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Persistent Pulmonary Hypertension of Newborn: Analysis of 494 cases in a Tertiary Care Hospital.

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Abstract:

Introduction: Persistent pulmonary hypertension (PPHN) or persistent fetal circulation (PFC) is a commonly encountered problem in neonatal and pediatric cardiac intensive care units and cause significant mortality and morbidity.

Aim/Objective : To show the outcome of patient of PPHN treated by a cheap, locally available NNF protocol.

Methods: It was a retrospective study conducted in pediatric cardiology department of a tertiary care hospital in Dhaka, Bangladesh from February 2014 to March 2019. After diagnosis in noninvasive cardiac laboratory (NIC Lab), all cases were admitted in neonatal and pediatric cardiac intensive care units for specific management using NNF protocol. After 72 hours, echocardiography was repeated, and outcome was analyzed.

Results: Out of total 494 cases, 80.56% cases were diagnosed at first week and 4.45% cases were diagnosed at 3rd week of life. Male patients (60.32%) outnumbered female. Babies were delivered by caesarean section in 92.31% cases. PPHN was found alone in 24.69% cases and rest along with other less severe congenital heart diseases. Severe pulmonary hypertension was observed in 63.56% cases. Right ventricular volume was increased in 93.52% cases. Hundred percent neonates were treated with high flow oxygen therapy by optiflow/ nasal cannula/ head box. Anti-failure treatment was offered in 73.27% cases, pulmonary vasodilators in 59.51% cases, inotropes in 15.18% cases. Outcome of treatment was analyzed after 72 hours by repeat echocardiography. Four hundred and seventy one (95.34%) cases were cured completely and only 1.01% expired.

Conclusion: PPHN is a life threatening condition in neonate only. Early diagnosis and proper management is must for survival. Management by low cost NNF protocol was found effective with 95.34% cure rate and only 1.01% mortality. This protocol may be used for treatment of PPHN in low cost set up.

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Introduction:

Persistent pulmonary hypertension (PPHN) is the persistence of the high pulmonary arterial pressure after birth which is a characteristic of the fetal circulation. It is characterized by the presence of elevated pulmonary vascular resistance and right to left shunt through the ductus arteriosus and/or foramen ovale. PPHN is associated with substantial infant mortality and morbidity.

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Survival of a newborn at birth requires an immediate and sustained fall in pulmonary vascular resistance from its elevated level in-utero to a low resistance, high flow pulmonary circulation after delivery. This rapid drop allows eightfold increase of blood flow to the lungs that enable it to exchange gases. Some infants do not achieve or sustain this normal decrease in pulmonary vascular resistance at birth leading to severe respiratory distress and hypoxemia which is known as persistent pulmonary hyperten sion of newborn (PPHN). 1,2 This is usually seen in newborn with respiratory distress syndrome, overwhelming sepsis, meconium aspiration syndrome, intrauterine hypoxemia or ischemia and neonatal hypoxemia or ischemia.[3] PPHN is a major clinical syndrome contributing significantly to high morbidity or mortality in both full term and premature neonates.[4-9] PPHN primarily affects full term and near term neonates, although some premature infants <32

weeks gestation show echocardiographic evidence of PPHN[3-9]. The incidence of PPHN in term and near term newborn infants is estimated to be 2 per 1000 live births, based on an observational study by Walsh Sukys et al[1] that included neonatal ICUs at 12 large academic centers during 1993–1994. Meconium aspiration syndrome (MAS) is the most common underlying diagnosis of PPHN, followed by primary PPHN. Other diagnoses include respiratory distress syndrome (RDS), pneumonia and/or sepsis, pulmonary vasoconstriction from asphyxia and pulmonary hypoplasia secondary to congenital diaphragmatic hernia or oligohydramnios. RDS in preterm neonates delivered by elective or indicated caesarean section at 34–37 weeks gestation has become a more frequent cause of PPHN.[10-13]

Persistent fetal circulation (PFC) was described as unripe birth of mankind by William Harvey in 1628.[7] PFC also known as persistent pulmonary hypertension of the newborn is defined as persistence of right to left atrial or ductal shunting or both in the presence of elevated right ventricular pressure. Mean pulmonary artery pressure at rest is > 25 mm of Hg in such situation with normal pulmonary capillary wedge pressure. PPHN results from abnormal vascular remodeling, increased pulmonary arterial resistance and exaggerated vascular activity. In utero the fetus derives its oxygen and nutrients from placenta through the umbilical vein. Most of this blood bypasses the liver and enter into right atrium (RA). From RA blood enters into left atrium through foramen ovale and subsequently pumped into Aorta. Negligible amount of blood that enter into right ventricle from RA is subsequently pumped into Aorta through ductus arteriosus bypassing lung as pulmonary vascular resistance is very high in fetus. So, fetal lung receives only 8% of ventricular output. Because a lower PVR generally promotes functional closure of the ductus and foramen ovale while a high PVR encourages PFC, it is useful to know which substances affect PVR. Factors known to lower PVR include oxygen, nitric oxide, prostacyclin, prostaglandins E_2 and D_2, adenosine, magnesium, bradykinins, atrial natriuretic factor, alkalosis, histamine, acetylcholine, beta-adrenergic stimulation and potassium channel activation. Oxygen and inhaled nitric oxide represent the foundation of therapy; oxygen induced pulmonary vasodilatation appears to be mediated by ATP through purinergic receptors and through activation of a calcium dependent potassium channel.[12,13,14] Factors that increase PVR are hypoxia, acidosis, endothelin-1, leukotrienes, thromboxanes, platelet activating factors, prostaglandin F_2-alpha, alpha-adrenergic stimulation and calcium channel activation. Thus, it is important to recognize clinical conditions that affect PVR and to treat them appropriately. Mechanisms that contribute to high pulmonary vascular resistance in the fetus are: Low oxygen tension, relatively low basal production of vasodilator products (PGI, nitric oxide), increased production of vasoconstrictors (endothelin and leukotrienes) and altered smooth muscle activity. During last trimester, the fetal pulmonary circulation becomes progressively responsive to vasoactive stimuli.[15-19] Immediately after birth, pulmonary artery pressure falls, and blood flow increases in response to birth related stimuli. Those includes establishment of air liquid interface, rhythmic lung distension, increased oxygen tension and altered production of vasoactive substances like nitric oxide and prostaglandin.[1,2] Mechanisms that lead to failure of fall in pulmonary resistance at birth include a) exposure to chronic or acute hypoxia at birth, b) chronic hypoxia in utero. c) Entrance of meconium into the airways d) septicemia e) cardiac malformations and others.[15,16] Most of the cases of PFC landed to complete recovery or death. Occasionally, there may be long term sequelae such as chronic lung disease,[17] cerebral infarction resulting in specific motor and/or cognitive deficits, and sensorineural hearing loss. An association with sudden infant death syndrome has also been suggested.

In modern neonatal intensive care unit, anticipation and early treatment of PFC and its complications in sick newborns are common events. So severe PFC are only seen in rare occasions. Various treatment protocol including High flow oxygen therapy, oral Sildenafil, High Frequency Ventilation (HFV), Extracorporeal Membrane Oxygenation (ECMO), inhaled nitric oxide (INO), NNF Protocol are used according to the need of the patient. [18] This study aimed to see the spectrum of the disease and its outcome in Bangladesh using cheap, locally available NNF protocol.

Materials and Methods:

This is a retrospective study carried out in the non-invasive cardiac laboratory of a tertiary hospital from February 2014 to March 2019. Out of total 16245 cases of color Doppler echocardiography in this period, 494 cases were diagnosed as persistent pulmonary hypertension (PPHN) of newborn or persistent fetal circulation (PFC) and were included in the study. After diagnosis, all the outpatient cases were admitted to the neonatal intensive care unit (NICU) or pediatric cardiac ICU (PCICU) for specific management. Some of the cases were already in NICU for their existing illness.

Echocardiography parameters which were noted in each case were:

- Measurement of pulmonary artery systolic and diastolic pressure
- Right ventricular dimension and thickness.
- Left Ventricular volume. (D shape)
- Presence of Atrial Septal Defect (ASD) or Patent Ductus Arteriosus (PDA), Patent foramen ovale (PFO) and direction of shunt through them.

Those who had right to left shunt through ASD or PFO or PDA were considered as persistent fetal circulation. Patients who had pulmonary hypertension associated with significant congenital lesions like large ventricular Septal defects, Aorto pulmonary window, Atrioventricular septal defects or other complex lesions were excluded from the study. Birth history, antenatal history of mother like history of hypertension or diabetes, H/O TORCH infection, gestational age of the baby, birth weight, APGAR score, mode of delivery were recorded. Treatment protocols used for the patient is known as NNF protocol which was innovated by author in 2001 and in use since then for PPHN. Retinopathy of prematurity (ROP) screening of all preterm babies were ensured.

Outcome of treatment was assessed by repeat echocardiography after 72 hours. Follow up of all cases were ensured by echocardiography after one month of discharge.

NNF Protocol [18] which was accepted in the international conference on Paediatric and Neonatal Nasal High Flow in New Delhi, India on 13th-14th April 2019 , used for treating PPHN are as follows:

First line treatment:

1. High flow oxygen therapy for 72 hours. (Optiflow®)
2. Tablet Captopril/Enalapril (Pulmonary Vasodilatation)
3. Injection Frusemide (After load reduction)
4. Injection Digoxin (To treat RV Dysfunction)
5. Sedatives to reduce oxygen consumption.

Second line treatment:

1. Nasal continuous positive airway pressure (CPAP)
2. Tablet Sildenafil.
3. Hyperventilation to reduce carbon dioxide in blood and thus allowed vasodilatation.
4. Some of the patient required high frequency ventilation due to profound hypoxemia and acidosis along with alkalinization.
5. Some of the patients required inotropic support with injection Dopamine and/or Dobutamine in low dose/ Injection Milrinone.
6. In preterm patients with significant PDA without right to left shunt, Injection Indomethacin or Syrup Ibuprofen or Paracetamol are used to close the ductus arteriosus.
7. Tab Bosentan (Tracleer) are used in some cases as pulmonary vasodilator.
8. Injection Magnesium Sulphate ($MgSO_4$) in selective cases.
9. Injection Prostaglandin in selective cases.

Third line management:

Inhaled Nitric Oxide (INO) and extra corporeal membrane oxygenation (ECMO) are not available in Bangladesh. These were not advised for any patient in this seris.

First two lines of management were used as per severity of the condition.

Informed consent of parents was taken as per Helsinki declaration.

Ethical approval was taken from the hospital ethical committee of Lab Aid cardiac Hospital. Data were collected from computerized records of the department of pediatric non-invasive cardiac laboratory and pediatric cardiology. Numerical and categorical data were described as frequency and percentage.

As it was a single variant study, comparative analysis was not required.

Results

Table I: Demographic profile of the patient. N=494

1. Age at diagnosis	no	percentage
First week of life	398	80.56
Second week of life	74	14.94
Third week of life	22	4.45
2. Sex		
Male	298	60.32
Female	196	39.67
3. Gestational age		
Preterm	239	48.38
Term	57	31.78
4. Associated neonatal condition		
Respiratory distress syndrome	162	32.79
Meconium aspiration syndrome	55	11.13
Diaphragmatic hernia	2	0.40

Table I showed demographic profiles of cases. Most of the cases were (80.56%) diagnosed at 1st week of life, least (4.45%) diagnosed at 3rd week. Out of 494 cases, 298 (60.32%) were male and 196 (39.67%) were female. Most of the cases were preterm (48.38%), term were 31.78% and post term were 19.83%. Respiratory distress syndrome was present in 32.79% cases and meconium aspiration syndrome in 11.13 % cases. Only 0.40 % cases had diaphragmatic hernia.

Fig I: Mode of delivery **N= 494**

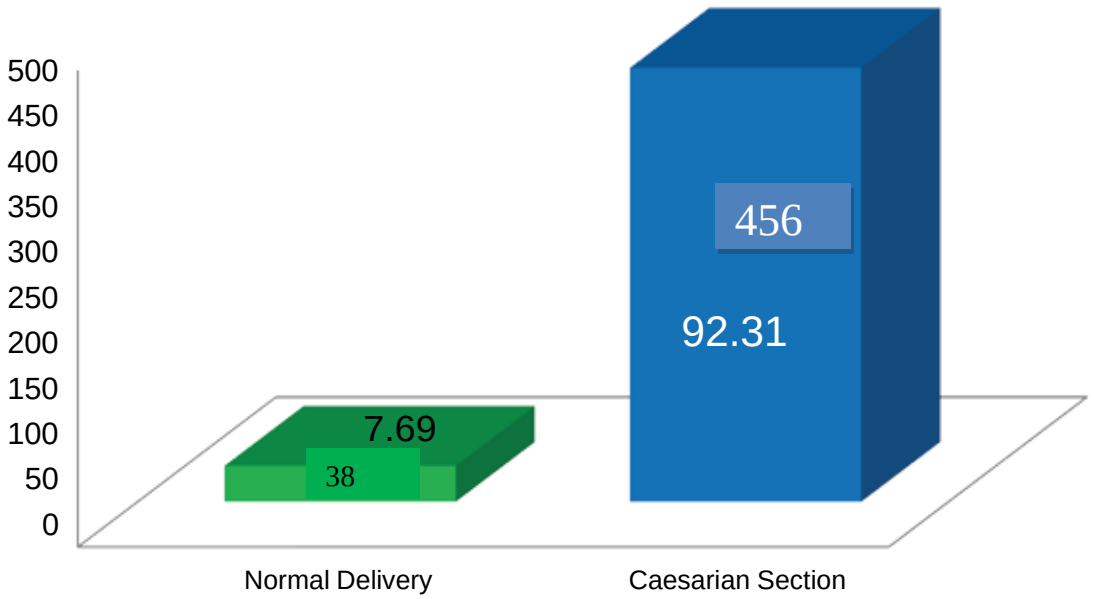

Fig II showed mode of delivery of study cases. Out of 494 cases, 92.31% had caesarean section and 7.69% had normal delivery.

Table II: Associated congenital heart diseases (CHD) in study cases. N=494

Disease	Number	Percentage
PPHN	122	24.69%
PFC+PDA+ASD	35	7.08%
PPHN+ ASD	92	18.62%
PPHN+ ASD+PDA	82	16.59%
PPHN+ PFO	29	5.87%
PPHN+PDA	46	9.32%
PPHN+PDA+ PFO	29	5.87%
PPHN+ASD+PDA+VSD	15	3.04%
PPHN+LPA/RPA STENOSIS	12	2.43%
PPHN+MVP	09	1.82%
PPHN+ CoA+ PDA	13	2.64%
Other Disease	10	2.03%

Table II showed associated CHD along with PPHN. One hundred twenty two (24.69%) cases had PPHN only. Atrial Septal Defect (ASD) was seen in 92 (18.62%) cases. Only patent ductus arteriosus (PDA) was found in 46 (9.32%) cases and Ventricular Septal Defect (VSD) along with ASD and PDA was found in 15 (3.03%) cases. Combination of ASD & PDA was found with PFC in 35(7.08%) cases and PPHN in 82(16.59%). Combination of left pulmonary artery stenosis (LPA) or right pulmonary artery stenosis (RPA) was seen in 12(2.43%) cases and Coarctation of Aorta (CoA) and PDA in 13(2.64%) cases. Mitral valve Prolapse (MVP) was seen in 9(1.82%) cases.

Table III: Distribution of Patients according to severity of pulmonary hypertension (Peak pulmonary artery pressure gradient measured from tricuspid regurgitation (TR) gradient). N=494

Severity of Pulmonary hypertension	Number	Percentage
Mild > 30-50 mm of Hg	65	13.16%
Moderate > 50-60 mm of Hg	115	23.28%
Severe > 60 mm of Hg	314	63.56%

Table III showed Severity of pulmonary hypertension classified by echocardiography from TR gradient. Sixty five (13.16%) cases had mild pulmonary hypertension, 115 (23.28%) cases had moderate pulmonary hypertension and 314 (63.56%) cases had severe pulmonary hypertension.

Table IV: Echocardiographic findings of Patients. N= 494 (Each Parameter).

Parameter	Echo Findings	Number	Percentage
Aortic Valve Velocity	Decreased< 0.8 M/sec	152	30.76%
	Increased>1.5 M/sec	00	00%
	Normal	342	69.23%
Right ventricular (RV) Volume (End diastolic)	Decreased< 70 ml/m^2	00	00%
	Increased> 100 ml/m^2	462	93.52%
	Normal	32	6.47%
Left ventricular (LV) Volume (End Diastolic)	Decreased< 60 ml/m^2	25	5.06%
	Increased> 110 ml/m^2	65	13.15%
	Normal	404	81.78%

Table IV showed echocardiographic findings of Patient with Pulmonary hypertension. RV volume was increased in 462 (93.52%) cases and LV volume was increased in 65 (13.15%) cases and decreased in 25(5.06%) cases.

Table V: Modalities of treatment offered to the patients (NNF Protocol). N= 494

Treatments modalities	Number	Percentage
High flow oxygen therapy (head box/ Nasal cannula/ Optiflow)	494	100%
Anti failure treatment	362	73.27%
Pulmonary vasodilator (Sildenafil)	294	59.51%
High frequency ventilation	32	6.44%
Extra corporeal membrane oxygenation(ECMO)	00	00%
Continuous positive airway pressure (CPAP)	150	30.36%
Inhaled Nitric Oxide (INO2)	00	00%
Inotropes (Dopamine, Dobutamine, Milrinone)	75	15.18%
Inj Indomethacin/ Ibuprofen/Paracetamol	24	4.85%
Correction of acidosis or alkalosis/ Hyperventilation	186	37.66%

Table V showed treatment protocol offered in NICU or PCICU: High flow oxygen therapy was offered to 494 (100%) cases, anti-failure with Frusemide, Captopril, and Digitalis were prescribed in 362 (73.27%) cases. Tablet Sildenafil was given to 294 (59.51%) cases. High frequency ventilation was given to 32 (6.44%) cases. CPAP applied in 150 (30.36%) cases. Dopamine and Dobutamine was used in 75 (15.18%) cases. Injection Indomethacin was used to close significant PDA in 24 (4.85%) cases. Corrections of acidosis or alkalosis were indicated in 186 (37.66%) cases. ECMO and inhaled nitric oxide (NO) was not advised.

Table VI: Outcome of treatment after 72 hours. N= 494

Variables	Number	Percentage
Cured	471	95.34%
Expired	05	1.01%
Develop IPAH	8	1.61%
Left with ASD, PDA& VSD	46	9.31%

Out of 494 cases, 471(95.34%) cases cured completely, 5 (1.01%) cases expired, 8 (1.61%) cases progressed to idiopathic pulmonary arterial hypertension, and 46 (9.31%) cases left with ASD, VSD, PDA in follow up.

Discussion:

Age at diagnosis is important, because earlier the initiation of treatment, better the outcome .[19]

In this study, 80.56% cases were diagnosed at first week of life (Table I). Males were more in number than females which correlates with other studies.[16] PFC can be primary or secondary to other factors. In our study preterm delivery was 48.38% and post term delivery was 19.83%. Respiratory distress syndrome was seen in 32.79% cases and Meconium aspiration syndrome in 11.13% cases and diaphragmatic hernia in 0.40% cases. Other studies correlate with these findings.[19-22] Any problems or situations can result in idiopathic PFC, including hypoxia, acidosis, hypothermia, hypoglycemia etc. Secondary PFC is most commonly seen in infants with lung diseases, the most common cause being meconium aspiration. The resulting hypoxia and acidosis cause pulmonary vasoconstriction and increased right-sided pressures. Other common causes are diaphragmatic hernia, hyaline membrane disease, sepsis syndrome and pulmonary thromboembolism. These babies usually present with cyanosis, respiratory distress, oxygen dependency, low cardiac output states, differential cyanosis etc.[19-23]

In our study caesarean delivery was observed in 92.21% cases which might have some influence on PPHN (Fig I). A study showed correlation between elective cesarean section and respiratory failure leading to ECMO .[20]

Chest X-ray may be normal or there may be oligemic lung fields, evidence of congenital diaphragmatic hernia etc. PPHN may be an isolated finding or may be associated with other congenital heart diseases which are not the cause of PPHN. In our series ASD, PDA were the commonest association (Table II).

Echocardiography is the most sensitive and specific investigation which helps to confirm the diagnosis of PPHN.[13] Parameters used in our settings are (Table 3 and Table 4):

a) Right ventricular dimension and thickness (RV volume 70-100ml/m^2)

b) Left ventricular dimension and output (LV volume 100-120ml/m^2)

c) Direction of shunt through holes in atrial, ventricular or ductus level

d) Calculation of pulmonary artery systolic and diastolic pressure from tricuspid and pulmonary regurgitation jet.

The patient who had decreased left ventricular size and aortic velocity had increased likelihood to need ECMO support, INO, high frequency ventilation etc.[24-29] Exposure to INO even for a brief period can sensitize the pulmonary circulation to rebound vasoconstriction during discontinuation of INO therapy. A significant drop in PaO_2 during withdrawal of INO can be avoided by weaning the dose gradually in steps from 20 ppm to the lowest dose possible (0.5 -1 ppm) for a period of time before its discontinuation[2]. Even in babies that show no response to INO, sudden discontinuation can precipitate pulmonary vasoconstriction and rapid deterioration. INO in combination with HFV results in better oxygenation in patients with severe PPHN[27].When INO therapy is used in non-ECMO centers; it should be continued during transport of the infant to ECMO center. Non-ECMO centers should establish treatment failure criteria for INO in collaboration with the nearest ECMO center so that transfer of an ill infant is not delayed while waiting for a response to INO.[29-30] Indications for treatment with ECMO include: (i) severe respiratory failure unresponsive to conventional treatment (FiO2=100%, hyperventilation, and drugs); (ii) birth weight over 2000 gram; (iii) less than seven days Of assisted ventilation;(iv) reversible pulmonary disease; (v) absence of congenital heart disease; and (vi) intraventricular hemorrhage or severe coagulopathy. Idiopathic PPHN patients have good survival with ECMO.[28]

In our study, only 25 cases had smaller left ventricular end diastolic volume (Table IV) and these cases required high frequency ventilation. Cases with right ventricular volume overload and high calculated pulmonary artery systolic pressure, few with right to left shunting through ASD or PDA were treated successfully with NNF Protocol composed of high flow nasal oxygen therapy along with administration of pulmonary vasodilator drugs (Table V). Oxygen is well known as a pulmonary vasodilator and should be started at 100%. Nevertheless, high oxygen concentrations should not be maintained for long periods, in order to prevent hyperoxia related injury. In some centers newer drugs are used for resistant PPHN which includes Cicletanine hydrochloride (Antihypertensive and diuretics), Recombinant Human Superoxide Dismutase, Vasoactive Intestinal Peptide (VIP) inhalation and oral pulmonary vasodilators such as Bosentan, Tadalafil etc. Off label use of Glucocorticoid was also reported.[28] Outcome of treatment at the end of therapy was assessed by doing echocardiography after 72 hours. A study on PPHN conducted in Combined Military Hospital ,Dhaka showed, out of 181 cases 173 cases (95.58%) cured completely, 02 patient(1.10%) expired and 3.31% patient developed IPAH where most of the patient received high flow oxygen by head box. In a study conducted in children's hospital of Philadelphia, out of 63 neonates 95% survived, 14% required ECMO, 52% required HFV, 67% INO and 35% required mechanical ventilation.[31] Most of the patient required expensive and invasive treatment modalities for ultimate cure. In our study we achieved high rate of cure without using any expensive and invasive treatment. PPHN was the commonest finding now and severe form of PFC was only seen in isolated occasion. Treatment protocol formulated (NNF protocol) and used for PPHN in our neonatal intensive care unit is cheap, affordable and effective which was proved from our low mortality rate.

Conclusion:

Respiratory failure and RV failure are the leading cause of death in newborn with PPHN. This condition is reversible but can cause very severe and unrelenting respiratory failure and death if remain untreated. Recent advancement in diagnostic procedure and treatment expanded the scope for survival in these patients. Some of our PFC cases died due to lack of INO & ECMO and from co-morbid conditions. As a resource constraint center, we are applying NNF protocol to treat our PPHN cases with good outcome. Availability of INO & ECMO will further improve our outcomes.

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Reference:

1. Walsh-Sukys MC, Tyson JE, Wright LL, et al. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. Pediatrics 2000;105:14–20. [PubMed]
2. Danhaive O, Margossian R, Geva T, et al. Pulmonary hypertension and right ventricular dysfunction in growth-restricted, extremely low birth weight neonates. J Perinatol 2005;25((7)):495–499. [PubMed]
3. Abman S H. Persistent pulmonary hypertension of Newborn: Pathophysiology and treatment. Pulmonary hypertension summer 2006 ; 5 (2) : 22 - 30.
4. Razzaq A, Quddusi A, I, Nizami N. Risk factors and mortality among newborns with persistent pulmonary hypertension. Pak J Med sci2013 sept-Oct; 29(5):1099-1104.
5. Heymann MA. Control of the pulmonary circulation in the perinatal period. Journal of Developmental Physiology 1984;6:281–90. [PubMed]
6. Cornfield DN, Reeves HL, Tolarova S. Oxygen Causes fetal pulmonary vasodilation through activation of a calcium dependent potassium channel. Proc Natl Acad Sci 1996;93:8089-8094.
7. ChrysalD'cunha MD. Koravangettshankaran MD.Persistent fetal circulation.Paediatr child health 2001; 6 (10):744-750.
8. Levin DL, Heymenn MA, Kiterman JA. Persistent pulmonary hypertension of newborn. J Pediatcs 1976; 89:626-633
9. Kinsella JP, Abman SH. Recent development in the pathophysiology and treatment of PPHN . J pediatr 1995;126:853 - 864.
10. Cassidy Delany , David N Comfield. Risk factors for persistent pulmonary hypertension in new born. Pulm Circ 2012 Jan-Mar ; 2(1) : 15-20. Doi: 10.4103/2045.8932.94818 .
11. Rasanen J, Wood DC, Debbs RH, Cohon J, Weiner S, Huhta JC. Reactivity of the human fetal pulmonary circulation to maternal hyper oxygenation increases during the second half of pregnancy. A randomized study. Circulation 1998; 97: 257-262.
12. Rudloph AM, Heymann MA, Lewis All. Physiology and pharmacology of the pulmonary circulation in the fetus and newborn. In :Hodson W, ed. Development of the lung. NY Marcel-Dekk1997:497-523.
13. Morin FC, Egan EA, Ferguson W, Lundgren CEG. Development of pulmonary vascular response to oxygen. AMJ Physiol 1988;254: 542- 546.
14. Crowley MR. Oxygen-induced pulmonary vasodilation is mediated by adenosine triphosphate in newborn lambs. Journal of Cardiovascular Pharmacology Jul 1997;30(1):102-9
15. Abman SH, Shanley PF Accurso FJ. Failure of postnatal adaptation of the pulmonary circulation after chronic intrauterine pulmonary hypertension in fetal lambs. J Clin Invest 1989;83:1849-1858.
16. Kumar VH, Hutchison AA, Lakshminrusimha S, Morin FC, 3rd, Wynn RJ, Ryan RM. Characteristics of pulmonary hypertension in preterm neonates. J Perinatol 2007;27:214–9. [PubMed]
17. Teitel DF, Iwamoto HS, Rudolph AM. Changes in the pulmonary circulation during birth-related events. Pediatr Res 1990;27:372–8. [PubMed]
18. International meeting on Paediatric and Neonatal Nasal High Flow ,April 2019 New Delhi-India; www.fphcare.com
19. Storme L, Aubry E, Rakza T, Houeijeh A, Debarge V, Tourneux P, et al. Pathophysiology of persistent pulmonary hypertension of the newborn: impact of the perinatal environment. Arch Cardiovasc Dis. 2013; 106:169–77. [PubMed]
20. Martin Kaszler, Mary Terse Carbone, Cynthia Cox, Robert E Schumacher, Pediatrics 1992; 89(4) : 670-672.
21. Van Meurs KP, Wright LL, Ehrenkranz RA, Lemons JA, Ball MB, Poole WK, et al. Inhaled nitric oxide for premature infants with severe respiratory failure. N Engl J Med. 2005;353:13–22. [PubMed]
22. N N Fatema. Persistent pulmonary hypertension of newborn : Analysis 181 cases over one year. Cardiovascular journal 2018 ; 11(1): 17-22.
23. Frostell C, Fratacci MD, Wain JC, et al. Inhaled nitric oxide. A selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. Circulation. 1991 Jun;83((6)):2038–2047. [PubMed]

24. N N Fatema M R Khan , M. S Kabir. Persistent pulmonary hypertension of newborn; analysis of 93 cases over one year. Bangladesh Journal of Cardiology 2012 March ;4 (1) : 25-29.

25. Hintz SR, Suttner DM, Sheehan AM, et al. Decreased use of neonatal extracorporeal membrane oxygenation (ECMO): how new treatment modalities have affected ECMO utilization. Pediatrics. 2000;106((6)):1339–1343. [PubMed]

26. Baquero H, Soliz A, Neira F, et al. Oral sildenafil in infants with persistent pulmonary hypertension of the newborn: a pilot randomized blinded study. Pediatrics. 2006;117((4)):1077–1083. [PubMed]

27. Clark RH, Kueser TJ, Walker MW, Southgate WM, Huckaby JL, Perez JA, et al. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. Clinical Inhaled Nitric Oxide Research Group. N Engl J Med 2000;342:469–74. [PubMed]

28. Janet Flicker. Nitric oxide may reduce need for extracorporeal membrane oxygenation. The Lancet 1996; 347(9012): 1397.

29. Roberts JD, Jr, Fineman JR, Morin FC, 3rd, Shaul PW, Rimar S, Schreiber MD, et al. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. The Inhaled Nitric Oxide Study Group. N Engl J Med. 1997;336:605–10. [PubMed]

30. Konduri GG, Kim UO. Advances in the diagnosis and management of persistent pulmonary hypertension of the newborn. Pediatr Clin North Am 2009;56:579–600. [PMC free article] [PubMed]

31. Peterson AL, Deatman S, Frommelt MA, Mussatto K, Frommelt PC. Correction of echocardiographic marker and therapy in persistent pulmonary hypertension of newborn.Pediatr Cardiol 2009; 30 (2); 160-5.