PREVALENCE AND CLINICAL CORRELATES OF PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN IN NEONATES WITH PERINATAL ASPHYXIA AT KENYATTA NATIONAL HOSPITAL – NEWBORN UNIT (KNH-NBU)

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Declaration

This research dissertation is my original work and has not been presented for the award of a degree in any other university for award.

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Dedication

I thank God for guiding me through this successful journey.

With so much respect, I dedicate this book to my father. I have no words to describe your continuous inspiration, encouragement, support and love.

Many thanks to my very supportive family.

My sincere gratitude to Professor Jowi for making this difficult study possible with her dedication.

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List of Abbreviations

PPHN -	Persistent Pulmonary Hypertension of Newborn
PA -	Perinatal Asphyxia
HIE -	Hypoxic Ischemic Encephalopathy
KNH -	Kenyatta National Hospital
NBU -	Newborn Unit
WHO -	World Health Organization
K^+ -	Potassium ion
Na^+ -	Sodium ion
FiO_2 -	Fraction of inspired Oxygen
NO -	Nitric Oxide
PVR -	Pulmonary Vascular Resistance
V/Q -	Ventilation Perfusion ratio
MAS -	Meconium Aspiration Syndrome
CPAP -	Continuous Positive Airway Pressure
BP -	Blood Pressure
sPAP -	Systolic Pulmonary Artery Pressure
mPAP -	Mean Pulmonary Artery Pressure
RAP -	Right Atrial Pressure
VmaxTR -	Peak velocity of Tricuspid Regurgitation
2D ECHO -	2-dimensional Echocardiography

Definitions of Terms

1. **PPHN:** is the failure of the normal circulatory transition at birth characterized by marked pulmonary hypertension leading to hypoxemia secondary to right-to-left shunting of blood at foramen ovale and ductus arteriosus(1).

2. **Perinatal Asphyxia:** Failure to initiate and sustain breathing at birth (2) plus clinical evidence of Hypoxic Ischemic Encephalopathy as defined by Sarnat and Sarnat staging (3).

3. **Hypoxic Ischemic Encephalopathy:** Acute non-static brain injury late antepartum or intrapartum caused by brain hypoxia and ischemia.

4. **Term Neonate:** A newborn infant delivered at or after 37 completed weeks of gestation and is in the first 28 days of life.

5. **Pulmonary Hypertension**: Mean Pumonary Atery Pressure of ≥ 20 mmHg calculated using modified Bernoulli's equation and Chemla's equation.

Abstract

Introduction

Perinatal asphyxia is the inability to start or maintain breathing after birth. Globally around 9 million cases of perinatal asphyxia are reported annually and in Kenya, it accounts for 29% of neonatal mortalities. This is a major risk factor for developing Persistent Pulmonary Hypertension of the Newborn (PPHN) as hypoxia and ischemia lead to an increase in PVR and both are associated with MAS. Severe PPHN in asphyxia can lead to higher mortality rates and longer hospital stays. Since PPHN is a treatable condition, early diagnosis can improve the outcomes in asphyxiated neonates. Echocardiography can be effectively used to diagnose PPHN by estimating mPAP.

Objective

To determine the prevalence of PPHN in neonates with birth asphyxia at KNH-NBU.

Methodology

A hospital-based prospective observational study among neonates with moderate to severe asphyxia admitted to the KNH-NBU. 49 neonates were recruited into the study. Echocardiography was performed to diagnose and determine the severity of PPHN.

Data analysis

Data was entered and analyzed using The R version 4.1.2. Continuous variables were presented in summary form using means and standard deviation. The Fishers exact test of association was used to compare the categorical variables.

Ethical considerations

Consent was obtained from the KNH-UoN Ethics committee. The ECHO findings were communicated to the attending doctor in real-time for better management of the patients.

Results

Out of 49 neonates 26 were found to have PPHN. In multivariate analysis Meconium stained liquor, Male gender and cesarean section delivery were found to be significant risk factors for developing PPHN in neonates with asphyxia.

Conclusions

The prevalence of PPHN was found to be high (53%) in the neonates with perinatal asphyxia. Asphyxiated Neonates born through meconium stained liquor were having higher risk for developing PPHN.

Introduction

Background

According to WHO, perinatal asphyxia is the failure to start and maintain breathing after birth (2). The absence of blood flow or gas exchange to the fetus in late pregnancy, during or after birth causes it. There is an incomplete or broad oxygen loss to the critical organs when placental or pulmonary gas exchange is reduced or interrupted. Hypoxemia and hypercapnia occurs as a result of this insult. The tissues and essential organs will incur an oxygen debt if the hypoxia is severe enough. Lactic acidosis and anaerobic glycolysis will occur. The neurologic consequences of perinatal hypoxia are known as neonatal hypoxic-ischemic encephalopathy (4).

In Kenya, neonatal mortality rate is high at 21 per 1,000 live births and perinatal asphyxia contributes to 29% of neonatal mortalities (5). In KNH- NBU Perinatal asphyxia accounts for up to 20% of admissions and the mortality rate in this group is documented at 31.1% by day 7 of life (6).

The following factors are evaluated in diagnosing asphyxia according to the American Academy of Paediatrics (AAP) and the American College of Obstetrics and Gynecology (ACOG) standards.

(i) Intense metabolic or mixed acidosis, pH <7.00 from the umbilical artery blood sample, if obtained,
(ii) Apgar score of 0–3 for longer than 5 min,
(iii) neonatal neurologic sequelae , and
(iv) several organ connections such as the kidney, lungs, liver, heart and intestines (7)

Perinatal asphyxia is associated with numerous multiorgan effects and its impact on the brain, resulting in hypoxic-ischemic encephalopathy (HIE) is one of the serious complications linked to unfavourable outcomes. "An acute non-static encephalopathy induced by intrapartum or late antepartum brain hypoxia and ischemia," according to the definition. The Sarnat and Sarnat grading system is used to classify HIE into three categories which are predictive of neurodevelopmental disability in newborns with perinatal asphyxia (3).

Pathogenesis and pathophysiology of HIE

The pathogenesis of neuronal damage in HIE is due to the deprivation of oxygen and energy in the form of glucose which results in an abnormal and toxic biochemical neuronal milieu that causes cell damage and death.

This initial insult in HIE, termed primary energy failure, results from oxygen deficiency leading to anaerobic metabolism and accumulation of lactate. Lactate accumulation is initially instrumental as an alternate source of energy but has a detrimental impact by causing an impairment in cardiovascular autoregulation capacity which worsens an already compromised circulation.

With hypoxia, there is reduced oxidative phosphorylation and decreased production of adenosine triphosphate (ATP). ATP depletion leads to of the transcellular ATP-dependent Na^+/K^+ ATPase pump failure. An influx of extracellular electrolytes (Na^+) into the intracellular compartment with passive diffusion of water intracellularly results in cell swelling and cell lysis by causing necrosis (cytotoxic oedema). The influx of Na^+ results in membrane depolarization and the release of glutamate, an excitatory amino acid, into the synaptic cleft and reduced uptake by the post-synaptic neuron.

Excessive release of glutamate triggers an excitotoxic cascade acting on 3 major ionotropic receptors: N-methyl-D-aspartate (NMDA) receptors, Kainate receptors (KA) and alpha-amino-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors. NMDA receptor activation causes voltage-gated Ca2+ channels to open and become active. Secondary cell death is caused by NMDA activation and intracellular calcium buildup, which activates lipases, proteases, caspases, endonucleases, and nitric oxide synthase. Apoptosis (cell death) is the result of this pathway (7).

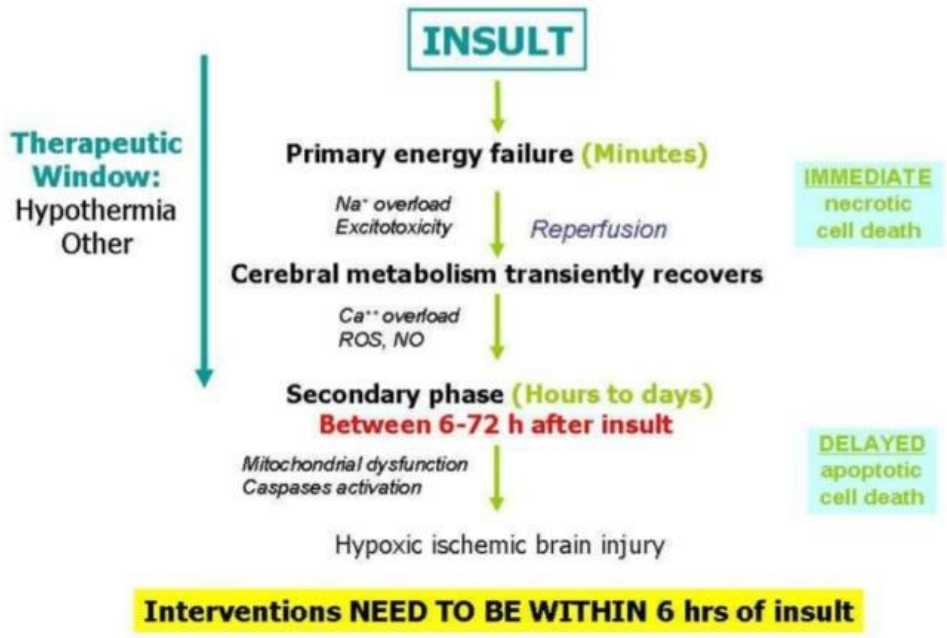

Figure 1: Schematic illustration of HIE pathophysiology

(Adapted from *Perinatal webinar: HIE)* (8).

Various factors increase the risk of perinatal asphyxia and include impaired maternal oxygenation, decreases blood flow from the mother to the placenta, and increased fetal oxygen requirement. The aetiology of perinatal asphyxia may be multiple and include maternal factors such as hypertension, hypotension, infection, hypoxia from cardiac/pulmonary disorder, and drug exposure.

Complications of Perinatal asphyxia

Perinatal asphyxia affects mainly the brain, kidneys, and heart and may manifest as multiorgan dysfunction. It also affects the pulmonary system causing high pulmonary vascular resistance (PVR), pulmonary haemorrhage, and pulmonary oedema are symptoms of persistent pulmonary hypertension in the newborn (9).

Persistent Pulmonary Hypertension of the Newborn (PPHN)

PPHN is described as a failure of the usual reduction in pulmonary vascular resistance at or shortly after birth, resulting in the shunting of unoxygenated blood into the systemic circulation across the foramen ovale or ductus arteriosus (9).

The prevalence of PPHN is 0.2% in developed countries but most likely higher in developing countries (10). Various risk factors have been associated to develop PPHN, common ones being meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), Pneumonia and Perinatal asphyxia.

Physiology of Fetal circulation and Neonatal transition

Low systemic vascular resistance, high pulmonary vascular resistance (PVR), and the existence of shunts characterize fetal circulation (foramen ovale and Ductus arteriosus). Since the placenta, not the lungs, serves as the organ for respiration, a high PVR is normal and vital for the fetus. The ductus arteriosus carries the majority of right ventricular output to the aorta, leaving just 13-21 percent of total ventricular output for the pulmonary vascular bed. Low fetal oxygen content, fluid-filled alveoli squeezing the pulmonary blood arteries, and vasoconstriction mediators including endothelin-1, thromboxane, and leukotriene all contribute to the elevated PVR in utero (11).

At birth, a marked increase in oxygen tension and rhythmic distention of lungs by breathing causes an 8-10-fold increase in pulmonary blood flow and pulmonary arterial pressure drops by 50%. Increased blood flow and oxygenation cause a rise in endothelial nitric oxide (NO) production. Using cyclic guanosine monophosphate, NO mediates pulmonary vasodilation (cGMP) (11).

Pathogenesis and Pathophysiology of PPHN

Late preterm and term newborns are more likely to have PPHN. When the PVR does not fall after delivery, PPHN develops, which is characterized by increased pulmonary vascular resistance and right-to-left shunting through the foramen ovale and/or ductus arteriosus, resulting in arterial hypoxia even with 100% FiO2 (12).

Mainly three types of pulmonary vasculature abnormalities underlie PPHN, which are;

1. Underdevelopment: When the diameter of the pulmonary vasculature is reduced, the PVR is fixed. Pneumoplasia can arise as a result of congenital diaphragmatic hernia (CDH), congenital pulmonary malformation (CPM), renal agenesis, and fetal growth limitation.
2. Maldevelopment: is seen as atypical muscle layer thickening of the pulmonary arterioles. Conditions leading to maldevelopment may include post-term delivery, meconium staining and MAS.
3. Maladaptation occurs when the pulmonary vascular bed develops normally but severe perinatal circumstances promote active vasoconstriction, interfering with normal postnatal PVR decline. Perinatal hypoxia, pulmonary parenchymal disorders, and pneumonia are among these ailments.

Whatever the origin, high PVR leads to aberrant smooth muscle growth and hypertrophy in the walls of tiny pulmonary arteries and arterioles, as well as right-to-left shunting and chronic systemic hypoxia. Increased stress on the heart is caused by high pulmonary and systemic resistances, resulting in right ventricular hypertrophy, tricuspid insufficiency, and right-sided heart failure (13).

PPHN in Perinatal asphyxia

Asphyxia is one of the main etiologies of developing Persistent Pulmonary Hypertension of the Newborn. According to a study by Ahmed et al., 19.5% of asphyxiated neonates developed PPHN (9). Hypoxemia and metabolic acidosis are the main factors causing PPHN in asphyxiated neonates. Failure to start breathing at birth causes hypoxia in the lungs and in the absence of oxygen, which is one of the vasodilators required to dilate Pulmonary arterioles and to constrict ductus arteriosus, PVR remains elevated after birth. Pulmonary vasoconstriction is aggravated by hypoxia and acidity, causing a cycle of right-to-left shunting, hypoxia, and acidosis (13). Ischemia, right and left ventricular dysfunction, coagulation abnormalities, hyperoxic resuscitation, and mechanical ventilation impacts are all direct causes of PPHN in hypoxia.

PPHN in asphyxia can also occur ramblingly since both are related to meconium aspiration syndrome. Meconium can obstruct the airway and also deactivate the surfactant leading to an increase in V/Q (Ventilation/Perfusion) ratios and intrapulmonary right-to-left shunting(1).

Literature Review

Prevalence of PPHN in Perinatal Asphyxia

Different studies have effectively linked PPHN as a complication of perinatal asphyxia. Two African studies linking PPHN, and perinatal asphyxia were identified in the literature. A study from Egypt concluded that the prevalence of PPHN in the NICU was 5% and birth asphyxia among others was associated with elevated risk for PPHN.

The other study in South Africa by Nchabeleng et al showed that 14% of the neonates with PPHN had an APGAR score of <6 at 5 minutes and birth asphyxia accounted for 6% of the single risk factor for developing PPHN.

A meta-analysis of 22 studies by Zhou et al., in China, showed that asphyxia is an important risk factor for developing PPHN with odds ratio of 3.9.

A prospective study from India by Ahmed et al., clearly investigated the prevalence of pulmonary hypertension in newborns with perinatal asphyxia, where they considered Pulmonary arterial pressures (PAP) of >25mmHg to be PAH and right-to-left blood shunting at foramen ovale or ductus arteriosus as diagnostic for PPHN. In their study, they found that the prevalence of PAH and PPHN was 44% and 19.5% respectively in the neonates with perinatal asphyxia.

Table 1 summarizes the above-mentioned studies on PPHN in perinatal asphyxia highlighting the study methods, and results.

Table 1: Summary of studiesdone on PPHN in perinatal asphyxia

Study title/ Author/ Year	Type of study and Sample size	Results
Prevalence and outcome of pulmonary arterial hypertension in newborns with perinatal asphyxia (9). **Ahmed et al. 2018, India**	Prospective observational study 41 neonates	The prevalence of PPHN in asphyxiated newborns is 19.5%.
A meta-analysis of the risk factors of Persistent Pulmonary Hypertension in newborns (14). **Zhou et al. 2021, China**	Meta-analysis of 22 studies	Perinatal asphyxia is an important risk factor in developing PPHN with odds ratio of 3.9
Prevalence and outcomes of persistent pulmonary hypertension of the newborn in a neonatal unit, Mankweng Hospital, Limpopo Province, South Africa (15) **Nchabeleng et al. 2021, South Africa**	A retrospective descriptive review of 6,776 neonates	Birth asphyxia accounted for 6% of the single risk factors for developing PPHN.
Pulmonary Hypertension Associated with Hypoxic-Ischemic Encephalopathy-Antecedent Characteristics and Comorbidities (16). **Lakshminrusimha et al. 2017, USA**	Prospective observational study 303 neonates	PPHN is common among infants with moderate/severe HIE and is associated with severe encephalopathy, lung disease, sepsis, systemic hypotension, and increased mortality.

Conceptual Framework

Conceptual Framework narration

The study aims to establish the prevalence of PPHN in neonates with perinatal asphyxia. Perinatal asphyxia has been considered a major risk factor for developing PPHN. Thus, independent variables that are investigated in this study include the severity of asphyxia, APGAR score, Sarnat staging, gestation age, birth weight, treatment with Therapeutic Hypothermia, and presence of MAS. The outcome/ dependent variable are the presence or absence of PPHN.

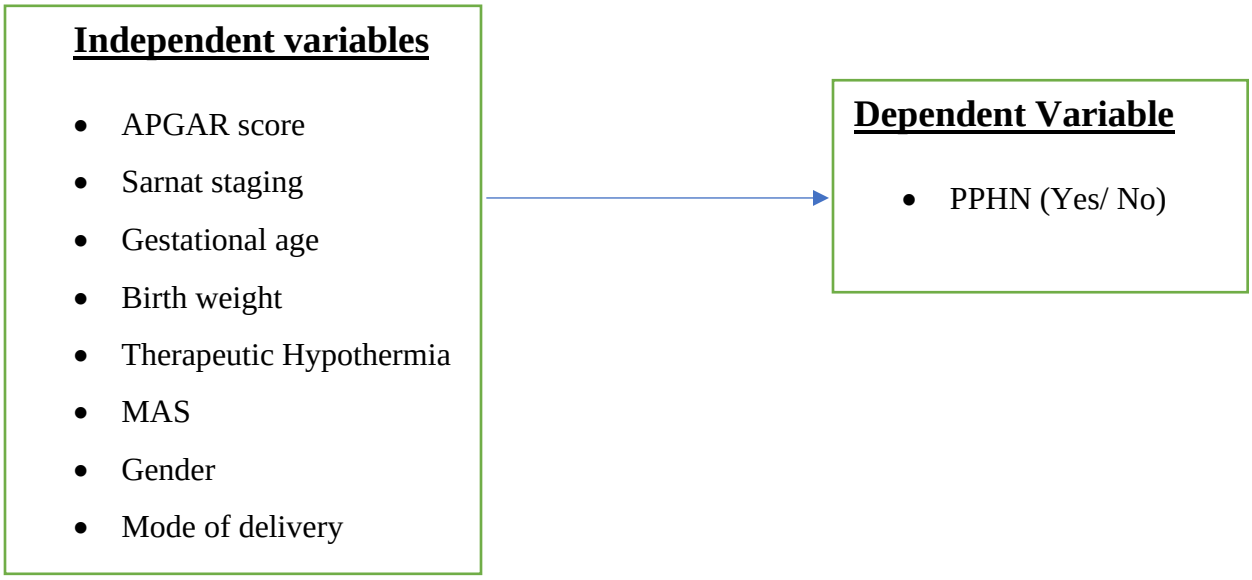

Figure 2 Conceptual framework

Justification and Utility

Asphyxia is one of the main risk factors for developing Persistent Pulmonary Hypertension (PPHN). Having PPHN increases the risk of mortality for these neonates or sometimes can be considered a contraindication to treat them with therapeutic hypothermia.

PPHN is a manageable condition and timely treatment can help reduce mortality and morbidity in asphyxiated neonates. The aspect of PPHN is mostly ignored in the management of these neonates. Having known the prevalence of PPHN in asphyxiated neonates can allow clinicians to actively investigate and treat PPHN in this subset of neonates.

Research question and study objectives

Research Question

What is the prevalence, severity, and clinical correlates of Persistent Pulmonary Hypertension of the Newborn (PPHN) in neonates admitted with Perinatal asphyxia at KNH newborn unit (NBU)?

Study objectives

Primary Objective

- To find the prevalence of PPHN in neonates with birth asphyxia at KNH-NBU.

Secondary objectives

- To describe the severity of PPHN in neonates with birth asphyxia at KNH-NBU.
- To assess the risk factors associated with PPHN in asphyxiated neonates e.g., Gestational age, Gender, Therapeutic Hypothermia, Meconium aspiration syndrome (MAS), Mode of delivery, severity of HIE and birth weight.

Methodology

Study design

The study was a **prospective observational study** conducted in a hospital setup. Although this study design is costly and time consuming it was chosen because of the advantages it provides over the retrospective study. The advantages being avoidance of recall bias or incomplete medical records, consistency in data collection and objective observations.

Study setting

The study was done at Kenyatta National Hospital (KNH) newborn unit. KNH is the national referral hospital in Kenya. KNH NBU serves the sick neonates born in KNH as well as the referrals from peripheral facilities, accommodating up to 110 neonates at any given point in time. The common conditions managed are perinatal asphyxia, Neonatal jaundice, neonatal sepsis, prematurity, and meconium aspiration among others.

The NBU also includes a Neonatal intensive care unit (NICU) with 7 beds and ventilators. Other equipment includes 10 CPAP machines, 6 phototherapy machines and 3 full-body cooling cradles. Perinatal asphyxia accounts for around 20% of the total admissions. KNH- NBU offers Therapeutic Hypothermia as a standard treatment for moderate and severe asphyxia and hence receives several referrals with a diagnosis of asphyxia.

Study population

Neonates admitted with a diagnosis of perinatal asphyxia at KNH-NBU were recruited into the study. The primary investigator examined neonates and diagnosis of perinatal asphyxia was based on,

1. ‘inability to commence and maintain breathing at birth’, and
2. Clinical signs of HIE as defined by Sarnat and Sarnat staging.

Inclusion criteria

- Term neonate
- Evidence of perinatal asphyxia by APGAR score of <5 at 10 minutes and/or need of resuscitation ≥ 10 minutes.
- Moderate or severe encephalopathy based on Sarnat and Sarnat staging

- Informed consent from the caregiver

Exclusion criteria

- Neonates with obvious congenital malformations
- Neonates with congenital heart diseases
- Caregiver declines to give consent

Sample size calculation

Cochran's Sample Size Formula was used as follows,

$$n = \frac{Z^2(pq)}{d^2}$$

Where:

d is the preferred level of precision (i.e., the margin of error), 0.1

p is the proportion of the population with the characteristic in question, 19.5% (0.195) as per a study done by Ahmed et al (9).

Q is 1 – p, (0.805)

$= (1.96^2 \times 0.195 \times 0.805)/0.1^2$

$= 60.304 \approx 61 \quad \therefore n = 61$ neonates

The sample population was 61 (n0) Neonates. Because of the small population of asphyxiated neonates being studied at KNH – NBU, a finite sample correction was done to obtain a convenient sample size, using

$$n = \frac{n0}{1 + \frac{n0-1}{N}},$$

N is estimated neonates with asphyxia in KNH NBU, which is 20% of total neonates admitted to the unit. Average admission in NBU is 300 monthly. 20% of 300 = 60. Duration of data collection is 4 months. N = 60×4 = 240.

$$N = \frac{61}{1 + \frac{61-1}{240}} = 48.8 = 49 \text{ neonates.}$$

Sampling Method

All children who met inclusion criteria and did not have exclusion criteria were enrolled into the study through consecutive sampling.

Study procedures

The principal investigator screened the patients and examined them to score the severity of perinatal asphyxia. 52 Neonates who met inclusion criteria were identified and recruited into the study after gaining the caregivers' informed permission. Ethical approval was sought from Kenyatta National Hospital Ethics and Research committee.

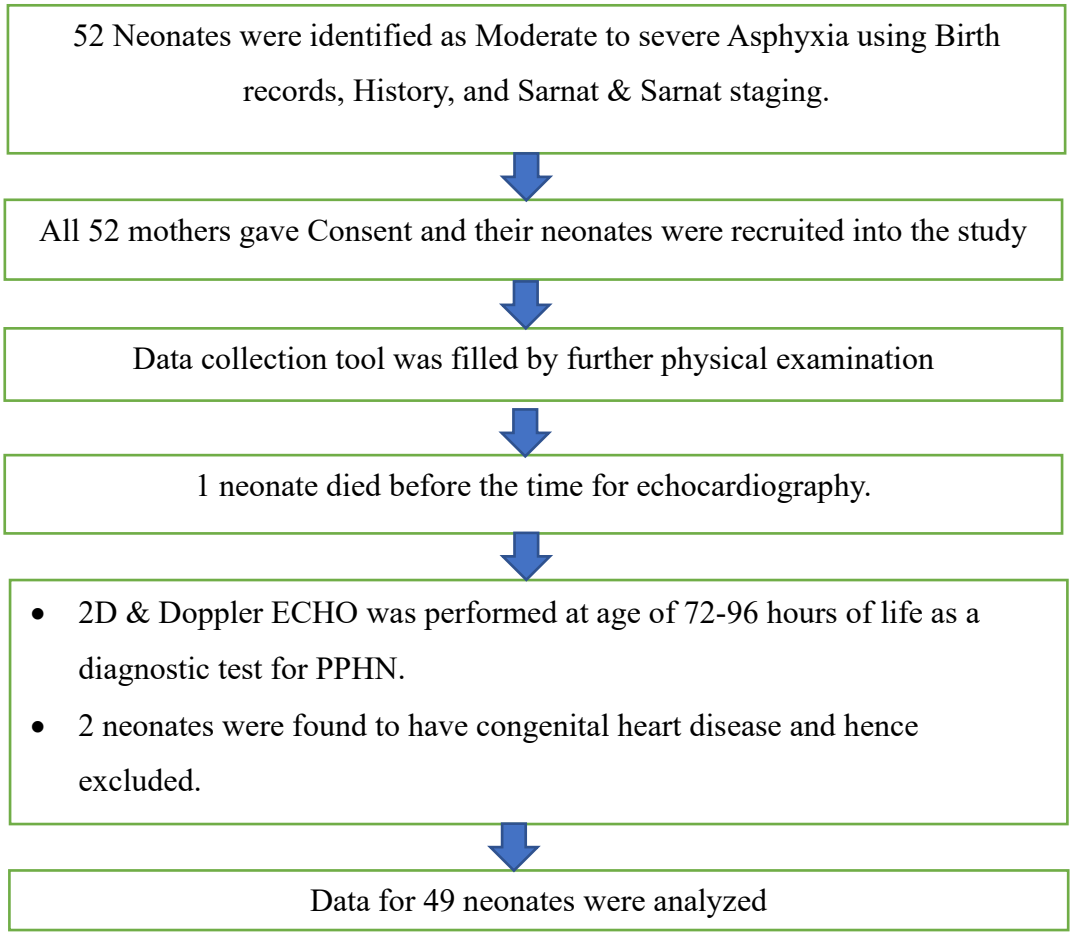

Figure 3: study procedure flow chart

The figure 3 shows the flow chart of the study participant enrollment process. Out of 52 children with moderate to severe asphyxia 2 had congenital heart diseases while 1 neonate died before

performing the echocardiography. Therefore total of 49 neonates underwent echocardiography and were included into the analysis.

Physical Examination

The investigator who was 2nd year pediatric resident performed the full examination of the neonate within 1st 24 hours of life. It included a general exam and focused systemic exam involving Cardiovascular, respiratory and Central nervous systems. Gestational age was assessed using the New Ballard's score and the Weight was taken using a calibrated digital Salter scale and measured to the nearest gram.

ECHO procedure for diagnosis and severity of PPHN

ECHOs was performed by the senior paediatric cardiologist and assisted by the principal investigator. It was performed when the neonate was between the ages of 72-96 hours to allow the Pulmonary artery pressures to drop normally as transition from Fetal to Neaonatal circulation (17). Transthoracic echocardiography was performed using a portable Vivid I colour echocardiography machine. The ECHO was performed when the neonate was asleep or calm. Cardiac measurements were done in accordance with the procedures of the American Society of Echocardiography (18) with emphasis on,

A. Pulmonary artery pressures,

Systolic pulmonary artery pressure (sPAP) was calculated by measuring the peak velocity of tricuspid valve regurgitation using modified Bernoulli's equation (19),

$sPAP \approx 4\times (VmaxTR)^2 + RAP$,

Where, VmaxTR = Peak velocity of tricuspid regurgitation in m/s,

RAP = Right atrial pressure in mmHg, assumed to be 10 mmHg

The Chemla's equation was then used to calculate the mean pulmonary artery pressure (mPAP) (20), $mPAP = (0.61 \times sPAP) + 2$ mmHg.

Pulmonary hypertension was considered when mPAP is > 20 mmHg (21).

The severity was categorized as,

- Mild: sPAP 30 – 39 mmHg
- Moderate: sPAP 40 – 60 mmHg
- Severe: sPAP > 60 mmHg (9).

B. **Myocardial performance,** checking for right and left ventricular functions.
C. **Shunting** of the blood through ductus arteriosus and open foramen ovale.

Other significant findings were also recorded. The digital images and videos from ECHOs were stored for future validation purposes. For the confidentiality purposes, the digital images were labeled with respective study numbers and not the names of the neonates.

Ethical considerations

The researcher sought approval from the KNH/UoN research and ethics committee. The patients were recruited into the study only after explaining the study details to the caregivers and obtaining their consent. No financial implications were transferred to the patients, nor were they given any compensation to participate in the study. The significant ECHO findings were communicated to NBU doctors in real time and the appropriate management was suggested for the patients by the paediatric cardiologist. At all times, the confidentiality of the patient was maintained. For reference purposes, the ECHO films were stored in the password protected computer bearing a study number and not the names of the patient.

3.8 Data management and analysis

Data management

Collected data was entered into excel spreadsheet, checked for completeness, cleaned, and stored in a password-protected personal computer. The data was then imported into R version 4.1.2 for analysis.

Data analysis

Categorical variables e.g., gender and severity of HIE were summarized as frequencies and proportions. Continuous variables e.g., the weight of the neonates was summarized using mean

and standard deviation since it was normally distributed. Skewed continuous variables e.g., gestation in weeks was summarized using median and standard deviation.

The proportion of neonates with PPHN was summarized using a proportion with 95% confidence intervals. The severity of PPHN was summarized using frequencies and proportions, and presented using a bar chart.

The association between the severity of HIE and development of PPHN was analyzed using Fisher's exact test. The association of other variables e.g., gender, meconium-stained liquor, therapeutic hypothermia with the outcome i.e., development of PPHN was analyzed using binary logistic regression. A multivariable logistic regression model was fitted to adjust for the effect of predictors on each other. Variables for the multivariable model were selected using purposeful selection (p values <0.25) but others e.g., gender and mode of delivery were added based on literature where they have been shown to be significant.

Results were interpreted at 5% significance level with p values less than 0.05 considered significant, odds ratios and confidence intervals for odds ratios.

RESULTS

Descriptive characteristics of the neonates

Among the 49 neonates who were recruited into the study, 28 (57%) were females and the rest were males. The mean birth weight of the neonates was 3218 grams with a standard deviation of 382 grams. One (2%) neonate was born with low birth weight, 47 (96%) were born with normal weights and 1 (2%) was born with macrosomia.

The median gestational age of the neonates was 39 weeks with an interquartile range of 38 to 40 weeks. Thirty-six (73%) of the neonates were born via spontaneous vaginal delivery and the rest were born via caesarean section (Table 2).

Table 2: Descriptive characteristics of the neonates (n=49)

Variable	Detail	Frequency/Median/Mean	Percent/IQR/SD
Gender	Male	21	43
	Female	28	57
Birth weight in grams	Mean	3218	382
Birth weight categories in grams	Low birth weight (1500-2499)	1	2
	Normal weight (2500-4000)	47	96
	Macrosomia (>4000)	1	2
Gestation in weeks	Median	39	(38, 40)
Mode of delivery	Spontaneous vaginal delivery	36	73
	Caesarean section	13	27

Clinical characteristics of the neonates

All the neonates who participated in this study had hypoxic ischaemic encephalopathy (HIE). Of the 49 neonates, 38 (77.6%) had moderate HIE and the rest had severe HIE. The median APGAR score for the neonates at 5 minutes was 5 with an interquartile range of 5 to 6 minutes.

Table 3: Clinical characteristics of the neonates (N = 49)

Variable	Detail	Frequency/Median	Percent/IQR
Hypoxic Ischaemic Encephalopathy severity	Moderate	38	77.6
	Severe	11	22.4
APGAR score at 5 minutes	Median	5	5, 6
Meconium-stained liquor	Yes	9	18.4
	No	40	81.6
Therapeutic cooling	Yes	35	71.4
	No	14	28.6
Systolic pulmonary arterial pressure	Median	32	17, 44

Out of the 49 neonates, 9 (18.4%) had meconium-stained liquor and the rest did not. Thirty-five (71.4%) of the neonates underwent therapeutic cooling and the rest did not. The median systolic pulmonary arterial pressure was 32 mmHg with an interquartile range of 17 to 44 mmHg (Table 3).

Prevalence of PPHN among neonates with birth asphyxia at KNH-NBU

The prevalence of PPHN among neonates with birth asphyxia at Kenyatta National Hospital-new born Unit was 53% (95% CI 38%, 67%) (Figure 4).

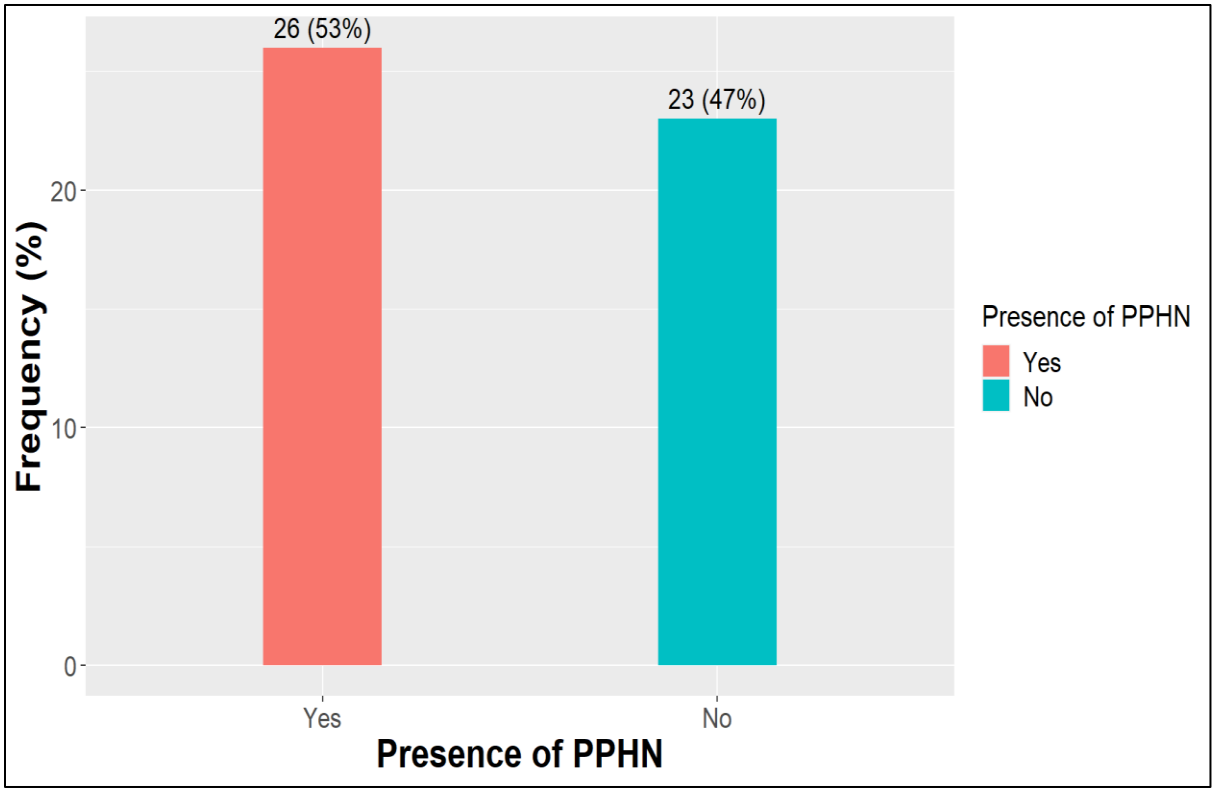

Figure 4: Prevalence of PPHN among neonates with birth asphyxia at KNH-NBU

Association between severity of HIE and development of PPHN

Table 4: Association between severity of HIE and development of PPHN

	Development of PPHN			
Severity of HIE	Yes n = 26	No n = 23	**Total** **N = 49**	P-value
Severe	5 (19%)	6 (26%)	11 (22%)	0.82
Moderate	21 (81%)	17 (74%)	38 (78%)	

Table 4 above shows the results of Fisher's exact test of association between severity of HIE and development of PPHN. The p value of 0.82 indicates that there was no association between the severity of hypoxic ischaemic encephalopathy and development of PPHN at 5% significance level.

Severity of PPHN in neonates with birth asphyxia at KNH-NBU

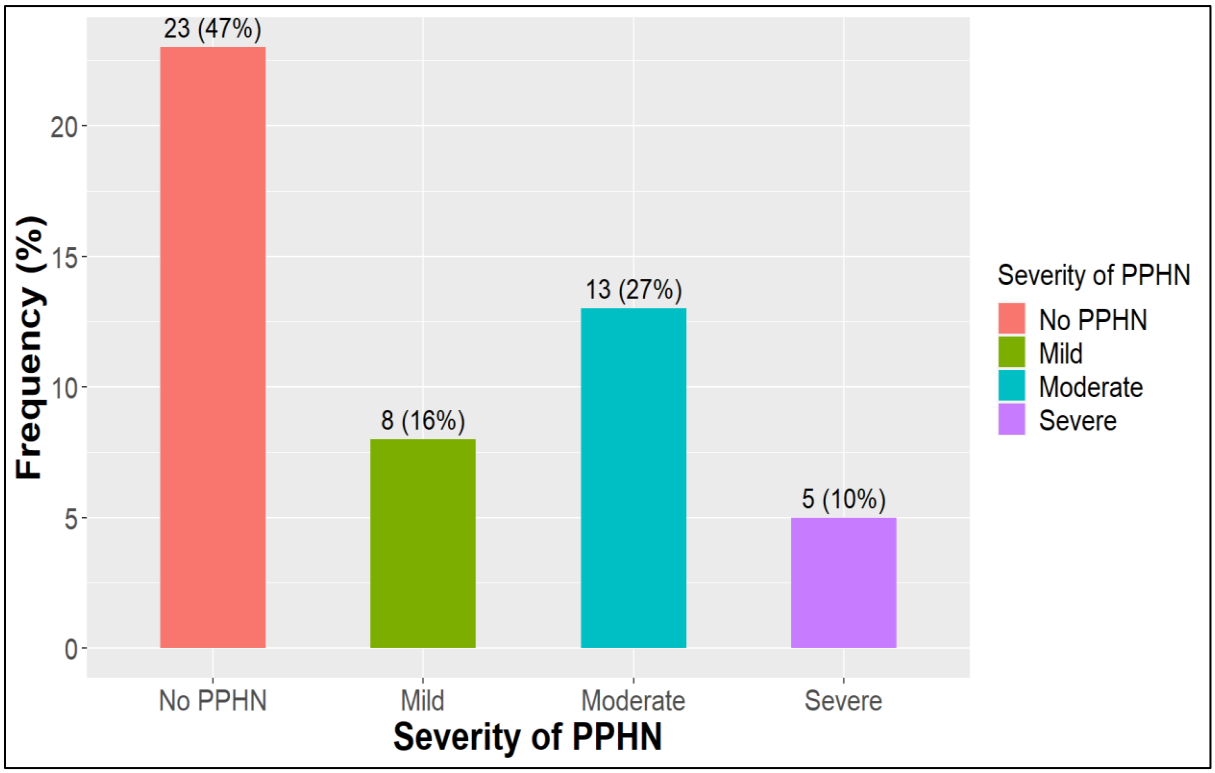

Figure 5: Severity of PPHN in neonates with birth asphyxia at KNH-NBU

In terms of severity persistent pulmonary hypertension (PPHN), 23 (47%) of the neonates did not have PPHN, 5(10%) had severe PPHN, 13 (27%) had moderate PPHN and 8 (16%) had mild PPHN.

Association between the severity of HIE and severity of PPHN

Table 5: Association between the severity of HIE and severity of PPHN

	Severity of PPHN					
Severity of HIE	**Severe n = 5**	**Moderate n = 13**	**Mild n = 8**	**None n = 23**	**Total N = 49**	**p-value**
Severe	3 (60%)	1 (8%)	1 (13%)	6 (26%)	11 (22%)	0.12
Moderate	2 (40%)	12 (92%)	7 (87%)	17 (74%)	38 (78%)	

There was no association between the severity of HIE and severity of PPHN, Fisher's exact test p value 0.12 at 5% significance level (Table 5).

Bivariate analysis

Risk factors predisposing asphyxiated neonates to PPHN

Of the five factors assessed, only meconium-stained liquor was significantly associated with development PPHN in neonates with birth asphyxia, p value 0.03 at 5% significance level. Neonates who got meconium-stained liquor were 9.78 times more likely to develop PPHN compared to neonates who did not get meconium-stained liquor OR 9.78 (95% CI 1.12, 85.65).

Table 6: Risk factors predisposing asphyxiated neonates to PPHN (N = 49)

Variable	**Detail**	**PPHN present**			
		Yes	**No**	**Crude OR (95% CI)**	**P value**
Gender	Male	12	9	1.33 (0.43, 4.16)	0.62
	Female	14	14	***Reference***	
Therapeutic cooling	Yes	19	16	1.19 (0.34, 4.12)	0.79
	No	7	7	***Reference***	
Meconium aspiration syndrome	Yes	8	1	9.78 (1.12, 85.65)	0.03
	No	18	22	***Reference***	
Gestational age in weeks		NA		0.95 (0.70, 1.29)	0.76
Weight in grams		NA		0.999 (0.997, 1.000)	0.15
Mode of delivery	CS	8	5	1.6 (0.44, 5.83)	0.47
	SVD	18	18	***Reference***	

Male neonates were 33% more likely to develop PPHN compared to female neonates OR 1.33 (95% CI 0.34, 4.12). Neonates who underwent therapeutic cooling were 19% more likely to develop PPHN compared to those who did not, OR 1.19 (95% CI 0.34, 4.12).

The results also show that increasing gestational age by 1 week reduced the odds of getting PPHN by 5% OR 0.95 (95% CI 0.70, 1.29). (Table 6)

Multivariable analysis

Variables for the multivariable model were selected using purposeful selection (Hosmer, Lemeshow and Sturdivant, 2013) with p values of less than 0.25 being considered. Two variables; meconium-stained liquor and weight were selected for this model. Gender and mode of delivery were added because literature has shown that they are significantly associated with PPHN.

Risk factors predisposing asphyxiated neonates to PPHN

Under multivariable analysis, meconium-stained liquor remained significant with a p value of 0.04 at 5% significance level.

After adjusting for weight, neonates who had meconium-stained liquor (MSL) were 9.37 times more likely to develop PPHN compared to those who did not get MSL AOR 9.37 (95% CI 1.47, 185.57). After adjusting for MSL, one unit increase in weight reduced the odds of developing PPHN by 0.001% AOR 0.999 (95% CI 0.997, 1.000).

Holding other factors constant, the odds of developing PPHN for male neonates were 25% more than those of female neonates, AOR 1.25 (95% CI 0.36, 4.43). Neonates who were delivered via caesarean section were 59% more likely to develop PPHN after controlling for the other factors in the model (Table 7).

Table 7: Risk factors predisposing asphyxiated neonates to PPHN (N = 49)

Variable	**Detail**	**PPHN present**			
		Yes	**No**	**Adjusted OR (95% CI)**	**P value**
Gender	Male	12	9	1.25 (0.36, 4.43)	0.72
	female	14	14	***Reference***	
Meconium-stained liquor	Yes	8	1	9.37 (1.47, 185.57)	0.04
	No	13	27	***Reference***	
Weight in grams		NA		0.999 (0.997, 1.00)	0.29
	CS	8	5	1.59 (0.39, 6.80)	0.52

Mode of delivery	SVD	18	18	***Reference***	

Discussion

From our study the prevalence of PPHN among the neonates with perinatal asphyxia admitted to KNH NBU between January 2023 to April 2023 was 53% (95% CI 38%, 67%). We did not find any other study in Africa to determine the magnitude of this problem.

Globally many studies have linked perinatal asphyxia as a risk factor for developing PPHN. However, very few studies have looked at prevalence of PPHN in the population of neonates with asphyxia.

There is a study by Ahmed et al in Uttar Pradesh, India where 41 neonates with severe asphyxia were followed up and Pulmonary hypertension was detected in 18 of them giving the prevalence of 43.9% (9). The pulmonary hypertension in this study was defined as PAP of >25mmHg, which was the definition for the same in years 2015,2016. However during the 6th World Symposium on Pulmonary Hypertension (WSPH) in 2018 changed the cut off for the diagnosis of Pulmonary Hypertension to mPAP of >20mmHg. This new cut off was used in our study which might have given us the higher prevalence compared to the old study by Ahmed and colleagues.

A study in Taiwan by Te- Kuei Hsieh et al determined that asphyxia is one of the major risk factors for babies born to Meconium stained liquor to develop PPHN (22) as meconium can obstruct the airway and also deactivate the surfactant leading to an increase in V/Q (Ventilation/Perfusion) ratios and intrapulmonary right-to-left shunting(1). Our study showed similar results as neonates who had meconium-stained liquor (MSL) were 9.37 times more likely to develop PPHN compared to those who did not get MSL AOR 9.37 (95% CI 1.47, 185.57).

Vijverberg Joanna et al compared neonates with asphyxia undergoing therapeutic hypothermia (TH) to those without therapeutic hypothermia and found that PPHN occurred 2.5 times more in the TH group (23). In our study we also had some neonates who did not receive therapeutic cooling due to reasons like unavailability of the cooling device or arriving to hospital later than 6

hours of life. And hence we had a chance to compare the two groups. Our study discovered that neonates who underwent therapeutic cooling were 19% more likely to develop PPHN compared to those who did not, OR 1.19 (95% CI 0.34, 4.12).

This study also found that Male neonates were 33% more likely to develop PPHN compared to female neonates OR 1.33 (95% CI 0.34, 4.12) in a bivariate analysis which is comparable to a study by Athar Razzaq et al in Pakistan, where they found male sex is a major risk factor for developing PPHN (24).

Study strengths

This study has several strengths that set it apart from previous articles in the literature. One of the strengths is the use of agreed-upon cut-off points for defining pulmonary hypertension. Unlike previous studies that employed varying cut-offs, this study adhered to the most recent expert consensus published in 2018, which established mPAP >20mmHg as the updated classification for pulmonary hypertension (21). To determine mPAP in this study, the researchers utilized the Chemla equation, which not only provides a simple calculation but also demonstrates excellent correlation with cardiac catheterization (20). Another advantage of this study is the opportunity to employ a non-invasive method for measuring pulmonary arterial pressures and evaluating severity of pulmonary hypertension.

The majority of studies conducted on persistent pulmonary hypertension of the newborn (PPHN) in the context of perinatal asphyxia have relied on retrospective designs. However, in this study, a prospective design was employed, which represents a notable strength. In the context of studying PPHN in perinatal asphyxia, a prospective design provides several advantages. It allows for the timely and accurate assessment of perinatal asphyxia, the severity of hypoxia, and other relevant factors associated with the development of PPHN.

During the study, echocardiography findings and diagnoses were informed to the caregivers and the NBU doctors in real time and the treatment PPHN was also suggested by the paediatrtic cardiologist depending on the severity. And hence this study became a source of quick consultation and allowed timely step up or step down for the treatment of PPHN.

Study Limitations

The consecutive sampling method used is non-probabilistic and may impede generalization (lower external validity) to the entire study population. EEG and MRI brain are ideal to determine the extent of HIE insult but was not considered in our study due to financial feasibility concerns. The small study sample in this study may have reduced the power of the study and the findings may not represent the true picture especially when compared to findings from literature.

Conclusions and recommendations

Conclusions

1. In this study, the prevalence of PPHN was found to be on the higher side (53%) in the neonates with moderate to severe perinatal asphyxia.
2. The presence of meconium stained liquor in babies with asphyxia is a major risk factor for developing PPHN.

Recommendations

1. Neonates with moderate to severe asphyxia should have echocardiography screening to rule out PPHN.
2. Echocardiography for asphyxiated neonates with meconium stained liquor should be considered early in order to treat of PPHN in timely manner.

References

1. Nair J, Lakshminrusimha S. UPDATE ON PPHN: MECHANISMS AND TREATMENT. Semin Perinatol. 2014 Mar;38(2):78–91.

2. WHO. Perinatal asphyxia [Internet]. [cited 2022 Jan 22]. Available from: https://www.who.int/teams/maternal-newborn-child-adolescent-health-and-ageing/newborn-health/about

3. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol. 1976;33(10):696–705.

4. Gebregziabher GT, Hadgu FB, Abebe HT. Prevalence and Associated Factors of Perinatal Asphyxia in Neonates Admitted to Ayder Comprehensive Specialized Hospital, Northern Ethiopia: A Cross-Sectional Study. Int J Pediatr. 2020:e4367248.

5. Shikuku DN, Milimo B, Ayebare E, Gisore P, Nalwadda G. Practice and outcomes of neonatal resuscitation for newborns with birth asphyxia at Kakamega County General Hospital, Kenya: a direct observation study. BMC Pediatr. 2018;18(1):167.

6. Maalim A. Short term outcomes of term neonates admitted with perinatal asphyxia in Kenyatta National Hospital newborn unit. 2011;67.

7. Morales P, Bustamante D, Espina-Marchant P, Neira-Peña T, Gutiérrez-Hernández MA, Allende-Castro C, et al. Pathophysiology of perinatal asphyxia: can we predict and improve individual outcomes? EPMA J. 2011;2(2):211–30.

8. Zanelli S. Hypoxic-Ischemic Encephalopathy: Practice Essentials, Background, Pathophysiology [Internet]. [cited 2022 Nov 14]. Available from: https://emedicine.medscape.com/article/973501-overview

9. Ahmed T, Abqari S, Shahab T, Ali SM, Firdaus U, Khan IA. Prevalence and outcome of pulmonary arterial hypertension in newborns with perinatal asphyxia. J Clin Neonatol. 2018;7(2):63.

10. Stark A. Persistent pulmonary hypertension of the newborn - UpToDate [Internet]. [cited 2022 Jan 22]. Available from: https://www.uptodate.com/contents/persistent-pulmonary-hypertension-of-the-newborn?source=history_widget

11. Tauber K. Persistent Pulmonary Hypertension of the Newborn (PPHN): Practice Essentials, Overview, Etiology. 2021 Aug 17 [cited 2022 Jan 25]; Available from: https://emedicine.medscape.com/article/898437-overview#a2

12. Teixeira-Mendonça C, Henriques-Coelho T. Pathophysiology of pulmonary hypertension in newborns: Therapeutic indications. Rev Port Cardiol Engl Ed. 2013;32(12):1005–12.

13. Lattari A. Persistent Pulmonary Hypertension of the Newborn - Pediatrics [Internet]. MSD Manual Professional Edition. [cited 2022 Jan 25]. Available from:

https://www.msdmanuals.com/professional/pediatrics/respiratory-problems-in-neonates/persistent-pulmonary-hypertension-of-the-newborn

14. Zhou R, Zheng YN, Zhang XY, Cheng YY. A Meta-Analysis of the Risk Factors of Persistent Pulmonary Hypertension in Newborns. Front Pediatr [Internet]. 2021;9. Available from: https://www.frontiersin.org/article/10.3389/fped.2021.659137

15. Nchabeleng MJ, Hamese MHK, Ntuli TS. Prevalence and outcomes of persistent pulmonary hypertension of the newborn in a neonatal unit, Mankweng Hospital, Limpopo Province, South Africa. South Afr J Child Health. 2021;15(2):102–6.

16. Lakshminrusimha S, Shankaran S, Laptook A, McDonald S, Keszler M, Vanmeurs K, et al. Pulmonary Hypertension Associated with Hypoxic-Ischemic Encephalopathy—Antecedent Characteristics and Comorbidities. J Pediatr. 2018;196.

17. Kang C, Zhao E, Zhou Y, Zhao H, Liu Y, Gao N, et al. Dynamic Changes of Pulmonary Arterial Pressure and Ductus Arteriosus in Human Newborns From Birth to 72 Hours of Age. Medicine (Baltimore). 2016 Jan 22;95(3):e2599.

18. Lai WW, Geva T, Shirali GS, Frommelt PC, Humes RA, Brook MM, et al. Guidelines and Standards for Performance of a Pediatric Echocardiogram: A Report from the Task Force of the Pediatric Council of the American Society of Echocardiography. J Am Soc Echocardiogr. 2006;19(12):1413–30.

19. de Boode WP, Singh Y, Molnar Z, Schubert U, Savoia M, Sehgal A, et al. Application of Neonatologist Performed Echocardiography in the assessment and management of persistent pulmonary hypertension of the newborn. Pediatr Res. 2018;84(1):68–77.

20. Chemla D, Castelain V, Provencher S, Humbert M, Simonneau G, Hervé P. Evaluation of Various Empirical Formulas for Estimating Mean Pulmonary Artery Pressure by Using Systolic Pulmonary Artery Pressure in Adults. Chest. 2008 Oct 1;135:760–8.

21. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019 Jan 24;53(1):1801913.

22. Hsieh TK, Su BH, Chen AC, Lin TW, Tsai CH, Lin HC. Risk factors of meconium aspiration syndrome developing into persistent pulmonary hypertension of newborn. Acta Paediatr Taiwanica Taiwan Er Ke Yi Xue Hui Za Zhi. 2004;45(4):203–7.

23. Joanna R. G. 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 Dec 12;35(25):4969–75.

24. Razzaq A, Iqbal Quddusi A, Nizami N. Risk factors and mortality among newborns with persistent pulmonary hypertension. Pak J Med Sci. 2013 Sep 1;29(5):1099–104.

25. Power BD, McGinley J, Sweetman D, Murphy JF. The Modified Sarnat Score in the Assessment of Neonatal Encephalopathy: A Quality Improvement Initiative. :4.

APPENDICIES

Appendix I: Sarnat and Sarnat Staging

A neonate must meet at least 3 criteria of any stage to be classified as that stage.

Table 8: Sarnat and Sarnat staging for severity of Hypoxic Ischemic Encephalopathy and by extension Perinatal asphyxia

A neonate requires 3 or more features to meet the criteria of any stage to be classified in that stage.	**Stage 1**	**Stage 2**	**Stage 3**
Level of consciousness	Alert: arouses to wakefulness or Hyper alert	Lethargic /Obtunded: delayed but complete response to external stimuli	Stupor/Coma: not arousable and is non-responsive to external stimuli.
Activity	Normal	Decreased	Absent
Muscle tone	Normal	Mild hypotonia	Flaccid
Seizures	None	Common: focal or multifocal	Uncommon: excluding decerebration
Reflexes			
Moro	Strong, low threshold	Weak, incomplete	Absent
Suck	Weak	Weak or absent	Absent
Autonomic system	Pupils equal and reacting to light. normal heart rate and respirations	Pupils constricted. bradycardia or periodic/irregular breathing	Pupils deviated/ dilated/non-reactive; variable heart rate or apnea.

(Adapted from The Modified Sarnat and Sarnat Score in the Assessment of Neonatal Encephalopathy: A Quality Improvement Initiative)(25)

Appendix II: Informed Consent

Study Title

Prevalence and clinical correlates of persistent pulmonary hypertension of the newborn (PPHN) in neonates with perinatal asphyxia at Kenyatta National Hospital – newborn unit (KNH-NBU)

Principal Investigator/and institutional affiliation: Nisarg Patel: Resident, department of paediatrics and child health, University of Nairobi

Co-Investigators and institutional affiliation: Prof. C Jowi, Prof. A Wasuna, University of Nairobi

Introduction: I would like to tell you about a study being conducted by the above-listed researchers. The purpose of this consent form is to give you the information you will need to help you decide whether or not your child should participate in the study. Feel free to ask any questions about the purpose of the research, what happens if your child participates in the study, the possible risks and benefits, the rights of your child as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions to your satisfaction, you may decide if you want your child to be in the study or not. This process is called 'informed consent. Once you understand and agree for your child to be in the study, I will request you to sign your name on this form. You should understand the general principles which apply to all participants in medical research: i) Your child's decision to participate is entirely voluntary ii) Your child may withdraw from the study at any time without necessarily giving a reason for his/her withdrawal iii) Refusal to participate in the research will not affect the services your child is entitled to in this health facility or other facilities.

May I continue? YES / NO

Background

Perinatal asphyxia is the failure to start and maintain breathing after birth. There is an incomplete or broad oxygen loss to the critical organs when placental or pulmonary gas exchange is reduced or interrupted. Hypoxemia and hypercapnia occur as a result of this. The tissues and essential organs will incur an oxygen debt if the hypoxia is severe enough. The neurologic consequences of perinatal hypoxia are known as neonatal hypoxic-ischemic encephalopathy. In Kenya, the neonatal mortality rate is high at 21 per 1,000 live births and perinatal asphyxia contributes to

29% of neonatal mortalities. In KNH- NBU Perinatal asphyxia accounts for up to 20% of admissions and the mortality rate in this group is documented at 31.1% by day 7 of life.

Purpose

To determine the prevalence and clinical features of persistent pulmonary hypertension of the newborn (PPHN) in neonates with perinatal asphyxia at Kenyatta National Hospital – Newborn unit (KNH-NBU)

Study procedures

The principal investigator will employ one research assistant who will assist with recruitment and data collection. The research assistant will be fully trained in research protocols. Screening of the neonates for asphyxia birth using records, history and physical examination. The parents are approached for consent when a baby meets the inclusion criteria. These babies are then recruited into the study. Physical examination will be done to fill the data collection tool. Performing doppler and 2D ECHO for the diagnosis of PPHN. Interviewing mothers to fill in mothers' characteristics. After data collection, the data will be entered into excel and imported into R for cleaning and analysis. The name of the infant will not appear in the ECHO films or any digital images. Instead, these images will bear the questionnaire number. We intend to store the films/images until August 2023.

Voluntary participation

Your decision for you or your child to participate in this study is voluntary. Once you understand and agree for your child to be in the study, the research personnel will request you to sign your name on this form.

Confidentiality

The data collected will be used solely for this study. We will keep everything you tell us as confidential as possible. We will use a code number to identify your child in a password-protected computer database and will keep all of our paper records in a locked file cabinet.

Benefits

There will be no financial benefit given to your child for participating in this study. Your child’s participation will not affect or delay their planned treatment. We will refer your child to the

appropriate clinic for care and support if necessary. Also, the information you provide will help us better understand the magnitude of persistent pulmonary hypertension of the newborn (PPHN) and its associated factors in neonates with perinatal asphyxia. This will help us improve the management of these babies.

Risk of Participation

We will not alter your child's planned treatment. The examinations carried out on your child will not cause any harm.

Right of withdrawal

You may withdraw your child from the study at any time without necessarily giving any reason for the withdrawal. The refusal or withdrawal of your child from this study will not affect the services your child is entitled to, in this health facility or other facilities.

CONSENT FORM (STATEMENT OF CONSENT)

The person being considered for this study is unable to consent for him/herself because he or she is a minor (a person less than 18 years of age). You are being asked to give your permission to include your child in this study.

Parent/guardian statement

I have read this consent form or had the information read to me. I have had the chance to discuss this research study with the study personnel. I have had my questions answered by him or her in a language that I understand. The risks and benefits have been explained to me. I understand that my participation and that of my child in this study is voluntary and that I may choose to withdraw at any time. I understand that all efforts will be made to keep information regarding me and my child's identity confidential.

Parent/legal Guardian signature /Thumb stamp: _____ Date __

Parent/legal Guardian printed name: _____

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given his/her consent.

Printed Name: _____ Date: _____ Signature:

In case you have any questions concerning the study, feel free to contact the following persons during official working hours:

PRINCIPAL INVESTIGATOR:
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Faculty of Health Sciences

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Department of Paediatrics and Child Health
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Regulatory Body

KNH-UON ERC

Telephone (254-020) 2726300 Ext 44102

Email: uonknh_erc@uonbi.ac.ke

Website: www.erc.uonbi.ac.ke

Appendix III: Data collection tool

Study Identification no. ……. Hospital no. …… Date: …….

Mother's details				
Age				
Parity				
ANC attendance	Yes [ ]	No [ ]		
If yes, the Number of ANC clinics attended				
Occupation	Unemployed [ ]	Self-employed [ ]	Informal employment [ ]	Formal employment [ ]
Place of delivery	Home [ ]	Clinic/dispensary [ ]	On transit to the hospital [ ]	Hospital [ ]
Duration of labour	<12hours [ ]	>12hours [ ]		
Significant Perinatal Events:				
Which medications did you take during pregnancy?.....				
Patient/ Neonate details				
Gender	Male [ ]	Female [ ]		
Date of birth (dd/mm/yy) :				
Time of birth :				
Age in hours :				
Gestational age in weeks :				
Birth weight (kgs) :				
APGAR score: 1 min …….. 5 min …… 10 min…….				
Mode of delivery	SVD [ ]	CS [ ]		

Vital signs at the time of ECHO	Temp:	Respiratory rate: spO2:	Heart rate:	BP:
Significant Respiratory exam findings:				
Significant Cardiovascular exam findings:				

ECHO Findings

ECHO number:

<table>
<tr><td colspan="2">VmaxTR (m/s^2): ……</td></tr>
<tr><td colspan="2">sPAP: (4 × …….^{2})+ 5 mmHg = ……...mmHg</td></tr>
<tr><td colspan="2">mPAP: (0.61 × ……..) + 2 mmHg = …… mmHg</td></tr>
<tr><td colspan="2">Shunting;</td></tr>
<tr><td>Foramen ovale:</td><td>Ductus arteriosus:</td></tr>
<tr><td colspan="2">Interventricular Septum deviation:</td></tr>
<tr><td colspan="2">Other significant findings:</td></tr>
</table>

Appendix IV: Budget Estimate in Kenya shillings

Commodity	Price per piece	Number of pieces	Total cost
Notebook	120	2	240
Ballpoint pens	20	10	200
Pencils	10	10	100
Eraser	30	2	60
Foolscaps	70	2	140
File	200	5	1000
Photocopying and printing		15,000	
Proposal booklet	2000	5	10,000
KNH-UON ERC fee	2000	1	2000
Ultrasound gel		5,000	
Research assistant		50,000	
Statistician		30,000	
Contingency		30,000	
Overall total		**143,740/-**	

Appendix V: Study Timeline

Activity	Dec. 2021/ Oct 2022		Nov/Dec 2022	Jan- Apr 2023	May/2023	June/2023
Proposal Development						
Ethical review						
Data collection						
Data analysis						
Final write-up of thesis						

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Ref: KNH-ERC/A/471

18th November, 2022

Dr. Nisarg Sitaram Patel
Reg. No.H58/37248/2020
Dept. of Paediatrics & Child Health
Faculty of Health Sciences
University of Nairobi

APPROVED
18 NOV 2022

Dear Dr. Patel,

RESEARCH PROPOSAL: PREVALENCE AND CLINICAL CORRELATES OF PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN(PPHN) IN NEONATES WITH PERINATAL ASPHYXIA AT KENYATTA NATIONAL HOSPITAL – NEWBORN UNIT(KNH-NBU) (P511/06/2022)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P511/06/2022.** The approval period is 18thNovember 2022 - 17th November 2023.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH-UoN ERC within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours sincerely,

DR. BEATRICE K.M. AMUGUNE
SECRETARY, KNH-UoN ERC

c.c. The Dean, Faculty of Health Sciences, UoN
The Senior Director, CS, KNH
The Assistant Director, Health Information Dept., KNH
The Chairperson, KNH- UoN ERC
The Chair, Dept. of Paediatrics & Child Health UoN
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