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A Prospective Study of Neonates with Persistent Pulmonary Hypertension of the Newborn: Prevalence, Clinical Outcomes, and Risk Factors

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ABSTRACT

Background: Persistent pulmonary hypertension of the newborn (PPHN) is caused by the inability of the pulmonary arteries to dilate at birth, which leads to severe hypoxemia. Several risk factors have been identified in association with its occurrence and prognosis. The present study aimed to determine the incidence of PPHN, describe neonates' characteristics, and evaluate the etiology, as well as mortality risk factors in newborns hospitalized due to PPHN at Bahrami Children's Hospital, Tehran, Iran, from 2017 to 2020.

Methods: A total of 49 neonates were included in the present study. The PPHN diagnosis was based on clinical criteria and echocardiography provided by neonatologists. Therefore, a complete history, physical examination, and laboratory data were gathered. Afterward, PPHN etiology was determined, and the patients were followed up for six months. Finally, PPHN prevalence was calculated and probable risk factors for its complications were investigated by using logistic regression analysis.

Results: The findings revealed that the prevalence of PPHN was 3.5% in the center under study, and the mortality rate, as well as complete recovery, were 24.5% and 63%, respectively. It was also found that factors, such as male gender, abnormal Apgar score at birth, and cesarean delivery, were high in a percentage of PPHN patients; however, they were not associated with PPHN mortality and morbidity. The only variable that had a significant association with mortality and morbidity was an abnormal white blood cell count.

Conclusion: The need for inotropic support was associated with poor outcomes. From the aspect of etiology, there exists higher mortality rates, complications, and poor prognosis among PPHN patients with underdevelopment, compared to the ones with maldevelopment.

Keywords: Developmental disorder, Mortality, Persistent pulmonary hypertension of the newborn, PPHN, Prevalence, Risk factor

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is a clinical syndrome that occurs at birth due to a lack of reduction in pulmonary vascular resistance, followed by inadequate pulmonary blood flow (1-5). This results in the shunting of non-oxygenated blood from the pulmonary circulation to the systemic circulation (4, 6). The extrapulmonary shunt is seen in severe cases of the disease, which leads to severe hypoxemia and thus, difficulty in responding to oxygen therapy, as well as vasodilator medications (3). The PPHN is one of the neonatal emergencies that require immediate interventions to prevent hypoxia, as well as other long-term and short-term consequences and complications (4, 7). Neonates with PPHN stand in great need of long-term follow-

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up for developmental neurological disorders, hearing impairment, chronic lung disease, and other health-related disorders after discharge (3, 4, 8, 9).

Previous studies indicated that PPHN occurs in one to two cases per thousand live births, as illustrated by a population-based study of neonates born above 33 weeks of gestational age (1, 2, 4). However, there are numerous differences among the statistics provided in different centers, varying from 0.43 to 6.82 cases per thousand live births (10). Although PPHN is more common in full-term and near-term infants (1, 2, 4), its occurrence is not uncommon in preterm infants with respiratory distress syndrome and bronchopulmonary dysplasia (3, 4, 11).

Numerous risk factors have been identified to cause this condition which is associated with high mortality and morbidity (1, 4, 12, 13). Mortality is reported to be around 10%-20% despite common treatments (1, 10, 14, 15), the most common causes of which are irreversible hypoxia, myocardial infarction, and failure. The mortality rate varies according to the underlying conditions; if there is an underlying disease (e.g., simultaneous infection with group B streptococcal infection), this rate has been reported to be up to 50% (14).

This study attempted firstly to investigate etiologies, risk factors, and prescribed treatments, as well as the prognosis, in neonates with PPHN, who were admitted to neonatal wards of Bahrami Children's Hospital, Tehran, Iran, from 2017 until 2020, and secondly, to compare the obtained results with other studies in this field.

Methods

Settings and patients

A prospective cross-sectional study was designed to review medical charts of patients admitted to the neonatal intensive care unit (NICU) of Bahrami Children's Hospital (a tertiary center), Tehran, Iran. The NICU of the hospital provides care for newborns younger than 30 days. It is worth mentioning that the study protocol was approved by the ethical review board (IR.TUMS.MEDICINE.REC.1396.4303).

Data collection

All neonates included in the present study had been hospitalized with respiratory distress or stable cyanosis whose cardiologist confirmed the diagnosis of PPHN for them by using echocardiography. On the other hand, infants with congenital heart disease were excluded from the study.

In total, 1,392 neonates, who had been admitted to NICU, were evaluated between October 2017 and March 2020. The PPHN was diagnosed in 49 patients, which was also confirmed by echocardiography and NICU specialists. These infants were included in the study and their outcome was assessed during a six-month follow-up period with a primary focus on the respiratory tract and neurological problems). Neonates' demographic characteristics and laboratory data, such as their gender, gestational age, birth weight, Apgar score, blood sugar level, blood calcium level, complete blood count, and their mothers' medical record, including gestational diabetes mellitus (GDM), smoking habits, as well as body mass index (BMI), were collected. The PPHN pathophysiology was also determined.

Definitions

Three main groups of abnormalities in the pulmonary arteries were defined below: (16-19)

1. Underdevelopment: In this abnormality, the number of pulmonary arteries was less than normal, which caused an increase in pulmonary blood pressure. Infants with pulmonary hypoplasia, including diaphragm hernia or cases of oligohydramnios and associated syndromes, were included in this group.

2. Maldevelopment: This abnormality was a disorder in the division and differentiation of alveoli, despite normal development of the lungs and a sufficient number of pulmonary vessels. These cases were not placed in the other two groups.

3. Maladaptation: Infants included in this group had normal vascular networks but lung adaptation changes in prenatal and postnatal conditions, such as pneumonia, meconium aspiration, or asphyxia.

Statistical analysis

All data were entered into the SPSS software (version 21, IBM Corp., Armonk, NY, USA) and were analyzed by the STATA software (version 14.2). Descriptive statistics were used to identify prevalence and percentages. However, due to rare outcome assumptions, prevalence confidence intervals were calculated by the binomial exact method. Furthermore, the association between mortality and probable risk factors was assessed with the implementation of logistic regression analysis. The significance level was considered lower than 0.05. In this study, two groups of complications and deaths were merged and

compared to the healthy group.

Results

This study included 49 neonates suffering from PPHN, who were selected out of 1,392 neonates admitted to the NICU of Bahrami Children's Hospital, Tehran, Iran. Among these 49 infants, 34 (69.4%) were male and 15 (30.6%) were female. The overall prevalence of PPHN in the center understudy was estimated to be 3.5% (95%CI: 2.6%-4.6%). Among these PPHN patients, 12 neonates (24.5%) died and 6 of them (12.2%) developed complications (developmental disorders in four neonates, developmental and hearing impairment in one neonate, and developmental disorder, as well as chronic lung disease, in another one of them).

The majority of neonates in the present study were full-term and they had a good birth weight, as well as a normal Apgar score (67.3%, 91.8%, 59.2%, respectively). None of them were post-term. A total of 32 neonates (65.2%) were delivered via cesarean section and the others through normal vaginal delivery (NVD). In terms of prenatal factors, six mothers (12.2%) had GDM during pregnancy; however, they did not suffer from any other underlying diseases, such as asthma, gestational hypertension, and hypothyroidism. Among neonates' mothers, 15 (30.6%) were exposed to second-hand smoke during their pregnancy, 36 (73.5%) had high pre-pregnancy BMI (BMI>27), and none had oligohydramnios. They also did not take non-steroidal anti-inflammatory drugs or selective serotonin reuptake inhibitors during pregnancy (Table 1).

Table 1. Demographic and clinical characteristics of neonates with persistent pulmonary hypertension of the newborn

Characteristic	Number of patients (n)	Percentage (%)
Admitted	49	100
Sex		
Male	34	69.4
Female	15	30.6
Gestational Age		
<37 weeks	16	32.7
≥37 weeks	33	67.3
Type of Delivery		
Normal Vaginal Delivery	17	34.8
Caesarean Section	32	65.2
Birth Weight		
≤90 percentile	45	91.8
>90 percentile	4	8.2
Apgar Score		
≤7	20	40.8
>7	29	59.2
Gestational Diabetes Mellitus		
Yes	6	12.2
No	43	87.8
Maternal Smoking		
Yes	15	30.6
No	34	69.4
Laboratory Data		
Hypocalcemia	9	18.4
Hypoglycemia	4	8.2
Leukocytosis or Leukopenia	20	40.8
Polycythemia	4	8.2
Positive Blood Culture	2	4.1
Treatment		
Inotrope	11	22.4
Sildenafil/Milrinone	4	8.2
Inotrope + Sildenafil/Milrinone	4	8.2
Inotrope + Sildenafil/Milrinone + Prostaglandin	7	14.3
Surgery + Medical	7	14.3
None	16	32.7
Prognosis		
Cured	31	63.3
Developmental disorder	4	8.2
Developmental disorder + Hearing impairment	1	2.0
Developmental disorder + Chronic lung disease	1	2.0
Deceased	12	24.5

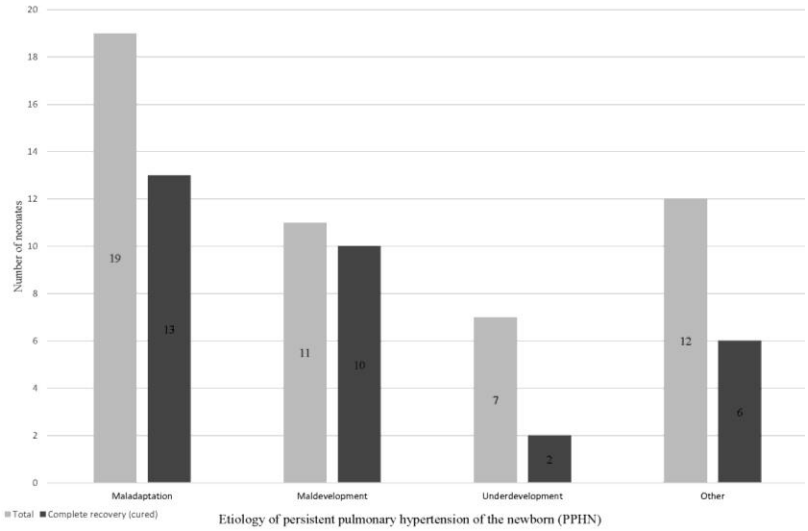

Figure 1.

The most common etiology of PPHN in this study was maladaptation (19 neonates or 28.8%) and the least common etiology was underdevelopment (7 neonates or 14.3%). The highest mortality and morbidity rates were among neonates whose PPHN etiology was underdevelopment (5 neonates out of 7 or 71.4% of them), and the highest rate of complete recovery was in patients with maldevelopment as the etiology of their disease (10 out of 11 neonates or 90.9% of them) (Figure 1).

The highest incidence of developmental disorders was in neonates with a mild disease that did not need medical treatments (three out of six neonates with developmental disorders did not receive any medications). In addition, all of those neonates that died in this study received at least one inotropic agent. It should be noted that there was no death among neonates who did not need medical treatments or those who needed surgery.

The main prenatal or natal risk factor connected with the prognosis of neonates was white blood cells (WBC) count in the peripheral blood sample whose decrease or increase was associated with mortality and morbidity in neonates (P-value=0.03, OR=3.84, 95%CI: 1.13-13.0). On the other hand, no significant relationship was discovered between prognosis and other factors (Table 2). Finally, the Fisher's exact test showed a significant difference between neonates suffering from PPHN, compared to the healthy group, in the etiologies of PPHN and the occurrence of complications and mortality (P-value=0.04).

Table 2. Logistic regression analysis for the risk factors of mortality and morbidity in neonates with persistent pulmonary hypertension of the newborn

Variable	Logistic regression analysis	
	OR (95%CI)	P-value
Sex Male Female	0.81 (0.22-2.90)	0.74
Gestational Age <37 weeks ≥37 weeks	2.21 (0.59-8.32)	0.24
Apgar Score ≤7 >7	0.38 (0.11-1.26)	0.11
Type of Delivery Normal Vaginal Delivery Cesarean Section	0.75 (0.22-2.51)	0.64
Smoking No Yes	0.81 (0.22-2.90)	0.74
White Blood Cell Count Normal Abnormal	3.84 (1.13-13.07)	0.03
Inotrope Administration No Yes	8.56 (2.21-33.17)	<0.01

Discussion

Persistent pulmonary hypertension of the newborn, also known as persistent fetal circulation, is a syndrome of failed vascular adaptation at birth due to delay or impairment in the normal descent in pulmonary vascular resistance occurring after birth (13). Respiratory failure in neonates has been conceded for over 40 years since its first explanation by Gersony et al. in 1969 (20).

The PPHN is a complex clinical syndrome with an estimated incidence of 1.9 per 1,000 live births (0.4-6.8/1000 live births) (21). About 10%-50%

of these neonates will die of this problem and 7%-20% of them develop long-term impairments, such as hearing impairment, chronic lung disease, and intracranial bleeding (22). Furthermore, in a population-based study in California, the incidence of PPHN was estimated at approximately 1 in every 500 live births (23). In a study conducted in the center understudy, the mortality rate was 24.5% (95%CI: 14.2%-38.9%) and the prevalence of complications, such as hearing impairment, among survivors was 16.2% (95%CI: 6.2%-32.0%), which was similar than the prevalence of other studies in the world. Moreover, the overall prevalence of PPHN in this center was higher, determined at 3.5% (95%CI: 2.6%-4.6%), probably because the center is a referral hospital.

In a study conducted by Kumar et al., it was reported that the associated risk factors with PPHN in preterm neonates were gestational age of less than 37 weeks, low Apgar score, premature rupture of membranes, oligohydramnios, pulmonary hypoplasia, and sepsis, which were independent predictors of the PPHN occurrence. In the same study, body weight at birth, intraventricular hemorrhage, and male gender had a close relationship with the mortality rate in patients (7). Another study evaluated other linked factors with PPHN, such as male gender, black or Asian mother, high body mass index during pregnancy (above 27), maternal diabetes, maternal asthma, cesarean delivery, age of delivery as 34 to 37 weeks or more than 41 weeks (compared to the age of delivery as 37 to 41 weeks), and gestational weight of above 90 percentile, compared to the gestational weight of between 10 to 90 percentiles (15). Other risk factors include ureaplasma infection, therapeutic hypothermia, which is used as a treatment for ischemic hypoxic encephalopathy, hypoglycemia, hypocalcemia, and polycythemia (4).

Some articles reported that WBC count (leukopenia or leukocytosis) is a risk factor that deteriorates neonates' health condition (24). Based on the obtained findings in the present study, there was a significant association between changing WBC count (decrease or increase in WBC count) and the rate of mortality and morbidity in affected patients. The P-value of this statistical test was significant (0.03), and the OR was 3.84 (95%CI: 1.13%-13.07%). However, it is necessary to conduct studies with a larger sample size to estimate the OR more accurately as the CI range of this study was wide (from a trivial relationship to a high size effect, and it was not possible to estimate the strength of the relationship between them).

Another independent variable, which was highly considered to have an impact on increasing the rate of mortality and morbidity, was the consumption of inotropic agents used as a treatment for these patients (25). All patients who died in this study had received inotrope (Dopamine) alone or with other medications. Similarly, the study by Harerimana et al. revealed that 72% of dead patients received inotropes, which was significantly higher than the group that survived (26). In 2018, an Asian multicenter retrospective study indicated that the use of inotropic agents had a significant impact on enhancing the risk of death in PPHN patients (27). In this study, a significant association was observed between the administration of inotropic agents, alone or alongside other medications, and mortality or long-term complications (P-value<0.01, OR=8.56, 95%CI: 2.21-23.17). It seems that the use of inotrope deteriorates a patient's health status, although there are many confounding variables in this relationship. One of the most important confounders is the deterioration and severity of PPHN in patients who were prescribed inotrope.

In a California report, based on a state-wide database that linked maternal and infant hospital discharges, female gender was a protective factor against the occurrence of the PPHN (23). In the present study, the number of male patients with PPHN was almost twice that of female patients with PPHN, and the prevalence of PPHN was higher in males than females. Similar to the results of the present study, in a study by Abdel Mohsen et al., the prevalence of PPHN in males was twice higher than that in females. Male gender was also one of the risk factors that appear to be associated with mortality in patients with PPHN. Regarding the prognosis and mortality of PPHN, Razzaq et al. conducted a study that showed the male gender doubled the chance of mortality line (28). However, no significant relationship was found between gender and prognosis in the present study. In the analysis of the female-to-male risk, no significant relationship was observed between gender and the risk of mortality and complications (P-value=0.7, OR=0.81, 95%CI: 0.22-2.90).

In the descriptive part of this study, among patients with PPHN, the prevalence of cesarean delivery was almost twice the NVD. Studies regarding PPHN infants have reported a high prevalence of cesarean delivery in these patients (1, 15, 28, 29). In a case-control study by Wilson et al. in the United States, the risk of developing

PPHN was five times higher in women who gave birth by elective cesarean section, compared to that in women who gave birth through NVD (30). However, it should be taken into consideration that the higher risk of PPHN in neonates born through cesarean section can be due to the effects of cesarean delivery itself or secondary to fetal disorders that led to the choice of cesarean section. The analytical analysis showed no significant relationship between the type of delivery (cesarean section, compared to NVD) and PPHN prognosis (P-value=0.64, OR=0.81, 95%CI: 0.22-2.51). A study by Razzaq et al. showed a similar conclusion and found no association between the type of delivery and the risk of complications (28).

Similar to this study, findings from many previous studies indicated normal Apgar scores in the majority of PPHN patients (about 59%) in the first minutes of life (26). It is true that in this study about 60% of patients with PPHN had normal Apgar scores, but no significant relationship was found between the first minutes Apgar score and the mortality rate, as well as the risk of complications, in these patients (P-value=0.11, OR=0.38, 95%CI: 0.12-1.26).

The maternal body mass index was above 27 in more than 73% of cases in this study. The majority of mothers (about 88%) did not have specific diseases; however, gestational diabetes was found in six of them (12%). Some previous studies indicated that there was a link between maternal obesity, diabetes, and neonatal PPHN (1, 15, 16). Diabetes and obesity cause endothelial dysfunction and inflammation, which may affect fetal lung growth (31). However, in this study, no significant association was found between the presence of GDM or high BMI in mothers and PPHN complications. Fifteen mothers (31%) were in contact with cigarettes during pregnancy. Recently, the results of a population-based study showed maternal smoking as an independent risk factor for PPHN in neonates (23). However, in this study, the relationship of smoking and non-smoking with neonatal morbidity or death was not significant (P-value=0.74, OR=0.81, 95%CI: 0.22-2.90).

The present study examined and compared the characteristics of patients in terms of disease prognosis. A significant relationship was seen between disease prognosis and pathophysiology of PPHN. More than 70% of patients with underdevelopment died, while the majority of patients (about 83%) with other etiologies survived. On the other hand, the maldevelopment etiology did not cause any infant mortality, and a developmental disorder occurred only in one neonate. The Fisher's exact test also showed that there was a significant difference between PPHN etiologies in terms of complications and mortality occurrence (P-value=0.04), which is explained by the difference between the two etiologies of maldevelopment and underdevelopment in terms of prognosis.

The strengths of this study were the complete prospective follow-up of all patients and no loss or missing data; however, there were two major limitations that could be addressed in future research attempts. The first limitation was the conduction of this study in a referral center which led to a higher prevalence of PPHN, in comparison with population-based studies. The second limitation was the sample size of this study. Due to the low prevalence of PPHN, conducting this study with a larger sample size requires registry systems and cooperation with various centers as a multicenter to determine more risk factors accurately. Therefore, studies with a larger sample size are highly recommended.

Conclusion

The prevalence of PPHN was about 3.5% in the center understudy, which was relatively high. Male gender, abnormal Apgar score at birth, and cesarean delivery were high in a percentage of PPHN patients; however, none of these variables were significantly associated with PPHN mortality and morbidity. The only history-related and para-clinical variable that had a significant connection with mortality and morbidity was the abnormal WBC count. Additionally, the use of inotrope increased mortality in patients; however, the cause is the onset of inotrope in deteriorated patients. In the aspect of etiology, underdevelopment etiology had higher mortality, complications, and poor prognosis, in comparison with PPHN patients with maldevelopment.

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Conflicts of interest

The authors declare no conflict of interest.

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