar-kers	AUC	Sensitivi-ty	Specifici-ty	TPR	FPR	p
NO	84.18%	87.50%	81.63%	40.00%	95.24%	0.134
EPO	83.04%	75.00%	87.76%	40.00%	91.49%	0.238
Ca^{+2}	82.74%	100.00%	66.67%	33.33%	96.55%	0.195
NO, EPO	87.76%	75.00%	97.96%	83.33%	94.12%	0.371
NO, Ca^{+2}	93.45%	100.00%	88.10%	58.33%	97.37%	0.240
EPO, Ca^{+2}	92.26%	100.00%	78.57%	43.75%	97.06%	0.138
NO, EPO, Ca^{+2}	94.64%	100.00%	78.57%	43.75%	97.06%	0.119

Note: AUC - area under the curve; PPV, positive predictive value; NPV, negative predictive value; p-section.

Our findings show that an increase in the levels of EPO, NO and a decrease in Ca^{+2} happens depending on the severity of the clinical course of NEC. The staging of the levels of our biomarkers reflects the patient's condition and the nature of the clinical course of the disease. Table 4 shows the results of the study.

Using ROC analysis, the following critical levels of the studied biomarkers were compiled, which determine the risk group of newborns for NEC disease: NO >41.70 μmol/l, EPO>13.10 mmol/l, Ca^{+2} <1.96 mmol/l.

The stimulation of NO production in endothelial cells depends on the concentration of EPO, induced by receptors (EPOR) and eNOS. The action of EPO on eNOS may be a physiologically linked mechanism to balance the increased hemoglobin-bound NO degradation due to hypoxia-induced increase in erythrocyte mass. Besides hypoxia, an increase in NO levels with low blood O_2 content

in newborns with NEC is also induced by iNOS, pro-inflammatory cytokines, and bacterial endotoxins.

The damaging effect of hypoxia and/or asphyxia is realized in two phases. During the first phase of acute hypoxia and/or asphyxia, there is an increase in EPO synthesis, which stimulates NO production. Increased NO synthesis not only induces acceleration of epithelial damage but also inhibits recovery mechanisms, by suppressing proliferation and migration of enterocytes. An imbalance between damaging and restorative mechanisms leads to persistent barrier insufficiency, bacterial invasion, sustained activation of inflammatory mediators, and consequently intracellular Ca^{+2} migration. This pathological process develops over several hours and persists for several days.

Consequently, a significant change in serum levels of EPO, NO, and Ca^{+2} compared to their values in the control group explains the pathogenesis of NEC in full-term newborns and can be used to improve the disease diagnostics.

A promising direction in modern medicine is statistical study of pathological processes. The testing model we propose helps in determining a course of action for specialists (in this case, neonatologists) and conducting analyses to make decisions about optimizing the tactics of treating patients with NEC. The pathogenesis of NEC is suitable for statistical analysis, due to the multifactorial nature of the pathological process, accompanied by dysfunction of the vascular endothelial layer (occurring during hypoxia) and the involvement of various organs and systems.

The result of the work was the creation of a mathematical model for the early identification of NEC and the detection of severe cases of the disease. The model we've developed can be utilized to identify the presence of NEC and to monitor the progression and severity of the pathological process.

Upon admission to the hospital in a full-term newborn with appropriate anamnestic and clinical data, determining the serum levels of NO, EPO, Ca^{+2} can reveal the development of NEC in the early

stages. Suggested model for NEC detection: where e=2.71 is a mathematical constant. The accuracy of the model is 95.83%.

$$p = \frac{1}{1 + e^{-(-17.994+0.183*NO+0.994*EPO-1.292*Ca^{+2})}}$$

The levels of biomarkers NO, EPO, Ca^{+2} are determined, then their values are substituted into the corresponding positions in the formula. If as a result p>0.556, then we can talk about the formation of NEC.

This model is presented to assess the severity of the necrotic process, which can be used in the dynamics of the disease. If, as a result, p>0.447, then we can talk about the deterioration of the patient's condition and the development of a severe degree of NEC. Model has an AUC of 86.89%.

$$p = \frac{1}{1 + e^{-(0.033*NO+0.226*EPO-1.515*Ca^{+2})}}$$

The role of NO in the differential diagnosis of necrotizing enterocolitis in full-term newborns. During the study, it was found that only 83 patients with NEC had an increase in the levels of NO, EPO and a decrease in Ca^{+2}. And in 17 patients with NEC+Sepsis, low values of NO, EPO and Ca^{+2} were determined, which made up the case-control group. It should be noted that in patients with NEC with a septic complication, the level of NO was lower than its values of patients with NEC I, NEC II, and NEC III ($p < 0.001$). With the combination of NEC+Sepsis, there is also a decrease in the level of EPO and an increase in the level of Ca^{+2}. Statistically significant decrease in the level of EPO was only detected when compared against patients with NEC III ($p = 0.01$) stages, and in the level of Ca^{+2} no statistically significant changes were found. That is, the greatest change in the levels of biomarkers in the blood of patients was observed only in the value of NO indicators. Changes in the level of NO can be used not only to identify a risk group for the development of NEC but also to detect severe forms and septic complications of the disease.

The serum levels of EPO, NO, Ca^{+2} were also used to construct the ROC curve. Due to the fact that the clinical picture of NEC II, NEC

III and NEC+Sepsis have similarities, these groups of patients were compared using ROC analysis. ROC analysis was performed taking into account different combinations of biomarkers in patients with NEC+Sepsis. The analysis results are shown in table 5.

Table 5

Comparison of diagnostic values of biomarkers and their combinations between patients with NEC and NEC+Sepsis

Biomar-kers	AUC	Sensitivi-ty	Specifici-ty	TPR	FPR	p
NO	82.42%	58.82%	93.98%	64.29%	90.70%	0.368
EPO	57.02%	41.18%	77.11%	24.00%	85.33%	0.194
Ca^{+2}	51.81%	92.86%	17.81%	16.90%	87.50%	0.155
NO, EPO	83.56%	70.59%	91.57%	61.11%	92.68%	0.329
NO, Ca^{+2}	86.69%	71.43%	95.89%	75.00%	93.33%	0.420
EPO, Ca^{+2}	61.79%	42.86%	84.93%	31.25%	87.32%	0.214
NO, EPO, Ca^{+2}	86.89%	71.43%	95.89%	75.00%	93.33%	0.422

Note: AUC - area under the curve; PPV, positive predictive value; NPV, negative predictive value; p-section.

The greatest diagnostic value is observed when using NO and combinations of NO+EPO, NO+EPO+Ca^{+2}. Thus, to differentiate NEC from NEC with a septic complication of the course, it is sufficient to use NO. The results obtained indicate a significant role of NO in the pathogenesis of NEC, which allows us to consider it as a promising marker in order to develop new approaches to the diagnosis and management of this pathology in full-term newborns. The detected changes highlight the clinical significance of determining NO levels in children with NEC, particularly as the disease progresses. Confirmed findings include an increase in NO production in cases of NEC and a decrease in cases of NEC accompanied by sepsis. Appropriate threshold values for NO levels for each pathological process can be used in the differential diagnosis of NEC from NEC with septic complication and in the development of a testing algorithm

in full-term newborns. We have found that NO is the biomarker with the highest specificity of the studied markers for determining the development of sepsis. If the level of NO value is <37.80 μmol/l, then we are justified to worry about the development of a septic complication of the clinical course of NEC. This critical level of NO in dynamics can be used to detect the development of sepsis, which can be used to optimize management of treatment tactics and timely correction of patient treatment.

In the routine blood test of newborn patients with NEC, in addition to Ca^{+2}, other parameters such as potassium, sodium, platelets, erythrocytes, leukocytes, hemoglobin, total bilirubin, sugar, and hematocrit were retrospectively studied. All patients showed changes in blood indicators. Comparing the parameters of these indicators in patients with NEC and NEC+Sepsis, a statistically significant difference was noted only in the levels of platelets and total bilirubin. The lowest platelet value was found in patients with NEC III 65.00 [39.75; 109.75], whereas for the NEC+Sepsis group it was 197.00 [61.25; 326.75]. The lowest total bilirubin level is observed in the case-control group at 176.00 [104.00; 208.00] compared to newborns with NEC III at 244.00 [220.00; 311.20].

The apparent difference in total bilirubin levels in patients can be explained by its anti-inflammatory and antioxidant properties. Presumably, the low total bilirubin level in the blood of NEC patients with septic complications is associated with the child's immunodeficient state. It is known that the basis of the hemolytic disease of the newborn and transfusion-associated anemia is hemolytic anemia, which is one of the risk factors for the development of NEC in full-term newborns. Increased erythropoiesis and hyperbilirubinemia in newborns with NEC have a causal relationship with the disease's pathogenesis.

To determine the diagnostic value of TBill and PLT, ROC analysis was used. Numerical data of TBill and PLT were considered both separately and in combination. The best results were obtained using TBill (AUC 89.09% DI [72.89%; 100.00%]; p 0.69) and the combination of TBill+PLT (AUC 88.64% DI [71.27%; 100%]; p

0.76). The diagnostic significance of PLT (AUC 76.29% DI [54.52%; 97.86%]; p 0.84) was not found to be sufficiently effective. The results of the ROC analysis are shown in Table 6.

Table 6

Comparison of diagnostic values of TBill, PLT and their combinations in patients with NEC III and NEC+Sepsis

Biomarkets	PPC	Sensitivity	Specificity	TPR	FPR	p
TBill	89.09%	90.09%	80.00%	90.00%	66.67%	0.69
PLT	76.19%	50.00%	100.00%	100.00%	42.86%	0.84
TBill + PLT	88.64%	90.09%	75.00%	90.00%	60.00%	0.76

Note: AUC - area under the curve; PPV, positive predictive value; NPV, negative predictive value; p-section.

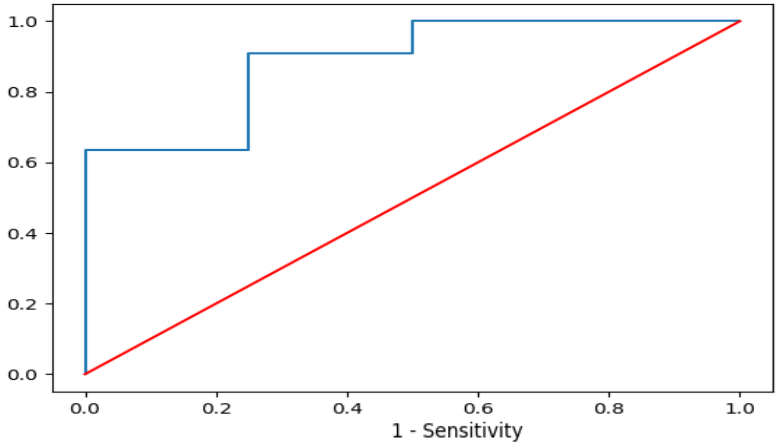

Figure 2. Curve – ROC TBill + PLT in the differential diagnosis of NEC with NEC + Sepsis

Drug treatment for severe forms of NEC is often insufficient to achieve good results. Timely detection of progression and differential diagnosis of NEC from diseases with similar symptoms is crucial for optimizing treatment and preventing various complications in newborns. The results of our study show that NO is a biomarker that can be used as part of an algorithm for differential diagnosis of severe

forms of necrotizing enterocolitis from septic processes during treatment of full-term newborns. Hyperproduction of NO in NEC, caused by hypoxic CNS damage and mesenteric hypoperfusion, accelerates intestinal epithelial damage, slows recovery mechanisms, leads to persistent barrier insufficiency, bacterial invasion, activation of inflammatory mediators, and ultimately the development of NEC. Hypoproduction of NO, caused by eNOS, with the generalization of the infectious process also contributes to intestinal damage in newborns. Therefore, the increased production of NO in NEC and decreased production in NEC+Sepsis are indicators of the pathological process in the newborn's intestine. The corresponding threshold values of NO levels for each pathological process can be used in the differential diagnosis of NEC from NEC with septic complications and in creating a testing algorithm for full-term newborns.

With the help of the compiled mathematical model, it becomes possible to identify the development of sepsis in patients with NEC. According to our study, it is sufficient to determine the level of serum NO. Using the test proposed below, it is possible to identify a septic complication of the clinical course of NEC in full-term newborns, where $p > 0.368$. The AUC of the model is 87.00%.

$$p = \frac{1}{1 + e^{-(1.573 - 0.056 * NO)}}$$

Timely determination of critical NO values will allow revealing the essence of pathological processes and differential diagnosis of NEC from sepsis, and thereby optimize early diagnosis and management of patients in the course of the disease.

CONCLUSIONS

1. Maternal anemia (40%, $p<0.01$), complications during childbirth (39%, $p<0.01$), and maternal infectious diseases (29%, $p<0.01$) are identified as antenatal and intranatal risk factors. These maternal factors contribute to intrauterine hypoxia, thereby increasing the risk of NEC in full-term newborns. Additionally, hypoxic lesions of the

central nervous system (67%) and early neonatal intestinal infections (22%) in the infant are the primary risk factors for the development of NEC in term newborns [2].

2. Even though a Caesarean section is not a direct risk factor for necrotizing enterocolitis, it contributes to creating unfavorable conditions that can exacerbates the clinical course and lead to adverse outcomes of the disease [3].

3. EPO, NO and Ca^{+2} are emerging biomarkers for detecting NEC in full-term newborns. A significant increase in EPO ($p < 0.001$) and NO ($p < 0.001$) levels, combined with a decrease in Ca+2 levels ($p < 0.001$) in the blood serum of patients compared to the control group, varies depending on the stage of the disease. These variations can be utilized for the early identification and diagnosis of severe forms of NEC in full-term newborns [4].

4. In full-term newborns, sepsis is a known complication of NEC. In the case of sepsis development within the NEC cohort, there is a noted decrease in NO levels to 35.60 μmol/l, which is lower than the levels observed in the initial stage of NEC (54.40 μmol/l). This significant variation in NO levels can be utilized as a specific biomarker to differentiate between NEC and NEC with sepsis [5].

5. Our mathematical testing algorithm, which is based on the serum levels of EPO, NO and Ca^{+2} facilitates the early identification of NEC, its more severe forms, and the septic complications associated with the disease's clinical course [9; 10].

PRACTICAL RECOMMENDATIONS

1. Neonates born to mothers who experienced a complicated pregnancy and delivered via Caesarean section, and who have been subjected to chronic and severe hypoxia during the antenatal and intranatal periods, should be considered at risk for the development of NEC. It is necessary to recommend intensive monitoring of these children in the early neonatal period.

2. To optimize early diagnosis and management of NEC in full-term newborns, diagnostic tests should include measuring levels of EPO,

NO, and Ca^{+2} in blood serum. High levels of NO and EPO, along with low levels of Ca^{+2} in the first days of the neonatal period, indicate the development of NEC. The interconnected changes in the levels of these biomarkers, corresponding to the disease's progression through its stages, can assist in timely detecting clinical complications and guide the adjustment of management and treatment strategies for this pathology as it evolves.

3. The detection of low NO biomarker levels in patients with NEC enables the identification of septic complications within the disease. We have developed a testing algorithm to ascertain the risk group of newborns for the development of sepsis.

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LIST OF ACCEPTED ABBREVIATIONS

NEC - necrotizing enterocolitis
NEC+Sepsis - necrotizing enterocolitis with septic complications
CS - caesarean section
EP - natural childbirth
GIT - gastrointestinal tract
HDN - hemolytic disease of newborns
IUI - intrauterine infection
IUGR - intrauterine growth retardation
CNS - central nervous system
ELISA - enzyme immunoassay
EPO - EPO
ABS - acid-base state of blood
O_2 - oxygen
NO - NO
eNOS - endothelial NO synthase
iNOS - inducible NO synthase
nNOS - neuronal NO synthase
NOc - sum of nitrates and nitrites
Ca^{+2} - Ca^{+2}
HGB - hemoglobin
HCT - hematocrit
WBC - leukocytes
RBC - red blood cells
TBil - total bilirubin

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