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PREDICTIVE FACTORS AND CLINICAL AND PARACLINICAL FEATURES OF URINARY TRACT DYSFUNCTION IN PRETERM INFANTS

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Summary

Acute kidney injury is a multifactorial clinical pathological syndrome that falls within the critical conditions of the early neonatal period and independently associates with high rates of morbidity and mortality. The frequency of acute kidney injury in critically ill preterm infants varies significantly, ranging from 25 % to 77 % according to different studies. Numerous scientific investigations describe an inversely proportional correlation between gestational age and birth weight. Of particular importance in terms of pathophysiology is the understanding of the concept of 'functional acute kidney injury,' clinically characterized by a reduction in glomerular filtration rate in the absence of markers of tubular damage. Consequently, it represents potentially reversible changes in renal function, sensitive to both the duration and depth of the alterations, which precede the development of injury.

***Aim** of the study: To conduct an analysis of clinical characteristics, risk factors, and results of paraclinical examinations in preterm infants with gestational ages of 25-31 and 32-33 weeks, who exhibited signs of severe functional disturbances in the urinary system during the early neonatal period as part of complex perinatal pathology.*

***Materials and Methods:** A comprehensive clinical and paraclinical examination was conducted on 93 preterm infants with severe perinatal pathology. Group I comprised 30 infants with gestational ages of 25-31 weeks, while Group II consisted of 32 infants with gestational ages of 32-33 weeks. Group III included 31 conditionally healthy preterm infants with gestational ages of 34-36 weeks.*

Verification of the diagnosis of renal dysfunction was performed according to the recommended international classification 'Kidney Disease: Improving Global Outcomes' with the modification by J. G. Jetton and D. J. Askenazi (2015). The degree of severity of polyorgan deficiency in perinatal pathology in newborns was assessed using the Neonatal Multiple Organ Dysfunction Score. The effectiveness of therapeutic interventions was evaluated using the Neonatal Therapeutic Intervention Scoring scale. The severity of the newborns' condition during observation was assessed using the Score for Neonatal Acute Physiology scale.

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

Statistical analysis of the obtained research results was performed using the software packages «Statistica 10» (StatSoft Inc., USA, 2010) and MedCalc Software (Version 16.1), with calculations including the odds ratio excess coefficient (Chi-squared), odds ratio (OR), and 95 % confidence interval (CI). Statistically significant differences between groups were considered at a significance level of $p < 0.005$.

The dissertation work was conducted within the scientific focus of the Department of Pediatrics, Neonatology, and Perinatal Medicine at Bukovinian State Medical University. The research themes included: a research project on 'Improvement of Prognostic, Diagnostic, and Therapeutic Approaches to Perinatal Pathology in Newborns and Infants, Optimization of Follow-up and Rehabilitation Schemes' (State registration number 0115U002768, duration from 01.2015 to 12.2019); and a research project on 'Chronobiological and Adaptive Aspects, as well as Features of Vegetative Regulation in Pathological Conditions in Children of Different Age Groups' (State registration number 0122U002245, duration from 01.2020 to 12.2024).

***Research Results:** The obtained results demonstrated statistically significant associations between the severity of perinatal pathology in preterm infants and the depth of dysfunction in the urinary system, as well as a complex set of factors complicating the course of pregnancy and childbirth in mothers, thereby influencing the postnatal adaptation of the child. Among the reasons for complicated pregnancies, notable factors included anemia, cardiovascular and urinary system pathology, TORCH infections, isthmo-cervical insufficiency, disturbances in fetal-placental blood flow, the threat of spontaneous abortion, and premature labor. Anomalies such as abnormal fetal presentation, fetal distress, premature rupture of membranes, and urgent cesarean section were more likely to occur in women in this group. The course of perinatal pathology in newborns with gestational ages less than 33 weeks at birth was predominantly severe, with some children diagnosed with multiple organ dysfunction syndrome, one manifestation of which was acute kidney injury. Changes in the indicators of general and biochemical blood analysis in newborns reflected low compensatory reserves of the neonatal organism in the context of experienced hypoxia and morpho-functional immaturity associated with premature birth.*

***Conclusions:** The formation of renal dysfunction in preterm infants in the early neonatal period has a complex polyetiological nature associated with a set of adverse factors during pregnancy and childbirth in mothers. Critically ill newborns represent a primary and challenging pediatric cohort in which this pathological syndrome is linked to high neonatal mortality rates and the development of functional and chronic pathology of the urinary system in later years, justifying the need for in-depth scientific research to consolidate perspectives on providing medical care to preterm infants.*

***Key words:** Preterm Infants; Renal Dysfunction; Risk Factors; Clinical Features; Laboratory Diagnostic Criteria.*

Introduction

One of the threatening pathological conditions contributing to a high incidence and mortality rate in perinatal pathology among preterm infants (PTIs) is acute kidney injury (AKI), with a frequency ranging from 25 to 56 % within this infant cohort [1-3]. Various studies have demonstrated that the epidemiology of renal dysfunction in children has significantly evolved over the past few decades. Scientific data on kidney diseases exhibit extraordinary variability, primarily due to differences in criteria used to

define the condition, the absence of a unified approach to diagnosis, and the nonspecific clinical manifestations [4-6].

According to Charlton D. R.'s literature, the frequency of early neonatal acute kidney injury (AKI) (within the first 7 days of life) varies, taking into account different gestational age (GA) cohorts: 22-28 weeks – 28 % of cases, 29-35 weeks – 14 % of cases, and ≥36 weeks – 27 % of cases. The average number of days from birth to the first episode of renal dysfunction is typically 2.8±1.8 days. Early manifestations of AKI are independently associated with higher mortality and longer hospitalization compared to infants without kidney disorders [7]. Askenazi D. J.'s study (2020) describes the frequency distribution of AKI among children of different GAs as follows: 43 % in newborns with GA <29 weeks, 18 % in children with GA between 29 and 36 weeks, and 37 % in infants with GA >36 weeks. Analyzing the scientific literature reveals some discrepancies in the frequency of pathology among newborn groups of different gestational ages. Numerous studies note a reverse correlation between GA, body weight, and the frequency of AKI during the early neonatal period [8-10].

According to the literature, functional impairments of the urinary system in preterm infants (PTIs) have a multifactorial etiology closely associated with gestational age and low birth weight, often coexisting with clinical signs of respiratory distress syndrome (RDS), arterial hypotension, and birth asphyxia [11,12]. The administration of nonsteroidal anti-inflammatory drugs, diuretics, anticonvulsant, and inotropic drugs has an adverse impact on the development of renal functions in PTIs [11-13].

In recent years, numerous scientific discussions have been ongoing regarding the well-known marker of kidney dysfunction – plasma creatinine level (SCr). It is noted that an elevation in plasma creatinine levels, as well as a decrease in diuresis, are only late consequences of kidney damage, not indicators of acute injury. Therefore, active research is underway to identify new biomarkers for the diagnosis of acute kidney injury (AKI). Additionally, various measurement techniques, specific medications, and the presence of hyperbilirubinemia can distort the actual values of SCr levels in the first few days of a newborn's life [14,15]. Leading researchers in the field of neonatal nephrology are focused on studying novel biomarkers of tubular and glomerular kidney damage, which have demonstrated high diagnostic and prognostic value, including plasma cystatin C (Cys-C), urinary fractions of alpha-1-microglobulin (α1-MG), beta-2-microglobulin (β2-MG), and microalbumin (MA) [16-19].

In our opinion, there is a need for scientific research to deepen the understanding of potential pathogenetic mechanisms underlying the development of functional impairments in the urinary system in newborns, taking into account the severity of perinatal pathology and gestational age at birth, particularly in preterm infants.

Research Aim: to conduct an analysis of clinical characteristics, risk factors, and results of paraclinical examinations in preterm infants with gestational ages of 25-31 and 32-33 weeks, who presented severe perinatal pathology and exhibited signs of functional impairments in the urinary system during the early neonatal period.

The study presents a comprehensive analysis of data from exchange cards of pregnant women (Form № 113/o), labor histories (Form № 096/o), and newborn development histories (Form № 112/o) for 93 preterm neonates (PTN) receiving treatment at the Neonatal Intensive Care Unit (NICU) of the Municipal Clinical Maternity Hospital No. 2, Chernivtsi, during the period from 2017 to 2021.

Observation groups were formed considering gestational age (GA) at birth and the presence or absence of severe perinatal pathology signs. Accordingly, Group I comprised 30 newborns with GA of 25-31 weeks, Group II included 32 infants with GA of 32-33 weeks, and Group III consisted of 31 infants with GA of 34-36 weeks. The examination results of Group III served as a basis for comparing the clinical and laboratory indicators of the newborns in the main study groups.

The analysis involved reviewing and synthesizing information from prenatal, labor, and neonatal records to extract relevant clinical and paraclinical data. Statistical processing was performed using the «Statistica 10» software (StatSoft Inc., USA) and MedCalc Software (Version 16.1), employing Chi-squared test, Odds ratio (OR), and 95 % Confidence Interval (CI) calculations. Statistical significance was considered at $p<0.005$.

The study adhered to the principles of Good Clinical Practice (1996), the Council of Europe Convention on Human Rights and Biomedicine (April 4, 1997), the Helsinki Declaration of the World Medical Association on Ethical Principles for Medical Research Involving Human Subjects (1964-2008), and Ukrainian Ministry of Health Order No. 690 dated September 23, 2009, with subsequent amendments according to Order No. 523 dated July 12, 2012. The research was conducted within the scientific themes of the Department of Pediatrics, Neonatology, and Perinatal Medicine at Bukovinian State Medical University.

Inclusion Criteria: Children born with a gestational age between 25-36 weeks and a weight ≥ 500 g and < 2500 g were eligible for inclusion. Parental informed consent for participation in the clinical study was required. Exclusion Criteria: Children with a weight < 500 g or ≥ 2500 g, gestational age < 25 weeks or ≥ 37 weeks, lack of informed parental consent for participation in the clinical study, congenital developmental defects, and early neonatal sepsis were excluded from the study.

The severity of multiple organ dysfunction in newborns with perinatal pathology was assessed using the Neonatal Multiple Organ Dysfunction Score (NEOMOD, 2001) [18]. According to recommended criteria, the newborn's condition was scored (10 and > points indicated severe organ failure, 7-10 points indicated moderate, and <7 points indicated mild). The condition of newborns in Groups I and II was considered very severe with a NEOMOD score exceeding 7 points.

The effectiveness of therapeutic interventions was evaluated using the Neonatal Therapeutic Intervention Scoring (NTISS) scale [19]. The severity of the newborns' condition over time was assessed using the Score for Neonatal Acute Physiology (SNAPPE II) scale, followed by the calculation of the predicted risk of in-hospital mortality [20].

The degree of renal dysfunction severity was determined using the classification developed by the Kidney Disease: Improving Global Outcomes (KDIGO) International Expert

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Group, as modified by J. G. Jetton and D. J. Askenazi [21]. This classification is based on an increase in plasma creatinine levels of more than 26.5 μmol/L (with two consecutive measurements within 48 hours) and/or an hourly urine output of less than 0.5 ml/kg/hour over 6 hours.

The research was conducted in accordance with the fundamental principles of Good Clinical Practice (GCP) from 1996, the Council of Europe Convention on Human Rights and Biomedicine (April 4, 1997), the Helsinki Declaration of the World Medical Association on ethical principles for conducting medical research involving human subjects (1964-2008), and the Ukrainian Ministry of Health Order No. 690 dated September 23, 2009 (with amendments according to the Ministry of Health of Ukraine Order No. 523 dated July 12, 2012).

Statistical processing of the study results was performed on a PC using the Statistica 10 software package (StatSoft Inc., USA, 2010) and Microsoft Excel (2010), Microsoft Office (2010), and MedCalc software (version 16.1). Differences between relative values were determined and analyzed using the Fisher's signed rank test. Statistical values were calculated by analyzing the following indicators: standard deviation (S), standard error (m), arithmetic mean of the sample (M), using the Shapiro-Wilk test (normal distribution with sample size greater than 30, $p<0.05$) and the Kolgomorov-Smirnov test.

Assessment of differences in qualitative characteristics between study groups was performed using MedCalc software (Statistical software package for biomedical research, 2023) with calculation of the coefficient of variation (Chi-squared), odds ratio (OR), 95 % confidence interval (95 % CI). Statistically significant differences between groups were considered at $p<0.05$.

The dissertation work was conducted within the scientific focus of the Department of Pediatrics, Neonatology, and Perinatal Medicine at Bukovinian State Medical University. The research themes included: a research project on 'Improvement of Prognostic, Diagnostic, and Therapeutic Approaches to Perinatal Pathology in Newborns and Infants, Optimization of Follow-up and Rehabilitation Schemes' (State registration number 0115U002768, duration from 01.2015 to 12.2019); and a research project on 'Chronobiological and Adaptive Aspects, as well as Features of Vegetative Regulation in Pathological Conditions in Children of Different Age Groups' (State registration number 0122U002245, duration from 01.2020 to 12.2024).

Results and discussion. According to the assessment of anthropometric indicators in the observed groups at birth, the average body weight was 1105.66±128.53 g in Group I (95 % CI 1188.70-1313.97, $p<0.0001$), 1547.83±141.48 g in Group II (95 % CI 743.92-874.41, $p<0.0001$), significantly lower compared to the comparison group – 2357.00±115.78 g. The body length was accordingly 35.36±1.05 cm (95 % CI 10.37-11.30, $p<0.0001$) in Group I, 35.96±1.24 cm (95 % CI 9.71-10.76, $p<0.0001$) in Group II, and 46.20±0.76 cm in the comparison group. Newborns in the study groups were gender-representative, with a predominance of males in both groups (Group I – 20 boys (66.60 %, CI 10.40; 95 % CI 3.06-35.28, p = 0.0002), Group II – 24 boys (75.00 %, CI 20.80; 95 % CI 5.61-77.09, $p<0.0001$)), compared to the comparison group (5 boys, 16.10 %).

According to the KDIGO diagnostic criteria [21], severe renal dysfunction associated with perinatal pathology was diagnosed in 16 children (53.33 %) in Group I, including 4 cases (13.33 %) based on combined criteria (decreased hourly diuresis and pathological increase in plasma creatinine level), 4 cases (13.33 %) based on an increase in plasma creatinine level only, and 8 cases (26.66 %) based on a decrease in hourly diuresis. Among the newborns in group II, this pathology was diagnosed in 11 children (34.38 %), including 3 cases (9.37 %) based on two criteria (hourly diuresis level and pathological increase in plasma creatinine), 4 cases (12.48 %) based on increased plasma creatinine, and 4 cases (12.48 %) where the diagnosis was made because of a decrease in hourly diuresis.

Analysis of medical history, spectrum of extragenital and gynecological pathology in mothers of newborns in the observation groups, as well as features of pregnancy and childbirth, allowed us to identify the main perinatal risk factors for functional disorders of the urinary system in preterm newborns, 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:

– Maternal somatic and obstetric-gynecological history:

– maternal age (group I OR 22.94, 95 % CI 2.75-109.97, p=0.0038; group II OR 13.63, 95 % CI 1.62-114.52, p=0.0161)

– Maternal anemia grade II-III (group I, OR 12.68, 95 % CI 1.51-109.27, p=0.0019),

– cardiovascular diseases (group I, OR 58.00, 95 % CI 10.71-314.09, $p<0.0001$; group II, BMI 21.19, 95 % CI 4.29-104.67, p=0.0002),

– Urinary tract diseases (Group I OR 98.57, 95 % CI 1.31-858.66, $p<0.0001$; Group II OR 34.00, 95 % CI 4.12-280.41, p=0.0011)

– TORCH infections (group I OR 15.00, 95 % CI 1.77-126.48, p=0.0128),

– induced and spontaneous abortions, stillbirths, and history of children under one year of age (group I, OR 20.00, 95 % CI 2.39-166.96, p=0.0057),

- -Pregnancy and delivery characteristics:

– Risk of spontaneous abortion and preterm delivery (group I, HR 12.85, 95 % CI 2.55-62.99, p=0.0193)

– Impaired fetal-placental blood flow (group I, OR 34.28, 95 % CI 4.12-284.94, p=0.0011; group II, OR 11.73, 95 % CI 1.38-99.40, p=0.00238)

– Abnormal fetal presentation (group I, OR 12.85, 95 % CI 1.51-109.27, p=0.0193)

– fetal distress (group I, OR 29.00, 95 % CI 5.73-146.77, $p<0.0001$; group II, OR 11.27, 95 % CI 2.29-55.52, p=0.0029),

– cervical incompetence (group I, OR 17.36, 95 % CI 2.07-145.61, p=0.0085),

– Premature rupture of membranes (group I OR 15.00, 95 % CI 1.77-126.48, p=0.128; group II OR 12.85, 95 % CI 1.51-109.27, p=0.0193),

– Urgent cesarean section (group I OR 29.00, 95 % CI 5.73-146.77, $p<0.0001$; group II OR 7.70, 95 % CI 1.63-66.25, p=0.0098)

Table 1

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

Indicators	Group I (n=30)	Group II (n=32)	Group III (n=31)
First pregnancy	10 (33,30)	10 (31,25)	7 (22,54)
Repeated pregnancy	20 (66,70)	22 (68,75)	24 (77,46)
The first birth	10 (33,30)	13 (40,62)	9 (28,98)
Repeated birth	20 (66,70)	19 (59,38)	22 (71,02)
Urban residents	18 (59,94)	17 (53,12)	9 (28,98)
Rural residents	12 (40,06)	15 (46,88)	22 (71,02)
Natural childbirth	10 (33,30)	10 (31,25)	22 (73,26)
Emergency cesarean section	20 (66,70)*	17 (53,12)*	2 (6,44)
Planned cesarean section	-	5(15,62)	7(22,54)
Extragenital pathology			
Cardiovascular Diseases	24 (79,92)*	19 (59,37)*	2 (6,44)
Diseases of the urinary system	23 (76,59)*	17 (53,12)*	1 (3,22)
Respiratory diseases	6 (19,38)	4 (12,50)	-
Diseases of the gastrointestinal tract	9 (29,97)	8 (25,00)	-
Diseases of the endocrine system	11 (36,63)	9 (28,12)	1 (3,22)
Acute viral infections during pregnancy	8 (26,64)	5 (15,60)	1 (3,22)
An old firstborn	13 (43,29)*	10 (31,25)*	1 (3,22)
A young firstborn	2 (6,66)	2 (6,25)	-
Complicated obstetric history			
Induced and spontaneous abortions, stillbirths, children who died before one year of age	12 (40,06)*	4 (12,50)	1 (3,22)
Infertility	7 (23,31)	4 (12,50)	1 (3,22)
In vitro fertilization	6 (19,98)	3 (9,37)	1 (3,22)
History of preterm labor	4 (3,33)	2 (6,25)	1 (3,22)
Gynecological Pathology			
Vaginitis	9 (29,97)	6 (18,75)	1 (3,22)
Infections of the TORCH group	10 (33,30)*	6 (18,75)	1 (3,22)
Abnormalities in the development of the uterus	5 (16,65)	5 (15,60)	-
Cervical Incompeence	11 (36,63)*	8 (25,00)	1 (3,22)
Course of Pregnancy			
Risk of miscarriage, premature birth	9 (29,97)*	7 (21,87)	1 (3,22)
Anemia of the II-III grade.	14 (46,62)*	9 (28,12)	2 (6,44)
Feto-placental insufficiency with development of fetal retardation syndrome	16 (53,33)*	9 (28,12)*	1 (3,22)
Childbirth Complications			
Fetal distress	20 (66,70)*	14 (43,75)*	2 (6,44)
Prenatal death of one fetus out of twins	2 (6,66)	2 (6,25)	-
Premature rupture of the membranes	10 (33,30)*	9 (28,12)	1 (3,22)
Premature detachment of a normally positioned placenta	7 (23,31)	5 (15,60)	1 (3,22)
Uterine bleeding	6 (19,98)	3 (9,37)	-
Abnormal fetal presentation	9 (29,97)*	4 (12,50)	1 (3,22)

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

The obtained data coincide with the results of recent studies on the prognosis of the development of disorders of the functional state of the urinary system in newborns [7-10].

Analyzing the peculiarities of the course of perinatal pathology in children of the study groups, it should be noted that postnatal adaptation disorders were caused by typical conditions characteristic of premature birth. In particular, in all 30 cases children of group I (100 %) had severe respiratory disorders (RD) (6 and > points on the Downes scale); the average duration of stay on artificial lung ventilation (ALV) was 7.60±3.52 days. Neurological symptoms were represented by severe hypoxic-ischemic damage (HI) of the central nervous system (100 %), all children had depression syndrome; 4 newborns (13.32 %) had signs of intraventricular hemorrhage (IVH) of the first degree, in 4 children (13.32 %) – signs of IVH II, in 2 children (6.66 %) – signs of IVH III-IV; in 4 children (13.32 %) – periventricular leukomalacia (PVL) was diagnosed.

Clinical signs of cerebral edema were detected in 4 newborns (13.32 %), cerebral coma was diagnosed in 4 children (13.32 %), and 8 newborns (26.64 %) had clinical signs of convulsive syndrome. It should

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be noted that all children of this group had clinical manifestations of multiple organ failure syndrome (MOFS) in the dynamics of observation. In particular, in 30 cases (100 %) there were lesions of CNS and RS, in 9 cases (29.97 %) – lesions of cardiovascular system (CVS), in 7 cases (23.31 %) – anemic syndrome, in 9 cases (29.97 %) – hemorrhagic syndrome, in 8 cases (26.64 %) – phenomena of disseminated intravascular coagulation (DIC). 18 newborns of group I (59.94 %) had signs of gastrointestinal tract (GIT) disorders, including decreased food tolerance, and 6 children (19.98 %) had complete intolerance to enteral feeding. Nonspecific enterocolitis (NEC) of the first degree was diagnosed in 6 newborns (19.98 %) and NEC of the second degree in 2 newborns (6.66 %). 9 children (29.97 %) of this group had signs of neonatal jaundice in the first week of life. Among the newborns of this group, 11 children (36.63 %) had low birth weight, 2 children (6.66 %) were small for gestational age.

The condition of all newborns of group I from the moment of birth and during the treatment in the NICU remained serious and did not show significant positive dynamics. The duration of stay in the NICU was 8.46±3.29 days, after which the children were transferred to further stages of treatment.

The neonates of group II had clinical manifestations of severe respiratory distress immediately after birth in 18 cases (44.0 %), moderate respiratory distress in 11 cases (40.0 %), and mild respiratory distress in 3 cases (16.0 %), the severity of which increased during the first day of life. The mean duration of stay on ALV in neonates was 7.60±3.52 days. In 17 cases (53.12 %) clinical signs of CNS HI with dominance of depression syndrome were noted, in 5 cases (15.62 %) clinical signs of neonatal encephalopathy were noted, in 4 newborns (12.50 %) grade I IVH was diagnosed, in 3 newborns (9.37 %) – grade II IVH, in 2 infants (6.25 %) grade III-IV CHD was diagnosed, in 1 infant (3.12 %) PVL was diagnosed. 2 infants (6.25 %) had clinical signs of cerebral edema, 1 infant (3.12 %) was diagnosed with cerebral coma, and 5 infants (15.62 %) had clinical signs of convulsive syndrome.

Clinical manifestations of POF syndrome were diagnosed in 9 children (28.12 %) of group II, with CNS and RS lesions in all cases; 3 infants (9.37 %) were diagnosed with CVS lesions, 1 case (3.12 %) – anemic and hemorrhagic syndrome; 4 children (12.48 %) had manifestations of DIC syndrome. In 8 newborns of this group (25.00 %) there were signs of gastrointestinal damage manifested by decrease in food tolerance, 2 children (6.25 %) had complete intolerance to enteral nutrition. In 2 children of this group (6.25 %) NEC I was diagnosed. There were signs of neonatal jaundice in 5 newborns (15.62 %). 9 children (28.12 %) of group II were born with low birth weight, 2 children (6.25 %) were born small for gestational age. The condition of 18 children (44.0 %) of this group was severe at birth, 14 children (56.0 %) had deterioration to severe during the first day of life and remained so throughout the period of treatment in the NICU. The average length of stay in the NICU of group II was 6.33±1.39 days, and the children continued treatment in the following stages of medical care.

The comparison group (group III) consisted of 31 conditionally healthy preterm infants with GA at 34-36/6 weeks. The average Apgar score at the end of the first minute of life was 6.83±0.37 points, at the end of the fifth minute – 7.83±0.37 points. Accordingly, all children had a satisfactory condition at birth and a favorable course of the early neonatal period in terms of postnatal adaptation. The number of hospital bed days was 3.96±0.31 days.

The hematopoietic system plays an important role in providing compensatory and adaptive mechanisms in conditions of premature birth, having certain characteristics in conditions of morphological and functional immaturity of the organism [25, 26]. The analysis of the complete blood count (CBC) on the first day of life in premature infants of the observation groups showed that the average values of most indicators differ between groups of newborns and have a clear correlation with the general condition and GA, respectively. The mean values of hematological parameters on the first day of life in children of the observation groups in comparison with the control indicators are shown in Table 2.

Table 2

Mean values of hematological parameters in preterm infants of the observation groups on day 1 of life (M±m)

Index	Group I (n=30)	Group II (n=32)	Group III (n=31)
Red blood cells (t/L)	4,59±0,23*	4,86±0,19*"	5,09±0,22
Hemoglobin (g/L)	168,23±7,41*	172,14±8,73*	198,25±6,28
Hematocrit (%)	50,07±2,05*	52,75±2,61*"	55,69±2,60
Thrombocytes (g/L)	205,93±9,8*	204,25±9,83*	246,12±6,26
White blood cells (g/L)	17,07±0,77*	16,86±0,78*	11,31±0,52
Rod nucleation (%)	10,76±0,51*	10,50±0,56*	7,12±0,34
Segmented (%)	49,66±2,24*	48,06±2,34*	57,38±2,69
Eosinophils (%)	1,60±0,72*	1,93±0,84	1,9±0,14
Lymphocytes (%)	36,40±1,37*	36,43±1,81*	32,58±1,40
Monocytes (%)	1,46±0,62*	2,00±0,87	2,12±0,34

*Note: * – significant difference compared to the control, p<0.05; "- significant difference between the observation subgroups, p<0.05.*

Summarizing the data obtained, it should be noted that the indicators of erythrocytes, hemoglobin, hematocrit and platelets were inversely correlated with the GW of newborns and had statistically significantly lower values compared to control values (p<0. 0001), probably indicating a weak adaptive response to the combined effect of intra-

and postnatal adverse factors against the background of severe combined somatic dysfunction, and also due to the suppression of hematopoietic activation under the conditions of hypoxia in MFD [25, 26]. Levels of leukocytes, especially polymorphonuclear neutrophils (PMN), were statistically significantly higher, which is characteristic of lower GA compared to controls ($p<0.0001$). A statistically significant lower level of eosinophils and monocytes was observed in children of group I compared to controls ($p<0.0001$), and the opposite was observed in the absolute level of lymphocytes – the indicators in children of groups I and II were higher compared to controls ($p<0.0001$).

The results of the analysis of the biochemical spectrum of blood serum in the study groups are shown in Table 3.

Table 3

Indicators of the biochemical spectrum of blood in preterm infants in the observation groups (M±m)

Index	Group I (n=30)	Group II (n=32)	Group III (n=31)
Total protein, g/L	50,44±2,60*	52,48±2,58*"	55,20±2,34
Urea, mmol/L	3,85±0,16*	3,84±0,21*	3,45±0,17
Total bilirubin, μmol/L	131,92±6,5*	119,16±5,86*"	79,94±3,98
Indirect bilirubin, μmol/L	129,59±4,7*	117,18±5,84*"	79,94±3,98
Direct bilirubin, μmol/L	2,33±0,11*	1,98±0,10"	-
Glucose, μmol/L	2,41±0,12*	2,51±0,11*"	3,34±0,15
Creatinine, μmol/L	79,93±3,89*	75,96±3,37*"	60,32±2,63
ALT, U/L	17,22±0,84*	15,66±0,75*"	10,26±0,44
ACT, U/L	48,00±2,33*	47,73±2,09*	38,41±1,76
Sodium, mmol/L	134,49±4,34*	136,89±6,02	140,49±4,12
Potassium, mmol/L	4,98±0,22*	5,25±0,19*"	5,43±0,25
Calcium, mmol/L	1,33±0,07*	1,36±0,07*	2,28±0,10
Chlorides, mmol/L	103,50±4,09*	104,79±2,82*	109,99±4,23

*Note: * – significant difference compared to the control, $p<0.05$; "- significant difference between the observation subgroups, $p<0.05$.*

The analysis of serum parameters allowed us to establish statistically significant associations between neonatal GA and the overall severity of the condition. With lower GA in children and severe perinatal pathology, a decrease in the level of total protein was noted, which can be explained by the complex effect of the depth of morphological and functional immaturity on protein metabolism and slowing down of anabolic processes [27], especially in newborns of groups I and II compared with the control ($p<0.0001$), as well as when comparing groups among themselves – between the indicators of group I and group II ($p=0.0029$). The analysis of average serum urea values showed a statistically significant inverse relationship between GA and plasma urea levels, which is probably due to a pronounced impairment of nitrogen metabolism against the background of a slowing down of the excretory function of «immature» kidneys with subsequent retention of degradation products in the body [28]. A significant increase in urea levels was also found to be inversely related to GA and the severity of the neonatal condition, with statistically significant differences found in children compared to controls ($p<0.0001$), as well as between the indicators of children in groups I and II ($p=0.0390$). The same trends were found for total serum bilirubin – an increase in its level at lower GA in all groups compared to control ($p<0.0001$), as well as when comparing the mean values of observation groups I and II ($p<0.0001$). According to the study, all neonates, regardless of the observation group, had a stable tendency to hypoglycemia ($p<0.0001$).

The classic marker of glomerular filtration rate is serum creatinine. Although the relevance of this indicator for the verification of the diagnosis of AKI in premature infants has been the subject of much debate in recent years, it is still the most widely used marker. Due to the morphologic and functional immaturity of the renal glomeruli and desynchronous nephrogenesis, an increase in creatinine levels can only be observed when 25-50 % of filtration capacity has already been lost. Preterm infants have higher values of this indicator compared to full-term infants and «late» preterm infants [29,30]. In the analysis of creatinine levels, it was found that the index was statistically higher in newborns of groups I and II compared to controls ($p<0.0001$), which mainly reflects the trend of postnatal evolution of renal function.

The study of the main indicators of electrolyte metabolism also showed certain trends in the difference of indicators, namely the presence of hyponatremia in newborns of group I in comparison with the control group ($p<0.0001$), hypokalemia in children of groups I and II ($p<0.0001$), hypocalcemia ($p<0.0001$) in newborns of groups I and II in comparison with the control group. Disturbances of calcium metabolism in the body in conditions of preterm birth (decreased intestinal reabsorption, increased urinary losses, etc.) indicate a redistribution of the concentration of free calcium ions with subsequent increase of lipid peroxidation (LPO) as a result of cell apoptosis on the background of moderate to severe hypoxic damage. [31,32] Serum chloride levels reflected the general trends of electrolyte imbalance in correlation with GA and were lower in neonates of groups I and II compared to controls ($p<0.0001$).

Thus, the formation of disorders of the functional state of the urinary system in critically ill IPH has a multifactorial etiology due to the combined adverse effects of prenatal and perinatal factors on the body of a pregnant woman and

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the fetus, and the development of severe, often combined perinatal pathology in the child after birth. The adaptation of premature newborns to the conditions of extrauterine existence occurs at a certain level of morphological and functional immaturity of the body, which is a trigger factor for the formation of organ and systemic disorders under hypoxia, which requires appropriate understanding and medical tactics in the implementation of intensive care measures in the early neonatal period.

Conclusions

1. The development of disorders of the functional state of the urinary system, including acute kidney injury in premature infants is statistically significantly associated with a burdened background of somatic and obstetric and gynecological pathology in the mother, which requires the attention of neonatologists to predict possible renal dysfunction to develop an appropriate plan for diagnosis and treatment of newborns.

2. The course of neonatal diseases in children with gestational age of 25-31 weeks and 32-33 weeks is characterized by a combination of simultaneous disorders of 2 or more organ systems in the clinical picture, which causes certain difficulties in differential diagnosis of somatic dysfunction.

3. A detailed analysis of the recommended laboratory parameters of general and biochemical blood counts allows us to draw conclusions about the disorders of compensatory and adaptive mechanisms in premature infants under conditions of hypoxia in perinatal pathology, reflecting the nature of postnatal adaptation and body reserves, which is important for the formation of an optimal intervention strategy in the treatment of prenatal pathology.

Prospects for further research. Significant variability of scientific data makes it expedient to study the prevalence, risk factors and possible etiopathogenetic mechanisms of development of disorders of the functional state of the urinary system in preterm infants, which will improve the quality of medical care of this cohort of newborns.

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ПРЕДИКТОРИ ТА КЛІНІКО-ПАРАКЛІНІЧНІ ОСОБЛИВОСТІ ПОРУШЕНЬ ФУНКЦІОНАЛЬНОГО СТАНУ СЕЧОВИДІЛЬНОЇ СИСТЕМИ У ПЕРЕДЧАСНО НАРОДЖЕНИХ ДІТЕЙ

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Резюме.

Гостре пошкодження нирок – мультифакторний клінічний патологічний синдром, що належить до критичних станів раннього неонатального періоду і незалежно асоціюється з високими показниками захворюваності та смертності. Частота гострого пошкодження нирок у критично хворих передчасно народжених дітей значно варіює і за різними даними новонароджених складає від 25 до 77 %. Численні наукові дослідження описують обернено пропорційну кореляцію між гестаційним віком та масою тіла при народженні. Важливим з погляду патофізіології є розуміння поняття «функціональне гостре пошкодження нирок», що клінічно характеризується зменшенням швидкості клубочкової фільтрації при відсутності маркерів тубулярного ураження та, відповідно характеризує потенційно оборотні, чутливі до часу та глибини зміни ниркових функцій, які лише передують розвитку пошкодження.

Мета дослідження. Провести аналіз даних клінічної характеристики, факторів ризику та результатів параклінічного обстеження у передчасно народжених дітей з гестаційним віком 25-31 та 32-33 тижнів, що мали в комплексі перинатальної патології важкого ступеню ознаки порушень функціонального стану сечовидільної системи впродовж раннього неонатального періоду.

Матеріал та методи дослідження. Проведено комплексне клініко-параклінічне обстеження 93 передчасно народжених дитини з важкою перинатальною патологією, з яких І групу склали 30 дітей з гестаційним віком 25-31 тиждень та ІІ групу – 32 дитини з гестаційним віком 32-33 тижні; до ІІІ групи увійшли 31 умовно здорових передчасно народжених дітей з гестаційним віком 34-36 тижнів.

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Верифікація діагнозу дисфункції нирок проводилась згідно рекомендованої міжнародної класифікації Kidney Disease: Improving Global Outcomes з модифікацією J. G. Jetton та D. J. Askenazi (2015). Для оцінки ступеню важкості поліорганної недостатності при перинатальній патології у новонароджених використано шкалу Neonatal Multiple Organ Dysfunction Score. Оцінку ефективності терапевтичних втручань проводили за допомогою шкали Neonatal Therapeutic Intervention Scoring. Оцінку важкості стану новонароджених в динаміці спостереження проводили за шкалою Score for Neonatal Acute Physiology.

Дослідження виконані з 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.).

Статистичну обробку отриманих результатів дослідження проведено з використанням пакету програмного забезпечення «Statistica 10» (StatSoft Inc., США, 2010) та MedCalc Software (Version 16.1) з розрахунком відношення шансів коефіцієнту ексцесу (Chi-squared), коефіцієнту співвідношення шансів, 95 % довірчого інтервалу (95 % Confidence Interval). Статистично значимі відмінності між групами вважались при значенні $p<0,005$.

Дисертаційна робота виконувалась в межах наукової тематики кафедри педіатрії, неонатології та перинатальної медицини Буковинського державного медичного університету: НДР на тему «Удосконалення напрямків прогнозування, діагностики і лікування перинатальної патології у новонароджених та дітей раннього віку, оптимізація схем катамнестичного спостереження та реабілітації» (*Державний реєстраційний номер* 0115U002768, термін виконання 01.2015 р. – 12.2019 р.); НДР на тему: *«Хронобіологічні й адаптаційні аспекти та особливості вегетативної регуляції при патологічних станах у дітей різних вікових груп» (Державний реєстраційний номер 0122U002245, термін виконання 01.2020 р. – 12.2024 р.)*

Результати дослідження. Отримані результати продемонстрували статистично значимі асоціації між важкістю перинатальної патології у передчасно народжених дітей та глибини дисфункції сечовидільної системи, а також, комплексом факторів, що ускладнювали перебіг вагітності та пологів у матері та, відповідно, постнатальну адаптацію дитини. Серед причин ускладненого перебігу вагітності відмічені анемія, патологія серцево-судинної та сечовидільної систем, істміко-цервікальна недостатність, порушення плодово-плацентарного кровотоку, загроза самовільного викидня та передчасних пологів. Вірогідно частіше у жінок даної групи відмічалися аномальне передлежання та дистрес плоду, передчасний розрив плідних оболонок, а також, ургентний кесарів розтин. Перебіг перинатальної патології в групах новонароджених з гестаційним віком менше 33 тижні при народженні був здебільшого важким, у тому числі, у деяких дітей було діагностовано синдром поліорганної невідповідності, одним з проявів якого було гостре пошкодження нирок. Зміни показників загального та біохімічного аналізу крові новонароджених відобразили низькі компенсаторні резерви організму новонароджених на тлі перенесеної гіпоксії та морфо-функціональної незрілості, що пов'язано з передчасним народженням.

Висновки. Формування ренальної дисфункції у передчасно народжених дітей в ранньому неонатальному періоді має складний поліетіологічний характер, асоційований з комплексом несприятливих факторів під час вагітності та пологів у матері. Критично хворі новонароджені є основною та найбільш складною педіатричною когортою, у яких даний патологічний синдром пов'язаний з високим рівнем смертності в неонатальному періоді та формуванням функціональної та хронічної патології сечовидільної системи у подальші роки життя, що обґрунтовую необхідність поглиблення наукових досліджень для узагальнення поглядів щодо надання медичної допомоги передчасно народженим дітям.

Ключові слова: передчасно народжені діти; реальна дисфункція; чинники ризику; клінічні особливості; критерії лабораторної діагностики.

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