РЕЗУЛЬТАТИ ДИСЕРТАЦІЙНИХ ТА НАУКОВО-ДОСЛІДНИХ РОБІТ

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PREDICTORS OF THE DEVELOPMENT OF HYPOXIC-ISHEMIC ENCEPHALOPATHY IN FULL-TERM AND PREMATURE INFANTS BORNFROM MOTHERS WITH METABOLIC SYNDROME IN THE EARLY NEONATAL PERIOD

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Summary

Recent studies have demonstrated a direct association between hypoxic-ischemic encephalopathy (HIE) and maternal overweight or obesity. HIE remains one of the leading causes of neonatal mortality and long-term neurological impairment in newborns. It represents a systemic condition affecting not only the central nervous system but also multiple peripheral organs, including the liver. One of the indirect biochemical indicators of hypoxic injury is elevated hepatic transaminase activity – specifically, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Particular emphasis has been placed on the involvement of nitric oxide (NO) in the pathophysiology of HIE

Objective*: to analyze and identify risk factors for hypoxic-ischemic encephalopathy in full-term and premature infants born to mothers with metabolic syndrome, to build clinical prognostic models.*

Materials and methods. *The study cohort consisted of 125 neonates. The study cohort consisted of 125 neonates. Group 1 included infants born to mothers with metabolic syndrome who were diagnosed with HIE (n = 45), while Group 2 included infants born to mothers without metabolic syndrome and without clinical manifestations of HIE (n = 79).). Nitrite concentrations were measured by quantifying the diazo compounds formed via reaction with sulfanilic acid, followed by a subsequent reaction with the Griess-Ilosvai reagent. The bioethical principles of the study were confirmed by the Commission on Ethical Issues and Bioethics of Poltava State Medical University (protocol No. 233 dated 21 December 2024). Statistical analysis was conducted using the STATA 14.0 software package. Statistical analysis was performed using the STATA 14.0 software package. The work was carried out within the research project of the Department of Paediatrics No. 1 with Neonatology of Poltava State Medical University ''To develop clinical and laboratory criteria, methods for predicting and preventing metabolic disorders in young children" (state registration number 0120U102856, term of completion 2020-2024).*

Results of the study and their discussion. *Initial clinical assessments were performed immediately postnatally. Among term infants, the most frequently diagnosed conditions included neonatal depression syndrome, respiratory distress syndrome, heart failure, seizures, and muscular dystonia. In preterm infants, depression syndrome, muscular dystonia, and seizures were the predominant clinical manifestations. HIE in term neonates is typically characterized by multisystem involvement, whereas in preterm infants, clinical signs are predominantly neurological. A metabolic profile analysis confirmed the multisystemic nature of HIE. On day one of life, AST and ALT levels in preterm infants with HIE were significantly elevated compared to preterm infants without HIE ($p = 0.055$ and $p = 0.049$, respectively). The urinary nitrite level in preterm infants with HIE was significantly higher compared to that in preterm infants without HIE ($p = 0.025$). Similar findings were observed in term infants, where those with HIE exhibited elevated urinary nitrite levels ($p = 0.042$). Based on these data, we developed predictive models for the early neonatal onset of HIE. After adjusting for gestational age and ALT or AST activity, urinary nitrite concentration proved to be a reliable prognostic marker for HIE in both preterm and term neonates. The areas under the ROC curves for models incorporating urinary nitrite levels, gestational age, and either ALT or AST were 0.9952 and 0.9279, respectively.*

Conclusions*. HIE in neonates is associated with multisystem involvement, affecting various organs in addition to the central nervous system. In light of the systemic nature of the condition, potential metabolic biomarkers were evaluated. Among these, serum ALT and AST levels, as well as urinary nitrite concentration, emerged as significant risk factors for early neonatal HIE in infants born to mothers with metabolic syndrome. Due to the heterogeneity of the cohort in terms of gestational age, multiple logistic regression analysis with obligatory adjustment for gestational age was employed to ensure accurate interpretation of the findings. A predictive model for HIE development was constructed, incorporating urinary nitrite and ALT levels. Newborns diagnosed with HIE and born to mothers with metabolic syndrome require close monitoring of ALT and AST levels during the early neonatal period. Furthermore, urinary nitrite concentration serves as an optimal biomarker for predicting HIE onset.*

Keywords: *Metabolic Syndrome, Hypoxic-Ischemic Encephalopathy, Newborns, Predictors of Hypoxic-Ischemic Encephalopathy, ALT, AST, Urinary Nitrites.*

Introduction

Maternal obesity represents a significant prenatal risk factor for obstetric complications, preterm birth [1], neonatal morbidity associated with asphyxia [2], and potentially for cognitive and behavioral disorders in offspring [3]. Robust evidence indicates that an elevated maternal body mass index is correlated with an increased risk of intrauterine fetal demise, stillbirth, and neonatal mortality [4]. Recent research has established a direct association between hypoxic-ischemic encephalopathy (HIE) and maternal overweight or obesity [5]. HIE is one of the primary causes of neonatal mortality and long-term neurological disability. Approximately one-third

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of infants diagnosed with HIE go on to develop neurological impairments such as psychomotor developmental delays, epilepsy, or cerebral palsy, and nearly 25% die within the first two years of life [6]. Despite the use of therapeutic hypothermia – whose efficacy is constrained by a limited therapeutic window and the severity of injury – there remains a critical need for early identification of biomarkers capable of accurately predicting both immediate and long-term adverse outcomes associated with HIE. HIE is systemic in nature, affecting not only the central nervous system but also other organs, including the liver. One indirect biochemical marker of hypoxic injury is the elevated activity of hepatic transaminases, specifically alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [7].

Furthermore, multiple studies have demonstrated significantly elevated ALT and AST levels in neonates with HIE, with these elevations correlating with the severity of encephalopathy. In the study by Choudhary et al., mean ALT and AST levels were significantly higher in newborns with HIE compared to controls, with enzyme activity increasing proportionally to the severity of HIE [8]. Similar findings were reported by Elsadek, who observed significantly elevated ALT and AST levels in neonates with perinatal asphyxia, again showing a strong correlation with the severity of encephalopathy [9].

It is well established that newborns, particularly preterm infants, exhibit a deficiency of L-arginine – the primary substrate for nitric oxide (NO) synthesis. Additionally, they present with elevated concentrations of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of NO synthase, which further impairs nitric oxide production [10, 11]. Consequently, the role of nitric oxide (NO) in the pathogenesis of hypoxic-ischemic encephalopathy (HIE) warrants special attention. NO is a critical vasoactive mediator involved in the regulation of vascular tone, the permeability of the blood-brain barrier, and plays a significant role in neuroinflammation and apoptosis [12]. Alterations in NO metabolite levels – specifically nitrates and nitrites in urine – are considered markers of endothelial dysfunction and the extent of ischemic tissue injury [13, 14]. Nitrites, as intermediate products of nitric oxide metabolism, possess high biological reactivity and accumulate rapidly in response to ischemia-reperfusion injury. Unlike nitrates, nitrite concentrations are more sensitive to acute fluctuations in nitric oxide metabolism, particularly in the context of inducible NO synthase activation triggered by hypoxia and inflammation [15]. The measurement of urinary nitrite levels represents a non-invasive diagnostic approach that can be adapted for neonatal monitoring. Nevertheless, there remains a paucity of comprehensive studies in both domestic and international scientific literature evaluating nitrite concentration as an independent predictive marker for the development of HIE.

Objective: To analyze and identify risk factors for hypoxic-ischemic encephalopathy in term and preterm infants born to mothers with metabolic syndrome during the early neonatal period and to develop clinical prognostic models.

Materials and methods. The study enrolled 125 neonates born at the Poltava Regional Clinical Hospital named after M. V. Sklifosovsky. The cohort included both preterm and term infants, as existing evidence indicates that women with metabolic syndrome (MS) have a higher incidence of preterm birth [16]. Two primary groups were defined: the first group included infants born to mothers with MS who developed HIE (n = 45), and the second group comprised infants born to mothers without MS and without clinical manifestations of HIE (n = 79). Group 1 was further stratified into two subgroups: Subgroup 1A (30 infants) consisted of preterm newborns with HIE, and Subgroup 1B (15 infants) included term newborns with HIE. Group 2 was divided into Subgroup 2A (19 infants), comprising preterm infants without HIE, and Subgroup 2B (60 infants), consisting of term infants without HIE.

The criteria for classifying mothers into the MS group were the presence of three or more of the following criteria: elevated blood pressure (>130/85 mm Hg), hypertriglyceridemia (>1.7 mmol/L), reduced HDL cholesterol (<1.3 mmol/L), obesity, or elevated fasting glucose (>5.5 mmol/L) [17].

Diagnostic criteria for the HIE group of newborns were: moderate or severe birth asphyxia, including Apgar score ≤7 at 1 minute and ≤5 minutes, and/or umbilical artery acidemia (pH <7.0); neurological symptoms persisting beyond 24 hours, including altered muscle tone, abnormal primitive reflexes, seizures, or signs of brainstem dysfunction.

Criteria for including children in the study: maternal metabolic syndrome, fulfillment of HIE diagnostic criteria, and admission to the post-intensive care unit.

The exclusion criteria were as follows: severe cardiac, hepatic or renal dysfunction at birth; hematological or congenital disorders; seizures attributable to electrolyte disturbances (hypocalcemia, hypoglycemia), birth trauma, intrauterine infections, inherited metabolic diseases or other congenital anomalies; previous therapeutic hypothermia.

Method of determining nitrates and nitrites in urine. Nitrite concentration was assessed by measuring diazo compounds formed in the reaction with sulfanilic acid, followed by coupling with α-naphthylamine (Griess reagent), producing red azo dyes with color intensity proportional to nitrite concentration. Nitrate concentration was determined by measuring nitrite after enzymatic reduction using hydrazine sulfate. For analysis, 0.2 mL urine aliquots were used [18, 19].

All studies were conducted in compliance with patient safety and ethical standards, following the principles of ICH Good Clinical Practice (1996), the Council of Europe Convention on Human Rights and Biomedicine (1997), the Declaration of Helsinki (1964/2000), and the Order of the Ministry of Health of Ukraine No. 690 (23.09.2009). The study protocol was approved by the Ethics and Bioethics Commission of Poltava State Medical University (Protocol No. 233, 21.12.2024).

Statistical analysis. For processing quantitative values, traditional methods of parametric and nonparametric statistics were employed. Qualitative characteristics, primarily expressed as percentages, were analyzed using nonparametric methods. For normally distributed data, the following statistical parameters were applied: mean (M) to determine central tendency; 95% confidence interval (CI) for the mean. Hypotheses regarding equality of

population means were tested using two-tailed Student's t-test. Comparisons of relative values (percentages) were performed using Fisher's exact two-tailed test. Relationships between count variables were assessed through binary and multiple Poisson regression analyses. All statistical analyses were conducted using STATA 14.0 software package.

The work was performed as part of the research project of the Department of Pediatrics No. 1 with Neonatology at Poltava State Medical University titled «Development of Clinical and Laboratory Criteria, Methods for Prediction and Prevention of Metabolic Disorders in Young Children» (state registration number 0120U102856, implementation period 2020-2024).

Research results and their discussion

Initial analysis focused on the clinical condition of neonates. The frequency of principal clinical symptoms and syndromes associated with asphyxia showed minimal variation between term and preterm infants. In term infants of Group 1, the most frequently observed conditions were depression syndrome, respiratory distress syndrome, heart failure, seizures, and muscular dystonia. Among preterm infants, depression syndrome, muscular dystonia, and seizures predominated (Table 1).

The clinical picture of HIE was multiorgan in both term and preterm infants, though with some differences in the frequency of the identified conditions between these groups. As expected, the most common pathology involved nervous system manifestations. It is quite logical that the most common pathology was manifestations from the nervous system. The frequency of depression syndrome and seizures was nearly identical in both term and preterm infants. Neurosonographic studies revealed that periventricular edema occurred significantly more frequently in term infants (Table 2).

Additionally, analysis of the resistance index (RI) of the anterior cerebral artery (ACA) showed that in preterm infants, RI values tended toward either extreme (0.8 or 0.6), while in term newborns these values clustered around median levels (Fig. 1)

Table 1

Frequency of the main clinical symptoms and syndromes associated with asphyxia among children of the examined groups, n (%)

Indicators	First group		p
	Group 1A (n=30)	Group 1B (n=15)	
Seizures	6 (20,0)	5 (33,3)	0,464
Depression	22 (73,3)	9 (60,0)	0,362
Muscular dystonia	12 (40,0)	4 (26,7)	0,514
Heart failure	4 (13,3)	7 (46,7)	0,026
Respiratory disorders	22 (73,3)	9 (60,0)	0,497
Oliguria	3 (10,0)	3 (20,0)	0,384
Food intolerance	6 (20,0)	3 (20,00)	0,998

Table 2

Rate of neurosonographic changes among infants of the examined groups, n (%)

Indicators	First group		p
	Group 1A (n=30)	Group1B (n=15)	
Periventricular edema	6 (20,0)	8 (53,33)	0,067
Subepyndema cysts	9 (30,0)	3 (20,0)	0,510
Ventriculodilatation	3 (10)	1 (6,67)	0,593
Hydrocephalic syndrome	4 (13,3)	2 (13,3)	0,429
IVH I-II	6 (20,0)	2 (13,3)	0,458

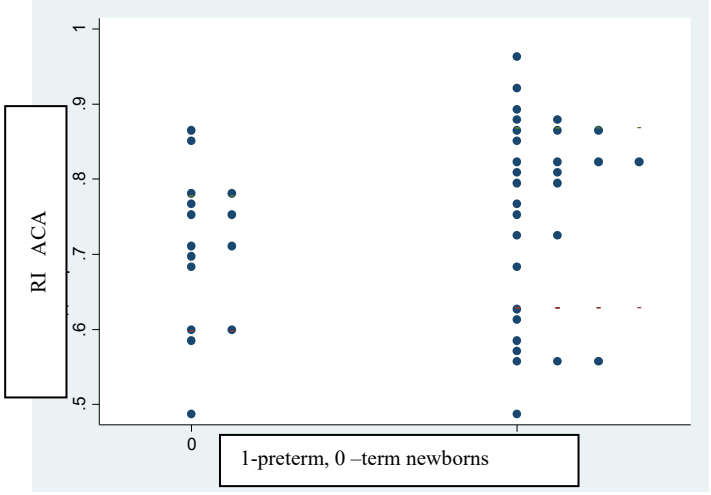

Fig. 1. Distribution of the IR index of the anterior cerebral artery in full-term and premature children with HIE

The frequency of respiratory disorders showed no significant difference between term and preterm infants (p=0.497, Table 1). Cardiovascular failure was diagnosed significantly more often in term infants compared to preterm infants (46.7% vs 13.3%, p=0.026, Table 1).

The obtained data suggest that HIE in term infants involves multiple organ system injuries, while in preterm infants most clinical manifestations primarily affect the nervous system. We propose that when such symptoms appear in preterm infants, their hypoxic origin should be primarily considered rather than attributed solely to organ system immaturity, as delayed detection and correction of early manifestations may lead to long-term adverse consequences.

To address one of our study objectives – developing a predictive model for HIE progression in term and preterm infants – we analyzed their metabolic profiles, which further confirmed the multiorgan manifestations of HIE.

Our findings showed that on the first day of life, preterm infants with HIE had significantly higher AST and ALT levels compared to preterm infants without HIE. In contrast, term infants demonstrated nearly identical ALT and AST levels regardless of HIE presence, with no statistically significant differences (Table 3).

Table 3

Mean values of metabolic indicators reflecting internal organ damage associated with asphyxia in study group infants on the first day of life, M (95% CI)

Indicators	First group		Second group		p
	Group 1A (n=30)	Group 1B (n=15)	Group 2A (n=19)	Group 2B (n=60)	
LDH, U/l	914,7 (771,7-1057,7)	776,1 (707,84-844,37)	1408,7 (241,3-3058,8)	1029,5 (676,8-8824,7)	0,412* 0,751#
AST, U/L	66,84 (39,09-94,6)	72,89 (30,91-114,87)	39,13 (31,35-46,91)	47,66 (38,94-56,39)	0,055* 0,220#
ALT, U/л	31,92 (17,68-46,16)	32,04 (7,17-58,57)	17,2 (12,95-21,45)	37 (5,28-68,71)	0,049* 0,767#
Creatinine, mmol/l	67,83 (58,51-77,15)	73,2 (58,56-87,83)	67,62 (59,85-75,39)	50,33 (33,42-67,24)	0,971* 0,011#
Glucose, mmol/l	3,70 (3,00-4,4)	4,31 (3,21-5,41)	3,93 (3,19-4,67)	4,58 (3,39-5,51)	0,677* 0,251#

*Note: *– p between groups 1A and 2A; # – p between groups 1B and 2B*

However, on day 6 of life, significantly higher AST levels were observed in term infants with HIE compared to those without HIE (p=0.034). This finding suggests prolonged effects of hypoxic damage and reduced compensatory capacity against hypoxia (Table 4).

Given the multiorgan nature of HIE-associated injuries, we focused on investigating nitric oxide's role in asphyxia pathogenesis and clinical manifestations, since vascular remodeling at birth requires interaction of multiple vasoactive mediators, with nitric oxide being predominant. Furthermore, this metabolite – along with others (interleukins, tumor necrosis factor alpha [TNF-α], free radicals) – plays a key role in blood-brain barrier permeability during hypoxia [20]. Therefore, we examined urinary nitrate/nitrite levels in the study groups (Table 5).

Urinary nitrite levels were significantly higher in preterm infants with HIE compared to those without HIE (p=0.025). Similar findings were observed in term infants – higher nitrite levels in HIE cases (Table 5). Regarding nitrates, levels were significantly elevated in preterm infants with HIE versus those without HIE. However, no such differences were found among term infants.

Table 4

Mean values of metabolic indicators reflecting internal organ damage in study group infants on day 6 of life, M (95% CI)

Indicators	First group		Second group		p
	Group 1A (n=30)	Group1B (n=15)	Group 2A (n=19)	Group 2B (n=60)	
LDH, U/l	776,1 (707,8-844,37)	-	1029 (854,3-1234,1)	-	0,751*
AST, U/L	60,7 (50,09-71,3)	72,73 (48,37-97,09)	43,83 (21,45-66,21)	44,0 (22,34-65,65)	0,130* 0,034#
ALT, U/л	16,67 (13,52-18,81)	42,86 (1,57-87,3)	22 (5,74-38,25)	35 (28,43-41,57)	0,419* 0,711#
Creatinine, mmol/l	72,26 (61,53-82,99)	62,22 (48,32-76,11)	77 (52,28-101,7)	67,33 (33,33-168,0)	0,698* 0,850#
Glucose, mmol/l	3,66 (3,07-4,26)	3,99 (3,34-5,63)	3,96 (3,39-4,53)	3,65 (3,3-4,05)	0,522* 0,692#

*Note: *– p between groups 1A and 2A; # – p between groups 1B and 2B*

Table 5

Average urinary nitrate levels in study group infants, M±m

Indicators	First group		Second group		p
	Group 1A (n=30)	Group 1B (n=15)	Group 2A (n=19)	Group 2B (n=60)	
Nitrates, nmol/l	3,95±0,72	3,44±0,31	2,16±0,17	1,97±0,456	0,036* 0,127#
Nitrites, nmol/l	1,76±0,35	1,62±0,10	0,80±0,06	0,76±0,152	0,025* 0,042#

*Note: *– p between groups 1A and 2A; # – p between groups 1B and 2B*

Nitric oxide serves as a crucial regulator in multiple systems, including vascular endothelium, smooth muscle cells, macrophages, and neurons [21]. Diminished NO production contributes to persistent pulmonary hypertension in newborns [22], while excessive NO is associated with septic shock [23]. The observed low plasma nitrite concentrations during the initial postnatal period may result from several factors: preterm infants frequently exhibit L-arginine deficiency, impairing NO synthesis, and demonstrate elevated asymmetric dimethylarginine (ADMA) levels – an endogenous NOS inhibitor – compared to adults [24]. Consequently, reduced L-arginine availability combined with increased ADMA may suppress eNOS activity in neonates, potentially explaining diminished plasma nitrite levels postnatally. Depressed nitrate/nitrite concentrations resulting from NO deficiency may indicate vascular ischemia, vasospasm, and oxidative stress severity. Furthermore, endothelial dysfunction characterized by impaired NO-mediated neurovascular protection may substantially contribute to cognitive impairment development. Experimental evidence confirms NO's pivotal role in neonatal hypoxic-ischemic brain injury pathogenesis [25].

The combined analysis of urinary nitrite with ALT/AST levels may enhance HIE prediction accuracy in neonates. This approach holds significant clinical relevance by enabling early identification of high-risk patients and facilitating timely preventive interventions. Our data facilitated development of predictive models for early neonatal HIE. After adjusting for gestational age (GA) and ALT/AST activity, urinary nitrite emerged as a robust predictive marker for HIE in both preterm and term infants. The corresponding areas under ROC curves for models incorporating urinary nitrite, GA, and ALT or AST reached 0.9952 and 0.9279, respectively (Table 6., Fig. 2).

Table 6

Prognostic models of the development of HIE based on the determination of nitrate in urine

Indicators	OR (95% CI)	β (95% CI)	p	Area under ROC curve
I model				
Nitrites, nmol/l	1,86 (1,80-1,92)	157,2 (129,5-184,8)	0,000	0,9952
GA, weeks	0,0002 (0.00018-0.0003)	-8,23 (–8,61-(–7,85)	0,0001	0,411
ALT, U/l	0,0004 (0.000061-0.0035)	-7,67 (–9,69-(–5,63)	0,00006	0,1923
II model				
Nitrates, nmol/l	3,18 (1,09-9.266	4,64 (1,17-8,10)	0,009	0,9279
GA, weeks	0,98 (0,95-1.02)	-0,19 (–061-0,23)	0,381	0,411
AST, U/l	0,95 (0.71-1.27)	-0,006 (–0,05-0,04)	0,765	0,3678

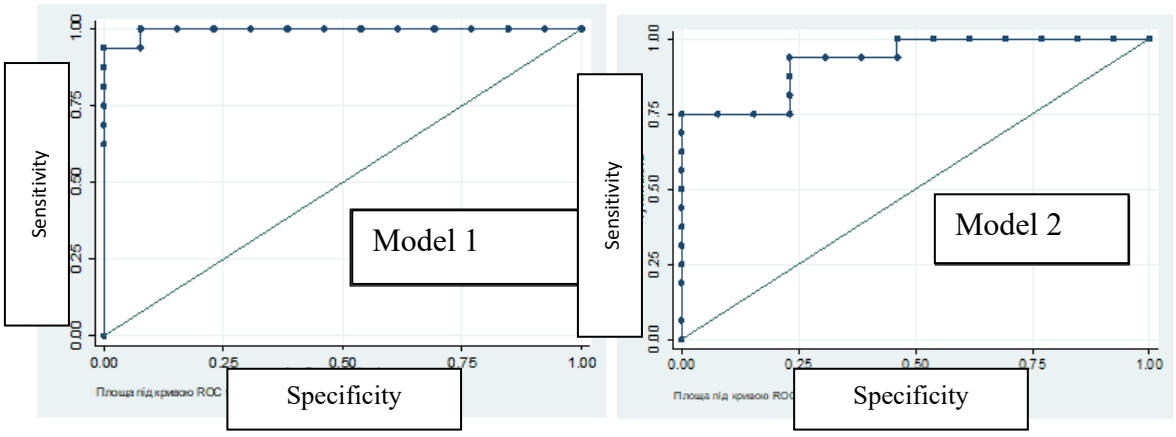

Fig. 2. ROC curves of predictive models for HIE development in neonates during the early neonatal period.

If we analyze the operational characteristics of the predictive models, then, as shown by the data presented in Table 7, the best sensitivity, specificity, positive and negative predictive value were found in the first predictive model, which contains the following criteria: urinary nitrite levels, GA and ALT.

Table 7

Operational characteristics of predictive models for HIE development (%)

Indicators	1 model	2 model
Sensitivity	93,75	75,0
Specificity	92,31	76,92
Positive predictive value	93,75	80,00
Negative predictive value	92,31	71,43
Correctly classified	93,10	75,86

Conclusions

HIE in neonates is associated with multiorgan system involvement. Considering this multiorgan pathology, we identified reliable metabolic markers for HIE risk during the early neonatal period in infants born to mothers with metabolic syndrome: serum ALT/AST levels and urinary nitrites. Given gestational age (GA) heterogeneity within our cohort, we employed multiple logistic regression analysis with GA adjustment for proper data interpretation. We developed a predictive model incorporating urinary nitrite and ALT levels. The elevated ALT levels may reflect maternal metabolic syndrome, as recent studies demonstrate that first-trimester ALT abnormalities can predict fetal macrosomia [26]. Therefore, neonates with HIE born to mothers with metabolic syndrome require mandatory ALT/AST monitoring during the early neonatal period. Urinary nitrite measurement represents an optimal biomarker for early HIE prediction.

Prospects for further research. Given the diagnostic challenges and absence of perfect algorithms for HIE and its complications identification, future studies with larger patient cohorts may yield novel diagnostic criteria among metabolic markers.

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ПРЕДИКТОРИ РОЗВИТКУ ГІПОКСИЧНО-ІШЕМІЧНОЇ ЕНЦЕФАЛОПАТІЇ У ДОНОШЕНИХ ТА ПЕРЕДЧАСНО НАРОДЖЕНИХ ДІТЕЙ ВІД МАТЕРІВ З МЕТАБОЛІЧНИМ СИНДРОМОМ У РАННЬОМУ НЕОНАТАЛЬНОМУ ПЕРІОДІ

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Резюме.

Останні дослідження свідчать про прямий зв'язок між гіпоксично-ішемічною енцефалопатією (ГІЕ) та надмірною масою тіла або ожирінням у матері. ГІЕ є однією з провідних причин неонатальної смертності та довготривалої неврологічної інвалідизації новонароджених. ГІЕ має системний характер і охоплює не лише центральну нервову систему, а й інші органи, зокрема печінку. Одним із непрямих біохімічних маркерів гіпоксичного ушкодження є підвищення активності печінкових трансаміназ – аланінамінотрансферази (АЛТ) та аспартатамінотрансферази (АСТ). Окрему увагу привертає участь оксиду азоту (NO) у патогенезі ГІЕ.

Мета: проаналізувати і виявити фактори ризику гіпоксично-ішемічної енцефалопатії у доношених та передчасно народжених дітей від матерів з метаболічним синдромом, побудувати клінічні прогностичні моделі.

Матеріали і методи. У дослідження було включено 125 новонароджених: у першу групу ввійшли немовлята, народжені матерями з метаболічним синдромом, і які мали ГІЕ (n=45), у другу групу – немовлята, які народились від матерів без метаболічного синдрому і без проявів ГІЕ (n=79). Концентрацію нітритів досліджували шляхом визначення діазосполук, що утворилися у реакції з сульфаніловою кислотою, з подальшим проведенням реакції з реактивом Грісса-Ілосвая). Біоетичні принципи виконання дослідження підтверджені комісією з етичних питань та біоетики Полтавського державного медичного університету (протокол № 233 від 21.12.2024 р.). Статистичний аналіз проводили за допомогою пакету прикладних програм STATA 14.0. Робота виконана у межах НДР кафедри педіатрії № 1 із неонатологією Полтавського державного медичного університету «Розробити клініко-лабораторні критерії, методи прогнозування та запобігання метаболічних порушень у дітей раннього віку» (державний реєстраційний номер 0120U102856, термін виконання 2020-2024 рр.).

Результати дослідження та їх обговорення. На початку дослідження було проведено аналіз клінічного стану дітей після народження. Найчастіше у доношених немовлят діагностувалися синдром пригнічення, синдром дихальних розладів, серцеву недостатність, судоми та м'язеву дистонію. Серед передчасно народжених найпоширенішими станами були синдром пригнічення, м'язева дистонія та судоми. ГІЕ у доношених немовлят супроводжується комплексом уражень інших органів та систем, у той час як у передчасно народжених дітей більшість клінічних проявів стосується нервової системи. Було проведене дослідження метаболічного профілю, який підтверджує мультиорганні прояви ГІЕ. Виявлено, що на першу добу життя у передчасно народжених немовлят з ГІЕ рівень АСТ та АЛТ був достовірно вищим за передчасно народжених немовлят без ГІЕ (p=0,055 та p=0,049). Рівень нітритів в сечі у передчасно народжених немовлят з ГІЕ був достовірно вищим за рівень нітритів передчасно народжених немовлят без ГІЕ (p=0,025), подібні зміни нами отримано і для доношених немовлят – вищий рівень нітритів у немовлят з ГІЕ (p=0,042). Ґрунтуючись на отриманих даних, ми розробили прогностичні моделі розвитку ГІЕ в ранньому неонатальному періоді. Після корекції на гестаційний вік та активність АЛТ або АСТ рівень нітритів в сечі є достовірним прогностичним маркером розвитку ГІЕ як у передчасно народжених, так і у доношених немовлят, при цьому площі під ROC кривими в моделях, що включають такі змінні перемінні як рівень нітритів в сечі, гестаційний вік та АЛТ або АСТ становлять 0,9952 і 0,9279 відповідно.

Висновки. ГІЕ у новонароджених супроводжується комплексом уражень інших органів та систем. Враховуючи поліорганність патології, було вивчено можливі метаболічні маркери і серед них виявлено достовірні фактори ризику розвитку ГІЕ у ранньому неонатальному періоді у новонароджених від матерів з метаболічним синдромом, а саме рівень АЛТ та АСТ сироватки крові та нітритів сечі. Зважаючи на неоднорідність групи дітей за гестаційним віком, для коректної інтерпретації отриманих даних було застосовано множинний логістичний регресійний аналіз з обов'язковою корекцію на гестаційний вік. Було побудовано прогностичну модель розвитку ГІЕ, яка включає рівень нітритів та рівень АЛТ. Новонароджені, які народилися з ГІЕ від матерів з метаболічним синдромом потребують обов'язкового контролю АЛТ та АСТ під час раннього неонатального періоду, а визначення нітритів в сечі є оптимальним біомаркером щодо прогнозування розвитку ГІЕ.

Ключові слова: метаболічний синдром, гіпоксично-ішемічна енцефалопатія, новонароджені, предиктори гіпоксично-ішемічної енцефалопатії, АЛТ, АСТ, нітрити сечі.

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