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Risk Factors and Clinical Outcome of Neonate with Persistent Pulmonary Hypertension

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Abstract

Background: Persistent pulmonary hypertension (PPHN) is the persistence of the high pulmonary arterial pressure after birth which is a characteristic of the fetal circulation. PPHN is associated with substantial infant mortality and morbidity.

Objective of the Study: To identify risk factors for PPHN in this study and to assess its outcome.

Methodology: This prospective Observational study was conducted from April 2019 to March 2020 in the Department of Neonatology and Pediatric Cardiology, BSMMU. All preterm, term and post-term newborns with perinatal risks factors in developing respiratory distress and clinically highly suspicious to PPHN in NICU at BSMMU were taken as the study population.

Neonates having respiratory distress, a difference >5% between preductal and postductal oxygen saturation and profound hypoxemia (PaO2 < 50 mm of Hg) on their arterial blood gas (ABG) was selected for echocardiography. The diagnosis of PPHN was confirmed by 2D color echocardiography, which was performed by designated pediatric cardiologist.

All data were analyzed by statistical package for social sciences (SPSS) version 21. Quantitative variables were compared by unpaired t-test and categorical variables by Chi-square test. p-value < 0.05 was considered as significant. To determine independent risk factors of outcome, binary logistic regression analysis was performed with the variables which were found significant by bivariate analysis. Odds ratio and 95% confidence intervals were calculated.

Result: Out of 75 neonates, 4 neonates were excluded and finally 71 patients were included for the study. Among them, 30 neonates were diagnosed as PPHN and classified as cases and remaining population were classified as control group. In univariate analysis, meconium aspiration (p < 0.002), Respiratory distress syndrome (p < 0.004), Perinatal asphyxia (p = 0.022) sepsis (p = 0.003) maternal diabetes mellitus (p = 0.006) maternal HTN (p = 0.010) were significantly associated with PPHN in neonates. Combining these variables in a logistic regression analysis showed that only four risk factors were significantly associated with PPHN. These were: Meconium aspiration (odds ratio = 11.01; 95% CI = 1.647 - 73.610, p = 0.013) were 11.010 times more likely to had PPHN than other group of PPHN. Similarly, neonates with respiratory distress syndrome (odds ratio = 19.84; 95% CI = 2.957 - 133.185, p = 0.002) were 19.844times, perinatal asphyxia (odds ratio = 7.25; 95% CI = 1.029 - 50.920346, p = 0.047) 7.238 times, and maternal DM (odds ratio = 80.37; 95% CI = 1.620 - 39.866, p = 0.011) were 8.037 times more likely to had PPHN than other group of PPHN.

Conclusion: Meconium aspiration, respiratory distress syndrome, birth asphyxia and maternal factor like diabetes mellitus are the major risk factors for PPHN in our study. Outcome in this study was found, about 83% of the neonates with PPHN was improved out of which 73% at first month and 10% at three months follow up.

Keywords: *Persistent Pulmonary Hypertension of Newborn (PPHN); Pulmonary Vascular Resistance (PVR); Persistent Fetal Circulation (PFC)*

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is a condition characterized by marked pulmonary hypertension resulting from elevated pulmonary vascular resistance (PVR) and altered pulmonary vasoreactivity, leading to right to left extrapulmonary shunting of blood across the foramen ovale and the ductus arteriosus, if patent [15]. Previously, this disorder was referred to as persistent fetal circulation (PFC) and is often secondary to an unsuccessful pulmonary transition at birth [28].

Unless identify and treated promptly, PPHN is a serious neonatal illness and associated with a significant morbidity and mortality that can be as high as 10 - 20% [25]. It results from failure of the neonate to make a postnatal transition from a high resistance fetal pulmonary circulatory state to a low resistance pulmonary circulation. This increased pulmonary vascular resistance and decreased pulmonary blood flow prevents adequate gas exchange in the lungs resulting in severe respiratory distress and hypoxemia in the neonate [26]. Although Persistent pulmonary hypertension is less common, but more significant cause of respiratory distress in newborns than others like transient tachypnea of newborn, respiratory distress syndrome and etc [30]. Overall an incidence of PPHN is 1 - 2 per 1000 live-births have been reported, and mortality rate ranging from 12 - 29% have been reported [9,35]. In Bangladesh, previous study reported the incidence of PPHN nearly 1.4% (181/13245 cases) with a mortality rate of 1.10% at Combined Military Hospital, Dhaka [13]. It is also reported a mortality rate of 25% at Al-Minya University Hospital, Egypt and 11% (range 4% - 33%) reported overall mortality rate in multicenter in USA [26,41].

In many multicenter studies which have found various risk factors associated with PPHN [10,33]. In Bangladesh, Meconium aspiration syndrome, birth asphyxia or ischemia, Respiratory distress syndrome, neonatal septicemia and diaphragmatic hernia were the most encounter risk factor for PPHN in Combined Military Hospital, Dhaka [13]. In additional, Post-term, cesarean section, maternal hypertension and diabetes mellitus were the risk factor for PPHN in Al-Minya University Hospital, Egypt [26]. Meconium aspiration syndrome (MAS) in newborns is the most common cause of PPHN causing acute respiratory failure and a mortality upto 10% [45]. Meconium mainly causes chemical pneumonitis and surfactant inactivation, resulting in mismatch of ventilation-perfusion. This hypoxemic state along with hypercarbia triggers the release of various cytokines (IL-1β, IL-8, TNF-α) and vasoconstrictors including endothelin and thromboxane causing pulmonary vasoconstriction and PPHN [37].

Persistent pulmonary hypertension (PPHN) complicates the course of approximately 10% of infants with respiratory failure and is a source of considerable mortality and morbidity in this population [34]. The sick infants may require mechanical ventilation, surfactant replacement, pulmonary vasodilators and hemodynamic support by volume expansion and/or inotropes (dopamine, dobutamine, and adrenaline). ECMO is the ultimate treatment option for those who do not respond to these therapies [21].

The newborn with PPHN is typically a term or late-preterm infant who does not have associated congenital anomalies and presents within hours of birth with severe respiratory failure that requires intubation and mechanical ventilation. Mechanical ventilation improves oxygenation. It reduces ventilation- perfusion (V/Q) mismatch by providing alveolar recruitment and adequate lung expansion [8].

Infants with RDS and MAS improve significantly from a combination of HFV and iNO therapy [19]. A combination of HFV along with iNO and surfactant replacement have shown to reduce the demand for ECMO [44]. When untreated, PPHN is frequently fatal, despite the introduction of treatments and advanced modes of mechanical ventilation, 10% to 20% of affected infants still die. In addition, infants who survive PPHN face increased risks for serious and long-term sequalae as a result of both the condition's hypoxemia and the aggressive treatments that PPHN often requires [16].

Materials and Methods

This prospective observational study will be conducted in the Department of Neonatology, BSMMU, Dhaka city after approval by Institutional Review Board (IRB) of BSMMU over a one year period. The study includes all admitted neonates presented with respiratory distress who have clinically highly suspicious to PPHN in NICU, BSMMU, Dhaka.

After taking informed written consent from the parents/guardians before enrollment in the subject field, meticulous history of the newborn from the attendance/mother and physical assessment will be done and required information will be recorded in a data collection form and assurance about confidentiality will be given.

Newborns gestational age will be calculated on the basis of New Ballard scoring. Anthropometry like weight, length, and head circumference will be measured at birth. The newborn infants weight will be taken without clothing soon after birth on an electronic scale with a precision of 10 gm [Model 914, SALTER]. The length will be measured by infantometer and OFC will be measured by measuring tape.

Newborns gestational age, gender, birth weight, Apgar score, Mode of delivery (vaginal/caesarean), Fetal growth at birth (SGA, AGA, LGA), Sex (Male/Female), Age at onset, cord stained with meconium/MAS, RDS, sepsis/pneumonia, IDM, respiratory support will be recorded.

All relevant laboratory investigations, including pulse oxymetry, septic work up, X-ray chest, ABG will be done. Neonates having respiratory distress, a difference > 5% between preductal and postductal oxygen saturation and profound hypoxemia (PaO_2 < 50 mm of Hg) on their arterial blood gas (ABG) will be selected for echocardiography. The diagnosis of PPHN will be confirmed by 2D color echocardiography, which will be performed by designated pediatric cardiologist. Echocardiography (Model no.GE Vivid 7) in neonates with stable vitals or those with need of minimum oxygen support will be performed in pediatric cardiology department and in those with vitals unstable portable echocardiography (GE Vivid i) will be done. Among those baby who will undergo echocardiography will diagnosed as PPHN if they will meet the following criteria:

1. Right to left or bidirectional hemodynamic shunting at the ductus arteriosus or at patent foramen ovale,
2. Tricuspid regurgitation jet pressure of > 40 mm of Hg.

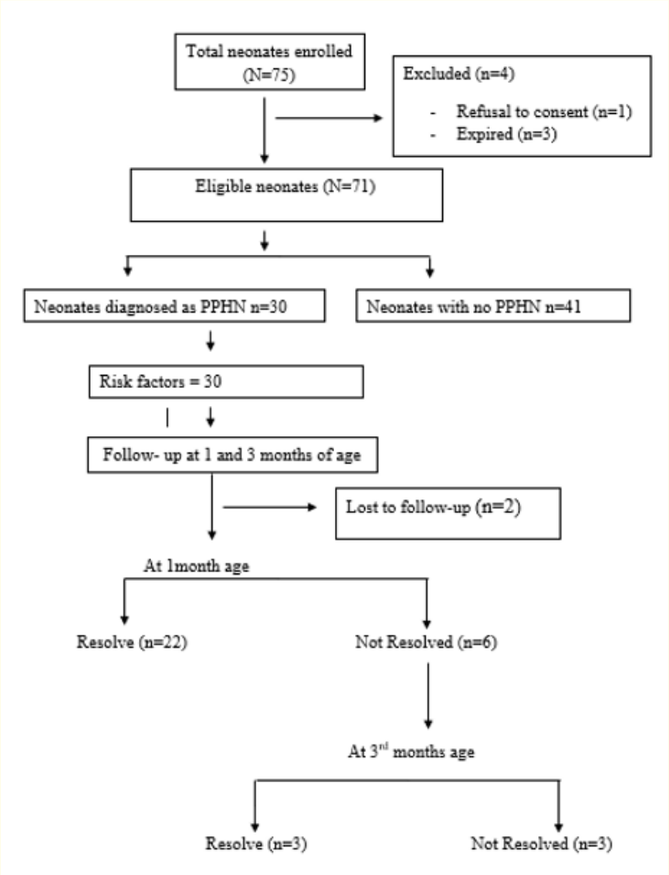
Once neonates will diagnosed as PPHN, they will be categorized into:

- Mild: 25 - 40 mm of Hg.
- Moderate: 40 - 60 mm of Hg.
- Severe: > 60 mm of Hg [1].

Follow-up of these neonate will be done at 1st and 3rd months of age to see the outcome of PPHN as resolved and not resolved by performing echocardiography by a Paediatric Cardiologist.

Selection of control group

Control group included all neonates with respiratory distress who are clinically suspicious for PPHN went for echocardiography where they did not meet the diagnostic criteria for PPHN.



Flow Chart: *Flow chart of at risk newborn enrollment and outcome.*

Data analysis

Data were analyzed using the statistical package for social sciences (SPSS) version 20. Quantitative data were expressed as mean± SD and categorical data were presented as proportion. All quantitative variables (between the groups of PPHN and non PPHN) were compared by unpaired t-test; categorical variables were compared by Chi-square test. P value < 0.05 was considered as significant. To determine independent predictors of outcome multivariate logistic regression analysis was performed, using variables found significant on univariate analysis. Odds ratios and 95% confidence intervals were calculated.

Results

During the study period, data were obtained from 75 neonates out of which 34 neonates were diagnosed as persistent pulmonary hypertension of newborn (PPHN) and classified as cases, and 41 neonates were no PPHN classified as control group. Among these 34 neonates diagnosed case PPHN, 2 neonate was died due to congenital diaphragmatic hernia and one due perinatal asphyxia so excluded. Finally, 71 neonates were analyzed in the study.

Out of 30 cases, 22 (73.3%) resolved, 6 (20%) not resolved and 2 follow up were lost due to COVID 19 pandemic at 1st month of age. Remaining 6 cases follow up done at 3rd months of age and found 3 (50%) resolved and 3 (50%) not resolved.

Characteristic	Finding Group A	Finding Group B
Gestational age (weeks) mean ± SD	35.27 ± 3.54	35.10 ± 2.97
Birth weight (g), mean ± SD	1713.53 ± 680.40	1993.29 ± 923.29
Sex		
Male	18 (60)	25 (61)
Female	12 (40)	16 (39)
Admission status		
Inborn	20 (66.7)	37 (90.2)
Outborn	10 (33.3)	04 (9.8)
Mode of delivery		
LUCS	26 (86.7)	36 (87.8)
NVD	4 (13.4)	05 (12.5)
Fetal growth at birth		
SGA	6 (20)	16 (39)
AGA	23 (76.77)	24 (58.4)
LGA	1 (3.3)	01 (2.4)
Respiratory distress	24 (80)	33 (80.5)
Birth asphyxia	9 (30)	03 (7.3)
Hypoglycemia	4 (13.3)	01 (2.4)
Hypocalcemia	7 (23.3)	05 (12.2)
Sepsis	19 (63.3)	10 (24.4)

Table 1: *Demographic and clinical characteristics of newborns with PPHN (Group A, n = 30) and without PPHN (Group B, n = 41).*

Characteristic	Finding Group A	Finding Group B	P-value
Gestational age (weeks) mean ± SD	35.27 ± 3.54	35.10 ± 2.97	0.828ns
Birth weight (g), mean ± SD	1713.53 ± 680.40	1993.29 ± 923.29	0.15ns
Sex			
Male	18 (60)	25 (61)	1.000ns
Female	12 (40)	16 (39)	
Admission status			
Inborn	20 (66.7)	37 (90.2)	0.018s
Outborn	10 (33.3)	04 (9.2)	
Mode of delivery	26 (86.7)	36 (87.8)	1.000ns
LUCS NVD	4 (13.4)	05 (12.5)	
Fetal growth at birth			
SGA	6 (20)	16 (39)	0.231ns
AGA	23 (76.77)	24 (58.4)	
LGA	1 (3.3)	01 (2.4)	
Respiratory distress	24 (80)	03 (7.3)	1.000ns
Hypoglycemia	4 (13.3)	01 (2.4)	0.155ns
Hypocalcemia	7 (23.3)	05 (12.2)	0.337ns
Sepsis	19 (63.3)	10 (24.4)	0.019s

Table 2: *Comparison of perinatal parameter and clinical finding between PPHN (Group A, n = 30) and without PPHN (Group B, n = 41).*

Parameter	Group A	Group B	P- value
Meconium aspiration			
Yes	13	4	0.002[s]
No	17	37	
Perinatal asphyxia			
Yes	9	3	0.022[s]
No	21	29	
Respiratory distress syndrome			
Yes	12	4	0.004[s]
No	18	26	
Transient tachypnea of newborn			
Yes	7	6	0.371[ns]
No	23	35	
Pneumonia			
Yes	6	2	0.063[ns]
No	24	39	
Sepsis			
Yes	19	11	0.003[s]
No	11	30	
Maternal DM			
Yes	17	9	0.006[s]
No	13	32	
Maternal HTN			
Yes	15	8	0.010[s]
No	15	33	

Table 3: *Comparing the parameter (cause) between PPHN (Group A, n = 30) and without PPHN (Group B, n = 41).*

Risk factors	Odds ratio	95% CI		P-value
		Lower limit	Upper limit	
Meconium aspiration	11.01	1.647	73.61	0.013[s]
Perinatal asphyxia	7.238	0.029	50.92	0.047[s]
Respiratory distress Syndrome	19.844	2.957	133.185	0.002[s]
Sepsis	2.477	0.557	11.028	0.234[ns]
Maternal DM	8.037	1.62	39.866	0.011[s]
Maternal HTN	0.497	0.582	10.724	0.218[ns]

Table 4: *Logistic regression analysis of neonatal and maternal factors associated with PPHN.*

Therapy	Number 30	Percentage (%)
Oxygen theray	30	100
Anti-failure treatment	10	33.3
Inotrope	4	13.3
Dopamine, Dobutamine	3	10
Pulmonary vasodilator	9	30
Sildenafil Milirone	1	3.3
Continuous positive airway pressure	9	30
Mechanical ventilator	5	16.7
High frequency ventilator	1	3.3

Table 5: *Treatment modality offered to the newborn with PPHN.*

	At 1st month of age (n = 30)	At 3rd month of age (n = 6)
Outcome	**Findings**	**Findings**
Resolved	22 (73.3)	3 (50)
Not resolved	6 (20)	3 (50)
Lost to follow up	2 (6.7)	0

Table 6: *Outcome of the neonates with PPHN at 1st month and 3rd month of age.*

Discussion

Persistence of pulmonary hypertension leading to respiratory failure in the neonate has been recognized for 40 years since its original description by Gersony in 1969. Since then, a number of risk factors have been attributed for this serious cause of respiratory failure in newborn infants [15]. The mortality rate of infants with PPHN was estimated to be around 10 - 20% even with the use of high-frequency ventilation, surfactant, iNO and ECMO but is much higher when these therapies are not available [36].

In this study, out of 71 total neonates, 30 neonates (18 male and 12 female) were diagnosed as having persistent pulmonary hypertension which was prospectively evaluated. The diagnosis of our cases depends on high clinical suspicion, echocardiography, and pulse oximetry and blood gas analysis.

This study showed most common cause for PPHN was mainly Meconium aspiration syndrome (43.3%) and infection/sepsis (63%). In different study, like in California, USA by Dr. Steurer also reported the similar findings [26,35]. Sepsis secondary to common neonatal bacteria can be complicated which lead to development of PPHN [32]. Bacterial endotoxin causes pulmonary hypertension from several mechanisms, including the release of thromboxane, endothelin and several cytokines [47]. Meconium cause mechanical obstruction to the airway, resulting in air trapping, hyperinflation, and increased risk for pneumothorax. Meconium components also inactivate surfactant, trigger an inflammatory response with the release of cytokines, and increase the production of the vasoconstrictors endothelin and thromboxane [11,37].

In this study, preterm neonates are at greater risk of developing PPHN, occurred as a complication of respiratory distress syndrome (RDS) 40% delivered by C-section. Previous studies by Mohsen., *et al*. 2013 showed that 18.7% RDS complicate with PPHN [26]. Deficient synthesis or release of surfactant, together with small respiratory units and a compliant chest wall, produces atelectasis and eventually results into hypoxia in RDS. Decreased lung compliance, small tidal volumes, increased physiological dead space and insufficient alveolar ventilation eventually result in hypercapnia. The combination of hypercapnia, hypoxia and acidosis produces pulmonary arterial vasoconstriction with increased right-to-left shunting through the foramen ovale and ductus arteriosus and within the lung itself and these are the reasons for PPHN in preterm with RDS (Walther., *et al*. 1992).

In this study, along with infection and prematurity, birth asphyxia account for (30%). In contract to previous study by author Mohsen, birth asphyxia was found 43.7% which is comparatively lower in our NICU [26].

Maternal hypertension and uncontrolled diabetes mellitus were also associated with maternal risk factor in our neonates. Insulin resistance are known to induce endothelial dysfunction and inflammation and might therefore have a direct impact on fetal lung development leading to hyaline membrane disease, hypoglycemia, hypocalcemia, macrosomia and fetal distress (Anderson., *et al*. 2005).

The primary goal of PPHN therapy is selective pulmonary vasodilation. Intravenous dilators, such as prostacyclin and tolazoline, may produce nonselective effects on the systemic circulation, leading to hypotension. In contrast, iNO is well suited for the treatment of PPHN and significantly reduce the need for ECMO. It is a rapid and potent vasodilator, and because NO is a small gas molecule, it can be delivered as inhalation therapy to airspaces approximating the pulmonary vascular bed (Clark., *et al*. 2000). Due to unavailability of iNO and ECMO, we used other modalities as pulmonary vasodilator drugs like oral sildenafil. In our study, nine neonate cases were treated with oral sildenafil, most of the neonates were moderate to severe PPHN. One neonate (outborn) were treated outside with oral milrinone in case of severe PPHN. In our NICU, we mainly used to treat with oral sildenafil and improvement with this drug is satisfactory.

In the previous study, author stated that oral sildenafil was administered easily and was tolerated as well as placebo and improved oxygenation index in infants with severe PPHN, which suggests that oral sildenafil, may be effective in the treatment of PPHN and underscores the need for a large, controlled trial [6]. Khorana., *et al*. 2011 in a retrospective study concluded that results confirm that sildenafil may be a useful adjuvant therapy for term neonates with pulmonary hypertension in centers lacking iNO and ECMO.

Outcome of neonates after follow-up at 1st month of age and 3rd months of age in this study showed, out of 30 neonates with cases PPHN, 22 (73.3) were improved (resolved) and 6 (20%) were not resolved and remaining 2 (6.7%) follow up was lost.

At 3rd month follow-up, remaining neonates showed 3 (50%) resolved and 3 (50%) not resolved which were under pediatric cardiology department under treatment.

Conclusion

Meconium aspiration, respiratory distress syndrome, sepsis and birth asphyxia are the major risk factors for PPHN in our study. Outcome in this study was found about 83% of the neonates with PPHN was improved out of which 73% at first month and 10% at three months follow up.

Limitation of the Study:

- Single center analysis.
- Sample size was small.

Recommendation

Further study with large sample size is recommended to validate the present study.

Conflict of Interest

Nil.

Source of Funding

Nil.

Author Contributions

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All authors contributed to the final version of the manuscript.

All authors read and approved the final manuscript.

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Bibliography

1. Ahmed T., *et al*. "Prevalence and outcome of pulmonary arterial hypertension in newborns with perinatal asphyxia". *Journal of Clinical Neonatology* 7.2 (2018): 63.
2. Abassi Z., *et al*. "Implications of the natriuretic peptide system in the pathogenesis of heart failure: diagnostic and therapeutic importance". *Pharmacology and Therapeutics* 102.3 (2004): 223-241.
3. Agrawal A and Agrawal R. "Persistent pulmonary hypertension of the newborn: Recent advances in the management". *International Journal of Clinical Pediatrics* 2.1 (2013): 1-1.
4. Alano MA., *et al*. "Analysis of nonsteroidal anti-inflammatory drugs in meconium and its relation to persistent pulmonary hypertension of the newborn". *Pediatrics* 107.3 (2001): 519-523.
5. Abman SH. "Abnormal vasoreactivity in the pathophysiology of persistent pulmonary hypertension of the newborn". *Pediatrics In Review* 20.11 (1999): e103-109.
6. Baquero H., *et al*. "Oral sildenafil in infants with persistent pulmonary hypertension of the newborn: a pilot randomized blinded study". *Pediatrics* 117.4 (2006): 1077-1083.
7. Bhat R and Vidyasagar D. "Delivery room management of meconium-stained infant". *Clinics in Perinatology* 39.4 (2012): 817-831.
8. Carlo WA., *et al*. "High-frequency jet ventilation in neonatal pulmonary hypertension". *American Journal of Diseases of Children* 143.2 (1989): 233-238.

9. Choudhary M., *et al*. "To study prevalence of persistent pulmonary hypertension in newborn with meconium aspiration syndrome in western Rajasthan, India: a prospective observational study". *The Journal of Maternal-Fetal and Neonatal Medicine* 29.2 (2016): 324-327.

10. Delaney C and Cornfield DN. "Risk factors for persistent pulmonary hypertension of the newborn". *Pulmonary Circulation* 2.1 (2012): 15-20.

11. Dargaville PA., *et al*. "Surfactant and surfactant inhibitors in meconium aspiration syndrome". *The Journal of Pediatrics* 138 (2001): 113-115.

12. Farrow KN and Steinhorn RH. "Phosphodiesterases: emerging therapeutic targets for neonatal pulmonary hypertension". *Phosphodiesterases as Drug Targets* (2011): 251-277.

13. Fraser WD., *et al*. "Amnioinfusion for the prevention of the meconium aspiration syndrome". *New England Journal of Medicine* 353.9 (2005): 909-917.

14. Fatema NN. "Persistent Pulmonary Hypertension of the Newborn: Analysis of 181 cases over one Year". *Cardiovascular Journal* 11.1 (2018): 17-22.

15. Gersony WM. " PFC" syndrome (persistence of the fetal circulation)". *Circulation* III (1969): 87-94.

16. Grigoriadis S., *et al*. "Prenatal exposure to antidepressants and persistent pulmonary hypertension of the newborn: systematic review and meta-analysis". *British Medical Journal* (2014): 348.

17. Gomella TL., *et al*. "Persistent Pulmonary Hypertension of Newborn". 7th edition. New Delhi: McGraw Hill Education (India) Pvt. Ltd (2013).

18. Hernández-Díaz S., *et al*. "Risk factors for persistent pulmonary hypertension of the newborn". *Pediatrics* 120.2 (2007): e272-282.

19. Kattwinkel J., *et al*. "Part 15: neonatal resuscitation: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care". *Circulation* 122.18-3 (2010): S909-919.

20. Khorana M., *et al*. "Outcome of oral sildenafil therapy on persistent pulmonary hypertension of the newborn at Queen Sirikit National Institute of Child Health". *Journal of the Medical Association of Thailand* 94.3 (2011): S64-73.

21. Kinsella JP and Abman SH. "Clinical approach to inhaled nitric oxide therapy in newborn with hypoxemia". *The Journal of Pediatrics* 136.6 (2000): 717-726.

22. Kinsella JP., *et al*. "Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn". *The Journal of Pediatrics* 131.1 (1997): 55-62.

23. Konduri GG. "New approaches for persistent pulmonary hypertension of newborn". *Clinics in Perinatology* 31.3 (2004): 591-611.

24. Konduri GG and Kim UO. "Advances in the diagnosis and management of persistent pulmonary hypertension of the newborn". *Pediatric Clinics* 56.3 (2009): 579-600.

25. Lakshminrusimha S and Steinhorn RH. "Pulmonary vascular biology during neonatal transition". *Clinics in Perinatology* 26.3 (1999): 601-619.

26. Lazar DA., *et al*. "The use of ECMO for persistent pulmonary hypertension of the newborn: a decade of experience". *Journal of Surgical Research* 177.2 (2012): 263-267.

27. Lewandowski K. "Extracorporeal membrane oxygenation for severe acute respiratory failure". *Critical Care* 4.3 (2000): 1-3.

28. Mhanna MJ and Puthiyachirakkal MA. "Pathophysiology, management, and outcome of persistent pulmonary hypertension of the newborn: a clinical review". *Frontiers in Pediatrics* 1 (2013): 23.

29. Mohsen AH and Amin AS. "Risk factors and outcomes of persistent pulmonary hypertension of the newborn in neonatal intensive care unit of Al-Minya University Hospital in Egypt". *Journal of Clinical Neonatology* 2.2 (2013): 78.

30. Mcmahon TJ., *et al*. "Analysis of responses to serotonin in the pulmonary vascular bed of the cat". *Journal of Applied Physiology* 75.1 (1993): 93-102.

31. Nair J and Lakshminrusimha S. "Update on PPHN: mechanisms and treatment". *In Seminars in Perinatology* 38.2 (2014): 78-91.

32. Navarrete CT., *et al*. "The role of endothelin converting enzyme inhibition during group B streptococcus-induced pulmonary hypertension in newborn piglets". *Pediatric Research* 54 (2003): 387-392.

33. Rao S., *et al*. "Current and future therapeutic options for persistent pulmonary hypertension in the newborn". *Expert Review of Cardiovascular Therapy* 8.6 (2010): 845-862.

34. Razzaq A., *et al*. "Risk factors and mortality among newborns with persistent pulmonary hypertension". *Pakistan Journal of Medical Sciences* 29.5 (2013): 1099.

35. Rasanen J., *et al*. "Role of the pulmonary circulation in the distribution of human fetal cardiac output during the second half of pregnancy". *Circulation* 94.5 (1996): 1068-1073.

36. Rocha G., *et al*. "Persistent pulmonary hypertension of non cardiac cause in a neonatal intensive care unit". *Pulmonary Medicine* (2012): 818971.

37. Simonneau G., *et al*. "Updated clinical classification of pulmonary hypertension". *Journal of the American College of Cardiology* 54.1 (2009): S43-54.

38. Rao S., *et al*. "Current and future therapeutic options for persistent pulmonary hypertension in the newborn". *Expert Review of Cardiovascular Therapy* 8.6 (2010): 845-8462.

39. Simonneau G., *et al*. "Updated clinical classification of pulmonary hypertension". *Journal of the American College of Cardiology* 54.1 (2009): S43-54.

40. Steinhorn RH. "Neonatal pulmonary hypertension. Pediatric critical care medicine: a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies 11.2 (2010): S79.

41. Steurer MA., *et al*. "Persistent pulmonary hypertension of the newborn in late preterm and term infants in California". *Pediatrics* 139.1 (2017).

42. Shaltout F., *et al*. "Magnesium sulphate versus sildenafil in the treatment of persistent pulmonary hypertension of the newborn". *International Journal of Clinical Pediatrics* 1.1 (2012): 19-24.

43. Soukka H., *et al*. "Endothelin-1, atrial natriuretic peptide and pathophysiology of pulmonary hypertension in porcine meconium aspiration". *Acta Paediatrica* 87.4 (1998): 424-428.

44. Steinhorn RH and Farrow KN. "Pulmonary hypertension in the neonate". *Neo Reviews* 8.1 (2007): e14-e21.

45. Teixeira-Mendonça C and Henriques-Coelho T. "Pathophysiology of pulmonary hypertension in newborns: Therapeutic indications". *Revista Portuguesa de Cardiologia* 32.12 (2013): 1005-1012.

46. Vain NE., *et al*. "Oropharyngeal and nasopharyngeal suctioning of meconium-stained neonates before delivery of their shoulders: multicentre, randomised controlled trial". *The Lancet* 364.9343 (2004): 597-602.

47. Verma B., *et al*. "Persistent pulmonary hypertension among neonates with sepsis". *Indian Journal of Pediatrics* 73 (2006): 250-251.

48. Walsh-Sukys MC., *et al*. "Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes". *Pediatric* 105.1 (2000): 14-20.

49. Winovitch KC., *et al*. "Persistent pulmonary hypertension of the newborn following elective cesarean delivery at term". *The Journal of Maternal-Fetal and Neonatal Medicine* 24.11 (2011): 1398-1402.

50. Wiswell TE. "Delivery room management of the meconium-stained newborn". *Journal of Perinatology* 28.3 (2008): S19-26.

51. Wang YF., *et al*. "Effects of inhaled nitric oxide in neonatal hypoxemic respiratory failure from a multicenter controlled trial". *Chinese Medical Journal* 124.08 (2011): 1156-1163.

52. Yoder BA., *et al*. "Changing obstetric practices associated with decreasing incidence of meconium aspiration syndrome". *Obstetrics and Gynecology* 99.5 (2002): 731-739.

Volume 11 Issue 7 July 2022