UNDERLYING DISEASE, MANAGEMENT STRATEGIES AND SURVIVAL RATE OF NEONATES DIAGNOSED WITH PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine
Johannesburg, 2020

DECLARATION

I, Motlalepula Portia Pitiri, declare that this dissertation report is my own work. It is being submitted for the degree of Master of Medicine in Paediatrics at the university of Witwatersrand Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signed: 

On this: 22 day of: March 2021

DEDICATION

To my husband Lebo, my daughter Warona, my mother Gomotsegang and my sister Kegomoditswe, thank you for your unwavering support throughout this journey.

PUBLICATION AND PRESENTATION ARISING FROM THE THESIS.

None

ABSTRACT

Background: Management of persistent hypertension of the new-born (PPHN) varies widely around the world. Therapeutic strategies used in management of PPHN in low-and middle-income countries (LMIC) are not well reported. Secondly, the diagnoses associated with PPHN and the survival rates of neonates with PPHN in LMIC is not well known.

Objective: To determine the underlying disease, management strategies and survival rate of near-term and term neonates (birth weight >2000 grams) diagnosed with PPHN.

Methods: This was a retrospective review of clinical records of near-term and term neonates who were admitted to Chris Hani Baragwanath Hospital (CHBAH), neonatal intensive care unit (NICU) from January 2012 to December 2013 with a diagnosis of PPHN.

Results: A total of 1262 neonates were admitted to NICU, of which 470 weighed >2000 grams. Fifty neonates were diagnosed with PPHN which was 4.0% of NICU admissions and 10.6% of near-term or term neonates admitted to NICU. Meconium aspiration syndrome with (44%) and without (42%) birth asphyxia was the most common underlying diagnosis associated with PPHN. Management strategies used were fluid boluses (80%), inotropes (80%), alkalinisation (68%), sildenafil (60%) and inhaled nitric oxide (6%). All-cause mortality rate was 36%. Non-survivors were more likely to have required rescue high frequency oscillatory ventilation than survivors (83.3% vs 25.0%, $p<0.001$)

Conclusion: PPHN accounts for about a tenth of near-term and term neonates requiring mechanical ventilation and is associated with high mortality rate. MAS is the most common underlying diagnosis in neonates with PPHN. Commonly used management strategies are fluids, inotropes, alkalinization and sildenafil.

ACKNOWLEDGEMENTS

To my supervisor Professor S Velaphi, thank you so much for your guidance, support and pearls of wisdom. You never gave up on me during my darkest days.

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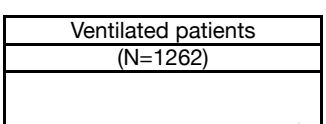

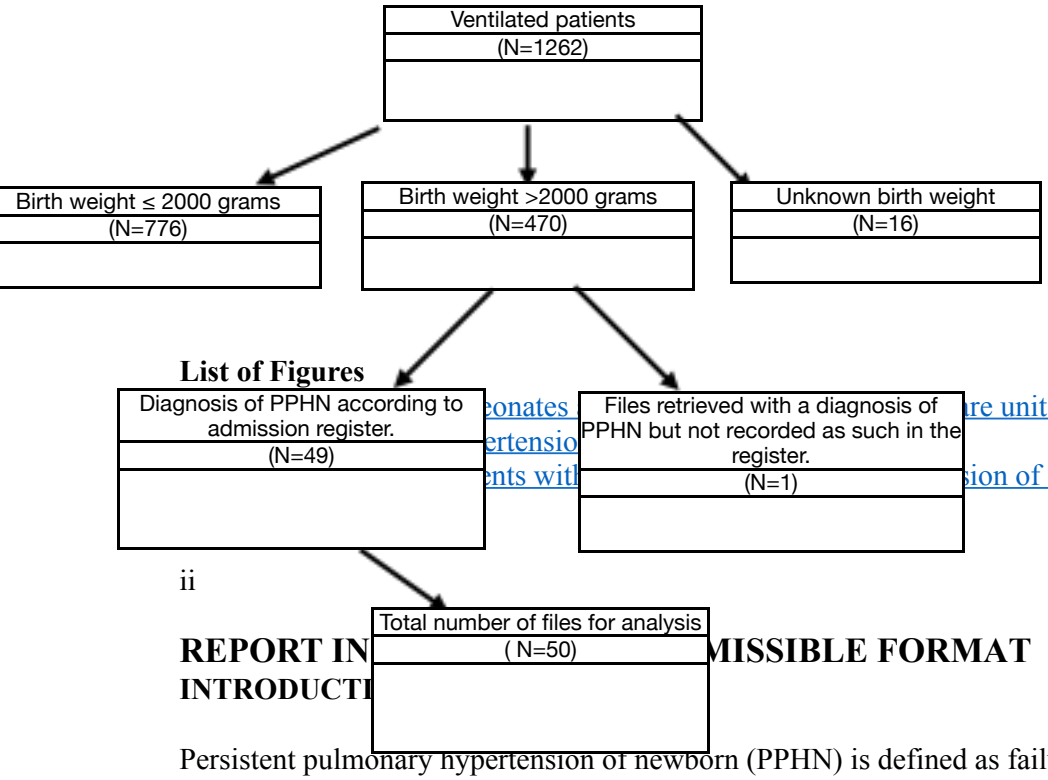

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REPORT IN MISSIBLE FORMAT

INTRODUCTI

Persistent pulmonary hypertension of newborn (PPHN) is defined as failure of normal fall in pulmonary vascular resistance (PVR) at or shortly after birth, leading to shunting of deoxygenated blood into the systemic circulation across foramen ovale or ductus arteriosus. Pulmonary vasoconstriction, vascular proliferation and remodelling contribute to elevated PVR in PPHN.[1] The incidence of PPHN is reported to be 0.43-6.8 per 1000 live births, with mortality rate ranging between 4% and 33%.[1, 2] About 14%-46% of the survivors develop long-term impairments such as hearing deficits, chronic lung disease, cerebral palsy and other neurodevelopmental disabilities.[3, 4]

The aetiology of PPHN can be classified into three groups; abnormally constricted pulmonary vasculature as a result of parenchymal diseases; hypoplastic pulmonary vasculature and normal parenchyma with remodelled pulmonary vasculature.[2] The common aetiologies of PPHN are meconium aspiration syndrome, birth asphyxia, neonatal septicaemia and post-term delivery.[3, 5-7] Echocardiography is the gold standard for definite diagnoses of PPHN and also assist to exclude congenital cyanotic cardiac disease.[7-9] The suspicion of PPHN can also be confirmed by measuring preductal and postductal arterial oxygenation. A difference in arterial partial pressure of oxygen (PaO_2) of 20 mmHg or a difference in oxygen saturation of >10% between right arm and lower limbs should be considered as suggestive of PPHN. Current therapies of PPHN include mechanical ventilation, vasodilators and extracorporeal membrane oxygenation (ECMO). Oral sildenafil has been used successfully to improve oxygenation in patients with PPHN especially in resource limited setting where facilities like inhaled nitric oxide (iNO) and ECMO are unavailable.[10-12] In low- and middle-income countries (LMIC) the availability iNO and ECMO is limited due to high costs and limited availability of trained physicians.[8] The neurodevelopmental and medical outcome among PPHN survivors treated with these advanced therapies is the same as compared with those treated with conventional therapies.[13, 14]

The use of different therapeutic strategies in management of neonates with PPHN in low- and middle-income countries (LMIC) is not well reported. Secondly the diagnoses associated with PPHN and the survival rates of neonates with PPHN in facilities based in these countries is also not well known. In this study we sought to determine underlying and/or associated diagnoses, management strategies and survival rates of newly born infants diagnosed with PPHN admitted to a public tertiary hospital from a LMIC.

management strategies and survival rates of newly born infants diagnosed with PPHN admitted to a public tertiary hospital from a LMIC.

METHODS

Study design:

This study was a retrospective review of clinical records of neonates diagnosed with PPHN and were admitted to a neonatal intensive care unit (NICU) of Chris Hani Baragwanath Academic Hospital (CHBAH) from 1 January 2012 to December 2013.

Study population and setting:

CHBAH is a public tertiary hospital situated in Soweto, Johannesburg, South Africa. It is a major referral center for clinics in the region and hospitals in the southern part of Gauteng. This hospital conducts about 20,000 in-hospital births per year and caters for secondary or tertiary level of healthcare care for about 8000 births conducted in the local community health centers or midwifery obstetric units. A diagnosis of PPHN was based on the difference in pre and postductal oxygen saturations of >10%. The study population included all neonates who were considered to be near-term and term (weighing > 2000 grams at birth) who were admitted to NICU at CHBAH with a diagnosis of PPHN. Neonates whose records could not be retrieved were excluded from the study.

Data collection:

The NICU admission register was reviewed for names of all neonates who weighed >2000 grams and had a diagnosis of PPHN recorded on admission or on discharge from NICU. Hospital records of these neonates with a diagnosis of PPHN were retrieved and reviewed for maternal and infant characteristics, underlying clinical diagnosis, management and outcomes at hospital discharge. Data on maternal characteristics included maternal age, human immunodeficiency status, presence of meconium staining of the amniotic fluid, place of birth, mode of delivery, and data on infant characteristics included birth weight, sex, gestational age, management strategies of PPHN and outcome at hospital discharge. All data were collected and entered into a structured data capturing sheet.

Data analysis:

All collected data were captured into a Microsoft Excel spreadsheet. Data were checked for incompleteness and inconsistencies and was analysed using the statistical software Stata/IC, version 15.1. Continuous variables namely maternal age, birth weight, and gestational age were checked for normality in distribution using histograms and the Shapiro-Wilk test and were presented as means with standard deviations or medians with interquartile ranges. Comparisons

Data analysis:

All collected data were captured into a Microsoft Excel spreadsheet. Data were checked for incompleteness and inconsistencies and was analysed using the statistical software Stata/IC, version 15.1. Continuous variables namely maternal age, birth weight, and gestational age were checked for normality in distribution using histograms and the Shapiro-Wilk test and were presented as means with standard deviations or medians with interquartile ranges. Comparisons of continuous variables between survivors and non-survivors were performed using Student t-test. Categorical and dichotomous variables were presented as frequencies and percentages. Comparison in categorical or dichotomous characteristics were performed using chi-square Fisher exact test. Bivariate analysis was performed using logistic regression to assess factors associated with the primary outcome, the mortality and was reported as odds ratios with 95% confidence intervals. For all analyses, differences were considered to be statistically significant if the p-value was <0.05.

Ethical consideration:

Permission to conduct this study was given by the hospital chief executive officer after the protocol was reviewed by the hospital protocol review committee. Ethical approval to conduct the study was given by the University of the Witwatersrand Human Research Ethics Committee. Informed consent was not obtained from patients as this was a retrospective audit of records and all data was kept confidential by the researcher.

RESULTS

A total of 1262 patients were admitted for mechanical ventilation in NICU at CHBAH from January 2012 to December 2013. Those who had a birth weight >2000 grams were 470. A total of 49 patients had diagnosis of PPHN recorded on admission and 1 recorded on discharge giving a total of 50 patients (10.6% of admissions weighing >2000grams). All 50 patients had their medical records retrieved (Figure 1). The median number of neonates admitted with PPHN per month was two with interquartile ranges of one and three, with the highest number of admissions per month being five patients, noted in July 2013 (Figure 2).

Figure 1: Flow chart of neonates admitted to neonatal intensive care unit with a diagnosis of persistent pulmonary hypertension of the newborn.

Figure 2: Number of patients with persistent pulmonary hypertension of the newborn by admission month

Figure 2: Number of patients with persistent pulmonary hypertension of the newborn by admission month

Maternal and infant characteristics of infants with PPHN are presented on Table 1. The mean maternal age was 28.4 (SD 5.75) years, 41.7% of mothers were HIV positive, 34.7% were primigravida and 86% had meconium stained amniotic fluid. Forty-nine (98%) mothers had complete records and one (2%) mother's maternal age, parity, gestational age and mode of delivery were unknown. Forty-seven (94%) of the 50 neonates had birth weight of > 2500 grams. The mean gestational age at delivery was 39.6 +/- 1.6 weeks, with 43 (89%) of them being of gestational age of 37 to 41 weeks and 4 (8.3%) were born at > 41 weeks' gestational age. Seventy one percent of patients had an Apgar score <7 at 5 minutes.

Table 1: Characteristics of neonates with persistent pulmonary hypertension of the newborn.

Characteristic	**n**	**(%)**
Maternal Characteristic		
Maternal age, in years (n = 49)		
<20	3	6.1
20-34	40	80
≥35	6	12.2
Human immunodeficiency virus status positive (n = 49)	20	41.7
Primigravida (n = 49)	20	41.7
Vaginal delivery (n = 49)	31	63.3
Meconium stained amniotic fluid (n = 50)	43	86
Infant Characteristics		
Male sex (n = 50)	27	54
Low birth weight (<2500 grams) (n = 50)	3	6
Gestational age (n = 48)		
Preterm (<37 weeks)	1	2.1
Term	43	89.6
Post-term	4	8.3
Apgar score <7 at 1 min (n = 49)	35	71.4

The underlying diagnoses were meconium aspiration syndrome (MAS) with birth asphyxia (44%; n=22), MAS without birth asphyxia (42%; n=21), congenital pneumonia (10%; n=5), birth asphyxia only (2%; n=1), and congenital diaphragmatic hernia (2%; n=1) (Table 2).

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Table 2: Underlying diagnosis in neonates admitted to neonatal intensive care unit with a diagnosis of persistent pulmonary hypertension of the newborn.

Diagnosis	**n**	**(%)**
Meconium aspiration syndrome with asphyxia	22	44
Meconium aspiration syndrome without asphyxia	21	42
Congenital pneumonia	5	10
Asphyxia only	1	2
Congenital diaphragmatic hernia	1	2

Management strategies included administration of normal saline bolus and use of inotropes in 40 neonates (80%), administration of sodium bicarbonate (alkalinisation) in 34 patients (68%) and oral sildenafil in 30 (60%) patients (Table 3). Only 3 (6%) patients were recorded as having received inhaled nitric oxide. All patients were managed with mechanical ventilation with 47 (94%) of them being started on conventional mechanical ventilation, and only 3 (6%) being started directly on high frequency oscillator ventilation. Amongst the 47 who were started on conventional mechanical ventilation, 20 (42.6%) were subsequently changed to high frequency oscillator ventilation.

Table 3: Different interventions used in management of neonates with persistent pulmonary hypertension of the newborn.

Intervention	**n**	**(%)**
Number managed with fluid (normal saline) bolus	40	80
Number managed with inotropes	40	80
Number managed with sodium bicarbonate (alkalinization)	34	68
Number ventilated with conventional mechanical ventilator (CMV) only	27	54
Number ventilated with CMV initial and subsequently changed to HFOV*	20	40
Number managed with sildenafil	30	60
Number managed with nitric Oxide	3	6

* - HFOV- High frequency oscillatory ventilation

There were 18 patients who had died at hospital discharge, giving the all-cause mortality rate of 36%. In comparing the non-survivors to survivors, the only difference found was that there were more patients who required to be changed to HFOV among the non-survivors than survivors (62% vs 38%, p=0.001) (Table 4). There were no differences in maternal characteristics, infant characteristics and diagnosis on admission.

Table 4: Comparison of characteristics, diagnosis and interventions used between non-survivors and survivors in neonates with persistent pulmonary hypertension of the newborn.

VARIABLE	**Non-survivors, N= 18 n (%)**	**Survivor, N = 32 n (%)**	**P-value**
Median maternal age, in years	27	30	0.499
Number with human immunodeficiency virus exposure	14 (77.8)	6 (18.8)	0.670
Primigravida	10 (55.6)	7 (21.9)	0.890
Vaginal delivery	18 (100)	13 (40.6)	0.325
Number with meconium stained amniotic fluid	16 (88.9)	27 (84.4)	0.660
Median Birth weight, in grams	3010	2900	0.705
Median gestational age, in weeks	40	40	0.603
Male sex	17 (94.4)	10 (31.3)	0.690
Meconium aspiration syndrome without asphyxia	10 (55.6)	12 (37.5)	0.321

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Male sex	17 (94.4)	10 (31.3)	0.690
Meconium aspiration syndrome without asphyxia	10 (55.6)	12 (37.5)	0.321
Meconium aspiration syndrome with asphyxia	6 (33.3)	16 (50)	0.254
Number given fluid (normal saline) bolus	15 (83.3)	25 (78.1)	0.815
Number given inotropes	16 (88.9)	24 (75.0)	0.251
Number given sodium bicarbonate	13 (72.2)	21 (65.6)	0.631
Number changed to high frequency oscillatory ventilation	15 (83.3)	8 (25.0)	**0.001**
Sildenafil	11 (61.1)	19 (59.4)	0.715
Nitric oxide	2 (11.1)	1 (3.1)	0.254

DISCUSSION

This retrospective study reviewed underlying diagnoses, modalities used in the management of newborns with PPHN and their outcomes at hospital discharge in a resource limited setting. The main findings in this study were that meconium aspiration syndrome with or without asphyxia was the most common underlying diagnosis. The common management strategies used were volume expanders, alkalinization and oral sildenafil. Only six percent of patients were managed with inhaled nitric oxide. This is likely due to high costs of iNO. PPHN is associated with high mortality, and neonates who are converted to high frequency ventilation are more likely to die. Louis D *et al* and Velaphi *et al* reported that MAS as the underlying cause of PPHN is associated with significant mortality.[5, 6]

Sixty percent of patients in this study were on sildenafil, suggesting that it is used as an alternative to iNO. Inhaled nitric oxide is the first line treatment strategy for treating PPHN as it is the local pulmonary vasodilator.[8] Inhaled NO improves oxygenation and reduces the need for ECMO in patients with diverse causes of PPHN.[15] In this study only six percent of patients were on iNO, most likely due to unavailability of iNO. The alternate pulmonary vasodilators are endothelin receptor antagonist such as bosetan, and phosphodiesterase-5 inhibitors such as sildenafil and tadafil. Hussain, et al showed that oral sildenafil can be successfully used to improve oxygenation patients with PPHN particularly in a resource limited setting where facilities like iNO and ECMO are not available.[11] Baquero et al demonstrated oxygen index improvement within 6 to 30 hours in all infants receiving oral sildenafil and significant improvement in oxygen saturation over time, different from the placebo group ($p<0,05$).[16] Mohsen et al used oral sildenafil in 16 cases (50%) that were randomly selected, 10 of them (62,5%) showed improvement and 6 (37.5%) discontinued medication due to unresponsiveness and shifted to other treatment modalities.[13] Lastly Uslu S et al showed that the time to adequate clinical response was significantly shorter in sildenafil group than intravenous magnesium sulphate group.[12]

In the absence of iNO, supportive measures such as maintenance of adequate systemic blood pressures, normothermia and correction of metabolic abnormalities such as metabolic acidosis become an alternative.[10] An international survey done by Nakwan et al demostrated that Dopamine was used as an initial inotropic agent, normal saline was the preferred initial fluid resusitation for hypotension, sedation and analgesia were routinely used as well in the supportive management of PPHN.[8] Gentle ventilating strategies with permissive hypercapnia are recommended to ensure adequate lung expansion with limited barotrauma. All neonates were ventilated, and 68% were managed with alkalization using sodium bicarbonate. Hyperventilation and alkali infusion of sodium bicarbonate to maintain an alkaline pH were strategies previously used but now considered outdated in high income countries. There are concerns of impaired cerebral perfusion, sensorineural deafness with respiratory alkalosis and produces transient effect of pulmonary dilatation and provides no short term or long-term benefits.[4, 7]

The limitations of the study were that PPHN was diagnosed based on clinical presentation of

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The limitations of the study were that PPHN was diagnosed based on clinical presentation of differential oxygen saturation of >10%, rather than echocardiogram which could assist in assessing severity of PPHN. The study design is cross-sectional and thus difficult to infer causality in terms of the PPHN and mortality. Moreover, due to a small sample size, we could not use multivariate analyses to explore possible confounding.

CONCLUSION

In conclusion, meconium aspiration syndrome with or without birth asphyxia was the most common underlying cause of PPHN. Neonates with PPHN have high mortality. Oral sildenafil appears to be used as an alternative pulmonary vasodilator in the absence of iNO.[17, 18] Future studies need to enrol large numbers in order to determine predictors of mortality in neonates with PPHN.

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APPENDIX

APPENDIX A: PROTOCOL

Title: Underlying disease, treatment modalities and survival rate of neonates diagnosed with persistent pulmonary hypertension of the newborn.

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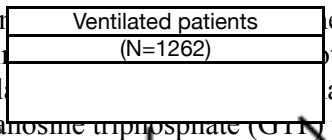
Degree: MMED (Paediatrics)
Supervisor: Professor Sithembiso Velaphi
MBChB (Natal), FC Paed (SA), and Certificate in Neonatology, Head of Paediatrics and Child Health at Chris Hani Baragwanath academic hospital.

Background

PPHN can be defined as failure of normal fall in pulmonary vascular resistance (PVR) at or shortly after birth, leading to shunting of deoxygenated blood into systemic circulation across foramen ovale or ductus arteriosus.[1] Incidence of PPHN is approximately 0.4-6.8/1000 live births with estimated mortality of 10-20%.[2] PPHN primarily affects full-term and near-term neonates.

Fetal lung receives 5-10% of cardiac output due to high PVR. Shortly after birth PVR decreases dramatically with resultant fall in pulmonary arterial pressure and an increase in pulmonary blood flow.[1] Various factors like expansion of lungs, shear stress, increase in Pa02 and Ph, and decrease in PaC02, helps decrease PVR by stimulating the release of nitric oxide (NO), prostacyclin (PGI2) and activating potassium channels.[2] Normal pulmonary tone is regulated by complex interactions between vasodilators (NO, PGI2) and vasoconstrictors (endothelin-1, thro



elial derived relaxing factor synthesized by oxidation of L-argi thelial nitric oxide synthatase (eNOS) enzymes.[3] At birth NO stimul ase (sGC) enzyme in vascular smooth muscle cells which converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP).

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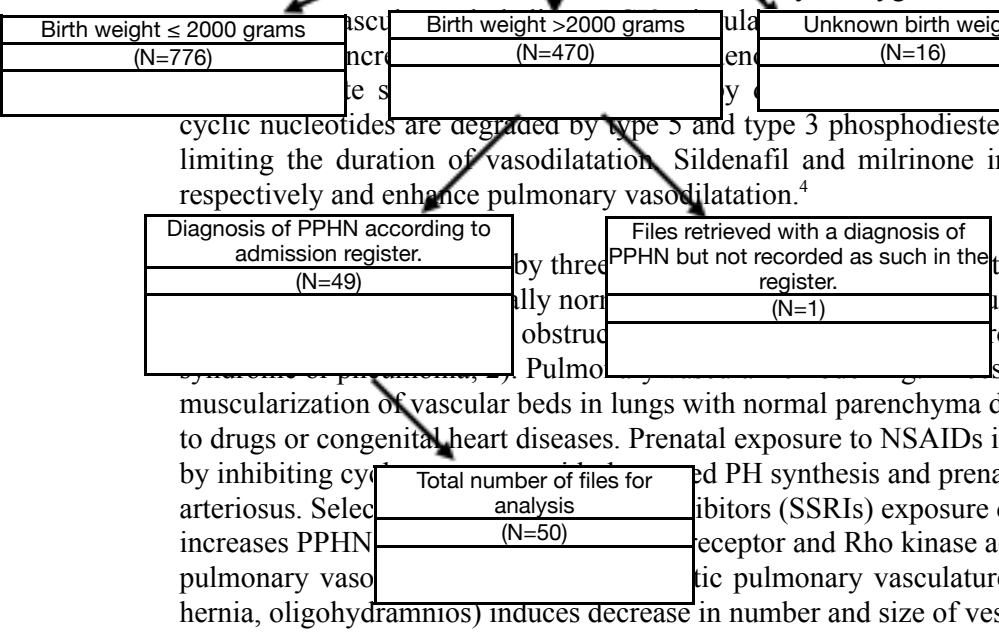

…by three… …tation: abnormal …ally nor… …uced by hypoxia due to obstruc… …rome, respiratory distress syndrome or pneumonia, 2). Pulmo… …ssive in-utero muscularization of vascular beds in lungs with normal parenchyma due to intrauterine exposure to drugs or congenital heart diseases. Prenatal exposure to NSAIDs increases the risk of PPHN by inhibiting cy… …ed PH synthesis and prenatal constriction of ductus arteriosus. Selec… …ibitors (SSRIs) exposure during late pregnancy increases PPHN… …eceptor and Rho kinase activation mediated pulmonary vaso… …tic pulmonary vasculature: (congenital diaphragmatic hernia, oligohydramnios) induces decrease in number and size of vessels.[5]

Pulmonary parenchymal diseases, including surfactant deficiency, pneumonia and meconium aspiration syndrome are associated with increased risk of PPHN. Abnormalities of pulmonary development contribute structurally to PPHN, either by pruning of the vascular tree, as occurs in congenital diaphragmatic hernia and other forms of pulmonary parenchymal hypoplasia, or malalignment of pulmonary arteries and veins, as seen in alveolar capillary dysplasia.[6] Sepsis of bacterial or viral origin can initiate PPHN by suppressing the endogenous nitric oxide production, endotoxin-mediated myocardial depression, and pulmonary vasoconstriction associated with release of thromboxanes. Prolonged fetal stress and hypoxemia lead to remodelling and abnormal muscularization of pulmonary arterioles.

Oxygen is a pulmonary vasodilator and should be initially administered in concentration to maintain normal oxygen saturation in an attempt to reverse pulmonary vasoconstriction. Maintain haemoglobin concentration between 15-16g/dl to preserve adequate tissue oxygenation.

Mechanical ventilation with permissive hypercapnia has demonstrated greater survival and lower incidence of brochopulmonary dysplasia. Routine use of alkalosis should be avoided as it decreases cerebral perfusion with resultant hearing loss and neurological disabilities among survivors. Surfactant may be considered in patient with meconium aspiration syndrome and hyaline membrane disease. Assisted ventilation in the form of conventional mechanical ventilation or high frequency oscillatory ventilation when peak pressures of conventional mechanical ventilation are 28-30cmH2O. Patients on ventilator support should be sedated if they breathe out of synchrony with the ventilator or if they become agitated as agitation may increase right to left shunting, as well as catecholamine release resulting in worsening of pulmonary vascular resistance. Inotropic support is also used to achieve systolic blood pressure of 50-70mmHg and mean arterial pressures of 45-55 as pulmonary arterial pressure in patients with PPHN is at or near normal to systemic pressures. Drugs or medication used to treat PPHN include the use of oral sildenafil, and inhaled nitric oxide. Infants who fail to respond to medical management with persistent oxygen index >40 and metabolic acidosis require treatment with extracorporeal membrane oxygenation.[7]

The long-term outcome of infants with PPHN depends on the underlying conditions and therapeutic interventions that were used. Neurodevelopmetal disabilities including cognitive delay and hearing impairment can be seen in 6.4% of PPHN survivors hence long term medical and neurodevelopmental follow up of these infants is warranted.[8] The mortality rate is about 10-20% in patients affected with PPHN despite treatments such as nitric oxide, high frequency oscillatory ventilator and extracorporeal membrane oxygenation.[6] This mortality rate is reported from developed countries where all resources needed in management of infants with PPHN are easily available. Secondly some of the conditions reported to be associated with PPHN like Meconium Aspiration Syndrome (MAS) and Perinatal asphyxia are more common in developing countries. Perinatal asphyxia refers to inadequate exchange of respiratory gases that occur during prepartum, following characteristics are essential in making a diagnosis of perinatal asphyxia:

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Objectives

a. To determine the prevalence of PPHN in babies admitted for mechanical ventilation during the neonatal period.
b. To determine the underlying diagnosis/conditions in patients who require mechanical ventilation and develop PPHN.
c. To determine the modalities or strategies used in management of neonates with PPHN.
d. To determine the survival rate to NICU and hospital discharge of neonates diagnosed with PPHN.

Methods

a. **Study design**

A retrospective audit of records of neonates who were admitted to CHBAH neonatal intensive care unit from 1 January 2013 to 31 December 2013.

b. **Sample population**

I. **Inclusion criteria**

Neonates weighing >2000 grams at birth who were admitted to NICU at Chris Hani Baragwanath academic hospital (CHBAH) with a diagnosis of PPHN.

II. **Exclusion criteria**

Neonates whose records cannot be retrieved

c. **Study procedure**

Hospital records of infants weighing >2000 grams on admission to NICU will be retrieved. Records of infants will be reviewed for written diagnoses of PPHN. Data on maternal pregnancy and labour details, maternal and infant demographics, infant clinical diagnoses, management of PPHN, survival rate to NICU discharge and survival rate to hospital discharge

d. **Data handling and collection**

Data will be collected and entered into prepared data sheet. The data sheet will capture clinical features and investigation done at presentation, conditions associated with PPHN, clinical course, length of stay in neonatal intensive care unit and complications.

e. **Data analysis**

Data will be entered into Microsoft excel spreadsheet and basic statistical analysis will be performed using Microsoft excel. Descriptive statistical analysis using means, median, percentages and standard deviation will be used for demographic data. A Statistician will be consulted for further assistance.

f. **Limitations**

The study relies on data of existing records. Patient's records that are incomplete records will weaken the study.

Ethical consideration

A consent will not be obtained from parents as this is a retrospective audit of records. The research protocol will be submitted to Postgraduate committee and Human research ethical committee of Wits for approval. Patient personal information will be kept confidential by the researcher.

g. **Cost/ Funding**

The costs will be covered by the investigator as there is no funding for this study. Costs involved will be for stationery, printing, photocopying and binding.

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h. **Timelines**

	Feb 2014	March 2014	Apr 2014	May 2014	June 2014	July 2014	Aug 2014	Sept 2014	Oct 2014	Nov 2014	Dec 2014	Jan 2015
Literature review												
Protocol preparation												
Protocol assessment												
Ethics approval												
Post graduate approval												
Data collection												
Data analysis												
Write-up report												

References

1. Lakshminrusimha S, Steinhorn RH. Pulmonary vascular biology during neonatal transition. Clinical Perinatology. 1999;26(3):601-619
2. Abman SH, Chatfield BA, Hall SL, McMurtry IF. Role of endothelium-derived relaxing factor during transition of pulmonary circulation at birth. Am J Physiol. 1990;259(6 Pt 2): H1921-1927.
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9. Tax N, Urlesberger B, Binder C, et al. The influence of perinatal asphyxia on peripheral oxygenation and perfusion in neonates. Early Human Development 89 (2013) 483-486.

Data collection sheet

Maternal characteristics

Maternal age: **Parity**: **Gestation:** **Booked:** Yes/No

HIV: Pos/ Neg/ Unknown **Drug usage:** NSAIDS/SSRI/ none/ Not recorded

Meconium stained liquor: Yes/ No/ Not recorded

Risk factors for sepsis: PROM >18hours: Yes/ No

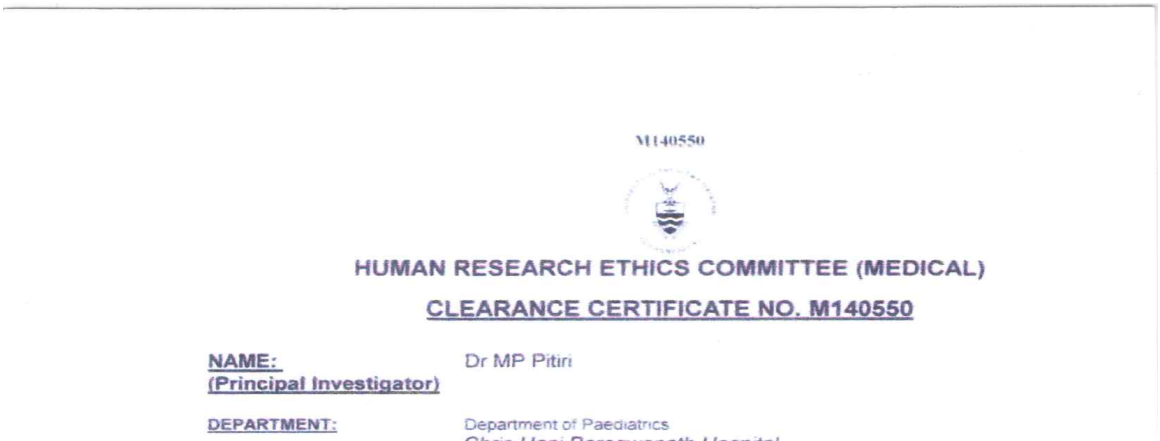
Fever (temperature >38): Yes/ No

Data collection sheet
Maternal characteristics
Maternal age: **Parity**: **Gestation:** **Booked:** Yes/No
HIV: Pos/ Neg/ Unknown **Drug usage:** NSAIDS/SSRI/ none/ Not recorded
Meconium stained liquor: Yes/ No/ Not recorded
Risk factors for sepsis: PROM >18hours: Yes/ No
Fever (temperature >38): Yes/ No
Tachycardia (pulse > 100): Yes/ No

Infant characteristics
Date of birth: **Weight:** **Gestational age (dates/U/S or Ballard score):**
Sex: **OFC:** **Length:**
Apgar: 1min 5min 10min 20min
Date of admission: **Date of discharge:** **Length of stay in NICU:**
Died: Yes/No
If yes, state the date and cause of death:
Resuscitation at birth: BMV: Yes/ No
Intubation for meconium: Yes/ No
Intubation for resuscitation: Yes: No
Chest compression: Yes/ No
Adrenaline: Yes/ No
Time to spontaneous breathing:
Diagnosis
Congenital pneumonia: Yes/ No **MAS:** Yes/ No **Birth asphyxia:** Yes/ No
HMD: Yes/ No Sepsis: Yes/ No **CDH:** Yes/ No
Other diagnoses: Yes/ No if yes state the diagnoses:
Investigations done on admission to NICU
White cell count: **Leucocytes:** **Platelets:** **CRP:**
Positive blood culture on admission: Yes/ No, if yes state the organism
Echocardiography: Done/ not done; If done, state the findings:

Management
Fluid bolus within 24 hours of admission: Yes/ No
Total fluids: Day 1: Day2:
Sodium bicarbonate: Yes/ No, if yes – bolus or infusion
Inotropes: Yes/ No
Sildenafil: Yes/No
Nitric oxide: Yes/ No
Mode of ventilation: NCPAP/ CMV/ HFOV
If CMV: Highest PIP: Highest Fio2: Highest rate:
If HFOV: Highest amplitude: Highest MAP: Low frequency: Highest Fio2:

APPENDIX B: ETHICS CLEARANCE CERTIFICATE



M140550

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140550

NAME: (Principal Investigator) Dr MP Pitiri

DEPARTMENT: Department of Paediatrics

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140550

NAME: (Principal Investigator)	Dr MP Pitiri
DEPARTMENT:	Department of Paediatrics Chris Hani Baragwanath Hospital
PROJECT TITLE:	Underlying Disease, Treatment Modalities and Survival rate of Neonates Diagnosed with Persistent Pulmonary Hypertension of the Newborn
DATE CONSIDERED:	30/05/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Sithe Velaphi
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	30/05/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House University

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**

Principal Investigator Signature M140550Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX C: PLAGIARISM DECLARATION

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS
SENATE PLAGIARISM POLICY:

I, Motlalepula Pitiri (Student number: 701149) am a student registered for the degree of Masters in Medicine in the academic year 2020. I hereby declare the following: - I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong. - I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise. - I have followed the required conventions in referencing the thoughts and ideas of others. - I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing. - I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: _____

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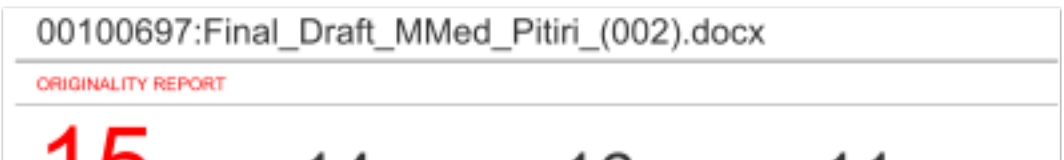
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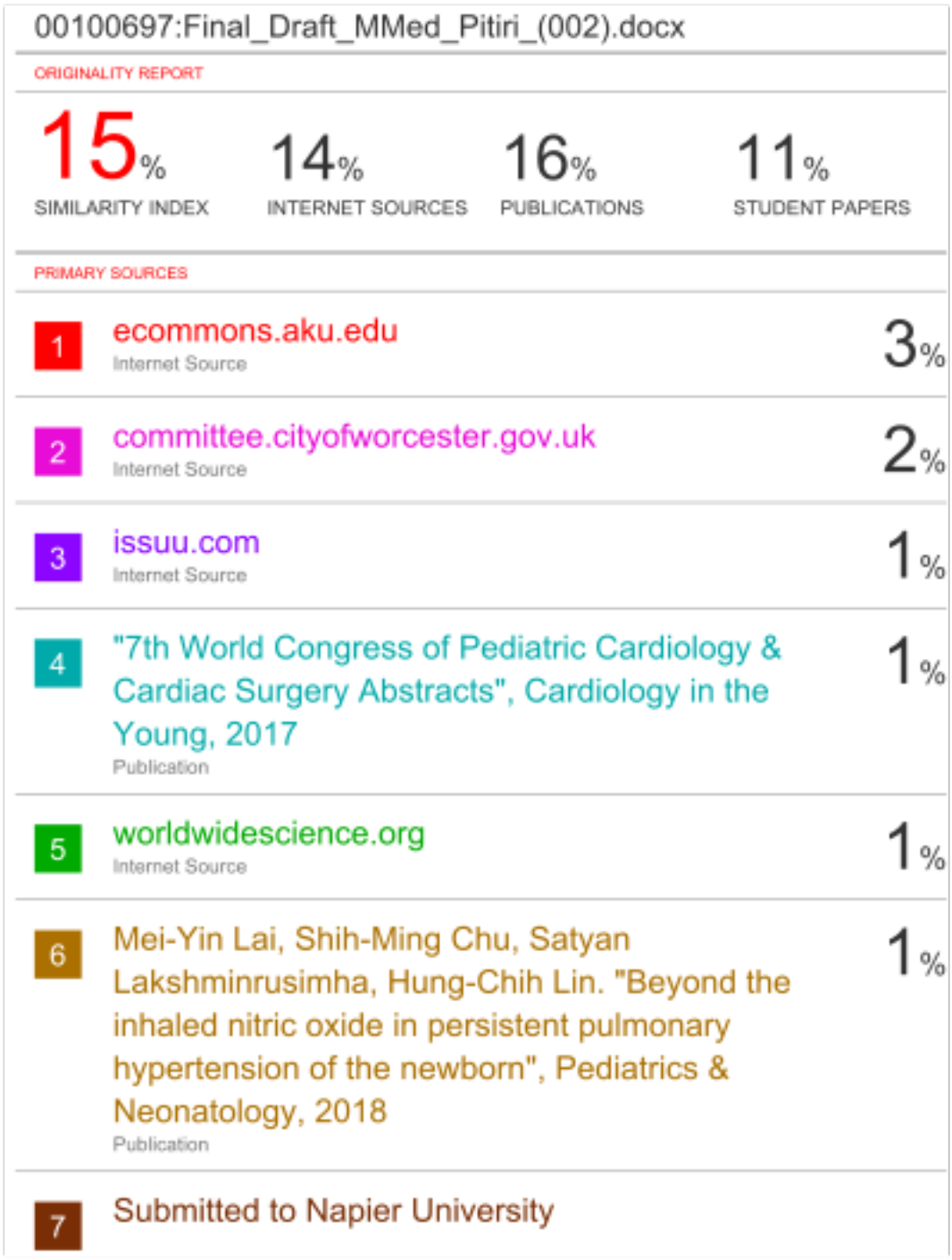
ORIGINALITY REPORT

15

APPENDIX D: TURNITIN REPORT



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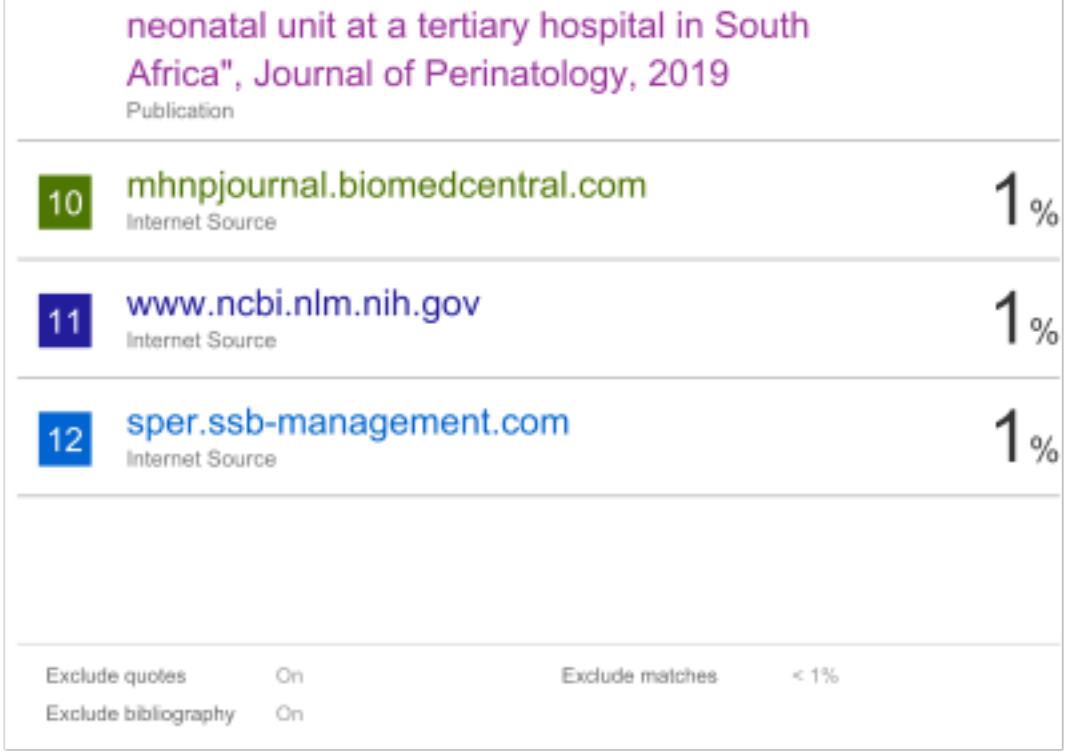

APPENDIX E: MANUSCRIPT SUBMITTED TO SOUTH AFRICAN JOURNAL OF CHILD HEALTH

UNDERLYING DISEASE, MANAGEMENT STRATEGIES AND SURVIVAL RATE OF NEONATES DIAGNOSED WITH PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

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ABSTRACT

Background: Management of persistent hypertension of the new-born (PPHN) varies widely around the world. Therapeutic strategies used in management of PPHN in low-and middle-income countries (LMIC) are not well reported. Secondly, the diagnoses associated with PPHN and the survival rates of neonates with PPHN in LMIC is not well known.

Objective: To determine the underlying disease, management strategies and survival rate of near-term and term neonates (birth weight >2000 grams) diagnosed with PPHN.

Methods: This was a retrospective review of clinical records of near-term and term neonates who were admitted to Chris Hani Baragwanath Hospital (CHBAH), neonatal intensive care unit (NICU) from January 2012 to December 2013 with a diagnosis of PPHN.

Results: A total of 1262 neonates were admitted to NICU, of which 470 weighed >2000 grams. Fifty neonates were diagnosed with PPHN which was 4.0% of NICU admissions and 10.6% of near-term or term neonates admitted to NICU. Meconium aspiration syndrome with (44%) and without (42%) birth asphyxia was the most common underlying diagnosis associated with PPHN. Management strategies used were fluid boluses (80%), inotropes (80%), alkalinisation (68%), sildenafil (60%) and inhaled nitric oxide (6%). All-cause mortality rate was 36%. Non-survivors were more likely to have required rescue high frequency oscillatory ventilation than survivors (83.3% vs 25.0%, $p<0.001$)

Conclusion: PPHN accounts for about a tenth of near-term and term neonates requiring mechanical ventilation and is associated with high mortality rate. MAS is the most common underlying diagnosis in neonates with PPHN. Commonly used management strategies are fluids, inotropes, alkalinization and sildenafil.

INTRODUCTION

Persistent pulmonary hypertension of newborn (PPHN) is defined as failure of normal fall in

INTRODUCTION

Persistent pulmonary hypertension of newborn (PPHN) is defined as failure of normal fall in pulmonary vascular resistance (PVR) at or shortly after birth, leading to shunting of deoxygenated blood into the systemic circulation across foramen ovale or ductus arteriosus. Pulmonary vasoconstriction, vascular proliferation and remodelling contribute to elevated PVR in PPHN.[1] The incidence of PPHN is reported to be 0.43-6.8 per 1000 live births, with mortality rate ranging between 4% to 33%.[1, 2] About 14%-46% of the survivors develop long-term impairments such as hearing deficits, chronic lung disease, cerebral palsy and other neurodevelopmental disabilities.[3, 4]

The aetiology of PPHN can be classified into three groups; abnormally constricted pulmonary vasculature as a result of parenchymal diseases; hypoplastic pulmonary vasculature and normal parenchyma with remodelled pulmonary vasculature.[2] The common aetiologies of PPHN are meconium aspiration syndrome, birth asphyxia, neonatal septicaemia and post-term delivery.[3, 5-7] Echocardiogram is the gold standard for definite diagnoses of PPHN and also assist to exclude congenital cyanotic cardiac disease.[7-9] The diagnoses of PPHN can also be confirmed by measuring preductal and postductal arterial oxygenation. A difference in arterial partial pressure of oxygen (PaO_2) of 20 mmHg or a difference in oxygen saturation of >10% between right arm and lower limbs should be considered as suggestive of PPHN. Current therapies of PPHN include mechanical ventilation, vasodilators and extracorporeal membrane oxygenator (ECMO). Oral sildenafil has been used successfully to improve oxygenation in patients with PPHN especially in resource limited setting where facilities like inhaled nitric oxide (iNO) and ECMO are unavailable.[10-12] In low- and middle-income countries (LMIC) the availability iNO and ECMO is limited due to high costs and limited availability of trained physicians.[8] The neurodevelopmental and medical outcome among PPHN survivors treated with these advanced therapies is the same as compared with those treated with conventional therapies.[13, 14]

The use of different therapeutic strategies in management of neonates with PPHN in low- and middle-income countries (LMIC) is not well reported. Secondly the diagnoses associated with PPHN and the survival rates of neonates with PPHN in facilities based in these countries is also not well known. In this study we sought to determine underlying and/or associated diagnoses, management strategies and survival rates of newly born infants diagnosed with PPHN admitted to a public tertiary hospital from a LMIC.

METHODS

This study was a retrospective review of clinical records of neonates diagnosed with PPHN and were admitted to a neonatal intensive care unit (NICU) of Chris Hani Baragwanath Academic Hospital (CHBAH) from 1 January 2012 to December 2013. CHBAH is a public tertiary hospital situated in Soweto, Johannesburg, South Africa. It is a major referral center for clinics in the region and hospitals in the southern part of Gauteng. This hospital conducts about 20,000 in-hospital births per year and caters for secondary or tertiary level of healthcare care for about 8000 births conducted in the local community health centers or midwifery obstetric units. A diagnosis of PPHN was based on the difference in pre and postductal oxygen saturations of >10%. The study population included all neonates who were considered to be near-term and term (weighing > 2000 grams at birth) who were admitted to NICU at CHBAH with a diagnosis of PPHN. Neonates whose records could not be retrieved were excluded from the study.

The NICU admission register was reviewed for names of all neonates who weighed >2000 grams and had a diagnosis of PPHN recorded on admission or on discharge from NICU. Hospital records of these neonates with a diagnosis of PPHN were retrieved and reviewed for maternal and infant characteristics, underlying clinical diagnosis, management and outcomes at hospital discharge. Data on maternal characteristics included maternal age, human immunodeficiency status, presence of meconium staining of the amniotic fluid, place of birth, mode of delivery, and data on infant characteristics included birth weight, sex, gestational age, management strategies of PPHN and outcome at hospital discharge. All data were collected and entered into a structured data capturing sheet.

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All collected data were captured into a Microsoft Excel spreadsheet. Data were checked for incompleteness and inconsistencies and was analysed using the statistical software Stata/IC, version 15.1. Continuous variables namely maternal age, birth weight, and gestational age were checked for normality in distribution using histograms and the Shapiro-Wilk test and were presented as means with standard deviations or medians with interquartile ranges. Comparisons of continuous variables between survivors and non-survivors were performed using Student t-test. Categorical and dichotomous variables were presented as frequencies and percentages. Comparison in categorical or dichotomous characteristics were performed using chi-square Fisher exact test. Bivariate analysis was performed using logistic regression to assess factors associated with the primary outcome, the mortality and was reported as odds ratios with 95% confidence intervals. For all analyses, differences were considered to be statistically significant if the p-value was <0.05.

Permission to conduct this study was given by the hospital chief executive officer after the protocol was reviewed by the hospital protocol review committee. Ethical approval to conduct the study was given by the University of the Witwatersrand Human Research Ethics Committee. Informed consent was not obtained from patients as this was a retrospective audit of records and all data was kept confidential by the researcher.

RESULTS

A total of 1262 patients were admitted for mechanical ventilation in NICU at CHBAH from January 2012 to December 2013. Those who had a birth weight >2000 grams were 470. A total of 49 patients had diagnosis of PPHN recorded on admission and 1 recorded on discharge giving a total of 50 patients (10.6% of admissions weighing >2000grams). All 50 patients had their medical records retrieved (Figure 1). The median number of neonates admitted with PPHN per month was two with interquartile ranges of one and three, with the highest number of admissions per month being five patients, noted in July 2013 (Figure 2).

Figure 1: Flow chart of neonates admitted to neonatal intensive care unit with a diagnosis of persistent pulmonary hypertension of the newborn.

Figure 2: Number of neonates with persistent pulmonary hypertension of the newborn

Figure 2: Number of neonates with persistent pulmonary hypertension of the newborn

Maternal and infant characteristics of infants with PPHN are presented on Table 1. The mean maternal age was 28.4 (SD 5.75) years, 41.7% of mothers were HIV positive, 34.7% were primigravida and 86% had meconium stained amniotic fluid. Forty-seven (94%) of the 50 neonates had birth weight of > 2500 grams. The mean gestational age at delivery was 39.6 +/- 1.6 weeks, with 43 (89%) of them being of gestational age of 37 to 41 weeks and 4 (8.3%) were born at > 41 weeks' gestational age.

Table 1. Characteristics of neonates with persistent pulmonary hypertension of the newborn.

Characteristic	Number	Percent
Maternal Characteristic		
Maternal age, in years (n = 49)		
<20	3	6.1
20-34	40	80
≥35	6	12.2
Human immunodeficiency virus status positive (n = 49)	20	41.7
Primigravida (n = 49)	20	41.7
Vaginal delivery (n = 49)	31	63.3
Meconium stained amniotic fluid (n = 50)	43	86
Infant Characteristics		
Male sex (n = 50)	27	54
Low birth weight (<2500 grams) (n = 50)	3	6
Gestational age (n = 48)		
Preterm (<37 weeks)	1	2.1
Term	43	89.6
Post-term	4	8.3
Apgar score <7 at 1 min (n = 49)	35	71.4

The underlying diagnoses were meconium aspiration syndrome (MAS) only (44%; n=22), MAS with birth asphyxia (42%; n=21), congenital pneumonia (10%; n=5), birth asphyxia only (2%; n=1), and congenital diaphragmatic hernia (2%; n=1) (Table 2).

Table 2. Underlying diagnosis in neonates admitted to neonatal intensive care unit with a diagnosis of persistent pulmonary hypertension of the newborn.

Diagnosis	Number	Percent
Meconium aspiration syndrome with asphyxia	22	44
Meconium aspiration syndrome without asphyxia	21	42
Congenital pneumonia	5	10
Asphyxia only	1	2
Congenital diaphragmatic hernia	1	2

Management strategies included administration of normal saline bolus and use of inotropes in 40 neonates (80%), administration of sodium bicarbonate (alkalinisation) in 34 patients (68%) and oral sildenafil in 30 (60%) patients (Table 3). Only 3 (6%) patients were recorded as having received inhaled nitric oxide. All patients were managed with mechanical ventilation with 47 (94%) of them being started on conventional mechanical ventilation, and only 3 (6%) being started directly on high frequency oscillator ventilation. Amongst the 47 who were started on conventional mechanical ventilation, 20 (42.6%) were subsequently changed to high frequency oscillator ventilation.

Table 3. Different interventions used in management of neonates with persistent pulmonary

oral sildenafil in 30 (60%) patients (Table 3). Only 3 (6%) patients were recorded as having received inhaled nitric oxide. All patients were managed with mechanical ventilation with 47 (94%) of them being started on conventional mechanical ventilation, and only 3 (6%) being started directly on high frequency oscillator ventilation. Amongst the 47 who were started on conventional mechanical ventilation, 20 (42.6%) were subsequently changed to high frequency oscillator ventilation.

Table 3. Different interventions used in management of neonates with persistent pulmonary hypertension of the newborn.

Intervention	Number	Percent
Number managed with fluid (normal saline) bolus	40	80
Number managed with inotropes	40	80
Number managed with sodium bicarbonate (alkalinization)	34	68
Number ventilated with conventional mechanical ventilator (CMV) only	27	54
Number ventilated with CMV initial and subsequently changed to HFOV*	20	40
Number managed with sildenafil	30	60
Number managed with nitric Oxide	3	6

* - HFOV- High frequency oscillatory ventilation

There were 18 patients who had died at hospital discharge, giving the all-cause mortality rate of 36%. In comparing the non-survivors to survivors, the only difference found was that there were more patients who required to be changed to HFOV among the non-survivors than survivors (62% vs 38%, p=0.001) (Table 4). There were no differences in maternal characteristics, infant characteristics and diagnosis on admission.

Table 4. Comparison of characteristics, diagnosis and interventions used between non-survivors and survivors in neonates with persistent pulmonary hypertension of the newborn.

Variable	Non-survivors N= 18 n (%)	Survivors N = 32 n (%)	P-value
Median maternal age, in years	27	30	0.499
Number with human immunodeficiency virus exposure	14 (77.8)	6 (18.8)	0.67
Primigravida	10 (55.6)	7 (21.9)	0.89
Vaginal delivery	18 (100)	13 (40.6)	0.325
Number with meconium stained amniotic fluid	16 (88.9)	27 (84.4)	0.66
Median Birth weight, in grams	3010	2900	0.705
Median gestational age, in weeks	40	40	0.603
Male sex	17 (94.4)	10 (31.3)	0.69
Meconium aspiration syndrome without asphyxia	10 (55.6)	12 (37.5)	0.321
Meconium aspiration syndrome with asphyxia	6 (33.3)	16 (50)	0.254
Number given fluid (normal saline) bolus	15 (83.3)	25 (78.1)	0.815
Number given inotropes	16 (88.9)	24 (75.0)	0.251
Number given sodium bicarbonate	13 (72.2)	21 (65.6)	0.631
Number changed to high frequency oscillatory ventilation	15 (83.3)	8 (25.0)	**0.001**
Sildenafil	11 (61.1)	19 (59.4)	0.715
Nitric oxide	2 (11.1)	1 (3.1)	0.254

DISCUSSION

This retrospective study reviewed underlying diagnoses, modalities used in the management of newborns with PPHN and their outcomes at hospital discharge in a resource limited setting. The main findings in this study were that meconium aspiration syndrome with or without asphyxia was the most common underlying diagnosis, common management strategies used are volume expanders, alkalinization and oral sildenafil. Only six percent of patients were managed with inhaled nitric oxide. This is likely due to high costs of iNO and unavailability of trained physicians. PPHN is associated with high mortality, and neonates who are converted to high frequency ventilation are more likely to die. Louis D *et al* and Velaphi *et al* reported that MAS as the underlying cause of PPHN is associated with significant mortality [5, 6]

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Sixty percent of patients in this study were on sildenafil, suggesting that it is used as an alternative to iNO. Inhaled nitric oxide is the first line treatment strategy for treating PPHN as it is the local pulmonary vasodilator.[8] Inhaled NO improves oxygenation and reduces the need for ECMO in patients with diverse causes of PPHN.[15] In this study only six percent of patients were on iNO, most likely due to unavailability of iNO. The alternate pulmonary vasodilators are endothelin receptor antagonist such as bosetan, and phosphodiesterase-5 inhibitors such as sildenafil and tadafil. Hussain, et al showed that oral sildenafil can be successfully used to improve oxygenation patients with PPHN particularly in a resource limited setting where facilities like iNO and ECMO are not available.[11] Baquero et al demonstrated oxygen index improvement within 6 to 30 hours in all infants receiving oral sildenafil and significant improvement in oxygen saturation over time, different from the placebo group ($p<0,05$).[16] Mohsen et al used oral sildenafil in 16 cases (50%) that were randomly selected, 10 of them (62,5%) showed improvement and 6 (37.5%) discontinued medication due to unresponsiveness and shifted to another treatment modalities.[13] Lastly Uslu S et al showed that the time to adequate clinical response was significantly shorter in sildenafil group than intravenous magnesium sulphate group.[12]

In the absence of iNO, supportive measures such as maintenance of adequate systemic blood pressures, normothermia and correction of metabolic abnormalities such as metabolic acidosis become an alternative.[10] An international survey done by Nakwan et al demostrated that Dopamine was used as an initial inotropic agent, normal saline was the preferred initial fluid resusitation for hypotension, sedation and analgesia were routinely used as well in the supportive management of PPHN.[8] Gentle ventilating strategies with permissive hypercapnia are recommended to ensure adequate lung expansion with limited barotrauma. All neonates were ventilated, and 68% were managed with alkalization using sodium bicarbonate. Hyperventilation and alkali infusion of sodium bicarbonate to maintain an alkaline pH were strategies previously used but now considered outdated in high income countries. There are concerns of impaired cerebral perfusion, sensorineural deafness with respiratory alkalosis and produces transient effect of pulmonary dilatation and provides no short term or long-term benefits.[4, 7]

The strength of this study is that all patients were inborn and therefore all data on underlying diagnosis and information on management strategies were complete. The limitations of the study were that PPHN was diagnosed based on clinical presentation of differential oxygen saturation of >10%, rather than echocardiogram which could assist in assessing severity of PPHN. The study design is cross-sectional and thus difficult to infer causality in terms of the PPHN and mortality. Moreover, due to a small sample size, we could not use multivariate analyses to explore possible confounding.

CONCLUSION

In conclusion, meconium aspiration syndrome with or without birth asphyxia was the most common underlying cause of PPHN. Neonates with PPHN have high mortality. Oral sildenafil appears to be used as an alternative pulmonary vasodilator in the absence of iNO.[17, 18] Future studies need to enrol large numbers in order to determine predictors of mortality in neonates with PPHN.

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APPENDIX F: AUTHOR GUIDELINES FOR SOUTH AFRICAN JOURNAL OF CHILD HEALTH

MANUSCRIPT PREPARATION
PREPARING AN ARTICLE FOR ANONYMOUS REVIEW

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this requirement are Editorials, Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Submitted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction prior to being sent for review, which will delay publication.

General:

- Manuscripts must be written in UK English (this includes spelling).
- The manuscript must be in Microsoft Word or RTF document format. Text must be 1.5 line spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes). Pages and lines should be numbered consecutively.
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

If you wish material to be in a box, simply indicate this in the text. You may use the table format – this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAJCH is a Journal on child health, therefore for articles involving genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53

- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

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- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

** NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

Research

Guideline word limit: 3 000 words (excluding abstract and bibliography)

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Where appropriate, sample size calculations should be included to demonstrate that the study is not underpowered. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

- May include up to 6 illustrations or tables.
- A max of 20 - 25references

Structured abstract

- This should be no more than 250words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
  - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
  - Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors. It should be able to be intelligible to the reader without referral to the main body of the article.
  - Do not include any references in the abstracts.

Here is an example of a good abstract.

***Scientific letters*/short reports**

These include case reports, side effects of drugs and brief or negative research findings.

Guideline word limit: 1500 words

- Abstract: unstructured, of about 100-150 words
- May include only one illustration or table
- A maximum of 6 references

These include case reports, side effects of drugs and brief or negative research findings.

Guideline word limit: 1500 words

- Abstract: unstructured, of about 100-150 words
- May include only one illustration or table
- A maximum of 6 references

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

Review articles

Review articlesshould always be discussed with the Editor prior to submission.

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners. They should be aligned to practice in South and/or sub-Saharan Africa and not a precis of reviews published in the international literature

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 400 words

Letters to the editor should relate either to a paper or article published by the SAJCH or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address.

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide evidence of consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant*

- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author.
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) consecutively as they are referred to in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:
Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:
Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:
Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted.*
If reference manager software is used, the reference list and citations in text are to be unformatted to plain text before submitting..

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
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  - Look for the correct, matching article in the list of results.
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- Volume and issue numbers should be given.
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  - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx/doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references
- Government Gazettes:

  National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

  In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.
- Provincial Gazettes:

  Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.
- Acts:

  South Africa. National Health Act No. 61 of 2003.
- Regulations to an Act:

  South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).
- Bills:

  South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.
- Green/white papers:

  South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.
- Case law:

  Rex v Jopp and Another 1949 (4) SA 11 (N)

  Rex v Jopp and Another: Name of the parties concerned

  1949: Date of decision (or when the case was heard)

  (4): Volume number

  SA: SA Law Reports

  11: Page or section number

  (N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

  NOTE: no . after the v
- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

From submission to acceptance

Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the *SAJCH* requirements.
- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
  - Anonymous manuscript (unless otherwise stated)

From submission to acceptance

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- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
  - Anonymous manuscript (unless otherwise stated)
  - Author Agreement form [forthcoming]
  - Manuscript
  - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
  - Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer Review Process

All manuscripts are reviewed initially by the Editor-in-Chief and only those that meet the scientific and editorial standards of the journal, and fit within the aims and scope of the journal, will be sent for external peer review. Each manuscript is reviewed by either one or two reviewers selected on the basis of their expertise in the field. A double blind review process is followed at SAJCH.

Authors are expected to receive feedback from reviewers and an editorial decision within approximately 6 weeks of submission. The time period of the entire review process may vary however depending upon the quality of the manuscript submitted, reviewers' responses and the time taken by the authors to submit the revised manuscript.

Manuscripts from review may be accepted, rejected or returned to the author for revision or resubmission for review. Authors will be directed to submit revised manuscripts within two months of receiving the editor's decision, and are requested to submit a point by point response to the reviewers' comments. Manuscripts which authors are requested to revise and resubmit will be sent for a second round of peer review, often to the original set of reviewers. All final decisions on a manuscript are at the Editor's discretion.

Production process

The following process should usually take between 4 - 6 weeks:

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).
2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.
3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.
4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.
5. The CE will finalise the article and then it will be typeset.
6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.
7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

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Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@hmpg.co.za,including the following details:

- Journal, volume and issue in which published
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