РЕЗУЛЬТАТИ ДИСЕРТАЦІЙНИХ ТА НАУКОВО-ДОСЛІДНИХ РОБІТ

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GENDER ASPECTS FOR THE MANAGEMENT OF PERSISTENT PULMONARY HYPERTENSION IN PREMATURE INFANTS

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Summary

Nowadays, premature birth continues to cause negative long-term consequences for subsequent morbidity and mortality of infants. Underdevelopment of pulmonary vessels on the background of insufficiency of the antioxidant system and diseases of the early neonatal period lead to the development of persistent pulmonary hypertension. Since pulmonary hypertension is a multifaceted pathology that requires a systematic approach to diagnosis and treatment, we considered the gender aspects of the management of persistent pulmonary hypertension in premature infants.

***The aim of the study:** To improve 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 diagnosis and treatment of pulmonary hypertension, taking into account the levels of oxidative stress as determined by the urinary 8-hydroxy-2-deoxyguanosine and gender differences.*

***Material and methods of the study.** The study included 100 premature infants born at a gestational age of 26/1-34/6 weeks: group I consisted of 50 children with respiratory distress syndrome, group II – 50 children with respiratory distress syndrome associated with perinatal asphyxia. Group I included 26 boys and 24 girls, group II included 25 boys and 25 girls. All newborns were assessed for the presence and severity of persistent pulmonary hypertension using echocardiography on the first and 3rd-5th days of life, and 44 infants were quantified for the urinary 8-hydroxy-2-deoxyguanosine (ng/ml) by enzyme-linked immunosorbent assay on the first and 3rd-5th days of life. The study was carried out in compliance with the requirements of bioethics within the framework of the planned scientific research work of the Department of Pediatrics № 3 and Neonatology of Kharkiv National Medical University (state registration number 0122U000025).*

***Results.** Gender differences in pulmonary hypertension were established in premature infants with respiratory distress syndrome: mean pulmonary artery pressure levels were significantly lower in girls in both groups, despite the aggravating effect of perinatal asphyxia. It was determined that in both groups of newborns by the 3rd-5th day of life, the number of cases of mild persistent pulmonary hypertension exceeded that in girls, which was observed due to a higher proportion of cases of moderate and severe persistent pulmonary hypertension in boys. According to the results of the analysis of cases of complications of the neonatal period, there were a greater number of episodes of bronchopulmonary dysplasia, intraventricular hemorrhages of grade II-IV, retinopathy of prematurity of stages I-III, hearing impairment (test not passed), anemia of prematurity, hypoxic-ischemic encephalopathy stages II-III in premature boys of both groups. A correlation was found between the content of urinary 8-hydroxy-2-deoxyguanosine as a biomarker of oxidative stress in premature infants and mean pulmonary artery pressure on the first and 3rd-5th day of life. Levels of urinary 8-hydroxy-2-deoxyguanosine on the 3rd-5th day of life were significantly higher in boys of both groups. The created algorithm of a differentiated approach to the management of persistent pulmonary hypertension includes the calculated diagnostic coefficient of the male sex (I=1.04) as a predictor of the development of severe pulmonary hypertension by the 3rd-5th day of life.*

***Conclusions.** 1. On the first day of life moderate and severe persistent pulmonary hypertension occurs in premature boys 3 times more often than in girls in the early neonatal period, and on the 3rd-5th day of life – 4 times more often. 2. Perinatal asphyxia complicates the course of persistent pulmonary hypertension in infants with respiratory distress syndrome to a greater extent in prematurely born boys, which is associated with the peculiarities of compensation for the effects of oxidative stress at birth. 3. In the developed algorithm of a differentiated approach to the management of persistent pulmonary hypertension, it should be taken into account that the diagnostic coefficient in male newborns is I=1.04, and is a predictor of the development of severe persistent pulmonary hypertension by the 3rd-5th day of life.*

***Keywords:** Persistent Pulmonary Hypertension; Premature Babies; Sexual Dimorphism; Oxidative Stress.*

Introduction

Persistent pulmonary hypertension (PPH) in preterm infants is a multifaceted pathology, with oxidative stress (OS) as an integral component of its pathophysiology [1-4]. A biomarker of OS in preterm infants is the urinary 8-hydroxy-2-deoxyguanosine (8-OHdG) [5-8]. Animal and clinical studies have shown that males have lower neuroendocrine reactivity and adaptability to oxidative stress, leading to higher morbidity and mortality rates [9].

We have previously published articles analyzing current medical literature highlighting the need to improve the management of PPH in a population of premature infants [10], the results of determining the urinary biomarker of OS and its correlation between OS levels and mean pulmonary artery pressure (mPAP) in premature infants with respiratory distress syndrome (RDS) and perinatal asphyxia in the early neonatal period [11, 12]. Data on the duration and types of respiratory support for preterm infants, taking

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into account OS levels [13], and the results of the creation and scientific substantiation of an algorithm for a differentiated approach to the management of PPH in preterm infants [9] were presented.

This article is a supplement to the previously presented results of scientific work on PPH management in premature infants, taking into account gender aspects.

The aim of the study is to improve 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 diagnosis and treatment of pulmonary hypertension, taking into account the levels of oxidative stress as determined by the urinary 8-hydroxy-2-deoxyguanosine and gender differences.

Material and methods. The study was conducted on the basis of the intensive care unit for premature infants of the MNPE «City Perinatal Center» of the Kharkiv City Council during 2020-2023. 100 prematurely born infants were examined, and divided into groups. The first group included 50 children with RDS (including 26 boys and 24 girls), the second group consisted of 50 children with birth asphyxia in association with RDS (including 25 boys and 25 girls). The clinical characteristics of the examined newborns are presented in Table 1. Inclusion criteria for the study: the presence of persistent pulmonary hypertension; gestational age 26/1-34/6 weeks; neonatal period; the presence of respiratory distress syndrome grades II-III; the presence of RDS in association with birth asphyxia; obtaining voluntary informed consent from the patient's parents/guardians to participate in the study. Exclusion criteria from the study: gestational age less than 26/1 weeks or more than 34/6 weeks; presence of congenital heart disease and hemodynamically significant patent ductus arteriosus; presence of necrotizing enterocolitis, sepsis; refusal of the child's parents/guardians to participate in the study [14].

On the first and on the 3rd-5th day of life, all children were determined for the presence and severity of PPH using echocardiography in accordance with modern international recommendations [15-18]. Urinary 8-OHdG level (ng /ml) as biomarker of oxidative stress was measured in 44 infants on the first and on the 3rd-5th day of life by ELISA using the DNA Damage ELISA reagent kit, Enzo Life Sciences (USA) according to the manufacturer's instructions.

Statistical analysis was performed using MS Excel, Statsoft software package. Statistics 7.0. (USA), MedCalc® Statistical Software, version 20.218 (MedCalc Software Ltd, Ostend (Belgium). Quality The parameters were analyzed using Fisher's exact test (φ) [19].

Table 1

Clinical characteristics of examined newborns by groups, n(%), M±m [14]

Group	Gestational age, weeks (M±m)	Body weight at birth, grams (M±m)	Boys, n (%)	Girls, n (%)	Total
1 (n=50) – RDS	30.66±2.60*	1399±542*	26 (52%)	24 (48%)	50
2 (n=50) – RDS + perinatal asphyxia	30.34±3.15*	1534±677*	25 (50%)	25 (50%)	50
Total n=100	Note: * – p >0.05 – no significant difference between groups				

Results. On the first day of life, in both groups of newborns, there was almost no significant difference in mPAP (mm Hg) between boys and girls. By the 3rd-5th day of life, a significant difference in the mean pulmonary artery pressure was established in both groups of children by gender: in girls of group I, by the 3rd-5th day of life, there was a more significant decrease in mPAP ($p<0.05$) than in boys. In group II, the following changes occurred: – the level of mPAP increased in boys and decreased in girls, despite the aggravating effect of perinatal asphyxia (Table 2).

Table 2

Gender characteristics of mPAP dynamics in premature infants with RDS and perinatal asphyxia, M±m [14]

Average mPAP (mmHg)	Group I (n=50)		Group II (n=50)	
	Boys (n=26)	Girls (n=24)	Boys (n=25)	Girls (n=25)
1 day of life	25.70±0.67*	24.53±0.45*	40.89±0.43*	39.42±0.32*
3rd-5th days of life	22.75±0.54*	20.94±0.84*	45.79±0.52*	37.99±0.78*

*Note: *p <0.05 –There is a significant difference between the groups.*

The results obtained indicate that birth asphyxia aggravates the course of PPH in children with respiratory distress syndrome, especially in male newborns, who are less adapted and have reduced compensatory mechanisms to the effects of perinatal asphyxia [14].

Analysis of cases of persistent pulmonary hypertension of varying degrees in children of both groups depending on gender allowed us to establish that: in the first day of life in boys of both groups the number of cases of mild PPH was 48% less than in girls (77.6% and 29.5%, respectively). This was due to the increased number of cases of moderate and severe PPH in boys of both groups by 38.5% and 9.6%, respectively.

The absence of ultrasound and clinical signs of PPH by the 3rd-5th day of life was registered in 20.4% of girls, which is 2 times more than in boys. The number of cases of mild PPH decreased in both sexes and was 5.9% in boys and 65.3% in girls. Regarding moderate and severe PPH, the following dynamics were observed: in girls – a decrease in the number of cases of moderate PPH by 4% and severe PPH by 4.1%. In boys – an increase in the number of cases of moderate and severe PPH by 8% and 6%, respectively (Table 3).

Table 3

Number of cases of persistent pulmonary hypertension of various degrees in premature infants of both groups depending on gender, n (%) [14]

Degree of pulmonary hypertension	Number of cases, n (%)			
	Boys n=51		Girls n=49	
	Life span			
	1	3-5	1	3-5
No	0 (0%)*	5 (9.8%)*	0 (0%)*	10 (20.4%)*
Mild	15 (29.5%)*	3 (5.9%)*	38 (77.6%)*	32 (65.3%)*
Moderate	29 (56.8%)*	33 (64.7%)*	9 (18.3%)*	7 (14.3%)*
Severe	7 (13.7%)*	10 (19.6%)*	2 (4.1%)*	0 (0%)*

*Note: *p <0.05 – is a significant difference between groups.*

The peculiarity of the number of cases of PPH of different severity by gender that we analyzed indicates a greater tendency to development of severe PPH in males, which is confirmed by modern literature data [20-22].

The following results of the analysis of complications of the neonatal period were obtained (Table 4). Among the children of group I, 19 (38%) children were discharged from the hospital without complications, the majority of them were girls (58.3%) and boys (19.2%). In group II, 12% of the total number of children did not develop complications, all – girls [14].

The number of cases of BPD in the group I was 8 children (16%), of which 2 cases (25%) were in girls, and 6 (75%) were in boys. In the group II, 13 children were diagnosed with BPD, which was 26%, of which 6 cases were in girls (46.2%), and 7 (53.8%) were in boys; this is 10% higher compared to Group I of children without perinatal asphyxia [14].

Retinopathy of prematurity stage II-III was detected in 13 infants of group I (26%), among them 5 cases (38.5%) were in girls, 8 (61.5%) were in boys. In the group II, the number of retinopathy of prematurity increased by 6% and amounted to 32%; of these, 7 cases (43.8%) were in girls, 9 (56.2%) were in boys [14].

IVH grade II-IV was detected in 4 children. group (8%), among them – 1 girl (25%), and 3 boys (75%). Regarding IInd group, the number of cases of IVH was 12%, including 2 girls (33.3%) and 4 boys (66.6%) [14].

Hearing impairment (failed screening test) in I group was observed in 6 children (12%), of whom 4 were boys (66.6%) and 2 were girls (33.3%). In the IInd group – 18% of children failed the test, including 5 boys (55.5%) and 4 girls (44.4%) [14].

Anemia of prematurity was observed in 9 children in the group I (18%), of which 3 were girls (33.3%) and 6 were boys (66.7%). In the II group – developed in 11 children (18%), of whom – 5 girls (45.5%) and 6 boys (54.5%) [14].

HIE grade II-III grade, in the Ist group was observed in 28 children (56%), of which 12 were girls (42%), and 16 were boys (58%). In the II group – in 36 children (72%), of whom – 10 girls (28%), and 26 boys (72%) [14].

The obtained data indicate that the number of cases and severity of complications of the neonatal period is higher in the group of children with perinatal asphyxia. Regarding gender characteristics in terms of the number of complications, prematurely born boys demonstrate a predisposition to an unfavorable course of PPH, and a higher risk of further morbidity, disability and mortality [14].

Table 4

Characteristics of complications of the neonatal period of premature babies of different groups, taking into account gender [14]

Complication	Group I (n=50)		Group II (n=50)	
	Boys (n=26)	Girls (n=24)	Boys (n=25)	Girls (n=25)
Without complications, n (%)	5 (26.3%)*	14 (73.7%)*	0 (0%)*	6 (100%)*
Bronchopulmonary dysplasia, n (%)	6 (75%)*	2 (25%)*	7 (53.8%)*	6 (46.2%)*
Retinopathy stages I-III, n (%)	8 (61.5%)*	5 (38.5%)*	9 (56.2%)*	7 (43.8%)*
IVH grade II-III, n (%)	3 (75%)*	1 (25%)*	4 (66.6%)*	2 (33.3%)*
Hearing impairment, n (%)	4 (66.6%)*	2 (33.3%)*	5 (55.5%)*	4 (44.4%)*
Anemia of prematurity, n (%)	6 (66.7%)*	3 (33.3%)*	6 (54.5%)*	5 (45.5%)*
HIE stage II-III, n (%)	12 (42%)*	10 (58%)*	10 (28%)*	26 (72%)*

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

In our previous work, it was determined that the best biomarker of oxidative stress, in premature infants, associated with PPH is the urinary 8-OHdG, and its correlation with mPAP has been established [11, 12, 13]. In this article, we present gender differences in the dynamics of the urinary 8-OHdG levels, ng/ml in premature infants (Table 5).

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Table 5

Gender differences in the dynamics of urinary 8-OHdG levels in premature infants with RDS and perinatal asphyxia, M±m [14]

8-OHdG level in urine, ng /ml	Group I (n=23)		Group II (n=21)	
	Boys (n=13)	Girls (n=10)	Boys (n=11)	Girls (n=10)
1 day of life	1.87±0.32*	1.77±0.27*	2.82±0.48*	2.24±0.30*
3rd-5th days of life	1.14±0.14**	0.90±0.21**	3.89±0.45**	1.78±0.19**

*Note: *p>0.05 – no significant difference between groups*
***p<0.05 – there is a significant difference between groups*

In both groups of examined infants on the first day of life, there was no significant difference (p>0.05) in the levels of the urinary 8-OHdG among boys and girls. On the 3rd-5th day of life, boys in both groups had a significant increase in the level of 8-OHdG in urine (p<0.05) compared to girls [14]. Thus, the male sex demonstrates reduced adaptability, reactivity and compensatory capabilities to counteract oxidative stress, which was confirmed by previous researchers [23, 24, 25]. Based on scientifically substantiated relationships between clinical, laboratory, radiological, gender aspects of premature infants with perinatal pathology and the identified diagnostic and prognostic values of the informativeness of 8-OHdG levels in urine, an algorithm for a differentiated approach to the diagnosis and treatment of PPG was developed. The calculated diagnostic coefficients showed that male gender is a predictor of the development of severe PPH by the 3rd-5th day of life (I=1.04) [14].

Conclusions

1. On the first day of life moderate and severe persistent pulmonary hypertension occurs in premature boys 3 times more often than in girls in the early neonatal period, and on the 3rd-5th day of life – 4 times more often.

2. Perinatal asphyxia complicates the course of persistent pulmonary hypertension in infants with respiratory distress syndrome to a greater extent in prematurely born boys, which is associated with the peculiarities of compensation for the effects of oxidative stress at birth.

3. In the developed algorithm of a differentiated approach to the management of persistent pulmonary hypertension, it should be taken into account that the diagnostic coefficient in male newborns is I=1.04, and is a predictor of the development of severe persistent pulmonary hypertension by the 3rd-5th day of life.

Prospects for further research. Prospects for further research include continuing to study the influence of gender in newborns with perinatal pathology, due to higher clinical instability and greater need for invasive interventions for oxidative stress in boys compared to girls. Further study of sexual dimorphism will allow the development of information-search systems for pathology management in neonatology.

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СТАТЕВІ АСПЕКТИ МЕНЕДЖМЕНТУ ПЕРСИСТУЮЧОЇ ЛЕГЕНЕВОЇ ГІПЕРТЕНЗІЇ У ПЕРЕДЧАСНО НАРОДЖЕНИХ ДІТЕЙ

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Резюме.

На сьогодні передчасні пологи продовжують спричиняти негативні довгострокові наслідки для подальшої захворюваності та смертності немовлят. Недорозвинення легеневих судин на фоні недостатності антиоксидантної системи та хвороб раннього неонатального періоду призводять до розвитку персистуючої легеневої гіпертензії. Оскільки легенева гіпертензія – багатогранна патологія, що потребує систематичного підходу до діагностики та лікування, ми розглянули статеві аспекти менеджменту персистуючої легеневої гіпертензії у передчасно народжених дітей.

Мета дослідження. Підвищення ефективності ведення передчасно народжених дітей з персистуючою легеневою гіпертензією з асфіксією та респіраторним дистрес-синдромом на підставі розробки алгоритму диференційованого підходу до діагностики та лікування легеневої гіпертензії з урахуванням рівнів оксидативного стресу за визначенням 8-гідрокси-2-дезоксигуанозину в сечі та статевих відмінностей.

Матеріал та методи дослідження. У дослідження було включено 100 недоношених немовлят, народжених у терміні гестації 26/1-34/6 тижнів: І групу складали 50 дітей з респіраторним дистрес-синдромом, ІІ групу – 50 дітей з респіраторним дистрес-синдромом у поєднанні з асфіксією при народженні. У І групі було 26 хлопчиків і 24 дівчинки, в ІІ групі – 25 хлопчиків і 25 дівчаток.

За допомогою ехокардіографії всім новонародженим було проведено визначення наявності та ступеню тяжкості персистуючої легеневої гіпертензії в першу та на 3-5 добу життя, а 44 немовлятам в першу та на 3-5 добу життя методом імуноферментного аналізу проводилось кількісне визначення рівня 8-гідрокси-2-дезоксигуанозину (нг/мл).

Дослідження виконано з дотриманням вимог біоетики в рамках планової науково-дослідної роботи кафедри педіатрії № 3 та неонатології Харківського національного медичного університету (№ держреєстрації 0122U000025).

Результати дослідження. Встановлено гендерні відмінності легеневої гіпертензії у передчасно народжених дітей з респіраторним дистрес-синдромом: рівні середнього тиску у легеневій артерії були достовірно нижчі у дівчаток в обох групах, незважаючи на обтяжуючий вплив перинатальної асфіксії. Визначено, що в обох групах новонароджених к 3-5 добі життя

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кількість випадків легкого ступеня персистуючої легеневої гіпертензії перевищувала у дівчаток, що спостерігалось за рахунок більшої частки випадків персистуючої легеневої гіпертензії помірного та тяжкого ступеня у хлопчиків. За результатами аналізу випадків ускладнень неонатального періоду було встановлено більшу кількість епізодів бронхолегеневої дисплазії, внутрішньошлуночкових крововиливів II-IV ступеню, ретинопатії недоношених I-III стадії, уражень слуху (тест не пройдено), анемії передчасно народжених дітей, гіпоксично-ішемічного ураження центральної нервової системи II-III ступеню у передчасно народжених хлопчиків обох груп. Встановлено кореляцію між вмістом 8-гідрокси-2-дезоксигуанозину в сечі як біомаркеру оксидативного стресу у передчасно народжених дітей з середнім тиском у легеневій артерії в першу та на 3-5 добу життя. Рівні 8-гідрокси-2-дезоксигуанозину в сечі на 3-5 добу життя достовірно вищі у хлопчиків обох груп. До створеного алгоритму диференційованого підходу до менеджменту персистуючої легеневої гіпертензії входить розрахований діагностичний коефіцієнт чоловічої статі дитини (I=1,04) як предиктора розвитку легеневої гіпертензії тяжкого ступеня к 3-5 добі життя.

Висновки. 1. В першу добу життя у передчасно народжених хлопчиків персистуюча легенева гіпертензія вираженого та тяжкого ступенів зустрічається в 3 рази частіше ніж у дівчаток в ранньому неонатальному періоді, а на 3-5 добу життя – в 4 рази частіше. 2. Перинатальна асфіксія погіршує перебіг персистуючої легеневої гіпертензії у дітей респіраторним дистрес-синдромом, більшою мірою у передчасно народжених хлопчиків, що пов'язано з особливостями компенсації до впливу оксидативного стресу при народженні. 3. У розробленому алгоритмі диференційованого підходу до менеджменту персистуючої легеневої гіпертензії потрібно враховувати, що діагностичний коефіцієнт у новонароджених чоловічої статі дорівнює I=1,04, і є предиктором розвитку персистуючої легеневої гіпертензії тяжкого ступеня к 3-5 добі життя.

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

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