НЕОНАТОЛОГІЯ, ХІРУРГІЯ ТА ПЕРИНАТАЛЬНА МЕДИЦИНА
NEONATOLOGY, SURGERY AND PERINATAL MEDICINE
Т. XIV, № 1(51), 2024
VOL. XIV, № 1(51), 2024
ISSN 2226-1230 (PRINT) ISSN 2413-4260 (ONLINE)
KEY TITLE: NEONATOLOGÌÂ, HÌRURGÌÂ TA PERINATAL'NA MEDICINA (ONLINE)
ABBREVIATED KEY TITLE: NEONATOL. HÌR. PERINAT. MED. (ONLINE)

UDC: 616.61-008.6-074-053.2:618.3-071.1
DOI: 10.24061/2413-4260. XIV.1.51.2024.5

RENAL DYSFUNCTION IN PRETERM INFANTS WITH PERINATAL PATHOLOGY: RISK FACTORS, SENSITIVITY AND SPECIFICITY OF LABORATORY MARKERS OF DAMAGE

A. V. Frunza, Yu. D. Hodovanets

Bukovinian State Medical University
(Chernivtsi, Ukraine)

Summary.

The main burden of neonatal morbidity in critically ill preterm infants, despite significant achievements and rapid development of care technologies, is most often associated with neonatal sepsis, perinatal asphyxia and the development of multiple organ failure syndrome. As a component of this syndrome, newborns with combined perinatal pathology in the early neonatal period manifest severe renal dysfunction up to acute kidney injury, which is closely correlated with increased mortality. The incidence of acute kidney injury in critically ill preterm infants varies widely, ranging from 25 to 77 % according to different neonatal data. A major problem in the field of neonatal nephrology is the lack of uniform approaches for the diagnosis of moderate and severe renal dysfunction at the subclinical stage, which would allow the timely formation of risk groups and the optimization of interventional strategies.

Aim of the study. *To analyze the data on clinical characteristics, risk factors, and results of additional paraclinical examinations in preterm infants with gestational age of 34-36/6 weeks who had severe and moderate perinatal pathology during the early neonatal period.*

Material and methods. *A comprehensive study of 91 premature infants with moderate and severe perinatal pathology was conducted, of which group I consisted of 30 children with severe perinatal pathology at 34-36/6 weeks' gestation, group II – 30 children with moderate perinatal pathology at 34-36/6 weeks' gestation; group III (control) consisted of 31 conditionally healthy premature infants at 34-36/6 weeks' gestation.*

The diagnosis of acute kidney injury in neonates in the comparison groups was made according to the International Criteria for Kidney Disease: Improving Global Outcomes as modified by J. G. Jetton and D. J. Askenazi (2015). The international scale Neonatal Multiple Organ Dysfunction Score was used to assess the severity of multiorgan dysfunction in perinatal pathology. The effectiveness of therapeutic interventions was assessed using the international scale Neonatal Therapeutic Intervention Scoring Scale, and the severity of the patient's condition in dynamics was assessed using the neonatal scale Score for Neonatal Acute Physiology.

Methods of laboratory research. *The study of the biochemical spectrum of urine in children of the observation groups, in particular, the determination of the level of markers of kidney damage – alpha-1-microglobulin, beta-2-microglobulin, microalbumin, cystatin C was carried out on the basis of the problematic research laboratory of the Bukovinian State Medical University of the Ministry of Health of Ukraine using the automatic analyzer «ACCENT-200» and «ACCENT-200 II CEN». Urine was collected on the 3rd day of life (between 48-72 hours of life), in sterile disposable containers, in the amount of at least 5 ml. At the same time, a blood sample for cystatin C determination was taken in the amount of 0.5-1.0 ml, in accordance with the rules of asepsis and antisepsis in disposable sterile tubes. A turbodimensional immunoassay was used to determine the concentration of cystatin C and urinary microalbumin. Determination of alpha-1-microglobulin was performed using an ACCENT-200 automated analyzer by measuring agglutination by change in absorbance (572 nm), with actual concentration determined by interpolation from a calibration curve constructed using calibrators of known concentration. The concentration of beta-2-microglobulin in urine was determined by the method of competitive chemiluminescence analysis.*

The studies were conducted in accordance with the basic provisions of GCP (1996), the Convention of the Council of Europe on Human Rights and Biomedicine (April 4, 1997), the World Medical Association Declaration of Helsinki on Ethical Principles for Research Involving Human Subjects (1964-2008), Order of the Ministry of Health of Ukraine No. 690 of September 23, 2009 (as amended by Order of the Ministry of Health of Ukraine No. 523 of July 12, 2012).

Statistical analysis of the results was performed using Statistica 10 software (StatSoft Inc., USA, 2010), MedCalc software (version 16.1) with calculation of chi-squared, odds ratio (OR), 95 % confidence interval (CI), statistically significant differences between the study groups were considered at a value of $p<0.005$. Receiver operating characteristic (ROC) curves, area under ROC (AUROC), sensitivity (SN), and specificity (SP) were analyzed using MedCalc software (version 16.1).

The research work was carried out within the framework of research of the Department of Pediatrics, Neonatology and Perinatal Medicine of the Bukovinian State Medical University: Research project «Improvement of directions of prognostication, diagnosis and treatment of perinatal pathology in newborns and infants, optimization of schemes of catamnestic observation and rehabilitation» (State registration number 0115U002768, term of implementation 2015-2019); Research project «Chronobiological and adaptive aspects and features of vegetative regulation in pathological conditions in children of different age groups» (State registration number 0122U002245, term of implementation 2020-2024).

Study results. *The data obtained showed statistically significant associations between the risk of severe renal dysfunction and a number of antenatal and postnatal factors that adversely affect the course of the early neonatal period. These included fetal distress during pregnancy and delivery, emergency cesarean section, risk of spontaneous abortion and preterm birth, and impaired fetal-placental blood flow. Statistically significant associations with the development of moderate and severe renal dysfunction are associated with a burdened history of maternal extragenital pathology, namely cardiovascular, urinary system, and anemia ($p<0.005$). The structure of perinatal pathology in preterm infants is often combined and difficult to diagnose. A significant proportion of newborns had clinical manifestations of multiple organ failure syndrome, including signs of renal dysfunction. Therefore, it is expedient to study a set of the latest potential biomarkers of renal dysfunction, such as cystatin C, alpha-1-microglobulin, beta-2-microglobulin and microalbumin, in order to create an appropriate prognostic model and timely form risk groups among this category of children.*

Conclusions. *The basis for the development of moderate and severe renal dysfunction in premature infants with perinatal pathology is polyetiology against the background of morphological and functional immaturity of the body, which has a clear relationship with gestational age and birth weight. The compensatory and adaptive properties of the «immature» kidneys at birth are limited, which, in the presence of combined pathology, plays a significant role in shaping the severity of the course of the disease. Early prognosis and diagnosis of renal dysfunction in the early stages of its development makes it possible to improve the quality and effectiveness of medical care and improve treatment outcomes.*

Key words: *Children; Preterm Infants; Acute Kidney Injury; Risk Factors; Clinical Characteristics; Laboratory Diagnostics.*

Introduction

In 2016, the international multidisciplinary group The Neonatal Kidney Collaborative (NKC) developed the AWAKEN (Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates) study program to investigate the population epidemiology of AKI, the main risk factors, the impact of fluid balance on the risk of acute kidney injury (AKI), and short-term outcomes in preterm infants (PICU). The prevalence of ARF reaches 10-30 % in neonates admitted to the neonatal intensive care unit (NICU) [1], with a higher incidence of AKI in newborn boys. In very low birth weight (VLBW) infants, the prevalence of AKI reaches 18 %, the mortality rate from AKI compared to no AKI in this pediatric group reaches 55 % versus 5 %, in extremely low birth weight (ELBW) infants, the prevalence of AKI is 13 %, the mortality rate from AKI compared to no AKI in this group is 70 % versus 22 %. In sick term and late preterm infants (34-36 weeks) the prevalence reaches 18 %, mortality – 22 % vs 0 %, in infants with sepsis – the prevalence is 26 %, mortality 70 % vs 25 % in the control group without sepsis, in newborns with asphyxia the prevalence of AKI reaches 38 %, mortality 14 % vs 2 % in the control group [2-5].

Numerous studies have demonstrated an inverse relationship between gestational age (GA), body weight and the incidence of AKI in the early neonatal period. The incidence of AKI in neonates, depending on the definition and method of study (KDIGO, AKIN, pRIFLE classification), ranges from 2.5 % to 17.6 % in NICU patients, can reach 40 % in VLBW neonates and up to 60 % in ELBW neonates [6]. Since the kidneys are the central organ of drug excretion, they are the main target of possible toxicity, especially in the development of typical conditions characteristic of premature infants (PI) (respiratory distress syndrome, perinatal asphyxia, severe infections, sepsis, hemodynamic instability, etc.) In hospitalized children, exposure to nephrotoxic drugs is one of the most common factors in the development of AKI, accounting for approximately 16 % of AKI cases [7, 8].

The main pathogenetic mechanisms of renal dysfunction in PI under conditions of perinatal pathology are inextricably linked to morphological and functional features, as well as compensatory and adaptive responses of the body against the background of preterm birth. In particular, understanding the mechanisms of postnatal renal adaptation is a key element in the prognosis and prevention of severe renal dysfunction, including the development of AKI.

The pathophysiological mechanisms in the setting of hypoxia and/or reperfusion injury are quite complex, but can be divided into 2 main pathways: microvascular and tubular [9-11]. The microvascular mechanism is an increase in vasospasm, endothelial dysfunction, and increased leukocyte adhesion with subsequent initiation of inflammatory mechanisms. The tubular mechanism is due to disruption of the cytoskeleton with initiation of cellular apoptosis, autophagy, and necrosis [9-11]. The consequence is the formation of a pathological «vicious circle» at the molecular and cellular level: vasoactive proinflammatory mediators activate a «positive» feedback cascade, resulting in decreased tubular and glomerular perfusion with their subsequent destruction (tubular component), which in turn leads to increased production of proinflammatory mediators and further deepening of ischemic, destructive and proinflammatory changes (microvascular component) [9-11].

In recent years, a significant amount of research has been devoted to the study of the latest biomarkers in the field of neonatal nephrology, as this pediatric cohort is the most challenging for the clinician. It is worth noting that despite the rapid development of this field, there is still no «gold standard» for the diagnosis of renal dysfunction in PI. The complexity of the scientific search is due to the fact that the validation of renal biomarkers for the diagnosis of severe renal dysfunction and AKI in PI is inextricably linked to GA, birth weight, as well as a complex of antenatal and postnatal factors that can significantly influence their levels [12,13]. This phenomenon may also be due to the inability of immature renal tubules to reabsorb proteins. As glomerulo-tubular differentiation continues up to 34 weeks, baseline levels of potential biomarkers may vary depending on GA. An in-depth study of the mechanisms of postnatal development of «immature» kidneys and the associated changes in laboratory parameters of common and advanced laboratory markers is needed to establish the relationship between biomarkers and the reported outcomes – the risk of severe renal dysfunction and AKI [12-14].

In view of the above, understanding how the levels of indicators in urine and plasma vary in children during the early neonatal period, depending on GA and body weight, the presence of concomitant combined pathology, and the search for the most effective indicator biomarkers is crucial for determining a further strategy for differential diagnosis and the formation of risk groups. The main problem remains the lack of results from multicenter studies, given the complexity of this pediatric cohort of newborns and the multifactorial nature and diversity of perinatal pathology.

Aim of the study: To analyze the risk factors, clinical characteristics, and results of additional paraclinical examinations in preterm infants of 34-36 weeks gestational age who had signs of renal dysfunction in the early neonatal period to determine their specificity and sensitivity in moderate and severe perinatal pathology.

Material and methods of the study.

ISSN 2226-1230 (PRINT) ISSN 2413-4260 (ONLINE)

In the course of the study, we analyzed data from pregnancy exchange cards (F No. 113/o), birth histories (F No. 096/o), and neonatal development histories (F No. 112/o) of 91 PIs treated in the neonatal intensive care unit (NICU) of the City Clinical Maternity Hospital No. 2 in Chernivtsi during 2017-2021.

The study groups were formed according to the severity of the underlying perinatal pathology. Group I consisted of 30 PIs with a gestational age of 34-36/6 weeks with severe forms of perinatal pathology; group II – 30 PIs with a gestational age of 34-36/6 weeks with clinical signs of moderate perinatal pathology; group III (control) consisted of 31 conditionally healthy PIs with a gestational age of 34-36/6 weeks at birth.

Inclusion criteria: neonates with gestational age of 25-36/6 weeks, weight ≥ 500 g and < 2500 g, and with informed parental consent to participate in the clinical trial. Exclusion criteria: weight < 500 g and ≥ 2500 g, gestational age < 25 weeks and ≥ 37 weeks, lack of informed parental consent to participate in the clinical trial, congenital malformations, early neonatal sepsis.

The severity of the neonatal condition was assessed using the Score for Neonatal Acute Physiology (SNAPPE II) [15]. In conditions of severe perinatal pathology, the severity of multiple organ failure syndrome (MOS) was determined using the Neonatal Multiple Organ Dysfunction Score (NEOMOD, 2001), where each individual child was assigned a score according to the results of the assessment of certain criteria. According to the score, 10 or more points indicated a severe degree of multiple organ dysfunction, 7-10 points – a moderate degree, <7 points – a mild degree [16]. All PIs in the first group of the study had a NEOMOD score of 10 points or more. Verification of the diagnosis of severe renal dysfunction, including AKI, was performed using internationally accepted Kidney Disease criteria: Improving Global Outcomes (KDIGO) as modified by J. G. Jetton and D. J. Askenazi (serum creatinine level greater than 26.5 μmol/L – 2-fold increase in consecutive measurements within 48 hours) and/or hourly diuresis less than 0.5 mL/kg/hour over 6 hours [17].

Methods of laboratory research

The study of the biochemical spectrum of urine in children of the observation groups, in particular, the determination of the level of markers of kidney damage – alpha-1-microglobulin, beta-2-microglobulin, microalbumin, cystatin C was carried out on the basis of the problematic research laboratory of the Bukovinian State Medical University of the Ministry of Health of Ukraine using the automatic analyzer «ACCENT-200» and «ACCENT-200 II CEN». Urine was collected on the 3rd day of life (between 48-72 hours of life), in sterile disposable containers, in the amount of at least 5 ml. Blood samples for cystatin C determination were taken at the same time, in the amount of 0.5-1.0 ml, in accordance with the rules of asepsis and antisepsis, in disposable sterile tubes. A turbodimensional immunoassay was used to determine the concentration of cystatin C and urinary microalbumin. Determination of alpha-1-microglobulin content was performed using an automated analyzer ACCENT-200 by determining agglutination by change in absorbance (572 nm), with determination of actual concentration by interpolation with a calibration curve established using calibrators of known concentration. The concentration of beta-2-microglobulin in urine was determined by the method of competitive chemiluminescence analysis.

The studies were conducted in accordance with the basic provisions of GCP (1996), the Convention of the Council of Europe on Human Rights and Biomedicine (April 4, 1997), the World Medical Association Declaration of Helsinki on Ethical Principles for Research Involving Human Subjects (1964-2008), Order of the Ministry of Health of Ukraine No. 690 of September 23, 2009 (as amended by Order of the Ministry of Health of Ukraine No. 523 of July 12, 2012).

Statistical analysis of the results was performed using Statistica 10 software (StatSoft Inc., USA, 2010), MedCalc software (version 16.1) with calculation of chi-squared, odds ratio (OR), 95 % confidence interval (CI), statistically significant differences between the study groups were considered at a value of $p<0.005$. Receiver operating characteristic (ROC) curves, area under ROC (AUROC), sensitivity (SN), and specificity (SP) were analyzed using MedCalc software (version 16.1).

The research work was carried out within the framework of scientific topics of the Department of Pediatrics, Neonatology and Perinatal Medicine of the Bukovinian State Medical University: Research work «Improvement of directions of prognosis, diagnosis and treatment of perinatal pathology in newborns and infants, optimization of schemes of catamnestic observation and rehabilitation» (State registration number 0115U002768, term of execution 01.2015-12.2019); Research work «Chronobiological and adaptive aspects and peculiarities of vegetative regulation in pathological conditions in children of different age groups» (State registration number 0122U002245, term of execution 01.2020-12.2024).

Results of the study and discussion

Group I included 30 children with severe perinatal pathology. In this subgroup, 8 children (26.64 %) were born at 34 weeks of gestation, 13 children (43.29 %) at 35 weeks of gestation, and 9 children (29.97 %) at 36/6 weeks of gestation. The mean birth weight of the newborns was 2288.50±217.05 g, body length 44.70±2.45 cm, head circumference 30.36±2.07 cm, chest circumference 31.23±1.52 cm. There were 18 boys (59.94 %) and 12 girls (40.06 %) in this group.

The average Apgar score at the end of 1 minute of life in the newborns of group I was 5.40±1.30 points, at the end of 5 minutes – 6.50±0.82 points. In 13 infants of this group (43.29 %) there were clinical signs of moderate respiratory distress immediately after birth, which increased in dynamics to severe; in 17 infants (56.71 %) severe respiratory distress was observed immediately after birth. The mean duration of artificial lung ventilation (ALV) in the children was 5.40±2.12 days. Clinical signs of severe hypoxic-ischemic central nervous system (HIS CNS) damage with dominance of depression syndrome were observed in 12 newborns (40.06 %); 6 children (24.00 %) had clinical signs of neonatal encephalopathy; 4 newborns (13. 32 %) had signs of first degree intraventricular hemorrhage (IVH), 1 child (3.33 %) had signs of IVH II; 6 children (16.65 %) had

signs of subependymal hemorrhage (SEH) I, 4 children (13.32 %) had signs of SEH II. Clinical signs of cerebral edema were observed in 4 neonates (13.32 %), and clinical signs of convulsive syndrome were observed in 4 neonates (13.32 %). Clinical manifestations of multiple organ failure syndrome (MOS) were observed in 8 children (26.64 %) of this group, of which 8 cases (26.64 %) had CNS and respiratory system (RS) damage, 4 cases (13, 32 %) – cardiovascular system (CVS) lesions, 2 newborns (6.66 %) had anemia, 2 children (6.66 %) had hemorrhagic syndrome, and 2 cases (6.66 %) had disseminated intravascular coagulation. In 6 neonates of the first observation group (19.98 %), lesions of the gastrointestinal tract (GIT) were observed, accompanied by signs of decreased food tolerance. In 8 IPAs (26.64 %) of this group, manifestations of jaundice of prematurity were noted in the first week of life. In 13 children of this group (43.29 %) the condition at birth was considered moderate, but during the first day of life it deteriorated to severe; in 17 children (56.71 %) the general condition at birth was considered severe. The mean length of hospital stay was 7.46±3.60 days.

Group II of the study consisted of 30 PIs with moderate perinatal pathology born at 34-36/6 weeks of gestation. Among the newborns of this group, 6 children (19.98 %) were born at 34 weeks gestational age, 15 children (49.95 %) – 35 weeks, and 9 children (30.07 %) – 36/6 weeks. The mean birth weight of the newborns was 2158.33±249.89 g, body length 45.36±2.09 cm, head circumference 31.63±1.24 cm, chest circumference 29.76±2.54 cm. There were 12 boys (40.06 %) and 18 girls (59.94 %) in group II.

The average Apgar score at the end of 1 minute of life in neonates of group II was 6.56±0.62 points, at the end of 5 minutes – 6.50±0.82 points. Among the clinical manifestations, 16 children (53.28) had moderate signs of RD at birth, and 14 newborns (46.72) had no signs of RD. Signs of diabetic fetopathy were found in 2 cases (6.66 %). In 5 newborns of this group (16.65 %) there were clinical manifestations of mild HIS CNS damage with predominance of depression syndrome; in 25 children (83.35 %) there were clinical manifestations of neonatal encephalopathy. In this group, 5 children (16.65 %) were small for gestational age at birth, 2 children (6.66 %) had low birth weight. In 8 children of this group (25.76 %) the neurosonography (NSG) showed grade I SEH, in 1 child (3.22 %) grade II SEH. In 4 newborns of this group (13.32 %) signs of conjugative jaundice were observed, and in 3 newborns (9.99 %) neonatal hypoglycemia was laboratory confirmed, which required appropriate medical correction. All infants were in moderate condition from birth (100 %). The number of hospital bed days for the neonates in the IIIA subgroup was 5.53±1.27.

Group III, which was created to compare the complex of clinical and laboratory parameters of the main study groups, included 31 conditionally healthy preterm infants with gestational ages of 34-36/6 weeks. Among the newborns in this group, 4 children (12.88 %) were born at 34 weeks of gestation, 11 children (35.42 %) at 35 weeks, and 16 children (51.52 %) at 36/6 weeks. The mean birth weight in this subgroup was 2357.00±115.78 g, length 46.20±0.76 cm, head circumference 32.53±0.73 cm, and chest circumference 30.50±1.47 cm. There were 5 boys (16.10 %) and 26 girls (83.90 %) in this group.

The average Apgar score at the end of 1 minute of life in newborns of group III was 6.83±0.37 points and at the end of 5 minutes – 7.83±0.37 points. All children had a stable condition at birth and a satisfactory course of the early neonatal period. The number of hospital bed days was 3.96±0.31 days.

According to the international KDIGO diagnostic criteria [17], 7 children (23.31 %) in group I of the study were diagnosed with AKI, of which 2 children (6.66 %) were diagnosed on the basis of combined criteria (decreased hourly diuresis and pathological increase in plasma creatinine), 2 children (6.66 %) – on the basis of increased plasma creatinine only, and 3 children (9.99 %) – on the basis of decreased hourly diuresis.

The analysis of the anamnesis data, the spectrum of gynecological and extragenital pathology in the mothers of the newborns of the study groups, the characteristics of pregnancy and delivery allowed us to determine the main perinatal risk factors for kidney damage in PI, which are presented in Table 1.

Summarizing the obtained statistical data, it should be noted that the following factors contribute to the risk of developing renal dysfunction in IPV in perinatal pathology:

1) Course of pregnancy and delivery:

- Risk of spontaneous abortion and preterm delivery (group I, OR 10.90, 95 % CI 1.27-93.69, p=0.0294)
- Impaired fetal-placental blood flow (group I, CSF 6.21, 95 % CI 1.21-31.77, p=0.0282; group II, CSF 10.90, 95 % CI 1.27-93.69, p=0.0294)
- Fetal distress (group I, CSA 5.27, 95 % CI 1.01-27.33, p<0.0477; group II, CSA 11.27, 95 % CI 2.29-55.52, p=0.0029),
- Urgent cesarean section (group I CSA 5.27, 95 % CI 1.01-27.33, p<0.0477; group II CSA 6.21, 95 % CI 1.21-31.77, p=0.0282).

2) Extragenital pathology and maternal obstetric and gynecologic history:

- Maternal anemia (group I, OR 6.21, 95 % CI 1.21-31.77, p=0.0282)
- cardiovascular diseases (group I, SES 39.87, 95 % CI 7.69-206.72, p<0.0001; group II, SES 18.96, 95 % CI 3.81-94.35, p=0.0003)
- Urinary tract diseases (group I, CSA 17.36, 95 % CI 2.07-145.61, p=0.0085).

Summarizing the data obtained on clinical characteristics and obstetric and gynecological history, it can be argued that the complicated course of labor and the burden of extragenital pathology in mothers, in particular the presence of pathology of the cardiovascular and urinary systems, have a significant impact on the risk of severe renal dysfunction in PI. Analyzing the spectrum of the main perinatal pathology in newborns, it should be noted that, according to our data, the dominant pathology was pathology of the RS and CNS. In a significant number of cases in group I, the development of MOS occurred, and it should be noted that severe renal dysfunction may be both a significant pathogenetic link in the underlying disease and an independent clinical syndrome, causing significant severity of the newborn's condition.

ISSN 2226-1230 (PRINT) ISSN 2413-4260 (ONLINE)
KEY TITLE: NEONATOLOGÌÂ, HÌRURGÌÂ TA PERINATAL'NA MEDICINA (ONLINE)
ABBREVIATED KEY TITLE: NEONATOL. HÌR. PERINAT. MED. (ONLINE)

Table 1

Anamnesis data, spectrum of extragenital and obstetric and gynecological pathology in mothers of newborns in the study groups, n (%)

Indicators	Group I (n=30)	Group II (n=30)	Group III (n=31)
First pregnancy	9 (29,97)	9 (29,97)	7 (22,54)
Repeated pregnancy	21 (69,93)	21 (69,93)	24 (77,28)
The first birth	9 (29,97)	12 (39,96)	9 (28,98)
Repeated birth	21 (69,93)	18 (59,94)	22 (70,84)
Urban residents	16 (53,28)	12 (39,96)	9 (28,98)
Rural residents	14 (46,62)	18 (59,94)	22 (70,84)
Natural childbirth	18 (59,94)	14 (46,62)	22 (70,84)
Emergency cesarean section	8 (26,64)*	9 (29,97)*	2 (6,44)
Planned cesarean section	4 (13,32)	7 (23,31)	7 (22,54)
Extragenital pathology			
Cardiovascular Diseases	22 (73,26)*	17 (56,61)*	2 (6,44)
Diseases of the urinary system	11 (36,63)*	3 (9,99)	1 (3,22)
Respiratory diseases	4 (13,32)	2 (6,66)	-
Diseases of the gastrointestinal tract	6 (19,98)	4 (13,32)	-
Diseases of the endocrine system	4 (13,32)	3 (9,99)	1 (3,22)
Acute viral infections during pregnancy	4 (13,32)	4 (13,32)	1 (3,22)
An old firstborn	2 (6,66)	1 (3,33)	1 (3,22)
Complicated obstetric history			
Induced and spontaneous abortions, stillbirths, children who died before one year of age	5 (16,65)	4 (13,32)	1 (3,22)
Infertility	5 (16,65)	4 (13,32)	1 (3,22)
In vitro fertilization	3 (9,99)	3 (9,99)	1 (3,22)
History of preterm labor	4 (13,32)	2 (6,66)	1 (3,22)
Gynecological Pathology			
Vaginitis	6 (19,98)	4 (13,32)	1 (3,22)
TORCH infections	5 (16,65)	2 (6,66)	1 (3,22)
Abnormalities in the development of the uterus	5 (16,65)	1 (3,33)	-
Cervical Incompetence	6 (19,98)	2 (6,66)	1 (3,22)
Course of Pregnancy			
Risk of miscarriage, premature birth	8 (26,64)*	5 (16,65)	1 (3,22)
Anemia of the II-III grade	9 (46,62)*	6 (28,12)	2 (6,44)
Feto-placental insufficiency with development of fetal retardation syndrome	9 (53,33)*	8 (28,12)*	1 (3,22)
Childbirth Complications			
Fetal distress	8 (26,64)*	9 (29,97)*	2 (6,44)
Prenatal death of one fetus out of twins	2 (6,66)	-	-
Premature rupture of the membranes	4 (13,32)	4 (13,32)	1 (3,22)
Premature detachment of a normally positioned placenta	4 (13,32)	3 (9,99)	1 (3,22)
Uterine bleeding	4 (13,32)	3 (9,99)	-
Abnormal fetal presentation	3 (9,99)	2 (6,66)	1 (3,22)

** – significant difference compared to the control, p<0.05*

In the course of the study, a panel of urinary and plasma biomarkers of kidney injury was analyzed, in particular to determine the relationship between them and the outcomes of interest – the risk of severe renal dysfunction and AKI. To determine the sensitivity and specificity of the most promising biomarkers (cystatin C (CysC), alpha-1-microglobulin (A1MG), beta-2-microglobulin (B2MG), urinary microalbumin (MA)), MedCalc software (version 16.1) was used to analyze the receiver operating characteristic (ROC) curves, area under ROC (AUROC), and sensitivity (SN).

Cystatin C is a low molecular weight protein of the thiol protease inhibitor group with a molecular weight of 13 kDa that is excreted by all cells of the human body, reabsorbed and catabolized in the proximal renal tubules, so that only trace amounts of this protein can be detected in urine in intact kidneys [18]. There are 2 main fractions of this protein: urinary, reflecting tubular dysfunction, and plasma, whose level changes are highly sensitive to glomerular filtration rate [19]. Cystatin C does not cross the placental barrier and therefore does not depend on the level of this protein in the mother's plasma. Cystatin C levels are variable depending on GA, birth weight and the presence of concomitant perinatal pathology and are independently associated with an increased risk of mortality in NICU patients [20,21].

According to the literature, an increase in the plasma level of cystatin C allows prediction of the development of AKI 24-48 hours before the appearance of a diagnostically significant increase in creatinine level, and thus allows detection of preclinical kidney damage without creatinine elevation [22]. This is due to the extracellular distribution of cystatin C, in contrast to the fact that plasma creatinine is distributed in the internal environment of the whole body, and therefore the increase in cystatin C levels is faster with a decrease in GFR. It is important to note that cystatin C levels do not undergo significant changes until after 40 weeks of postconceptional age due to the constant «recruitment» of new nephrons, although numerous studies have shown that preterm birth «interrupts» the pathohistological and pathophysiological pathways of postnatal renal ontogeny [23,24].

The results of the study describe an inversely proportional correlation between plasma cystatin C and GA at birth, but not with respect to postconceptional age. In particular, significantly higher levels of both plasma and urinary fractions of cystatin C are observed in groups of ELBW and VLBW preterm infants with severe perinatal pathology [23,24], and the level of cystatin C in plasma or urine is inversely proportional to kidney volume and reflects the state of nephrogenesis [25].

Alpha-1-microglobulin is a low molecular weight glycoprotein with a mass of 27 kDa that is reabsorbed by renal tubular cells, belongs to the group of proteins that bind heme and free radicals, and has protective properties, particularly against mitochondria [26, 27]. In tubular dysfunction, urinary levels of alpha-1-microglobulin increase, particularly in preterm infants, who have increased urinary excretion of this protein, which, according to the literature, is inversely correlated with GA. Taking into account the involvement of alpha-1-microglobulin in balancing the reactions of the antioxidant defense system, the increase in this indicator may indirectly indicate the intensity of the cascade of biochemical reactions associated with pathological oxidative stress in the setting of preterm birth and interrupted nephrogenesis [28,29].

Beta-2-microglobulin is a low molecular weight protein (11.8 Da) that forms the light chain of the major histocompatibility complex class I, is found on the cell membrane surface of all nucleated cells, is almost completely reabsorbed in the intact kidney, and is catabolized in the tubules [30-31]. This protein does not cross the placenta; according to the literature, its concentration is inversely related to GW. Beta-2-microglobulin levels are a sensitive indicator of tubular dysfunction in neonates with moderate to severe asphyxia [30-32]. According to the literature, beta-2-microglobulin levels are significantly higher in preterm infants compared to term infants and gradually decrease with increasing postconceptional age [30-32]. This can be explained not only by the mechanisms of tubular differentiation that are actively taking place during the neonatal period, but also by the balance of the antioxidant defense system, as beta-2-microglobulin partially represents the severity of proinflammatory changes in the body of the AKI due to hypoxic stress [30-32].

Microalbuminuria [30-32] precedes proteinuria by its mechanism of occurrence, as there is a steady excretion of low molecular weight proteins in the presence of immature glomeruli and/or their damage. The reduction of the filtration surface in immature kidneys with a reduced number of nephrons leads to a decrease in renal function (Brenner's theory of hyperfiltration). It is microalbuminuria that precedes a decrease in glomerular filtration rate (GFR), and some studies have shown that in premature infants, microalbuminuria and subsequent proteinuria are associated with the loss of podocytes that provide ultrafiltration mechanisms. Persistent microalbuminuria has been shown to be a predictor of permanent renal dysfunction, particularly in chronic kidney disease [30-32].

The ROC curves of the above biomarkers as well as their sensitivity and specificity data in neonates of the study groups are shown in Diagrams 1-3 and Tables 2-4.

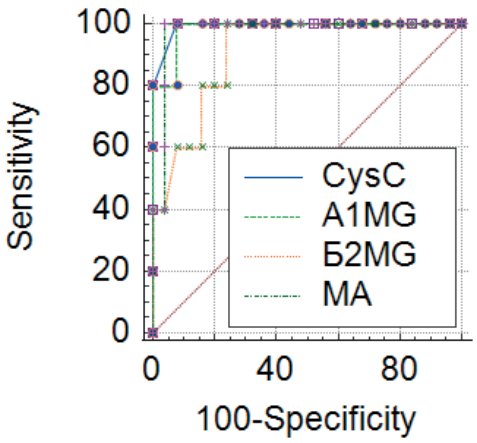

Diagram 1. Summary analysis of ROC curves of laboratory biomarkers of kidney injury in neonates of study group I

Table 2

Analysis of ROC curves of laboratory biomarkers of renal injury in neonates in Study Group I

Index	AUC	Standard error	p	95% DI
CisC, mg/L	0,992	0,00973	<0,0001	0,870-1,000
MA, mg/L	0,976	0,0259	<0,0001	0,843-1,000
α1MG, mg/L	0,984	0,0195	<0,0001	0,856-1,000
β2MG, mg/L	0,908	0,0596	<0,0001	0,745-0,982

ISSN 2226-1230 (PRINT) ISSN 2413-4260 (ONLINE)
KEY TITLE: NEONATOLOGIÂ, HIRURGIÂ TA PERINATAL'NA MEDICINA (ONLINE)
ABBREVIATED KEY TITLE: NEONATOL. HIR. PERINAT. MED. (ONLINE)

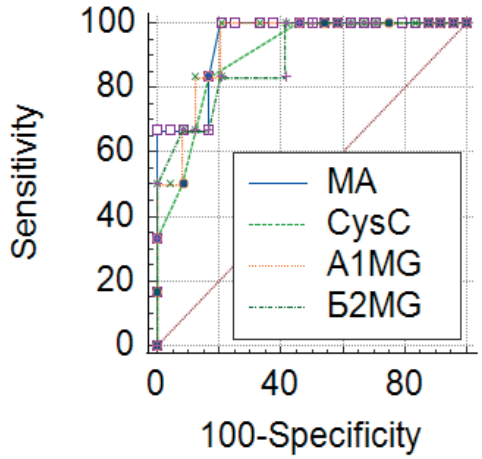

Diagram 2. Summary analysis of ROC curves of laboratory biomarkers of renal injury in neonates in study group II

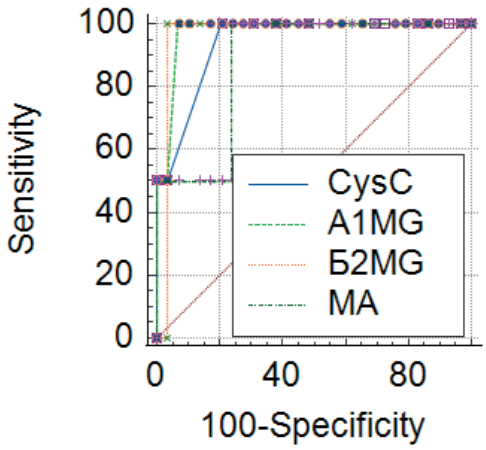

Diagram 3. Summary analysis of ROC curves of laboratory biomarkers of renal injury in neonates in study group III

Table 3

Analysis of ROC curves of laboratory biomarkers of renal injury in neonates in Study Group II

Index	AUC	Standard error	p	95% DI
CisC, mg/L	0,899	0,0601	<0,0001	0,734-0,979
MA, mg/L	0,941	0,0455	<0,0001	0,790-0,994
α1MG, mg/L	0,931	0,0473	<0,0001	0,775-0,991
β2MG, mg/L	0,892	0,0748	<0,0001	0,725-0,975

Table 4

Analysis of ROC curves of laboratory biomarkers of renal injury in neonates in Study Group III

Index	AUC	Standard error	p	95% DI
CisC, mg/L	0,940	0,0648	<0,0001	0,792-0,993
MA, mg/L	0,879	0,127	0,0029	0,712-0,968
α1MG, mg/L	0,974	0,0321	<0,0001	0,843-1,000
β2MG, mg/L	0,966	0,0345	<0,0001	0,830-0,999

Summarizing the results of the analysis of the ROC curves in the newborns of the study groups, it can be noted that these biomarkers are highly sensitive and specific not only for the detection of possible renal dysfunction, but also for the formation of a risk group – in PIs with moderate perinatal pathology, who are at risk of developing severe renal dysfunction. Thus, according to our data, the level of cystatin C in conditionally healthy PIs (group III of the study) was 0.73±0.03 mg/l, in PIs with moderate perinatal pathology (group II) – 0.98±0.04 mg/l, in PIs with severe perinatal pathology (group I) – 1.06±0.04 mg/l. Analysis of the results of cystatin C levels in blood plasma of newborns of the study groups showed that the highest values of cystatin C levels in blood plasma were observed in group I of newborns with severe perinatal pathology ($p < 0.0001$), and cystatin C levels in group II of the study were statistically significantly higher in comparison with the control group, as well as when comparing the groups among themselves (pIII-II <0. 0001, pIII-IB <0.0001, pIII-III <0.0001), which not only reflects a violation of glomerular filtration mechanisms against the background of severe morphological and functional immaturity, but may also indicate subclinical dysfunction of severe degree against the background of combined perinatal pathology in critically ill PIs.

The analysis of beta-2-microglobulin levels in the PIs of the study groups showed an inversely proportional correlation of this marker with GA, with the highest values in group I ($p < 0.0001$) compared to the control. Thus, the level of B2MG in conditionally healthy PIs (study group III) was 1.43±0.07 mg/l, in group II PIs with moderate perinatal pathology – 1.86±0.08 mg/l, in PIs with severe perinatal pathology (group I) – 3.85±0. 18 mg/l (pIII-II <0.0001, pIII-IB <0.0001, pIII-III <0.0001), which not only reflects the severity of tubular dysfunction, but also allows us to speak to some extent about the degree of hypoxic renal damage.

Analysis of alpha-1-microglobulin levels in preterm infants of the study groups showed an inversely proportional correlation of this marker with GA, with the highest values in group I ($p < 0.0001$). The level of α1MG in the control group (study group III) was 8.64±0.40 mg/l, in group II of PIs with moderate perinatal severity – 11.79±0.27 mg/l, in PIs with severe perinatal pathology (group I) – 15.43±0.54 mg/l (pIII-II <0.0001, pIII-IB <0.0001, pIII-III <0.0001). When comparing the groups by severity

of disease, statistically significant differences were also found between group I and group II ($p < 0.0001$). This may also indicate that "late" preterm infants, in terms of the formation of mechanisms of postnatal renal adaptation from an anatomical and physiological point of view, resemble "conditionally mature" kidneys in newborns at 37 weeks and older.

Analysis of microalbuminuria levels in PIs of the study groups showed that the highest values were observed in newborns of group I with severe forms of perinatal pathology ($p<0.0001$) and were statistically significantly higher in children of group II compared to controls. The level of MA in the control group (study group III) was 5.08±0.21 mg/l, in group II of PIs with moderate perinatal pathology – 8.20±0.23 mg/l, in PIs with severe perinatal pathology (group I) – 14.89±0.41 mg/l (p III-II <0.0001, p II-IIB <0.0001, p II-III <0.0001). The results of the study, which showed not only an inverse correlation between GA and weight, but also an inverse correlation with the index of total urinary protein, indicate that when interpreting the general urine analysis, overt proteinuria occurred only in neonates with severe perinatal pathology in critically ill preterm infants, whereas microalbuminuria at 34-36 weeks of age was mostly latent and, in the presence of concomitant perinatal pathology, may indicate preclinical moderate tubular dysfunction.

Thus, the development of renal dysfunction in PIs of the study groups is influenced by a complex of factors that, in combination with moderate or severe perinatal pathology, can cause the development of renal dysfunction, including the most threatening pathological syndrome – acute kidney injury. However, this condition is potentially reversible with timely early prognosis with the appropriate formation of risk groups for the development of renal dysfunction in PIs, including the use of minimally invasive, highly sensitive and specific biomarkers of renal damage, as well as to some extent to improve differential diagnostic approaches to determine the severity of disorders.

Conclusions

1. The development of severe and moderate urinary system dysfunction in premature infants in the presence of perinatal pathology is based on multifactorial etiological factors and a significant amount of potentially nephroaggressive interventions aimed at maintaining vital activity and ensuring the body's adaptation to the conditions of extrauterine life.
2. Differential diagnosis of urinary system dysfunction by routine methods, taking into account the high frequency of multisystem mismatch in critically ill premature infants with combined perinatal pathology, is significantly difficult in the context of diagnosing an isolated syndrome against the background of morphological and functional immaturity of the body.
3. The identification of modern promising biomarkers of urinary system damage in premature infants is the main problem of neonatal nephrology, since the search for a set of ideal biomarkers is significantly limited due to the physiological characteristics of the organism of this pediatric cohort.

Prospects for further research. A significant diversity of literature data is due to the lack of large-scale multicenter studies, although in recent years the attention of scientists and leading clinicians has been focused on the search for new unified strategies for prognosis and differential diagnosis to cover the problem at the preclinical stage of pathology development. This creates the need for further in-depth study of the main mechanisms of pathogenesis of renal dysfunction, taking into account the gestational age of newborns in association with perinatal pathology.

Conflicts of interest. There are no actual or potential conflicts of interest related to this publication.

Funding sources. The article was published without financial support.

References:

1. Al-Mouqdad MM, Huseynova R, Khalil TM, Asfour YS, Asfour SS. Relationship between intraventricular hemorrhage and acute kidney injury in premature infants and its effect on neonatal mortality. Sci Rep. 2021; 24;11(1):13262. doi: https://doi.org/10.1038/s41598-021-92746-3

2. Savrun T., Kocherha Z., Chekotun TV, Bykovska OA, Kyslov YO. Doslidzhennia hostroho urazhennia nyrok u peredchasno narodzhenykh novonarodzhenykh, yaki zaznaly vplyvu perynatalnoi hipoksii.[Study of acute kidney injury in premature neonates exposed to perinatal hypoxia]. 2017; 4(62): 71-76. doi: https://doi.org/10.26724/2079-8334-2017-4-62-71-76

3. Frunza AV. Hostre poshkodzhennia nyrok u peredchasno narodzhenykh ditei: perynatalni chynnyky ryzyku. [Acute kidney injury in premature infants: perinatal risk factors.] Neonatolohiia, khirurhiia ta perynatalna medytsyna. 2019;2 (32):45-52.
doi: https://doi.org/10.24061/2413-4260.IX.2.32.2019.7

4. Phrunza A, Hodovanets Y, Babintseva A, Kovtyuk N, Makarova O. Laboratory Diagnostic Criteria of Renal Impairment in Premature Newborns with Severe Perinatal Pathology. International Conference on Innovations in Science and Education. Proceeding of CBU in Medicine. 2021;1: 12-17. doi: https://doi.org/10.12955/pmp.v1.91

5. Hodovanets Y, Frunza. Predyktory ta kliniko-paraklinichni osoblyvosti porushen funktsionalnoho stanu sechovydilnoi systemy u peredchasno narodzenykh ditei. [Predictive factors and clinical and paraclinical features of urinary tract dysfunction in preterm infant]. Neonatolohiia, khirurhiia ta perynatalna medytsyna. 2023; 13 (4(50):40-48.
doi: https://doi.org/10.24061/2413-4260.XIII.4.50.2023.5

6. Lee CC, Chan OW, Lai MY, Hsu KH, Wu TW, Lim WH, Wang YC, Lien R. Incidence and outcomes of acute kidney injury in extremely-low-birth-weight infants. PLoS One. 2017; 12(11): e0187764. doi: https://doi.org/10.1371/journal.pone.0187764

7. Joyce EL, Kane-Gill SL, Fuhrman DY, Kellum JA. Drug-associated acute kidney injury: who's at risk? Pediatr Nephrol. 2017, 32(1):59-69. doi: https://doi.org/10.1007/s00467-016-3446-x

8. Gallo D, de Bijl-Marcus KA, Alderliesten T, Lilien M, Groenendaal F. Early Acute Kidney Injury in Preterm and Term Neonates: Incidence, Outcome, and Associated Clinical Features. Neonatology. 2021;118(2):174-179. doi: https://doi.org/10.1159/000513666

9. Raina R, Chakraborty R, Tibrewal A, Sethi SK, Bunchman T. Advances in pediatric acute kidney injury. Pediatr Res. 2022, 91(1):44-55. doi: https://doi.org/10.1038/s41390-021-01452-3

10. Nieuwenhuijs-Moeke GJ, Pischke SE, Berger SP, Sanders JSF, Pol RA, Struys MMRF, Ploeg RJ, Leuvenink HGD. Ischemia and Reperfusion Injury in Kidney Transplantation: Relevant Mechanisms in Injury and Repair. J Clin Med. 2020, 17;9(1):253. doi: https://doi.org/10.3390/jcm9010253

11. Selewski DT, Akcan-Arikan A, Bonachea EM, Gist KM, Goldstein SL, Hanna M, Joseph C, Mahan JD, Nada A, Nathan AT, Reidy K, Staples A, Wintermark P, Boohaker LJ, Griffin R, Askenazi DJ, Guillet R; Neonatal Kidney Collaborative. The impact of fluid balance on outcomes in critically ill near-term/term neonates: a report from the AWAKEN study group. Pediatr Res. 201, 85(1):79-85. doi: https://doi.org/10.1038/s41390-018-0183-9

12. Starr MC, Charlton JR, Guillet R, Reidy K, Tipple TE, Jetton JG, Kent AL, Abitbol CL, Ambalavanan N, Mhanna MJ, Askenazi DJ, Selewski DT, Harer MW; Neonatal Kidney Collaborative Board. Advances in Neonatal Acute Kidney Injury. Pediatrics. 2021, 148(5): e2021051220. doi: https://doi.org/10.1542/peds.2021-051220

13. Xu X, Nie S, Xu H, Liu B, Weng J, Chen C, Liu H, Yang Q, Li H, Kong Y, Li G, Wan Q, Zha Y, Hu Y, Xu G, Shi Y, Zhou Y, Su G, Tang Y, Li Y, Su L, Chen R, Cao Y, Gao P, Zhou S, Zhang X, Luo F, Xu R, Gao Q, Hou FF. Detecting Neonatal AKI by Serum Cystatin C. J Am Soc Nephrol. 2023, 1;34(7):1253-1263. doi: https://doi.org/10.1681/asn.0000000000000125

14. Sokou R, Tritzali M, Piovani D, Konstantinidi A, Tsantes AG, Ioakeimidis G, Lampridou M, Parastatidou S, Iacovidou N, Kokoris S, Nikolopoulos GK, Kopterides P, Bonovas S, & Tsantes A. Comparative Performance of Four Established Neonatal Disease Scoring Systems in Predicting In-Hospital Mortality and the Potential Role of Thromboelastometry. Diagnostics. 2021, 11(11), 1955. doi: https://doi.org/10.3390/diagnostics11111955

15. Richardson, D K, Corcoran JD, Escobar, GJ, Lee SK. SNAP-II and SNAPPE-II: Simplified newborn illness severity and mortality risk scores. The Journal of pediatrics. 2001, 138(1), 92-100. doi: https://doi.org/10.1067/mpd.2001.109608

16. Cetinkaya M, Köksal N, Özkan H. A new scoring system for evaluation of multiple organ dysfunction syndrome in premature infants. American journal of critical care: an official publication, American Association of Critical-Care Nurses. 2012, 21(5), 328-337. doi: https://doi.org/10.4037/ajcc2012312

17. KDIGO AKI Work Group: KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012, 2:1-138. https://kdigo.org/guidelines/acute-kidney-injury/

18. Capelli I, Vitali F, Zappulo F, Martini S, Donadei C, Cappuccilli M, Leonardi L, Girardi A, Aiello V, Galletti S, Faldella G, Poluzzi E, DE Ponti F, Gaetano M. Biomarkers of Kidney Injury in Very-low-birth-weight Preterm Infants: Influence of Maternal and Neonatal Factors. In Vivo. 2020, 34(3):1333-1339. doi: https://doi.org/10.21873/invivo.11910

19. Fang F, Hu X, Dai X, Wang S, Bai Z, Chen J, Pan J, Li X, Wang J, Li Y. Subclinical acute kidney injury is associated with adverse outcomes in critically ill neonates and children. Crit Care. 2018, 10;22(1):256. doi: https://doi.org/10.1186/s13054-018-2193-8

20. Yang Y, Wu Y, Pan JJ, Cheng R. Change of cystatin C values in preterm infants with asphyxia-From two centers of China. J Clin Lab Anal. 2017, 31(5): e22070. doi: https://doi.org/10.1002/jcla.22070

21. Correa LP, Marzano ACS, Silva Filha R, Magalhães RC, Simoes-E-Silva AC. Biomarkers of renal function in preterm neonates at 72h and 3weeks of life. J Pediatr (Rio J). 2021, 97(5):508-513. doi: https://doi.org/10.1016/j.jped.2020.11.006

22. Salem F, Johnson TN, Hodgkinson ABJ, Ogungbenro K and Rostami-Hodjegan A. Does «Birth» as an Event Impact Maturation Trajectory of Renal Clearance via Glomerular Filtration? Reexamining Data in Preterm and Full-Term Neonates by Avoiding the Creatinine Bias. The Journal of Clinical Pharmacology, 2021, 61: 159-171 doi: https://doi.org/10.1002/jcph.1725

23. Filler G, Ferris MED. Discrepant changes of urinary cystatin C and other urinary biomarkers in preterm neonates. J Pediatr. 2021, 97(5):473-475. doi: https://doi.org/10.1016/j.jped.2021.02.002

24. Kandasamy Y, Rudd D. Cystatin C: A more reliable biomarker of renal function in young infants? A longitudinal cohort study. Acta Paediatr. 2021, 110(4):1341-1345. doi: https://doi.org/10.1111/apa.15538

25. Barbati A, Aisa MC, Cappuccini B, Zamarra M, Gerli S, Di Renzo GC. Urinary Cystatin-C, a marker to assess and monitor neonatal kidney maturation and function: validation in twins. Pediatr Res. 2021, 89(4):932-939. doi: https://doi.org/10.1038/s41390-020-0965-8

26. Levin-Schwartz Y, Curtin P, Svensson K, Fernandez NF, Kim-Schulze S, Hair GM, Flores D, Pantic I, Tamayo-Ortiz M, Luisa Pizano-Zárate M, Gennings C, Satlin LM, Baccarelli AA, Tellez-Rojo MM, Wright RO, Sanders AP. Length of gestation and birth weight are associated with indices of combined kidney biomarkers in early childhood. PLoS One. 2019, 31;14(12): e0227219. doi: https://doi.org/10.1371/journal.pone.0227219

27. Romantsik O, Agyemang AA, Sveinsdóttir S, Rutardóttir S, Holmqvist B, Cinthio M, Mörgelin M, Gumus G, Karlsson H, Hansson SR, Åkerström B, Ley D, Gram M. The heme and radical scavenger α1-microglobulin (A1M) confers early protection of the immature brain following preterm intraventricular hemorrhage. J Neuroinflammation. 2019, 7;16(1):122. doi: https://doi.org/10.1186/s12974-019-1486-4

28. Hansson M, Gustafsson R, Jacquet C, Chebaane N, Satchell S, Thunberg T, Ahlm C, Fors Connolly AM. Cystatin C and α-1-Microglobulin Predict Severe Acute Kidney Injury in Patients with Hemorrhagic Fever with Renal Syndrome. Pathogens. 2020, 18;9(8):666. doi: https://doi.org/10.3390/pathogens9080666

29. Van den Eynde J, Salaets T, Louw JJ, Herman J, Breysem L, Vlasselaers D, Desmet L, Meyns B, Budts W, Gewillig M, Mekahli D. Persistent Markers of Kidney Injury in Children Who Developed Acute Kidney Injury After Pediatric Cardiac Surgery: A Prospective Cohort Study. J Am Heart Assoc. 2022, 5;11(7): e024266. doi: https://doi.org/10.1161/jaha.121.024266

30. Batista Muñoz A, Hadley S, Iriondo Sanz M, Agut Quijano T, Camprubí Camprubí M. Role of beta-2-microglobulin as a biomarker in very preterm and extremely preterm infants with CNS inflammation. PLoS One. 2019, 7;14(5): e0216498. doi: https://doi.org/10.1371/journal.pone.0216498

31. Nagai S, Fujioka K, Minamikawa S, Nozu K, Iijima K. Bilateral Renal Hypoplasia with High β2-Microglobulinuria in the Neonatal Period. Kobe J Med Sci. 2021 Aug 2;67(1): E34-E37. PMID: 34344855; PMCID: PMC8622258. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8622258/

32. Levin-Schwartz Y, Curtin P, Svensson K, Fernandez NF, Kim-Schulze S, Hair GM, Flores D, Pantic I, Tamayo-Ortiz M, Luisa Pizano-Zárate M, Gennings C, Satlin LM, Baccarelli AA, Tellez-Rojo MM, Wright RO, Sanders AP. Length of gestation and birth weight are associated with indices of combined kidney biomarkers in early childhood. PLoS One. 2019, 31;14(12): e0227219. doi: https://doi.org/10.1371/journal.pone.0227219

ДИСФУНКЦІЯ НИРОК ПЕРЕДЧАСНО НАРОДЖЕНИХ ДІТЕЙ З ПЕРИНАТАЛЬНОЮ ПАТОЛОГІЄЮ: ФАКТОРИ РИЗИКУ, ЧУТЛИВІСТЬ ТА СПЕЦИФІЧНІСТЬ ЛАБОРАТОРНИХ МАРКЕРІВ УРАЖЕННЯ

А. В. Фрунза, Ю. Д. Годованець

Буковинський державний медичний університет
(м. Чернівці, Україна)

Резюме.

Основний тягар неонатальної захворюваності серед критично хворих передчасно народжених дітей, незважаючи на вагомі досягнення та стрімкий розвиток технологій виходжування, на сучасному етапі найчастіше пов'язують із неонатальним сепсисом, перинатальною асфіксією та розвитком синдрому поліорганної невідповідності. Як складова даного синдрому у новонароджених, що мали комбіновану перинатальну патологію впродовж раннього неонатального періоду, маніфестує важка ренальна дисфункція аж до виникнення гострого пошкодження нирок, що тісно корелює з підвищенням летальності. Частота гострого пошкодження нирок у критично хворих передчасно народжених дітей значно варіює і за різними даними новонароджених складає від 25 до 77 %. Суттєвою проблемою у галузі неонатальної нефрології залишається відсутність уніфікованих підходів до діагностики дисфункції нирок середнього та важкого ступеню на субклінічному етапі, що дозволило би своєчасно формувати групи ризику та оптимізувати інтервенційні стратегії.

Мета дослідження. Провести аналіз даних клінічної характеристики, факторів ризику та результатів додаткового параклінічного обстеження у передчасно народжених дітей з гестаційним віком 34-36/6 тижнів, що мали перинатальну патологію важкого та середнього ступеню впродовж раннього неонатального періоду.

Матеріал та методи дослідження. Проведено комплексне дослідження 91 передчасно народженої дитини з перинатальною патологією середнього та важкого ступеню, з яких I групу склали 30 дітей гестаційним віком 34-36/6 тижнів з важкою перинатальною патологією та II групу – 30 дітей з гестаційним віком 34-36/6 тижнів, що мали перинатальну патологію середнього ступеня важкості; до III (контрольної) групи увійшли 31 умовно здорова передчасно народжена дитина з гестаційним віком 34-36/6 тижнів.

Діагностику гострого пошкодження нирок у новонароджених дітей груп порівняння було проведено згідно Міжнародних критеріїв Kidney Disease: Improving Global Outcomes у модифікації за J. G. Jetton та D. J. Askenazi (2015). Для оцінювання ступеня важкості поліорганної невідповідності за умов перинатальної патології було використано міжнародну шкалу шкалу Neonatal Multiple Organ Dysfunction Score. Ефективність терапевтичних інтервенцій було оцінено з використанням міжнародної шкали Neonatal Therapeutic Intervention Scoring, а важкість стану пацієнтів у динаміці – за допомогою неонатальної шкали Score for Neonatal Acute Physiology.

Дослідження біохімічного спектру сечі у дітей груп спостереження, зокрема визначення рівня маркерів ураження нирок – альфа-1-мікроглобуліну, бета-2-мікроглобуліну, мікроальбуміну, цистатину С було проведено на базі проблемної науково-дослідної лабораторії Буковинського державного медичного університету МОЗ України з використанням автоматичного аналізатору «ACCENT-200» та «ACCENT-200 II CEN». Забір сечі проводився на 3-у добу життя дитини (у проміжку між 48-72 годинами життя), у одноразові стерильні контейнери, у кількості не менше 5 мл. Забір крові для визначення рівня цистатіну С було проведено у аналогічні терміни, у кількості 0,5-1,0 мл, із дотриманням правил асептики та антисептики у одноразові стерильні пробірки. Для визначення концентрації цистатіну С та мікроальбуміну сечі було використано турбодиметричний імунологічний метод. Визначення вмісту альфа-1-мікроглобуліну було проведено за допомогою автоматичного аналізатору ACCENT-200 шляхом визначення аглютинації за зміною абсорбції (572 нм), з визначенням актуальної концентрації шляхом інтерполяції з калібрувальною кривою побудованої за калібраторами з відомою концентрацією. Визначення концентрації бета-2-мікроглобуліну у сечі було проведено з використанням методу конкурентного хемілюмініцентного аналізу.

Дослідження виконувалися із дотриманням основних положень GCP (1996 рік), Конвенції Ради Європи про права людини та біомедицину (від 4 квітня 1997 р.), Гельсінської декларації Всесвітньої медичної асоціації про етичні принципи проведення наукових медичних досліджень за участю людини (1964-2008 рр.), наказу МОЗ України № 690 від 23.09.2009 р. (із змінами, внесеними згідно з Наказом Міністерства охорони здоров'я України № 523 від 12.07.2012 р.).

Статистичний аналіз отриманих результатів здійснено за допомогою програмного забезпечення «Statistica 10» (StatSoft Inc., США, 2010), MedCalc Software (Version 16.1) з розрахунком відношення шансів коефіцієнту ексцесу (Chi-squared), коефіцієнту співвідношення шансів (КСШ, Odds ratio, OR), 95 % довірчого інтервалу (95 % Confidence Interval, CI), статистично значимі відмінності між групами дослідження було враховано при значенні $p<0,005$. За допомогою MedCalc Software (Version 16.1) було проведено аналіз ROC-кривих (Receiver Operating Characteristic Curve – операційних характеристичних кривих), AUROC (Area Under ROC) – площа під операційною характеристичною кривою, а також чутливості (ЧТ, Sensitivity) та специфічності (СП, Specificity).

Дисертаційна робота виконувалась у межах науково-дослідних робіт кафедри педіатрії, неонатології та перинатальної медицини Буковинського державного медичного університету: НДР «Удосконалення напрямків прогнозування, діагностики і лікування перинатальної патології у новонароджених та дітей раннього віку, оптимізація схем катамнестичного спостереження та реабілітації» (Державний реєстраційний номер 0115U002768, терміни виконання 2015-2019 рр.); НДР «Хронобіологічні й адаптаційні аспекти та особливості вегетативної регуляції при патологічних станах у дітей різних вікових груп» (Державний реєстраційний номер 0122U002245, терміни виконання 2020-2024 рр.)

Результати дослідження. Отримані дані продемонстрували статистично значимі асоціації між ризиком розвитку важкої дисфункції нирок та низкою антенатальних та постнатальних факторів, що несприятливо впливають на перебіг раннього неонатального періоду. Відмічено дистрес плоду під час вагітності та пологів, ургентний кесарев розтин, загроза самовільного викидня та передчасних пологів, порушення плодово-плацентарного кровотоку. Статистично значимі асоціації щодо розвитку дисфункції нирок помірного та важкого ступеню мають обтяжений анамнез щодо екстрагенітальної патології у матері, а саме, патології серцево-судинної, сечовидільної системи та анемії ($p<0,005$). Структура перинатальної патології у передчасно народжених дітей дуже часто є комбінованою та складною для діагностики. Значна частина новонароджених мала клінічні прояви синдрому поліорганної недостатності, в комплексі якого були ознаки дисфункції нирок. Це обумовлює доцільність вивчення

ISSN 2226-1230 (PRINT) ISSN 2413-4260 (ONLINE)
KEY TITLE: NEONATOLOGÌÂ, HÌRURGÌÂ TA PERINATAL'NA MEDICINA (ONLINE)
ABBREVIATED KEY TITLE: NEONATOL. HÌR. PERINAT. MED. (ONLINE)

комплексу новітніх потенційних біомаркерів ренальної дисфункції, зокрема таких як цистатін С, альфа-1-мікроглобулін, бета-2-мікроглобулін та мікроальбумін для створення відповідної прогностичної моделі та своєчасного формування груп ризику серед зазначеної категорії дітей.

Висновки. Основою розвитку ренальної дисфункції помірного та важкого ступеню у передчасно народжених дітей за умов перинатальної патології є поліетіологічність на фоні морфо-функціональної незрілості організму, що має чіткий зв'язок із гестаційним віком та масою тіла при народженні. Компенсаторно-пристосувальні особливості «незрілих» нирок на момент народження є лімітованими, що за наявності поєднаної патології відіграє суттєву роль для формування важкості перебігу захворювань. Своєчасне прогнозування та діагностика дисфункції нирок на ранніх етапах її розвитку надає можливість підвищення якості та ефективності медичної допомоги та покращення результатів лікування.

Ключові слова: діти; передчасно народжені діти; гостре пошкодження нирок; чинники ризику; клінічні особливості; лабораторна діагностика.

Contact Information:
Alina Frunza – Postgraduate student, Department of Pediatrics, Neonatology and Perinatal Medicine, Bukovinian State Medical University (Chernivtsi, Ukraine).
e-mail: frunzaalina@ukr.net
ORCID ID: http://orcid.org/0000-0002-9178-5004
Researcher ID: http://www.researcherid.com/rid/AAY-1624-2021

Yuliya Hodovanets – PhD, Doctor of Medicine, Professor, Professor of Department of Pediatrics, Neonatology and Perinatal Medicine, Bukovinian State Medical University (Chernivtsi, Ukraine).
e-mail: yul.godovanets@gmail.com
ORCID ID: http://orcid.org/0000-0003-0922-8696
Resercher ID: http://www.researcherid.com/rid/S-8224-2016
Scopus Author ID: https://www.scopus.com/authid/detail.uri?authorId=57205579303

Контактна інформація:
Фрунза Аліна Владиславівна – аспірант кафедри педіатрії, неонатології та перинатальної медицини Буковинського державного медичного університету (м. Чернівці, Україна).
e-mail: frunzaalina@ukr.net
ORCID ID: http://orcid.org/0000-0002-9178-5004
Researcher ID: http://www.researcherid.com/rid/AAY-1624-2021

Годованець Юлія Дмитрівна – доктор медичних наук, професор, професор кафедри педіатрії, неонатології та перинатальної медицини Буковинського державного медичного університету (м. Чернівці, Україна).
e-mail: yul.godovanets@gmail.com
ORCID ID: http://orcid.org/0000-0003-0922-8696
Resercher ID: http://www.researcherid.com/rid/S-8224-2016
Scopus Author ID: https://www.scopus.com/authid/detail.uri?authorId=57205579303

Received for editorial office on 23/12/2023
Signed for printing on 10/02/2024