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Risk Factors of Persistent Pulmonary Hypertension of Newborn (PPHN) in Different Gestation

Nargis Ara Begum[1, *], Sharmin Afroze[2], Runa Laila[1], Shahnaz Parvin Siddiqua[1], Mohammad Toyobur Rahaman[1]

[1]Department of Neonatology, United Hospital Limited, Dhaka, Bangladesh

[2]Department of Neonatology, Dr. M R Khan Shishu (Children) Hospital & Institute of Child Health, Dhaka, Bangladesh

Email address:
nargisdr@yahoo.com (N. A. Begum), mumu.sharmin8@gmail.com (S. Afroze), dr.runa.laila.09@gmail.com (R. Laila), naznova@yahoo.com (S. P. Siddiqua), dr.toyob@gmail.com (M. T. Rahaman)

[*]Corresponding author

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Abstract: Persistent Pulmonary Hypertension of Newborn (PPHN) is a critical neonatal problem resulting from failed circulatory adaptation at birth, associated with substantial perinatal morbidity as well as mortality. Despite significant advancement in management of PPHN across the globe, it still remains a challenge especially in developing countries like Bangladesh. So the study was conducted over five years in United Hospital Limited to determine the risk factors of PPHN in relation to gestational age. All PPHN cases diagnosed by echocardiogram were included in the study and divided into term (≥ 37 wks) and preterm group (<37 wks). Among 157 of PPHN cases, 66% were male, 59% were preterm, mean gestational age and birth weight were 35.6 ± 2.54 wks and 2598.22 ± 760.353 gm respectively. Maternal asthma (p 0.01) and pre-eclamptic toxemia (p 0.010) were significant risk factors for persistent pulmonary hypertension of newborn. PPHN was found high in neonates with Respiratory Distress Syndrome (p 0.000) and Meconium Aspiration Syndrome (p 0.000). Most (96%) of the babies were discharged to home.

Keywords: Persistent Pulmonary Hypertension, Risk Factors, Persistent Fetal Circulation

1. Introduction

Persistent Pulmonary Hypertension of Newborn (PPHN) is a condition characterized by marked pulmonary hypertension resulting from elevated pulmonary vascular resistance(PVR) and altered pulmonary vaso-reactivity, that leads to right to left extra-pulmonary shunting of blood across the foramen ovale and the ductus arteriosus [1]. Though PPHN is less common causes of respiratory distress in newborns but it has significant impact on morbidity and mortality [2]. PPHN occurs in 1-2 infants/1000 live births [3] and mortality rate ranging from 4–33% [4]. High pulmonary pressure is normal and necessary state for the fetus. In fetal life, most of the right ventricular output crosses the ductus arteriosus to the aorta and only 5-10% of the combined ventricular output is directed to the pulmonary vascular bed. This high pulmonary vascular tone in fetus is due to increased pulmonary vasoconstrictors (low oxygen tension, endothelin-1, leukotriene's and Rho kinase) and decreased vasodilators (prostacyclin and nitric oxide) [5]. In some newborns, the normal decrease in pulmonary vascular tone does not occur and eventually results in PPHN. Inadequate pulmonary perfusion leads to refractory hypoxemia, respiratory distress and acidosis [6]. There are several maternal risk factors associated with the occurrence of PPHN which includes the following: maternal asthma, maternal diabetes, pre-conception maternal overweight, chorioamnionitis, antenatal exposure to selective serotonin reuptake inhibitors and non-steroidal anti-inflammatory drugs, infection (mainly by Group B *Streptococcus*) and cesarean section etc. Important

neonatal risk factors are male gender, 2nd twin, hypothermia, hypocalcemia and polycythemia [7-9]. The diagnosis of PPHN is challenging as risk factors are not evaluated properly and diagnostic facilities are not available in all centers. Regardless of the etiology, PPHN should be diagnosed and treated as soon as possible to avoid hypoxia and its short term and long-term morbidities. Despite initiation of latest treatments like high flow oxygen, sildenafil and advanced modes of mechanical ventilation, there is still 10- 20% mortality [10-12]. In addition, infants who survive develop long-term sequelae (e.g. chronic lung disease, seizures and neuro-developmental problems) as a result of hypoxemia and the aggressive treatment [13-14]. There are few studies on PPHN in our country. Thus an observational study was conducted to identify risk factors for PPHN.

2. Method

2.1. Study Procedure

This observational study was conducted in the Neonatal Intensive Care Unit (NICU) of United Hospital which is one of the largest tertiary care hospitals of Dhaka city. This 500 bedded hospital provides one-stop multidisciplinary health services. Annually 150-200 neonates with varying clinical entity get admitted in the NICU of this hospital. We commonly found neonates having PPHN. So this observational study was designed to identify risk factor of PPHN in antenatal as well as perinatal period. The duration of the study was from January 2013 to December 2017 which was conducted as per guideline of the institutional review board (IRB). All NICU admitted neonates underwent echocardiography from three days of life onwards according to our unit protocol. Among them, diagnosed PPHN cases were included in the study and were divided into term (≥37wks) and preterm group (<37wks) for assessing risk factors. Various demographic characteristics like parity, type of gestation, antenatal risk factors (e.g. pre-eclamptic toxemia/PET, gestational diabetes, antepartum hemorrhage/APH, asthma and infection etc.), mode of delivery, need of resuscitation, neonatal respiratory conditions (e.g. meconium aspiration syndrome/MAS, respiratory distress syndrome/RDS, pneumonia etc.) were recorded and compared between two groups. Other informations of neonatal morbidities such as coagulopathy, acute kidney injury (AKI), intraventricular hemorrhage (IVH), thrombocytopenia, dyselectrolytemia, hypocalcemia were also collected and analyzed. All PPHN newborns were managed according to the unit protocol (treatment included high flow oxygen, continuous positive airway pressure (CPAP), mechanical ventilator, high frequency oscillatory ventilation (HFOV), MgSO4, sildenafil and Milrinone). Data were entered in a predesigned proforma and compared among both groups.

2.2. Statistical Analysis

Social Package of Statistical Science (SPSS version 20) was applied for the final analysis. Chi-square test was used to find out the risk factors. Unadjusted odds ratios were also calculated between categorical variables and the outcome variable.

3. Results

3.1. Baseline Characteristics

We identified 157 neonates having PPHN among 1056 admitted newborns (prevalence14%) during the study period. Sixty six percent babies were male. Among the cases, 93 (59%) were born before 37 weeks of gestation and 64 (41%) after 37 weeks. Table 1 shows that inborn babies were more (69%) than outborn (31%). Mean gestational age was 35.6±2.54 wks and mean birth weight was 2598.22±760.353 gm. The predominant preterm group was late preterm (68%).

Table 1. *Baseline characteristics of neonates with PPHN, admitted in NICU (N=157).*

Characteristics	N(Percentage)
Gender	
Male	103 (66%)
Female	54(34%)
Type of admission	
Inborn	108 (69%)
Outborn	49 (31%)
Mode of delivery	
NVD	16 (10.2%)
LUCS	139 (89%)
Gestational Age Category	
<37weeks	93 (59%)
Extreme pre-term(<28 wks)	0
Very pre-term(28-32 wks)	18 (19%)
Moderate pre-term(33-34 wks)	12 (13%)
Late pre-term(35-36 wks)	63 (68%)
≥37weeks	64 (41%)

Based on echocardiography, mild, moderate and severe variety of PPHN cases were 57%, 18% and 25% respectively (Figure 1).

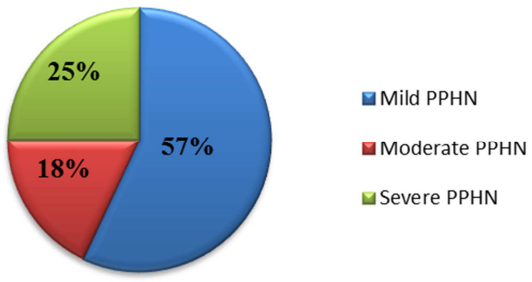

Figure 1. *Distribution of 157 PPHN cases (confirmed by echocardiogram).*

3.2. Antenatal Risk Factors

Maternal APH, maternal PET, asthma, gestational diabetes were observed in mothers of babies who had persistent pulmonary hypertension in postnatal period (Table 2).

Table 2. *Comparison of maternal risk factors for developing PPHN among two groups.*

Maternal Morbidity	Group-1(Preterm, <37wksGA) n=93(%)	Group-2(Term, ≥37wksGA), n=64(%)	Pvalue
APH	8 (8.6)	4 (6.2)	0.76
PET	28 (30)	8 (13)	0.01
Asthma	12 (13)	1 (1.5)	0.01
GDM	37 (40)	23 (36)	0.73
UTI	16 (17)	7 (11)	0.36

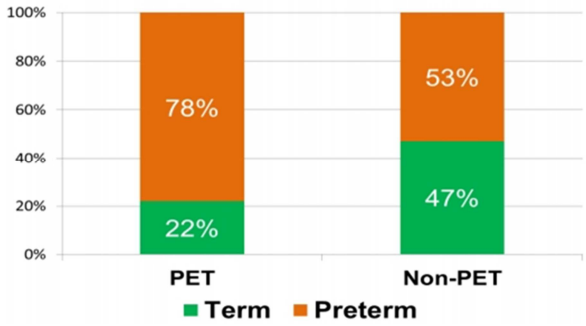

Figure 2. *Proportion of preterm among PET and non-PET mothers.*

PET was found significant (p=0.01) risk factor for PPHN (78% versus 53%). About 78% preterm babies' mothers had PET compared to 53% preterm babies mother didn't have PET (Figure2). Odds of having preterm is 3.1 times (OR=3.12; p=0.010) among mothers who had PET compared to mothers who did not have PET.

Similarly maternal asthma was another significant (p=0.010) risk factor for PPHN. About 92% preterm babies' mothers had asthma compared to 56% preterm babies' mother who did not have asthma (Figure3). Odds of having preterm is 9.6 times (OR=9.60; p=0.032) among asthmatic mothers compared to non-asthmatic mothers.

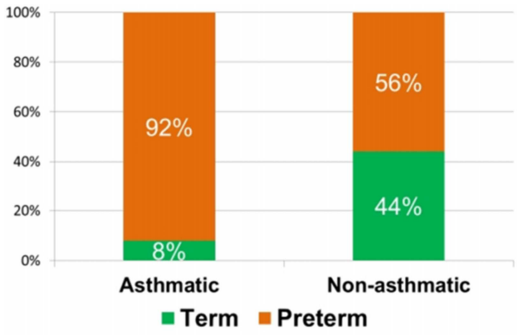

Figure 3. *Proportion of preterm among asthmatic and non-asthmatic mothers.*

3.3. Perinatal Risk Factors

Table 3. *Comparison of neonatal morbidities among both groups having PPHN.*

Neonatal Morbidities	Group-1(Preterm, <37 wksGA), n=93(%)	Group-2(Term, ≥37 wks GA), N=64(%)	P value
Perinatal asphyxia	11 (12)	8 (13)	1
RDS	43 (46)	9 (14)	0.000
MAS	0	9 (14)	0.000
Cong. pneumonia	13 (14)	14 (29)	0.205
TTNB	5 (5.3)	3 (5)	1
Sepsis	60 (65)	51 (80)	0.05
CHD	48 (52)	28 (44)	0.515
Jaundice	70 (75)	46 (72)	0.06
Coagulopathy	21 (23)	7 (11)	0.089
AKI	12 (13)	5 (8)	0.434
IVH	10 (11)	3 (4.7)	0.242
Thrombocytopenia	10 (11)	5 (8)	0.591
Dyselectrolytemia	30 (32)	18 (28)	0.602
Hypocalcemia	50 (54)	31 (48)	0.521
Birth Defect	6 (6.4)	10 (16)	0.105
Syndromes	6 (6.4)	5 (8)	0.759
Associations			
CCAM (Congenital cystic adenomatoid malformation)	0	2	0.165
CDH (Congenital Diaphramatic Hernia)	0	1	0.408

Most of the newborns were delivered by LUCS (89%). Among the delivery variables, 23% neonates with PPHN required some form of resuscitation like suction, tactile stimulation or bag mask ventilation (Figure 4).

Meconium Aspiration Syndrome (MAS) in term neonates was significantly associated with PPHN (p<0.05) shown in Table 3.

Respiratory Distress Syndrome (RDS) was also found significant (p<0.001) risk factor for PPHN in preterm babies (Table 3). Odds of having preterm is 5.5 times (OR=5.46; p<0.001) among mothers whose babies had RDS compared to mothers whose babies did not have RDS (Figure 5).

Seventy percent newborns with PPHN responded well to high flow O2. Besides O2 therapy, other respiratory supports

like CPAP, SIMV and medications were required more in preterm group than term but these were not statistically significant (Table 4). Ninety six percent babies were discharged to home.

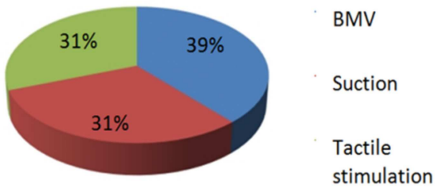

Figure 4. *Types of delivery room resuscitation- required in 23% of all PPHN cases.*

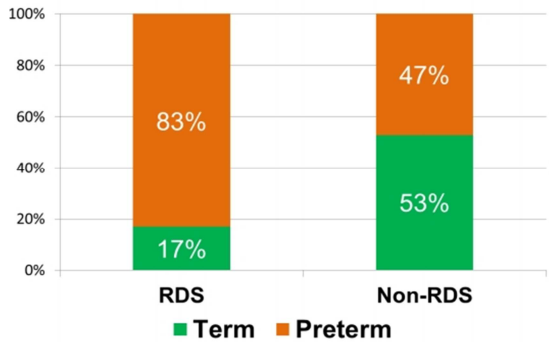

Figure 5. *Proportion of preterm with PPHN cases for having RDS.*

Table 4. *Management required in PPHN cases.*

Management	Group-1(Preterm, <37wksGA) n=93(%)	Group-2(Term, ≥37wksGA), n=64(%)	Pvalue
Respiratory support			
Only O2	37 (40)	24 (26)	0.868
CPAP	15 (16)	5 (8)	0.149
SIMV	21 (23)	11 (17)	0.430
HFOV	0	1 (1.5)	0.408
B. Drugs			
MgSO4	18 (19)	13 (20)	0.519
Sildenafil	14 (15)	13 (20)	0.399
Milrinone	0	3 (4.6)	0.06
Surfactant	14 (15)	6 (9.3)	0.339

4. Discussion

Persistent pulmonary hypertension of the newborn (PPHN) is a frequent cause of hypoxemic respiratory failure in term and late preterm infants affecting 0.43 to 6.8 per 1000 live births [15-16]. In our study 14% of the admitted newborns have PPHN which is slightly higher; might be due to increased number of critically sick newborns referred from other hospitals. According to Martina AS et al, the incidence of PPHN in late preterm age group is much higher and more likely to be due to RDS or infection than in term infants [17]. In our study PPHN was also higher in late pre-term (68%) babies. It is noted by many authors like Razzaq A, Quddusi AI, Nizami Nand Fatema NN in their work that males developed PPHN more than females [2, 28]. We also got PPHN more among males (66%). However, female sex is protective against severe RDS because of advanced fetal pulmonary maturity, which might explain the protective effect of female sex on PPHN [17]. Another important risk factor for PPHN is caesarian section which is found significant in most of the studies. It is found that the risk for PPHN was 7 times higher after cesarean section deliveries when compared with vaginal deliveries [7]. In normal labor; there is increased release of endogenous prostaglandins and catecholamines. These substances along with physical compression from birth canal result in increased clearance of lung fluid, which is absent in cesarean section delivery [2]. In our study both group of babies with PPHN were delivered by LUCS but it was not found statistically significant. It may be due to increased referral of complicated delivery cases to our hospital. Maternal asthma has been identified as a risk factor for PPHN because this condition causes placental insufficiency and thus contributes to fetal hypoxemia, which has been shown to induce pulmonary hypertension [18-19]. Furthermore Hernandez-Diaz S et al. stated that genetic predisposition to lung disorders or unknown environmental exposures could increase the risk for both asthma in the mother and PPHN in the fetus [7]. But Ahmed T et al. did not get any association between maternal asthma and fetal PPHN [20]. We have found a significant risk for PPHN among mothers with asthma in our study. We also got maternal PET as a significant risk factor for developing PPHN in newborns which is consistent with various studies [21-24]. It has been reported by many authors that RDS and PPHN are associated [17, 21]. 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 it-self and these are the reasons for PPHN in preterm with RDS [17]. Among the well-recognized risk factors for PPHN, meconium aspiration syndrome is another one; although it's incidence has decreased in recent years due to a reduced number of post-term deliveries [25]. Whether PPHN is a direct consequence of meconium aspiration or is a surrogate marker for in utero stress still remains unknown. Meconium inactivates surfactant, causes lung inflammation and alveolar hypoxia resulting in pulmonary vasoconstriction. Meconium in the airway leads to obstruction, gas trapping and lung over distention and elevation of leukotrienes, platelet activating factors, thromboxanes which further

increase the pulmonary vascular resistance [25-27]. In our study, MAS has been found as a significant risk factor for PPHN in term babies which is consistent with the findings of Cassidy Delaney and David N. Cornfield [26]. Other than risk factors we also tried to find out the need of medications and therapy for PPHN among these two groups. Preterm group required more support than the term. The optimal approach to the management of PPHN remains controversial till now. Many authors concluded that conventional therapy is effective in the management of PPHN. We also found that most of the newborns (70%) responded well with high flow O2 [28-29]. Most of the patients showed favorable outcome of PPHN cases [28].

5. Conclusion

Pre-eclamptic toxemia and maternal asthma are significant risk factors for PPHN, more in preterm babies than the term. RDS in preterm and MAS in term babies are strongly associated with PPHN.

6. Recommendation

a) To convey the message to the obstetricians regarding strong relationship of maternal PET and asthma with PPHN; this will help them to pick up the cases for timely prevention.
b) As significant association was found between PPHN and RDS in pre-term baby and MAS in term; neonatologists should treat these cases with special care.

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