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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

THE EARLY DIAGNOSTICS AND THE PROGNOSIS OF ISCHEMIC NEPHROPATHY IN LOW BIRTH WEIGHT INFANTS

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GENERAL DESCRIPTION OF WORK

Relevance. The pathology of low birth weight infants has a large share in the structure of the causes of perinatal morbidity and mortality[1], whereas reproductive losses and the costs of complex treatment of such children cause significant social injury and economic disbenefit[2,3]. According to WHO, the number of children with low birth weight, including newborns with developmental delay, ranges from 6.5% in developed European countries to 31.1% in Central Asia[4].

At the same time, low birth weight newborns present a significant problem, since events related to intrauterine development of the fetus make themselves known decades later[5]. Many pathological factors affecting the child in the perinatal period, directly or indirectly, impair the function of the kidneys in the newborn. The reduction of regional blood flow leads to a decrease in renal perfusion, which, against the background of functional immaturity of the renal tissue at the time of birth, causes the early development of ischemic nephropathy (IN) in newborns[6].

However, the absence of noticeable signs of nephropathy in newborns in the first days of life, due to their nonspecificity, veiled by the anatomical and physiological features of the kidneys, the severity of neurological symptoms cause significant difficulties for

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[1]*Khalid, M., Andreoli, S.P.* Kidney injury in the neonate. In: Oh W., Baum M., eds. Nephrology and Fluid/Electrolyte Physiology: Neonatology Questions and Controversies. 3rd Ed. Philadelphia: Elsevier, – 2019. – p. 291-314.

[2]*Lei, C.* Effectiveness and renal functions safety of treatments used for neonates with patent ductus arteriosus: a prospective cohort study / C.Lei, H.Liu, H.Wang [et al.] // Med. Sci. Monit., – 2019. May, 17. 25, – p. 3668-3675. doi:10.12659/MSM.914181.

[3]*Jetton, J.G., Sorenson, M.* Pharmacological management of acute kidney injury and chronic kidney disease in neonates // Semin Fetal Neonatal. Med., – 2017. Apr. 22 (2), – p. 109-115.

[4]*BO3, 2021.* https://www.who.int/maternal_child_adolescent/topics/newborn/care_of_preterm/ru/

[5]*Ольхова, Е.Б.* Острая почечная недостаточность у новорожденных // Ультразвуковая и функциональная диагностика, – 2004. № 4, – с. 30-41.

[6]*Nada, A., Bonachea, E.M., Askenazi, D.J.* Acute kidney injury in the fetus and neonate // Semin Fetal Neonatal. Med., – 2017. Apr. 22 (2), – p. 90-97.

the early diagnosis of renal pathology in the neonatal period, and in the absence of timely and adequate therapy, they contribute to the chronicity of the process or can be fatal[7]. In this regard, the search for new, more informative diagnostic markers indicating the development of pathological processes in the renal tissue at the preclinical stage is a relevant issue.

In recent years, a number of studies have been carried out to determine the most informative markers of the kidney, and, in particular, the tubular apparatus[8].

KIM-1 (Kidney Injure Molecule) is a kidney injury molecule, a transmembrane glycoprotein that is not detected in the urine of a healthy kidney, but is synthesized by the epithelial cells of the proximal tubules in a very high concentration after ischemic damage, persisting until the tubular function is fully restored[9].

NGAL is a neutrophilic gelatinase-associated lipocalin. Expressed into plasma by many organs when damaged, such as the lungs and liver, but an early and sharp rise in urine and serum NGAL levels is observed with tubular injury associated with ischemia in acute renal failure (ARF) due to acute tubular necrosis or tubulo-interstitial nephropathy[10].

Plasma NGAL is freely filtered by glomeruli. A decrease in glomerular filtration as a result of renal pathology leads to the accumulation of NGAL in the systemic circulation.

Serum cystatin C is a low molecular weight endogenous inhibitor

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[7]*Chaturvedi, S., Ng, K.H., Mammen, C.* The path to chronic kidney disease following acute kidney injury: a neonatal perspective // Pediatr. Nephrol., – 2017. Feb. 32 (2), – p. 227-241.

[8]*Stojanovic, V.D.* Urinary kidney injury molecule-1 rapid test predicts acute kidney injury in extremely low-birth-weight neonates / V.D.Stojanovic, N.A.Barisic, N.M.Vuckovic [et al.] // Pediatr. Res., – 2015. 78 (4), – p. 430-435.

[9]*Mehmet, Y.O.* Urinary markers of acute kidney injury in newnorns with perinatal asphyxia. / M.Y.Oncel, F.E.Canpolat, S.Arayici [et al.] // Journal of Renal Failure. – 2016. 38 (6), – p. 882-888.

[10]*Liao, B.* Evaluation of a diagnostic test of serum neutrophil gelatinase-associated lipocalin (NGAL) and urine KIM-1 in contrast-induced nephropathy (CIN) / B.Liao, W.Nian, A.Xi [et al.] // Med Sci. Monit., – 2019. Jan; 19. 25, – p. 565-570. doi:10.12659/MSM.912569.

of cysteine proteinase. The synthesis of this substance does not depend on the metabolic processes of the body due to the fact that it does not participate in the metabolism of substances. Based on the above, serum cystatin C, in contrast to serum creatinine, can be called an almost ideal endogenous biomarker of renal function[11, 12].

The above markers were studied mainly in the adult population, with the exception of a few studies carried out in newborns. There are no scientific studies related to diagnosing the risk of ischemic nephropathy in the early adaptation period in low birth weight infants, and assessing the severity level using the above markers in combination.

Object of study. Low birth weight (LBW) newborns (birth weight less than 2500 g), regardless of the degree of maturity, the presence or absence of clinical signs of post-hypoxic disorders of the urinary system.

Purpose of the study – to reveal the clinical and laboratory features of hypoxic-ischemic kidney damage in low birth weight infants with the determination of the most informative diagnostic and prognostic markers.

Research objectives:

1. To identify the most significant pre- and perinatal risk factors for hypoxic-ischemic kidney damage in low birth weight infants.
2. To develop specific preclinical markers of hypoxic-ischemic kidney damage in the blood and the urine in low birth weight infants, and based on the determination of their level, to establish the degree of ischemic nephropathy.
3. To determine the clinical significance of KIM-1 and NGAL in the urine and Cystatine C in the serum, in the case of ischemic nephropathy in low birth weight infants corresponding to the

[11] *Chen, D.* Serum cystatin C: A potential predictor for hospital-acquired acute kidney injury in patients with acute exacerbation of COPD / D.Chen, C.Cao, L.Jiang [et al.] // Respir. Dis., – 2020. Jan-Dec. 17, – 1479973120940677. doi:10.1177/1479973120940677.

[12] *Li, Y.* Urine interleukin-18 and cystatin-C as biomarkers of acute kidney injury in critically ill neonates / Y.Li, C.Fu, X.Zhou [et al.] // Pediatr. Nephrol., – 2012. 27 (5), – p. 851-860.

gestational age and newborns with intrauterine growth retardation.

4. To reveal the correlation dependence between the state of renal hemodynamics according to the results of the Doppler ultrasound examination and the markers of renal damage.

5. Predict the course and the outcome of ischemic nephropathy in low birth weight infants in the early neonatal period.

Research methods. All children underwent clinical, functional and biochemical research methods. Along with the generally accepted methods for assessing renal function in the urine, biomarkers of renal tubular apparatus damage KIM-1 and NGAL, and Cystatine-C in the blood plasma were determined. All newborns were examined for the presence of TORCH infections by an enzyme-linked immunosorbent assay. Instrumental research methods included: neurosonography, ultrasound of the abdominal organs, echocardiography.

The main provisions of the dissertation submitted for discussion:

– A history of chronic pyelonephritis in the mother and its exacerbation during pregnancy, placental insufficiency and preeclampsia, threatened abortion, cerebral ischemia of the 2^{nd} - 3^{rd} degree are the most significant pre- and perinatal risk factors contributing to the development of IN in LBW newborns.

– The increase in the levels of kidney damage biomarkers KIM-1 and NGAL in the urine in the first days of life is an early diagnostic and prognostic marker of ischemic nephropathy.

– In newborns with IUGR, there is a significant increase in KIM-1 and NGAL in the urine compared to newborns appropriate for their gestational age, at all degrees of IN.

– The severity of ischemic nephropathy is determined by the severity and the duration of hypoperfusion and renal hemodynamic disorders.

Scientific novelty of the research.

– Leading maternal and neonatal risk factors for the development of ischemic nephropathy have been identified in low birth weight infants.

– The influence of the pathogenetic mechanisms of IN on early

neonatal adaptation of low birth weight infants have been studied.

− The earliest and most informative markers of kidney damage in low birth weight infants at the preclinical stage of acute renal failure were identified.

− The frequency and severity of hypoxic-ischemic kidney damage in low birth weight infants was determined, as well as a comparative characteristic of kidney damage in different groups of children with low birth weight.

− Predictive algorithms for the course and outcome of IN and the risk of complications have been developed.

Practical significance of the research. Early markers of kidney damage in low birth weight infants have been developed. This will make it possible to diagnose nephropathy at the preclinical stage and begin timely treatment, and reduce mortality and the incidence of disability in children.

Approaches to antenatal prevention of ischemic nephropathy in low birth weight infants have been substantiated.

The course and the outcome of ischemic nephropathy in premature infants corresponding to the gestational age and children with intrauterine growth retardation were predicted.

Approbation of work. The main provisions of the dissertation were discussed and reported at the interdepartmental meeting of the Departments of Pediatrics at Azerbaijan Medical University (27.11.2018, protocol No. 6), at the scientific seminar of the Dissertation Council ED 2.27 operating at AMU (25.06.2021, Protocol No. 5), as well as at "The 5th Congress of the European Academy of Paediatric Societies EAPS" (Barcelona, Spain, 2014), 10th International Scientific Practical Conference "Global Science. Development and Novelty "(Munich, Germany, 2019), International Black Sea Coastline Countries symposium - VI (Giresun, Turkey, 2021).

Implementation of the results into practice. The results of the study were introduced into the clinical work of the maternity hospital № 5 named after Sh. Aleskerova and in the departments of intensive care and pathology of premature newborns of the Research Institute of Pediatrics named after K. Farajova.

The name of the organization where the research was implemented. The research was implemented at the Department of Childhood Diseases-2 of the Azerbaijan Medical University.

The connection of the work with the plans of scientific research. The research work is part of a project supported by the Scientific Development Fund under the Presidential Office of the Republic of Azerbaijan. The name of the project: "The role of perinatal factors in the formation of the neurosomatic status of premature newborns".

Published works. On the topic of the dissertation, 21 scientific works were published, of which 9 were articles (4 - abroad) and 12 were theses (9 - abroad).

The volume and the structure of the dissertation. The dissertation is presented on 166 computer pages (186253 characters) and consists of an introduction (5,5 pages, 8346 symbols), a literature review (28 pages, 45069 symbols), chapters of materials and methods (10 pages, 14584 symbols), 3 chapters of our own research (59 pages, 70879 symbols), conclusion (24 pages, 41541 symbols), conclusions (1.5 pages, 1918 symbols), practical recommendations (0.5 pages, 804 symbols), bibliography (31 pages), which includes 290 sources – 3 works are in Azerbaijani, 63 - in Russian and 134 - in English. The dissertation is illustrated by 25 tables and 7 graphs.

MATERIALS AND RESEARCH METHODS

The work was carried out in the maternity hospital № 5 named after Sh. Aleskerova and in the departments of intensive care and pathology of premature newborns of the Research Institute of Pediatrics named after K. Farajova in 2011-2018.

The main study group includes newborns weighing less than 2500 g at birth (newborns corresponding to the gestational age and newborns small for their gestational age); newborns who have undergone ante- and intranal hypoxia and asphyxia; newborns with pronounced clinical manifestations of impaired renal function.

In accordance with the purpose and objectives of this study, 150 newborns involved in this study were divided into 3 groups: Group 1 - 72 children with manifestations of ischemic nephropathy (main

group), of which 33 newborns were with IUGR, group 2 - 28 children (comparison group), 3rd - 50 healthy newborns (20 full-term, 30-premature (control group).

Depending on the severity of ischemic nephropathy (IN), the newborns of the main group were further divided into 3 subgroups: subgroup 1A - 36 infants with IN of 1st degree severity, 1B - 20 infants with IN of 2nd degree severity, 1C - 16 infants with IN of 3rd degree severity. Three (15%) newborns from 1B, and five (31.25%) low birth weight newborns from subgroup 1C died in the early (5 days) and late (10-13 days of life) neonatal period, as a result of multiple organ failure.

The division of the newborns of the main group into 3 subgroups, depending on the severity of ischemic nephropathy, was made on the basis of the classification proposed by Baybarina E.N. et al. (1999), who proposed to take the serum values of creatinine and urea and hourly urine output as the basis.

The comparison group (group 2) included low birth weight infants whose mothers had a burdened obstetric and gynecological history, extragenital pathology, pathological course of pregnancy and childbirth, contributing to the development of antenatal fetal hypoxia, but without kidney damage.

The control group was formed by the method of random sampling (conditionally healthy full-term and premature infants with gestational age less than 37 weeks and the correspondence of the child's weight at birth to gestational age and with the absence of burdened heredity for diseases of the urinary system).

In all examined newborns, risk factors for the development of kidney pathology were analyzed by collecting data from the social and biological anamnesis of their mothers.

At birth, the condition of the newborns was assessed using the Apgar and Silverman scale. The Apgar assessment in full-term newborns was carried out at 1-5 minutes. Premature babies were assessed at 1 and 15 minutes and 2 hours after birth.

Physical development of newborns (weight and length of the child's body, head and chest circumference) was assessed using the sigma table for this region.

Morphofunctional maturity of a newborn child was assessed using the table of Bollard et al. Considering that the state of the muscle tone, along with maturity, is also determined by the state of the central nervous system, infants with severe forms of damage to the nervous system were assessed according to V. Hoffner's table, consisting only of morphological criteria.

The work analyzed the results of clinical, functional and biochemical research methods: general urine analysis, clinical and biochemical blood tests (with the determination of urea, creatinine, electrolytes, acid-base state, glucose).

Instrumental research methods included: neurosonography, ultrasound of the abdominal organs, echocardiography. The state of the urinary system was assessed by an ultrasound examination of the kidneys and Doppler sonography of the segmental renal artery.

According to the indications, a chest x-ray was taken. An echographic examination of the brain and a Doppler study of the blood flow in the renal artery were carried out using an ultrasound diagnostic apparatus "Medison Sonocex 6" with a transducer with a frequency of 5 and 7.5 MHz.

The following indicators of renal hemodynamics were studied:

- time-averaged maximum speed (TAMX, cm/sec).
- end diastolic velocity (Ved, cm/sec);
- Resistance Index (RI)

Furthermore, indicators of daily and hourly urine output (ml/kg/hour) were investigated. To determine the urine output, a transurethral Foley catheter was used. The amount of urine output was measured by the direct measurement of the volume of urine within an hour and during the day.

The functional state of the kidneys was assessed based on the data of determining the plasma creatinine concentration by the photometric (colorimetric) method according to Yaffe on the FLEXORE analyzer (Netherlands) without preliminary deproteinization. The filtration capacity of the neonatal glomerular apparatus was calculated on the basis of renal urine output, and glomerular filtration rate (GFR) was calculated according to the modified Schwarz formula.

In addition, the severity of kidney damage in all children of the

study group was assessed using the RIFLE scale, based on plasma creatinine and GFR.

Along with the generally accepted methods for assessing renal function, biomarkers of the renal tubular apparatus damage KIM-1 and NGAL, and Cystatine-C in the blood plasma were determined in the urine.

Sampling of the urine and the blood samples for the determination of the above biomarkers was carried out twice: on the 1^{st}-3^{rd} and 7^{th}-10^{th} days of life.

The concentration of KIM-1 was determined using the corresponding reagent kit from Arqutus Medical, BioAssayWorks. The NGAL concentration was determined using the corresponding kit from RayBiotech, Inc. (USA).

NGAL in the urine was determined by a quantitative sandwich enzyme-linked immunosorbent assay (BioVendorsHuman Lipocalin-2 ELISA).

KIM-1 in the urine was determined by a quantitative sandwich enzyme-linked immunosorbent assay (Quantikine Human TIM-1 Immunoassay).

The level of cystatin C in the blood serum was determined by the method of enzyme-linked immunosorbent assay (ELISA) using the Human Cystatin C ELISA reagent kit from BioVendor (Czech Republic).

The obtained digital data of the study were statistically processed by parametric and nonparametric methods of statistical analysis. The data of patients of certain groups were combined into variation series, the arithmetic mean values (M), standard deviations (σ) and mean errors of the arithmetic mean (m) were calculated according to generally accepted formulas. Statistical processing of the results was carried out using standard mathematical analysis programs (Microsoft Excel 7.0 and SPSS 20).

RESEARCH RESULTS AND THEIR DISCUSSION

In order to identify the risk factors for the development of IN, an analysis of the ante- and intranatal anamnesis of the examined low-birth-weight infants was carried out and it was found that all study

groups were characterized by a high proportion of maternal somatic diseases, among which the highest rates were chronic pyelonephritis (27.8%), anemia (54.2%) and gastrointestinal diseases (43.1%) in mothers of newborns from the main group.

In the group of mothers who gave birth to low birth weight newborns during pregnancy, there were significantly more threats of termination of pregnancy in the first (51.4%) and second half (65.3%), gestosis in the first (20.8%) and second half of the pregnancy (58.3%) compared with the control group ($p<0.01$). Ultrasound examination of the fetus during the pregnancy in all groups of women showed a high incidence of signs of placental insufficiency, which ranged from 20.0% in the control group to 44.4% in the main group.

The birth weight of low birth weight newborns of the main group ranged from 980 g to 2300 g and averaged 1600±68.0 g, body length 41.6±0.8 cm, head circumference 28.4±0.3 cm; chest circumference - 26.2±0.6 cm.

Physiological loss of body weight was 12.1±1.7% and was significantly higher compared to the control group ($p<0.05$). The initial body weight was restored by 17.0±1.2 days of life.

Delay in intrauterine development of the fetus according to the hypotrophic (asymmetric) type of the first degree was noted in 21 (63.6%) newborns, according to the hypoplastic (symmetric) type in 12 (36.4%) premature babies.

The general condition of the examined newborns at birth was assessed using the Apgar scale. According to the results, from subgroup 1A in 16 (44.4%) children the general condition was assessed as severe and in 6 (16.6%) - extremely severe, which required respiratory support in the form of CPAP and mechanical ventilation. 8 (22.2%) were born in a moderate condition; 6 (16.6%) newborns were satisfactory. In subgroup 1B, 4 (20%) children were born in a state of moderate severity, in severe and extremely severe 12 (60%) and 4 (20%), respectively. In subgroup 1C, 2 (12.5%) newborns were moderately severe, 6 (37.5%) children were severe, and 8 (50.0%) extremely severe. Most of the newborns from the control group were in moderate condition and only 7 (23.3%) of premature infants from subgroup 2B were in a state of moderate severity.

8 (11.1%) newborns of the main group were born without asphyxia, and 13 (18.0%) children were born with 6-7 points on the Apgar scale, but in the next hours of life their condition worsened and they were transferred to the neonatal ICU. Moderate and severe asphyxia was found in 26 (36.1%) and 25 (34.7%) children.

In the main group, 55 (76.3%) newborns in the early neonatal period were diagnosed with perinatal damage of the central nervous system. Among children of the main group, cerebral ischemia of the 2^{nd} degree of severity was diagnosed in 23 (31.9%) newborns, cerebral ischemia of the 3^{rd} degree - in 8 (11.1%) newborns.

It is known that the severity of hypoxic-ischemic encephalopathy (HIE) correlates with the severity of IN, which we observed in our study. In low birth weight infants of subgroups 1B and 1C, that is, with II and III degree IN, the Apgar score was significantly lower than in infants of the 1A subgroup and control groups, and the frequency and severity of CNS lesions accompanied by various clinical syndromes were significantly higher in newborns with IN of the II and III degrees of severity.

Most of the newborns of the main group had edema of varying severity that had manifested itself from the first days of life. Edema syndrome, which is a clinical sign of renal dysfunction, was more pronounced in the first week of life and persisted until the end of the second week of life in 68 (97.2%) children of the main group.

Analysis of dynamic changes in the indicators of the urinary syndrome in low birth weight infants revealed that the urine output in the first week of life was significantly lower than in children of the control group ($p<0.01$). At the same time, it was found that in the diagnosis of ischemic nephropathy, the urine output level below 1.5 ml / kg / h is of great statistical significance. Along with this, we found that the levels of creatinine and urea, which characterize the filtration function of the kidneys, significantly increased in relation to the control group. The highest concentrations (3-4 times higher than normal) of creatinine and urea were found on the $5\text{-}7^{th}$ day of life (creatinine 1.20±0.02 mg/dl in group 1A, 1.94±0.05 mg/dl and 2, 64±0.06 mg/dl in groups 1B and 1C, respectively; urea 30.4±2.02 mmol/L, 42.0±2.05 mmol/L and 54.0±2.44 mmol/L in 1A, 1B and

1C groups, respectively). These indicators, despite the decrease in the dynamics (from the 10^{th}-14^{th} day of life), remained significantly high ($p>0.05$) in newborns of subgroup 1C at the end of the neonatal period on the 28^{th}-30^{th} day of life compared to the control group.

Considering that electrolyte and metabolic changes reflect the degree of renal dysfunction, their levels in the newborns of the main group were analyzed. The individual analysis carried out by us showed that in the majority of children with ischemic nephropathy of the I degree of severity in the early neonatal period, the concentration of potassium and sodium, against the background of the maximum value of creatinine, remained within the physiological values, averaging 4.64±0.16 mmol/L, 142.4±1.75 mmol/L, respectively. In newborns with the II degree of severity, the concentrations of potassium and sodium on the 1^{st} day of life were 4.51±0.25 mmol/L and 141.5±1.6 mmol/L, respectively. This data indicates that the kidneys still manage to regulate homeostasis - the constancy of the internal environment of the body (Chart 1).

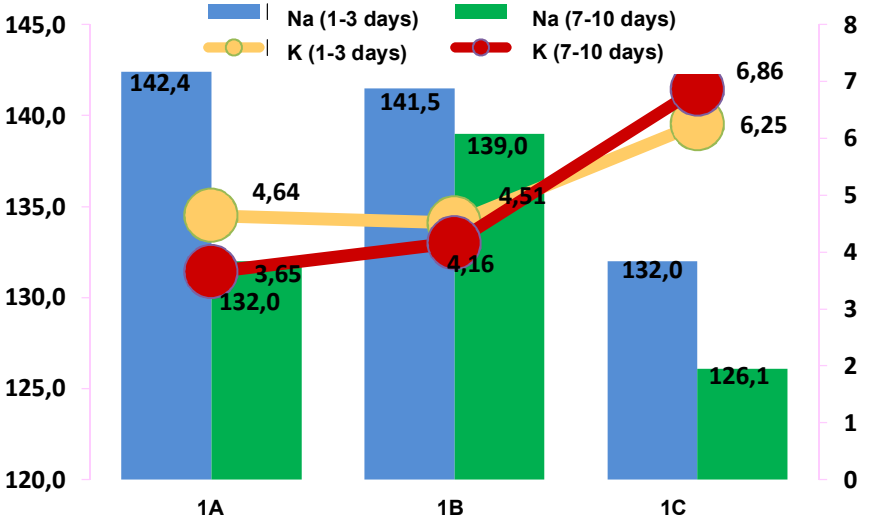


Chart 1. Plasma sodium and potassium concentrations in low birth weight infants with IN

On the 1st day of life, there was a significant increase in the serum potassium concentration up to 6.26±0.15 mmol/L in 10 (62.5%) children and hyponatremia - 132.0±1.51 mmol/L in 8 (50.0%) children. These results were observed in newborns with III degree IN significantly more often than in children with I and II degree of kidney ischemia. These indicators returned to normal only by the end of the second week of life: a decrease in potassium to 5.21±0.38 mmol/L and an increase in sodium to 141.0±1.21 mmol /L.

The concentration of potassium within the standard values was detected in 6 (37.5%) children, and sodium in 8 (50.0%) children with IN of the 3rd degree. Thus, by the end of the neonatal period in children with ischemic renal dysfunction, clinical symptoms from the urinary system persisted in half of newborns with grade I and II IN and in most newborns with grade 3 IN.

In order to diagnose IN in low birth weight infants, we used Doppler ultrasonography of the renal arteries as an additional research method. To assess renal hypoperfusion, we determined the following indicators of renal hemodynamics: time-averaged maximum velocity (TAMX, cm/sec), end diastolic velocity (Ved cm/sec), resistance index (RI).

All infants with IN showed signs of renal hypoperfusion (decreased TAMX), manifested by a decrease in the time-averaged maximum blood flow rate, and/or intrarenal hemodynamic disorders, which were manifested by the pathological variants of the blood flow, a decrease in Ved, as well as signs of increased vascular resistance (RI), marked as an increase in RI. Cases of a pathological type of blood flow ("diastolic steal") were noted in the first three days of life in low birth weight infants with IN of I, II, III degrees of severity in 8.31%, 20.0%, and 68.7% of cases, respectively. The pendulum like type of blood flow was revealed in low birth weight infants with IN of the 2nd, 3rd degree of severity of 10.0% and 32.1% of cases, respectively, on the 7-10th days of life.

In the main group, diastolic "stealing" was noted in 8.31% of newborns in the first two days of life. It should be noted that in these infants, by the end of the early neonatal period, a change in the pathological type of blood flow to normal was noted.

A resistance index above the norm was registered in 36 (50.8%) children of the main group. By the end of the early neonatal period (7-10 days of life), all Doppler findings were normal; time-averaged maximum blood flow velocity - 13.1±0.21 cm/sec, end diastolic velocity - 13.6±0.21 cm/sec, vascular resistance index - 0.75±0.015.

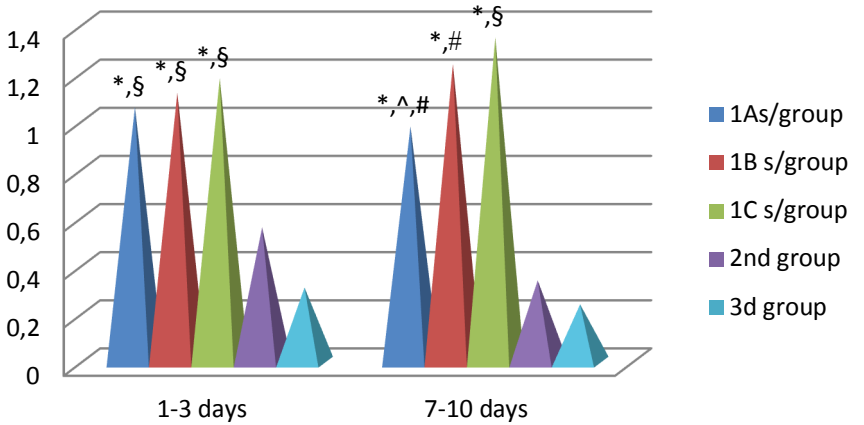
Thus, the development of ischemic nephropathy in low birth weight infants was preceded by a decrease in renal blood flow, the degree of hypoperfusion of which determined the severity of nephropathy. High numbers of the resistance index can be due to both the immaturity of the renal structures of the morphological and functional types, and the presence of extrarenal pathology.

In the study of the levels of biomarkers declared in our study, it was found that in newborns of the subgroup 1A of the main group with IN of I degree severity on the 1^{st}-3^{rd} day of life, the average level of KIM-1 in the urine was 1,06±0.08 ($p < 0.05$), in subgroup 1B with II degree IN was 1.12±0.04, IN of the III degree in subgroup 1C, the relative value of KIM -1 in urine was 1.18±0.10 ng/dL which significantly differed from the value of this indicator of healthy children (control group and newborns of the comparison group).

On the following days of life (7-10 days), the urine level of KIM-1 in newborns with grade 1 IN decreased to 0.98±0.09 ng/dL, which was 4 times higher than in the control group , and in newborns with II and III degree IN, the level of KIM-1 in urine on the $7\text{-}10^{th}$ day of life increased and amounted to 1.24±0.10 ng/dL and 1.36±0.12 ng/dL, respectively ($p<0.05$) compared with the values of this indicator in healthy children (control group and comparison group) (Chart 2).

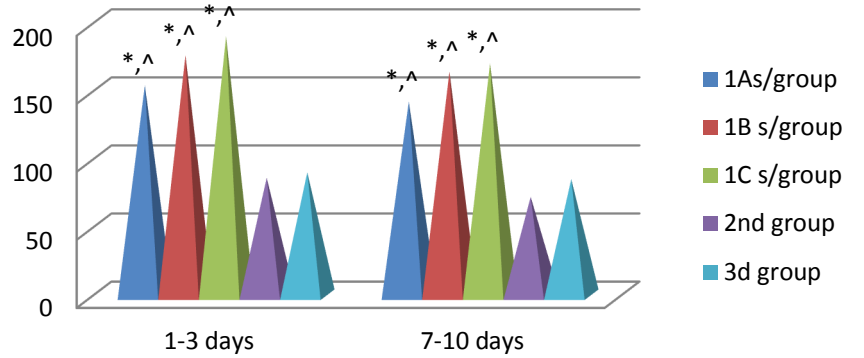
A study of the level of NGAL in urine in LBW infants with IN established the following. On the 1^{st}-3^{rd} days of life in newborns with the 1^{st} degree of severity was 154±14.6 ng/dL ($p<0.05$), with the 2^{nd} degree - 176±15.0 ng/dL ($p<0.05$), with IN of the 3^{rd} degree of severity - 150±18.4 ng/dL ($p<0.05$), which significantly differed from the value of this indicator in healthy children (up to 13±9.4 ng/dL) and newborns of the comparison group (86.4±6.8 ng/dL). On the $7\text{-}10^{th}$ day of life, the average NGAL concentration in the urine in children with I degree IN decreased to 142±10.2 ng/dL ($p < 0.05$), with grade 2 IN to 164±12 , 6 ng/dL ($p < 0.05$), with the 3^{rd} degree of severity up

to 170±15.0 ng/dL (p <0.05), which significantly differed from the NGAL value of healthy children and children of the comparison group (chart 3).



*Note: the differences are statistically significant when * - p <0.05 in relation to the control group; at ^ - p <0.05 - in relation to group 1B; # - p <0.05 - compared with group 1B, § - p <0.05 - in relation to the comparison group.*

Chart 2. KIM-1 level (ng/dL) in urine in LBW newborns



*Note: the differences are statistically significant at ^ - p <0.05 in relation to the comparison group; * - at p <0.05 in relation to the control group.*

Chart 3. Level of NGAL ng / ml in urine in low birth weight infants (M±m)

Thus, an increase in the urine levels of KIM-1≥0.68 ng/dL and NGAL≥164.0 ng / ml in urine on the 1-3rd day of life in low birth weight infants exposed to perinatal hypoxia demonstrated a greater vulnerability of the tubular apparatus.

When analyzing the values of the cystatin C index in subgroups with varying degrees of ischemic nephropathy, a significant increase in cystatin C was revealed in subgroup 1C relative to both 1A (0.664±0.015 mg / l; p <0.001) and 1B subgroup (p = 0.002) in the first days after birth, which indicates a pronounced decrease in the filtration capacity of the renal glomeruli in this category of newborns. When comparing these indicators with the data of the comparison group and the control group, a significant difference was found only in relation to newborns of the 1C subgroup (p <0.001).

When studying the concentration of this substance in the dynamics of the neonatal period, its decrease was noted in the study groups. The exception was newborns of subgroup 1B. The highest concentrations of cystatin C were typical for newborns with severe nephropathy, and the indicators significantly differed from those of children with grade 1 IN and indicators of children from the comparison group (p <0.05) (table 1).

Table 1

Cystatin C levels in LBW infants with IN

Cystatin C mg/dl	Newborns with IN			Comparision group n=28	Control group n=50
	1-st degree n=36	2-nd degree n=20	3-d degree n=16		
1-3-days	0,587±0,01	0,60±0,007	0,664±0,015 ¶*^σ	0,588±0,01	0,585±0,011
7-10-days	0,542±0,013	0,606±0,018	0,646±0,014 ¶^	0,542±0,02	0,568±0,009

*Notes: ¶ – the differences are statistically significant in relation to the 1st subgroup; * – the differences are statistically significant in relation to the 2nd subgroup; ^ – the differences are statistically significant in relation to the comparision group; σ – the differences are statistically significant in relation to the control group.*

High KIM-1 and NGAL values in LBW infants with IN who have undergone perinatal hypoxia is an anticipated result of tubular epithe-

lium damage. Along with this, the high content of these markers in low birth weight infants from the first days of life, apparently, were due to both the severity of chronic intrauterine hypoxia, developing against the background of preeclampsia, and cardiorespiratory disorders that maintain renal tissue hypoxia.

At the next stage of the study, we carried out a detailed correlation analysis between biomarkers of kidney damage and the level of createnine in blood plasma, as well as RI (resistance index) in the renal artery in the dynamics of the early neonatal period in all examined newborns.

A direct correlation was found between KIM-1 and NGAL ($r = 0.902$ $p<0.01$) on days 1-3 and 7-10 of life ($r = 0.930$ $p <0.01$) of newborns of the main group. Highly sensitive correlations between RI and KIM-1 were also established, both on days 1-3 ($r = 0.78$ $p <0.01$) and on days 7-10 ($r = 0.69$ $p < 0.01$), RI and uNGAL (1-3 days of life $r = 0.85$ $p <0.01$) and (7-10 days $r = 0.806$ $p <0.01$). A direct correlation was observed between plasma creatinine and KIM-1 ($r = 0.79$ $p <0.01$); plasma creatinine and NGAL ($r = 0.69$ $p <0.01$) only on the 7^{th}-10^{th} day. This indicates the high sensitivity of both biomarkers to the damage of the renal tubules from the moment of injury and in the dynamics of the early neonatal period,

At the next stage of the study, we conducting a comparative analysis of markers characterizing the functional status of the kidneys in low birth weight infants, depending on the correspondence of their anthropometric parameters to gestational age. The following data was obtained (Table 2).

The level of creatinine between the subgroups on days 1-3 and 7-10 days of life had a significant difference only in the 2^{nd} degree of nephropathy, where the level of this substance prevailed in the subgroup of newborns with IUGR. The highest creatinine values were found in grade 3 nephropathy in the IUGR subgroup; however, there was no statistically significant difference between the subgroups.

KIM-1 in newborns with IUGR significantly exceeds the values of this marker in relation to the 2^{nd} subgroup, both in the 1^{st} and 2^{nd} degrees of nephropathy. III degree IN is characterized by the highest concentrations of this protein with almost the same values in the subgroups of this group.

Table 2

Comparative analysis of markers characterizing the functional status of the kidneys in low birth weight infants depending on the correspondence of their anthropometric parameters to gestational age

	Newborns with IUGR with IN of 1st degree n = 16	Premature AGA newborns with IN of the 1st degree n = 20	Newborns with IUGR with IN of 2nd degree n = 9	Premature AGA newborns with IN of the 2nd degree n = 11	Newborns with IUGR with IN of 3rd degree n = 8	Premature AGA newborns with IN of 3rd degree n = 8
Creatinine, mg/dl 1-3 days	0.74±0.03 1.08-1.5	0.72±0.02 0.99-1.61	0.44±0.03 1.5-1.9	0.86±0.03 0.5-2.05	0.71±0.03 1.42-2.12	0.98±0.04 1.2-2.44
Creatinine, mg/dl 7-10 days	1.2±0.02 1.01-1.37	1.15±0.06 0.94-1.46	1.9±0.04 1.7-2.2	1.2±0.08 * 0.43-2.41	2.03±0.06 1.2-2.85	1.9±0.12 1.33-3.33
KIM-1, ng/dL 1-3 days	1.12±0.03 * 0.74-1.36	0.4±0.9 0.59-1.28	1.15±0.04 * 0.93-1.37	0.6±0.04 0.36-1.54	1.14±0.04 0.59-1.44	1.14±0.04 0.85-1.76
KIM-1, ng/dL 7-10th days	1.08±0.04 * 0.63-1.24	0.8±0.09 0.42-1.22	1.3±0.04 * 1.03-1.52	0.53±0.06 1.21-1.7	1.3±0.03 0.8-1.57	1.3±0.05 0.9-2.06
NGAL, ng / mL 1-3rd days	171±6.08 97.6-196.0	121±13.7 62.7-190.0	180±6.5 * 145.0-217.0	109±6.4 56.0-245.0	183.0±6.6 106.0-258.0	175.0±7.8 115.0-297.0
NGAL, ng / mL 7-10th days	145.0±5.5 109.0-236.0	136.0±10.6 101.0-184.0	168±5.5 * 138.0-199.0	96±6.3 46.0-223.0	170±5.04 * 95.0-213.0	159.0-6.6 106.0-257.0
Cystatine-C, mg / L 1-3rd days	0.62±0.03 0.56-0.68	0.587±0.01 0.54-0.62	0.66±0.02 0.61-0.72	0.60±0.07 0.53-0.66	0.70±0.03 * 0.68-0.72	0.66±0.015 0.61±0.72
Cystatine-C, mg / L 7-10th days	0.57±0.03 0.53-0.62	0.54±0.013 0.52-0.68	0.67±0.02 0.61-0.73	0.64±0.014 0.53-0.77	0.77±0.02 * 0.68-0.8	0.64±0.014 0.56-0.76
Resistance Index (Rİ) 1-3rd days	0.83±0.02 0.81-0.83	0.8±0.007 0.77-0.82	0.88±0.007 0.84-0.93	0.87±0.02 0.81-0.98	0.97±0.01 0.93-1.02	0.98±0.01 0.92-1.1
Resistance Index (Rİ) 7-10th days	0.8±0.04 0.75-0.8	0.77±0.02 0.68-0.9	0.8±0.006 0.78-0.87	0.81±0.02 0.75-0.92	0.87±- .009 0.84-0.92	0.88±0.02 0.83-0.99

*Note: * - difference within one subgroup, in relation to newborns without IUGR, at $p<0.05$.*

The level of NGAL in urine on days 1-3 with grade II IN and 7-10 days with grade III IN significantly prevailed in the subgroup of newborns with IUGR.

A high index of resistance in all three groups, indicating an increase in peripheral vascular resistance in the kidneys, did not have significant differences in the subgroups of the main group.

Thus, the kidneys of newborns with IUGR demonstrate a greater vulnerability of the tubular apparatus of the kidneys compared to prematurity with a weight corresponding to gestational age, which confirms the high sensitivity of the kidneys to unfavorable factors of the antenatal period, which reduce intrauterine growth of the fetus.

High KIM-1 values, reflecting the histotoxic hypoxia of kidney tissues from the first days of life to the end of the early neonatal period, indicate the severity of tubular disorders in newborns with IUGR already at IN of I degree. Despite the absence of a significant difference in the level of creatinine between subgroups with III degree IN, the level of NGAL in newborns with developmental delay is statistically significantly higher than the indicator of the same name in newborns without IUGR, which shows the possibility of developing the terminal stage of AKI in this category of newborns. When assessing the glomerular renal function, it was found that the level of Cystatin C, both in the first and in the second measurement, in newborns with IUGR with IN of the I and II degrees does not significantly exceed the indicators of the children corresponding to their gestational age, while, as among low birth weight infants with III degree IN, the values of this marker statistically significantly prevail in newborns with developmental delay both on the 1^{st}-3^{rd} days of life and on the 7th-10^{th} day of life. An increase in the concentration of this marker by the end of the early neonatal period in this group of children tells us about a violation of the restoration of glomerular filtration against the background of both anatomical and functional immaturity of the glomerular apparatus.

As for the renal artery resistance index taken separately, it does not always reflect the severity of renal tissue damage, since hypoxia triggers arteriovenous shunting with blood supply to juxtamedullary nephrons and damage to the cortex even with normal IR values.

Based on the results obtained, it can be assumed that newborns with IUGR constitute a risk group for the development of AKI, which must be taken into account when managing this group of children with the prevention of impaired water-salt metabolism, polypharmacy, especially nephrotoxic drugs. Assessment of renal functions only on the basis of creatinine does not allow for an objective assessment of the degree of damage to the tubular apparatus, which requires the use of more sensitive markers in order to prevent severe AKI.

In order to predict the development of certain complications in the dynamics of the disease, we found that a sharp increase in the value of KIM-1 and NGAL in the urine in the early neonatal period in children with IN in relation to healthy newborns indicating the possibility of developing a complication of IN.

The work developed a prognostic method for individual prediction of a favorable and unfavorable outcome of IN in low birth weight infants based on 19 most significant signs (Table 3).

The analysis of clinical manifestations in newborns with IN in the early neonatal period shows that an unfavorable outcome of IN can be observed if the pathological process occurs against the background of severe respiratory, cardiovascular insufficiency of the 2^{nd}-3^{rd} degree and ischemic brain damage. Among the laboratory data, the most informative was serum creatinine on the 7^{th}-10^{th} day of life. When determining the prognosis of IN in newborns, the biomarkers of kidney damage KIM-1 and NGAL in the urine were especially significant, and the frequency of an unfavorable outcome of IN in the observed newborns depends on the level of the studied biomarkers (KIM-1 and NGAL).

When comparing the informativeness of the prognostic coefficients developed by us in newborns of the main and control groups, it was found that the outcome of IN can be evaluated with a high degree of reliability (95%). Thus, in the main group, a favorable outcome was found in 83.7% of newborns, an unfavorable outcome in 75.8%, an uncertain prognosis in 16.6% and 24.2% of newborns, respectively.

Table 3

Predicting the outcome of ischemic nephropathy in newborns in the early neonatal period

Name of signs		Odds			
		PC 1	CI 1	PC 2	CI 2
Mother's age up to 20 years old and over 30 years old		+2.5	0.34	-2.5	0.30
Anemia of pregnancy		+2.5	0.30	-2.5	0.24
Chronic pyelonephritis		+3.0	0.45	-2.5	0.32
We take the threat of interruption. in the 1st half		+3.0	0.46	-2.8	0.32
We take the threat of interruption. in the 2nd half		+3.4	0.48	-3.0	0.34
Placental insufficiency		+3.6	0.51	-3.0	0.31
Polyhydramnios		+3.0	0.41	-2.8	0.30
Malnutrition		+2.5	0.31	-2.5	0.28
Severe birth asphyxia		+3.6	0.54	-3.2	0.36
Availability of DN 2-3rd step.		+4.2	0.88	-2.6	0.34
The presence of SSN 2-3rd step.		+4.0	0.82	-2.5	0.32
In neurosonogram: IVC or PVC		+4.0	0.84	-2.4	0.31
Serum creatinine (mg/dl)	On the 1-3rd day of life> 0.95	+3.4	0.46	-3.0	0.32
	At 7-10th days of life> 0.81	+3.6	0.48	-3.2	0.34
Serum Urea (mg/dl)	1-3rd day> 14.2	+3.0	0.38	-3.0	0.31
	7-10th day> 16.4	+3.2	0.36	-2.8	0.28
Ved	1-3rd day> 10.2	+3.0	0.36	-3.0	0.30
	7-10th day> 11.0	+2.8	0.34	-2.8	0.26
TAMX	1-3rd day> 11.4	+3.0	0.38	-3.0	0.34
	7-10th day> 13.8	+3.0	0.36	-3.0	0.32
KIM-1 (ng/dL)	1-3rd day> 0.52	+4.6	0.91	-3.6	0.65
	7-10th day> 0.32	+4.8	0.94	-3.4	0.56
NGAL (ng / ml)	1-3rd day> 110	+4.8	0.96	-3.5	0.62
	7-10th day> 104	+4.4	0.92	-3.4	0.46
CYSTATIN C (mg/l)	1-3rd days> 0.9	+3.2	0.86	-3.6	0.64
	7-10th days> 0.9	+3.8	0.67	-3.2	0.62

The advantage of biochemical parameters in predicting the course and outcome of IN is that if, based on anamnestic and clinical and laboratory data, there is a reliable prognosis in 42.0% of cases, when using biochemical markers of kidney damage, the correct prognosis is established in 80.0% of newborns.

Thus, the use of the developed prognostic algorithm makes it possible to predict the further course and outcome of IN already in the

early neonatal period, as well as to organize preventive and therapeutic measures in a timely manner.

CONCLUSIONS

1. The most significant pre- and perinatal risk factors contributing to the development of IN in low birth weight infants are: the mother has a history of chronic pyelonephritis and its exacerbation during pregnancy (27.8%), fetoplacental insufficiency (44.4%), the threat of interruption of the second half pregnancy (65.3%), severe birth asphyxia (34.7%), cerebral ischemia of the 2-3rd degree (31.9% and 11.1%, respectively) [1, 9, 10, 12].

2. An increase in the levels of KIM-1≥0.68 ng/dl and NGAL≥164.0 ng/ml in the urine on the 1st-3rd days of life, in low birth weight infants exposed to perinatal hypoxia, demonstrate greater vulnerability of the tubular apparatus and are an early diagnostic marker of ischemic nephropathy, and their continued high levels in urine by 7-10 days of life, indicates an unfavorable prognosis [2, 6, 7].

3. In newborns with IUGR, there is a significant increase in KIM-1 and NGAL in the urine compared to children corresponding to gestational age ($p < 0.05$), with all degrees of IN, which is due to the severity and duration of chronic antenatal hypoxia in this category of newborns [3-5, 18, 19].

4. A statistically significant increase in Cystatine C ($p<0.05$), which is a marker of damage to the glomerular apparatus in both premature AGA newborns and children with IUGR, is observed only in severe IN, which does not exclude the primary nature of tubular changes, while glomerular damage can develop at later stages of the disease and is secondary [16, 17, 20, 21].

5. The seriousness of ischemic nephropathy is determined by the severity and duration of hypoperfusion and renal hemodynamic disorders. Significant positive correlation between the renal vascular resistance index and KIM-1 ($r = 0.78$ $p < 0.01$) and the renal vascular resistance index and NGAL ($r = 0.85$ $p < 0.01$) from the first days of life indicate the presence of ultrastructural changes in the renal tubu-

lar apparatus in response to the adverse effects of perinatal stress on renal blood flow [8, 11, 14].

6. When predicting the risk of developing IN in newborns, the biomarkers of kidney damage KIM-1 and NGAL in urine turned out to be especially significant (KIM-1 on days 1-3, PC 1 = +4.6; CI1 = 0.91, on 7-10- th day PC1 = +4.8, CI 1 = 0.94); (NGAL on the 1-3rd day - PC1 = +4.8; CI1 = 0.96; on the 7-10th day PC1 = 4.4; CI1 = 0.92). Moreover, the frequency of an unfavorable outcome of IN in the observed newborns depends on the level of the studied biomarkers [13, 15].

PRACTICAL RECOMMENDATIONS

1. In low birth weight infants who have undergone perinatal hypoxia, it is recommended to determine the indicators of KIM-1 and NGAL in the urine on days 1-3 and 7-10 of life.

2. In the case of an increase in the levels of biomarkers of kidney damage - KIM-1 and NGAL in the urine on days 1-3 of life in low birth weight infants with a serum creatinine level> 1.5 mg/dl, such children should be identified as a high-risk group for IN.

3. Predicting the probability of developing IN in the early neonatal period in low birth weight infants can be made possible using a prognostic table, which includes prognostic and informative criteria: pregnancy complications (fetoplacental insufficiency, chronic intrauterine fetal hypoxia), cerebral ischemia II-III degree and cardiorespiratory disorders in newborns decrease in TAMX in the renal artery, NGAL content in urine ≥ 164.0 ng/dL, KIM-1 ≥ 0.68 ng/dL on days 1-3 of life.

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LIST OF CONDITIONAL ABBREVIATIONS

AGA	- appropriate for gestational age
AKI	- acute kidney injury
ARF	- acute renal failure
CNS	- central nervous system
CPAP	- continuous positive airway pressure
GFR	- glomerular filtration rate
IN	- ischemic nephropathy
IUGR	- intrauterine growth retardation
LBW	- low birth weight infants
SGA	- small for gestational age
Hb	- hemoglobin
KIM-1	- kidney injury molecule
NGAL	- neutrophil gelatinase associated lipocaline
RI	- resistance index
TAMX	- time-averaged maximum speed
Ved	- end diastolic velocity

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