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ABSTRACT

of the dissertation for the degree of Doctor of Science

EARLY DIAGNOSIS AND PREDICTION OF THE FUNCTIONAL DISORDERS IN LOW BIRTH WEIGHT INFANTS AT DIFFERENT GESTATIONAL AGE

Specialty: 3220.01 – Pediatrics

Field of science: Medicine

Applicant: **Nushaba Farhad Panahova**

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The work was performed at the Department of 2nd Children's Diseases of Azerbaijan Medical University

Scientific consultant: doctor of medical science, professor
Safikhan Shamil Hasanov

Official opponents: Honored scientist,
doctor of medical science, professor
Ibrahim Isa Isayev

doctor of medical science
Raksana Yusif Mammadova

doctor of medical science, professor
Kamal Mudafe Hajiyev

Doctor of medical science, associate professor
Andrey Mikhailovich Loboda

Dissertation council ED 2.27 of Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at Azerbaijan Medical University

The chairman of the Dissertation Council:
doctor of medical science, professor
Yagub Ziyaddin Gurbanov

Scientific Secretary of the Dissertation Council:
doctor philosophy in medicine, associate professor
Tora Akif Sadigova

The chairman of the scientific seminar:
Honored scientist,
doctor of medical science, professor
Amaliya Abdulla Eyyubova

İMZANI TƏSDİQ EDİRƏM
Azərbaycan Tibb Universitetinin
ELMİ KATİBİ
Tibb elmləri doktoru, professor
Nazim Adil oğlu Pənahov
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GENERAL DESCRIPTION OF THE WORK

Relevance of the theme: The medical community is tirelessly combining its efforts to solve the problems of maternal and child health, which against the background of demographic problems of our time, have become politically and socially important. Low birth weight remains an extreme dilemma of clinical neonatology and developmental physiology. Although the development of perinatal medicine has improved the chances of survival in low-birth-weight infants, the period of early adaptation in this category of patients is extremely stressful with the development of numerous life-threatening conditions [1, 2]. In turn, this is followed by an increase in mortality in later periods of a child's life, formation of delayed somatic and neurological complications[3]. One of main causes of morbidity and mortality, formation of disablement in young children are pronounced homeostatic changes in the child's body, resulting from negative multietiological effects of various factors on a developing fetus during gestation and birth[4]. In most cases, desadaptative syndrome is the result of "traumatic" effects of pre- and intranatal hypoxia on the fetus.

Involvement of the central nervous system (CNS) in the pathological process is a natural complication of hypoxia, which is mani-

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fested as hypoxic-ischemic encephalopathy[5]. Under conditions of perinatal hypoxia, in response to insufficient oxygen supply, peripheral spasm and centralization of the fetal blood circulation occurs with an increase in blood flow to vital organs - the brain, myocardium and adrenal glands ("brain sparing effect")[6]. It is a question of an elective blood supply to vital organs at the expense of reduction of blood flow in donor organs and tissues, which is followed by hypoxic-ischemic damage to their structural components, which in turn, limits the ability to adequately change their functions for optimal mode of activity in postnatal ontogenesis by disrupting their compensatory-adaptive capabilities [7]. The immediate factors that determine intensity of functional changes on part of various organs are: different ability of organs and tissues to resist hypoxia, nature of damaging factor and initial state of organ or system itself. Development of functional disorders during hypoxia most often occurs gradually and is evident by dysfunction of several organs, which is often a complete surprise to clinician. This is caused by the fact that clinical manifestations of organ dysfunctions depend on severity of underlying pathology and have nonspecific future, which leads to underestimation of patients' severity at an early stage [8]. Along with complications of neonatal period, the further state of health of low birth weight infants gives rise to a whole range of complex medical and

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social problems associated with possibilities of rehabilitation of this contingent of children and improvement of their quality of life [9], since along with an increase in the number of surviving newborns, the percentage of early disablement is growing [10]. Most often these are premature babies with hypoxic-ischemic damage to CNS, with outcomes such as minimal brain dysfunction, neurosensory disorders, infantile cerebral paralysis (CP), with cognitive, psycho-emotional and behavioral disorders persistent in preschool and school age [11], not to mention the whole range of functional and transient problems - high number of infectious diseases, deficiency conditions, low rates of physical development [12]. However, lack of outpatient service doctors' full awareness in matters of physiology, growth and development peculiarities of children born preterm or small for gestational age creates prerequisites for both underestimating the existing disorders, and for overdiagnosis and polypharmacy [13, 14].

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Thus, improvement of methods for early diagnosis and prediction of perinatal pathologies are the most important tasks of modern neonatology, solution of which will allow preserving the health and quality of life of survived low birth weight newborns, along with a decrease in neonatal and infant mortality.

Object of study. Newborns at different gestational age (29-41 weeks) exposed to perinatal hypoxia.

Aim of the study:

Development of early diagnostic and prognostic markers of functional disorders in low birth weight infants of various gestational ages.

Objectives of the study:

1. To identify the most significant pre- and perinatal risk factors for development of functional disorders in low birth weight newborns;
2. To establish the structure and severity of functional disorders in low birth weight infants depending on gestational age;
3. To assess the features of organ dysfunctions depending on the correspondence of body weight to gestational age;
4. To determine the intestinal barrier state depending on the nature of structural changes on neurosonography;
5. To establish the role of cardiorespiratory disadaptation in the development of organ disorders in the course of early neonatal period;
6. To determine the earliest and most informative diagnostic markers of damage to CNS, liver, intestines and kidneys;
7. Clarify the pathogenesis of organ dysfunctions in low birth weight newborns exposed to perinatal hypoxia;
8. To determine predictors of adverse outcomes of organ lesions in low birth weight infants;
9. To develop a mathematical model for predicting possible mortality of low birth weight newborns based on the results of a comprehensive analysis of anamnesis, clinical and laboratory data;
10. To evaluate the features of somatic health formation and con-

sequences of perinatal CNS lesions in the dynamics of the first three years of life depending on antenatal and neonatal risk factors.

Research methods. Clinical-laboratory and instrumental methods of investigation. The method of enzyme immunoassay was used to determine the level of organ-specific markers in peripheral blood and urine samples.

Key theses to be defended:

1. Burdened obstetric history, along with a complicated course of pregnancy, plays a role in realization of functional disorders in low birth weight newborns; a maternal history of anemia, preeclampsia, and threatened termination of pregnancy should be considered as a likely predictor of acute kidney injury in low birth weight infants;
2. Nature of functional disorders depends on duration and severity of perinatal hypoxia and is determined by gestational age and maturity of newborns; lesion of peripheral organs in the group of very premature infants small for gestational age is accompanied by depletion of antioxidant capacity;
3. Reliable relationship between the level of antibodies to glutamate receptors and markers of liver, kidney and intestinal damage proved by correlation method indicates that along with posthypoxic and reperfusion mechanisms, a certain role in the damage of these organs is played by the violation of central regulation of their functional status;
4. Ischemic-reperfusion complications of perinatal hypoxia are accompanied by lesions of the intestinal barrier, translocation of endotoxin and the development of endotoxemia further aggravating damage to organs and systems, as evidenced by the significant correlation between the levels of lipopolysaccharide-binding protein and organ-specific markers;
5. Evaluation of autoantibodies to NR2 receptors will predict the development of periventricular leukomalacia and lipopolysaccharide-binding protein will predict the development of necrotic enterocolitis from the first days of postnatal ontogenesis;

6. Pregnancy complicated by preeclampsia in combination with intrapartum asphyxia, respiratory distress syndrome, necrotic enterocolitis and certain clinical and laboratory parameters (pH, Hb, albumin, ALT, AST, IFABP) that reflects destabilization of the internal environment have prognostic outcome for mortality; the prediction regression model created on the basis of these indicators allow to determine the risk of neonatal mortality on the individual level;
7. Prediction of somatic and neurological pathology in postneonatal period will allow optimizing the immediate and long-term outcomes of low birth weight newborns with hypoxic lesions of CNS.

Scientific Novelty:

- On the basis of a comprehensive analysis of clinical and anamnestic data and the results of laboratory and instrumental research methods, significant ante- and intranatal factors of a high risk of developing functional disorders in low birth weight newborns were determined;
- The influence of gestational age and IUGR on the structure and severity of functional disorders was determined
- On the basis of regression analysis, the most informative criteria for early diagnosis of functional disorders with prediction of perinatal outcomes were determined
- The understanding of the structure of the causes of perinatal morbidity and mortality among low birth weight infants of various gestational ages has been expanded upon
- The criteria for predicting deviations in somatic status and the development of severe neurological pathology leading to disability in children with low birth weight have been systematized.

Theoretical and practical significance of the research:

Use of early highly sensitive markers of lesion in certain organs and body systems allows the determination of preclinical diagnosis of functional disorders in low birth weight infants and implementation of timely pathogenetically substantiated correction of these changes.

Identification of perinatal predictors of organ lesions in low birth weight infants will provide an opportunity to substantiate a complex of therapeutic and prophylactic measures for functional disorders, which will positively affect health of these infants and reduce duration of their hospitalization and material expenditures.

Calculation of probability of fatal outcome risk makes it possible to identify newborns requiring increased attention with implementation of prophylactic measures to prevent the development of life-threatening conditions. Identification of these markers will allow preventing aggressive treatment tactics.

System for predicting implementation of neurological and somatic pathologies in subsequent years of life, depending on the perinatal and neonatal risk factors and level of organo-specific markers in the neonatal period, can be used in an outpatient setting to carry out a differentiated approach during clinical examination of these children, and the timely implementation of preventive and rehabilitation measures in the outpatient-polyclinic setting.

Approbation and implementation.

The main provisions of the dissertation were presented and discussed at the interdepartmental meeting (22.05.2018, protocol №12) and the scientific seminar of the Dissertation Council ED 2.27 at AMU (21.05.2021, protocol №4).

Main results of the dissertation were reported and discussed at: I Medical Congress of Turkish-Speaking Countries (Baku, 2011), 4th Congress of Pediatric Communities of the European Academy (Istanbul, 2012), Congress of Pediatricians of Turkish-Speaking Countries (Baku, 2015), Maternal, Fetal, Neonatal Medicine I World Congress (London, 2017), Scientific and Practical Conference dedicated to the 90th anniversary of Farajova Pediatrics Research Institute (Baku, 2017), 7th Congress of Pediatric Societies of the European Academy (Paris, 2018), Maternal, Fetal, Neonatal Medicine II World Congress (London, 2019), Topical Issues of Modern Medicine V International Scientific-Practical Web-Conference of Caspian States, Astrakhan, October 9-10, 2020.

Place of research. The research work was carried out at the

clinical bases of the Department of 2nd Children's Diseases of Azerbaijan Medical University.

Publications. 45 papers reflecting main provisions of research were published on the topic of thesis. Of these: 29 articles, 4 of which are in scientific journals included in the Thomson Reuters List, chapters of the 2 books, 14 thesis of reports in the materials of scientific conferences.

The results of the study were introduced into the daily clinical work of the department of anesthesiology and resuscitation of newborns and the department of pathology of premature newborns of the K. Farajova Research Institute of Pediatrics.

The data obtained in the course of research were introduced into the educational process of the Department of Childhood Diseases when teaching the section "neonatology", with the inclusion of the relevant data in educational and methodological complexes.

Volume and structure of the dissertation. The dissertation is presented in Russian on 353 pages (365.900 characters), consists of introduction (12.300 characters), literature review (68.600 characters), descriptions of materials and research methods (48.400 characters), 3 chapters of presenting the results of own research (56.600 + 88.600 + 43.000 characters), conclusions, resume, practical recommendations (48.400 characters), list of used sources, including 471 titles. The paper is illustrated by 86 tables, 75 graphics.

MATERIAL AND RESEARCH METHODS

Research work is a part of the project supported by Science Development Foundation under the Presidential Administration of the Azerbaijan Republic. Project title: "The role of perinatal factors in the formation of the neurosomatic status of premature newborns. A comparative, controlled, three-stage study conducted with the approval of the Local Ethics Committee at the Azerbaijan Medical University. The work was carried out from 2010 to 2014 at the educational bases of the Department of 2nd Children's Diseases of AMU in 5th Maternity Hospital named after Sh. Alasgarova and at the Sci-

entific Research Institute of Pediatrics named after K. Farajova.

287 newborns of different gestational age (29-41 weeks) were recruited for this study and divided into a main and a control groups.

Control group consisted of 50 apparently healthy newborns born to mothers with physiological course of pregnancy and childbirth, in turn subdivided into 2 subgroups: 22 newborns born at term and 28 – born preterm. Control group newborns met the following criteria: Apgar score at 1 minute was higher than 5 points, physiological course of adaptation period, and absence of neurological symptoms.

Main group included 237 newborns born to mothers with burdened anamnesis, whose main diagnosis upon admission to Resuscitation and Intensive Care Unit of Farajova Pediatrics Research Institute was perinatal hypoxic encephalopathy. Purpose of creating the main group was to assess dynamics of organ disorders in low birth weight infants exposed to perinatal hypoxia. Depending on gestational age, main group newborns were divided into 3 groups: group 1 included newborns born at term, at 37-41 weeks of gestation (n=82); group 2 included infants with a gestational age of 33-36 weeks (n=100); group 3 consisted of very premature infants with gestational age of 29-33 weeks (n=55). Infants whose anthropometric data appropriate for their gestational age (AGA), Subgroup A (1A=47, 2A=68, 3A=39), and small to gestational age (SGA), Subgroup B (1B=35, 2B=32, 3B=16), were identified in each group. Exclusion criteria: stillbirth, newborns with clinical manifestation of congenital bacterial and TORCH infections confirmed by laboratory methods, congenital malformations (except for minor developmental anomalies that do not pose a threat to life), multiple pregnancies.

Assessment of antenatal history was carried out on the basis of results of prospective examination of pregnant women admitted to Sh. Alasgarova Maternity Hospital and retrospective data of newborns' mothers admitted Resuscitation and Intensive Care Unit of Farajova Pediatrics Research Institute.

At birth, each infant was assessed under Apgar scale to determine the severity of hypoxia. Newborns' physical development, cor-

respondence of their anthropometric indicators to gestational age was assessed based on centile tables and according to table developed at Neonatology Department under Professor N.Taghiyev's guidanc. Assessment of nervous system state and encephalopathy severity was carried out during the first 24 hours of life according to the scale proposed by Sarnat N., Sarnat M., 1976 as modified by Stoll B., Kliegman R., 2004.

All newborns underwent neurosonographic research in neonatal period dynamics in order to objectify clinical signs of CNS damage and monitor transformation of revealed structural cerebral disorders. Hemorrhagic changes were assessed according to the classification developed by Papile which distinguishes 4 degrees of cerebral hemorrhage. Periventricular leukomalacia (PVL) was diagnosed based on increased echogenicity of periventricular zones with formation of small fronto-parietal cysts.

Along with neurosonography, analysis of Echo data, ultrasound examination of kidneys with assessment of morphometric characteristics on apparatus with convection sensor of 2.5-5.0 MHz frequency were carried out with measurement of blood flow, X-ray examination of thorax and abdominal cavity.

To assess the functional status of newborns, in addition to routine analyses, markers reflecting both compensatory and protective capabilities, and the degree of damage to organs and systems in response to hypoxic damage were determined in peripheral blood samples taken on days 1-3 and 7-10 of life:

Markers of nervous system lesion: neurospecific enolase (NSE) and antibodies to NR2 receptors (aNR2) in peripheral blood serum;

Kidney injury markers - kidney injury molecule-1(KIM-1), lipocalin-2, liver fatty acid-binding protein (L-FABP) in urine, lipocalin-2 in blood;

Intestinal lesion markers – intestinal fatty acid-binding protein (I-FABP), mucin (MUC-2), trefoil factor (ITF) in peripheral blood serum, I-FABP in urine;

Liver lesion markers - L-FABP, ALT, AST in peripheral blood serum.

To assess endotoxemia degree, lipopolysaccharide-binding protein (LPB) in peripheral blood serum was determined.

To determine the level of organ-specific markers in blood and urine, we used a quantitative method based on enzyme-linked immunosorbent assay (ELISA) using the "sandwich" method.

To identify intestinal microflora balance, dejection was analyzed for dysbacteriosis.

To rule out intrauterine TORCH infections as a cause of newborn' condition severity, we used serological blood immunoassay. To rule out intrauterine sepsis, bacteriological examination of biological media and C-reactive protein determination were performed from the first day of life.

For statistical processing of results, the SPSS Statistics 20 Software Package was used. The indicators of the groups were compared by parametric -Student's t-test (in the case of normal distributions) and nonparametric - Mann-Whitney U-test by analysis methods. The analysis of variance was carried out by the method of one-factor analysis one-way ANOVA. To assess relationship between clinical and laboratory parameters, correlation analysis was used with identifying Spearman's rank correlation coefficient. To assess relationship between studied parameters, which have a quantitative expression, the step by step linear regression method was used. To create predictive algorithms for determining the risk of morbidity in subsequent years of life depending on level of organo-specific markers, we used the step by step linear regression method. To determine informativeness (diagnostic sensitivity (DP) and diagnostic specificity (DS)) and threshold values (cutoff) of studied parameters, the method ROC analysis was used.

RESEARCH RESULTS AND DISCUSSION

The role of antenatal factors in the formation of functional disorders in low birth weight infants

Newborns of mothers with burdened obstetric history (BOH) were characterized by significantly low Apgar score (5,79±0,29

against 6,46±0,16, p=0,48), high frequency of RDS (38,5% against 25%, p=0,041) and microcirculatory disorders (53,8% against 25,5%, p<0,05). At the same time, significantly lower NSE level in the group of newborns of mothers with BOH (52,2±5,7 ng/ml against 62,2±1,7 ng/ml) may indicate adaptation of brain structures to stressful situations, i.e. children exposed to several damaging effects in prenatal period demonstrate less pronounced response of neurocytes to asphyxia during labor (table 1).

Table 1

NSE level in newborns of the study groups in dynamics of neonatal period

NSE	Group	Mean	Mean error	95% DI		P	p1
				LB	HB		
1-3th DOL	BOH- (n=60)	57,6	2,2	53,0	62,1	<0,001	
	BOH+ (n=16)	55,0	5,4	42,5	67,6	<0,001	0,844
	Control (n=15)	25,0	1,8	21,3	28,8		
7-10th DOL	BOH- (n=32)	62,2	1,7	58,7	65,8	<0,001	
	BOH+ (n=19)	52,2	5,7	38,3	66,1	<0,001	0,018
	Control (n=15)	17,5	1,1	15,3	19,8		

Note:
p-reliability of the difference in relation to the control group
p1-reliability of the difference between the subgroups of the main group

An increase in the level of plasma lipocalin from the first day of life (213,72±11,57 ng/ml – in BOH + subgroup, 152,12±31,01 ng/ml - in BOH -subgroup) and LBP (38,4±3,01 ng/ml– in BOH + subgroup, 28,17±2,9 ng/ml– in BOH - subgroup) to the end of early neonatal period indicates vulnerability of newborns of mothers with BOH to inflammatory processes (table 2).

In newborns whose mothers suffered from anemia (anemia+ subgroup) during current pregnancy, birth asphyxia (Apqar score – 5,170±32 - anemia+ subgroup, 6,09±0,28 – anemia- subgroup) and respiratory distress syndrome (27,7% - anemia+ subgroup ,15,9% - anemia- subgroup) contribute to persistence of newborn’s hypoxic

condition in postnatal period, which is accompanied by more pronounced pattern of peripheral organ injury. In turn, ischemic intestinal damage, as evidenced by high concentration of I-FABP, in anemia+ subgroup (11.15±5.46 ng/ml) in relation both to anemia+ subgroup (5.45±2.29 ng/ml) and control group (2.74±0.29 ng/ml), induces a regenerative response in form of increase in expression of trefoil factor (29,7±6,0 ng/ml – anemia+ subgroup, 18,4±7,2 ng/ml – anemia- subgroup -, p=0,29), aimed at restoring intestinal mucous barrier and preventing bacterial translocation.

Table 2

LBP level in newborns of study groups in dynamics of neonatal period

LBP	Group	Mean	Mean error	95% DI		p	p1
				LB	HB		
1-3-th DOL	BOH- (n=45)	31,67	2,59	26,45	36,88	<0,001	
	BOH+ (n=24)	30,11	3,25	23,35	36,86	<0,001	0,914
	Control (n=15)	7,92	1,14	5,59	10,25		
7-10-th DOL	BOH- (n=40)	28,17	2,91	22,21	34,14	<0,001	
	BOH+ (n=21)	38,40	3,01	32,02	44,78	<0,001	0,034
	Control (n=15)	14,85	1,80	11,17	18,53		

Note:
p-reliability of the difference in relation to the control group
p1-reliability of the difference between the subgroups of the main group

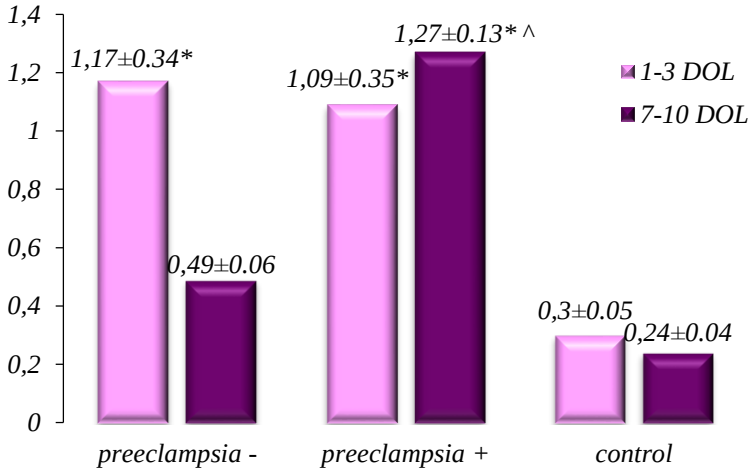
However, absence of parallel increase in another structural component of mucin-2 (11,1±1,4 ng/ml – anemia+ subgroup 13,0±1,9 ng/ml - anemia+ subgroup-, p=0,835) protective mucous barrier indicates failure of this compensatory mechanism which manifested itself clinically in the form of gastrointestinal syndrome. Assessment of condition of tubular apparatus of the kidneys of newborns born to mothers with anemia demonstrates a reliably high level of lipocalin (181,2±10.9 ng/ml) compared to control group (90,3±4,5 ng/ml) and anemia- subgroup (85,8±5,4 ng/ml) of newborns (p<0.001). Plasma concentration of liver FABP in the anemia + subgroup (2,55±0,4 ng/ml) significantly exceeds that in the anemia-

subgroup (1,51±0,31, p = 0,02).

Analyzing the perinatal outcomes of children born to mothers with gestosis, it was found that pregnancy complicated by preeclampsia has a significant effect on condition of fetus and newborn, being associated with fetal growth retardation (60,5% - preeclampsia+ subgroup, 27,3% - preeclampsia- subgroup, p=0,002) and risk of delivering children in a state of asphyxia (5,22±0,37- preeclampsia+ subgroup, 6,09±0,28, - preeclampsia- subgroup -, p=0,06) with increased mortality rate (p<0.05). However, absence of statistically significant difference in the level of markers reflecting organ dysfunction between newborns of subgroups preeclampsia+ and preeclampsia- indicates that chronic hypoxia is an universal damaging factors has a pronounced adverse effect on the course of metabolic and physiological processes in body, regardless of the causes that give rise to it. Exception was kidneys, damage of which was more pronounced and persistent in newborns born to mothers with preeclampsia. Kidney damage is accompanied by simultaneous involvement of glomerular and tubular apparatus in pathological process. Moreover, in contrast to glomerular filtration, damage to tubular epithelium is more prolonged. KIM-1 level study revealed its significant increase in the subgroups of main group from the first days of life. However, by day 7-10 of life, concentration of this marker in subgroup preeclampsia- tended to decrease, while in the group of newborns of mothers with preeclampsia its level continued to remain at high values and significantly differed from indicators of control group and subgroup preeclampsia- (p<0.05 - in relation to preeclampsia- subgroup -; p<0.001 - in relation to control group) (graphic 1).

Urinary lipocalin level in newborns of preeclampsia- subgroup did not differ from values of control group (85,8±5,5 ng/ml vs 9s,3±4,5 ng/ml, p=0,69). In preeclampsia+ subgroup, concentration of this marker during the first 10 days of life (167,1±30,3 ng/ml -1-3 DOL, 163,1±9,7 ng/ml – 7-10 DOL) reliably exceeded that in control group and in preeclampsia - subgroup (p<0.001). Preeclampsia and chronic intrauterine hypoxia lead to decrease in the number of neph-

rons with predominance of embryonic glomeruli in newborns. Thus, lower maturity at birth and more intensive development in early postnatal period contribute to a greater susceptibility of renal tubular epithelium to hypoxia.

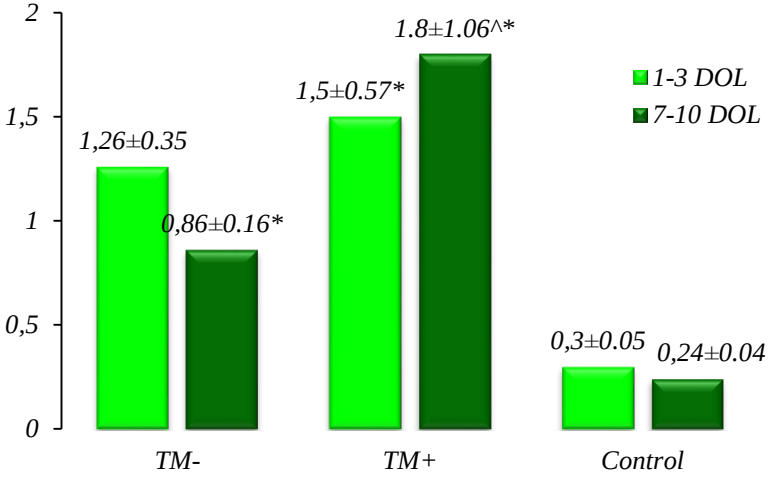


Note: statistically significant difference in relation to:
* - p <0.05 - to the control group
^ – p <0,05 – to compare subgroup

Graphic 1. KIM-1 level in newborns of study subgroups.

In perinatal pathology structure of newborns born to mothers with threatened miscarriage (TM), attention is drawn by severity of intrauterine malnutrition (50% - TM+ subgroup vs 45,9% - TM- subgroup, p=0,04). Urinary system of newborns was the most sensitive and vulnerable in this pregnancy pathology, which must be taken into account when managing newborns born to mothers with TM. As endogenous cause of inflammation, chronic hypoxia was manifested by persistent increase in urinary concentrations of lipocalin (212,2±6,8 ng/ml – TM+ subgroup vs 151,5±14,7 ng/ml – TM- subgroup , p=0,01). High concentration of ischemia marker KIM-1 in urine reflects the state of histotoxic hypoxia of renal tissue (graphic 2). On the one hand, LFABP increase confirms kidney ischemia and, on the

other hand, is an adaptive mechanism in response to impaired fatty acid oxidation during tissue hypoxia (12,68±2,05 – TM+ subgroup, ng/ml, 6,94±1,79 ng/ml – TM+ subgroup, p=0,045)



Note: statistically significant difference in relation to:
* - p <0.05 - to the control group
^ – p <0,05 – to compare subgroup

Graphic 2. KIM-1 level in newborns of study subgroups

Vaginally delivered low birth weight infants with complicated course of pregnancy, compared with babies delivered by cesarean section, are characterized by more pronounced maladjustment disorders of early neonatal period. As evidenced by a low Apgar score (5,81±0,23 ng/ml – in cesarean section + subgroup vs 5,12±0,24 ng/ml – in cesarean section - subgroup, p=0,046), perinatal stress causing a cascade of ischemia-mediated pathological processes in organs and tissues against the background of functional immaturity and instability of brain structures of low birth weight newborns developing in terms of chronic intrauterine hypoxia affects adversely their neurological status and gastrointestinal tract.

Vaginally delivered newborns (subgroup caesarean-) are characterized by a significantly high frequency of the syndrome of inhibi-

tion of the central nervous system (p = 0.039). When analyzing the data obtained by ultrasound and Doppler examination of the brain, no statistically significant difference was found in relation to PVL between the subgroups, although grade 3 intraventricular hemorrhage and dilatation of the lateral ventricles (p = 0.007) were detected, exclusively in vaginally delivered newborns. At the same time, immunochemical analysis did not reveal a significant effect of the method of delivery on indicators reflecting the state of the central nervous system. The level of antibodies to NMDA receptors at the 1st measurement did not differ in the compared subgroups (3,96 ± 0,32 ng/ml - in the cesarean- subgroup, 3,92 ± 0,45 ng/ml - in the cesarean + subgroup, p = 0,99). In dynamics, the decrease in the level of antibodies was more pronounced in vaginal delivery newborns (3,36 ± 0,32 ng / ml - in the Caesarean- subgroup, 3,72 ± 0,73 ng/ml - in the caesarean + subgroup, p = 0,79). The content of NSE in the cesarean + subgroup had some tendency to decrease, and in the cesarean- subgroup, on the contrary, to increase (55,6 ± 2,9 ng / ml - in the cesarean- subgroup, 66,1 ± 2,4 ng/ml - in the cesarean subgroup, cesarean +, p = 0,99, 1-3 days; 60,75 ± 2,5 ng / ml - in the subgroup of cesarean-, 58,75 ng/ml ± 3,64 - in the subgroup of cesarean +, p = 0,27).

Clinical manifestations of gastrointestinal disorders are accompanied in this category of newborns by increase of intestinal ischemia markers –IFABP (5,56±0,94 ng/ml – in cesarean section- subgroup vs 3,14±0,9 ng/ml – in cesarean section + subgroup, p=0,08) and secretory products of Goblet cells – ITF (27,8±4,8 ng/ml – in cesarean section- subgroup vs 16,2±3,1 ng/ml – in cesarean section + subgroup, p=0,05), which demonstrates severity of ischemia and inflammatory changes in intestine. Thus, caesarean section is justified in low birth weight infants in presence of perinatal risk.

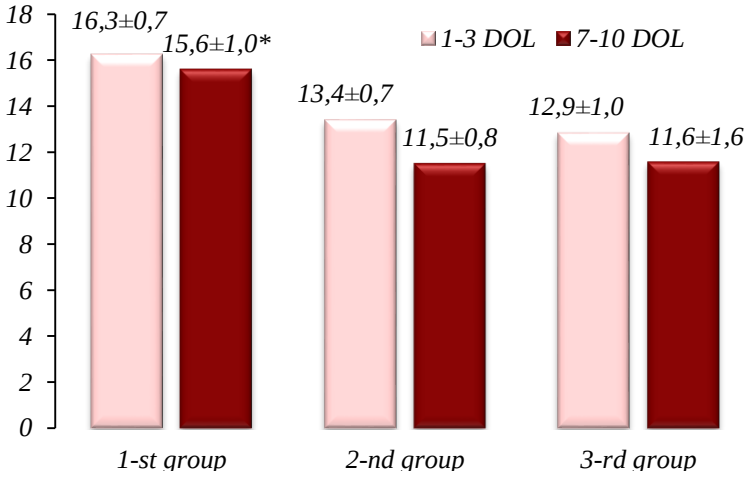
Influence of perinatal pathologies on the nature and severity of organ dysfunctions.

When analyzing the level of organospesific markers depending on gestational age the highest values of kidney injure molecule (KIM-1) in the first day of life were found in full-term infants, twice exceeding the same indicators of preterm infants, which indicates a

more pronounced nature of responses in mature children in reaction to renal tissue ischemia (1,66±0,14 ng/ml - in the 1st group vs 1,02±0,11 ng/ml – in the 2nd group və 0,84±0,13 ng/ml – in the 3 rd group, p<0,001).

Plasma concentration of L-FABP in newborns of main groups did not reliably exceed the values of control groups (p>0,05). Although we did not find reliable intergroup differences depending on gestational age, a relatively high concentration of this protein was found in full-term infants (2,69±0,41 ng/ml), and the lowest was in group of very premature infants (2,24±0,51 ng/ml) , which is apparently due to the low functional reserves of the liver in immature newborns.

Level of MUC-2 in premature infants at the first measurement has practically the same values in groups 2 and 3 and is insignificantly inferior to full-term infants' indicator. On days 7-10, difference between term and preterm babies becomes statistically significant, indicating a low reparative capacity of intestinal barrier in premature newborns (p=0,05) (graphic 3).



Note: *- p<0.01 – reliability of difference between 1st and 2nd groups

Graphic 3. Mucin-2 level in compared groups.

In contrast to secretory mucins, expression of intestinal trefoil factor in the first days of neonatal period both in term and preterm newborns significantly exceeds the same indices of healthy newborns ($p<0,05$). In dynamics, level of this marker decreases in all three groups, while remaining above the indicators of control groups. Days 1-3 are characterized by dominance of this indicator in the group of very preterm babies, where ITF significantly exceeded the values of not only the same indicator of term babies, but also newborns included in 2nd group (33,0±5,5 ng/ml – in the 3rd group, 25,8±4,2 ng/ml – in the 1st və 19,1±1,8 ng/ml – in the 2nd group, $p<0,05$)

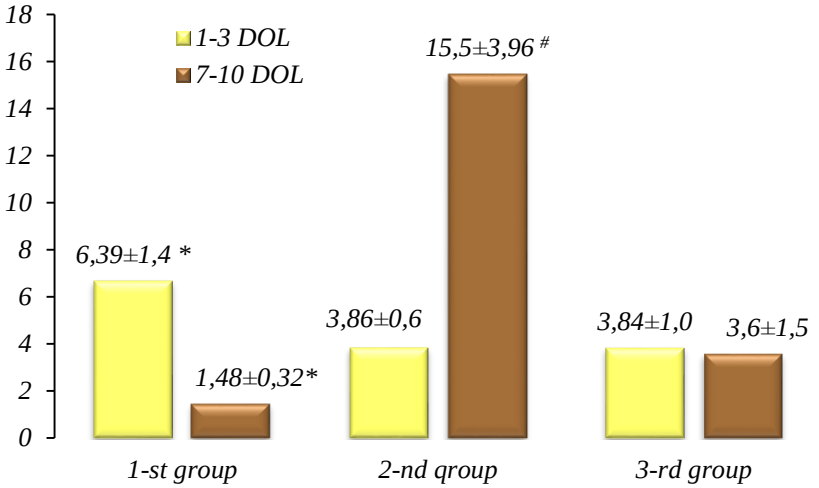
The highest I-FABP level at the beginning of the perinatal period is observed in term newborns, which is associated, apparently, with the ability of mature enterocytes to produce this protein. In dynamics, level of this indicator in full-term newborns decreasing by 3,7 times does not differ from indicators of healthy newborns (1,48 ±0,32 ng/ml vs 2,95±0,33 ng/ml).

In group 2, content of this protein increases sharply (15,49±3,96 ng/ml), significantly differing from indicator of the first days and at the same time IFABP of the group 2 of 7-10 days reliably differs in comparison with corresponding indicator of 1st and 3rd groups (graphic 4).

In comparison with the level of organ-specific markers, depending on the correspondence of body weight to gestational age, the most pronounced increase in NSE value was found in the SGA subgroup of very preterm infants compared with the level of this marker in the AGA subgroup ($p = 0,008$) (graphic 5).

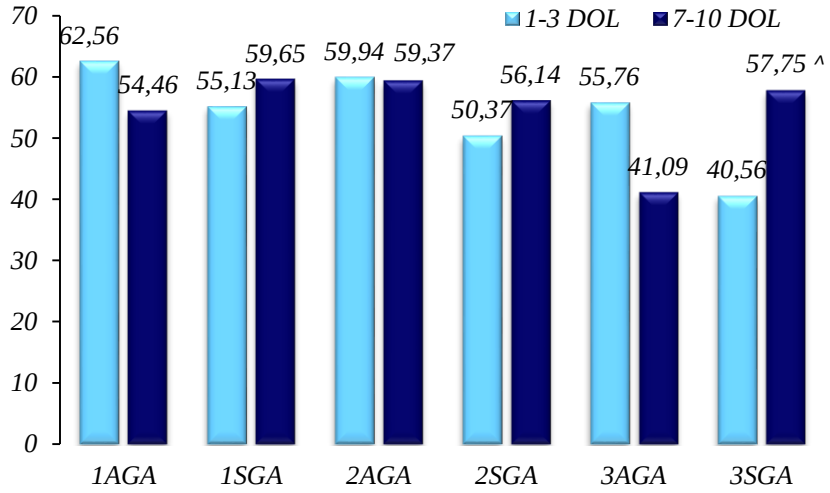
When assessing the state of kidneys, KIM-1 concentration in AGA subgroup of group 1 reliably exceed indicators of SGA newborns on the first day of life (2,06±0,2 ng/ml compare to 1,19±0,14 ng/ml, $p=0,002$).

In dynamics, level of this marker in AGA newborns sharply decreases, while in newborns SGA it remains at high levels (1,97 ng/ml), statistically reliably exceeding the values of AGA subgroup (0,7±0,076 ng/ml, $p < 0,001$).



*- p<0.05 – reliability of difference between 1 and 2 groups
- p<0.05 – reliability of difference between 2nd and 3rd groups

Graphic 4. Serum IFABP level in compared groups



^- reliability of difference between the subgroups of group 3

Graphic 5. NSE level in subgroups of main group.

Analysis of the level of plasma and urinary lipocalin concentrations between AGA and SGA subgroups showed that days 1-3 are characterized by significantly high level of plasma lipocalin concentration in AGA subgroup compared to SGA subgroup (177±40,6 ng/ml – SGA subgroup vs 80,7±41,9 ng/ml – AGA subgroup, p=0,012), while by days 7-10 plasma concentration of this substance increases in 2.5 times in SGA subgroup (168,0±33,7 ng/ml, p=0,05), slightly exceeding the indicators of AGA newborns. In the second group, at the first measurement, lipocalin level in SGA subgroup blood is lower, and in the second measurement, the value of this marker significantly increases (p=0,05), it becomes higher than the indices of AGA subgroup newborns in absence of significant difference between subgroups (p=0,89). An increase in the concentration of markers of kidney damage in the dynamics of the early neonatal period indicates a high sensitivity and vulnerability of the tubular apparatus of the kidneys of newborns small for gestational age, which is apparently due to an insufficient number of cortical nephrons and the inability of immature kidneys to quickly adapt to increased metabolic loads of postnatal ontogenesis.

The level of LFABP in urine in the SGA subgroup of the 1st group is tenfold, and in the 2nd group it is more than two times higher than the similar indicators of AGA newborns (8,97 ± 3.31 ng/ml vs 0,83 ± 0,24 ng /ml, p = 0,63 - 1st group; 10,23 ± 3,82 ng /ml vs 4,56 ± 1,08 ng/ml, p = 0,75 - 2nd group) in the absence of statistical significance between subgroups. In group 3, the level of this marker in SGA infants, on the contrary, is not significant lower than the indicator of newborns corresponding to gestational age (12,94 ± 4,36 ng/ml - in the GBS subgroup vs 2,29 ± 0,67 ng/ml - in the SGA subgroup, p = 0,43). The dynamics of the plasma concentration of this protein (pLFABP) is characterized by a significant decrease in the SGA subgroup of term infants (p <0.05).

Statistically significant differences in respect of intestinal ischemia marker (IFABP) were found between the subgroups of group 2. In premature infants of group 2, concentration of this marker increases 2,4 times in AGA subgroup and 8,8 times in newborns small

to gestational age, with reliability of this increase in SGA subgroup (9,97±4,28 ng/ml – AGA subgroup vs 24,9±6,83 ng/ml – SGA subgroup, p=0,05). Apparently, the onset of enteral feeding against the background of immaturity of the digestive tract in newborns small for gestational age is accompanied by regional hemodynamic disorders and intestinal ischemia.

The level of the main components of mucosal secretions in newborns small to gestational age for 1-3 days of the postnatal period exceeds the level of the same indicators in the subgroup of SGA. This difference was significant in relation to mucin (20,6±0.1 ng/ml vs. 15,2±0,7 ng/ml, p=0,035) in group 1, in relation to ITF (54.1±2.8 ng/ml vs. 19.8±3.7 ng/ml, p<0.001) – in group 2. In dynamics, we observed a decrease in these indicators in newborn babies SGA (41.4 ± 8.4 ng/ml 1-3 DOL 15,7 ± 2,7 ng / ml - on 7-10 DOL). In dynamics, we observed a decrease in these indicators in newborn small for gestational age (41,4 ± 8,4 ng/ml 1-3 days, 15,7 ± 2,7 ng / ml - on 7-10 days of life, p <0.05).

Thus, chronic hypoxia is characterized by multiorgan, multifunctional disorders manifested at systemic level. Their severity depends on duration and manifestation of adverse factor impact. In absence of significant difference in relation to neurospecific markers in groups 1 and 2, dynamics of their content in group 3 indicates a delayed feature of CNS lesion in very preterm infants small to gestational age. Kidney damage in SGA newborns depends on gestational age. High values of KIM-1 and lipocalin from the first days of life in combination with increase in urinary LFABP compared to newborns corresponding to gestational age in groups 1 and 2 indicate that damage to renal tubular apparatus of kidneys is accompanied by activation of antioxidant protection. In group 3, decrease in LFABP urinary concentration with increase in renal ischemia markers demonstrates failure of compensatory mechanisms in very preterm infants small to gestational age. Characteristic feature of intestinal dysfunction in newborns SGA was depletion of protective components of mucous barrier against the background of intestinal ischemia, which was most pronounced in Group 2 of infants. Significant increase in an-

tiendotoxin protection marker in very preterm infants small for gestational age reflects severity of bacterial translocation in this group of newborns.

At the next stage, we studied influence of perinatal pathologies on feature and sequence of organ dysfunctions in newborns of main group.

It was found that low birth weight infants who are exposed to acute birth asphyxia are characterized by high detection rate of organ and systemic disorders of posthypoxic genesis. High levels of both NSE (60,86±2,6 ng/ml – asphyxia+ subgroup, 47,49±9,4 ng/ml – asphyxia- subgroup, 25,03±1,83 ng/ml – control group) and aNR2 (4,46±0,83 ng/ml – asphyxia+ subgroup, 3,06±0,45 ng/ml – asphyxia- subgroup , 1,13±0,05 ng/ml – control group) in the first days of life indicate that perinatal hypoxia initiates processes leading to increase in permeability of cell membranes, death of neurons due to necrosis and/or apoptosis, disruption of integrity of blood-brain barrier structure, and penetration into systemic circulation cerebral antigens, which stimulating the immune system to produce anti-brain antibodies.

Disorders of systemic and peripheral circulation, disturbances in absorption and delivery of oxygen to tissues, accompanying perinatal asphyxia, develop a number of pathophysiological and pathobiochemical cascades leading to secondary damage to renal parenchyma. Urinary lipocalin on the 1st-3rd day in newborns exposed to acute asphyxia is almost twice higher than the indicators of the asphyxia-subgroup (178,8±69,1 ng/ml - asphyxia + subgroup, 99,3±14,8 ng/ml - asphyxia - subgroup, p=0,05). Renal tissue damage in newborns born in a state of acute asphyxia is accompanied by stress of antioxidant protection in the renal tissue, as evidenced by an increase in the level of urinary L-FABP significantly exceeding the indicator of the control group and the asphyxia- subgroup (17,02±3,4 ng/ml - asphyxia+ subgroup vs 6,3±0,6 ng/ml - asphyxia- subgroup, p=0,046).

Involvement of gastrointestinal tract (GIT) in the pathological process is an expected result of severe hypoxic lesion. The cause of

GIT damage in newborns who have exposed asphyxia in the first minutes of life is hemodynamic disorders, including regional ones with a decrease in blood circulation in the mesenteric arteries. Intestinal ischemia and inflammatory response, as evidenced by significant increase in urinary IFABP (5,06±0,2 ng/ml – asphyxia+ subgroup vs 0,76±0,1 ng/ml – asphyxia- subgroup, $p<0,05$) and ITF (37,3±9,0 ng/ml – asphyxia+ subgroup vs 15,58±3,7 ng/ml asphyxia- subgroup, $p=0,05$), is not accompanied by compensatory increase in antiendotoxin aggression marker in group of newborns exposed to birth asphyxia.

Asphyxia of low-weight newborns is characterized by stages of development of organ pathology with early involvement of the central nervous system and kidneys in the process and delayed damage of the intestinal barrier.

Further, when studying the influence of CNS lesion feature on level and dynamics of organo-specific markers, it was found that there are high levels of neurospecific proteins in newborns of main group, which reflects destructive changes in CNS, even in absence of changes in neurosonography. High values of antibodies to NR2 (6,76±1,23ng/ml – PVL subgroup vs 3,34±0,04 ng/ml – vs subgroup without change in neurosonography, $p<0,05$) and LBP (45,54±0,91 ng/ml – PVL subgroup vs 27,72±3,06 ng/ml – subgroup without change in neurosonography, $p<0,05$) reflect a deeper and more combined feature of damage (hypoxia-ischemia, inflammation) of CNS in periventricular leukomalacia.

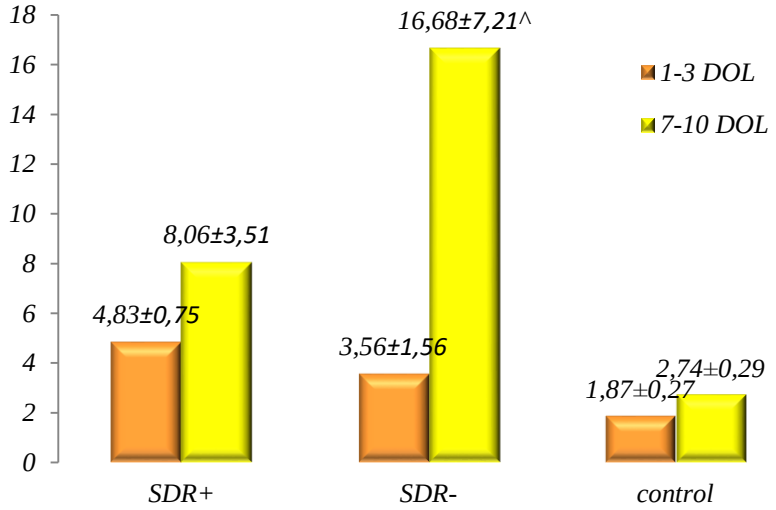
High IFABP values in newborns with hemorrhagic lesions of the central nervous system (8,01 ± 1,22 - in newborns with hemorrhagic lesions vs 2,02 ± 0,57 ng / ml - in newborns without structural changes on neurosonography, $p = 0,08$) on days 1-3 and an increase in this indicator by days 7-10 (8,47 ± 3,39 ng/ml) is apparently due to reperfusion complications in response to enteral nutrition.is apparently caused by reperfusion complications in response to enteral nutrition, intestinal colonization, and contact with bacterial components after oxygen deprivation period. High ITF level (39,12±7,62 ng/ml – in newborns with hemorrhagic lesions vs 16,7±5,3 ng/ml – in new-

borns without structural changes on neurosonography, p=0,03) in combination with low concentration of MUC2 (12,47±1,64 ng/ml - in newborns with hemorrhagic lesions vs 17,43±1,09 ng/ml - in newborns without structural changes on neurosonography, p=0,04) reflects depletion of secretory function of goblet cells in newborns with structural changes while maintaining the ITF stimulating effect on mucin production in response to inflammation. Disruption of MUC and ITF interaction reduces protective properties of mucins and regenerative potential of mucous membrane of large intestine in patients with severe damage to CNS.

In order to identify the effect of RDS on the level of organ-specific markers, newborns of the main group were divided into 2 subgroups: the 1st subgroup with the presence of respiratory distress syndrome (RDS +), the 2nd subgroup without the presence of this syndrome (RDS-). In newborns with RDS, the level of antibodies to NR2 on the first day of life (3,76±0,24 ng/ml) is higher than the values of the control group (1,13±0,05 ng/ml), but significantly lower than the values of newborns without respiratory disorders (3,76±0,24 ng/ml, $p<0,05$), despite the high frequency of cerebral hemorrhages in newborns with RDS.This appears to be due to the low immune response of the immature newborns that make up this subgroup. In dynamics, the level of this marker decreases in both subgroups of newborns, but in the subgroup of newborns without RDS, this decrease is more pronounced and is aligned with the indicator of children with respiratory disorders ($p_{1-2} = 0,044$ - for 1-3 days of life , $p_{1-2} = 0,644$ - for 7-10 days of life). The level of another neurospecific marker (NSE) at the first measurement also predominates in the subgroup of newborns without RDS. Despite the fact that the dynamics of this indicator by subgroups has a multidirectional character with an increase in the subgroup with RDS and a decrease in newborns without RDS, there were no significant differences between the subgroups (52,87 ± 4,1 ng/ml - in the 1st subgroup, 59,4 ± 3,3 ng/ml - in the 2nd subgroup, $p_{1-2} = 0,630$ - for 1-3 days of life; 61,85 ± 3,8 ng/ml - in the 1st subgroup, 56, 5 ± 5,8 ng/ml - in the 2nd subgroup, $p_{1-2} = 0,220$ - for 7-10 days of life). High values of KIM-1 in new-

borns of both subgroups on the first day of life indicate damage to the apical membrane of the proximal renal tubules, which is the zone most sensitive to the effects of damaging factors. In dynamics, the level of this marker in newborns without RDS, decreasing twofold, does not differ significantly from the indicators of the control group, while in the group of infants with RDS, persistence of hypoxia against the background of respiratory disorders maintains the ischemic state of this organ, as evidenced by there is a reliably high value of this indicator in comparison with the control group ($p < 0.05$) (1,17 ± 0,37 ng/ml - in the 1st subgroup vs 1,06 ± 0,26 ng/ml - in the 2nd subgroup, 0,98 ± 0,27 ng/ml - in the control group, $p = 0,612$ - between the 1st and 2nd subgroups for 1-3 days of life; 0,98 ± 0, 27 ng/ml - in the 1st subgroup, 0.53 ± 0.23 ng/ml - in the 2nd subgroup, 0,24 ± 0,04 ng/ml - in the control group, $p = 0,182$ - between subgroups of the main group for 7-10 days of life). At the same time, the level in the urine of the liver form of the fatty acids binds protein which reduces the processes of peroxidation under ischemia/reperfusion conditions is low in newborns with RDS in relation to the subgroup of infants without RDS (9,1±2,0 ng/ml vs 22,7±8,1 ng/ml, p=0,154 – 1-3 DOL, 7,2±1,6 ng/ml vs 13,73±4,4 ng/ml, p=0,175 – 7-10 DOL). The concentration of this protein in the blood is also characterized by a significant decrease by the end of the first week of life in newborns with RDS ($p < 0,05$) (2,31 ± 0,29 ng/ml - in the 1st subgroup, 2,66 ± 0.79 ng/ml - in the 2nd subgroup, 1,57 ± 0.08 - in the control group ng/ml, $p_{1-2} = 0,725$ - for 1-3 DOL ; 1,32 ± 0,20 ng / ml - in the 1st subgroup, 2,46 ± 0.83 ng/ml - in the 2nd subgroup, 0,86 ± 0,10 ng / ml - in the control group, $p_{1-2} = 0,269$ - for 7-10 DOL).

The I-FABP level on day 1 to 3 of life in hypoxia-exposed neonates of both subgroups is higher than that of the control group, both in plasma and in urine. The dynamic value of this marker in newborn infants with RDS increased 2-fold, but its significant rise by day 7-10 was seen in the subgroup of newborn infants without respiratory impairment ($p<0.05$), indicating significant ischemia of intestinal mucosa in this subgroup (graphic 6).

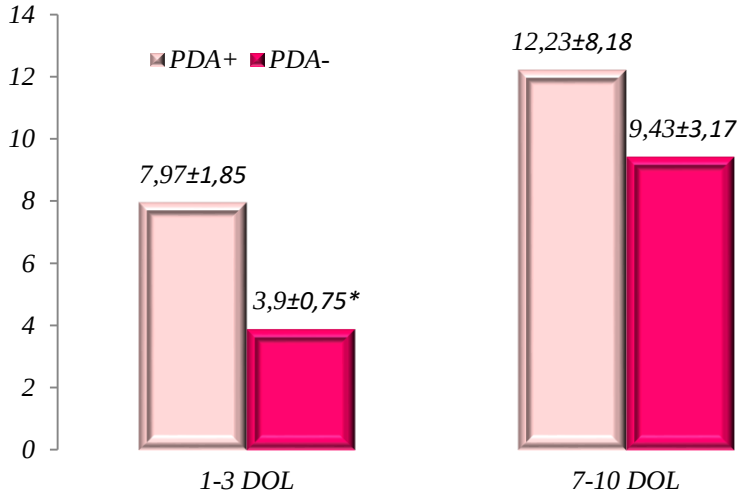


Graphic 6. Plasma IFABP concentration in newborns with respiratory distress syndrome.

A certain role in the absence of a sharp increase in İFABP, apparently, is played by the later onset of enteral nutrition in newborns with RDS due to the severity of respiratory disorders. Analysis of mucin levels (14,55 ± 1,13 ng /ml - in the 1st subgroup, 16,16 ± 1,13 ng/ml - in the 2nd subgroup, 17,6 ± 1,38 - in the control group ng/ml, p1-2 = 0,326 - for 1-3 days of life, 10.77 ± 1,6 ng/ml - in the 1st subgroup, 14,84 ± 1,36 ng /ml - in the 2nd subgroup, 15,69 ± 1,56 ng/ml - in the control group, p_{1-2} = 0,107 - for 7-10 days of life), providing the visco-elastic properties of the intestinal mucous barrier, reveals a statistically significant decrease by the end of the early neonatal period compared with the first days of life in newborns with respiratory distress syndrome ($p < 0.05$). Apparently, this is due to the rapid depletion of the goblet cells against the background of their immaturity due to the low gestational age of the newborns that make up this subgroup.

Thus, a distinctive feature of functional disorders in newborns with respiratory disorders is that these changes in this subgroup of infants occur against a background of reduced antioxidant protection, which can further aggravate damage to the structural and functional properties of cell membranes, delaying the recovery process.

Patent ductus arteriosus (PDA), "stealing" splanchnic blood flow and causing mesenteric hypoperfusion, is associated with increased risk of intestinal mucosa ischemic damage (graphic 7).



Note: *p<0,05 – reliability of difference between the subgroups

Graphic 7. Plasma IFABP concentration in newborns with PDA.

Reliably high IFABP values (p=0,03) are associated with insufficient secretory activity of goblet cells, which are manifested in a statistically significant decrease in ITF ((15,0±0,63 ng/ml – in PDA+subgroup, 35,8±4,9 ng/ml – PDA- subgroup, p=0,014).

Along with the study of the effect of open arterial flow on the functional status of organs and systems of low birth weight infants,

we also analyzed the level of organospecific markers depending on the duration of the “capillary refill time” symptom, which is an indirect marker of peripheral blood flow. Depending on the time of "capillary refill time", the newborns of the main group were divided into 3 subgroups. The first subgroup included 12 newborns with the duration of the "capillary refill time" symptom 0-3 seconds, the second subgroup - 34 newborns with the duration of the "capillary refill time" symptom 4-6 seconds, the third subgroup - 14 infants with a “capillary refilling time” duration of 7–10 seconds.

In our study, on the first day of the postnatal period, the level of NSE and antibodies to NR2 receptors in newborns 2nd (3,9 ± 0,28 ng/ml - aNR2, 114,9 ± 6,7 ng/ml - NSE) and the 3rd (3,4 ± 0,37 ng/ml - aNR2, 129,5 ± 1,5 ng/ml - NSE) subgroups slightly exceeded those of the 1st subgroup (2.8 ± 0.48 ng/ml - aNR2, 95,9 ± 17,9 ng/ml - NSE), in the absence of a significant difference ($p > 0,05$). Unlike markers of nervous system damage, the level of KIM-1, indicating acute ischemic necrosis of the renal tubules, in newborns of the 3rd subgroup significantly ($p < 0,05$) exceeds that in the 1st subgroup (0,35 ± 0,06, 0,9 ± 0,04 ng/ml - indicators of the 1st and 3rd subgroups, respectively). When assessing the level of urinary NGAL, a sensitive predictor of acute kidney injury, higher values of this substance were found in newborns of both the 2nd (180,3 ± 22,8 ng/ml) and 3rd subgroups (173,7 ± 31 , 6 ng/ml) compared with the 1st subgroup of infants (69,23 ± 15,8 ng/ml), but this difference has no statistical significance. The level of secretions of goblet cells, which form a protective mucous gel on the surface of intestinal epithelial cells, has a multidirectional character in the studied groups. Both in the 2nd (33,6 ± 5.7 ng/ml) and in the 3rd subgroup (51,3 ± 2,9 ng /ml) ITF in the first days of life has significantly high values compared to newborns 1st subgroup (12,9 ± 3,7 ng/ml, $p < 0,05$). In contrast, the level of mucin-2, decreasing by the end of the early neonatal period by 2,7 times in newborns of the 3rd subgroup (6,87 ± 2,75 ng/ml), significantly differs from the indicators of the 1st subgroup (16,20 ± 0,4 ng/ml, $p < 0,05$), which does not exclude a decrease in the regenerative potential of the intestinal mucosa in newborns with

pronounced perfusion disorders. Thus, “capillary refill time” can be used as an additional method to assess the state of individual organs and systems and to timely correct peripheral blood flow disorders in conditions of perinatal hypoxia.

Increase in the level of mesenteric ischemia (IFABP - 21,84±0,84 ng/ml – in gastrointestinal disorders subgroup vs 6,44±2,7 ng/ml – in subgroup without gastrointestinal disorders, p=0,05) marker in the group of newborns with gastrointestinal disorders is followed by tension of antiendotoxin immunity (39,1±6,4 ng/ml– in gastrointestinal disorders subgroup vs 28,8±2,1 ng/ml – in subgroup without gastrointestinal disorders, p=0,05) and absence of compensatory mechanisms of intestinal mucosa protection in the form of increase in the level of MUC-2 and ITF, which reduces protective properties of mucins and regenerative potential of colon mucosa in low birth weight newborns.

Diagnostic and prognostic significance of organ-specific markers.

To assess significance of studied markers in diagnosis of hypoxic damage to CNS, liver, kidneys and intestines, we performed ROC analysis with calculation of sensitivity, specificity and threshold value of each biomarker (table 3). When analyzing the data of ROC curves, it was found that the largest area under ROC curves in both full-term and preterm infants was established for antibodies to glutamate receptors, which indicates both diagnostic significance of this indicator and greater vulnerability of CNS in comparison with other organs in anoxic conditions. High sensitivity and specificity allows to asses this model as ideal. Balance accuracy of the diagnosis ($BAD=\frac{PPV+NPV}{2}$) when using aNR2 is 97.85. The diagnostic significance for kidney damage in term newborns was urinary lipocalin, in the group of premature infants, along with urinary lipocalin, a reliable result was also calculated for KIM-1.Concerning the intestinal damage markers, urinary IFABP, trefoil factor and mucin were reliable for term infants, and only the first two factors for preterm infants. The largest area under ROC curve was found for uFABP.

Table 3

Areas under ROC curves of studied biomarkers in venous blood serum on days 1-3 of life of preterm infants with CNS hypoxic lesions

Marker	Areas under ROC	P	DB	Susceptibility%	Susceptibility%	Sn+Sp	BAD
aNR2	0,997	<0,001	1,57	100	96,4	1,96	98,75
NSE	0,522	0,738	46,43	92,3	29,9	1,93	61,1
sIFABP	0,577	0,286	2,427	41	100	1,41	77,45
KIM-1	0,705	0,01	0,235	76,9	75,0	1,52	71,7
sLipocalin	0,587	0,217	145,7	32,6	96,4	1,29	70,75
uLipocalin	0,341	0,018	57	54,5	85,7	1,4	68,6
uFABP	0,512	0,873	8,49	41,4	100	1,41	81,3
LBP	0,937	<0,001	11,13	0,98	85,7	1,84	94,3
sIFABP	0,569	0,334	3,164	41,5	92,9	1,34	70,75
uIFABP	0,857	<0,001	0,72	83,3	100	1,83	95,15
ITF	0,703	0,01	18,35	65,4	92,9	1,58	74,55
Muc-2	0,356	0,068	11,7	44,4	92,9	1,37	81,9

For deeper understanding of functional disorder pathogenesis in low birth weight infants with hypoxic-ischemic damage to central nervous system, we performed a correlation analysis between markers of damage to CNS and peripheral organs. Mathematical and statistical assessment of relationship was conducted between the content of antibodies to NR2 measured on the first day, and KIM-1 level (r=0,33, p=0,05), plasma lipocalin concentrations (r=0,38, p=0,045) and LFABP (r=0,36, p=0,025), as well as urinary concentration of IFABP (r=0,55, p=0,036). Reliable positive dependence between these markers indicates the common pathogenetic mechanisms of development of hypoxic-ischemic lesions of neuron, epithelial cells of kidney proximal tubules, enterocytes and hepatocytes. Positive correlation between LBP level on days 1-3 and intestinal FABP on days 7-10 (r=0,51, p=0,043) does not exclude the fact that there is decrease in blood flow accompanied by intestinal ischemia under endotoxin influence. In turn, ischemic damage to intestine can cause organ damage through neutrophils' activation. Direct relationship

between IFABP and plasma lipocalin (r=0,37, p=0,03), a source of which, along with the kidneys, can also be activated neutrophils, confirms this assumption. Direct significant correlation between LBP and hepatic FABP plasma concentration (r=0,32, p=0,023), and blood creatinine in the first days of life indicates the role of endotoxin aggression in liver and kidney damage, along with hypoxia.

Thus, organ dysfunction in newborns exposed to perinatal hypoxia is caused by violation of central regulation mechanisms of peripheral organ functional status on the one hand and by endotoxin aggression on the other hand. To confirm prognostic significance of markers studied by us in perinatal pathology diagnosis, we performed regression analysis. When trying to predict periventricular leukomalacia and intraventricular hemorrhage, which are severe consequences of perinatal hypoxia, we found that a high concentration of antibodies to NR2 receptors in the first days of life is a reliable factor in PVL formation (table 4).

Table 4

Predicting periventricular leukomalacia

	B	Mean error	Vald	Asymp.	Exp (B)
aNR2 1-3 DOL	0,536	0,241	4,955	0,026	1,709
aNR2 7-10 DOL	0,295	0,305	0,938	0,333	1,344
NSE 1-3 DOL	0,063	0,048	1,732	0,188	1,065
NSE 7-10 DOL	-0,058	0,043	1,784	0,182	0,944

No statistically significant model was obtained when assessing LFABP effect measured on days 1-3 of life on aminotransferase and bilirubin fraction parameters measured on days 5-7 of life. Considering that the De Ritis ratio reflects perinatal stress effect on hepatocyte functional status better than the values of ALT and AST taken separately, we studied relationship of LFABP with this coefficient and obtained reliable regression. High LFABP values in the first days correlate with low values of De Ritis ratio indicating destabilization of hepatocyte membranes (p=0,048). When comparing predictive

significance of kidney damage markers, we found that plasma lipocalin has a significant direct relationship with creatinine level (p=0,033) and negative with albumin level (p=0,015). At the same time, we did not establish a statistically significant dependence of creatinine on urinary concentrations of lipocalin, KIM-1 and LFABP (p>0.05). High concentrations of these markers were predictive regarding renal perfusion (table 5).

Table 5

Selected biomarkers affecting renal resistance index and their regression coefficients

Independent variables	Вета	B	p-level
uLipokalin	0,359	0,002	0,018
KIM-1	0,339	0,190	0,011
мLFABP	0,322	0,005	0,033

The results of scientific studies indicate the negative effect of LPS on blood flow in renal artery by increasing the ratio of nitrites to nitrates which in turn promotes vasodilation and decrease in renal blood flow by increasing the level of nitric oxide. Taking it into account we compiled a regression model of dependence of renal artery IR on LBP level measured in the first days of life. High concentrations of lipopolysaccharide-binding protein lead to vasodilation in anterior renal artery, which probably is reflected in GFR (table 6). This can explain foregoing significant direct correlation between LBP and creatinine.

Table 6

Biomarkers affecting the renal artery resistance index and their regression coefficients

Independent variables	Вета	B	P-level
LBP, 1-3 DOL	0,679	1,432	0,05
LBP, 7-10 DOL	0,224	0,522	0,047

Another pathological condition that complicates the neonatal

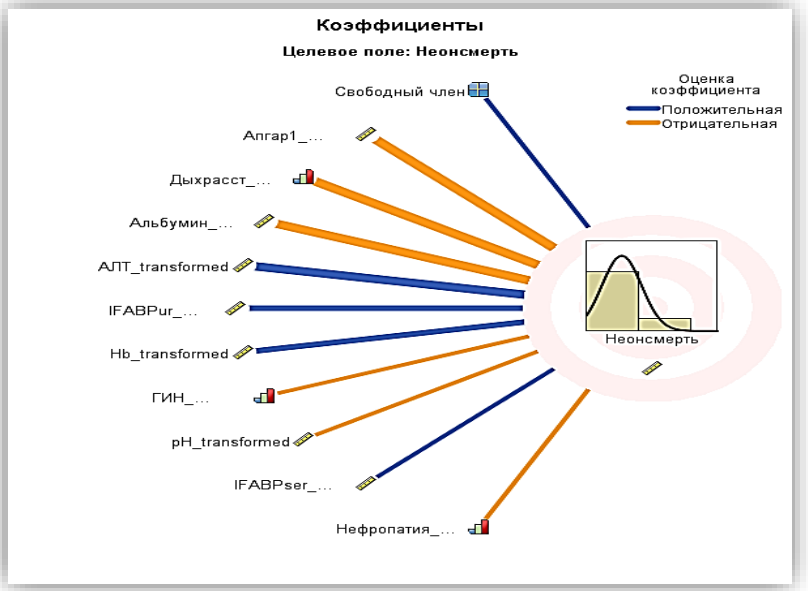
period course is necrotizing enterocolitis (NEC). Performed regression analysis revealed a positive regression between LBP measured in the first days of life and NEC (p=0,05, OR=1,03, $\chi 2$=3.5). The discovered pattern allows us to use LBP as a predictor of the development of NEC and to make a choice of tactics for the treatment of low-weight newborn children.

Fatal outcome prediction.

Analysis of infant mortality state at the present stage indicates that the greatest losses in mortality of children under 1 year of age shift into neonatal period of child's life. In a comparative analysis of the clinical and laboratory data of surviving and deceased newborns, pronounced metabolic changes were established in the form of dyslectrolythemia, hypoalbuminemia (30% in the group of survivors, 60% in the group of deceased), hypo- (30% in the group of survivors, 73% - in the group of deceased) and hyperglycemia in the group of deceased children (2% - in the group of survivors, 6% - in the group of deceased). The interpretation of the blood gas composition of these children indicates a hyperventilating variant of respiratory failure in the group of surviving children (72.73%) and a hypoxemic or parenchymal type in the group of deceased children (100%), accompanied with decreased total functional surface of alveolar-capillary membranes and expressed disturbance of ventilation-perfusion interrelations.

To predict the lethal outcome of low birth weight newborns, a regression model was built in this study. The regression model for predicting the survival of low-weight newborn infants exposed to chronic intrauterine hypoxia takes into account the combined influence of the most significant factors. When conducting a discriminant analysis with step-by-step addition of indicators that improve the quality of the model, 84 variables were analyzed, consisting of clinical, laboratory and instrumental indicators with the determination of the most significant ones affecting the differences between the aggregates. In addition to complicated course of pregnancy (preeclampsia), the factors determining the immediate unfavorable outcome include a low Apgar score at the 1^{st} and 5^{th} minutes of life. Results of

the study also confirm significant relationship between gestational age and increased risk of early neonatal death in low birth weight infants (graphic 8).



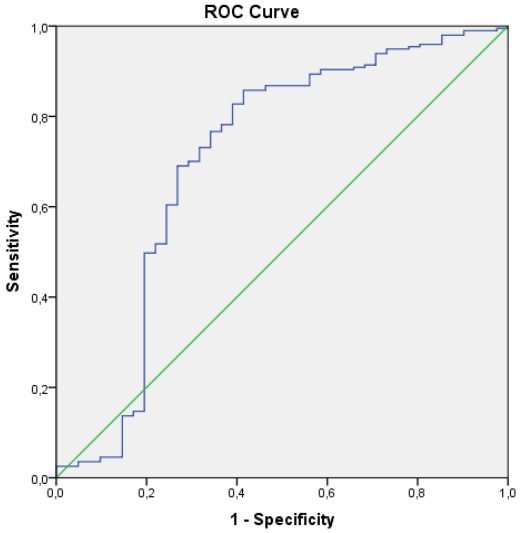
Graphic 8. Correlation dependencies selected indicators with the output variable.

Dead newborns are characterized by multiple organ lesions with a predominance of clinical manifestations of severe respiratory disorders (92,68% - in the group who died versus 17,35% - in the group who survived, p <0,001), as well as cardiovascular failure (63,41% - in the group of deaths versus 20,91% - in the group of survivors, p <0,001). The ROC data of the clinical outcome analysis in the main group indicate the possibility of using IFABP (cutoff 1,12 ng/ml) in conjunction with other clinical and laboratory data to determine the group of newborns with a fatal outcome.

To calculate the probability of death, a regression equation was compiled:

Neonatal mortality = 417.828 + 4.185 * nephropathy – 6.541 * Apgar1min + 12.695 * RDS + 0.244 * Hb + 267.24 * ALT – 2.03 * Albumin + 48.198 * pH + 3.495 * NEC + 2.613 * IFAB

After the conducted "exam", it was found that a lethal outcome is expected at values equal to or exceeding 0,65 (qrapfic 9). The accuracy of the model was 77.6%, sensitivity - 85.3%, specificity - 61%, total diagnostic weight (DC) – 81.1%.



Area	Std. Error	Asymptotic Sig.	Asymp. 95% Confidence Interval	
			Lower Bound	Upper Bound
0,704	0,055	0,000	0,597	0,811

Graphic 9. The result of the ROC analysis for the "exam".

Violation of central regulation mechanisms of vital systems against the background of hypoxic damage to CNS aggravating newborns' condition contributes to development of vicious circle with a fatal outcome. Considering the rather large load of liver and intestines for transformation and excretion of intermediate metabolic products formed under conditions of perinatal hypoxia, the defeat of

these organs cannot underestimate as factors of unfavorable outcomes of neonatal morbidity and mortality.

Prediction of pathologies of early childhood.

At present, there is no doubt that overwhelming number of pathological conditions leading to severe disablement in adulthood is formed in early ontogenesis. Along with antenatal period conditions, the 1st week of postnatal ontogenesis is defined as the first and most important critical period of individual development. In critical periods, the child's body is especially sensitive to action of stimuli unfavorable for a given period of child development, especially in case of immaturity of certain structures and/or functions, which can lead to occurrence of dysfunction of various organs and systems, forming a "vicious circle" of somatic and neurological pathology progression.

Considering the foregoing, it is of interest to study dependence of formation of neurological status and various somatic diseases on influence of unfavorable perinatal risk factors and functional status of various organs and systems. We succeeded in carrying out follow-up observation in 140 children under 3 years of age of 237 newborns in main group examined by us in neonatal period. Considering that main diagnosis of examined children was CNS perinatal hypoxic lesion, we were interested in neurological status of these children. Analysis revealed that 22 children were diagnosed by a neurologist with minimal cerebral dysfunction, 16 children with cerebral palsy, and 1 with autism. Among somatic diseases, iron deficiency anemia was detected in 27 cases, rickets in 23, hypotrophy in 15, allergic pathology in 19 children, 36 children were included in FIC Group (frequently ill children). Some of examined children suffered from several pathologies at the same time, which may be due to common nature of these conditions. 27 children constituted health group 1.

Malnutrition is a chronic eating disorder characterized by underweight in relation to height and age. Regression analysis of antenatal risk factors established a reliable effect of mother's age on possibility of hypotrophy development ($\chi 2=5.62$, OR=1.2, CI-1.035-1.443, p=0.018). When analyzing perinatal risk factors, it was found that those the most unfavorable in relation to development of malnu-

trition are low gestational age (OR=1.54, $\chi 2$=6.094, CI-0.463-0.915, p=0.014) and high frequency of respiratory therapy (OR=2.54, $\chi 2$=6.09, CI-1,333-4,863, p=0,005). Prevalence of CNS inhibition syndrome (OR=7,35, $\chi 2$=8,093, CI-1,86-29,05) and convulsive syndrome (OR=3,583, $\chi 2$=2,107, CI-0,639-20,081) in clinical picture of CNS lesions are evidence in favor of hypoxic encephalopathy severity in group of malnutrition children. Intolerance to enteral nutrition in neonatal period increased the risk of developing malnutrition in infancy by 3,5 times (OR=3,5, $\chi 2$=3,515, CI-0,945-12,966). Among organo-specific markers, a significant difference was established in relation to LFABP urinary level (p1-3<0,001, p7-10<0,001), which has low concentrations in group of newborns with subsequent development of malnutrition (1,72±0,76 ng/ml vs 25,13±2,7 ng/ml, p<0,001). Plasma concentration of this protein, which reflects antioxidant potential of liver, was also reduced in malnutrition group in neonatal period dynamics with reliable difference in the 2nd measurement (p=0,069 in the first, p=0,036 in the second measurement). When assessing the markers of intestinal epithelium integrity, it was found that IFABP plasma concentration in hypotrophic patients exceeded the same indicator of normotrophics by almost 3 times on Days 1-3 and 2 times by Days 7-10 of life (p1-3=0,06, p7-10=0,566 - difference reliability for Days 1-3 and 7-10). In comparative analysis of plasma concentration of markers produced by goblet cells of intestinal mucosa, we found a statistically significant difference in relation to mucin, which has higher values in malnutrition group (17,7±0,41 ng/ml vs 9,28±1,88 ng/ml p=0,003 - difference reliability by days 7 -10).

The next deficiency condition widespread in pediatric population is iron deficiency anemia. When analyzing antenatal anamnesis data, the mother's age was a significant risk factor (OR=1,174, $\chi 2$=5,548, CI–1.027-1,431, p=0,018), as in hypotrophy. Number of births also had reliably significant effect on development of this pathology (OR=2,219, $\chi 2$=4,736, CI – 1,082-4,551, p=0,03). SGA syndrome had a negative effect on iron absorption processes (OR=3,83, $\chi 2$=6,15, CI - 326-11,08, p=0,013). Perinatal encephalopathy, in par-

ticular, convulsive syndrome increases the risk of developing an iron deficiency state fivefold (OR=5,02, $\chi 2$=4,734, CI – 1,73-21,45, p=0,013), and CNS function inhibition - fourfold (OR=3,54, $\chi 2$=3,975, CI – 1,022-12,24, p=0,046). Intolerance to enteral nutrition played a significant role in realization of this pathology (OR=3,20, $\chi 2$=4,12, CI – 1,04-9,842, p=0,042). Possible damage to GIT in neonatal period, persisting in form of a syndrome of malabsorbtion, is accompanied by development of sideropenia in these children.

When studying the state of intestinal mucous barrier, a significant difference in mucin level was not established (p_{1-3}=0,746, p_{7-10}=1,0), with a reliably low ITF concentration on days 1-3 in the group of children with iron deficiency anemia (p1-3=0,021). Despite the low concentration of this substance in the first days after birth, its content increases almost tenfold in dynamics, unreliably exceeding the indicators of group 2 (p_{7-10}=0,408).

Trying to predict rickets, the only antenatal factor that significantly influenced the development of this pathology was the mother's age (OR = 1,14 $\chi 2$ = 4,45, CI – 1,009-1,288, p = 0,035). When assessing the neurological status in neonatal period, it was found that the risk of developing rickets is increased by CNS inhibition syndrome for 3 times (OR=3,68, $\chi 2$=3,95, CI = 1,018-13,270, p=0,047). Among biochemical parameters, the most indicative were the hepatic transferases level, which increased the risk of rickets. Mucin level in group with rickets has high values (16,98±0,61 ng/ml) reliably differing from the indicators of group without rickets on days 7-10 of life (9,28±1,88 ng/ml, p_{7-10}=0,014). Possibly, increase in the level of this component of intestinal mucosa has a compensatory character in terms of its ischemia against the background of perinatal hypoxia. One of the important risk factors for rickets development is perinatal hypoxic CNS damage. Level of neurospecific enolase in group without rickets was high (57,1±4,31 ng/ml) from the first day of life with reliable significant difference from indicator of children with rickets (37,3±9,13 ng/ml, p_{1-3}=0,054). In dynamics on days 7-10, the level of this marker in the group of children with rickets increases almost

twofold (60,95±1,3 ng/ml) and reliably differs from the indicator of days 1-3 of life ($p<0,05$), and intergroup difference in relation to NSE disappears ($p_{7-10}=0,353$). The delayed nature of this protein increase in the group of children with rickets does not exclude an increase in permeability of blood-brain barrier and secondary energy disorders against the background of post-ischemic reperfusion.

Due to significant prevalence of allergic diseases in children, the problem of early prediction and prevention of allergic pathology is becoming more urgent. Analysis of medical and biological history of examined children's groups in our study showed that among the antenatal factors BOH (OR=4 $\chi 2$=4,795, CI – 1,157-13.834, p=0,029), and number of births (OR=2,23 $\chi 2$=4.501, CI – 1,063-4,761, p=0,034) have reliable value in atopy development among antenatal risk factors.

In our study, convulsive syndrome increased the risk of developing this pathology by 5 times (OR=5,12 $\chi 2$=4,246, CI – 1,083-24,20, p=0,03). During comparative analysis of neurospecific markers, there is no statistically significant difference in NSE level in compared groups ($p_{1-3}=0,46$, $p_{7-10}=0,42$ - reliability of difference at Days 1-3 and 7-10 of life. Discrepancy of the level of neuroimmunochemical markers to severity CNS damage may indicate a violation of regulation processes of molecular homeostasis in brain tissue against the background of failure of protective function of innate immunity. Immaturity of immunity in group of children with allergies is also indicated by reliably low level of plasma (34,33±2,35 ng/ml vs 87,67±9,88 ng/ml, p=0,004) and urinary (5,5±1,64 ng/ml vs 51,6±11,87 ng/ml, p=0,001) concentration of lipocalin compared with the level of that in a group of children without atopy. Low level of this substance with a high concentration of KIM-1 testifies in favor of decrease in renoprotective properties ($p_{1-3}=0,175$, $p_{7-10}=0,073$). Intestinal FABP concentration on days 1-3 of life prevailed in group with atopy almost threefold and had statistical reliable difference from group without atopy indicator (7,31±2,58 ng/ml vs 2,24±0,59 ng/ml, $p_{1-3} = 0,03$). Damage to intestinal barrier integrity was accompanied by active secretion of goblet cells in newborns of group with

atopy, as indicated by high values of mucin-2 and intestinal trefoil factor. Significant increase was found in relation to mucin, both on days 1-3 and 7-10 of life (p1-3=0,002, p7-10=0,004).

Trying to predict the frequent illness of children, as is one of the most debated problems in pediatrics, it was found that among obstetric history data, the risk factors were BOH (OR=2,5 $\chi 2$=2,71, CI – 0,842-7,285, p=0,1), number of pregnancies (OR=1,4 $\chi 2$=3,98, CI – 1,006-2,058, p=0,046) and childbirth (OR=2,5 $\chi 2$=2,71, CI – 0,842-7,285, p=0,1).

Mean urinary lipocalin level in frequently ill children group (FIC) was reliably lower both on days 1-3 and 7-10 (9,63±3,54 ng/ml – in group FIC vs 51,6±11,87 ng/ml – in group of episodically ill children, p_{1-3}=0,001, 9,25±2,32 ng/ml — in group FIC vs 43,29±8,76 ng/ml – in group of episodically ill children, p_{7-10} =0,001), it indicates the safety of their renal tubules. Despite the fact that lipocalin is synthesized by epithelial cells, hepatocytes, and renal tubules cells, neutrophils are main cellular source of plasma lipocalin. Lipocalin more reliably than myeloperoxidase and lactoferrin reflects neutrophil activation, and its low values may reflect defect in neutrophil chemotaxis and degranulation in response to inflammatory stimuli.

Low content of this substance in acute period of disease has a protective nature preventing neutrophilic infiltration of organs and tissues. However, decrease in this marker in FIC group indicates that low lipocalin values reflect failure of immune responses starting from the first days of postnatal life. Plasma (p1-3=0.003 p7-10=0.428) and urinary concentration of LFABP (p1-3=0.001 p7-10=0.003) in newborns constituting FIC group are lower than those of newborns included in episodically ill children group. Given that synthesis of this protein also occurs by macrophages, its low level may indicate immaturity of macrophage-monocyte system.

Until now, there is no unified conceptual theory about specific causes of infantile cerebral paralysis (CP) formation, as this disease actually always has a polyetiological nature of development. When analyzing anamnestic data, it was revealed that significant factors triggering realization of this condition were mother's age (OR=1,093

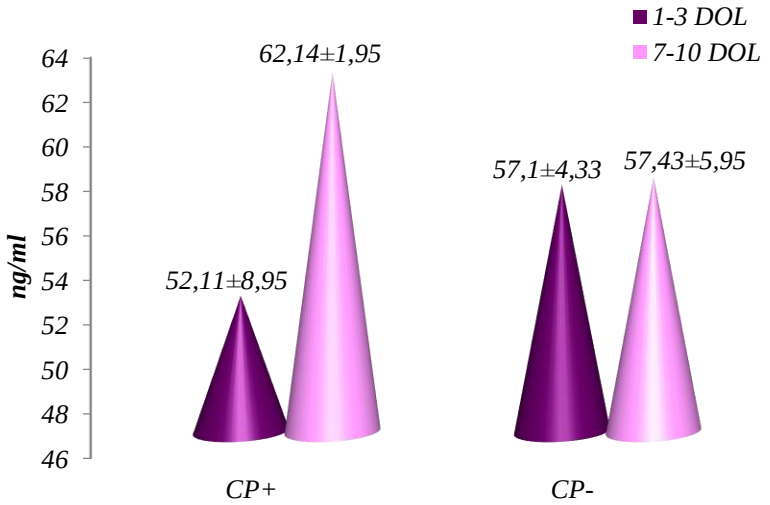
$\chi 2$=9,12, CI – 1,093-1,521, p=0,003), number of pregnancies (OR=1,5 $\chi 2$=4,25, CI – 1,020-2,201, p=0,039) and childbirth (OR=1,93 $\chi 2$=4,45, CI – 1,048-3,571, p=0,035). Literary information on influence of the number of births and pregnancies on the risk of this pathology formation is contradictory. Our data coincide with the results of Srinivasa SR et al, indicating that cerebral palsy is more often detected in children from the third and subsequent pregnancies. A short intergenitic interval plays certain role in this situation.

Among the factors of perinatal risk, a certain contribution to infantile cerebral paralysis development was made by low gestational age (OR=1,36 $\chi 2$=4,49, CI – 0,555-0,977, p=0,034), and birth weight (OR=1,0 $\chi 2$=4,04, CI – 0,997-1,000, p=0,045). Risk factors were also a high frequency of hypoxia attacks (OR=3,75 $\chi 2$=3,27, CI – 0,898-15,65, p=0,07) and, accordingly, the need for respiratory therapy OR=2,04.0 $\chi 2$=5,23, CI – 1,107-3,748, p=0,022). When assessing CNS state in the group of children with CP, it was found that syndrome of inhibition increases possibility of developing this pathology 3.8 times (OR=3,82 $\chi 2$=3,49, CI – 0,936-15,579, p=0,06), and convulsive syndrome increases this possibility 4.8 times (OR=4,78 $\chi 2$=3,545, CI – 0,938-24,336, p=0,06).

When studying the level of neurospecific markers, it was found that in absence of a reliable difference between the level of aNR2 in the studied groups (p_{1-3}=0,137, p_{7-10}=0,107 - reliability of difference at Days 1-3 and 7-10 of life), concentration of this marker in newborns with subsequent development of cerebral palsy increases in the dynamics of early neonatal period (4,34±0,51 ng/ml, 1-3 DOL, 4. 62±0,69 ng/ml, 7-10 DOL) while the opposite tendency is observed in group of favorable neurological outcome (4,34±0,51 ng/ml 1-3 DOL, 4, 62±0,69 ng/ml 7-10 DOL).

The average value of a marker of damage to neuronal nature cells, NSE, in neonatal period in blood serum of children with cerebral palsy did not significantly exceed the level in children of comparing group (p<0,05) (graphic 10). It is known that one of the factors affecting white substance of CNS is lipopolysaccharide or endotoxin. Damaging effect of this substance on nervous system is real-

ized by increasing production of cytokines and initiation of inflammation in nervous tissue due to endothelial dysfunction. Systemic endotoxinemia origin may be associated with translocation of gram-negative bacteria from intestine into bloodstream against the background of intestinal ischemia or transient disbacteriosis. Intestinal ischemia marker in newborns with subsequent development of cerebral palsy is 2 times higher than that in comparison group (14,09±0,595 ng/ml – CP+ group vs, 6,0±4.49 ng/ml – CP- group, p=0,38).



Graphic 10. Plasma NSE concentration in neonatal period of compared group.

At the same time, lipopolysaccharide-binding protein level in the group of newborns with cerebral palsy does not differ reliably from that in group of newborns with favorable neurological outcome without (37,41±5,96 ng/ml – CP+ group vs 36,84±4,13 ng/ml– CP- group, p = 0,942). Thus, formation of symptom complex of infantile cerebral palsy is facilitated by a combination of the following perina-

tal factors that have the greatest prognostic significance: maternal age, frequent pregnancies and childbirth, gestational age, birth weight, hypoxia attacks requiring respiratory therapy, and perinatal encephalopathy severity. Absence of a significant intergroup difference in neurospecific marker content indicates their diagnostic value only in the acute period of disease, in absence of significance for prognosis of child's distant psychomotor development. Relatively high values of intestinal ischemia and mucin marker in newborns with unfavorable neurological outcome does not exclude the role of intestinal permeability in formation of this severe pathology.

Thus, older maternal age, frequent pregnancies and childbirth, a high need for respiratory therapy, and perinatal hypoxic damage to CNS are the most common predictors of adverse somatic and neurological outcomes. Reliably low values of lipocalin and LFABP reflecting the inadequacy in immune responses and a deficiency of antioxidant potential with severity of perinatal pathologies in newborns with deviations in neurological and somatic status at subsequent stages of ontogenesis, indicate the role of immaturity in the implementation of pathological conditions in early childhood age.

FINDINGS

1. A burdened obstetric history, as well as a complicated course of pregnancy can be identified as risk factors for disadaptation of certain organs and systems in early postnatal ontogenesis. Damage to central nervous system did not depend on the causes of chronic intrauterine hypoxia. Analysis of markers, reflecting the functional status of peripheral organs, demonstrate the greatest sensitivity of kidneys of newborns born to mother with preeclampsia (KIM-1 1,27±0,13 ng/ml vs 0,49±0,06 ng/ml, $p<0,001$), anemia (lipocalin 181,2±10,9 ng/ml vs 85,8±5,4 ng/ml, $p<0,001$) and threatened abortion (lipocalin 212,4±6,8 ng/ml vs 151,6±14,7 ng/ml, $p<0,01$). A significant increase in LFABP concentration (2,55±0,42 ng/ml vs 1,51±0,31 ng/ml, $p=0,02$) reflects a compensatory increase in antioxidant poten-

tial of newborns' liver in response to negative effects of anemia and preeclampsia [9,15,20].

2. Intensity of responses from peripheral organs in chronic intrauterine hypoxia depends on newborns' gestational age. Despite the severity of perinatal pathologies, the level of renal and intestinal ischemia markers (IFABP and KIM-1) in the group of very premature infants is lower than in mature children (KIM-1 0,84±0,12 ng/ml vs 1,66±0,135 ng/ml, p<0,001, İFABP 3,6±1,5 ng/ml vs 15,49±3,96, p<0,001) [32, 33].
3. Prolonged nature of intrauterine hypoxia was reflected in the nature of organ dysfunctions in newborns small for gestational age. With reliably high values of markers reflecting damage to nervous system (NSE), kidney (KIM-1) and intestine (IFABP), there is a rapid depletion of antioxidant potential of liver and kidneys (LFABP 2,5±0,65 ng/ml – 1-3 DOL, 1,3±0,3 ng/ml – 7-10 DOL, p<0,05) and inhibition of protective function of intestinal goblet cells (ITF 41,4±8,4 ng/ml – 1-3 DOL, 15,7±2,7 ng/ml – 7-10 DOL, p<0,05) [4, 21, 28].
4. In newborns with hemorrhagic nature of CNS lesion, a statistically significant increase in ITF (39,12±7,62 ng/ml, p=0,03) and IFABP (8,47±3,39 ng/ml, p=0,026) demonstrates a compensatory increase in protective properties of intestinal mucosa against the background of intestinal ischemia. Statistically reliable increase in aNR2 (6,76±1,23 ng/ml, p=0,04) and LBP level (45,54±0,91 ng/ml, p=0,001), as well as decrease in MUC2 (12,47±1,64 ng/ml, p=0,038) in newborns with ischemic nature (PVL) of CNS damage reflects decrease in protective capabilities of intestinal mucous barrier with increase in endotoxin aggression against the background of NMDA receptor destruction [12, 34].
5. Low level of urinary LFABP (9,1±2,0 ng/ml vs 22,7±8,1 ng/ml, p=0,05) and sharp decrease in LFABP (2,31±0,29 ng/ml – 1-3 DOL vs 1,32±0,2 ng/ml – 7-10 DOL, p=0,05) and MUC-2 (14,44 ng/ml - 1-3 DOL vs 10,77±1,6 ng/ml – 7-10 DOL, p=0,05) in peripheral blood samples in the course of early neo-

natal period in newborns with RDS, indicates deficiency of intracellular antioxidant pool and compromised of intestinal mucous barrier along with immaturity of surfactant system of the .

6. High levels of IFABP in peripheral blood (12,23±8,18 ng/ml vs 7,97±1,85 ng/ml, p=0,031) and urine with low levels of intestinal trefoil factor (15,0±6,3 ng/ml vs 27,4±4,9 ng/ml, p=0,014) indicates a high risk of gastrointestinal disorders in newborns with hemodynamically significant patent ductus arteriosus [18].
7. Antiendotoxin immunity tension from the first days of life in newborns with NEC (LBP 39,1±6,4 ng/ml vs 28,8±2,1 ng/ml, p=0,05) is followed by increase in mesenteric ischemia marker in absence of activation of compensatory defense mechanisms of intestinal mucous barrier (MUC-2 14,84 ng/ml vs 10,77 ng/ml, p=0,61), which reduces regenerative potential of colon mucosa in small birth weight newborns with perinatal CNS damage [24,41].
8. Statistically significant positive correlation liver, kidney, intestinal damage marker's with antibodies to NR2 receptors and LBP ($p<0,05$) demonstrates that organ dysfunction in newborns exposed to perinatal hypoxia is caused by violation of central regulation mechanisms of peripheral organ functional status on the one hand, and endotoxin aggression on the other hand [31].
9. Reliably low LBP values (28,16±2,59 ng/ml vs 32,55±2,6 ng/ml, $p<0,05$) and high values of intestinal ischemia marker (IFABP 2,45±0,71 ng/ml vs 1,0±0,12 ng/ml, $p<0,05$) in blood and urine in the first days of life in infants with lethal outcome as compared with survived children indicate the role of endotoxin aggression in development of the unfavorable outcome development [10, 14].
10. Low birth weight newborns with perinatal hypoxic encephalopathy are in risk group for development of severe neurological and somatic pathology. The most significant risk factors for formation of pathology in infancy and early childhood are burdened obstetric history, frequent childbirth with short interge-

netic interval. Thus, frequent childbirth increases the risk of developing IDA and atopy by 2,2 times, infantile cerebral palsy by 1,9 times. Fetal growth restriction also increases risk of developing iron deficiency condition (OR=3,8). Burdened obstetric history 4 times increases the risk of developing allergic diseases.

11. Low gestational age, severity of CNS damage, and dependence on respiratory therapy are unfavorable risk factors of the neonatal period. Low gestational age affects possibility of developing postnatal malnutrition (OR=1,5) and CP (OR=1,36). Inhibition of CNS function syndrome increases the risk of developing CP (OR=3,8), malnutrition (OR=7,35), IDA (OR=3,5), rickets (OR =3,68), frequent respiratory infection (OR=5,2). Convulsive syndrome is a risk factor for development of CP (OR=4,8) and allergies (OR=5,12). Dependence on respiratory therapy in neonatal period increases risk of malnutrition by 2,5 times, FIC – 1,8 times [45].
12. High values of intestinal ischemia marker (IFABP), increased production of goblet cells (MUC-2 17,7±0,41ng/ml vs 9,28±1,88 ng/ml, p=0,003) in combination with low plasma (0,78±0,18 ng/ml vs1,86 ±0,41 ng/ml, p=0,036) and urinary concentrations of LFABP reflecting the antioxidant potential of liver and kidneys in neonatal period is associated with the development of deficient and atopy states at subsequent stages of formation these children [43].

PRACTICAL RECOMMENDATIONS

1. In low birth weight infants at different gestational ages exposed to perinatal hypoxia, serum level of antibodies to NR2 receptors can be used as early diagnostic criteria for CNS damage (DP-2,13 ng/ml - for full-term, 1,75 ng/ml - for preterm newborns), for kidney damage - level of urinary lipocalin (DP-62.85 ng/ml - for term, 57 ng/ml - for preterm newborns) and KIM-1 (DP-0.24 ng/ml - for preterm newborns), for intestinal

damage barrier - level of urinary IFABP (DP-0.941 ng/ml - for term, 0.72 ng/ml - for preterm newborns), ITF (DP-21.35 ng/ml - for full-term, 18.35 - for preterm newborns) and MUC-2 (DP-20.9 ng/ml - for term newborns).

2. Predicting periventricular leukomalacia from the first days of life based on a level of neurospecific marker (aNR2) will identify a high-risk group for the development of this pathology with Doppler monitoring of cerebral blood flow and with an early start of rehabilitation measures.
3. In consideration of high sensitivity of kidneys to perinatal risk factors (threatened miscarriage, anemia, preeclampsia, birth asphyxia), avoid polypharmacy and prescription of nephrotoxic drugs, intensively control water-salt metabolism and acid-base state, excretory function of the kidneys, observe the regimens of infusion therapy with correction of hypovolemia and prevention of hypervolemia.
4. In preterm infants exposed to perinatal hypoxia, based on the level of lipopolysaccharide-binding protein (LBP), early prediction of necrotizing enterocolitis is possible with a differentiated approach to the feeding regimen and the appointment of antibiotic therapy from the first days of life.
5. The model created by us will make it possible to predict mortality in low birth weight infants with hypoxic lesions of CNS and to intensify monitoring of newborns at risk for death with timely correction of critical conditions.
6. The capillary refill time can be used as a noninvasive informative method to assess the condition of individual organs and systems with timely correction of peripheral blood flow disorders
7. To minimize disabling consequences of perinatal pathology and improve quality of life of low birth weight newborns with hypoxic lesions of CNS, it is necessary outpatient observation with arrangement of complex and differentiated rehabilitation taking into account predicted outcome with participation of highly qualified medical staff.

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LIST OF ABBREVIATIONS

AGA – appropriate for gestational age
ALT – Alanine Aminotransferase
AST – Aspartate Aminotransferase
BOH – burdened obstetric history
CNS – central nervous system
CP – cerebral palsy
DOL – day of life
IDA – Iron Deficiency Anemia
EchoKG – echocardiography
FIC – frequently ill children
GFR – glomerular filtration rate
GIT – gastro-intestinal tract
IFABP – intestinal fatty acid binding protein
ITF – intestinal trefoil factor
KİM-1 – kidney injury molecule
LBP – lipopolysaccharide binding protein
LFABP – liver fatty acid binding protein
LPS – lipopolysaccharide
MUC – mucin
NEC – necrotizing enterocolitis
NMDA – N-metil D-aspartat receptor
NSE – neuron-specific enolase
OR – Odds Ratio
PDA – patent ductus arteriosus
PVL – periventricular leukomalacia
SGA – small for gestational age
RDS – respiratory distress syndrome
TM – threatened micarriage
TORCH – a syndrome that combines a number of specific infections

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