РЕЗУЛЬТАТИ ДИСЕРТАЦІЙНИХ ТА НАУКОВО-ДОСЛІДНИХ РОБІТ

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TO THE ISSUE OF THE DEVELOPMENT AN ALGORITHM FOR A DIFFERENTIATED APPROACH TO THE MANAGEMENT OF PERSISTENT PULMONARY HYPERTENSION IN PREMATURE INFANTS

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Summary

The management of premature infants with persistent pulmonary hypertension (PPH) remains a major problem in modern neonatology. In recent years, scientific studies have identified the role of oxidative stress (OS) in the development and course of PPH. The reserve for reducing mortality and optimizing the management of premature infants with respiratory distress syndrome (RDS) and asphyxia is the development of an algorithm for a differentiated approach to the management of PPH in premature infants, taking into account the severity and dynamics of OS, and its implementation into clinical practice.

Aim of the study. *To increase the effectiveness of management of premature infants with persistent pulmonary hypertension with asphyxia and respiratory distress syndrome based on the development of an algorithm for a differentiated approach to the management of pulmonary hypertension taking into account the levels of oxidative stress as determined by urinary 8-hydroxy-2-deoxyguanosine (8-OHdG).*

Material and methods. *100 premature infants between 26/1-34/6 weeks of gestation were included in the study: group I consisted of 50 infants with RDS, group II – 50 newborns with RDS associated with perinatal asphyxia. The presence and severity of PPH was determined in all infants on the first and third to fifth day of life by echocardiography (EchoCG), and quantitative determination of 8-OHdG level (ng/ml) – in 44 infants on the first day, and in dynamics – on the third to fifth day of life by enzyme-linked immunosorbent assay (ELISA). For radiographic evaluation of PPH, all infants underwent chest radiography with determination of Moore's, Schwedel's and cardiothoracic index (CTI). The research was conducted in compliance with bioethical requirements as part of the planned scientific work of the Department (state registration number 0122U000025).*

Results. *It was found that the characteristics of pulmonary hypertension in premature infants with RDS were significantly lower levels of mean pressure in the pulmonary artery (mPAP) on the first and 3-5 days of life than in children with perinatal asphyxia. It was noted that the factors with high diagnostic significance determining the occurrence of persistent pulmonary hypertension are: birth weight <1500 g; presence of perinatal asphyxia; low Apgar score on the 1st (1-3 points) and on the 5th minute of life (<7 points); gestational age <30 weeks; non-appropriateness for gestational age; male sex. Furthermore, it was found that urinary 8-OHdG levels as a biomarker of OS in preterm infants with RDS and perinatal asphyxia correlated with mPAP on the first and third to fifth days of life, and that urinary 8-OHdG levels had a high diagnostic value for determining the risk of developing severe PPH on the third to fifth days of life. The diagnostic significance of the data of the comprehensive radiological assessment of PPH – the radiological indices of Moore, Schwedel, CTI for the development of severe PPH was analyzed and the correlations between the indices and mPAP and between the indices and the level of 8-OHdG were established. The Schwedel index showed the highest reliability in all cases.*

Conclusion. *On the basis of scientifically established relationships between clinical, laboratory, radiological and gender aspects of premature infants with perinatal pathology and the identified diagnostic and prognostic values of urinary 8-OHdG, an algorithm for a differentiated approach to the management of PPH was developed. Determination of the degree of OS and mPAP in premature infants allows us to adjust and individualize the tactics of respiratory support in the management of premature infants, thus improving the quality of medical care of premature infants with RDS and perinatal asphyxia. In prematurely born children in perinatal centers, additional determination of the severity of RDS based on the level of 8-OHdG in urine allows to predict the adverse course of PPH and the development of complications: bronchopulmonary dysplasia, intraventricular hemorrhage III-IV grade, retinopathy II-III grade, hearing impairment, hypoxic-ischemic lesions of the central nervous system II-III grade in prematurely born children.*

Key words: *Premature infants; Persistent Pulmonary Hypertension; Oxidative Stress.*

Introduction

Oxidative stress (OS) is a component of the pathophysiology of neonatal lung disease associated with persistent pulmonary hypertension (PPH) [1-4]. The most sensitive OS biomarker in preterm infants is urinary 8-hydroxy-2-deoxyguanosine (8-OHdG) [5-8], which shows a high correlation with mean pulmonary artery trunk pressure and duration of respiratory support [9]. In this article, we add to the body of scientific work on the development of a differentiated approach to the management of PPH. Previously, we published data on the analysis of modern medical literature with the determination of the need to improve the diagnosis and treatment of PPH in premature infants [10] and the results of the search for the optimal urinary OS biomarker correlating between the levels of OS and mPAP in premature infants with RDS and asphyxia [11,

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12]. Data were also presented on the type and duration of respiratory support and its relationship with the dynamics of OS levels in preterm infants with PPH [13], and the results of the scientifically established algorithm for a differentiated approach to the management of PPH in preterm infants [9].

Aim of the study – to increase the effectiveness of the treatment of premature infants with persistent pulmonary hypertension with asphyxia and respiratory distress syndrome based on the development of an algorithm for a differentiated approach to the management of pulmonary hypertension taking into account the level of oxidative stress as determined by urinary 8-hydroxy-2-deoxyguanosine.

Material and methods

The study was conducted in 2020-2023 on the basis of the intensive care unit for premature infants of the Kharkiv Municipal Perinatal Center. Were studied 100 premature infants, divided into groups. The first group consisted of 50 infants with RDS (26 boys and 24 girls), the second group – 50 infants with perinatal asphyxia associated with RDS (25 boys and 25 girls). The clinical characteristics of the groups are shown in Table 1. Inclusion criteria of the study: persistent pulmonary hypertension; gestational age 26-34 weeks; neonatal period; respiratory distress syndrome IInd-IIIrd degree; RDS associated with perinatal asphyxia; obtaining voluntary informed consent of the patient's parents/caregivers to participate in the study. Exclusion criteria: gestational age less than 26 weeks or more than 34 weeks; congenital heart disease and patent ductus arteriosus; necrotic enterocolitis, sepsis; refusal of parents/caregivers to participate in the study [14].

Clinical and echocardiographic criteria were used to determine the presence and severity of PPH in all infants during the first and dynamic 3-5 days of life. Among the clinical criteria, the oxygenation index (OI) was the most important. Echocardiographic criteria, according to international recommendations, include: assessment of the rate of tricuspid regurgitation, measurement of systolic pressure in the right ventricle, assessment of the state of the right ventricle and the interventricular septum, blood shunt, ratio of pulmonary artery acceleration time to right ventricular ejection time [15-18]. The mean pressure in the pulmonary artery trunk was determined according to the international standards for the diagnosis of pulmonary hypertension [19]. Quantitative determination of urinary 8-OHdG (ng/ml) was performed in 44 infants on day 1 of life and again on days 3-5 by the ELISA method using the DNA Damage ELISA reagent kit, Enzo Life Sciences (USA), according to the manufacturer's instructions. Radiographic assessment of PPH severity was performed according to the criteria of Spuzyak MI et al. (2006) [20].

The algorithm of the differentiated approach was based on the study of clinical and anamnestic data of the studied groups of children, the ultrasound criteria of PPH, the dynamics of OS levels, the determined prognostic threshold value of 8-OHdG, and comparison with the indicators of comprehensive radiographic evaluation of pulmonary hypertension in premature infants with RDS and perinatal asphyxia.

The study was part of the research plan of the Department of Neonatology of the Kharkiv Medical Academy of Postgraduate Education «Study of the peculiarities of the course of oxidative stress diseases in newborns» (January 2022 – December 2024), state registration number 0122U000025.

The research design was discussed and approved at the meeting of the Medical and Ethical Committee of the Kharkiv Medical Academy of Postgraduate Education (Protocol No. 5 dated December 18, 2000). All parents gave informed consent to the study of their children.

Statistical analysis was performed using standard packages of MS Excel, Statsoft Statistica 7.0. (USA), MedCalc® Statistical Software, version 20.218 (MedCalc Software Ltd, Ostend (Belgium). Qualitative parameters were analyzed using Fisher's exact test (φ). A heterogeneous sequential Wald procedure [21] was used to determine the diagnostic coefficients (DC) and informativeness (I) of the studied features. The prognostic threshold for quantitative indicators was determined using ROC analysis with the construction of a curve between the sensitivity and specificity of the diagnostic method.

Table 1

Clinical characteristics of patient groups, n (%), M±m [14]

Indicator	Group I n=50	Group II n=50
Gestational age, weeks	30.66±2.60*	30.34±3.15*
Birth weight (g)	1399±542*	1534±677*
Boys, n (%)	26 (52 %)	25 (50 %)
Girls, n (%)	24 (48 %)	25 (50 %)
Apgar score, M±m		
1st minute of life	4.08±0,24*	3.08±0.27*
5th minute of life	5.95±0,25**	4.50±0.26**
Pulse oximetry, % M±m		
SpO_2 on the 1st day of life	92.41±1.62**	90.65±1.49**
SpO_2 on the 3rd –5th day of life	94.04±1.30**	91.00±1.26**
Cord blood gas analyses, M±m		
pH	7.27±0.01**	7.01±0.03**
PO_2, mm Hg	34.82±0.47**	24.95±0.42**
PCO_2, mm Hg	33.87±0.38**	46.58±0.40**
BE_b	-2.2±0.80**	-13.69±0.46**

Continuation of Table 1

Indicator	Group I n=50	Group II n=50
Blood bas analyses, M±m		
pH on the 1st day of life	7.24±0.06**	7.04±0.12**
pH on the 3rd –5th day of life	7.33±0.05**	7.189±0.09**
PO_2, mm Hg on the 1st day of life	31.25±2.10*	30.43±4.10*
PO_2, mm Hg on the 3rd –5th day of life	38.67±4.04**	30.35±3.18**
PCO_2, mm Hg on the 1st day of life	52.00±4.75**	80.80±14.76**
PCO_2, mm Hg on the 3rd –5th day of life	38.16±5.65**	64.67±8.51**
BE_b on the 1st day of life	-3.85±2.03**	-11.56±3.40**
BE_b on the 3rd –5th day of life	-0.63±4.35**	-6.56±4.69**
IO on the 1st day of life, M±m	16.43±2.79*	17.87±2.89*
IO on the 3rd –5th day of life, M±m	8.50±4.69**	16.00±1.31**
A-aDO_2 on the 1st day of life, M±m	183.26±48.12*	210.27±59.25*
A-aDO_2 on the 3rd –5th day of life, M±m	65.86±8.43**	160.80±51.75**
Type of delivery and unipara, n (%)		
Cesarean section	46 (92 %)	31 (62 %)
Natural childbirth	4 (8 %)	19 (38 %)
First delivery	38 (76 %)	31 (62 %)
Unipara	12 (24 %)	19 (38 %)
Maternal anamnesis and course of pregnancy		
Maternal age, years (M±m)	26.5±1.90**	32.3±1.85**
Severe gestosis, n (%)	12 (24 %)	34 (68 %)
RDS prophylaxis, n (%)		
Full	49 (98 %)	46 (92 %)
Partial	1 (2 %)	4 (8 %)
Not conducted	0 (0 %)	0 (0 %)
Surfactant therapy		
LISA, n (%)	28 (56 %)	6 (12 %)
INSURE, n (%)	12 (24 %)	7 (14 %)
Through additional port of endotracheal tube, n (%)	2 (4 %)	37 (74 %)
Not conducted, n (%)	8 (16 %)	0 (0 %)
Respiratory support, M±m		
MAP, см H_2O on the 1st day of life	11.47±0.64*	12.86±0.49*
MAP, см H_2O on the 3rd –5th day of life	10.57±1.56**	13,35±0.58**
FiO_2, % on the 1st day of life	31.45±6.75**	45,96±7.53**
FiO_2, % on the 3rd –5th day of life	21.16±0.98**	37,78±3.45**
Complications and average length of hospital stay		
No complications, n (%)	19 (38 %)	6 (12 %)
Bronchopulmonary dysplasia, n (%)	8 (16 %)	13 (26 %)
Retinopathy II-III stage, n (%)	13 (26 %)	16 (32 %)
IVG II-IV dg, n (%)	4 (8 %)	6 (12 %)
Hearing impairment (failed test), n (%)	6 (12 %)	9 (18 %)
Anemia of prematurity I dg., n (%)	9 (18 %)	11 (22 %)
Hypoxic ischemic encephalopathy II-III dg., n (%)	28 (56 %)	36 (72 %)
Average length of hospital stay, days	37.66±3.79**	43.31±2.94**

*Note: * – p >0.05 – no difference between groups*

*** – p < 0.05 – significant difference between groups*

SpO_2 – saturation; pH – blood acidity; PO2 –partial pressure of oxygen in the blood; PCO_2 – partial pressure of carbon dioxide in the blood; BE_b – deficiency of bases; IO – oxygenation index; A-aDO_2 – alveolar-arterial oxygen gradient; MAP – average pressure in the respiratory tract; FiO_2 – fraction of oxygen in the inhaled mixture; IVG – intraventricular gemorrage.

Results and discussion

At the first stage of research there was presented a characteristics of indicators of PPH and factors that determine the occurrence of PPH; were determined their diagnostic and prognostic significance in prematurely born children in the gestational age of 26-34 weeks with asphyxia and RDS. Against the background of treatment and selection of the most optimal tactics of respiratory support (traditional mechanical ventilation with PEEP of at least 6 cm H2O, high-frequency mechanical ventilation,

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non-invasive mechanical ventilation, CPAP), the average mPAP, mm Hg, was measured by the Echo CG method as an indicator of PPH in both groups in the first and in dynamics on the 3rd-5th day of life. On the first day of life, the average value of mPAP in group I was significantly lower than in group II. In the dynamics of observation on the 3rd-5th day of life, the average mPAP significantly decreased in the group of infants with RDS, and increased in the group with perinatal asphyxia (Table 2).

The above evidence supports the aggravating effect of perinatal asphyxia on the course of PPH and defines asphyxia as a factor determining the development of PPH in premature infants, which is confirmed by modern scientific and medical literature [22, 23].

Table 2

The mean value and dynamics of mPAP (mm Hg) in premature infants with RDS and perinatal asphyxia, M±m [14]

Indicator	Group I n=50	Group II n=50
Mean mPAP on the 1st day of life	25.00±0.56*	40.19±0.40*
Mean mPAP on the 3rd –5th day of life	21.77±0.73**	43.08±0.71**

*Note: * – p < 0.05 – significant difference between groups*
*** – p < 0.05 – significant difference between groups*

We evaluated the diagnostic significance and power of the main clinical and anamnestic data of premature infants, the course of pregnancy, the method of delivery, and analyzed their influence as factors determining the development of persistent pulmonary hypertension of various degrees (Table 3).

Table 3

Diagnostic significance of clinical and anamnestic data of premature infants with persistent pulmonary hypertension [9, 14]

Indicator	Gradation	DC	I
Birth weight, g	<1500	-3.8	4.35
	≥1500	+11.6	
Perinatal asphyxia	present	-6.0	3.60
	not present	+6.0	
Apgar score on the 5th minute of life	1-3 points	-9.0	3.49
	4-6 points	-0.5	
	≥7 points	+23.8	
Gestational age, weeks	26-29	-9.7	3.24
	30-34	+3.3	
Type of delivery	natural childbirth	-8.0	1.68
	Cesarean section	+1.9	
Apgar score on the 1st minute of life	1-3 points	-4.3	1.13
	>3 points	+2.4	
Appropriation for gestational age	non-appropriative	-12.5	1,13
	appropriative	+1,8	
Placental disfunction during pregnancy	present	-2.6	1.11
	not present	+3.8	
Infants's sex	male	-3.0	1.04
	female	+3.1	
Arterial hypertension during pregnancy	present	-5.9	0.60
	not present	0.9	

Note: The sign (+) indicates about favorable course of PPH, and the sign (–) indicates about the development of significant/severe PPH on the 3-5th day of life.

The following clinical and diagnostic factors are of high diagnostic significance for an unfavorable course of PPH: mean pulmonary artery pressure on day 3-5 of life > 31.9 mm Hg (I=7.0), oxygenation index on day 3-5 of life > 8 (I=4.35), body weight at birth <1500 g (I=4.30). (I=7.0), oxygenation index on day 3-5 of life > 8 (I=4.35), birth weight <1500 g (I=4.30), perinatal asphyxia (I=4.22), Apgar score at 5 minutes of life < 7 points (I=3.49), gestational age < 30 weeks (I=3.24), mean pulmonary artery pressure on day 1 of life > 34 mm Hg. (I=1.98), natural childbirth (I=1.68), small for gestational age (I=1.13), male sex (I=1.04), placental dysfunction during pregnancy (I=1.11), maternal hypertension during pregnancy (I=0.60) [14]. The obtained results are consistent with modern literature data [24, 25, 26].

The second stage was to study the value of urinary 8-OHdG in premature infants with asphyxia and RDS in the early neonatal period and to determine the clinical significance of its levels at different degrees of PPH (Table 4).

Table 4

Value of the urinary 8-OHdG (ng/ml) and its dynamics in premature infants with RDS and perinatal asphyxia, M±m

Value of the urinary 8-OHdG, ng/ml	Group I (n=23)	Group II (n=21)
First day of life	1.83±0.29*	2.27±0.39*
3rd –5th day of life	1.06±0.28*	4.10±0.42*

*Note: * –p < 0.05 – significant difference between groups*

The obtained data indicate that on the first day of life there is almost no significant difference between the studied groups of children. On the 3rd-5th day of life, in the first group of children there is a significant decrease in the studied urinary OS biomarker ($p<0.05$), in the second group – a significant increase by 1.8 times ($p<0.05$). Our results indicate that perinatal asphyxia has a detrimental effect on the degree of oxidative stress, reduced adaptability and reactivity to OS in premature infants.

To evaluate the possibility of using the biomarker of oxidative stress in clinical practice in the management of premature infants, we analyzed the diagnostic and prognostic significance of the dynamics of 8-OHdG levels in the first and 3-5 days of life. The DC values (Table 5) indicate that a decrease in urinary 8-OHdG in premature infants is associated with a favorable course of PPH, and the absence of a decrease in the studied indicator indicates the probable development of severe PPH. The above is also confirmed by our correlation analysis between mPAP and the level of urinary 8-OHdG, ng/ml in premature infants [14].

Urinary 8-OHdG as a biomarker of OS in preterm infants with RDS correlates with mean pulmonary artery pressure on day 1 ($r=0.85$, $p<0.001$) and day 3-5 ($r=0.84$, $p<0.001$). A correlation was found between the level of urinary 8-OHDG in preterm infants with RDS associated with perinatal asphyxia and mPAP on the first ($r=0.82$, $p<0.05$) and on the third to fifth days of life ($r=0.80$, $p<0.05$). The gender characteristics of the dynamics of 8-OHdG levels in premature infants with RDS and asphyxia with perinatal pathology confirm the reduced adaptability and reactivity of boys to oxidative stress in the early neonatal period: on the first day of life in both groups of studied newborns there is no significant difference ($p>0.05$) in the levels of 8-OHdG in urine between boys and girls. On the 3-5th day of life, a significant increase in urinary 8-OHdG levels was observed in boys in both groups ($p<0.05$) compared with girls.

Table 5

Diagnostic significance of determining the dynamics of urinary 8-OhdG in premature infants with PPH

Indicator	Gradation	DC	I
Decrease of the 8-OHdG levels on the 3rd – 5th day of life	don't decreased	-7.8	6.39
	decreased	+9.3	

Note: The sign (+) indicates about favorable course of PPH, and the sign (–) indicates about the development of significant/severe PPH on the 3-5th day of life.

It was found that the level of urinary 8-OHdG on the 3rd – 5th day of life has a high diagnostic significance for determining the risk of developing severe PPH (I=6.39): a decrease in the level of urinary 8-OHdG indicates a favorable course of PPH, and an increase – about the risk of developing severe PPH. The prognostic significance of decreased levels of urinary 8-OHdG on the 3rd – 5th day of life indicates a decrease in the probability of developing complications in the neonatal period (I=3.25).

Clinical and laboratory correlations between mean pulmonary artery pressure, 8-OHdG levels and the need for respiratory support in premature infants revealed that the more intensive the dynamics of 8-OHdG reduction, the shorter the duration of respiratory support required by the infants to establish spontaneous breathing ($r=0.80$, $p<0.001$). The high diagnostic value of the duration and type of respiratory support for the prognosis of the course of PPH in premature infants was established: the risk of developing severe PPH is indicated by: duration of HFOV > 48 hours (I=3.03), duration of traditional mechanical ventilation > 72 hours (I=2.49), when nIV/CPAP is not the only type of respiratory support (I=1.56). The prognostic significance of the duration and type of respiratory support for predicting the course of PPH in preterm infants was determined: the following factors indicate the risk of complications in the neonatal period: duration of traditional mechanical ventilation > 72 hours (I=2.65), duration of HFOV > 48 hours (I=1.46), when nIV/CPAP is not the only type of respiratory support (I=1.08).

Perinatal asphyxia worsens the course of RDS in preterm infants with higher levels of mPAP ($p<0.05$), 3.5 times more cases of severe pulmonary hypertension ($p<0.05$), higher levels of OS ($p<0.05$), and longer duration of ventilatory support ($p<0.05$).

In the third stage we determined the diagnostic and informative value of predictors of PPH formation in premature infants with asphyxia and RDS. According to the results of the ROC analysis, the signs indicating the development of an unfavorable course of PPH are: the level of urinary 8-OHdG on the 3rd-5th day of life > 2.5 ng/ml; mPAP level on the first day of life > 34 mm Hg; mPAP level on the 3rd-5th day of life > 31. 9 mm Hg; Moore's index on the first day of life > 42 %; Moore's index on the 3rd-5th days of life > 43 %, Schwedel's index on the first day of life > 0.4 cm, Schwedel's index on the 3rd-5th days of life > 0.5 cm, CTI on the first day of life > 60 %; CTI on the 3rd-5th days of life > 60 %, oxygenation

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index on the first day of life > 16, oxygenation index on the 3rd-5th days of life > 8. High specificity was demonstrated by ROC curves for urinary 8-OHdG levels and radiologic indices on days 3-5 of life. High sensitivity was demonstrated by ROC curves for mean pulmonary artery pressure on days 1 and 3-5 of life, Moore's index on day 1, oxygenation index on days 3-5 of life.

Thus, reliable predictors of the progressive course of persistent pulmonary hypertension in premature infants with RDS and perinatal asphyxia are: the level of the urinary 8-OHdG > 2.5 ng/ml on the 3rd-5th day of life, the Schwedel index on the 3rd-5th day of life > 0.5 cm. Favorable course of PPH in premature infants is evidenced by: mPAP on the first day of life ≤ 34 mm Hg, mPAP on the 3-5th day of life ≤ 31.9 mm Hg, Moore's index on the first day life ≤ 42 %, oxygenation index on the 3rd-5th day of life ≤ 8 [14].

On the basis of the obtained informative indicators of complex radiological assessment of the degree of PPH and dynamics of OS levels, the final stage of the work was carried out – a differentiated approach to the diagnosis and treatment of PPH in premature infants with asphyxia and RDS was developed. The developed algorithm (Table 6) is used by algebraic summation of DC until the diagnostic threshold is reached, which for the 95 % level of confidence is ≥ –13.0, and for the 99 % level – DC ≥ –20. If there is a «-» sign next to the sum of DC of all indicators, there is a risk of developing severe PPH, which requires correction of ventilator parameters and increased treatment, and a «+» sign indicates a favorable course of PPH.

Table 6

Algorithm of a differentiated approach to management of persistent pulmonary hypertension in premature infants [9, 14]

Indicator	Gradation	DC	I
mPAP on the 3rd – 5th day of life, mmHg	≤31.9	+9.0	7.0
	>31.9	-9.0	
Decrease of the 8-OHdG levels on the 3rd – 5th day of life	decreased	-7.8	6.39
	don't decreased	+9.3	
Surfactant therapy	conducted	+4.0	6.07
	don't conducted	-6.1	
Oxygenation index on the 3rd –5th day of life	≤8	+5.0	4.35
	>8	-4.2	
Birth weight, g	<1500	-3.8	4.30
	≥1500	+11.6	
Perinatal asphyxia	present	-6.0	4.22
	not present	+6.0	
Schwedel's index on the 3rd –5th day of life, cm	0.4-0.5	+8.5	3.60
	>0.5	-5.0	
Apgar score on the 5th minute of life	1-3 points	-9.0	3.49
	4-6 points	-0.5	
	>7 points	+23.8	
Gestational age, weeks	26-29	-9.7	3.24
	30-34	+3.3	
Moore's index on the 3rd –5th day of life, %	36-43 %	+6.7	3.23
	>43 %	-6.3	
Oxygenation index on the first day of life	≤16	+6.2	3.20
	>16	-6.4	
Duration of the HFOV, hours	<48	+3.1	3.03
	>48	-9.5	
Duration of TMV, hours	<72	+3.4	2.49
	>72	-6.9	
CTI on the 3rd –5th day of life, %	50-60 %	+3.4	2.49
	>60 %	-6.9	
mPAP on the 1stday of life, mmHg	≤34	+4.0	1.98
	>34	-4.6	
Type of delivery	natural childbirth	-8.0	1.68
	Cesarean section	+1.8	
NIV/CPAP- the only one type of respiratory support	yes	+7.2	1.56
	no	-2.0	
Apgar score on the 1st minute of life	1-3 points	-4.3	1.13
	>4 points	+2.4	
Appropriation for gestational age	non-appropriative	-12.5	1.13
	appropriative	+1.8	
Placental disfunction during pregnancy	present	-2.6	1.11
	not present	+3.8	
Infants's sex	male	-3.0	1.04
	female	+3.1	
Arterial hypertension during pregnancy	present	-5.9	0.60
	not present	0.9	

Note: The sign (+) indicates about favorable course of PPH, and the sign (–) indicates about the development of significant/severe PPH on the 3-5th day of life.

If the diagnostic threshold was not reached when adding the DC of all algorithm indicators, the diagnosis is considered uncertain.

Conclusions

1. In our research, the development of an algorithm for a differentiated approach to the management of PPH, taking into account the complex radiological assessment of pulmonary hypertension, OS levels as determined by urinary 8-OHdG in premature infants at gestational age of 26-34 weeks with respiratory distress syndrome and perinatal asphyxia is scientifically based.

2. The pathogenetic significance of urinary 8-OHdG in the development of PPH was determined and substantiated by the ELISA method, and a direct strong correlation was established between the OS indicator and the mPAP level in premature infants with RDS and with RDS associated with perinatal asphyxia in the early neonatal period. Perinatal asphyxia has been shown to exacerbate the degree and course of pulmonary hypertension in premature infants with RDS.

3. Diagnostic and prognostic determinants of the development and course of pulmonary hypertension in premature infants with RDS and perinatal asphyxia were determined. It was found that a decrease in urinary 8-OHdG levels on the 3rd to 5th day of life is a prognostic sign of a favorable course of PPH (I=6.39).

4. On the basis of scientifically substantiated correlations between clinical, laboratory, radiological, gender aspects of premature infants with perinatal pathology and the identified diagnostic and prognostic values of the informative value of urinary 8-OHdG levels, an algorithm for a differentiated approach to the management of PPH was developed.

5. Determination of the degree of OS and mPAP in premature infants allows to optimize the tactics of respiratory support in the management of premature infants, thus improving the quality of medical care of premature infants with RDS and perinatal asphyxia.

6. In premature infants in perinatal centers, additional determination of the severity of PPH on the basis of urinary 8-OHdG level allows to predict the adverse course of PPH and development of complications: bronchopulmonary dysplasia, intraventricular hemorrhage of III-IV degree, retinopathy of II-III degree, hearing impairment, hypoxic-ischemic lesions of the central nervous system of II-III degree in premature infants.

Prospects for further research. Prospects for further research are to carry out a catamnestic observation of premature infants in order to study the influence of OS on the development of complications.

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ДО ПИТАННЯ СТВОРЕННЯ АЛГОРИТМУ ДИФЕРЕНЦІЙОВАНОГО ПІДХОДУ ДО МЕНЕДЖМЕНТУ ПЕРСИСТУЮЧОЇ ЛЕГЕНЕВОЇ ГІПЕРТЕНЗІЇ У ПЕРЕДЧАСНО НАРОДЖЕНИХ ДІТЕЙ

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Резюме.

Ведення передчасно народжених дітей з персистуючою легеневою гіпертензією (ПЛГ) залишається актуальною проблемою сучасної неонатології. Наукові дослідження останніх років визначають роль оксидативного стресу (ОС) у розвитку та перебігу ПЛГ. Резервом для зниження летальності та оптимізації ведення недоношених новонароджених з респіраторним дистрес-синдромом (РДС) та асфіксією є розробка та впровадження в клінічну практику алгоритму диференційованого підходу до менеджменту ПЛГ у передчасно народжених дітей з урахуванням вираженості та динаміки ОС.

Мета дослідження. Підвищення ефективності ведення передчасно народжених дітей з ПЛГ з асфіксією та РДС на підставі розробки алгоритму диференційованого підходу до ведення легеневої гіпертензії з урахуванням рівнів оксидативного стресу за визначенням 8-гідрокси-2-дезоксигуанозину (8-OHdG) в сечі.

Матеріал та методи дослідження. В дослідження було включено 100 передчасно народжених дітей у терміні гестації 26/1-34/6 тижнів: I групу склали 50 дітей з РДС, групу II – 50 дітей з РДС у поєднанні з асфіксією при народженні.

Визначення наявності та ступеню тяжкості ПЛГ було проведено всім дітям в першу та на 3-5 добу життя за допомогою ехокардіографії (ЕхоКГ), а кількісне визначення рівня 8-OHdG (нг/мл) – 44 дітям в першу, та в динаміці – на 3-5 добу життя методом імуноферментного аналізу (ІФА). Для променевої оцінки ПЛГ всім дітям проводилось рентгенологічне дослідження органів грудної клітини (Rö ОГК) з визначенням індексів Мура, Шведеля та кардіоторакального індексу (КТІ).

Дослідження виконано з дотриманням вимог біоетики в рамках планової наукової роботи кафедри (№ держреєстрації 0122U000025).

Результати дослідження. Встановлено, що особливостями легеневої гіпертензії у передчасно народжених дітей з РДС були достовірно нижчі рівні середнього тиску у стовбурі легеневої артерії (mPAP) в першу, та на 3-5 добу життя, ніж у дітей з перинатальною асфіксією.

Визначено, що чинниками з високою діагностичною значущістю, детермінуючими виникнення персистуючої легеневої гіпертензії є: маса тіла дитини при народженні <1500 г, наявність перинатальної асфіксії, низька оцінка за шкалою Апґар на 1 (1-3 бали) та на 5 хвилинах життя (<7 балів), термін гестації <30 тижнів, невідповідність маси тіла дитини гестаційному віку, чоловіча стать дитини.

Встановлено, що вміст 8-OHdG як біомаркера ОС в сечі у передчасно народжених дітей з РДС та перинатальною асфіксією корелює з mPAP в першу та на 3-5 добу життя, а рівні 8-OHdG в сечі мають високу діагностичну значущість для визначення ризику розвитку ПЛГ тяжкого ступеня на 3-5 добу життя.

Проаналізовано діагностичну значущість даних комплексної променевої оцінки ПЛГ – рентгенологічних індексів Мура, Шведеля, КТІ на розвиток ПЛГ тяжкого ступеня та встановлено кореляційні зв'язки між індексами та mPAP, та між індексами та рівнем 8-OHdG. Індекс Шведеля показав найбільш високу достовірність у всіх випадках.

Висновки. На підставі науково обґрунтованих взаємозв'язків між клінічними, лабораторними, променевими, гендерними аспектами передчасно народжених дітей з перинатальною патологією та виявлених діагностично-прогностичних значень інформативності рівнів 8-OHdG в сечі розроблено алгоритм диференційованого підходу до менеджменту ПЛГ. Визначення ступеня ОС та mPAP у передчасно народжених дітей дозволяє скоригувати та індивідуалізувати тактику респіраторної підтримки при веденні недоношених новонароджених, таким чином покращивши якість надання медичної допомоги недоношеним новонародженим з РДС та перинатальною асфіксією.

У передчасно народжених дітей в перинатальних центрах додаткове визначення тяжкості ОС на підставі рівня 8-OHdG в сечі дозволяє прогнозувати несприятливий перебіг ПЛГ та розвиток ускладнень: бронхолегеневої дисплазії, внутрішньошлуночкового крововиливу III-IV ступеня, ретинопатії II-III стадії, уражень слуху, гіпоксично-ішемічного ураження ЦНС II-III ступеня у передчасно народжених дітей.

Ключові слова: передчасно народжені діти; персистуюча легенева гіпертензія; оксидативний стрес.

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