PHENOTYPES OF PERSISTENT PULMONARY HYPERTENSION IN NEWBORNS (clinical observations)

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ABSTRACT

Background. Persistent Pulmonary Hypertension of the Newborn (PPHN) is a potentially life-threatening condition caused by abnormal postnatal transition from fetal to neonatal circulation. The COVID-19 pandemic and genetic syndromes, such as trisomy 21, have highlighted new challenges in its diagnosis and treatment.

Aim. To analyze clinical observations of the development of persistent fetal circulation of various origins in full-term newborns, to spread awareness among the medical community regarding the features of the diagnosis of this pathological condition after birth by analyzing the causes of cardiovascular system dysfunction, the difficulties of diagnosis in modern conditions.

Materials and Methods. The study was based on clinical and instrumental examinations of neonates diagnosed with PPHN in the early neonatal period. Doppler echocardiography, pulse oximetry, and standard clinical assessment were used. Two clinical cases of PPHN in a newborn from a mother with COVID-19 (COronaVIrus Disease 2019) and in newborn with trisomy 21 were analyzed.

Results and Conclusions. In the first case, maternal COVID-19 infection resulted in impaired maternal-placental circulation, fetal hypoxia, and impaired pulmonary adaptation of the newborn with severe PPHN requiring intensive support. In the second case, PPHN in a neonate with trisomy 21 was prolonged and characterized by poor response to standard therapy. The results of the study emphasize that the pathogenesis of PPHN varies depending on the etiology – infectious or genetic and is accompanied by ventricular dysfunction. An interdisciplinary approach is important for timely assessment of signs of heart failure with early echocardiographic assessment and changes in treatment. Further studies are needed to develop early diagnostic and treatment algorithms.

Keywords: *COVID-19, trisomy 21, fetal hypoxia, right-left shunt, echocardiography, Doppler*.

Abbreviations

Ao diameter – Aorta diameter.
COVID-19 – COronaVIrus Disease 2019.
Doppler EchoCG – Doppler Echocardiography.
FS – linear Fractional Shortening.
HR – Heart Rate.
IVSd – Interventricular Septum thickness, Diastole.
LAD – Left Atrial Diameter.
LVEDd – Left Ventricle End Diastolic diameter.
LVEF – Left Ventricular Ejection Fraction.
LVPWd – Left Ventricular Posterior Wall thickness in diastole.
PAD – Pulmonary Artery Diameter.
PDA – Patent Ductus Arteriosus.
PG – Pressure Gradient.
PG AoV – Pressure Gradient Aortic Valve.
PG Desc Ao – Pressure Gradient in the Descending Aorta.
PG PV – Pressure Gradient Pulmonary Artery Valve.
PPHN – Persistent Pulmonary Hypertension of the Newborn.
RAD – Right Atrial Diameter.
RVEDd – Right Ventricle End-Diastolic diameter.
SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus 2.

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Introduction

Persistent pulmonary hypertension of the newborn across various gestational ages remains a critical issue, as it is a potentially life-threatening condition. This underscores the importance of timely recognition and specialist care [1]. PPHN (also known as persistent fetal circulation) results from the abnormal transition from fetal to neonatal circulation in the early neonatal period [2]. This syndrome is characterized by a pathological rise in pulmonary artery pressure due to pulmonary vascular malformations, maladaptation to postnatal circulation, or impaired development or growth of the newborn [1; 2], such as prematurity or intrauterine growth retardation. The condition involves postnatal persistence of right-to-left shunting at the level of the patent foramen ovale and patent ductus arteriosus in the presence of increased pressure in the right ventricle [3; 4].

PPHN can be primary or secondary. In the primary type, morphological changes in the vessels lead to high pressure in the right ventricle and pulmonary circulation. Secondary PPHN is characteristic of newborns with various somatic pathologies, as a result of which hypoxia and acidosis cause pulmonary vasoconstriction and increased pressure in the pulmonary circulation [3; 4].

Etiologies include parenchymal lung diseases (e.g., meconium aspiration syndrome, congenital pneumonia, respiratory distress syndrome, sepsis) [2]. Separately, idiopathic persistent pulmonary hypertension in newborns is considered, the cause of which is excessive thickness of the smooth muscles of the pulmonary vessels. Sometimes different etiological factors are combined.

Despite its multifactorial origin, recent epidemiological studies have demonstrated that PPHN is associated with antenatal events (preeclampsia, chorioamnionitis, and other perinatal causes). These lead to abnormal growth and dysfunction of the pulmonary vessels and may increase the risk of developing pulmonary arterial hypertension in later life [5].

If persistent pulmonary hypertension is suspected, one of the necessary diagnostic methods is Doppler echocardiography, as it can confirm the presence of right-to-left shunting and can assess the severity of pulmonary hypertension. [4; 6].

The consequences of persistent pulmonary hypertension can be diverse (cardiorepiratory failure, chronic lung disease, cerebral infarction), leading to specific motor and/or cognitive deficits or death [1; 4].

The **aim** of the study was to analyze clinical observations of the development of persistent fetal circulation of various origins in full-term newborns, to spread awareness among the medical community regarding the features of the diagnosis of this pathological condition after birth by analyzing the causes of cardiovascular system dysfunction, the difficulties of diagnosis in modern conditions.

Materials and Methods

The study was based on the analysis of our own clinical observations. Clinical and instrumental examinations were performed in newborns with persistent pulmonary hypertension in the early neonatal period. The complex of clinical and diagnostic measures included: clinical research methods, Doppler echocardiography, pulse oximetry. To achieve the set goal, comparative descriptive and analytical methods were used.

The parents of the examined newborns were informed about the clinical and instrumental study and gave their consent to its conduct. The Ethics and Bioethics Commission of Kharkiv National Medical University established that the mentioned studies were conducted in accordance with the ethical norms and principles controlling human medical research.

Results

Clinical case 1.

Newborn O., (birth weight 3050 g, length 52 cm, head circumference 37 cm, thoracic circumference 36 cm, Apgar score 6/7) was born from the second pregnancy with an uncomplicated course, the second physiological birth at a gestational age of 38 weeks. Four days before the birth, the mother fell ill with COVID-19 of moderate severity, and had a fever during childbirth. Prenatally, during ultrasound screenings, no cardiovascular system pathology was detected in the fetus.

After birth, the child's condition was severe due to the development of cardiovascular disorders (marble skin, episodes of desaturation up to 84% with agitation). There was persistent central cyanosis. Oxidant test detected refractory hypoxemiae, the HR was 60 bpm, auscultation above the lungs showed puerile breathing. On auscultation, the heart sounds were rhythmic, and the systolic murmur was detected in the 2nd intercostal space on the left, as well as at the projection point of the mitral and tricuspid valves, $2^{nd}/3^{rd}$ according to the gradation of the intensity of heart murmurs according to Levin's scale [7], The HR was [128–160] bpm, and blood pressure was 70/38 mmHg.

The abdomen was soft and painless. Pulsation on the femoral arteries was present. According to the data on the acid-base balance, metabolic acidosis was revealed.

Doppler echocardiography (*Fig. 1*) showed the following measurements: LVEDd 13.7 mm, IVSd 3.4 mm, LVPWd 4.6 mm, LAD 10.9 mm, RVEDd 12.4 mm, RAD 14.0 mm, LVEF 60%, FS 30%, Ao diameter 9.0 mm, PG Desc Ao 8.5 mmHg, PG AoV 3.5 mmHg, PAD 11.0 mm, PG PV 3.8 mmHg.

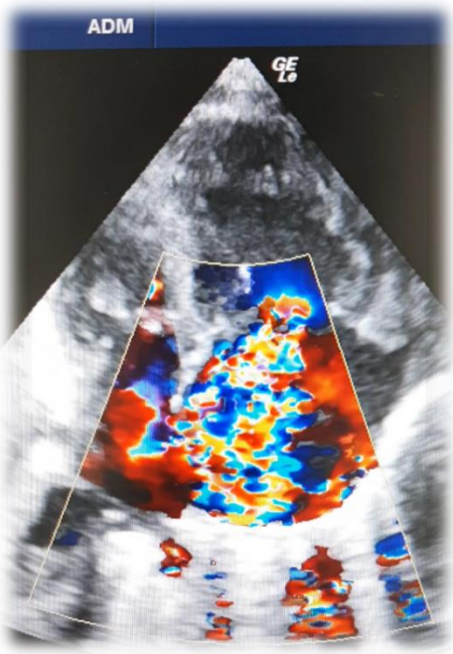

Fig. 1. Newborn O., 1 day of life. Dilatation of the right chambers, mainly the right atrium, tricuspid regurgitation of the 3rd degree, right-left shunt at the level of the patent foramen ovale.

Blood flow in the abdominal aorta was pulsatile, with a maximal flow velocity (V_{max}) of 46.0 cm/s. There was right ventricular dilation; tricuspid regurgitation of the 2nd degree, mitral regurgitation of the 1st degree (PG of the regurgitation jet was 55 mm Hg). The average pressure in the pulmonary artery trunk was [58–60] mm Hg. The PDA was functioning, 2.6 mm; the patent foramen ovale was 2.9 mm, right-left shunt. Diastolic dysfunction of the ventricles was of abnormal relaxation type. Persistent pulmonary hypertension of the newborn, severe pulmonary hypertension with right-to-left shunt through PDA and foramen ovale were diagnosed. Therapy included compliance with the warm chain, control of normovolemia, respiratory support, correction of electrolyte, glucose, calcium, and magnesium levels; administration of diuretics according to weight and water balance, as well as monitoring of acid-base balance, blood pressure, saturation, and indicators of central hemodynamics. On the third day, the child's condition stabilized; Doppler EchoCG showed a decrease in the linear dimensions of the right chambers, a functioning PDA with a diameter of up to 1.2 mm, a patent foramen ovale, 2.8 mm, left-right shunt, LVEF 64%, FS 32%. The average pressure in the pulmonary artery trunk was [32–34] mmHg.

Clinical case 2.

Newborn J. (birth weight was 3200 g, length 51 cm, head circumference 37 cm, thoracic circumference 36 cm, Apgar score 6/7 points) was born from the third uncomplicated pregnancy and third physiological birth at 39 weeks of gestation. No pathologies of the cardiovascular system were detected in the fetus during prenatal ultrasound screenings.

After the birth, the child's condition was severe due to the development of cardiovascular disorders (marble skin, episodes of desaturation up to 76%), and persistent central cyanosis. The child's phenotype is trisomy 21. On clinical examination, saturation was [76–78]%. Oxidant test demonstrated refractory hypoxemia, HR of 60 bpm; auscultatory findings above the lungs, and puerile breathing were detected. On auscultation, the heart sounds were rhythmic, and a systolic murmur was heard in the 2nd intercostal space on the left, at the point of projection of the tricuspid valves, 2nd/3rd according to the gradation of intensity of heart murmurs corresponding to Levin's scale [7], and splitting of the second sound over the pulmonary artery was revealed, with an HR of [130–160] bpm. Blood pressure was 74/37 mmHg. The abdomen was soft and painless. Liver was +2 cm below the costal arch. Acid-base balance was comsistent with metabolic acidosis.

Chest X-ray (*Fig. 2*) revealed cardiomegaly, cardiothoracic index (CT ratio or CTR) – 0.75; and thymomegaly.

Ultrasound examination of the heart (*Fig. 3*) demonstrated LVIDd 16.8 mm, IVSd 3.6 mm, LVPWd 4.6 mm, LAD 12.1 mm, RVIDd 14.8 mm, RAD 14.9 mm, EF [58–60]%, FS [28–30]%, Ao diameter 9.7 mm, PG Desc Ao 9.1 mm Hg, PG AoV 3.9 mm Hg, PAD 11.6 mm, PG PV 3.6 mm Hg. Blood flow in the abdominal aorta was pulsatile, with a maximal flow velocity (V_{max}) of 41.0 cm/s. There was right ventricular dilation; tricus-

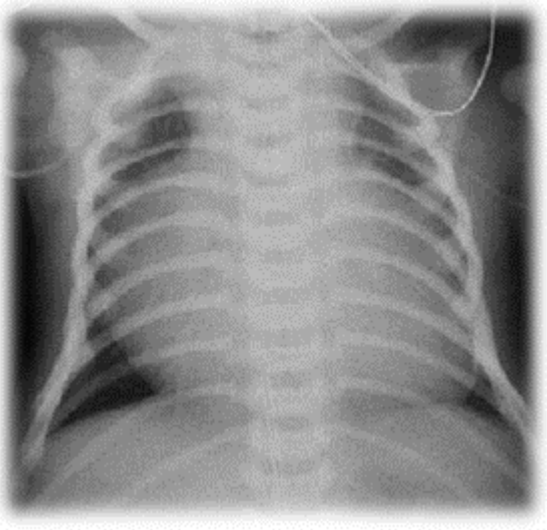

Fig. 2. Newborn J., 1 day of life. Thymomegaly, cardiomegaly. CTR 0.75.

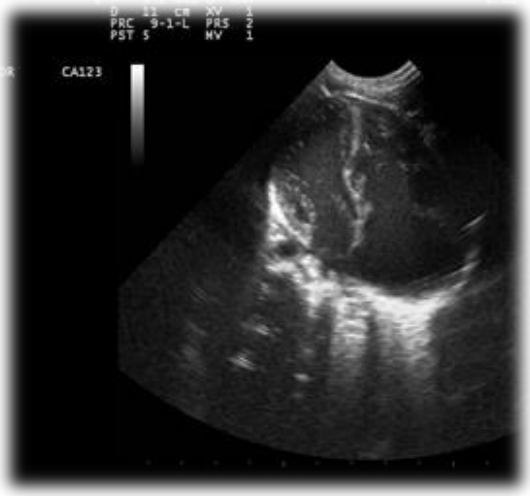

Fig. 3. Newborn J., 1 day of life. Right ventricular dilatation, third-degree tricuspid regurgitation, excision of the MPP into the left atrium (right-left shunt at the level of the patent foramen ovale).

pid regurgitation of the 2nd–3rd degree, PG of the regurgitation jet was 63 mm Hg. The average pressure in the pulmonary artery trunk was [65–70] mm Hg. PDA was 3.1 mm, patent foramen ovale was 3.9 mm, and the right-left shunt. Diastolic ventricular dysfunction was classified by the type of abnormal relaxation. It was found that persistent pulmonary hypertension of the newborn, severe pulmonary hypertension with right-to-left shunt through PDA and foramen ovale. Therapy according to modern standards of neonatal management included maintenance of warm chain, control of normovolemia, respiratory therapy, correction of electrolyte disorders, glucose, administration of diuretics under control of weight and water balance, daily monitoring of acid-base balance, blood pressure, saturation, central hemodynamics, mean pressure in the pulmonary artery trunk and direction of shunting at the level of fetal communications. The disease had a wave-like course with episodes of desaturation, systolic and diastolic dysfunction, with a decrease in EF to 56% and long-term preservation of bidirectional shunting at the level of the patent foramen ovale. On the sixth day, the child's condition stabilized, with a decrease in the linear dimensions of the right ventricles on the Doppler EchoCG, PDA with a diameter of up to 1.4 mm, a patent oval foramen of 3.8 mm, left-right shunt, LVEF 62%, FS 31%, mean pressure in the pulmonary artery trunk [34–35] mm Hg.

Discussion

Our knowledge on the impact of maternal COVID-19 infection on the development of neonatal persistent pulmonary hypertension is limited. An increase in the number of cases of PPHN in full-term and premature infants has been identified during the COVID-19 pandemic. According to the results of the examinations, if a pregnant woman is sick with COVID-19, the risk of premature birth increases, which disrupts an important stage of adaptation of the child, the beginning of pulmonary breathing; due to prematurity, the level of surfactant in the lungs is reduced, which leads to the development of respiratory distress syndrome. Such newborns may also develop complications of respiratory adaptation, such as transient tachypnea [8].

The pathogenesis of COVID-19 is associated with the toxic effect of the virus on the vessels, which is accompanied by the destruction of the vascular endothelium and stimulation of the body's hyperinflammatory response due to impairment of the immune system regulation. The neonatal immune system responds to proinflammatory cytokines transmitted from the mother, contributing to vasoconstriction in the pulmonary circulation. In turn, endothelial damage and hyperergia can contribute to hypercoagulation accompanied by the subsequent formation of micro- and microthrombi, as well as maladaptation of the angiotensin-converting enzyme-2 action. As a result, there is a decrease in the diffusing capacity of the lungs (restrictive ventilation disorders persist for

[3–6] months after recovery, as after acute respiratory distress syndrome) [9; 10].

Thus, placental SARS-CoV-2 infection disrupts uteroplacental blood flow and leads to fetoplacental insufficiency, fetal hypoxia, and delayed development of pulmonary structures, which debuts with clinical manifestations of respiratory disorders. Impaired adaptation of pulmonary circulation can lead to prolonged preservation of the fetal type of circulation because of endothelial dysfunction and reduced nitric oxide production. This condition requires respiratory support, mechanical ventilation, or high-frequency oscillatory ventilation of the lungs with a highly oxygenated inhaled mixture, as well as sedative therapy due to severe hypoxemia.

Hyperoxia test (breathing 100% oxygen for [10–15] minutes) can help distinguish persistent pulmonary hypertension and heart disease from lung parenchymal disease; however, it is not always performed due to the general availability of echocardiography and the potential adverse effects of hyperoxia [1].

It is also important to note the direct effect of the virus on the myocardium, pericardium, and cardiac conduction system due to the tropism for angiotensin-converting enzyme-2 receptors; thus, the immune response can cause cardiomyocyte death and lead to the replacement of desmosomal proteins with fibro-adipose tissue [11–13], which makes it advisable to dynamically monitor the state of the respiratory and cardiovascular systems in children in the first year of life after suffering persistent pulmonary hypertension.

Children with trisomy 21 develop pulmonary hypertension, including immediately after birth as persistent pulmonary hypertension of the newborn, with a frequency of up to 28%, which accounts for [5–17]% of cases registered in international pediatric pulmonary hypertension registries [14]. Studies have shown that patients with trisomy 21 are predisposed to the development of increased pulmonary vascular resistance and pulmonary arterial hypertension. The cause of this pathological condition is abnormal lung development in conditions of reduced pulmonary vascular surface area and the presence of endothelial dysfunction with higher levels of endothelin-1 and lower levels of nitric oxide, increased hemodynamic stress, increased pulmonary vascular resistance, and postcapillary disease, which contributes to the development of persistent pulmonary hypertension and early progression of pulmonary vascular transformation in patients with trisomy 21 [15; 16]. Early pulmonary artery remodeling may occur due to congenital interferonopathy, intrinsic endothelial dysfunction, or other metabolic conditions. Increased hemodynamic stress may occur due to congenital heart disease or a functioning patent ductus arteriosus, causing persistent pulmonary hypertension of the newborn. Increased pulmonary vascular resistance may occur due to acquired lung disease and abnormalities in the capillaries or postcapillaries [16].

It has been proven that the course of pulmonary hypertension in patients with trisomy 21 is usually associated with late closure of fetal communications, the development of persistent pulmonary hypertension, and is transient [17].

Thus, in newborns with trisomy 21, the course of persistent pulmonary hypertension tends to be prolonged, with periods of decompensation and poor response to standard therapy (ventilation, exogenous surfactant, diuretics, cardiotonic drugs).

Conclusion

1. The course of pulmonary hypertension of newborns in the early neonatal period largely depends on its cause.

2. The detection of PPHN cases during the COVID-19 pandemic indicates that the intrauterine impact of maternal COVID-19 infection, impaired maternal-placental circulation, and fetal hypoxia are key triggers for the development of persistent pulmonary hypertension in newborns, which affects the formation of fetal pulmonary hemodynamics, in particular, an increase in pulmonary vascular resistance and a disruption of its normal decrease after birth.

3. Persistent pulmonary hypertension in children with trisomy 21 syndrome is transient, and special clinical vigilance should be paid to the detection and monitoring of myocardial function, since right ventricular dysfunction significantly worsens the prognosis.

4. A multidisciplinary approach is crucial for the timely assessment of signs of heart failure, facilitated by early echocardiographic assessment and timely adjustments of therapy.

Prospects for further research. To prevent the development of adverse long-term consequences of persistent fetal circulation, it is important to continue research, including multicenter studies, with subsequent early development of an algorithm for early monitoring and treatment of persistent pulmonary hypertension in neonatal units during the COVID-19 pandemic.

DECLARATIONS

Statement of ethics

The authors have no ethical conflicts to disclose.

Data transparency

Data can be requested from the authors.

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Consent to publication

All authors give their consent to publication.

References

1. Jordan P, Cooper P, Budhwani A, Kunneth LS, Patel IA, Omohundro A, et al. Persistent pulmonary hypertension of the newborn. Prog Pediatr Cardiol. 2025;76:101777. DOI: 10.1016/j.ppedcard.2024.101777.

2. Nandula PS, Shah SD. Persistent Pulmonary Hypertension of the Newborn. Treasure Island (FL): StatPearls Publishing; 2023. Available at: https://www.ncbi.nlm.nih.gov/books/NBK585100 [accessed 30 Jun 2025].

3. Stark AR, Eichenwald EC. Persistent pulmonary hypertension of the newborn (PPHN): Clinical features and diagnosis. UpToDate, 21 Aug 2024 [Internet]. Available at: https://www.uptodate.com/contents/persistent-pulmonary-hypertension-of-the-newborn-pphn-clinical-features-and-diagnosis [accessed 30 Jun 2025].

4. Mandell E, Kinsella JP, Abman SH. Persistent pulmonary hypertension of the newborn. Pediatr Pulmonol. 2021;56(3):661-9. DOI: 10.1002/ppul.25073. PMID: 32930508.

5. Rosenzweig EB, Abman SH, Adatia I, Beghetti M, Bonnet D, Haworth S, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J. 2019;53(1):1801916. DOI: 10.1183/13993003.01916-2018. PMID: 30545978.

6. Hansmann G, Koestenberger M, Alastalo TP, Apitz C, Austin ED, Bonnet D, et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. J Heart Lung Transplant. 2019;38(9):879-901. DOI: 10.1016/j.healun.2019.06.022 PMID: 31495407.

7. Freeman AR, Levine SA. The clinical significance of the systolic murmur: a study of 1,000 consecutive "non-cardiac" cases. Ann Intern Med. 1933;6(11):1371. DOI: 10.7326/0003-4819-6-11-1371.

8. Stolojanu C, Doros G, Bratu ML, Ciobanu I, Munteanu K, Iacob ER, et al. COVID-19 and Its Potential Impact on Children Born to Mothers Infected During Pregnancy: A Comprehensive Review. Diagnostics (Basel). 2024;14(21):2443. DOI: 10.3390/diagnostics14212443. PMID: 39518410.

9. Michelen M, Manoharan L, Elkheir N, Cheng V, Dagens A, Hastie C, et al. Characterising long COVID: a living systematic review. BMJ Glob Health. 2021;6(9):e005427. DOI: 10.1136/bmjgh-2021-005427. PMID: 34580069.

10. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-42. DOI: 10.1001/jama.2020.2648. PMID: 32091533.

11. Corrado D, Link MS, Calkins H. Arrhythmogenic right ventricular cardiomyopathy. N Engl J Med. 2017;376(1):61-72. DOI: 10.1056/NEJMra1509267. PMID: 28052233.

12. Wu Q, Zhou L, Sun X, Yan Z, Hu C, Wu J, et al. Altered lipid metabolism in recovered SARS patients twelve years after infection. Sci Rep. 2017;7(1):9110. DOI:10.1038/s41598-017-09536-z. PMID: 28831119.

13. Agarwal AK, Garg R, Ritch A, Sarkar P. Postural orthostatic tachycardia syndrome. Postgrad Med J. 2007;83(981):478-80. DOI:10.1136/pgmj.2006.055046. PMID: 17621618.

14. Hopper RK, Abman SH, Elia EG, Avitabile CM, Yung D, Mullen MP, et al. Pulmonary hypertension in children with Down syndrome: results from the Pediatric Pulmonary Hypertension Network Registry. J Pediatr. 2023;252:131-40.e3. DOI: 10.1016/j.jpeds.2022.08.027. PMID: 36027975.

15. Nguyen CP, Kanaan U, Garcia RU, Ferguson ME, Wilson HC. Evaluation of clinical and echocardiographic factors associated with postoperative pulmonary arterial hypertension requiring medical therapy in infants with trisomy 21 undergoing atrioventricular septal defect repair. Prog Pediatr Cardiol. 2025;76(1):101801. DOI: 10.1016/j.ppedcard.2024.101801.

16. Bush DS, Ivy DD. Pulmonary hypertension in the population with Down syndrome. Cardiol Ther. 2022;11:33-47. DOI: 10.1007/s40119-021-00251-5. PMID: 35037192.

17. Bush D, Galambos C, Ivy DD, Abman SH, Wolter-Warmerdam K, Hickey F. Clinical Characteristics and Risk Factors for Developing Pulmonary Hypertension in Children with Down Syndrome. J Pediatr. 2018;202:212-219.e2. DOI: 10.1016/j.jpeds.2018.06.031. PMID: 30025669.

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