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Original Article

Characteristics of Newborn with Persistent Pulmonary Hypertension (PPHN) Admitted In Neonatal Intensive Care Unit in a Tertiary Care Hospital

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ABSTRACT

Objectives: To find the frequency, aetiologies, treatment options and outcomes in neonates with persistent pulmonary hypertension of the new-born and to identify risk factors associated with severe pulmonary hypertension.
Study Design: Prospective longitudinal study.
Place and Duration of Study: Neonatal Intensive Care Unit, Fatima Memorial Hospital, Lahore Pakistan, from Apr to Oct 2020.
Methodology: All neonates admitted to the Neonatal Unit with signs and symptoms suggestive of PPHN and confirmed on echocardiography were included in the study. Multiple maternal and neonatal risk factors leading to PPHN were identified.
Results: A total of 70 neonates with persistent pulmonary hypertension were identified. The all-cause mortality rate was 18.6% (13 of 70). Pneumonia was the primary cause of pulmonary hypertension (64.3%). Pneumonia was the primary cause of pulmonary hypertension (64.3%). Out of 72, 46(65.7%) were male and 24(34.3%) were female. The mean gestational age was 35.38±3.39 weeks. On binary logistic regression analysis, severe pulmonary hypertension showed a significant association with maternal septic risk factors (OR 0.26, p=0.03, emergency section (OR 3.69, p=0.05).
Conclusions: The persistent pulmonary hypertension of newborns in the current study was higher than in Western countries. Pneumonia and sepsis are the primary aetiologies of developing PPHN. Maternal septic risk factors and emergency section are associated with an increased risk of severe pulmonary hypertension.

Keywords: Hypoxic ischemic encephalopathy (HIE), Neonatal intensive care unit, Pneumonia, Persistent pulmonary hypertension of the newborn (PPHN).

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INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) results when these circulatory adaptation fails, leading to hypoxemic respiratory failure.[1] The incidence of PPHN in Asian countries ranges from 1.2 to 4.6 per 1000 live births,.[2] which is higher compared to the USA, where the incidence is 1.[8] per 1000 live births.[3] Multiple maternal and neonatal factors have been pointed out as risk indicators for PPHN.[4]

Most neonates with PPHN present with respiratory distress and cyanosis within the first 24 hours after birth.[5] They may have low APGAR scores and need delivery room interventions, including oxygen therapy, bag and mask ventilation, and endotracheal intubation.[6,7] Echocardiography remains the gold standard diagnostic tool in PPHN and helps classify disease severity.[8]

General management includes maintenance of normal temperature, electrolytes, glucose, and intravascular volume. Ionotropic support (Milrinone, Dopamine, and Dobutamine) may be required to improve cardiac output. Internationally, inhaled Nitric oxide (iNO) is well-documented for treating PPHN. Other current treatment options are Sildenafil, Milrinone, Prostaglandin analogues, Bosentan, Iloprost and Magnesium sulfate.[9,10] The mortality rate of PPHN in developed countries is between 7 and 10 per cent. Survivors of severe PPHN and/or extracorporeal membrane oxygenation (ECMO) treatment are at increased risk of developmental delay, motor disability, hearing deficits, and chronic health problems compared with individuals without PPHN.[3] There is limited data related to associations of severe PPHN in our country. No study has been conducted earlier to identify the maternal and neonatal risk factors responsible for severe PPHN. This study may document associations of risk factors with severe pulmonary hypertension and available treatment options associated with different grades.

METHODOLOGY

The prospective longitudinal study was conducted at Fatima Memorial Hospital Lahore Neonatal ICU from April to October 2020. The sample size was

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calculated using a WHO calculator, taking a reported prevalence of pulmonary hypertension of 5%.[11] Ethical approval was obtained from Institutional Review Board (FMH-01-2020-IRB-713-M).

Inclusion Criteria: Neonates of either gender admitted to the Neonatal Unit with signs and symptoms suggestive of PPHN and confirmed on echocardiography were included in the study.

Exclusion Criteria: Neonates with no echocardiographic evidence of PPHN or congenital heart defect were excluded from the study.

Informed consent was obtained from parents prior to enrollment in the study.The criterion for diagnosis of pulmonary hypertension was set as normal structural cardiac anatomy with flattened or displaced ventricular septum and Doppler studies showing right-to-left shunt through the patent ductus arteriosus and/or foramen ovale. Echocardiography was done with simultaneous BP monitoring, and grades of pulmonary hypertension were defined.

Multiple maternal and neonatal risk factors leading to PPHN were identified. Sepsis was defined as leukocytosis >30,000, leukopenia <5000 or ANC <1500 or platelets <100 or CRP > 5 or positive blood culture.[12]

Respiratory distress syndrome (RDS) was defined as respiratory distress requiring oxygen within 6 hours of birth and X-ray suggestive of RDS. Meconium aspiration syndrome (MAS) was documented when there was a history of meconium-stained amniotic fluid or respiratory distress with or without suggestive X-ray chest. Hypoxic ischemic encephalopathy (HIE) was a history of delayed cry at birth or 5 minutes APGAR <7.[13] Maternal risk factors were documented as fever or vaginal discharge or lower abdominal pain or leukocytosis or UTI, or chorioamnionitis in the mother during her pregnancy.

Before starting data collection, the data collection team was trained and assessed for uniformity of data collection. All the neonates fulfilling the criterion were assessed for age, gender, maternal and neonatal risk factors of persistent pulmonary hypertension, given treatment and short-term outcome, i.e., mortality of enrolled babies. Data was collected on a specially designed PPHN proforma. All children were managed according to institutional guidelines.

Statistical Package for Social Sciences (SPSS) version 26.0 was used for the data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency & percentages. Independent sample t-test and Chi-square test were applied to explore the inferential statistics. The association of different clinical variables with the diagnosis of Severe PPHN was determined using binary logistic regressions. The *p*-value of 0.05 or less was taken as significant.

RESULTS

During the study period, 1446 babies were admitted to neonatal units, while 272 required care in NICU. From the data of 272 babies in NICU, 72(26.4%) babies were diagnosed with PPHN, confirmed on echocardiography. Out of 72, 46(65.7%) were male and 24(34.3%) were female. The mean gestational age and weight were 35.38±3.39 weeks and 2428+884.1 gm. Gestational illness was observed in 40(57.1%), septic risk factors were 42(60%), anetal steroids was observed in 18(25.7%) and anemia in 21(30%) (Table-I).

Table-I: Distribution of Maternal Risk Factors (n=70)

	Yes	No
Gestational Illness	40(57.1%)	30(42.9%)
Septic Risk Factors	42(60%)	28(40%)
Antenatal Steroids	18(25.7%)	52(74.3%)
Anemia	21(30%)	49(70%)

Demographic characteristics of antenatal and natal factors and possible etiologies were divided into severe and non-severe persistent pulmonary hypertension groups. Of the 70 infants, 12(17.1) had mild pulmonary hypertension, while 58(82.9) had moderate to severe hypertension. Septic risk factors were the most common maternal factors associated with PPHN 38(90.5%) and significant in infants with severe PPHN as compared to the Group without severe PPHN 4(9.5%) *p*0.038). Pneumonia was the most common aetiology of PPHN (82.2%) (Table-II). Binary logistic regression was applied. Severe PPHN patients were significantly associated with septic risk factors and emergency section. The following variables were included in the final full regression model: sepsis, septic risk factors, emergency section, RDS, HIE, TTN, and MAS (Table-III).

DISCUSSION

This study explored the causes of persistent pulmonary hypertension, treatment options and outcomes in neonates. Based on echocardiography, most neonates diagnosed with PPHN were categorized in the moderate to severe PPHN group (82.8%). On binary logistic regression analysis, Severe PPHN patients were significantly associated with septic risk factors and emergency section.

Table-II: Descriptive characteristics of Study Population with and without Severe Pulmonary Hypertension (n=70)

Risk Factors	Neonates with Severe Pulmonary Hypertension (n=58)	Neonates without Severe Pulmonary Hypertension (n=12)	*p*-value
Gender–Male	7(15.2%)	39(84.8%)	0.554
Gender-Female	5(20.8%)	19(79.2%)	
Gestational Age (weeks)	34.63±3.32	35.5±3.4	0.37
Birth Weight(gm)	2526.2±859.80	1953.3±880.95	0.040
Maternal Age (years)	29.32±4.61	28.91±4.23	0.77
Maternal Body mass index (kg/m2)	29.83±4.19	30.58±3.70	0.565
Septic Risk Factors	38 (90.5%)	4 (9.5)	0.038
Maternal Hypertension	14 (73.7)	5 (26.3)	0.21
Smoking	5 (100)	0	0.291
Anemia	18 (85.7)	3 (14.3)	0.67
Liquor	10 (83.3)	2 (16.7)	0.96
Spontaneous vaginal delivery	12 (92.3)	1 (7.7)	0.31
Emergency Section	26 (74.3)	9 (25.7)	0.057
Pneumonia	37 (82.2)	8 (17.8)	0.85
Respiratory distress syndrome	17 (89.5)	2 (10.5)	0.37
Meconium aspiration syndrome	16 (100)	0	0.038
Transient tachypnea of newborn	2 (50)	2 (50)	0.07
Hypoxic ischemic encephalopathy	17 (94.4)	1 (5.6)	0.13
Sepsis	35 (81.4)	8(18.6)	0.68
Oxygen	46 (83.6)	9 (16.4)	0.740
Sildenafil	35(94.6)	2(5.4)	0.006
Milrinone	14 (100)	0	0.057
Continuous positive airway pressure	43(81.1)	10(18.9)	0.499
Conventional ventilation	37 (88.1)	5 (11.9)	0.154

In a study by multiple Asian centres, incidence ranged from 1.3-4.6 per 1000 live births.[4] The mean gestational age in mothers having babies with pulmonary hypertension recorded by Nakwan *et al.* was 39.1±1.6 weeks.[11] However, in our study, the mean gestational age was recorded to be 35.38±3.39 weeks. The global prevalence of pre-term birth is 9.6%, but the pre-term birth rate in Pakistan is higher, i.e., 15·7%. More pre-term neonates are exposed to risk factors leading to the development of PPHN.[12,13]

In a study by Choudhary *et al.*, the mean birth weight was recorded to be 2900±300.[14] But in our study population, it was lower, 2428±884.1g. This might be attributed to the developing country status, lack of good health facilities, poor maternal health and malnutrition

Maternal sepsis and septic risk factors are significantly associated with the development of pulmonary hypertension, as documented in a previous study.[15] Caesarean section possessed an almost 5-fold increased risk of developing PPHN compared to a demographically well-matched control population.[16] We found that the emergency section was significantly associated with developing severe PPHN (OR 3.69, CI 0.94- 24.03, *p*-value 0.05).

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.17 In our study, RDS was recorded in 19(27.1%) neonates as aetiology of PPHN.

Meconium aspiration syndrome (MAS) is a common cause of morbidity and mortality in neonates.

Table-III: Binary Logistic Regression associations of Different Clinical Variables with Severe Pulmonary Hypertension (n=70)

Factors		Study Parameter		*p*-value	Odds Ratio	95% Confidence Interval	
		Mild	Severe			Lower	Upper
RDS	Yes	2(10.5%)	17(89.5%)	0.865	0.482	0.179	7.71
	No	10(19.6%)	41(80.6%)				
MAS	Yes	0(0.0%)	16(100%)	0.998	1.28	0.00	
	No	12(22.2%)	42(77.8%)				
TTN	Yes	2(50%)	2(50%)	0.438	5.66	0.018	5.68
	No	10(15.2%)	56(84.8%)				
HIE	Yes	1(5.6%)	17(94.4%)	0.523	0.219	0.186	27.16
	No	11(21.2%)	41(78.8%)				
Sepsis	Yes	8(18.6%)	35(81.4%)	0.518	1.314	0.335	8.73
	No	4(14.8%)	23(85.2%)				
Maternal Septic Risk Factor	Yes	4(9.5%)	38(90.5%)	0.037	0.263	0.032	0.899
	No	8(28.6%)	20(71.4%)				
Emergency Section	Yes	9(25.7%)	26(74.3%)	0.05	3.69	0.942	24.03
	No	3(8.6%)	32(91.4%)				

Chemical pneumonitis can lead to persistent pulmonary hypertension of the newborn (PPHN) with irreversible hypoxia.[18] In a previous study the most common cause of PPHN was MAS 89(27.1%), which is the most common cause of PPHN reported in the developing world.[19] In our study, it was not the most frequent cause of PPHN 16(22.9%).

Fetal hypoxemia associated with severe HIE exacerbates pulmonary vasoconstriction. One study documented the incidence of PPHN as 23% in the HIE group.[19] We found HIE as a risk factor in 25.7% of neonates with severe pulmonary hypertension. In a study by Deshpande *et al*., 49% of neonates with proven LOS in the study group had pulmonary hypertension.[20] The high mortality rate in severe cases indicates the necessity of inhaled Nitric oxide and extracorporeal membrane oxygenation that would further enhance the outcome.

LIMITATIONS OF STUDY

Due to the lack of advanced therapeutic modalities for PPHN, i.e., inhaled NO and ECMO, it is difficult to comment on the effectiveness of other treatment options. However, the Group with severe pulmonary hypertension required Sildenafil, Milrinone and HFOV significantly compared to the Group without severe PPHN.

Due to a lack of prolonged follow-up, we cannot comment on the neurological deficits and cognitive delays, which may occur in patients with prolonged ventilation. We only documented mortality as the acute outcome of the study.

CONCLUSION

Persistent pulmonary hypertension of the newborn (PPHN) is an important differential diagnosis of babies admitted to NICU with respiratory symptoms. There are four strong predictors of severe PPHN: sepsis, hypoxic-ischemic encephalopathy, emergency caesarean section and maternal septic risk factors. Babies with these risk factors should be closely monitored for the development of PPHN, which can complicate the course of illness due to severe PPHN.

Authors Contribution:

Following authors have made substantial contributions to the manuscript as under:

FS: & FY: Conception, study design, drafting the manuscript, approval of the final version to be published.

ZA: & RG: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

SGA: & ZH: Critical review, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Sardar S, Pal S, Mishra R. A retrospective study on the profile of persistent pulmonary hypertension of newborn in a tertiary care unit of Eastern India. J Clin Neonatol 2020; 9(1): 18. http://dx.doi.org/10.4103/jcn.JCN_68_19
2. Nakwan N, Jain S, Kumar K, Hosono S. An Asian multicenter retrospective study on persistent pulmonary hypertension of the newborn: incidence, etiology, diagnosis, treatment and outcome. J Matern Fetal Neonatal Med 2020; 33(12): 2032-2037. https://doi.org/10.1080/14767058. 2018.1536740
3. Steurer MA, Jelliffe-Pawlowski LL, Baer RJ, Partridge JC, Rogers EE, Keller RL, et al. Persistent pulmonary hypertension of the newborn in late preterm and term infants in California. Pediatrics 2017; 139(1). https://doi.org/10.1542/peds.2016-1165
4. Razzaq A, Quddusi AI. Risk factors and mortality among newborns with persistent pulmonary hypertension. Pak J Med Sci 2013; 29(5): 1099. https://doi.org/10.12669/pjms.295.3728
5. Lakshminrusimha S, Keszler M. Persistent pulmonary hypertension of the newborn. Neoreviews 2015; 16(12): e680-e92. https://doi.org/10.1542/neo.16-12-e680
6. Teng RJ, Wu TJ. Persistent pulmonary hypertension of the newborn. J Formos Med Assoc 2013; 112(4): 177-184. https://doi.org/10.1016/j.jfma.2012.11.007.
7. 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. N Eng J Med 2000; 342(7): 469-474. https://doi.org/10.1056/nejm200002173420704
8. Ahmed T, Abqari S, Shahab T, Ali M, Firdaus U. Prevalence of pulmonary Arterial hypertension on echocardiography in newborns with maternal risk factors. Int J Pregnancy Child Birth 2017; 3(1). https://doi.org/10.15406/ipcb.2017.03.00053
9. Pedersen J, Hedegaard ER, Simonsen U, Infanger M, Grimm D. Current and future treatments for persistent pulmonary hypertension in the newborn. Basic Clin Pharmacol Toxicol 2018; 123(4): 392-406. https://doi.org/10.1111/bcpt.13051
10. Steinhorn RH. Advances in neonatal pulmonary hypertension. Neonatology 2016; 109(4): 334-344. https://doi.org/10.1159/000444895
11. Nakwan N, Pithaklimnuwong S. Acute kidney injury and pneumothorax are risk factors for mortality in persistent pulmonary hypertension of the newborn in Thai neonates. J Matern Fetal Neonatal Med 2016; 29(11): 1741-1746. https://doi.org/10.3109/14767058.2015.1060213
12. Begum NA, Afroze S, Laila R, Siddiqua SP, Rahaman MT. Risk factors of persistent pulmonary hypertension of newborn (PPHN) in different gestation. Am J Pediatr 2019; 5(3): 142-147. https://doi: 10.11648/j.ajp.20190503.20
13. Shaikh K, Premji SS, Rose MS, Kazi A, Khowaja S, Tough S, et al. The association between parity, infant gender, higher level of paternal education and preterm birth in Pakistan: a cohort study. BMC Pregnancy Childbirth 2011; 11(1): 1-10. https://doi.org/10.1186/1471-2393-11-88
14. Choudhary M, Meena MK, Chhangani N, Sharma D, Choudhary JS, Choudhary SK, et al. To study prevalence of persistent pulmonary hypertension in newborn with meconium aspiration syndrome in western Rajasthan, India: a prospective observational study. J Matern Fetal Neonatal Med 2016; 29(2): 324-327. https://doi.org/10.3109/14767058.2014.1000296

15. Agarwal P, Shankaran S, Laptook AR, Chowdhury D, Lakshminrusimha S, Bonifacio SL, et al. Outcomes of infants with hypoxic ischemic encephalopathy and persistent pulmonary hypertension of the newborn: results from three NICHD studies. J Perinatol 2021; 41(3): 502-511. https://doi.org/10.1038%2Fs41372-020-00905-7
16. Alwan S, Friedman JM, Chambers C. Safety of selective serotonin reuptake inhibitors in pregnancy: a review of current evidence. CNS Drugs 2016; 30(6): 499-515. https://doi.org/10.1007/s40263-016-0338-3
17. Chettri S, Bhat BV, Adhisivam B. Current concepts in the management of meconium aspiration syndrome. The Indian J Pediatr 2016; 83(10): 1125-1130. https://doi.org/10.1007/s12098-016-2128-95567577
18. Lakshminrusimha S, Shankaran S, Laptook A. Pulmonary hypertension associated with hypoxic-ischemic encephalopathy-antecedent characteristics and comorbidities. J Pediatr 2018; 196: 45-51. e3. https://doi.org/10.1016/j.jpeds.2017.12.055
19. Joanna RG V, Lopriore E, Te Pas AB, Rijken M, van Zwet EW, de Bruine FT, et al. Persistent pulmonary hypertension in neonates with perinatal asphyxia and therapeutic hypothermia: a frequent and perilous combination. J Matern Fetal Neonatal Med 2022 ; 35(25): 4969-4975. https://doi.org/10.1080/14767058.2021.18941
20. Deshpande S, Suryawanshi P, Holkar S, Singh Y, Yengkhom R, Klimek J, et al. Pulmonary hypertension in late onset neonatal sepsis using functional echocardiography: a prospective study. J Ultrasound 2022 Jun; 25(2): 233-239. https://doi.org/10.1007/s40477-021-00590-y

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