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STATISTICAL DATA AND ANALYSIS OF LITERATURE SOURCES ON PATHOPHYSIOLOGICAL MECHANISMS OF THE CROSSTALK BETWEEN ACUTE KIDNEY AND LIVER INJURY IN PRETERM NEWBORNS DURING THE EARLY NEONATAL PERIOD

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Summary

Acute kidney injury (AKI) and acute liver failure (ALF) are common and potentially dangerous complications in neonates admitted to the NICU. This article reviews data on the adverse effects of AKI on liver function and the development of ALF in preterm neonates. Infants with hemodynamically significant patent ductus arteriosus (hsPDA) are highlighted.

Aim. *To analyze risk factors and the incidence of liver damage in preterm newborns who experienced AKI during the early neonatal period.*

Materials and methods. *The study retrospectively analyzed the medical history of 74 preterm infants admitted to the anesthesiology and neonatal intensive care unit. Patients were examined using a complex of general clinical, biochemical, immunoenzymatic, and instrumental methods, as well as measuring the urinary neutrophil gelatinase-associated lipocalin (NGAL) biomarker and performing statistical analysis. Scientific research was conducted in accordance with the provisions of GCP (1996), the Convention of the Council of Europe on Human Rights and Biomedicine (April 4, 1997), the Declaration of Helsinki of the World Medical Association on the Ethical Principles for Conducting Scientific Research with Human Participation (1964-2008), and the Order of the Ministry of Health of Ukraine No. 690 dated September 23, 2009 (as amended by the Order of the Ministry of Health of Ukraine No. 523 dated July 12, 2012).*

The distribution of patients was carried out depending on the AKI development, that was diagnosed and stratified by the severity based on the neonatal modification of the 2012 KDIGO criteria. AKI was diagnosed according to the Pediatric Acute Liver Failure Study Group recommendations: prothrombin time ≥20 seconds after vitamin K administration or International Normalized Ratio values ≥2 units).

Results. *AKI was diagnosed in 36.5% of all preterm infants studied and 77.8% of them had hsPDA. ALF manifestations were mostly detected on day 5 and accounted for 79.3% of infants with AKI, 3 times more frequent in its severe course ($p<0.05$) and 4.2 times more frequent than in those without AKI signs ($p<0.05$). Correlation analysis of blood creatinine levels on days 3 and 10 showed a direct association with the development of AKI ($\rho=0.496$, $p<0.05$ and $\rho=0.456$, $p<0.05$, respectively). At the same time, AKI was 3.4 times ($p<0.05$) more severe when combined with ALF. An increase in bilirubin levels to levels indicating the need for phototherapy was directly correlated with the development of AKI ($\rho=0.544$, $p<0.05$). Episodes of hypoglycemia and the need for its additional correction were directly correlated with the severity and duration of AKI ($\rho=0.349$, $p<0.05$ and $\rho=0.556$, $p<0.05$, respectively). In addition, 78% of the children were predisposed to lactic acidosis.*

The diagnostic value of urinary NGAL for AKI in preterm infants was 229.7±94.82 (208.5; 176-297.3). An NGAL concentration of 249.0±113.27 (210; 185.5-302) tripled the odds of developing AKI ($p<0.05$). Elevated urine NGAL was an independent prognostic factor for 28-day mortality. Unfortunately, all 6 infants with urine NGAL levels above 250 μg/L developed severe AKI with ALF manifestations and died in the neonatal period. Analysis of the perinatal history of the studied preterm infants showed a statistically significant association between AKI and ALF in those infants whose mothers had a history of renal disease, chronic infection, or chorioamnionitis.

Conclusions. *Understanding the impact of acute kidney injury on liver function in preterm infants can help address the issues of early diagnosis, management and prevention of acute liver failure and improve outcomes of care for these infants. Identification of early pathological manifestations using biomarkers and analysis of patient history are needed to prevent complications caused by the complex and potentially dangerous vicious circle related to kidney-liver crosstalk.*

Keywords: *Neonates; Preterm Infants; Jaundice; Clinical and Laboratory Diagnostics; Acute Kidney Injury; Acute Liver Failure.*

Introduction

Acute kidney injury (AKI) and acute liver failure (ALF) are common and potentially dangerous complications in newborns admitted to the anesthesiology and intensive care unit. Literature reviews and meta-analyses have shown large discrepancies in data on the occurrence of these conditions, that could be associated with different study group compositions and gestational ages as well as various work streams of departments [1, 2].

A study by J. G. Jetton et al. [3] has reported a frequency of AKI ranging from 18% in very low-birth-weight neonates, 38% – with asphyxia, to 71% in those who required extracorporeal membrane oxygenation. According to a multicenter study conducted in 2017, the incidence of AKI in newborns according to the neonatal modification of the 2012 KDIGO criteria was 29.9% [4], while this rate was significantly higher (57.5%) in preterm infants with hemodynamically significant patent ductus arteriosus (hsPDA). This is due to the fact that preterm infants with hsPDA are considered the most vulnerable category since ductal left-to-right blood shunting results in hypoperfusion of organs, including the kidneys [5].

As for the present situation with regard to ALF, the following can be mentioned. Although isolated studies have reported incidence of 17/100,000 across all age groups, there are no accurate estimates of ALF development in newborns and children of other ages. The basis for the diagnosis of ALF, according to the Pediatric Acute Liver

Failure Study Group, is the presence of a liver-based coagulopathy not corrected with vitamin K. The mortality rate from ALF is as high as 55-70% [6, 7]. It should be taken into account that the neonatal period is characterized by substantial physiological changes associated with the fetal hemoglobin replacement, making it difficult to diagnose ALF. Concomitant kidney-liver diseases determine survival rates and are tightly correlated with the need for early intervention and treatment of identified dysfunctions [8-10]. Several studies have shown AKI-induced systemic low-grade inflammation. Inflammatory cytokines released in AKI (IL-6, IL-17A and tumor necrosis factor-alpha (TNF-α)) promote oxidative stress, increased hepatic vascular permeability and endothelial dysfunction, which in turn causes immune cell migration initiating inflammatory responses to liver cells and resulting in apoptosis, fatty degeneration, and hepatocellular necrosis [9, 11, 12].

The aim of the study. To analyze risk factors and the incidence of liver damage in preterm newborns who experienced acute kidney injury during the early neonatal period.

Materials and methods. The study retrospectively analyzed medical histories of 74 preterm newborns who were admitted to the Anesthesiology and Neonatal Intensive Care Unit with a mobile neonatal team from the community enterprise «Regional Medical Center of Family Health, DRC».

In the examinations of patients, a complex of general clinical, biochemical, immunoenzymatic, instrumental methods were used, as well as urine neutrophil gelatinase-associated lipocalin (NGAL) biomarker was measured (using the ELISA Kit reagent, 96), and a statistical analysis was performed.

The distribution of patients was carried out depending on the AKI development, that was diagnosed and stratified by the severity based on the neonatal modification of the 2012 KDIGO criteria [4]. AKI was diagnosed according to the Pediatric Acute Liver Failure Study Group recommendations: prothrombin time ≥20 seconds after vitamin K administration or International Normalized Ratio values ≥2 units) [6].

To attain the stated objectives, a set of statistical research methods was used, namely, independent samples were subjected to the Mann-Whitney and Kruskal-Wallis tests, the Wilcoxon signed-rank test and the McNemar index were used for dynamics assessment, the $\chi 2$ test and the Fisher's exact test – for contingency tables, the Spearman (rank) correlation was employed to assess the degree of associations between variables. The study results were statistically analyzed using the STATISTICA 6.1® software product (StatSoft Inc., serial number AGAR909E415822FA).

The study was approved by the Biomedical Ethics Committee of Dnipro State Medical University (DSMU). Scientific research was carried out in compliance with the provisions of GCP (1996), the Council of Europe Convention on Human Rights and Biomedicine (dated April 4, 1997), the World Medical Association Declaration of Helsinki on the Ethical Principles for Conducting Scientific Research with Human Participation (1964-2008), and the Order of the Ministry of Health of Ukraine No. 690 dated September 23, 2009 (as amended by the Order of the Ministry of Health of Ukraine No. 523 dated July 12, 2012).

The work was supported by the research project of the Department of Propaedeutics of Children's Diseases and Pediatrics No. 2 of DSMU: «Diagnosis and Treatment of Kidney Injury in Children with Somatic Diseases». State registration number: 0124U000052, project timeline: 2024-2027.

Results and discussion. All the children were admitted to the department on the 1st day after birth. Gestational age of the examinees was 32.6±1.93, the mean weight was 2037.8±552.60 g. The sex ratio: males – 43 (58.1%), females – 31 (41.9%). It is interesting to note the significant predominance of males in hsPDA group, as there were 28 males (70.0%) and 12 (30%) females, while in the group with PDA or closed ductus arteriosus – 8 (47.1%) and 7 (41.2%), respectively. No differences were found in Apgar Scores assessed at the 1st and 5th minutes of life. None of the infants was diagnosed with congenital liver diseases.

The nosological structure of the studied groups is presented in Figure 1.

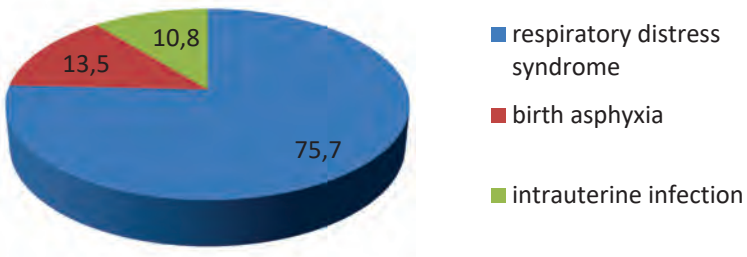

Fig. 1. Nosological structure of the studied groups, %.

HsPDA was detected in 40 infants, non-hsPDA – in 17, and 17 infants had closed their ductus by the time of the examinations. Patent ductus arteriosus was considered hemodynamically significant according to the following criteria: large diameter of ductus arteriosus (≥1.5 mm in newborns weighing <1500 g, >1.4 mm/kg in newborns weighing ≥1500 g); ductal left-to-right shunting and increasing, pulsatile flow pattern; left atrium-to-aortic root ratio >1.4; high diastolic flow velocity in the pulmonary artery >0.2 m/s; retrograde diastolic blood flow in descending aorta in the post-ductal descending aorta; regional circulatory disturbances[13].

AKI was diagnosed in 27 (36.5%) of 74 examined infants on the 3rd day of life, predominantly in those with

hsPDA. Among these children, AKI occurred in 52.5% of cases, which was 2.2 times more often than that in children with non-hsPDA ($p<0.05$) and 4.4 times more frequently as compared to infants with a closed ductus arteriosus ($p<0.007$). So, according to the study, the presence of hsPDA was a predictor of AKI development. An association between the PDA diameter and the serum creatinine level has been found. AKI stage II-III has been shown to prevail in the case of a PDA diameter of more than 2 mm [5].

Additional analyses have revealed ALF manifestations in most infants with AKI, more commonly seen on day 5. The clinical features of ALF have been identified in 79.3% of children with AKI, 3 times more often ($p<0.05$) in its severe course and 4.2 times more often than in those without AKI signs ($p<0.05$) (Figure 2).

The dynamics of symptom onset has testified that kidney injury was primary. This makes total sense, since patients with manifestations of congenital hepatitis were excluded from the study.

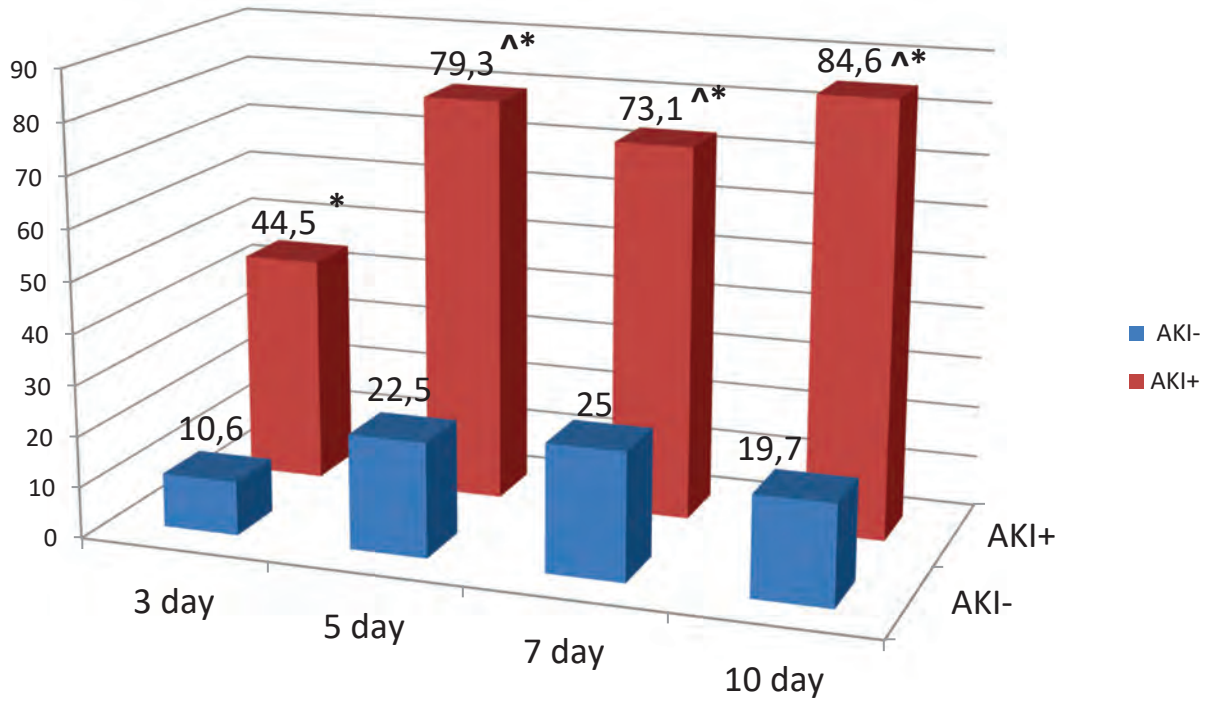

Fig. 2. The occurrence of ALF in the examined infants regarding the presence of AKI, %.

*Note: * – statistically significant differences compared to the presence of AKI. Differences between independent samples were tested using the Kruskal-Wallis and Mann-Whitney criteria. ^ – significant differences from the values on the 1st day; (p<0.05) values from the Wilcoxon signed-rank test.*

What we have found to be interesting were the results obtained from the correlation analysis. Serum creatinine levels on the 3rd and 10th days were directly corelated with the ALF development ($\rho=0.496$, $p<0.05$ and $\rho=0.456$, $p<0.05$, respectively), and worsening severity of AKI by 3.4 times ($p<0.05$) was associated with the ALF presence.

An increase in serum bilirubin levels to concentrations requiring phototherapy was directly correlated with the AKI development ($\rho=0.544$, $p<0.05$). Since preterm infants with comorbidities develop complications at lower serum bilirubin levels, there is no hyperbilirubinemia value that would be deemed non-toxic. A liver damage, irrespective of etiology, reduces the number of hepatocytes and can impair the uptake of indirect bilirubin from blood plasma and decrease transport and clearance of direct bilirubin through the bile ducts, as well as causes a decrease in albumin synthesis [14-16]. Therefore, these infants experienced a prolongation of neonatal jaundice for an average of 1.3±0.2 weeks. This condition required additional control of serum bilirubin levels to prevent bilirubin encephalopathy, that is characterized by a delayed development of physiological reflexes (more than 3 weeks by postconceptual age).

In fact, glucose metabolism is maintained by the state of the liver and kidneys, since gluconeogenesis occurs mainly in the liver and partially in the renal cortex. The gluconeogenic principal regulatory enzymes of renal gluconeogenesis are expressed in the proximal tubular epithelial cells, while the enzymes responsible for glycolysis are mainly functioning in the distal tubular cells [10]. Hence, blood glucose levels and the need for correction have been evaluated. It has been shown that episodes of hypoglycemia and the need for additional correction were directly correlated with the AKI severity and duration ($\rho=0.349$, $p<0.05$ and $\rho=0.556$, $p<0.05$, respectively). This has confirmed the data obtained by N. K. Rad et al. regarding potentially abnormal glucose metabolism in children with AKI. Researchers have also found that thiamine (vitamin B1) reduced the rate of glycolysis and increased lactate clearance and glucose production [10]. Thus, thiamine regulates cellular metabolism in proximal renal tubular cells and reduces mortality in patients with acute renal failure, which might be a subject of further examinations in newborns. The findings obtained in this study have revealed 78% of children with underlying risk

for lactic acidosis. Such being the case, it is challenging to differentiate lactic acidosis due to its multifactorial origin and potential links to hypoxia or other causes. Therefore, in patients with an unstable glucose profile and severe lactic acidosis, a suspicion of the possible ALF occurrence and appropriate diagnostics are deemed to be reasonable.

In relation to early diagnosis of AKI as well as the crosstalk between the liver and kidney, papers focused on specific biomarkers have been reviewed to identify relevant critical indicators that facilitate early detection and assessment of pathological conditions involving both the kidneys and the liver [11, 17]. The diagnostic value of urinary NGAL for the detection of AKI in preterm infants has been found to be 229.7±94.82 (208.5; 176-297.3). At a value of 249.0±113.27 (210; 185.5-302), infants had threefold increased chances of developing AKI ($p<0.05$). An increase in the urine NGAL level was an independent prognostic factor for 28-day mortality.

The liver and kidneys are central organs to numerous homeostatic functions and have close pathophysiological interrelationships. The presence of liver injury significantly increases the mortality and disability rate in patients with any other conditions [8, 10], that has been confirmed by our study. All 6 children with urinary NGAL levels above 250 μg/L who developed severe AKI and ALF manifestations (marked coagulopathy, impaired synthetic and metabolic liver functions) and hsPDA, unfortunately, died in the neonatal period.

A vicious circle is triggered by interrelations between kidney-induced liver injury and liver-induced kidney disease. The following factors are conducive to crosstalk between the liver and kidneys: ischemia, reperfusion, release of pro-inflammatory cytokines, metabolic acidosis, oxidative stress and altered enzyme activity [16, 18, 19].

The analysis of the perinatal history of the examined preterm neonates has shown a statistically significant association between AKI and ALF in those children whose mothers had a history of kidney disease ($p<0.009$), foci of chronic infection ($p<0.005$), chorioamnionitis ($p<0.009$), early gestosis ($p<0.03$), and threatened miscarriage ($p<0.04$). Similar data have been obtained from the analysis of infants with ALF, but the greatest associations have been shown with chorioamnionitis ($p<0.007$) and early gestosis ($p<0.04$).

Furthermore, these children were at high risk of developing necrotizing enterocolitis ($p<0.007$) and intraventricular hemorrhage ($p<0.005$) in later life. Perhaps this is due to the molecular mechanisms of interactions between remote organs in AKI, including leukocyte activation and infiltration, inflammatory cytokine influences and endothelial damage, accompanied by oxidative stress and production of reactive oxygen species [20, 21].

Thus, our data have confirmed the direct association between renal hypoperfusion resulting from hsPDA functioning and the AKI development with the vicious circle induction generated by renal-induced liver damage that significantly increased the mortality rate [8, 9, 20, 21].

Conclusions. Acute kidney injury has been detected in 36.5% of all the examined preterm infants, 77.8% of whom had hemodynamically significant patent ductus arteriosus. Clinical manifestations of acute liver failure have mostly been identified in 79.3% of infants with acute kidney injury on the 5th day, that was 3 times more often in its severe course and 4.2 times more often compared to those without signs of acute kidney injury.

Understanding the impact of acute kidney injury on liver functions in preterm infants may help address the issues of early diagnosis, management, and prevention of acute liver failure, as well as improve the outcomes of nursing care for them. Appropriate follow-up by a nephrologist and hepatologist along with the identification of early pathological manifestations using biomarkers and medical history analysis are essential to prevent complications caused by the complex and potentially dangerous vicious cycle related to the kidney-liver crosstalk.

The results obtained have presented the feasibility of further studies.

Conflict of interest. The authors declare no conflict of interest.

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ВЗАЄМОЗВ'ЯЗОК ГОСТРОГО УРАЖЕННЯ НИРОК І ПЕЧІНКИ В РАННЬОМУ НЕОНАТАЛЬНОМУ ПЕРІОДІ У НЕДОНОШЕНИХ НОВОНАРОДЖЕНИХ

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Резюме.

Гостре ураження нирок та гостра печінкова недостатність є поширеними й потенційно небезпечними ускладненнями у новонароджених, які знаходяться на лікуванні у відділенні анестезіології та інтенсивної терапії. Потребують аналізу дані щодо шкідливого впливу гострого ураження нирок на функцію печінки та розвиток гострої печінкової недостатності у недоношених новонароджених, особливо з гемодинамічно значущою відкритою артеріальною протокою.

Мета. Аналіз факторів ризику та частоти ураження печінки у недоношених новонароджених, які мали гостре ураження нирок у ранньому неонатальному періоді.

Матеріали і методи дослідження. У ході дослідження проведено ретроспективний аналіз історій хвороб 74 недоношених новонароджених дітей, які перебували на лікуванні у відділенні анестезіології та інтенсивної терапії для новонароджених. До обстежуваних пацієнтів застосовано комплекс загальноклінічних, біохімічних, імуноферментних, інструментальних методів, а також визначення рівня біомаркеру – ліпокалін-2, асоційованого з желатиназою нейтрофілів (Neutrophil gelatinase–associated lipocalin – NGAL) в сечі, статичний аналіз. Проведений розподіл хворих залежно від розвитку гострого ураження нирок, діагностика та стратифікація ступеня тяжкості якого виконувалась за критеріями неонатальної модифікації KDIGO. Гостру печінкову недостатність діагностували згідно з рекомендацією Pediatric Acute Liver Failure Study Group: протромбіновий час ≥20 секунд після введення вітаміну К або значення показника Міжнародного нормалізованого співвідношення ≥2 Од). Наукові дослідження виконані з дотриманням 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 досліджень за участю людини (1964-2008 рр.), наказу МОЗ України № 690 від 23.09.2009 р. (із змінами, Наказ МОЗ України № 523 від 12.07.2012 р.). Статистична обробка результатів проведена з використанням програмного забезпечення «STATISTICA» (StatSoft Inc., USA, Version 10). Порівняння кількісних показників з нормальним розподілом проведено з використанням t-критерію Стьюдента, вірогідність відмінностей вважалася статистично значущою при $p<0,05$.

Результати. Гостре ураження нирок виявлено у 36,5% обстежених недоношених дітей загалом і в 61,9% дітей з гемодинамічно значущою відкритою артеріальною протокою. Ознаки гострої печінкової недостатності найчастіше виявлялись на

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5 добу і складали 79,3% дітей з гострим ураженням нирок, втричі частіше ($p<0,05$) при його тяжкому перебігу і в 4,2 рази частіше, ніж за дітей без ознак гострого ураження нирок ($p<0,05$). При кореляційному аналізі рівень креатиніну крові на 3-ю та 10-у добу прямо залежав від розвитку гострої печінкової недостатності ($\rho=0,496$, $p<0,05$ і $\rho=0,456$, $p<0,05$, відповідно). А розвиток гострої печінкової недостатності підсилював тяжкість гострого ураження нирок в 3,4 рази ($p<0,05$). Підвищення рівня білірубіну до цифр, які свідчили про потребу фототерапії, прямо корелювало з розвитком гострого ураження нирок ($\rho=0,544$, $p<0,05$). Епізоди гіпоглікемії та потреба в додатковій її корекції прямо корелювали з тяжкістю гострого ураження нирок та його тривалістю ($\rho=0,349$, $p<0,05$ і $\rho=0,556$, $p<0,05$, відповідно). Крім того, діти мали також схильність до лактатацидозу у 78%. Діагностична здатність NGAL сечі щодо гострого ураження нирок у недоношених дітей склала 229,7±94,82 (208,5; 176-297,3). При концентрації NGAL в сечі, що дорівнювала 249,0±113,27 (210; 185,5-302) шанси щодо розвитку гострої печінкової недостатності у дітей збільшувались у три рази ($p<0,05$). Підвищення рівня NGAL у сечі було незалежним прогностичним фактором 28-денної смертності. Всі 6 дітей з рівнем NGAL сечі вище 250 мкг/л, на жаль, мали тяжке гостре ураження нирок та ознаки гострої печінкової недостатності і загинули в неонатальному періоді. Аналіз перинатального анамнезу обстежених недоношених дітей виявив статистично значущий зв'язок щодо гострим ураженням нирок та гострою печінковою недостатністю у тих дітей, матері яких мали захворювання нирок в анамнезі, хронічні вогнища інфекції, хоріоамніоніт.

Висновки. Гостре ураження нирок виявлено у 36,5% обстежених недоношених дітей загалом і у 61,9% дітей з гемодинамічно значущою відкритою артеріальною протокою. Ознаки гострої печінкової недостатності найчастіше виявлялися на 5 добу і складали 79,3% дітей з гострим ураженням нирок, що було втричі частіше при його тяжкому перебігу і в 4,2 рази частіше в порівнянні з дітьми без ознак гострого ураження нирок.

Розуміння впливу ниркової недостатності на функцію печінки може допомогти вирішити проблеми ранньої діагностики, управління та профілактики гострої печінкової недостатності. Належне спостереження нефролога та гематолога, а також ідентифікація ранніх проявів патологічних станів за допомогою біомаркерів є необхідними для запобігання ускладнень, спричинених складним і потенційно небезпечним порочним колом нирково-печінкової взаємодії.

Ключові слова: новонароджені; недоношені новонароджені; жовтяниця; клініко-лабораторна діагностика; гостре ураження нирок; гостра печінкова недостатність.

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