# THE STUDY OF GASTROINTESTINAL DISTRESS MARKERS IN CHILDREN OF GESTATIONAL AGE LESS THAN 32 WEEKS WITH PATHOLOGICAL CONDITIONS OF THE NEWBORN PERIOD

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**ABSTRACT**

**Background.** Feeding intolerance in preterm infants is currently one of the most common clinical problems in neonates, causing a delay in complete enteral absorption of food components and may lead to prolonged hospitalization. Prevention and control of nutritional deficiencies in children play an important role in improving the survival rates of premature babies.

**Aim.** To study the clinical and paraclinical features of food intolerance in premature babies under 32 weeks of gestation in perinatal pathology.

**Materials and Methods.** Clinical and paraclinical features of gastrointestinal disorders in perinatal pathology were analyzed in 54 severely preterm infants (group 1); the control group included 50 conditionally healthy newborns at 34–36/6 weeks gestational age (group 2). Laboratory tests included a biochemical analysis of blood serum, which characterizes the functional state of the hepatobiliary system and pancreas, as well as coprofiltrate parameters. Statistical analysis of the data was carried out using Statistica 13.0 (StatSoft Inc., USA). Quantitative values in samples with normal distribution were assessed using Student's t-test, with statistical significance $p<0.0001$. Approval of the Bioethics Commission of the Bukovinian State Medical University (Protocol No.2 on February 9, 2015).

**Results.** The clinical criteria for nutritional deficiency, which have shown their significance in the course of studies in newborns, are as follows: residual gastric volume greater than 50%, regurgitation and vomiting, enlarged liver, including hepatolienal syndrome; flatulence, blood in coprofiltrate, acholic stools, jaundice, edema, endotoxemia. The detected changes in blood chemistry parameters confirming enteral nutrition deficiency included: increased levels of Alanine Aminotransferase, Aspartate Aminotransferase and Lactate Dehydrogenase (cytolysis syndrome), Gamma-glutamyl Transferase, Alkaline Phosphatase and Bilirubin (cholestasis syndrome); decreased levels of Total Protein with increased levels of Cholesterol (liver and cell failure syndrome); low levels of Amylase, Lipase, Trypsin, and Leucine Aminopeptidase (pancreatic dysfunction); high levels of Calprotectin, Albumin, Alpha-1-Antitrypsin, and Faecal Elastase-1; decreased levels of PMN Elastase (inflammation of the intestinal mucosa).

**Conclusions.** Our findings demonstrate that the use of set of clinical and laboratory parameters allows early diagnosis of food intolerance in preterm infants, which enables appropriate correction of treatment in perinatal pathology.

***Keywords:*** *preterm infants, food tolerance disorders, clinical and laboratory diagnostics.*

## Introduction

Every year [10–16]% of children are born prematurely in different countries. Premature birth, especially in extremely premature infants, due to immaturity under hypoxia in the presence of negative factors in the prenatal period and during childbirth, is a leading cause of severe neonatal pathology. This category of children has a high risk of developing negative long-term consequences, including impaired nervous and physical development, as well as the formation of functional and chronic diseases [1; 2].

Feeding intolerance in preterm infants is currently one of the most common clinical problems

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in neonates, causing a delay in complete enteral absorption of food components and may lead to prolonged hospitalization. This pathology occurs in preterm infants with a frequency ranging from 33.80% to 53.45% [3]. Most commonly, food intolerance occurs in neonates with a gestational age of less than 32 weeks and a weight of less than 1500 g. Prevention and control of Nutritional Deficiencies (ND) in children play an important role in improving the survival rates of Premature Babies (PB). Therefore, this aspect of medical care is very important for early diagnosis to ensure timely, effective and safe intervention. Typically, the clinical manifestations of digestive dysfunction in neonates are an increase in gastric residual volume, vomiting, abdominal distention, and blood in the stool [4].

Clinical and laboratory criteria for GastroIntestinal Disorders (GID) in neonates are actively discussed in world scientific publications. It should be noted that currently there are no generalized approaches to defining laboratory criteria for food intolerance. In addition, these disorders should be discussed taking into account the peculiarities of the digestive system in premature infants, since the limits of indicators may differ depending on the gestational age and severity of the disease. At present, the pathogenetic mechanisms of GID are also insufficiently studied, which also does not allow to generalize clinical and laboratory criteria for food intolerance. In view of the above, conducting research to clarify the risk factors and clinical and paraclinical features of food intolerance in newborns, including PBI, is an important area of research at the current stage of development of neonatology, pediatrics and pediatric gastroenterology.

**Aim** of the study was to investigate the risk factors and clinical and paraclinical features of food tolerance disorders in perinatal pathology in children with gestational age at birth less than 32 weeks, taking into account the pathophysiological mechanisms of combined dysfunction of the hepatobiliary system, pancreas and intestine.

**Materials and Methods**

Considering the aim and objectives of the study, we analyzed the risk factors and clinical manifestations of GID in 54 children born at a gestational age of less than 32 weeks (group 1). The comparison group (group 2) consisted of 50 conditionally healthy children with a gestational age of 34–36/6 weeks. The correspondence of the signs of morphological and functional maturity with the gestational age at birth was determined taking into account the gestational age at the time of delivery, the data of anthropometric examination of the child at birth, with the evaluation of the indicators of the Ballard scale [5] and percentile tables. The criteria for inclusion in the main study group were: gestational age at birth less than 32 weeks, presence of clinical signs of severe perinatal pathology, including manifestations of GID, and presence of informed consent of the parents of the newborn to participate in the study. Exclusion criteria were: gestational age at birth greater than 32 weeks, confirmed congenital malformations, lack of parental consent to participate in the study. Data from pregnant women's exchange cards, birth histories and neonatal development records were studied.

Nosologic diagnoses were made according to International Classification of Diseases X, including the sections used: Disorders of the digestive system of the fetus and newborn (P75–P78); Problems with feeding of the newborn (P92). The condition of children after birth was assessed by the Apgar score, in the dynamics of observation – by the Score for Neonatal Acute Physiology (SNAPPE II). The Neonatal Multiple Organ Dysfunction Score (NEOMOD, 2001) was used to diagnose Multiple Organ Failure Syndrome (MODS) [6–9].

Clinical evaluation of the tolerability criteria was performed according to the recommended methodology, taking into account the age characteristics of the neonates. Laboratory tests included biochemical analysis of cord blood serum. The planned list included the determination of the following indicators: Total Protein, Bilirubin and its fractions; Glucose, Urea, Uric Acid, Cholesterol and Triglycerides; Alanine AminoTransferase (AlAT), Aspartate AminoTransferase (AsAT), Lactate DeHydrogenase (LDH), Gamma-Glutamyl Transferase (GGT) and ALkaline Phosphatase (ALP) activity; Amylase, Lipase, Trypsin and Leucine Aminopeptidase (LAP) levels. To clarify the indicators of enteric function of the intestine, we used the indicators of coprofiltrate: the level of Albumin, α-1-Antitrypsin (A1AT), Fecal Elastase-1 (FE-1), PMN-Elastase and Fecal Calprotectin (FC). The studies were performed in the Biochemical Laboratory of the Municipal Non-Profit Enterprise "City Clinical Maternity Hospital No.2" of Chernivtsi City Council, German-Ukrainian Laboratory "BUKINTERMED", Chernivtsi, Ukraine; Cottbus Public Laboratory of Medicine, Microbiology and Infectious Epidemiology, Cottbus, Germany (Accreditation Certificate D-ML-19676-01-00

according to DIN EN ISO 15189:2014, valid until November 25, 2019).

The research was conducted in accordance with the provisions of GCP (1996), the Convention of the Council of Europe on Human Rights and Biomedicine (1997), the Declaration of Helsinki of the World Medical Association on Ethical Principles for Research Involving Human Subjects (1964–2008), Order of the Ministry of Health of Ukraine No.690 on September 23, 2009 (as amended by Order of the Ministry of Health of Ukraine No.523 on July 12, 2012). Approval of the Bioethics Commission of the Bukovinian State Medical University (Protocol No.2 on February 9, 2015).

Statistical processing of the results was performed using Statistica 13.0 (StatSoft Inc., USA). Statistical values were determined considering standard deviation (S), standard error (m), arithmetic mean of the sample (M), using Shapiro-Wilk test (normal distribution with a sample size greater than 30, $p<0.05$) and Kolgomorov-Smirnov test. The quantitative indicators in samples with normal distribution were evaluated using the Student's t-test, the statistical significance of the results was determined at $p<0.0001$.

The research was carried out within the framework of the research work of the Department of Pediatrics, Neonatology and Perinatal Medicine of BSMU on the topic: "Improvement of prognosis, diagnosis and treatment of perinatal pathology in newborns and infants, optimization of schemes of catamnestic observation and rehabilitation" (State Registration No.0115U002768) and research on the topic: "Chronobiological and adaptive aspects and peculiarities of vegetative regulation in pathological conditions in children of different age groups" (State Registration No.0122U002245).

**Results and Discussion**

Group 1 consisted of 36 boys (66.67%) and 18 girls (33.33%). Anthropometric characteristics of children at birth were as follows: weight [1105.66± ±128.53] g, body length – [35.36±1.05] cm, head circumference – [26.58±2.06] cm, trunk circumference – [24.86±2.04] cm. Among the newborns of group 2 there were 23 (46.0%) boys and 27 (54.0%) girls with birth weight [2364.00±113.67] g, body length – [45.21±0.75] cm, head circumference – [31.59±0.71] cm, and trunk circumference – [30.51±1.46] cm. In comparison, anthropometric parameters showed significant differences, as they differed according to gestational age at birth – group 2 included children born at 34–36/6 weeks of gestation, which is considered almost full-term. Despite a certain percentage of maternal somatic pathologies and risk factors during pregnancy and childbirth, newborns of this group did not have any adaptation disorders in the neonatal period, so their study results were used as controls for the evaluation of laboratory parameters in children of study group 1.

The analysis of the somatic history of the women in group 1 showed that the birth of children before 32 weeks was observed in the following cases: 66.67% – in repeated pregnancy and childbirth, 42.59% – in age-matched first-time mothers, 66.67% had an emergency cesarean section. Compared with group 2, group 1 mothers were more likely to have somatic pathology, namely cardiovascular system – 43 (79.63%) and 3 (6.0%) cases, respectively, $p<0.0001$; urinary system – 42 (77.78%) and 3 (6.0%) cases, $p<0.0001$; GIS – 26 (48.15%) and 3 (6.0%) cases, $p<0.0001$; endocrine system – 19 (35.19%) and 3 (6.0%) cases, $p=0.0003$; respiratory system – 16 (29.63%) and 4 (8.0%) cases, $p=0.0163$; grade 2–3 anemia was diagnosed in 26 (48.15%) and 3 (6.0%) cases, respectively, $p<0.0001$.

The study of the peculiarities of the obstetrical and gynecological anamnesis of the women of group 1 showed the following: induced and spontaneous abortions, stillbirths, deaths of children under 1 year of age – 22 (40. 74%) cases, while the frequency of this indicator in group 2 was 1 (3.22%), $p<0.0001$; in vitro fertilization – 10 (18.52%) and 1 (3.22%) cases, $p=0.0138$; infertility – 13 (24.07%) and 2 (6.45%) cases, $p=0.0138$; preterm labor – 2 (3.70%) cases in the main group. Gynecological pathology in women was represented by: cervical insufficiency – 20 (37.04%) and 1 (3.22%) cases, $p<0.0001$; vaginitis – 16 (29.36%) and 2 (6.45%) cases, $p=0.0023$; TORCH infections – 18 (33.33%) and 1 (3.22%) cases, $p=0.0001$; uterine developmental abnormalities were detected in 9 (16.67%) cases.

Placental insufficiency during pregnancy was much more common in women of group 1, with fetal growth retardation detected in 29 (53.70%) cases, while in group 2 – only in 1 (3.22%) case, $p<0.0001$; threatened miscarriage and/or preterm delivery – in 16 (29.63%) and 2 (6.45%) cases, respectively, $p=0.0025$. Complications during labor included: fetal distress – 36 (66.67%) and 2 (6.45%) cases, $p<0.0001$; premature rupture of membranes – 18 (33.34%) and 1 (3.22%) cases, $p<0.0001$; abnormal presentation of the fetus – 17 (31.48%) and 1 (3.22%) cases, $p=0. 0002$; premature detachment of a normally located placenta – 13 (24.07%) and 1 (3.22%) cases, $p=0.0023$; ute-

rine bleeding – 11 (23.37%) cases in women of group 1. In addition, in 4 (7.47%) cases in women of group 1, a prenatal death of a twin fetus was diagnosed.

Newborns of group 1 had certain peculiarities of postnatal adaptation, which led to further development of severe pathological conditions in the neonatal period. The Apgar score of children of this group was [4.20±1.11] points at the 1st minute and [5.52±1.12] points at the 5th minute, which was significantly lower in comparison with the indicators of group 2 – [6.85±0.24] points and [7.82±0.35] points, respectively. The severity of the condition of children in group 1 was due to: Asphyxia – 32 (59.26%) cases; respiratory disorders – 54 (100%) cases; primary pulmonary atelectasis – 50 (92.59%) cases; hyaline membrane disease – 38 (70.37%) cases; 4 (7.41%) newborns were diagnosed with congenital pneumonia. Among children of group 1, 18 (33.33%) cases had pronounced signs of morphological and functional immaturity – 19 (35.19%) cases.

According to our data, all children in group 1 had signs of Multiple Organ Disfunction Syndrome (MODS), which included the following lesions: central nervous system and respiratory system – 54 (100.00%) cases each, cardiovascular system – 16 (29.63%) cases, hemorrhagic syndrome – 17 (31.48%) cases, anemic syndrome – 15 (27.78%) cases, disseminated intravascular coagulation – 14 (25.93%) cases. Convulsive syndrome was diagnosed in 15 (27.78%) newborns, 8 (14.81%) children had cerebral edema and/or were diagnosed with cerebral coma. Intraventricular hemorrhage of grade 1, 2, and 3–4 was diagnosed in 8 (14.81%) and 4 (7.41%) neonates, respectively. Signs of periventricular leukomalacia were observed in 8 (14.81%) children of group 1. It should be noted that in 11 (20.37%) cases of newborns of this group ulcerative Non-Specific Enterocolitis (UNEC) of the first degree was diagnosed, in 4 (7.41%) cases – UNEC of the second degree.

All 54 (100.00%) children in the main group showed, along with other symptoms of early neonatal disease, signs of nutritional dysfunction resulting in inadequate enteral absorption of the main components and requiring adequate supplementation by the administration of Parenteral Nutrition (PN). According to the literature, the disruption of the feeding schedule is usually caused by the child's inability to achieve complete enteral nutrition within the specified time, which is manifested either by a decrease in the number of feedings or their interruption due to the appearance of signs of malnutrition during feeding. Because the presence of nutritional dysfunction is easier to diagnose with an established feeding schedule, some studies have used the time to achieve total Enteral Nutrition (EN) or the need to interrupt EN with the addition of formula as criteria for assessing PN [9; 10]. A multicenter randomized trial published in 2002 concluded that the color of gastric residue in preterm infants does not always confirm PN [11]. The 2015 Canadian Guidelines for the Feeding of Very Low Birth Weight (LBW) Infants state that the yellow or green color of gastric residual volume alone cannot be used as a guide to diagnose LBW and also note that the use of abdominal circumference measurements to diagnose LBW is not recommended. [12] According to recent published scientific data, food intolerance in PB is usually manifested by an increase in Residual Gastric Volume (RGV) greater than 50% of previous feeding volume, accompanied by vomiting and/or bloating, and blood in stool [4].

Considering the purpose of the planned research, we raised the question of determining the clinical signs of ND in PB more broadly. Considering the expediency of generalizing the main diagnostic criteria characterizing the combined nature of the formation of Functional Gastrointestinal Disorders (FGID), we analyzed the probable clinical and paraclinical signs of dysfunction of the hepatobiliary system, pancreas and intestine in severe forms of perinatal pathology in this category of newborns.

The findings showed that the signs of ND in PB of less than 32 weeks gestational age were: residual stomach volume of more than 50% – in all 54 (100.00%) children; regurgitation and/or vomiting – in 32 (59.26%) cases; increased liver size and/or hepatolienal syndrome – in 54 (100.00%) and 43 (79.63%) cases, respectively, in neonates of the main and comparison groups; 48 (88.89%) children of group 1 had intestinal flatulence, 28 (51.85%) cases had blood in stool and 8 (14.81%) cases had acholic stool; 50 (92.59%) children had jaundice; 48 (88.89%) newborns had edema; 45 (83.33%) newborns had signs of endotoxemia.

The results of biochemical blood tests in the main group of PBIs showed significant homeostasis disorders. The data obtained, considered the indicators in the comparison groups, are presented in *Table 1*.

The analysis of the biochemical spectrum of blood serum revealed deviations of indicators, which, to a certain extent, allow to determine the

*Table 1. Biochemical parameters of newborn blood serum (M±m)*

| Parameter | Group 1 (n=54) | Group 2 (n=50) |
|---|---|---|
| Total Protein, g/l | 50.44±2.60* | 55.20±2.34 |
| Total bilirubin, μmol/l | 131.92±6.50* | 79.94±3.98 |
| Direct bilirubin, μmol/l | 2.33±0.11 | – |
| Indirect bilirubin, μmol/l | 129.59±4.70* | 79.94±3.98 |
| Alanine Aminotransferase, U/l | 17.22±0.84* | 10.26±0.44 |
| Aspartate Aminotransferase, U/l | 48.00±2.33* | 38.41±1.76 |
| Lactate Dehydrogenase, U/l | 1185.12±91.6* | 776.9±29.39 |
| Alkaline Phosphatase, U/l | 361.40±12.38* | 346.6±19.79 |
| Gamma-glutamyl Transferase, U/l | 127.82±8.47* | 108.9±9.87 |
| Cholesterol, mmol/L | 3.54±0.37* | 2.21±0.15 |
| Triglycerides, mmol/L | 0.57±0.06* | 0.72±0.05 |
| Glucose, mmol/L | 2.41±0.12* | 3.34±0.15 |
| Urea, mmol/L | 3.85±0.16* | 3.45±0.17 |
| Creatinine, μmol/l | 79,93±3,89* | 60.32±2.63 |
| Amylase, U/l | 5.34±0.29* | 25.0±0.23 |
| Lipase, U/l | 12.46±0.63* | 21.5±0.21 |
| Trypsin, μg/l | 235.43±11.77* | 427.4±11.15 |
| Leucine Aminopeptidase, U/l | 27.15±1.36* | 39.96±0.27 |

Note: * – significant difference between the comparison groups ($p<0.0001$).

main pathophysiological principles of food intolerance in severe forms of perinatal pathology. A significant decrease in the level of total protein was noted, which indicates a lack of protein-synthesizing function of the liver and may cause the development of hypoproteinemic and hemorrhagic syndromes. The consequence of hypoproteinemic syndrome, due to the decrease in albumin content, is decreased plasma oncotic pressure, which can cause edema syndrome. Hemorrhagic syndrome develops in newborns as a result of insufficient synthesis of proteins that are blood coagulation factors (fibrinogen, prothrombin, proconvertin, and proaccelerin) [13]. High levels of urea and creatinine are characteristics of disorders of protein metabolism, as the main source of nitrogen from amino acids and their degradation products, as well as urea-forming function of the liver and renal excretory function. The results of the PB examination also showed an increased level of cholesterol in the blood serum, which is a manifestation of hepatocyte cytolysis and is due to the activation of lipid peroxidation in the absence of an antioxidant defense system [14]. The data analysis also showed an increased level of total bilirubin, mainly due to the indirect fraction, which is associated with increased hemolysis due to postnatal physiological processes of the red blood cell, as well as pathological processes, in particular bilirubin metabolic disorders and cholestasis. A decrease in triglyceride levels indicates immature lipid metabolism in the PBI body and inadequate intestinal absorption. According to the literature, a decrease in this indicator is also associated with inadequate or absent enteral nutrition. Decreased glucose levels in neonates are associated with impaired gluconeogenesis in the liver and may be due to inadequate intake. The increase in ALP activity is explained by the activation of glucose release from tissues after dephosphorylation [15; 16].

High levels of AlAT and AsAT activity indicate activation of cytolytic processes in neonatal liver under hypoxia. The function of AlAT and AsAT is also related to the transamination process, which plays a key role in intermediate metabolism, ensuring the synthesis and breakdown of amino acids such as glutamic acid, aspartic acid and alanine. When converted to keto acids, which are components of the tricarboxylic acid cycle, they become a source of energy in the body. A significant increase in AlAT and AsAT in the acute period of hypoxic injury can also be explained by certain compensatory mechanisms aimed at providing cells with energy in the form of ATP, the formation of important biochemical molecules – acetyl CoA, NAD, FAD [17].

The results of the research also showed an increase in the enzymatic activity of GGT, which indicates both an increase in the activity of the glutathione system and glutathione-dependent enzymes, and the activation of cytolytic processes in the liver. An increase in LDH, which ensures the integration of carbohydrate and lipid metabolism, in children of the main group indicates a dysregulation of anabolism and catabolism, anaerobic and aerobic glycolysis [14]. Taking into account the main pathophysiological mechanisms of formation of HS dysfunction, the complex of signs of ND in PBI includes cytolysis syndrome (increased enzymatic activity of AlAT, AsAT and LDH), cholestasis syndrome (increased activity of GGT and ALT, cholesterol and bilirubin levels) and hepatocellular failure syndrome (decreased total protein and increased cholesterol levels).

The study of the indicators of the functional state of the pancreas showed a significant decrease in enzymatic activity, which confirms the insufficiency of its exocrine function in the presence of signs of ND in the PBI. A review of the current literature shows an insufficient number of scientific studies on exocrine insufficiency of the pancreas both in the general population and in patients with various diseases that lead to impaired functional state of the pancreas. However, it should be noted that the interest of researchers in this problem has increased in recent years. It is believed that exocrine insufficiency of the pancreas should be considered not as a dysfunction of a single organ, but as a general syndrome of digestive disorders. Accordingly, the aspects of diagnosis and treatment should include a more holistic approach [18; 19].

The study of laboratory markers of intestinal ND was performed with the determination of A1AT, FE-1, PMN-elastase, albumin and FC in the coprofiltrate of newborns. The results are presented in *Table 2*.

Analysis of the results showed significant differences in coprofiltrate indices in newborns of the main group under conditions of hypoxic damage to the body. In particular, signs of inflammation of the intestinal mucosa are confirmed by high levels of calprotectin. It is assumed that the increase of this indicator is due to its release from activated neutrophils. In the feces, it reflects the transepithelial migration of granulocytes into the intestinal lumen, confirming the inflammatory rather than functional nature of the disease [20]. Increased permeability of the intestinal mucosa due to inflammatory exudation from the altered epithelium also leads to protein loss and impaired parietal absorption. This may result in increased translocation of endotoxins and opportunistic pathogens from the intestinal lumen into the general circulation. The results obtained also showed a decrease in PMN-elastase, which is secreted by granulocytes and regulates inflammatory and immune responses, in the coprofiltrate of newborns. The decrease indicates the insufficiency of this compound in the regulation of intestinal anti-inflammatory mechanisms in PBI. References also suggest the possibility of cholestasis in severe forms of hypoxic inflammation [21–23]. A1AT, which is considered an acute-phase protein and a primary inhibitor of serine proteases in inflammation, was significantly elevated in group I neonates. According to the literature, A1AT is synthesized mainly by liver endoplasmic reticulum, polymorphonuclear neutrophils, alveolar macrophages, enterocytes, monocytes and Paneth cells. A1AT is an antiprotease that neutralizes excess proteases, inhibits chemotaxis and neutrophil adhesion. It is able to inhibit the release of proinflammatory interleukins, scavenge reactive oxygen species, and thus activate the body's anti-inflammatory response [24; 25]. Newborns in group 1 had slightly higher levels of FE-1, but the difference was not significant. Analysis of the literature

*Table 2. Comparative characteristics of the biomarkers of the coprofiltrate in the newborns of the comparison groups (M±m)*

| Parameter | Group 1 (n=54) | Group 2 (n=50) |
|---|---|---|
| Calprotectin, µg/g | 392.47±19.63* | 64.74±3.11 |
| Albumin, µg/g | 39.24±2.94* | 11.28±0.90 |
| PMN - Elastase, ng/g | 89.32±4.49* | 257.53±17.30 |
| α-1-Antitrypsin, µg/g | 358.42±2.89* | 241.15±18.90 |
| Fecal Elastase-1, µg/g | 289.58±14.49* | 246.98±16.79 |

Note: * – significant difference between the comparison groups ($p<0.0001$).

shows that the increase in the level of FE-1 can usually be earlier than that of other enzymes, especially in the subclinical stage of hypoxic inflammation [23]. In our opinion, the absence of a significant difference between the indices of the comparison groups may indicate the imperfection of this mechanism in PBI under conditions of significant immaturity of the organism.

Thus, in view of the obtained data, it can be concluded that ND in premature infants is caused by combined disorders of the functional state of the hepatobiliary system, pancreas and intestine. The pathophysiological mechanisms are based on hypoxic inflammation of the body, which has a negative impact on the formation of compensatory mechanisms, starting from the subcellular level of disorders. Detection of these changes, starting from the biochemical level, will improve the diagnosis of gastrointestinal disorders to prevent the development of severe dysfunction in the acute period of neonatal diseases, prevent the development of functional and chronic pathology in the later years of life.

**Conclusions**

1. Disturbances of the functional state of the gastrointestinal system in premature infants are caused by combined dysfunction of the hepatobiliary system, pancreas and intestine against the background of hypoxic damage and morphological and functional immaturity of the body.

2. Clinical signs of nutritional deficiency in newborns, taking into account the frequency of cases, include: residual volume of more than [50.00–100.00]%; regurgitation and/or vomiting – 59.26%; increased liver size (100%) and/or hepatolienal syndrome – 79.63%; flatulence – 88.89%, blood in coprofiltrate – 51.85%; acholic stools – 14.81%; jaundice – 92.59%; edema – 88.89%; endotoxemia – 83.33%.

3. The pathophysiologically substantiated biochemical markers of gastrointestinal disorders in premature infants are from the hepatobiliary system include increased activity of AlAT, AsAT and LDH (cytolysis syndrome); increased activity of GGT and ALP, cholesterol and bilirubin levels (cholestasis syndrome); decreased level of total protein and increased level of cholesterol (cholestasis syndrome and hepatic cell failure syndrome). Insufficiency of external secretory function of pancreas manifests by decreased level of amylase, lipase, trypsin and leucine aminopeptidase; inflammation and increased permeability of the intestinal mucosa (increased levels of calprotectin, albumin, alpha-1-antitrypsin, fecal elastase-1; decreased PMN elastase).

**Prospects for further research** are the comparison of clinical and laboratory parameters characterizing HBS dysfunction in PBI with regard to gestational age at birth.

**DECLARATIONS:**

**Disclosure Statement**

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations rele-vant to the subject matter or materials included.

**Statement of Ethics**

The authors have no ethical conflicts to disclosure.

**Data Transparency**

The data can be requested from the authors.

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**Consent for publication**

All authors give their consent to publication.

**References**

1. Rynhach NO, Moiseienko RO, Gojda NG. Neonatal mortality in Ukraine against COVID-19 pandemic: do not lose vigilance. Modern Pediatrics. Ukraine. 2022;7(127):86-94. DOI: 10.15574/SP.2022.127.86.

2. Ohuma EO, Moller AB, Bradley E, Chakwera S, Hussain-Alkhateeb L, Lewin A, et al. National, regional, and worldwide estimates of preterm birth in 2020, with trends from 2010: a systematic analysis. Lancet. 2023;402(10409):1261-71. DOI: 10.1016/S0140-6736(23)00878-4. PMID: 37805217.

3. Embleton ND, Jennifer Moltu S, Lapillonne A, van den Akker CHP, Carnielli V, Fusch C, et al. Enteral Nutrition in Preterm Infants (2022): A Position Paper from the ESPGHAN Committee on Nutrition and Invited Experts. J Pediatr Gastroenterol Nutr. 2023;76(2):248-68. DOI: 10.1097/MPG.0000000000003642. PMID: 36705703.

4. Evidence-Based Medicine Group, Neonatologist Society, Chinese Medical Doctor Association. Clinical guidelines for the diagnosis and treatment of feeding intolerance in preterm infants (2020). Zhongguo Dang Dai Er Ke Za Zhi. 2020;22(10):1047-55. DOI: 10.7499/j.issn.1008-8830.2008132. PMID: 33059799.

5. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. J Pediatr. 1991;119(3):417-23. DOI: 10.1016/s0022-3476(05)82056-6. PMID: 1880657.

6. Muktan D, Singh RR, Bhatta NK, Shah D. Neonatal mortality risk assessment using SNAPPE- II score in a neonatal intensive care unit. BMC Pediatr. 2019;19:279. DOI: 10.1186/s12887-019-1660-y. PMID: 31409303.

7. Ozcan B, Kavurt AS, Aydemir O, Gencturk Z, Baş AY, Demirel N. SNAPPE-II and risk of neonatal morbidities in very low birth weight preterm infants. Turk J Pediatr. 2017;59(2):105-12. DOI: 10.24953/turkjped.2017.02.001. PMID: 29276862.

8. Sokou R, Tritzali M, Piovani D, Konstantinidi A, Tsantes AG, Ioakeimidis G, et al. Comparative Performance of Four Established Neonatal Disease Scoring Systems in Predicting In-Hospital Mortality and the Potential Role of Thromboelastometry. Diagnostics (Basel). 2021;11(11):1955. DOI: 10.3390/diagnostics 11111955. PMID: 29276862.

9. Costa S, Maggio L, Alighieri G, Barone G, Cota F, G Vento. Tolerance of preterm formula versus pasteurized donor human milk in very preterm infants: a randomized non-inferiority trial. Ital J Pediatr. 2018;44(1):96. DOI: 10.1186/s13052-018-0532-7. PMID: 30115086.

10. Quigley M, Embleton ND, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database Syst Rev. 2018;6(6):CD002971. DOI: 10.1002/14651858.CD002971.pub4. PMID: 29926476.

11. Mihatsch WA, von Schoenaich P, Fahnenstich H, Dehne N, Ebbecke H, Plath C, et al. The significance of gastric residuals in the early enteral feeding advancement of extremely low birth weight infants. Pediatrics. 2002;109(3):457-9. DOI: 10.1542/peds.109.3.457. PMID: 11875141.

12. Dutta S, Singh B, Chessell L, Wilson J, Janes M, McDonald K, et al. Guidelines for feeding very low birth weight infants. Nutrients. 2015;7(1):423-42. DOI: 10.3390/nu7010423. PMID: 25580815.

13. Weeks CL, Marino LV, Johnson MJ. A systematic review of the definitions and prevalence of feeding intolerance in preterm infants. Clin Nutr. 2021;40(11):5576-86. DOI:10.1016/j.clnu.2021.09.010. PMID: 34656954.

14. Godovanets O. Markers of intracellular energy supply under conditions of hypoxia in premature babies. Child`s Health. 2024;19(6):354-61. DOI: 10.22141/2224-0551.19.6.2024.1739.

15. Godovanets OS. Clinical and laboratory aspects in diagnostics of the functional state of the hepatobiliary system in preterm infants. Actual Problems of the Modern Medicine: Bulletin of Ukrainian Medical Stomatological Academy. 2023;23(4):16-23. DOI: 10.31718/2077-1096.23.4.16.

16. Burge K, Vieira F, Eckert J, Chaaban H. Lipid Composition, Digestion, and Absorption Differences among Neonatal Feeding Strategies: Potential Implications for Intestinal Inflammation in Preterm Infants. Nutrients. 2021;13(2):550. DOI: 10.3390/nu13020550. PMID: 31783485.

17. Bussler S, Vogel M, Pietzner D, Harms K, Buzek T, Penke M, et al. New pediatric percentiles of liver enzyme serum levels (alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase): Effects of age, sex, body mass index, and pubertal stage. Hepatology. 2018;68(4):1319-30. DOI: 10.1002/hep.29542. PMID: 28926121.

18. Hopson P, Patel, S, Bornstein J, Mehta D, Horvath K. Isolated amylase deficiency in children and its clinical implication. Journal of Pediatric Gastroenterology and Nutrition. 2019;68(6):854-60. DOI: 10.1097/mpg.0000000000002317. PMID: 30889125.

19. Hopson P, Smadi Y, Mehta V, Patel S, Mehta D, Horvath K. Assessment of exocrine pancreatic function in children and adolescents with direct and indirect testing. Front Pediatr. 2022;10:908542. DOI: 10.3389/fped. 2022.908542. PMID: 36452348.

20. Vidova V, Benesova E, Klanova J, Thon V, Spacil Z, et al. Simultaneous quantitative profiling of clinically relevant immune markers in neonatal stool swabs to reveal inflammation. Sci Rep. 2021;11:10222. DOI: 10.1038/s41598-021-89384-0. PMID: 33986356 PMCID: PMC8119937.

21. Godovanets O, Nechytaylo Y. Clinical characteristics and possibilities of laboratory diagnostics of gastrointestinal diseases in perinatal pathology of premature infants. Neonatol. hìr. perinat. med. 2024;14(2(52): 28-33. DOI: 10.24061/2413-4260.XIV.2.52.2024.5.

22. Rigo J, Hascoet JM, Picaud JC, Mosca F, Rubio A, Saliba E, et al. Comparative study of preterm infants fed new and existing human milk fortifiers showed favourable markers of gastrointestinal status. Acta Paediatr. 2020;109(3):527-33. DOI: 10.1111/apa.14981. PMID: 31435957.

23. Wieczorek-Filipiak M, Drzymala-Czyz S, Szczepanik M, Miskiewicz-Chotnicka A, Wenska-Chyzy E, Moczko JA, Walkowiak J. Fecal elastase-1 in healthy children up to 2 years of age: a cross-sectional study. Dev Period Med. 2018;22(2):123-7. DOI: 10.34763/devperiodmed.20182202.123127. PMID: 30056398.

24. Rigo J, Hascoet JM, Picaud JC, Mosca F, Rubio A, Saliba E, et al. Comparative study of preterm infants fed new and existing human milk fortifiers showed favourable markers of gastrointestinal status. Acta Paediatr. 2020;109(3):527-33. DOI: 10.1111/apa.14981. PMID: 31435957.

25. Korkmaz B, Horwitz MS, Jenne DE, Gauthier F. Neutrophil elastase, proteinase 3, and cathepsin G as therapeutic targets in human diseases. Pharmacol Rev. 2010;62(4):726-59. DOI: 10.1124/pr.110.002733. PMID: 21079042.

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