PORTUGUESE JOURNAL OF PEDIATRICS

PERMANYER

Check for updates

NARRATIVE REVIEW

Persistent pulmonary hypertension of the newborn, part 1: understanding the physiological, clinical and diagnostic foundations. A review

Hipertensão pulmonar persistente do recém-nascido, parte 1: compreensão dos fundamentos fisiológicos, clínicos e de diagnóstico. Uma revisão

Gustavo Rocha

Department of Neonatology, Centro Hospitalar Universitário de São João, Porto, Portugal

Abstract

Persistent pulmonary hypertension of the newborn (PPHN) is a life-threatening neonatal condition resulting from the failure of normal cardiopulmonary transition after birth. This leads to persistently elevated pulmonary vascular resistance and right-to-left extrapulmonary shunting, causing severe hypoxaemia. This narrative review was based on articles retrieved from the PubMed database up to 1 June 2025. This first article in a two-part series provides a comprehensive overview of the haemodynamic adaptations required for a successful foetal-to-neonatal circulatory transition and explains how their disruption contributes to the pathophysiology of PPHN. The clinical manifestations are examined, with emphasis on key signs such as hypoxaemia and differential cyanosis. The main diagnostic modalities are also reviewed, including echocardiography, pre- and post-ductal oxygen saturation measurements, and relevant laboratory tests. A thorough understanding of these physiological and clinical foundations is essential for the timely recognition and management of PPHN. The therapeutic approach is presented in Part 2.

Keywords: Echocardiography. Newborn. Oxygenation. Persistent foetal circulation. Persistent pulmonary hypertension.

Resumo

A hipertensão pulmonar persistente do recém-Nascido (HPPRN) é uma condição neonatal potencialmente fatal, resultante de falência na transição cardiopulmonar normal após o nascimento. Esta situação leva à manutenção de uma resistência vascular pulmonar elevada e consequente desvio da circulação extrapulmonar da direita para a esquerda, causando hipoxemia grave. Esta revisão narrativa baseou-se em artigos extraídos da base de dados PubMed até 1 de junho de 2025. Este primeiro artigo, de uma série de dois, apresenta uma visão abrangente das adaptações hemodinâmicas necessárias para uma transição circulatória bem-sucedida do feto para o recém-nascido, e explica como a sua disrupção contribui para a fisiopatologia da HPPRN. As manifestações clínicas são apresentadas, com ênfase nos sinais-chave, como a hipoxemia e a cianose diferencial. São igualmente revistos os principais meios de diagnóstico, incluindo a ecocardiografia, as medições da saturação de oxigénio pré e pós-ductal, e os exames laboratoriais relevantes. Uma compreensão aprofundada destes fundamentos fisiológicos e clínicos é essencial para o reconhecimento atempado e a abordagem eficaz da HPPRN. A abordagem terapêutica é apresentada na Parte 2.

Correspondence:
Gustavo Rocha
E-mail: gusrocha@sapo.pt

Received: 18-09-2025
Accepted: 17-10-2026
https://pjp.spp.pt

Available online:
Port J Pediatr. (ahead of print)
DOI: 10.24875/PJP.25000069

2184-3333 / © 2026 Portuguese Society of Pediatrics. Published by Permanyer. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keypoints

What is known?

- Persistent pulmonary hypertension of the newborn (PPHN) is a severe condition caused by the failure of the normal circulatory transition after birth.
- It is characterised by persistent high pulmonary vascular resistance and severe hypoxaemia.
- Risk factors include perinatal asphyxia, meconium aspiration, infection and pulmonary or cardiac malformations.

What is added?

- An updated review of the pathophysiological mechanisms underlying the failure of the pulmonary vascular resistance to drop.
- The incorporation of recent findings on genetic markers for PPHN.
- A comprehensive review of the echocardiographic parameters used in PPHN diagnosis and severity assessment.

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is a condition that typically affects near-term and term infants within the first few hours or days of life.[1] It occurs when pulmonary vascular resistance (PVR) remains abnormally high after birth, making it difficult for blood to become adequately oxygenated.[1] The term "persistent foetal circulation" is often used synonymously with PPHN, as it reflects the failure to establish normal neonatal circulation.[1] This condition may arise from multiple underlying causes and involves complex, multifactorial pathophysiological mechanisms.[2,3]

The definitions of pulmonary hypertension (PH) and pulmonary arterial hypertension (PAH) have been updated in recent years. PPHN is classified as a subgroup within Group 1 (PAH) in the most recent clinical classifications of PH.[4,5]

In the neonatal intensive care unit (NICU), PPHN remains one of the most challenging conditions to manage due to the critical nature of the illness, which often requires multidisciplinary, comprehensive and continuous high-level care.[6] Despite advances such as inhaled nitric oxide (iNO) and neonatal extracorporeal membrane oxygenation (ECMO), early mortality associated with PPHN remains at 10%-15%.[6] Among survivors, long-term morbidities are common and may include neurodevelopmental delays, cognitive impairments and hearing abnormalities.[7-12]

This narrative review, Part 1 of a two-part series, provides a comprehensive overview of the pathophysiology, classification, genetics, clinical features and diagnostic approaches of PPHN. Management and treatment strategies are addressed in Part 2. The complete review is based on articles retrieved from the PubMed medical literature database, with no restrictions on date or language. The literature search was conducted on 1 June 2025, using the following terms: persistent pulmonary hypertension of the newborn, persistent foetal circulation, pulmonary hypertension, pulmonary artery pressure, neonate, newborn, infant, paediatric, oxygenation, nitric oxide (NO), prostacyclin, endothelin (ET), Rho-kinase, bosentan, phosphodiesterase (PDE), sildenafil, milrinone, iloprost, epoprostenol, treprostinil, dopamine, dobutamine, norepinephrine, epinephrine, vasopressin, hydrocortisone, prostaglandin E1, ECMO and genetics.

Physiological haemodynamic changes during the foetal-to-neonatal transition

At birth, PVR must rapidly and significantly decrease to allow an eightfold increase in pulmonary blood flow, enabling a successful transition to postnatal life. The transition from foetal to neonatal circulation enables the neonate to shift from placental to pulmonary gas exchange.[13] This process involves complex and coordinated cardiovascular, respiratory and biochemical changes that occur within minutes to hours after birth.[13-15]

Initiation of respiration and pulmonary vascular changes

With the onset of spontaneous breathing, the lungs expand and alveolar fluid is rapidly absorbed into the pulmonary interstitium and lymphatics.[16,17] This leads to a dramatic decrease in PVR, promoting a significant increase in pulmonary blood flow.[18] The pulmonary circulation then becomes the primary site of oxygen exchange, replacing the placenta.[19,20]

The rise in alveolar oxygen tension directly contributes to the vasodilation of the pulmonary vasculature, further lowering PVR.[21] Simultaneously, enhanced oxygen delivery and reduced carbon dioxide levels modulate the expression of vasoactive substances, including decreased levels of the vasoconstrictor ET-1 and increased production of NO and prostacyclin, both vasodilators.[22,23]

Clamping of the umbilical cord and increased systemic vascular resistance

The clamping of the umbilical cord abruptly interrupts the low-resistance placental circulation, resulting in a rise in systemic vascular resistance (SVR).[24] This haemodynamic shift increases left ventricular afterload and leads to the functional closure of foetal circulatory shunts.[25] The interruption of umbilical venous return also contributes to decreased right atrial pressure.[25]

Functional closure of foetal shunts

During foetal life, three major vascular shunts, the ductus venosus, foramen ovale and ductus arteriosus, are essential to bypass the liver and the non-functioning foetal lungs.[26,27] Following birth, these shunts undergo functional and, eventually, anatomical closure:

- Ductus venosus: This vessel diverts oxygenated blood from the umbilical vein to the inferior vena cava, bypassing the liver. It closes functionally within hours after the umbilical flow stops and anatomically within days to weeks.[27]
- Foramen ovale: This opening in the atrial septum allows blood to flow from the right to the left atrium in utero. Postnatally, increased pulmonary venous return elevates left atrial pressure, exceeding right atrial pressure, leading to the functional closure of the foramen ovale. Anatomical fusion occurs in most infants within the first year of life.[27]
- Ductus arteriosus: A blood vessel that connects the aortic isthmus with the left pulmonary artery, allowing blood to bypass the lungs during foetal life. After birth, increased PaO_2 and decreased circulating prostaglandin E_2 levels lead to ductal constriction, with functional closure usually occurring within the first 24-72 hours, followed by anatomical closure over the following weeks.[27]

Establishment of adult-type circulation

The above changes result in the establishment of a serial circulation, where deoxygenated blood returns to the right heart, is pumped through the now low-resistance pulmonary circuit, becomes oxygenated inside the lungs, and is then distributed systemically via the left heart.[28] Cardiac output becomes dependent on both right and left ventricular function, and the neonatal myocardium begins to adapt to increased workload and systemic pressures.[29]

Impact of early vs. delayed umbilical cord clamping

The timing of umbilical cord clamping has a significant impact on haemodynamic stability and circulatory adaptation during the foetal-to-neonatal transition.[30] Early cord clamping (ECC), typically performed within the first 15-30 seconds after birth, results in the abrupt cessation of umbilical venous return, leading to a sudden decrease in right atrial preload and an increase in SVR.[31] This can cause transient cardiovascular instability, particularly in preterm or compromised infants, by reducing left ventricular filling and potentially impairing cardiac output during the critical initial minutes after birth.[32]

In contrast, delayed cord clamping (DCC), defined as clamping performed at ≥ 60 seconds after birth or following the cessation of umbilical pulsations, allows for a more gradual transition.[33] It facilitates placental transfusion, increasing neonatal blood volume by approximately 20%-30%, thereby enhancing preload, improving systemic perfusion and supporting higher haemoglobin levels.[34] DCC has also been associated with improved iron stores, a reduced need for transfusions and a decreased incidence of intraventricular haemorrhage and necrotising enterocolitis in preterm infants.[34-37]

By maintaining umbilical venous return during the initiation of ventilation, DCC contributes to smoother cardiopulmonary transition, better ventilation – perfusion matching and more stable pulmonary and systemic circulations in the immediate postnatal period.[37]

Factors impacting foetal pulmonary vascular resistance and transition at birth

During the foetal-to-neonatal transition, significant physiological changes take place that result in the progressive decrease of PVR. Several factors contribute to the modulation of PVR during this critical period, and are summarised in Table 1.[3]

Categories and aetiologies of PPHN

PPHN is rarely familial, and few genetic causes have been identified.[38] The estimated prevalence of PPHN is 1.9 per 1000 live births; however, this figure is based on a study involving infants referred to level III NICUs, where mechanical ventilation and other advanced therapies were required.[38] The aetiology of PPHN is heterogeneous and can be broadly classified into four

Table 1. Main factors that contribute to the modulation of pulmonary vascular resistance during the foetal-to-neonatal transition[3]

Factor	Category	Mechanism of action
Nitric oxide (NO)	Vasodilator	Produced by endothelial cells; activates cGMP, leading to smooth muscle relaxation
Prostacyclin (PGI_2)	Vasodilator	Arachidonic acid derivative; increases cAMP, causing vasodilation in smooth muscle cells
Endothelin-1 (ET-1)	Vasoconstrictor	Potent endothelium-derived peptide; induces vascular smooth muscle contraction
Rho-kinase	Vasoconstrictor/modulator	Increases calcium sensitivity in smooth muscle, promoting vasoconstriction
Oxidative stress	Negative modulator	Reduces NO bioavailability and contributes to endothelial dysfunction
Alveolar oxygenation	Vasodilation stimulus	Elevated PaO_2 stimulates NO and PGI_2 release and suppresses ET-1 production
Lung expansion	Mechanical factor	Opens alveoli and capillaries, reducing PVR and improving pulmonary perfusion
Pulmonary fluid clearance	Mechanical factor	Facilitates alveolar ventilation and gas exchange, supporting vasodilation
Umbilical cord clamping	Haemodynamic factor	Increases systemic vascular resistance and redirects blood flow to the lungs

cAMP: cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate; ET: endothelin; PaO_2: partial pressure of oxygen in arterial blood; PG: prostaglandin; PVR: pulmonary vascular resistance

Table 2. Categories and typical causes of persistent pulmonary hypertension of the newborn

Classification	Description	Typical causes	Pathophysiology
Maladaptation	Structurally normal vessels with failure to dilate functionally	Perinatal asphyxia, meconium aspiration, pneumonia, respiratory distress syndrome, transient tachypnoea of the newborn, caesarean section without labour, severe acidosis, hypocalcaemia, idiopathic	Persistent vasoconstriction, endothelial dysfunction
Maldevelopment	Abnormal vascular structural development	Prematurity, bronchopulmonary dysplasia, foetal growth restriction, Trisomy 21, alveolar-capillary dysplasia, surfactant protein deficiencies, in-utero ductal closure, environmental "toxins", maternal diabetes, obesity, smoking, arterio-venous malformation	Reduced vascular branching, thickened vessel walls
Hypoplasia	Underdeveloped lungs and pulmonary vasculature	Congenital diaphragmatic hernia, oligohydramnios, Potter sequence, giant omphalocele	Decreased number of vessels, reduced vascular bed
Intravascular obstruction	Physical blockage within pulmonary vessels	Meconium emboli, microthrombi, polycythaemia	Increased vascular resistance due to vessel occlusion and/or hyperviscosity

Adapted from references 3 and 6

main categories: maladaptation, maldevelopment, hypoplasia and intravascular obstruction of the pulmonary vasculature, described in Table 2.[3,6,38-40]

Maladaptation refers to cases where the pulmonary vessels are structurally normal but fail to dilate properly after birth.[3] This form of PPHN is commonly associated with perinatal asphyxia, meconium aspiration syndrome (MAS), pneumonia or other conditions leading to pulmonary vasoconstriction and endothelial dysfunction. Primary or idiopathic causes represent about 10% of the cases in this category.[3]

Maldevelopment involves the abnormal structural development of the pulmonary vasculature, characterised by reduced vascular branching, thickened vessel walls and a reduced vascular bed.[41] This category is often linked to conditions such as bronchopulmonary

Table 3. Genes and molecular pathways associated with persistent pulmonary hypertension of the newborn[46-68]

Gene	Pathway/function	Pathophysiological mechanism	Clinical implications
BMPR2	TGF-β/BMP signalling	Endothelial dysfunction and vascular remodelling	Associated with familial and severe forms of PAH; may overlap with PPHN
ENG	TGF-β/angiogenesis	Disorganised endothelium and increased vascular proliferation	Linked to vascular remodelling in neonatal PPHN
ACVRL1 (ALK1)	TGF-β receptor signalling	Impaired endothelial cell differentiation and angiogenesis	Implicated in hereditary PAH and neonatal forms of PPHN
CRHBP	Foetal hypothalamic-pituitary-adrenal axis regulation	Altered glucocorticoid response affecting lung maturation	Potential marker for stress-related PPHN
NOS3 (eNOS)	NO production	Decreased NO synthesis and impaired vasodilation	May predict poor response to iNO therapy
GUCY1A1 GUCY1B1	Nitric oxide receptor (soluble guanylate cyclase)	Impaired NO-cGMP signalling	Associated with NO resistance and reduced iNO efficacy
PDE5A	cGMP degradation	Enhanced breakdown of cGMP, leading to vasoconstriction	Targeted by sildenafil in PPHN management
CAV1	eNOS regulation via caveolae	Dysfunctional NO signalling and endothelial instability	Seen in PAH; may contribute to NO unresponsiveness in neonates
CPS1	NO production	Reduced availability of L-arginine, which is the substrate for the enzyme NOS; decreased NO production	Pulmonary vasculature fails to dilate properly due to deficient NO signalling
FOXF1	Pulmonary vascular development	Alveolar capillary dysplasia with misaligned pulmonary veins	Consider in severe, refractory PPHN, especially with gastrointestinal anomalies
SFTPB SFTPC ABCA3	Surfactant metabolism	Surfactant deficiency causing alveolar collapse and hypoxaemia	Consider in neonatal respiratory failure with secondary PPHN

BMP: bone morphogenetic protein; cGMP: cyclic guanosine monophosphate; iNO: inhaled nitric oxide; NO: nitric oxide; eNOS: endothelial nitric oxide synthase; PAH: pulmonary arterial hypertension; PPHN: persistent pulmonary hypertension of the newborn; TGF: transforming growth factor

dysplasia or prematurity, where impaired foetal vascular growth leads to compromised pulmonary circulation.[42]

Hypoplasia denotes an underdevelopment of the lungs and their vasculature, resulting in a decreased number of pulmonary vessels and a markedly reduced vascular surface area.[42] This type of PPHN is typically seen in congenital anomalies such as congenital diaphragmatic hernia (CDH) or in cases of oligohydramnios, which limit lung growth in utero.[42]

Intravascular obstruction is characterised by physical blockage within the pulmonary vessels, such as microthrombi, emboli (e.g., MAS-related emboli), polycythaemia with hyperviscosity or other occlusive processes that increase PVR.[43,44] This mechanism further impedes pulmonary blood flow and contributes to elevated pulmonary artery pressures.[43,44]

Understanding these categories is critical for tailoring therapeutic approaches, as each subtype may respond differently to interventions aimed at reducing PVR and improving oxygenation.[45]

Genetic basis of PPHN

Although PPHN is frequently associated with perinatal conditions such as MAS, sepsis and perinatal asphyxia, mounting evidence suggests that genetic factors play a substantial role in its aetiology, particularly in idiopathic or refractory cases, as shown in Table 3.[46]

Pulmonary arterial hypertension genes and the TGF-ß pathway

Several genes implicated in heritable PAH have also been associated with PPHN, highlighting shared molecular mechanisms.[47] The transforming growth factor-beta (TGF-β) signalling pathway plays a central role in pulmonary vascular development and remodeling:[47]

- *BMPR2* (*bone morphogenetic protein receptor type II*): the most frequently mutated gene in heritable PAH. Loss-of-function variants can impair pulmonary endothelial integrity and reduce antiproliferative signalling, contributing to PPHN.[48]

- *ENG* (*endoglin*) and *ACVRL1* (*ALK1*). These genes, also part of the TGF-β family, are associated with vascular remodelling and endothelial cell proliferation. Their dysfunction may disrupt vascular homeostasis and pulmonary vasodilation.[49,50]

Variants in these genes are often inherited in an autosomal dominant manner with variable penetrance and may also predispose to PPHN when combined with environmental stressors.[50]

TBX4 *and developmental lung disorders*

T-BOX transcription factor 4 (*TBX4*) has emerged as a key gene in the context of neonatal PH, particularly when associated with abnormal lung development.[51] *TBX4* regulates mesenchymal–epithelial interactions during lung morphogenesis. Pathogenic variants in *TBX4* are classically associated with small patella syndrome, but are increasingly recognised in infants with lung hypoplasia, alveolar dysplasia and idiopathic PPHN. *TBX4*-related PH may be isolated or syndromic and often requires molecular confirmation for diagnosis.[51,52]

CRHBP *and the foetal stress response axis*

The *corticotropin-releasing hormone binding protein* (*CRHBP*) gene regulates the availability of corticotropin-releasing hormone (CRH) during foetal development.[53] Altered CRH signalling may affect glucocorticoid-driven pulmonary maturation, particularly in the setting of intrauterine stress or inflammation. Variants or the dysregulation of *CRHBP* can impair the foetal hypothalamic–pituitary–adrenal axis, potentially contributing to abnormal pulmonary vascular tone at birth. Though data is still emerging, *CRHBP* is a promising candidate in explaining susceptibility to PPHN, especially in the context of prenatal insults such as chorioamnionitis or maternal stress.[53]

Nitric oxide pathway genes

The NO-cGMP pathway is essential for pulmonary vasodilation after birth.[54] Genetic alterations in this pathway are increasingly recognised in both the pathogenesis of PPHN and in variable responsiveness to iNO.[21] Key genes include:

- *NOS3*, which encodes endothelial nitric oxide synthase (eNOS). Reduced expression or functional polymorphisms are associated with decreased NO production and a diminished vasodilatory response.[55]
- *GUCY1A1*/*GUCY1B1*, which encode the α and β subunits of soluble guanylate cyclase (sGC), the NO receptor. Mutations may impair cGMP generation, resulting in NO resistance.[56,57]
- *PDE5A*, which encodes phosphodiesterase 5A, which degrades cGMP. Its overexpression reduces NO signalling. Pharmacologic inhibition (e.g., sildenafil) is used therapeutically.[58]
- *CAV1* (*Caveolin-1*), which regulates eNOS localisation and activity. Mutations have been linked to familial PAH and abnormal NO signalling.[59]
- *CPS1*. Variants in the *CPS1* gene, which encodes carbamoyl phosphate synthetase 1, have been implicated in the pathogenesis of PPHN.[60] *CPS1* plays a critical role in the urea cycle, facilitating the removal of excess ammonia from the body. Disruptions in this metabolic pathway can lead to the reduced availability of L-arginine, the substrate for NO synthesis, which is essential for pulmonary vasodilation. Consequently, variants in *CPS1* may contribute to impaired NO production, adversely affecting pulmonary vascular function and promoting the development of PPHN. Recent studies have identified *CPS1* as one of the risk genes for PPHN, highlighting the importance of genetic screening in neonates presenting with this condition.[60]

These genes not only contribute to disease susceptibility but may also serve as predictors of treatment response in neonates with PPHN.[21]

Genetic syndromes and other monogenic conditions

In some cases, PPHN represents a manifestation of a broader genetic syndrome or developmental lung disorder.

Alveolar capillary dysplasia with misalignment of pulmonary veins (ACD/MPV): Mutations in the *FOXF1* gene lead to aberrant capillary alignment and abnormal pulmonary venous drainage, typically presenting as severe, early-onset PPHN that is refractory to therapy and often associated with gastrointestinal anomalies.[61,62]

Surfactant deficiency syndromes: Mutations in the *SFTPB*, *SFTPC* and *ABCA3* genes can present with secondary PPHN due to alveolar instability leading to hypoxaemia.[63]

TBX4 syndrome: already discussed, but relevant in the differential diagnosis in syndromic or familial cases of PPHN with skeletal features.[64]

Chromosomal abnormalities such as Trisomy 21 (Down syndrome), which is associated with increased

Table 4. Maternal drugs associated with persistent pulmonary hypertension of the newborn and proposed mechanisms[69-74]

Drug/class	Proposed mechanism	Evidence
Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g., fluoxetine, paroxetine, sertraline)	Increased foetal serotonin → → pulmonary vasoconstriction	Strong (multiple studies)
Non-steroidal anti-inflammatory drugs (NSAIDs) (e.g., ibuprofen, indomethacin)	Premature ductus arteriosus closure → increased pulmonary afterload	Moderate to strong
Tricyclic antidepressants (e.g., amitriptyline)	Potential vasoconstrictive effects similar to SSRIs	Limited evidence
Benzodiazepines (e.g., diazepam)	Unclear; conflicting data	Weak/inconclusive
Illicit drugs (e.g., cocaine)	Foetal vasoconstriction, chronic hypoxia	Strong (observational data)
Beta-blockers	May cause neonatal hypotension or bradycardia, affecting pulmonary flow	Weak/controversial
Tocolytics (e.g., ritodrine, terbutaline)	Possible interference with lung maturation or cardiac output	Weak/limited evidence

vascular reactivity and structural cardiac anomalies, and deletions like 22q11.2 or 1q41-q42, which may present with congenital heart disease (CDH) and secondary PPHN, have been linked to pulmonary vascular complications.[65-67] In addition to the genetic variants mentioned above, a recent study identified variants in PPHN patients, and reported *CPS1*, *NOTCH3* and *SMAD9* as risk genes for late preterm and term PPHN.[68]

Clinical and translational implications

Understanding the genetic basis of PPHN has significant implications for diagnosis, prognosis and individualised treatment strategies.[68] Genetic testing, including gene panels and whole-exome sequencing, is increasingly recommended for neonates presenting with idiopathic or severe/refractory PPHN, associated congenital anomalies or a family history of PH.[68] Identifying pathogenic mutations can guide therapeutic decisions, such as predicting responsiveness to iNO or the use of PDE5 inhibitors, while also providing valuable information regarding prognosis, the risk of disease progression and recurrence risk in future pregnancies. Consequently, genetic counselling becomes an integral component of patient management. Ongoing research that incorporates genomics, transcriptomics and epigenetics will be essential for advancing precision medicine approaches in PPHN.[68]

Maternal drugs associated with PPHN

Several maternal medications have been associated with an increased risk of PPHN, especially when administered during the third trimester, as shown in Table 4. These drugs may interfere with the normal perinatal cardiopulmonary transition by altering pulmonary vascular tone, promoting vasoconstriction or inducing premature closure of the ductus arteriosus.

Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine and sertraline, are among the most studied and are thought to elevate foetal serotonin levels, leading to pulmonary vasoconstriction and impaired postnatal vascular relaxation.[69-71] Non-steroidal anti-inflammatory drugs (NSAIDs), including indomethacin and ibuprofen, can cause premature ductal closure, increasing right ventricular afterload and disrupting normal pulmonary circulation.[72]

Other drugs, including tricyclic antidepressants, benzodiazepines, certain beta-blockers and tocolytics, have also been implicated, although the evidence is less consistent. Illicit drug use, such as cocaine, is a recognised risk factor due to its potent vasoconstrictive and hypoxia-inducing effects.[72-74]

Given these associations, the use of specific medications during pregnancy, particularly in the later stages, should be carefully evaluated due to the potential risk of adverse neonatal outcomes such as PPHN.

Pathophysiology

The pathophysiology of PPHN involves complex molecular and enzymatic mechanisms that disrupt the balance between vasodilation and vasoconstriction in the pulmonary vasculature.[75-77] In PPHN, transition fails due to persistent vasoconstriction, vascular

remodelling or underdevelopment of the pulmonary vascular bed, as described above.[75-77]

At the molecular level, NO plays a central role in pulmonary vasodilation.[78] Synthesised by eNOS, NO activates soluble guanylate cyclase (sGC) in vascular smooth muscle cells, increasing intracellular cyclic guanosine monophosphate (cGMP) levels, which induces relaxation of the vascular smooth muscle.[79] In PPHN, eNOS expression and activity are often reduced, and there is increased breakdown of NO by reactive oxygen species (ROS), such as superoxide anion, which reacts with NO to form peroxynitrite, a potent oxidant that further impairs vasodilation and damages the endothelium.[80,81]

Prostacyclin (PGI_2), a product of arachidonic acid metabolism via cyclooxygenase (COX) and prostacyclin synthase, is another critical vasodilator.[82] PGI_2 activates adenylate cyclase, increasing cyclic adenosine monophosphate (cAMP), which also promotes pulmonary vascular relaxation. In PPHN, prostacyclin synthesis is frequently diminished, contributing to increased vascular tone.[82,83]

Conversely, vasoconstrictor pathways are upregulated in PPHN. ET-1, a potent vasoconstrictor, is elevated and acts primarily through the endothelin-A receptor on smooth muscle cells to promote vasoconstriction and vascular smooth muscle proliferation.[84] Similarly, thromboxane A_2 (TXA_2), another arachidonic acid metabolite, promotes vasoconstriction and platelet aggregation, further exacerbating hypoxaemia.[85,86]

Furthermore, increased expression of PDEs, particularly PDE5, contributes to the degradation of cGMP, thereby blunting the vasodilatory effects of NO.[87] Therapeutic strategies often target these enzymatic pathways using iNO, PDE inhibitors (e.g., sildenafil) and prostacyclin analogues to restore the balance between vasodilation and vasoconstriction.[88,89]

Haemodynamically, PPHN is characterised by elevated pulmonary arterial pressure, right ventricular hypertrophy and, in severe cases, right heart failure.[90] The high PVR leads to the persistence of foetal circulatory right-to-left shunts through the foramen ovale and ductus arteriosus, resulting in systemic hypoxaemia.[75]

In conclusion, the pathophysiology of PPHN involves a multifaceted interplay between impaired vasodilator mechanisms (e.g., NO and prostacyclin pathways), enhanced vasoconstrictor signalling (e.g., ET-1 and TXA_2), oxidative stress and enzymatic dysregulation. Understanding these pathways is essential for the development of targeted therapies.[90]

Clinical features

PPHN is a serious condition in which labile hypoxaemia is a hallmark feature.[91] It refers to rapidly fluctuating oxygen saturation levels (SpO_2) or arterial oxygen tensions (PaO_2) that can vary significantly over short periods of time, often without any major changes in ventilatory settings or apparent clinical deterioration. This instability in oxygenation reflects the dynamic nature of pulmonary vascular resistance in affected neonates, which can change abruptly in response to minimal stimuli such as handling, noise or changes in body position. The intermittent right-to-left shunting of blood through foetal circulatory pathways (e.g., the ductus arteriosus or foramen ovale), driven by elevated and unstable pulmonary artery pressures, leads to episodes of hypoxaemia that are often refractory to conventional oxygen therapy. Recognition of this labile pattern is crucial for differentiating PPHN from other causes of neonatal respiratory distress and for guiding appropriate management.[92]

Clinically, one of the hallmark signs of PPHN is central cyanosis that is refractory to oxygen therapy.[91] Despite administration of high concentrations of oxygen, these infants continue to exhibit low SpO_2, often below 85%, due to the presence of extra-pulmonary shunting. Tachypnoea and other signs of respiratory distress, including nasal flaring, grunting and the use of accessory muscles, are also commonly observed. In more severe cases, the neonate may develop respiratory failure and require immediate respiratory support.[91]

Haemodynamic instability is another important clinical feature.[93] Affected neonates often present with hypotension, prolonged capillary refill time and poor peripheral perfusion, indicating inadequate cardiac output.[93] Although not always present, heart murmurs may be heard in cases involving significant ductal flow or structural cardiac anomalies.[93]

A distinctive finding that supports the diagnosis is a differential (greater than 10%) in pre- and post-ductal oxygen saturation, with higher saturation in the right upper extremity (pre-ductal) compared to the lower limbs or left upper extremity (post-ductal), suggesting right-to-left shunting through a patent ductus arteriosus.[75] Arterial blood gas analysis demonstrates profound hypoxaemia with low partial pressure of arterial oxygen with an elevated alveolar-arterial (A-a) oxygen gradient.[94]

Differentiating between primary and secondary PPHN

PPHN can be broadly classified into primary (idiopathic) and secondary forms, a distinction that is

clinically relevant as it impacts both management and prognosis.[91]

In primary PPHN, there is no identifiable underlying pulmonary or cardiac pathology.[91] The condition is thought to result from a failure of the normal postnatal decrease in PVR, possibly due to abnormal muscularisation of the pulmonary arterioles or impaired vasodilation mechanisms.[91] These infants typically have structurally normal lungs and hearts, and imaging studies such as chest radiography may appear unremarkable. The diagnosis is made largely by exclusion, after ruling out other causes of hypoxaemia and cyanosis.[91]

In contrast, secondary PPHN occurs in association with a variety of conditions that contribute to increased PVR or impaired gas exchange.[43] Common causes include MAS, transient tachypnoea of the newborn (TTN), neonatal pneumonia or sepsis, respiratory distress syndrome (RDS) in preterm infants, CDH and pulmonary hypoplasia due to conditions such as prolonged oligohydramnios or renal agenesis.[95] In these cases, PH arises as a consequence of hypoxia, inflammation, acidosis or anatomical underdevelopment of the pulmonary vasculature.[43,95]

The differential diagnosis includes cyanotic congenital heart defects, such as transposition of the great arteries, tricuspid atresia, pulmonary atresia and total anomalous pulmonary venous return.[96,97] Unlike the functional shunting seen in PPHN, these heart defects involve fixed anatomical right-to-left shunts.[96,97]

Other less common differential diagnoses include central nervous system disorders that lead to hypoventilation and hypoxaemia, such as hypoxic–ischemic encephalopathy or severe intraventricular haemorrhage.[98,99]

Accurate differentiation among these conditions relies heavily on echocardiography, which helps assess pulmonary pressures, cardiac anatomy and the presence of ductal or foramen ovale shunting. Chest radiography, blood gas analysis and the response to oxygen therapy also contribute to the diagnostic process. Recognition of whether PPHN is primary or secondary, and the exclusion of mimicking conditions, is essential for guiding targeted treatment and improving outcomes.[1]

Diagnostic evaluation

Infants typically present within the first few hours or days after birth. A thorough prenatal history should be obtained upon NICU admission, including details of maternal medical conditions and any drug exposure.[100] Clinicians should also assess prenatal and perinatal factors such as chorioamnionitis, meconium-stained amniotic fluid and perinatal asphyxia, as these are associated with the development of PPHN, as shown in Table 5.[100]

The diagnostic process begins with a high index of suspicion in term or late preterm neonates presenting with cyanosis, respiratory distress and hypoxaemia that is unresponsive to supplemental oxygen.[91,92] Key diagnostic indicators include a pre- and post-ductal SpO_2 difference greater than 10%, persistently low PaO_2 despite high inspired oxygen fraction (FiO_2) and an elevated Oxygenation Index (OI), calculated as: OI = (Mean Airway Pressure × FiO_2 × 100) / PaO_2. The OI is a crucial tool for assessing the severity of PPHN and guiding treatment decisions. It reflects the balance between oxygen delivery and ventilation, helping clinicians determine the appropriate level of respiratory support. An OI greater than 15 strongly suggests significant hypoxaemia.[101-103] Also, the Oxygen Saturation Index (OSI) represents a validated non-invasive surrogate for the OI in the evaluation of disease severity among neonates with PPHN. By substituting arterial PaO_2 with preductal SpO_2 [(Mean Airway Pressure × FiO_2 × 100) /SpO_2], the OSI enables continuous bedside monitoring and reduces the need for repeated arterial blood sampling. Several studies have demonstrated a good correlation between OSI and OI within moderate oxygen saturation ranges (85%-95%). Nonetheless, interpretation should account for the nonlinear relationship between SpO_2 and PaO_2, particularly at saturation extremes (below 85% and above 95%). Although the OSI is promising and has already been validated in neonates, there are still no formal guidelines recommending its exclusive use for decisions regarding the initiation of iNO or ECMO; further prospective studies are needed to standardise cutoff values and protocols.[104-107]

A chest radiography may appear normal or reveal an underlying pulmonary pathology such as SAM or pneumonia.[108] Lung ultrasound (LUS) has an important complementary role in evaluating potential secondary causes. LUS demonstrates higher sensitivity and specificity than a chest X-ray for several neonatal pulmonary disorders that may precipitate or coexist with PPHN, including RDS, TTN, MAS, pneumonia, pneumothorax and pleural effusion. In addition, LUS provides a bedside, radiation-free tool to monitor lung aeration and recruitment, allowing for the individualised adjustment of ventilatory strategies.[109] LUS should be regarded as a valuable adjunct in the comprehensive evaluation of neonates with suspected or confirmed PPHN. Chest CT and MRI may be justified when there is a need to clarify the underlying pulmonary pathology, such as

Table 5. Risk factors and common conditions predisposing to persistent pulmonary hypertension of the newborn[1,3,39-46,65,69-77,92,94,95]

During pregnancy
Preconception maternal obesity
Maternal ethnicity: Black or Asian
Foetal arrhythmia
Maternal asthma
High altitude
Illicit drug use
Use of anti-inflammatory medications (e.g., maternal aspirin, ibuprofen, naproxen, indomethacin; these inhibit prostaglandin production and may cause premature ductal closure)
Use of selective serotonin reuptake inhibitors (SSRIs)
Smoking
Foetal growth restriction
Maternal diabetes
Large for gestational age foetus
Post-term pregnancy
Late preterm birth
Meconium-stained amniotic fluid
Chorioamnionitis
Genetic or familial predisposition
In the newborn
Aspiration syndromes: meconium; blood; amniotic fluid
Idiopathic pulmonary hypertension ("black lung": abnormal vascular remodelling)
Hyaline membrane disease (neonatal respiratory distress syndrome)
Asphyxia
Hypoxia
Low Apgar score
Pulmonary hypoplasia: congenital diaphragmatic hernia; oligohydramnios; space-occupying lesions (e.g., congenital cystic adenomatoid malformation, congenital lobar emphysema)
Hypoglycaemia
Hypocalcaemia
Hypothermia
Acidosis
Pneumothorax, pneumomediastinum, pulmonary interstitial emphysema
Polycythaemia/hyperviscosity, hyperleukocytosis
Severe congenital anaemia
Sepsis/pneumonia
Caesarean section
Transient tachypnoea of the newborn (particularly after caesarean without labour)
Congenital heart disease, especially: total anomalous pulmonary venous return; hypoplastic left heart syndrome; transient tricuspid insufficiency (transient myocardial ischemia); coarctation of the aorta; critical aortic stenosis; Ebstein anomaly; transposition of the great arteries; endocardial fibroelastosis; atrioventricular septal defect
Cerebral arteriovenous malformations: clinical presentation depends on the volume of shunted blood bypassing brain tissue and returning to the heart: often presents during the neonatal period with signs of congestive heart failure and PPHN
Alveolar-capillary dysplasia
Hereditary surfactant protein disorders
Congenital pulmonary lymphangiectasia
Bronchopulmonary dysplasia
Central nervous system disorders, neuromuscular diseases, upper airway obstruction

pneumonia, congenital alveolar proteinosis, alveolar-capillary dysplasia or pulmonary lymphangiomatosis.[110] CT angiography (angio-CT) can be useful in evaluating cardiovascular anomalies that are not fully clarified by echocardiography, particularly in cases of obstructed anomalous pulmonary venous return and vascular malformations.[111] Cardiac MRI provides good visualisation of the right ventricle and congenital heart defects, as well as of the pulmonary circulation through angiographic techniques.[112]

Echocardiography remains the cornerstone of diagnosis, confirming elevated pulmonary artery pressures, demonstrating right-to-left shunting at the foramen ovale or ductus arteriosus, and ruling out structural congenital heart disease.[75,113] Table 6 summarises the echocardiographic parameters used for the diagnosis and severity assessment of PPHN.[75,113,114] Not all parameters are used in isolation to classify severity; a comprehensive assessment is essential. In neonatology, many of these findings are qualitative and require

Table 6. Echocardiographic parameters for the diagnosis and severity assessment of persistent pulmonary hypertension of the newborn[75,113,114]

Parameter	Findings	Clinical significance	Severity grading
Right-to-left or bidirectional shunting (via the ductus arteriosus or foramen ovale)	Seen on colour Doppler	Diagnostic hallmark of PPHN; direction indicates pressure gradient	Right-to-left or bidirectional shunting may support the diagnosis of PPHN when interpreted alongside other echocardiographic findings.
Tricuspid regurgitation (TR) jet velocity	Peak TR velocity measured using continuous-wave Doppler, when a measurable jet is present	Estimates right ventricular systolic pressure (RVSP)	Allows for the estimation of the right ventricular systolic pressure (RVSP) using the modified Bernoulli equation. Interpretation requires adequate Doppler signal quality and consideration of systemic blood pressure and RV function.
Interventricular septal flattening or leftward bowing	Seen in parasternal short axis	Suggests elevated RV pressure and pressure overload	Mild: normal septal motion Moderate: septal flattening Severe: D-shaped LV
Pulmonary artery acceleration time (PAAT)	Shortened (< 40 ms)	Indicates increased pulmonary vascular resistance	Shorter times = more severe (e.g., < 30 ms suggests severe PPHN)
Right ventricular hypertrophy (RVH)	Thickened RV free wall (> 5 mm), subjective in neonates	Indicates chronic RV pressure overload	More prominent in moderate-to-severe cases
Right ventricular dilatation	Enlarged RV cavity relative to LV	Suggests volume or pressure overload of the RV	Moderate-to-severe if RV >> LV
Reduced left ventricular output	Low LV stroke volume and cardiac output	Due to decreased pulmonary venous return (from shunting)	Severe: compromised LV preload/ output
Estimated RVSP (via TR jet + RA pressure)	Estimated RVSP relative to systemic blood pressure	Estimated RVSP below, approximately equal to, or above systemic systolic blood pressure	Estimated RVSP relative to systemic systolic blood pressure: Mild: < 2/3 systemic Moderate: ~systemic Severe: sSystemic
Systolic flattening of the interventricular septum (D-shaped LV)	Observed in short axis during systole	Correlates with elevated RV pressure; severity marker	Mild: normal shape Moderate: flattened Severe: D-shaped LV
Patent ductus arteriosus (PDA) flow pattern	Right-to-left or bidirectional	Confirms persistent foetal circulation	May support the diagnosis of PPHN when interpreted alongside other echocardiographic findings. Mild: left-to-right Moderate: bidirectional Severe: right-to-left
Foramen ovale flow direction	Right-to-left or bidirectional	Supports diagnosis of PPHN	Similar grading as PDA
Biventricular function assessment	May show RV dysfunction; LV underfilling	Important for prognosis and therapeutic decisions	Severe if significant dysfunction or low cardiac output

LV: left ventricle; PDA: patent ductus arteriosus; PPHN: persistent pulmonary hypertension of the newborn; RV: right ventricle.

interpretation by professionals experienced in functional neonatal echocardiography.

Additionally, the echocardiographic assessment of biventricular function is critical, as impaired right ventricular performance and reduced cardiac output are associated with poor outcomes.[75,115] In exceptional and highly specific situations, cardiac catheterisation may be required to rule out congenital heart disease.[116] This method allows for the assessment of pulmonary artery pressure, PVR, cardiac output and oxygen saturations.[117] It also enables the performance of acute pulmonary vasoreactivity testing.[118]

Laboratory evaluation should include arterial blood gases and lactate, which typically show marked hypoxaemia.[109] A comprehensive biochemical panel including glucose, electrolytes, renal function and liver

function tests is indicated in the evaluation of critically unwell patients. To rule out sepsis, a full blood count with differential, C-reactive protein (CRP) and blood cultures are recommended.[109] If ECMO is being considered, coagulation studies and a cranial ultrasound should be obtained prior to cannulation.[109] Brain natriuretic peptide (BNP), a marker of ventricular strain, is often elevated in PPHN; levels exceeding 550 pg/mL have been associated with the diagnosis and severity of the condition.[119] Genetic testing is indicated when the clinical context is suggestive or if there is a family history or a previous child affected by PPHN.[68]

In low-resource settings, the diagnosis and management of neonates with PPHN present significant challenges. Limited availability of iNO, advanced imaging modalities such as echocardiography and other specialised interventions often restrict the ability to make timely and precise treatment decisions. Consequently, clinicians must frequently rely on clinical assessment, basic monitoring parameters and non-invasive surrogates such as the OSI to guide therapy. These constraints highlight the need for simplified, validated protocols that can be applied effectively in resource-limited settings.

Conclusion

PPHN remains a serious and potentially life-threatening condition. A thorough understanding of its complex pathophysiology is essential for early recognition and appropriate intervention. Accurate and timely diagnosis relies heavily on clinical suspicion and echocardiographic evaluation, which also allows for the assessment of severity and monitoring of the therapeutic response. PPHN should always be approached in a multidisciplinary context.

Although advances in management have improved survival, morbidity remains significant. Therefore, prevention strategies, early diagnosis and individualised care remain central to improving both short- and long-term outcomes.

The second part of this review will address the current therapeutic strategies and emerging treatments for PPHN.

Fundings

This research received no external funding.

Conflicts of interest

The author declares no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

References

1. Mukherjee D, Konduri GG. Pediatric Pulmonary Hypertension: Definitions, Mechanisms, Diagnosis, and Treatment. Compr Physiol 2021;11(3):2135-2190. doi:10.1002/cphy.c200023.
2. Distefano G, Romeo MG, Parisi MG, Magro G. Aspetti fisiopatologici e terapeutici della persistenza della circolazione fetale. Revisione della letteratura ed osservazioni istologiche personali [Physiopathologic and therapeutic aspects of persistent fetal circulation. Review of the literature and personal histological observations]. Pediatr Med Chir 1992;14(4):387-98.
3. Sankaran D, Lakshminrusimha S. Pulmonary hypertension in the newborn- etiology and pathogenesis. Semin Fetal Neonatal Med 2022;27(4):101381. doi:10.1016/j.siny.2022.101381.
4. Ratwatte S, Celermajer DS. The latest definition and classification of pulmonary hypertension. Int J Cardiol Congenit Heart Dis 2024;17:100534. doi:10.1016/j.ijcchd.2024.100534.
5. Kovacs G, Bartolome S, Denton CP, Gatzoulis MA, Gu S, Khanna D, et al. Definition, classification and diagnosis of pulmonary hypertension. Eur Respir J 2024;64(4):2401324.
6. Ball MK, Seabrook RB, Bonachea EM, Chen B, Fathi O, Nankervis CA, et al. Evidence-Based Guidelines for Acute Stabilization and Management of Neonates with Persistent Pulmonary Hypertension of the Newborn. Am J Perinatol 2023;40(14):1495-1508. doi:10.1055/a-1711-0778.
7. Hendricks-Muñoz KD, Walton JP. Hearing loss in infants with persistent fetal circulation. Pediatrics 1988;81(5):650-6. PMID: 2451802.
8. Walsh-Sukys MC, Tyson JE, Wright LL, Bauer CR, Korones SB, Stevenson DK, et al. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. Pediatrics 2000;105(1 Pt 1):14-20. doi:10.1542/peds.105.1.14.
9. Lipkin PH, Davidson D, Spivak L, Straube R, Rhines J, Chang CT. Neurodevelopmental and medical outcomes of persistent pulmonary hypertension in term newborns treated with nitric oxide. J Pediatr 2002;140(3):306-10. doi:10.1067/mpd.2002.122730.
10. Konduri GG, Sokol GM, Van Meurs KP, Singer J, Ambalavanan N, Lee T, Solimano A. Impact of early surfactant and inhaled nitric oxide therapies on outcomes in term/late preterm neonates with moderate hypoxic respiratory failure. J Perinatol 2013;33(12):944-9. doi:10.1038/jp.2013.83.
11. Aleem S, Robbins C, Murphy B, Elliott S, Akinyemi C, Paredes N, et al. The use of supplemental hydrocortisone in the management of persistent pulmonary hypertension of the newborn. J Perinatol 2021;41(4):794-800. doi:10.1038/s41372-021-00943-9.
12. Robertson CM, Tyebkhan JM, Hagler ME, Cheung PY, Peliowski A, Etches PC. Late-onset, progressive sensorineural hearing loss after severe neonatal respiratory failure. Otol Neurotol 2002;23(3):353-6. doi:10.1097/00129492-200205000-00022.
13. Yigit MB, Kowalski WJ, Hutchon DJ, Pekkan K. Transition from fetal to neonatal circulation: Modeling the effect of umbilical cord clamping. J Biomech 2015;48(9):1662-70. doi:10.1016/j.jbiomech.2015.02.040.
14. Finnemore A, Groves A. Physiology of the fetal and transitional circulation. Semin Fetal Neonatal Med 2015;20(4):210-6. doi:10.1016/j.siny.2015.04.003.
15. Morton SU, Brodsky D. Fetal Physiology and the Transition to Extrauterine Life. Clin Perinatol 2016;43(3):395-407. doi:10.1016/j.clp.2016.04.001.
16. Helve O, Pitkänen O, Janér C, Andersson S. Pulmonary fluid balance in the human newborn infant. Neonatology 2009;95(4):347-52. doi:10.1159/000209300.
17. Katz C, Bentur L, Elias N. Clinical implication of lung fluid balance in the perinatal period. J Perinatol 2011;31(4):230-5. doi:10.1038/jp.2010.134.
18. Teitel DF, Iwamoto HS, Rudolph AM. Changes in the pulmonary circulation during birth-related events. Pediatr Res 1990;27(4 Pt 1):372-8. doi:10.1203/00006450-199004000-00010.

19. Holmes H, Saini BS, Moir OJ, Darby JRT, Morrison JL, Sun L, et al. Pulmonary Vascular Regulation in the Fetal and Transitional Lung. Clin Perinatol 2024;51(1):1-19. doi:10.1016/j.clp.2023.11.003.
20. Petersson J, Glenny RW. Gas exchange and ventilation-perfusion relationships in the lung. Eur Respir J 2014;44(4):1023-41. doi:10.1183/09031936.00037014.
21. Steinhorn RH, Lakshminrusimha S. Oxygen and pulmonary vasodilation: The role of oxidative and nitrosative stress. Semin Fetal Neonatal Med 2020;25(2):101083. doi:10.1016/j.siny.2020.101083.
22. Wang X, He B. Endothelial dysfunction: molecular mechanisms and clinical implications. MedComm (2020). 2024;5(8):e651. doi:10.1002/mco2.651.
23. Rapoport RM. Nitric oxide inhibition of endothelin-1 release in the vasculature: in vivo relevance of in vitro findings. Hypertension 2014;64(5):908-14. doi:10.1161/HYPERTENSIONAHA.114.03837.
24. Hooper SB, Binder-Heschl C, Polglase GR, Gill AW, Kluckow M, Wallace EM, et al. The timing of umbilical cord clamping at birth: physiological considerations. Matern Health Neonatol Perinatol 2016;2:4. doi:10.1186/s40748-016-0032-y.
25. Chioma R, Finn D, Healy DB, Herlihy I, Livingstone V, Panaviene J, et al. Impact of cord clamping on haemodynamic transition in term newborn infants. Arch Dis Child Fetal Neonatal Ed 2024;109(3):287-293. doi:10.1136/archdischild-2023-325652.
26. Tan CMJ, Lewandowski AJ. The Transitional Heart: From Early Embryonic and Fetal Development to Neonatal Life. Fetal Diagn Ther 2020;47(5):373-386. doi:10.1159/000501906.
27. Zampieri F, Thiene G, Basso C, Zanatta A. The three fetal shunts: A story of wrong eponyms. J Anat 2021;238(4):1028-1035. doi:10.1111/joa.13357.
28. Remien K, Majmundar SH. Physiology, Fetal Circulation. 2023 Apr 26. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–
29. Ostadal B, Kolar F, Ostadalova I, Sedmera D, Olejnickova V, Hlavackova M, et al. Developmental Aspects of Cardiac Adaptation to Increased Workload. J Cardiovasc Dev Dis 2023;10(5):205. doi:10.3390/jcdd10050205.
30. Rabe H, Gyte GM, Díaz-Rossello JL, Duley L. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database Syst Rev 2019;9(9):CD003248. doi:10.1002/14651858.CD003248.pub4.
31. Hooper SB, Polglase GR, te Pas AB. A physiological approach to the timing of umbilical cord clamping at birth. Arch Dis Child Fetal Neonatal Ed 2015;100(4):F355-60. doi:10.1136/archdischild-2013-305703.
32. Zaramella P, Freato F, Quaresima V, Secchieri S, Milan A, Grisafi D, et al. Early versus late cord clamping: effects on peripheral blood flow and cardiac function in term infants. Early Hum Dev 2008;84(3):195-200. doi:10.1016/j.earlhumdev.2007.04.003.
33. Stenning FJ, Hooper SB, Kluckow M, Crossley KJ, Gill AW, Wallace EM, et al. Transfusion or Timing: The Role of Blood Volume in Delayed Cord Clamping During the Cardiovascular Transition at Birth. Front Pediatr 2019;7:405. doi:10.3389/fped.2019.00405.
34. Chaparro CM. Timing of umbilical cord clamping: effect on iron endowment of the newborn and later iron status. Nutr Rev. 2011 Nov;69 Suppl 1:S30-6. doi:10.1111/j.1753-4887.2011.00430.x.
35. Hemmati F, Sharma D, Namavar Jahromi B, Salarian L, Farahbakhsh N. Delayed cord clamping for prevention of intraventricular hemorrhage in preterm neonates: a randomized control trial. J Matern Fetal Neonatal Med 2022;35(19):3633-3639. doi:10.1080/14767058.2020.1836148.
36. Garg BD, Kabra NS, Bansal A. Role of delayed cord clamping in prevention of necrotizing enterocolitis in preterm neonates: a systematic review. J Matern Fetal Neonatal Med 2019;32(1):164-172. doi:10.1080/14767058.2017.1370704.
37. Fait Tomáš, Janota Jan. Delayed umbilical cord clamping - benefits and risks. Ceska Gynekol 2022;87(6):424-426. English. doi:10.48095/cccg2022424.
38. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, et al; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Surgery and Anesthesia; and the American Thoracic Society. Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society. Circulation. 2015;132(21):2037-99. doi:10.1161/CIR.0000000000000329. Erratum in: Circulation 2016;133(4):e368. doi:10.1161/CIR.0000000000000363.
39. Grigoriadis S, Vonderporten EH, Mamisashvili L, Tomlinson G, Dennis CL, Koren G, et al. Prenatal exposure to antidepressants and persistent pulmonary hypertension of the newborn: systematic review and meta-analysis. BMJ 2014;348:f6932. doi:10.1136/bmj.f6932.
40. Perkin RM, Levin DL, Clark R. Serum salicylate levels and right-to-left ductus shunts in newborn infants with persistent pulmonary hypertension. J Pediatr 1980;96(4):721-6. doi:10.1016/s0022-3476(80)80753-0.
41. Young KC, Schmidt AF, Tan AW, Sbragia L, Elsaie A, Shivanna B. Pathogenesis and Physiologic Mechanisms of Neonatal Pulmonary Hypertension: Preclinical Studies. Clin Perinatol 2024;51(1):21-43. doi:10.1016/j.clp.2023.11.004.
42. Varghese NP, Tillman RH, Keller RL. Pulmonary hypertension is an important co-morbidity in developmental lung diseases of infancy: Bronchopulmonary dysplasia and congenital diaphragmatic hernia. Pediatr Pulmonol 2021;56(3):670-677. doi:10.1002/ppul.25258.
43. Nair J, Lakshminrusimha S. Update on PPHN: mechanisms and treatment. Semin Perinatol 2014;38(2):78-91. doi:10.1053/j.semperi.2013.11.004.
44. Kallimath A, Kolkur K, Malshe N, Klimek J, Suryawanshi P. Hemodynamics in neonates with polycythemia before and after partial exchange transfusion: an observational study. Front Pediatr 2024;11:1296184. doi:10.3389/fped.2023.1296184.
45. Kaplish D, Vagha JD, Rathod S, Jain A. Current Pharmaceutical Strategies in the Management of Persistent Pulmonary Hypertension of the Newborn (PPHN): A Comprehensive Review of Therapeutic Agents. Cureus 2024;16(9):e70307. doi:10.7759/cureus.70307.
46. Liu X, Mei M, Chen X, Lu Y, Dong X, Hu L, et al. Identification of genetic factors underlying persistent pulmonary hypertension of newborns in a cohort of Chinese neonates. Respir Res 2019;20(1):174. doi:10.1186/s12931-019-1148-1.
47. Botney MD, Bahadori L, Gold LI. Vascular remodeling in primary pulmonary hypertension. Potential role for transforming growth factor-beta. Am J Pathol 1994;144(2):286-95.
48. Cuthbertson I, Morrell NW, Caruso P. *BMPR2* Mutation and Metabolic Reprogramming in Pulmonary Arterial Hypertension. Circ Res 2023;132(1):109-126. doi:10.1161/CIRCRESAHA.122.321554.
49. Jiao YR, Wang W, Lei PC, Jia HP, Dong J, Gou YQ, et al. 5-HTT, BMPR2, EDN1, ENG, KCNA5 gene polymorphisms and susceptibility to pulmonary arterial hypertension: A meta-analysis. Gene 2019;680:34-42. doi:10.1016/j.gene.2018.09.020.
50. Montani D, Günther S, Dorfmüller P, Perros F, Girerd B, Garcia G, et al. Pulmonary arterial hypertension. Orphanet J Rare Dis 2013;8:97. doi:10.1186/1750-1172-8-97.
51. Tsoi SM, Jones K, Colglazier E, Parker C, Nawaytou H, Teitel D, et al. Persistence of persistent pulmonary hypertension of the newborn: A case of de novo TBX4 variant. Pulm Circ 2022;12(3):e12108. doi:10.1002/pul2.12108.
52. Prapa M, Lago-Docampo M, Swietlik EM, Montani D, Eyries M, Humbert M, et al; NIHR BioResource for Translational Research–Rare Diseases; National Cohort Study of Idiopathic and Heritable PAH; PAH Biobank Enrolling Centers' Investigators. First Genotype-Phenotype Study in TBX4 Syndrome: Gain-of-Function Mutations Causative for Lung Disease. Am J Respir Crit Care Med 2022;206(12):1522-1533. doi:10.1164/rccm.202203-0485OC.
53. Byers HM, Dagle JM, Klein JM, Ryckman KK, McDonald EL, Murray JC, et al. Variations in CRHR1 are associated with persistent pulmonary hypertension of the newborn. Pediatr Res 2012;71(2):162-7. doi:10.1038/pr.2011.24.
54. Cookson MW, Abman SH, Kinsella JP, Mandell EW. Pulmonary vasodilator strategies in neonates with acute hypoxemic respiratory failure and pulmonary hypertension. Semin Fetal Neonatal Med 2022;27(4):101367. doi:10.1016/j.siny.2022.101367.
55. Villanueva ME, Zaher FM, Svinarich DM, Konduri GG. Decreased gene expression of endothelial nitric oxide synthase in newborns with persistent pulmonary hypertension. Pediatr Res 1998;44(3):338-43. doi:10.1203/00006450-199809000-00012.
56. Dasgupta A, Bowman L, D'Arsigny CL, Archer SL. Soluble guanylate cyclase: a new therapeutic target for pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. Clin Pharmacol Ther 2015;97(1):88-102. doi:10.1002/cpt.10.
57. Chester M, Seedorf G, Tourneux P, Gien J, Tseng N, Grover T, et al. Cinaciguat, a soluble guanylate cyclase activator, augments cGMP after oxidative stress and causes pulmonary vasodilation in neonatal pulmonary hypertension. Am J Physiol Lung Cell Mol Physiol 2011;301(5):L755-64. doi:10.1152/ajplung.00138.2010.
58. Poitras EL, Gust SL, Kerr PM, Plane F. Repurposing of the PDE5 Inhibitor Sildenafil for the Treatment of Persistent Pulmonary Hypertension in Neonates. Curr Med Chem 2021;28(12):2418-2437. doi:10.2174/0929867327666200923151924.
59. Mathew R. Critical Role of Caveolin-1 Loss/Dysfunction in Pulmonary Hypertension. Med Sci (Basel) 2021;9(4):58. doi:10.3390/medsci9040058.
60. El-Khazragy N, El Barbary M, Fouad H, Abdelgawad A, Rabie D. Association between genetic variations in carbamoyl-phosphate synthetase gene and persistent neonatal pulmonary hypertension. Eur J Pediatr 2021;180(9):2831-2838. doi:10.1007/s00431-021-04053-8.
61. Pradhan A, Che L, Ustiyan V, Reza AA, Pek NM, Zhang Y, et al. Novel FOXF1-Stabilizing Compound TanFe Stimulates Lung Angiogenesis in Alveolar Capillary Dysplasia. Am J Respir Crit Care Med 2023;207(8):1042-1054. doi:10.1164/rccm.202207-1332OC.
62. Lin Y, Jiang JB, Xia B, Cao J, Yu AZ, Huang WM. [Alveolar capillary dysplasia with misalignment of the pulmonary veins: a case report and literature review]. Zhonghua Er Ke Za Zhi 2020;58(10):838-842. doi:10.3760/cma.j.cn112140-20200427-00441.

63. Lei C, Wan C, Liu C. ABCA3 mutation-induced congenital pulmonary surfactant deficiency: A case report. Medicine (Baltimore) 2024;103 (13):e37622. doi:10.1097/MD.0000000000037622.
64. Austin ED, Elliott CG. TBX4 syndrome: a systemic disease highlighted by pulmonary arterial hypertension in its most severe form. Eur Respir J 2020;55(5):2000585. doi:10.1183/13993003.00585-2020.
65. Bush DS, Ivy DD. Pulmonary Hypertension in the Population with Down Syndrome. Cardiol Ther 2022;11(1):33-47. doi:10.1007/s40119-021-00251-5.
66. Unolt M, DiCairano L, Schlechtweg K, Barry J, Howell L, Kasperski S, et al. Congenital diaphragmatic hernia in 22q11.2 deletion syndrome. Am J Med Genet A 2017;173(1):135-142. doi:10.1002/ajmg.a.37980.
67. Kantarci S, Donahoe PK. Congenital diaphragmatic hernia (CDH) etiology as revealed by pathway genetics. Am J Med Genet C Semin Med Genet 2007;145C(2):217-26. doi:10.1002/ajmg.c.30132.
68. Liu X, Mei M, Chen X, Lu Y, Dong X, Hu L, et al. Identification of genetic factors underlying persistent pulmonary hypertension of newborns in a cohort of Chinese neonates. Respir Res 2019;20(1):174. doi:10.1186/s12931-019-1148-1.
69. Chambers CD, Hernandez-Diaz S, Van Marter LJ, Werler MM, Louik C, Jones KL, Mitchell AA. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. N Engl J Med 2006;354(6):579-87. doi:10.1056/NEJMoa052744.
70. Alwan S, Bandoli G, Chambers CD. Maternal use of selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. Clin Pharmacol Ther 2016;100(1):34-41. doi:10.1002/cpt.376.
71. Byatt N, Freeman MP. Exposure to selective serotonin reuptake inhibitors in late pregnancy increases the risk of persistent pulmonary hypertension of the newborn, but the absolute risk is low. Evid Based Nurs 2015;18(1):15-6. doi:10.1136/eb-2014-101786.
72. Van Marter LJ, Leviton A, Allred EN, Pagano M, Sullivan KF, Cohen A, Epstein MF. Persistent pulmonary hypertension of the newborn and smoking and aspirin and nonsteroidal antiinflammatory drug consumption during pregnancy. Pediatrics. 1996 May;97(5):658-63.
73. Reis M, Källén B. Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. Psychol Med 2010;40(10):1723-33. doi:10.1017/S0033291709992194.
74. Xu C, Bao Y, Ding H, Wang K, Yang Q, Zhu J. The association between antenatal indomethacin exposure and persistent pulmonary hypertension of the newborn in extremely preterm infants. Sci Rep 2025;15(1):16962. doi:10.1038/s41598-025-01259-w.
75. Singh Y, Lakshminrusimha S. Pathophysiology and Management of Persistent Pulmonary Hypertension of the Newborn. Clin Perinatol 2021;48(3):595-618. doi:10.1016/j.clp.2021.05.009.
76. Mandell E, Kinsella JP, Abman SH. Persistent pulmonary hypertension of the newborn. Pediatr Pulmonol 2021;56(3):661-669. doi:10.1002/ppul.25073.
77. Distefano G, Sciacca P. Molecular physiopathogenetic mechanisms and development of new potential therapeutic strategies in persistent pulmonary hypertension of the newborn. Ital J Pediatr 2015;41:6. doi:10.1186/s13052-015-0111-0.
78. Cookson MW, Kinsella JP. Inhaled Nitric Oxide in Neonatal Pulmonary Hypertension. Clin Perinatol 2024;51(1):95-111. doi:10.1016/j.clp.2023.11.001.
79. Moncada S. Nitric oxide. J Hypertens Suppl 1994;12(10):S35-9.
80. Konduri GG, Ou J, Shi Y, Pritchard KA Jr. Decreased association of HSP90 impairs endothelial nitric oxide synthase in fetal lambs with persistent pulmonary hypertension. Am J Physiol Heart Circ Physiol 2003;285(1):H204-11. doi:10.1152/ajpheart.00837.2002.
81. Afolayan AJ, Eis A, Alexander M, Michalkiewicz T, Teng RJ, Lakshminrusimha S, et al. Decreased endothelial nitric oxide synthase expression and function contribute to impaired mitochondrial biogenesis and oxidative stress in fetal lambs with persistent pulmonary hypertension. Am J Physiol Lung Cell Mol Physiol 2016;310(1):L40-9. doi:10.1152/ajplung.00392.2014.
82. Del Pozo R, Hernandez Gonzalez I, Escribano-Subias P. The prostacyclin pathway in pulmonary arterial hypertension: a clinical review. Expert Rev Respir Med 2017;11(6):491-503. doi:10.1080/17476348.2017.1317599.
83. Cosa N, Costa E Jr. Inhaled pulmonary vasodilators for persistent pulmonary hypertension of the newborn: safety issues relating to drug administration and delivery devices. Med Devices (Auckl) 2016;9:45-51. doi:10.2147/MDER.S99601.
84. Rosenberg AA, Kennaugh J, Koppenhafer SL, Loomis M, Chatfield BA, Abman SH. Elevated immunoreactive endothelin-1 levels in newborn infants with persistent pulmonary hypertension. J Pediatr 1993;123(1):109-14. doi:10.1016/s0022-3476(05)81552-5.
85. Reyes JL. Arachidonic acid metabolites and haemodynamics of the neonate. Pediatr Nephrol 1993;7(6):841-4. doi:10.1007/BF01213371.
86. Santhosh KT, Sikarwar AS, Hinton M, Chelikani P, Dakshinamurti S. Thromboxane receptor hyper-responsiveness in hypoxic pulmonary hypertension requires serine 324. Br J Pharmacol 2014;171(3):676-87. doi:10.1111/bph.12487.
87. Padda IS, Tripp J. Phosphodiesterase Inhibitors. 2023 Jun 26. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–.
88. Kelly LE, Ohlsson A, Shah PS. Sildenafil for pulmonary hypertension in neonates. Cochrane Database Syst Rev 2017;8(8):CD005494. doi:10.1002/14651858.CD005494.pub4.
89. Wu Y, Liu HM, Gu L, Li QW, Zhu L. Prostacyclins and pulmonary arterial hypertension in children. Eur Rev Med Pharmacol Sci 2022;26(1):37-45. doi:10.26355/eurrev_202201_27745.
90. Kaplish D, Vagha JD, Rathod S, Jain A. Current Pharmaceutical Strategies in the Management of Persistent Pulmonary Hypertension of the Newborn (PPHN): A Comprehensive Review of Therapeutic Agents. Cureus 2024;16(9):e70307. doi:10.7759/cureus.70307.
91. Lakshminrusimha S, Keszler M. Persistent Pulmonary Hypertension of the Newborn. Neoreviews 2015;16(12):e680-e692. doi:10.1542/neo.16-12-e680.
92. Bhagwat AP, Sharath HV, Seth NH, Puri SN. Persistent Pulmonary Hypertension of Newborns Secondary to Labile Hypoxemia Associated With Cyanosis: A Case Series. Cureus 2024;16(2):e54016. doi:10.7759/cureus.54016.
93. Siefkes HM, Lakshminrusimha S. Management of systemic hypotension in term infants with persistent pulmonary hypertension of the newborn: an illustrated review. Arch Dis Child Fetal Neonatal Ed 2021;106(4):446-455. doi:10.1136/archdischild-2020-319705.
94. Bendapudi P, Rao GG, Greenough A. Diagnosis and management of persistent pulmonary hypertension of the newborn. Paediatr Respir Rev 2015;16(3):157-61. doi:10.1016/j.prrv.2015.02.001.
95. Arshad MS, Adnan M, Anwar-Ul-Haq HM, Zulqarnain A. Postnatal causes and severity of persistent pulmonary Hypertension of Newborn. Pak J Med Sci 2021;37(5):1387-1391. doi:10.12669/pjms.37.5.2218.
96. Singh Y, Lakshminrusimha S. Perinatal Cardiovascular Physiology and Recognition of Critical Congenital Heart Defects. Clin Perinatol 2021;48(3):573-594. doi:10.1016/j.clp.2021.05.008.
97. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013;62(25 Suppl):D34-41. doi:10.1016/j.jacc.2013.10.029. Erratum in: J Am Coll Cardiol 2014;63(7):746. Erratum in: J Am Coll Cardiol 2014;63(7):746. doi:10.1016/j.jacc.2013.12.004.
98. Yum SK, Seo YM, Kwun Y, Moon CJ, Youn YA, Sung IK. Therapeutic hypothermia in infants with hypoxic-ischemic encephalopathy and reversible persistent pulmonary hypertension: short-term hospital outcomes. J Matern Fetal Neonatal Med 2018;31(23):3108-3114. doi:10.1080/14767058.2017.1365123.
99. Novak CM, Ozen M, Burd I. Perinatal Brain Injury: Mechanisms, Prevention, and Outcomes. Clin Perinatol 2018;45(2):357-375. doi:10.1016/j.clp.2018.01.015.
100. Jain A, McNamara PJ. Persistent pulmonary hypertension of the newborn: Advances in diagnosis and treatment. Semin Fetal Neonatal Med 2015;20(4):262-71. doi:10.1016/j.siny.2015.03.001.
101. Konduri GG, Solimano A, Sokol GM, Singer J, Ehrenkranz RA, Singhal N, et al; Neonatal Inhaled Nitric Oxide Study Group. A randomized trial of early versus standard inhaled nitric oxide therapy in term and near-term newborn infants with hypoxic respiratory failure. Pediatrics 2004;113(3 Pt 1):559-64. doi:10.1542/peds.113.3.559.
102. Bui-Binh-Bao S, Nguyen Thi D, Hoang Mai L, Do Ho Tinh T, Nguyen TTB. Assessing hypoxic respiratory failure in mechanically ventilated neonates: A comparative study of oxygen saturation index and oxygenation index. PLoS One 2024;19(5):e0304278. doi:10.1371/journal.pone.0304278.
103. Bendapudi P, Rao GG, Greenough A. Diagnosis and management of persistent pulmonary hypertension of the newborn. Paediatr Respir Rev 2015;16(3):157-61. doi:10.1016/j.prrv.2015.02.001.
104. Muniraman HK, Song AY, Ramanathan R, Fletcher KL, Kibe R, Ding L, et al. Evaluation of Oxygen Saturation Index Compared With Oxygenation Index in Neonates With Hypoxemic Respiratory Failure. JAMA Netw Open 2019;2(3):e191179. doi:10.1001/jamanetworkopen.2019.1179.
105. Maneenil G, Premprat N, Janjindamai W, Dissaneevate S, Phatigomet M, Thatrimontrichai A. Correlation and Prediction of Oxygen Index from Oxygen Saturation Index in Neonates with Acute Respiratory Failure. Am J Perinatol 2024;41(2):180-186. doi:10.1055/a-1673-5251.
106. Bui-Binh-Bao S, Nguyen Thi D, Hoang Mai L, Do Ho Tinh T, Nguyen TTB. Assessing hypoxic respiratory failure in mechanically ventilated neonates: A comparative study of oxygen saturation index and oxygenation index. PLoS One 2024;19(5):e0304278. doi:10.1371/journal.pone.0304278.
107. Tsurukawa S, Zuiki M, Naito Y, Kitamura K, Matsumura U, Kanayama T, et al. Oxygenation saturation index in neonatal hypoxemic respiratory failure. Pediatr Int 2024;66(1):e15753. doi:10.1111/ped.15753.
108. Nandula PS, Shah SD. Persistent Pulmonary Hypertension of the Newborn. 2023 Jul 31. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–.

109. Del Rey Hurtado de Mendoza B, Sánchez-de-Toledo J, Bobillo Perez S, Girona M, Balaguer Gargallo M, Rodríguez-Fanjul J. Lung Ultrasound to Assess the Etiology of Persistent Pulmonary Hypertension of the Newborn (LUPPHYN Study): A Pilot Study. Neonatology 2019;116(2):140-146. doi:10.1159/000499047.
110. Hysinger EB, Higano NS, Critser PJ, Woods JC. Imaging in neonatal respiratory disease. Paediatr Respir Rev 2022;43:44-52. doi:10.1016/j.prrv.2021.12.002.
111. Shen Q, Pa M, Hu X, Wang J. Role of plain radiography and CT angiography in the evaluation of obstructed total anomalous pulmonary venous connection. Pediatr Radiol 2013;43(7):827-35. doi:10.1007/s00247-012-2609-6.
112. Ramirez-Suarez KI, Tierradentro-García LO, Otero HJ, Rapp JB, White AM, Partington SL, et al. Optimizing neonatal cardiac imaging (magnetic resonance/computed tomography). Pediatr Radiol 2022;52(4):661-675. doi:10.1007/s00247-021-05201-w.
113. de Boode WP, Singh Y, Molnar Z, Schubert U, Savoia M, Sehgal A, et al; European Special Interest Group 'Neonatologist Performed Echocardiography' (NPE). Application of Neonatologist Performed Echocardiography in the assessment and management of persistent pulmonary hypertension of the newborn. Pediatr Res 2018;84(Suppl 1):68-77. doi:10.1038/s41390-018-0082-0.
114. Boyd SM, Kluckow M, McNamara PJ. Targeted Neonatal Echocardiography in the Management of Neonatal Pulmonary Hypertension. Clin Perinatol 2024;51(1):45-76. doi:10.1016/j.clp.2023.11.006.
115. Peterson AL, Deatsman S, Frommelt MA, Mussatto K, Frommelt PC. Correlation of echocardiographic markers and therapy in persistent pulmonary hypertension of the newborn. Pediatr Cardiol 2009;30(2):160-5. doi:10.1007/s00246-008-9303-3.
116. Shibbani K, Kenny D. Updates in interventional cardiology in children with cardiac disease. Eur J Pediatr 2025;184(7):400. doi:10.1007/s00431-025-06236-z.
117. Wacker J, Joye R, Genecand L, Lador F, Beghetti M. Pulmonary vascular disease as a complication of pediatric congenital heart diseases. Transl Pediatr 2023;12(5):1041-1052. doi:10.21037/tp-23-64.
118. Zhang C, Li Q, Liu T, Gu H. [Cardiac catheterization and pulmonary vasoreactivity testing in children with idiopathic pulmonary arterial hypertension]. Zhonghua Er Ke Za Zhi 2014;52(6):468-72.
119. Reynolds EW, Ellington JG, Vranicar M, Bada HS. Brain-type natriuretic peptide in the diagnosis and management of persistent pulmonary hypertension of the newborn. Pediatrics 2004;114(5):1297-304. doi:10.1542/peds.2004-0525. Erratum in: Pediatrics 2005;115(5):1454.