UNIVERSITY of RWANDA

Short term outcomes of premature babies born to mothers with pregnancy induced hypertension at Rwanda military hospital (RMH) and Kigali university teaching hospital (CHUK)

A dissertation submitted in partial fulfillment of the requirements for the degree of

Masters of Paediatrics and Child Health

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DECLARATION

I declare that solely I have composed this dissertation and that it has not been submitted, in whole or in part, in any previous application for a degree, except where states otherwise by reference or acknowledgment, the work presented is entirely my own.

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May all those not cited here but contributed in one way or another to the completion of this work receive the expression of my deep gratitude.

CERTIFICATION FOR EXAMINATION

The undersigned certify that they have read and hereby recommend for acceptance by the University of Rwanda a dissertation entitled **"Short term outcomes of premature babies born to mothers with pregnancy induced hypertension at Rwanda military hospital (RMH) and Kigali university teaching hospital (CHUK)"** in partial fulfillment of the requirements for the degree of Master of Medicine (Pediatrics) of the University of Rwanda.

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ABSTRACT

Background: Pregnancy-induced hypertension (PIH) is one of the most common diseases which complicate pregnancies and contribute to neonatal morbidity and mortality(1). Description of PIH effects on neonatal outcomes are various in different settings and their pattern is unknown in Rwanda.

Objectives: This study aimed to evaluate the effect of maternal PIH on neonatal morbidity and mortality in premature infants in comparison with preterm neonates born to mothers without PIH

Methods: Preterm neonates (<37 weeks gestational age(GA)) from mothers with PIH and those from mothers without PIH were evaluated prospectively and retrospectively at RMH and CHUK. SPSS 25, independent t-test, odds ratio and Chi-square were used for analysis.

Results: Hundred sixteen (116) neonates of mothers with PIH (group for study) and hundred sixteen (116) neonates of mothers without PIH (control of study) were enrolled. There was a significant difference between the study and control group with increased cesarean delivery (95.6% Vs 59.4%), small gestational age (58.8% Vs9.4%), gestational age (mean GA: 32.0±2.3 weeks Vs 30.9±2.9 weeks), decreased male sex (42.2% Vs 56.8%) and dexamethasone doses received (mean dose number: 1.5±1.4 Vs 1.9±1.4) with neonates born to mothers with PIH. There was a difference between two groups of study with a decrease of RDS(52.5% Vs 61.2%) increased NEC (10.3% Vs 5.1%) and primary hospital stay(31.0±28 days Vs22.7±18.2 days) in premature babies born at 32 weeks and earlier, lower neonatal sepsis (59.4% Vs 76.7%) and delayed time of death (mean:31.0±28. days Vs 22.7±18.2days) for neonates born to mothers with PIH. No difference was seen between the two groups in terms of ventilation, oxygenotheurapy duration, BPD, ROP, NEC, IVH, and jaundice.

Conclusions: This study showed that cesarean delivery rates, SGA, and GA were higher, dexamethasone doses received and male gender were lower for neonates born to mothers with PIH. Although no difference was found for mortality and other perinatal outcomes, neonates born to mothers with PIH had decreased RDS, increased NEC and prolonged primary hospital stay in premature babies born at 32 weeks and earlier, delayed death, and lower neonatal sepsis.

Keywords (Mesh-terms): Perinatal outcomes, neonatal outcome, Pregnancy-induced hypertension, hypertensive disorders of pregnancy, Pre-eclampsia, Premature infant, Easter Africa, and Rwanda

Glossary of Terms

BPD: bronchopulmonary dysplasia

C/S: Cesarean section

CBHI: community-based health insurance

CHUK: University teaching hospital of Kigali

CI: confidence interval

CMHS: college of medicine and health sciences

CPAP: continuous positive airway pressure

ELBW: extremely lower birth weight (<1000g)

EoNNS: early-onset neonatal sepsis

GA: gestational age

HDP: hypertensive disorder of pregnancy

HDP: hypertensive disorder of pregnancy

HIC: high-income country

IRB: Institutional Review Board

KMC: kangaroo mother care

LBW: Low Birth Weight (<2500g)

LMIC: low and middle-income country

LoNNS: late-onset neonatal sepsis

MOH: Ministry of health

MV: mechanical ventilation

NEC: necrotizing enterocolitis

NICU: neonatal intensive care unit

OPD: outpatient department

PIH: pregnancy-induced hypertension

PLT: platelet

RMH: Rwanda Military Hospital

RMH: Rwanda military hospital

ROP: Retinopathy of prematurity

SDG: sustainable development goals

SGA: small for gestational age

SPSS: statistical package for social sciences.

SVD: spontaneous vaginal delivery

VEGF: vascular endothelial grow factor

VLBW: very low birth weight (<1500g)

WBC: white blood cell

WHO: ward health organization

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CHAPTER I: INTRODUCTION

1.1. Background

Pregnancy-induced hypertension (PIH) is among the most common diseases that complicate pregnancies and are among the causes of adverse outcomes for fetus, mothers and neonates (1). PIH was estimated around 5-10% of pregnancies with variation regarding ethnicity , region and settings (2). It has been described that the rate of prematurity increases once associated with PIH either by spontaneous delivery or provider-induced delivery(3). Its auxiliary effect concerning outcomes of neonates remains with controversy. It was reported that PIH increase fetal survival by maturating organs; however, available litteratures describing this are still conflicting(4).

Rates of PIH-related morbidity reported in middle and low-income countries tend to be higher (10–20%) than those reported in high-income countries (HICs) (5–9%)(5). LMICs incidence estimates are restricted to hospital-based cross-sectional surveys. Therefore, these are likely to be overestimated (5). PIH consist of gestational hypertension, pre-eclampsia, superimposed preeclampsia, and eclampsia(6). Studies showed that its prevalence was significantly higher in Central and Western Africa, with pre-eclampsia as the most prevalent at 66,2%(7).WHO estimates prematurity prevalence at 18% and similar findings were seen in Kenya in 2018 with PIH as a risk factor of prematurity at 32%(8). Hypotheses are attempting to explain the pathogenesis of PIH, but the definitive cause is generally unknown and the key point in management and diagnosis consist of early detection and delivery of the placenta (9,10).

Gestational age at the time of delivery was shown to be the main prognostic factor for neonatal mortality and adverse neonatal outcomes in severe PIH(2). It is not easy to identify pregnancy with PIH whose neonates will have bad outcomes, but some evidence from HIC showed that recurrent PIH, chronic hypertension, and severe hypertension are linked with bad outcomes (10). Only limited studies have investigated neonatal outcomes of infants born to PIH mothers; however, results are conflicting. PIH was found to have a protective effect on neonatal outcomes in some of these studies, whereas some others reported higher neonatal morbidity and mortality risk associated with PIH(2,8,9).

1.2. Problem statement /Rationale of the study

Outcomes of premature neonates born to mothers with PIH are described in different literature, but their pattern is not known in our population and settings. Our study intended to raise awareness of medical health personal working at tertiary and district hospitals in terms of maximizing preventive measures regarding those adverse outcomes associated with PIH.

1.3. Research aim and objectives

1.3.1. Research aim

This study aims to evaluate the effect of maternal PIH on neonatal morbidity and mortality in premature infants in comparison with preterm infants born to mothers without PIH.

1.3.2. Objectives

1. To evaluate and compare mortality and survival at discharge.
2. To evaluate and compare short-term respiratory outcomes in terms of oxygen treatment duration and need, continuous positive airway pressure (CPAP) or mechanical ventilation (MV) need and duration, respiratory distress syndrome (RDS), and bronchopulmonary dysplasia (BPD).
3. To evaluate and compare other morbidities including jaundice, necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), and neonatal sepsis (NNS).
4. To evaluate and compare the duration of primary hospital stay.

CHAPTER II: LITERATURE REVIEW

PIH pathophysiology is still completely unclear but the recently published research proposes that it might be a disease of placentation triggered by reduced activity or half-life of nitric oxide (NO). Abnormal placental formation and implatation result hypoperfusion and hypoxia with releases different factors into the feto-maternal circulation, specifically oxidative stress which initiates endothelial malfunction and other feto-maternal consequences(11). Normal pregnancy is associated with known physiological changes like changes in neutrophils, hyperlipidemia, procoagulant property, and inflammation; PIH can lead to enhancement of these conditions and placental dysfunction causing fetal complication and later contribute to neonatal mortality and morbidity(12).

The effects of PIH on outcomes of neonates is still not well cleared. It is speculated that it help the fetus surviving via maturating the organ through some stress oxidant. However, we are still having controversy of data regarding its association with mortality, short-term respiratory outcomes, BPD, IVH, NEC, NNS, ROP, and primary hospital stay. It remains unclear whether PIH's impact on neonatal outcomes is influenced by gestational age (GA) or the severity of PIH (2,9,13).

2.1. Respiratory outcomes

Recent literature shows that PIH is associated with an altered angiogenic state resulting from decreased umbilical cord vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) levels in infants born to PIH mothers. The appropriate angiogenic state is necessary for normal pulmonary vascular development and also for maintaining the alveolar structure of the lungs(14); on the other hand, several studies like (U. A.Sidramappa et al,2013) as well as (Winn et al,2000) done in the USA, showed that PIH is associated with lung maturation (15–18). Regarding RDS, different results from literature like (Bursal Duramaz et al,2017) and (M. Çetinkaya et al,2009) found that no difference was seen between PIH and non-PIH neonates (Bursal: 49.3% Vs 56.3%, M. Çetinkaya:15.7% Vs 6.1%, p> 0.05)(1,2). Differently, (Yu-Hua et al,2019) found that RDS incidence was lower in PIH neonates comparing to non-PIH (28.9% vs. 44%;uOR: 1.16 (95% CI, 1.02–1.31) (19). Razak et al(2017) stated that no association was found between invasive ventilation, duration of invasive ventilation, and duration of oxygen between the neonates born to PIH mothers and normotensive, however, association was seen between severe PIH regarding invasive ventilation and surfactant administration(uOR: 3.26; 95% CI: 1.11 -9.61)(4). M. Çetinkaya et al (2009) found that duration on mechanical ventilation and total oxygen duration was statistically different between the groups (12.9+19. 7 days Vs 4.9+ 5.7 days, p= 0.09).

Several studies point out that PIH has an impact on BPD. Hilal et al(2010) found that the incidence of BPD in preterm infants born to preeclamptic mothers was significantly higher compared with those born to normotensive mothers (38.5% Vs 19.5%, p< 0.05)(20), similar to L Gemmell et al(2016) suggested that neonates of mothers PIH had higher BPD (42% Vs 34%; P:0.01)(18). Bursal Duramaz et al(2017) the same as M. Çetinkaya et al(2009) found that no difference between group and control(Çetinkayaet al: 21.6% Vs 15.2% , Bursal et al: 19.3% Vs 16.7%, p> 0.05)(1,2).

2.2. Other perinatal outcomes

Necrotizing enterocolitis is a serious condition encountered in neonates and is among the reason for adverse outcomes in preterm infants (1,18). Even if mechanism of NEC is multi-factorial; intestinal immaturity, enteral feeds, the intestinal microbiome, inflammation, and local ischemia or reperfusion injury are obvious underlying factors predisposing to NEC(21). Diversity of results linking NEC to PIH via increased intestinal susceptibility due to inflammatory stress oxidants. Yang et al(2018) found in their nationwide population-based study in Taiwan that The incidence of NEC was higher in the PIH than in the matched non-PIH (0.16 Vs 0.03%, p< 0.05), they found also that maternal PIH was associated with an increased risk of subsequent neonatal NEC development (OR: 1.86, 95% CI, 1.08–3.21, P=.026)(21). Similarly, meta-analysis of Razak et al(2018) found a significant association between NEC and preeclampsia(uOR: 2.79; 95%CI: 1.57 to 4.96; I2 = 0%, 3 studies; 878 subjects)(4).Differently of fore mentioned studies, M. Çetinkaya et al,2009. (45.1 Vs 30.3%, *P*=0.25) and Bursal Duramaz et al,2017 (15.7% Vs 11.1%, *> 0.05*) found that no difference was between group and control regarding NEC(1,2).

Prematurity is an independent risk of ROP (22), though several risk factors, including small gestational age, low birth weight, and postnatal oxygen therapy, are known to be associated with the development of ROP(23). Dysregulation of circulating antiangiogenic factors plays an important role in the pathogenesis of both preeclampsia and ROP and Certain individual studies have shown that PIH is protective over ROP, possibly due to the oxidative stress exerted on fetal development(23). Razak et al(2018): aOR: (0.83; 95% CI: 0.72-0.96) and YU et al(2012) : (aOR, 0.66; 95% CI, 0.50–0.87 for all preterm births) found the adjusted odds were lower in neonates born to PIH, Hsin-Chung Huang, et al(2015) and a systematic review of Priscilla. L et al(2016) didn't find any difference between the PIH and non PIH offsprings(OR: 0.89; P = 0.38; adjusted OR: 1.35; P = 0.18) (4,24,25).

IVH is among premature infants complication and among major morbidity that may lead brain insults resulting in long-term neurological disability(22). Different literature links IVH and PIH effect to the premature babies via fetal endogenous corticosteroid secretion from uteroplacental insufficiency(18). L Gemmell et al(2016) found that infants born to pregnancy without PIH had a higher severe brain injury (IVH

3 to 4/) (18), similar to Eva Morsing et al (2016) who saw an association between reduced prevalence of severe IVH and exposure to PIH after adjustment for GA(OR 0.17, 95% CI 0.05–0.57)(26). Bursal Duramaz et al (2018) and M. Çetinkaya et al(2009) showed that no difference seen between PIH and non PIH neonates (Çetinkaya et al: 21.6% Vs 15.2%,Bursal et al: 19.3% Vs 16.7%, p> 0.05)(1,2).

Little is known regarding the link between PIH and Jaundice, scanty data are available and among them Brian K. Lee et al(2016) showing that there are an attributable fraction of risk factors for non-hemolytic neonatal jaundice for neonates born to mothers with gestational hypertension(Risk: 1.5%,95% CI0.4%, 2.8%)(27).

Neonates born to mothers with PIH are prone to transient(days to weeks) neutropenia related to uteroplacental insufficiency, which could be the reason of increased neonatal infections(12)(1)PIH neonates are found to be associated with nosocomial sepsis as was seen by M. Çetinkaya et al(2009) in Turkey and Hsin-Chung Huang et al(2015) in Taiwan (M. Çetinkaya et al: 49% Vs 21%, p= 0.02, Chung Huang et al: 25.1% Vs 20.7%, p=0.0062). Many studies showed that no difference between PIH and normotensive neonates in terms of neonatal sepsis: Eva morsing et al(2016) and Bursal Duramaz et al(2018) found that no difference between group and control (Eva morsing et al: 36% Vs 34%, p> 0.05, Bursal Duramaz et al:15.7 % Vs 11.1%, p> 0.05)(1,12).

2.3. Mortality

Prematurity is still among the major contributor to neonatal mortality in Rwanda (45%)(28). The determinants of neonatal mortality may be attributed to newborn, mother, or health system factors(29), some studies still pointing out that neonates born to mothers without PIH have higher mortality comparing to PIH offspring. L Gemmell et al (2016) found that infants from pregnancies without HDP had a higher mortality before discharge (13% Versus 11%;P:0.01)(18), similar to Razak et al(2018) who saw that there is a relation between maternal PIH and mortality (aOR: 0.65; 95% CI: 0.54 to 0.79; I2 = 93%; 3 studies; 1 804 382 subjects)(4). Berhe et al(2020) found that mortality is was higher in PIH comparing to the non-PIH group (15% Vs 2.5%, p< 0.05(30). Bursal Duramaz et al (2018) and M. Çetinkaya et al (2009) found that no difference in terms of neonatal mortality between 2 group (Bursal Duramaz et al: 7.9% Vs 11.8%, p*>0.05*, M. Çetinkaya et al: 34% Vs 39%, p=0.39). Regarding death time, D. Chacha et al(2020) found that maternal causes of neonatal mortality contributed mainly to early death, and Berhe et al(2020) found that early neonatal mortality was more frequent in the PIH group comparing to non-PIH (5% Vs 1%, uOR: 5.22, 95% CI: 1.87-14.49, aOR: 3.22, 95% CI: 1.06-9.74)(29)(30). Chen et al(2018) found that for both early death and late neonatal death, non-PIH was more frequent (31):

- Early neonatal death: early preterm babies (average for GA: 22.8 Vs 111.0, small for GA: 85.3 Vs 307.2)and late preterm babies(average for GA:1.0 Vs 1.5, small for GA: 2.2 Vs 9.1)
- Late neonatal death: early preterm babies (average for GA: 12.5 Vs 24.3, small for GA: 40.4 Vs 67.1) and late preterm babies (average for GA:0.5 Vs 0.8, small for GA: 1.5 Vs 4.5)

CHAPTER III: MATERIALS AND METHODS

3.1. Study description

This project consists of a retrospective and prospective study conducted at CHUK and RMH, by comparing perinatal outcomes of Premature babies (<37 weeks) between those born to mothers with PIH and non-PIH mothers.

After local ethics committee approval, candidates of prospective part were enrolled once meeting criteria and signed informed consent, and two weeks follow up was done based on medical records at two sites. For retrospective candidates, a complete review of the file and open clinic data was done, files found with missing data were not considered. Socio-demographic data, obstetric and neonatal data were collected using a questionnaire. Data entry was done using SPSS 25 software for analysis.

3.2. Study design

Prospective and retrospective Cross-sectional comparative study

3.3. Study site

University Teaching Hospital of Kigali (**CHUK)** and Rwanda Military Hospital **(RMH).** The study was conducted in two teaching hospitals: First in CHUK, a teaching hospital with different departments that receives patients from the Northern, some parts of southern and western province, and three Kigali district hospitals. CHUK's neonatology unit is equipped with eleven incubators, seven radiant warmers, nine cribs, and a block with four beds for Kangaroo mother care (KMC) where preterm infants spend some weeks before being discharged. It is also equipped to provide non-invasive respiratory support with five CPAP machines, and nasal oxygen. On some occasions depending on the availability of a bed in the Pediatric intensive unit (PICU), the neonate can be also admitted to PICU. For an average total of 30 hospitalized newborns, there are four nurses allocated during the day and three on the night shift who work hand in hand with at least two residents under the supervision of a neonatologist and/or a pediatrician. There are on average 650 patients per year hospitalized in the Neonatology unit with different conditions.

Because of time-constraint and COVID-19 pandemic challenges, to enroll sufficient patients during the period of data collection, the study was expanded to Rwanda military hospital (RMH), a military-based hospital, referral, and teaching hospital in Kigali. RMH receives many patients from the eastern province and some from one district hospital in Kigali. Being the only public hospital equipped with neonatal intensive care (NICU), it receives neonates from all parts of Kigali and the countryside depending on the availability of a free bed in the NICU. NICUis equipped with four neonatal ventilators machine and can also provide non-invasive respiratory support through four CPAP machines and oxygen therapy. RMH's neonatology unit is

made of ten incubators, four radiant warmers, ten cribs, and a KMC ward with six beds. There are on average 500 patients in the neonatology unit and 120 in NICU per year hospitalized neonates with different conditions.

3.4. Study population:

Premature Neonates (GA less than 37weeks) born either to mothers with PIH or without PIH.

3.4.1. Inclusion criteria

All preterm babies born with gestational age less than 37weeks GA were admitted to the neonatal unit or neonatal intensive care unit.

3.4.2. Exclusion criteria

- Neonates born with congenital abnormalities or chromosomal anomalies
- Neonates born with APGAR score less than five at five minute
- Neonates born to mothers with diabetes
- Neonates transferred or counter referred to another hospital other than the study site
- Neonates with incomplete, lost information in the file or lost for ROP follow-up.

3.5. Study period

This study was carried out prospectively from May to June 2021 and was extended retrospectively from April 2020 till April 2021 at CHUK and from January 2021 till April 2021 at RMH.

3.6. Sampling and enrollment

Considering available data, the population size of the group (Preterm babies born to mother with PIH) is about half of the control (preterm baby born to mother without PIH)(8), this is why we had always a big number of neonates in the control group. Stratified sampling was used in the control group by considering each month as strata and the first candidates meeting the criteria of selection were selected. If a candidate was found with the exclusion criteria, the following neonate in strata was considered. Unit admission registry books were used during this process. Details are provided in below **Figure I.**

3.7. Procedures at enrolment

All neonates meeting criteria admitted in the neonatology unit (and neonatal intensive care unit) at CHUK and RMH were enrolled in prospective part for the study group and those sampled for the control group. Candidates enrolled from May 2021 were observed during admission and prospective two weekly based longitudinal follow up was done in both the neonatology unit of the university teaching hospital of Kigali (CHUK) and Rwanda military hospital (RMH) NICU and neonatology.

Data collection was done by two data collectors (including the principal investigator at CHUK and a hired trained neonatal nurse at RMH working hand in hand with the principal investigator). Before starting data collection, the principal investigator organized a one-day session for explaining to the hired nurse at RMH the purpose and procedure for the study, the ethical considerations, and exercises of filling questionnaire were done. After assessing fulfillment of selection criteria, data collectors explained the purpose of the study and requested for signing written consent from the caretaker (one of the parents, or carer taker for patients to whom parents were not available like a critically ill mother in a context of nonavailable father). Counter-referred participants and those who missed for ROP follow-up were excluded **(Figure I).**

3.8 Sample size calculation:

The sample size was calculated using the formula:

$$n = \frac{\left(Z_{1-\beta} + Z_{1-\alpha}\right)^2 \left[(R+1) - p_2(R^2+1)\right]}{p2(1-R)^2}$$

Where:

$Z_{1-\alpha}$ is a value from standard normal distribution corresponding to the desired confidence level

($Z_{1-\alpha}$=1.96 for 95% CI)

$Z_{1-\beta}$ being the power of 80%

P_1 = proportion in the exposed group

P_2= proportion in non exposed group

R = risk ratio or relative risk (P_1/P_2)=0.32/0.68=0.47

Considering a study that was conducted in Kenya (one of the East-African countries)(8), it estimated PIH to be 32% compared to 68% for other causes of prematurity, our sample size was estimated to be 116 for each group of study with a total of **232**.

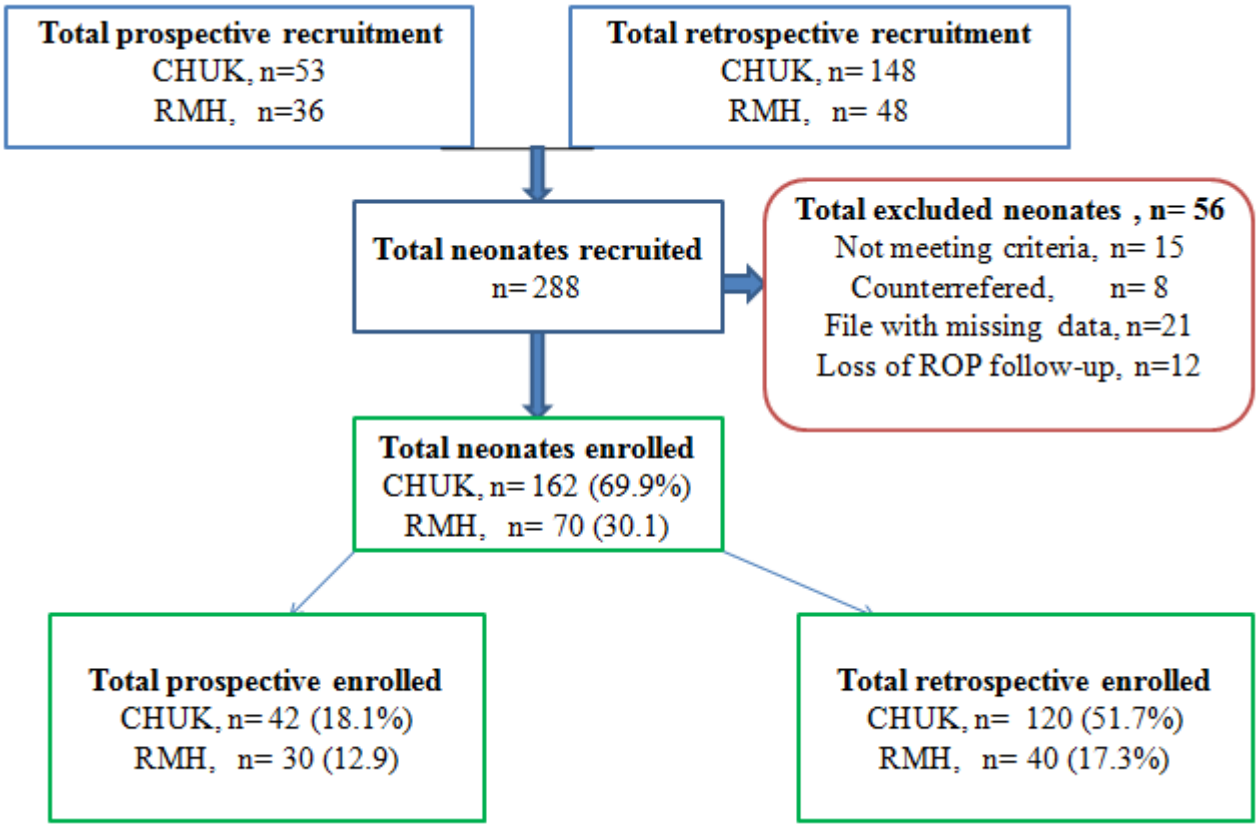

Figure I. Participant flow

3.9. Data collection:

- Data collection was done using a questionnaire
- The questionnaire was developed based on current literature and needed aspects to be evaluated in the study.
- Data collection was done prospectively from admission till discharge (or death), and follow-up at one month of discharge for ROP outcome and consisted of two weekly bases. Reference was made on medical and nursing documentation and OPEN CLINIC information.
- Complete file and OPEN CLINIC review were done for retrospective candidates.
- Electronic (Open clinic) ophthalmologist documentation was used for ROP.

3.10. Data Management:

During data collection, questionnaires were identified with the number and initials of the patient. All soft data were kept in a password-protected document.

3.11. Statistical analysis

Data analysis was done using SPSS 25; Descriptive data analysed, mainly mean ± standard deviation (SD) and median. Comparison of outcomes between 2 groups of study (Neonate born to mother with PIH and those born to mother without PIH), independent t-test was performed and results were interpreted according to Levene's test (based on equal or non-equal variance assumption). For assessing relation between variables, chi-square and odd Ratio with a confidence of 95% were used. For all statistical tests used ***p*-value <0.05** was considered to be significant.

3.12. Outcomes definition

The following outcomes of interest were defined as follows:

1) Mortality: defined as mortality recorded up to discharge

2) BPD was considered as need of oxygen or pressure ventilation either at 36 weeks GA or 28 days postnatal.

3) Short-term respiratory outcomes was defined and evaluated as follow:

a) Need of invasive (mechanical ventilator) and non-invasive (CPAP)ventilation support or surfactant therapy

b) Duration of ventilation support

c) Duration of oxygen therapy

d) RDS at diagnosis defined by signs of respiratory distress (high respiratory rate, recessions, grunting , and central cyanosis) with or without radiologic findings with air bronchograms and ground grace appearance) noticed shortly after delivery in a premature baby less than 33weeks gestational age.

4) IVH was defined as germinal matrix bleeding seen by trans-fontanelle ultrasound performed by a radiologist and graded by the Papile grading system.

6) NEC was defined by abdominal signs of modified bell staging from stage Ia up to above stages.

7) ROP diagnosed and staged according to the international classification of ROP during the hospital stay or at the first month of follow-up by ophthalmologist.

8) Neonatal sepsis is defined by non specific clinical signs (unstable vital signs, seizures, respiratory distress,seizures, abdominal distension, and vomiting) and abnormal routine laboratory tests mainly high WBC (>25000 /mm3) or low WBC (<5000 /mm3), low PLT (<50000/mm3) or high PLT (>450000/mm3) and elevated C-reactive protein (CRP) above 1mg/dL with or without hemoculture isolated organism.

9) Neonatal jaundice is defined by phototherapy bilirubin level according to the day of life and gestational age

10) Number of days for the hospital stay, counted since admission till the day of discharge or death

11) PIH is defined as hypertension (blood pressure ≥ 140/90mmHg) with or without proteinuria (≥ 300 mg/24 hours) merging after 20 weeks

11) Small for gestational age was defined by weight for age and sex below 10 percent.

3.14. Ethical considerations.

Confidentiality

- Questionnaires were identified with the number and initials of patients
- Hard copy data collection forms already filled were kept in a locked cupboard.
- Soft data were kept in a password-locked document.

Informed consent

For prospective participants, parents (or caretakers) provided informed consent after receiving the explanation of the rationale of the study and asking questions for better understanding. If one of the parents is not available (critical mother or deceased mother in the context of non-available father), the caretaker was allowed to sign the informed consent

Incentives for candidates

There were no financial benefits to the caregivers or the infants for participating in the study.

Funding & Sponsors

No funding was sought for this project. The PI used his funds to finance this project.

Potential conflict of interest

The PI is a post-graduate in Pediatrics and this thesis is part of the requirements for graduation

Risk of the study

No physical, social or legal risk was identified

The emotional risk could occur as a parent was asked to sign informed consent of critically ill neonate, this was mitigated by a proper and deep explanation by collector and when needed with the help from the medical team, explaining that the study is not intervention research, just it is the observation of care and disease status of the baby.

No financial risk was identified as all data were collected from the usual routine care of the premature baby.

No risk to researchers was identified

Ethical approval

This study is the result of the proposal which was submitted to the University of Rwanda Institutional Review Board (IRB) IRB Ref: CMHS/IRB/160/2021 and the Research Ethics Committee (REC) of the university teaching hospital of Kigali/ CHUK (Ref: EC/CHUK/072/2021) and Rwanda military hospital /RMH (Ref RMH IRB/040/2021) for review and approval.

CHAPTER IV: RESULTS

In total 288 neonates were recruited for the study, and after considering all exclusion criteria only 232 enrolled. **:** 116 neonates of mothers with PIH (group for study) and 116 neonates of mothers without PIH (control of study) were retained for study with 70 candidates (30.1%) admitted at RMH and 162 (69.9%) from CHUK. CBHI was the commonest insurance used, n=1889(81%), followed by RSSB/RAMA, n=29(12.5%). The most frequent maternal level of education was secondary level, n=107 (46.1%). Maternal non Pregnancy-induced hypertension diagnosis as cause of prematurity consisted of preterm premature rupture of membrane (PPROM), n=43(18.5%), Preterm labor n=31(13.4%), Placenta previa n=17 (7.5%), Abruptio placenta n=6 (2.6%), chorioamnionitis n=7(3%) and other causes n=12 (5.0%). PIH diagnosis as causes of prematurity consisted of Superimposed Preeclampsia n=14 (6%), gestational hypertension n=3 (1.3%), Preeclampsia n=18 (7.8%), severe Preeclampsia n=60 (25.9%) and eclampsia n=21 (9.1%). Features of uteroplacental insufficiency were evident in 66 out of 93(70.9%) and most cases were seen in severe preeclampsia, n= 44 (47.3%).

4.1. Neonatal and maternal characteristic findings

Difference between the study group and control was seen in the following characteristics **($p<0.05$)**: the mean gestational age at birth, small for gestational, Cesarian delivery, mean of dexamethasone doses received, and sex ratio. Details are provided in **Table I.**

Table I.Neonatal and maternal characteristics findings

Characteristics	**Studygroup(n=116)**	**Controlgroup(n=116)**	***P*value**
Maternal age (years)	30.6±6.0	30.9±5.7	*>0.05*
Maternal Gravidity	2.6±1.7	2.8±1.8	*> 0.05*
Maternal Parity	2.1±1.4	2.1±1.5	*> 0.05*
Refereed/non refereed mother	94/22	92/24	*>0.05*
Mother from Kigali, n (%)	48(41.3)	41(35.3)	*>0.05*
Antenatal care visit	2.4±1.1	2.1±1.0	*> 0.05*
Dexamethasone dose	1.5±1.4	1.9±1.4	***< 0.05***
Sex (male/ female)	49/67	66/50	***< 0.05***
Cesareandelivery, n (%)	111(95.6)	69(59.4)	***< 0.05***
Gestationalage at birth (week)	32.0±2.3	30.9±2.9	***< 0.05***
BirthWeight(Kg)	2.03±6.8	1.66±1.92	*> 0.05*
Small for gestationalage (SGA),n(%)	59(58.8)	11(9.4)	***< 0.05***

4.2. Perinatal outcomes findings

Regarding mortality and survival at discharge, no difference was seen between group and control ($p > 0.05$), but a significant difference was seen in terms of the time of the death occurred (21.2±42.0 days for the study group and 5.6±8.5 days for control) **($p < 0.05$)**. Details are in **Table II.**

Table II.Survival at discharge and mortality

Perinatal outcomes	**Study group, n=116**	**Control group, n=116**	***p*-value**
Mortality, n(%)	22 (18.9)	27 (23.2)	> 0.05
Survival to discharge, n(%)	94 (81%)	89 (76.7%)	> 0.05
Time of death, (days)	21.2±42.0	5.6±8.5	**< 0.05**

Neonatal sepsis was found different within two groups of study **(*p*< 0.05)** as 69 neonates(59.4%) in the study group were found to have sepsis and 89 (76.7%) in control with higher LoNNS in the study group (32.7%) and higher EoNNS in the control group (37.9%). For other outcomes, no difference was seen. Among the two groups, no single candidate received surfactant. For more details refer to below **table III**.

Table III. Perinatal outcomes findings

Perinatal Outcomes	**Study group (n=116)**	**Control group (n=116)**	***P value***
RDS, n (%)	76 (65.5)	83 (71.5)	*> 0.05*
Need of MV, n (%)	5 (4.3)	5 (4.3)	*> 0.05*
Duration on MV, (day)	0.35±2.8	0.27±1.4	*> 0.05*
Need of CPAP, n (%)	79 (68.1)	87 (75)	*> 0.05*
Duration on CPAP, (day)	3.7±8.1	4.2±6.0	*> 0.05*
BPD, n (%)	7 (6.0)	11 (9.4)	*> 0.05*
Total duration of oxygenotheurapy (day)	9.3±19.4	10.2±12.5	*> 0.05*
NEC, n (%)	16 (13.7)	9 (7.7)	*> 0.05*
ROP, n (%)	22 (18.9)	23 (19.8)	*> 0.05*
IVH, n (%)	17 (14.6)	24 (20.6)	*> 0.05*
Jaundice, n (%)	51 (43.9)	61 (52.5)	*> 0.05*
Neonatal sepsis (confirmed and suspected), n (%)	69 (59.4)	89 (76.7)	***< 0.05***
EoNNS, n (%)	21 (18.1)	44 (37.9)	*> 0.05*
LoNNS, n (%)	38 (32.7)	25 (21.5)	*> 0.05*
Duration on phototherapy (day)	1.2±1.5	1.59±1.7	*> 0.05*
Primary hospital stay (day)	23.0±23.4	19.3±16.7	*> 0.05*

Table IV.Subgroup analysis

Subgroup	**25 -32 weeks GA**			**33 – 36 weeks**		
Perinatal Outcomes	**Study group (n=116)**	**Control group (n=116)**	***P value***	**Study group (n=116)**	**Control group (n=116)**	***P value***
RDS, n (%)	61 (52.5%)	71(61.2%)	**< 0.05**	15(12.9%)	12(10.3%)	>0.05
Need of MV, n (%)	3(2.5%)	3(2.5%)	>0.05	2(1.7%)	2(1.7%)	>0.05
Duration on MV, (day)	0.5±3.8	0.2±1.0	>0.05	0.1±0.6	0.3±1.9	>0.05
Need of CPAP, n (%)	56(48.5%)	69(59.4%)	>0.05	23(19.8%)	18(15.5%)	>0.05
Duration on CPAP, (day)	5.6±10.5	5.6±6.7	>0.05	1.5±2.9	1.7±3.3	>0.05
BPD, n (%)	7(6.0%)	10(8.6%)	>0.05	0(0.0%)	1(0.8%)	>0.05
Total duration of Oxygenotheurapy (day)	14.3±25.5	12.2±13.6	>0.05	3.7±4.8	6.0±8.6	>0.05
NEC, n (%)	12(10.3%)	6(5.1%)	**< 0.05**	4(3.4%)	3(2.5%)	>0.05
ROP, n (%)	17(14.6%)	20(17.2%)	>0.05	5(4.3%)	3(2.5%)	>0.05
IVH, n (%)	16(13.7%)	21(18.1%)	>0.05	1(0.8%)	3(2.5%)	>0.05
Jaundice, n (%)	34(29.3%)	45(38.7%)	>0.05	17(14.6%)	16(13.7%)	>0.05
Neonatal sepsis (confirmed and suspected), n (%)	46(39.6%)	67(57.7%)	**< 0.05**	23(19.8%)	22(18.9%)	>0.05
EoNNS, n (%)	16(13.7%)	34(29.3%)	>0.05	5(4.3%)	10(8.6%)	>0.05
LoNNS, n (%)	26(22.4%)	15(12.9%)	>0.05	12(10.3)	10(8.6%)	>0.05
Duration on phototherapy (day)	1.62±1.6	1.8±1.7	>0.05	0.93±1.5	1.1±1.6	>0.05
Primary hospital stay (day)	31.0±28	22.7±18.2	**< 0.05**	14.2±12.1	13.2±11.6	>0.05
Mortality, n(%)	17(14.6%)	25(21.5%)	>0.05	5(4.3%)	2(1.7%)	>0.05
Time of death, (days)	24.9± 48.2	5.4± 8.7	< **0.05**	10.5±6.3	7.5±7.7	>0.05

4.3. Subgroup analysis and the relationship between variables

Participants were classified according Gestational age, with **subgroup group 1**: 25-32 weeks, and **subgroup 2**: 33-36 weeks. subgroup 1 made of 136 neonates (61 from group of study, 75 from the control of study), and subgroup 2 consisted of 96 neonates (55 from the group of study and 41 from the control of study).

Subgroup analysis showed the following findings: Difference between study and control group was seen regarding neonates who had RDS, NEC, neonatal sepsis, primary hospital stay, and death time **($p < 0.05$)**. For more details, refer to above **table IV**.

Relationship between variables was evident between **($p < 0.05$)**: birth weight and GA ($p < 0.05$, OR: 16.8, 95% CI 8.7-32.5), time of death, and type of neonatal infection was seen as follow: death happened ≤ 7days (EoNNS 27 Vs LoNNS 2), ≥8 days (EoNNS: 2 Vs LoNNS 9), primary hospital stay and total duration on oxygen(OR: 25.2, 95% CI: 8.6-74), and duration on CPAP (OR: 11.6, 95% CI: 4.2-31.3), and neonatal sepsis (OR: 3.8, 95% CI: 2.1-7). No relationship was seen between outcomes with the different diagnoses of PIH.

CHAPTER V: DISCUSSION

The study looked at "Short term outcomes of premature babies born to mothers with pregnancy-induced hypertension at Kigali university teaching hospital (CHUK) and Rwanda military hospital (RMH)" and was aiming at evaluating the effect of maternal PIH on neonatal morbidity and mortality in premature infants in comparison with premature neonates born to pregnancy without PIH. In this study, outcomes of neonates found between the 2 groups of study tend to be generally.

5.1 Survival to discharge and mortality

Our study found that there was no difference between neonates born to PIH and non-PIH mothers in terms of survival at discharge and mortality, and a difference was seen regarding the time at which death occurred with delayed death for PIH neonates.

Mortality

Diversity of findings in different settings regarding mortality depend on the quality of care (antenatal care, intrapartum and newborn care) among health care facilities(30). Similar to our study findings, most studies like those done in Turkey of Bursal Duramaz et al (2016) and M. Çetinkaya et al(2009) found no difference in terms of neonatal mortality between the two groups of study. On the other hand, Berhe et al (2020) in their prospective cohort study of 782 neonates done in Ethiopia found that mortality was higher in the PIH group and this difference was attributed to system-based care(antenatal and perinatal)(30). This difference in our result to the study done in Ethiopia can be attributed to system-based care but also our small sample size and recruitment method can't be ignored.

Death time

Some studies mentioned the difference in terms of death time between neonates born to mothers with PIH and non-PIH even though C. D. Mangu et al(2020) in their study done in Tanzania found that maternal causes of neonatal mortality contribute mainly to early death(29). Different to our findings, Chen et al(2013) in their population-based study of 5753 preterm babies in Taiwan, found that for both early death and late neonatal death, non-PIH had more death and these findings were related to the effect that PIH might serve some adaptive role for the fetus via uteroplacental dysfunction(31). Our results differ from those found in Taiwan and this might be related to sample size, but also considering the relation found between death time and neonatal infection type, high early neonatal sepsis in non-PIH neonates might contribute to their early death found.

5.2. Respiratory outcomes

Short term respiratory outcomes

In this study, no difference between PIH and non-PIH neonates was seen in terms of short-term respiratory outcomes, but subgroup analysis showed a difference for RDS in neonates of 25-32 weeks GA with decreased RDS in PIH neonates.

Respiratory distress syndrome

Similar to our findings, several studies like the one done by Ting-An Yen et al(2013) in their population-based study involved 8653 very low birth weight(VLBW) neonates in Taiwan found a lower incidence of RDS in PIH compared to non-PIH, attributed to lung maturation associated with PIH(19). A European study by Stylianou-Riga et al(2021); stated that early-onset infection tended to be associated with increased RDS(32). Considering higher early neonatal infection in non-PIH, this lower RDS in PIH neonates compared to non-PIH should be interpreted with caution.

Other short term respiratory outcomes

For other short term respiratory outcomes, notably total duration on oxygen, need of MV and CPAP, duration on mechanical ventilation and CPAP; no difference was seen between the two groups of study and similar findings were seen by Razak et al (2017) in their systematic review and meta-analysis as well as Bursal Duramaz et al(2018).

Bronchopulmonary dysplasia

This study didn't found the difference between PIH and non-PIH neonates regarding BPD. Several studies point out that PIH has an impact on BPD like Hilal et al (2010) in their prospective study of 332 premature (≤ 32 weeks GA) neonates in Turkey, found that incidence of BPD in preterm infants born to preeclamptic mothers (38.5%) was significantly higher compared with those born to normotensive mothers (19.5%) and they considered the role VEGF in the pathophysiology of BPD (20). On the other hand, Bursal Duramaz et al (2018), as well as M. Çetinkaya et al (2009), found that no difference between PIH and non-PIH neonates regarding BPD similar to our study results. Sample size and recruitment method might be related to the difference of our study results and those found by Hilal et al (2010)

5.3. Other perinatal outcomes

Our study findings showed the difference between two groups of study with increased NEC, prolonged primary hospital stay with 25 to 32weeks GA neonates, and lower neonatal sepsis for PIH neonates. Other perinatal outcomes notably IVH, ROP, and jaundice no difference was found.

Intraventricular hemorrhage

L Gemmell et al (2016) and in their intercontinental retrospectively study of 27 846 preterm neonates and Eva Morsing et al (2016) in their study done in Sweden of 1152 premature neonates, found that neonates from PIH pregnancies had a higher IVH(18)(26). Differently, Bursal Duramaz et al (2018) and M. Çetinkaya et al (2009) showed that no difference was seen regarding both the PIH group and normotensive group, similar to our findings. Our study findings differ from the previously mentioned intercontinental study and this might be related to the effect of our small sample size and system-based care.

Retinopathy of prematurity

Similar to our findings, Hsin-Chung Huang et al (2015) in their national-level study involved 21 NICU VLBW infants found that no association between PIH with the risk of ROP in VLBW infants(24). On the other hand, YU et al (2012) in their large US study involved 19 hospitals with 8758 preterms; found that preeclampsia was linked with reduced ROP(23). This difference in results of the last-mentioned study might be related to system-based care.

Necrotising enterocolitis

Different findings are available relating PIH and NEC and similar to our findings, Yang et al (2018) found in their nationwide population-based study in Taiwan that the incidence of NEC was higher in the PIH cohort (0.16%) than in the matched non-PIH (0.03%), they found also that maternal PIH was associated with an increased risk of subsequent neonatal NEC development and this was attributed to possible placental insufficiency, fetal hypoxemia, and an elevated proinflammatory cytokines level, resulting in increased fetal intestinal susceptibility(21). Again, Razak et al (2017) found that in subgroup analysis increased odds for NEC in preeclampsia, linked to fetal hypoxia and oxidative stress from compromised placental circulation(4). Though previously mentioned studies have similar findings with our study, we can assume that larger studies in our settings are needed regarding NEC in premature neonates from PIH pregnancies focusing on the 25 to 32 weeks gestational age group.

Neonatal jaundice

Little is known regarding the link between PIH and Jaundice, few data are available and among them, Brian K. Lee et al (2016) in their 1 019 220 neonates study done in Sweden showed that there attributable fractions of risk factors for nonhemolytic neonatal jaundice for neonates born to mother with gestational hypertension(27). Differently, our study did not show the difference in terms of neonatal jaundice and duration on phototherapy between PIH and non-PIH offsprings and this difference may be explained by our small sample size and settings which differ from the study done in Sweden.

Neonatal sepsis

In this study, we found the difference between PIH and non-PIH neonates regarding neonatal sepsis with lower neonatal sepsis and higher LoNNS in PIH neonates. Several studies like Hsin-Chung Huang et al(2015) in their large population-based study in Taiwan found a significant difference between two groups of study with higher neonatal infection rate in the PIH group, attributed to neutropenia found in the PIH group(24,25). This difference of our study to the one done in Tailland might be explained by our small size sample and maternal risk of infection for non-PIH neonates because PIH neonates had more late neonatal. Similar studies are needed to exclude the effect of maternal causes of infection notably PPROM and chorioamnionitis and investigation of neutropenia at birth as the attributable cause of increased frequency of late neonatal sepsis in PIH.

Primary hospital stay

Our study found the difference in terms of primary hospital stay for neonates with 32 weeks GA and earlier as PIH neonate stayed longer compared to non-PIH. Ting-An Yen et al (2013) in their VLBW population-based study in Taiwan, found that PIH neonates had shorter hospital stays compared to non-PIH, being a group with fewer comorbidities(19). This difference of our result to the study done in Taiwan could be explained by sample size difference, but also we can't ignore a found relation between neonatal sepsis and primary hospital stay as is the only perinatal comorbidity found related to the primary hospital stay and differ in two groups of study.

CHAPTER VI. CONCLUSION AND RECOMMENDATIONS

6.1. Conclusion

This study found the difference between neonates born to PIH and normotensive mothers with higher Cesarean delivery; GA, SGA, lower dexamethasone doses received, and lower male gender in the PIH neonates group. Neonatal morbidity (BPD, ventilation, total duration on oxygen, IVH, ROP, Jaundice) and mortality were similar between two groups of study but significant difference was seen with the decrease of RDS, increase NEC, prolonged primary hospital stay in premature babies born at 32 weeks and earlier, delayed death and lower neonatal sepsis with more late neonatal sepsis for neonates born to mothers with PIH.

6.2. Strength and limitation

Strength: This is the first comparative study done to assess the effect of pregnancy-induced hypertension on preterm neonates by assessing multiple perinatal outcomes in Rwanda.

Limitations: This study had prospective and retrospective participants and the majority was retrospective, further studies may consider only prospective data over a longer period.

the participant had a wide range of gestational age and involved only a small number of neonates who required NICU settings, further studies would look into premature babies born at 33weeks and below while focusing on neonates in ICU settings.

6.3. Recommendations

Based on this study global findings, no particular recommendations regarding management of premature babies born to PIH mothers, but we believe with improved similar study in future could bring different points of clarification and improving management of premature babies born to mothers with PIH.

Recommandation to the future researchers

- To narrow gestational age looking outcomes only in 32weeks and below of GA, prospective study for a longer period.
- To consider a study with the control group of mothers without infection risk (PPROM and chorioamnionitis to be excluded) for proper assessment of the effect of PIH on neonatal infection

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APPENDIX 1. QUESTIONNAIRE OF DATA COLLECTION

TOPIC : SHORT TERM OUTCOMES OF PREMATURE BABIES BORN TO MOTHERS WITH PREGNANCY INDUCED HYPERTENSION AT UNIVERSITY TEACHING HOSPITAL OF KIGALI AND RWANDA MILITARY HOSPITAL.

Initial : NO:

Hospital ID : RMH/CHUK

Maternal detail:

Age		Parity	Reffered Y / N	Origin N S E W	Dexamethasone received Y / N
Gravidity	Birth wt	Gest age at birth	Features of UPI on Doppler U/S Y / N not done	Level of education Pr S high school	Mode of delivery C/s SVD

Maternal Diagnosis:

Normotensive DX :	Superimposed preeclampsia	Preeclampsia	Severe preeclampsia	Eclampsia

Respiratory outcomes:

RDS Y / N	MV Y / N Days on MV	Tot Duration on O2(days)
CPAP Y / N Duration	Surfactant Y / N	BPD at DX Y / N

Others outcomes:

NEC Y / N	ROP Y / N	IVH Y / N Clinical U/S
Jaundice Y / N	Days on phototherapy	
Sepsis Y / N Eo NNS LoNNS CRP hemoculture clinical	Hospital stay(days)	Death Y / N Day of life at death

APPENDIX 2. INFORMED CONSENT FORM

AMASEZERANO YO KWEMERA KUJYA MU BUSHAKASHATSI KU BUSHAKE

Inyitoy'ubushakashatsi "SHORT TERM OUTCOMES OF PREMATURE BABIES BORN TO MOTHERS WITH PREGNANCY INDUCED HYPERTENSION AT UNIVERSITY TEACHING HOSPITAL OF KIGALI AND RWANDA MILITARY HOSPITAL"

Ayamasezerano agizwe n'ibicebibiriaribyo:

Igice cy'isaranganyamakuru (kugusangizaamakuruajyanyen'ububushakashatsi

Igicecyemezakwitabiraububushakashatsi (ahogusinyamugihewemeyekujyamuriububushakashatsi

I. **Igicecya1: Isaranganyamakuru**

Nitwa BAZAMBANZA Djamar, Turigukora ubushakashatsi kukuburwayi bumwe na bumwe bukunz kugaragara kumpinja zavutse igihe kitaragera, hagereranywa ipinja zavutse kubabyeyi bafite indwara z'umuvuduko wakomotse kugutwita n'izavutse kubabyeyi badafite ibibazo by'umuvuduko.

Ngiye kubasangiza amakuru ajyanyen'ububushakashatsi nanabashishikariza kubwitabwira.

Indwara z'umuvuduko wakomotse kugutwita zitera ibibazo bitandukanye igihe umunbyeyi atwite bikagira ingaruka zitandukanye k'umwana atwite. Kugeza uyumunsi ni bike cyane bizwi kubibazo byizompinja zivuka igihe kitaragera kuri abo babyeyi bafite indwara z'umuvuduko ukomoka kugutwita ugereranyije n'abana bavuka kubabyeyi badafite izondwara.

Ibizava muri ububushakshatsi bizongerera ubumenyi abavuzi bakurikirana izompinja bityo bibebyakongera iremery'ubuvuzizihabwa.

Ni ubushakashatsi buzakorerwa abana bari mubitaro bya CHUK n'ibitarobya Gisirikare bya Kanombe bavutse batagejeje igihe. Ntakintu nakimwe abashakatsatsi bazazikoraho uretse kureba nogukurikiranai mivurirwe yazo.

Kwitabira ubu bushakashatsi ni ubushakebwawe.Ni uburenganzira bwawe guhitamo kubwitabira cyangwa kutabwitabira. Ubaye uhisemo kubwitabira cyangwa kutabwitabira, ntakintu nakimwe bihindura uko umwana yitabwagaho, azakomeza ahabwe serivisi nk'ibisanzwe.

Mu gihe uhise mo kwitabira ubu bushakashatsi, ntamafaranga cyangwa izindi nyungu uzahabwa.Ububushakashatsi ntakibazo nakimwe bwatezaumwana. Amakuruyoseuzatanga muri ububushakashatsi ntahandi azakoreshwa, ni ibanga,nta wundi muntu azasangizwa.

Abagize iri tsinda ry'abashakashatsi nibo bonyine bazayabona. Umwirondoro wabitabira ububushakashatsi nawo uzajyawandikwa muburyo butaziguye.

Biremewe kutitabira ububushakashatsi mugihe wumva utabishaka. Biranewe guhagarika gukomeza kubwitabira igihe cyose wabishakira. Ni amahitamo yawe, kandi uburenganzira bwawe buzakomeza kubahirizwa mubijyanye n'ubuvuzi.

Umwemubabyeyi b'umwana niwe wemerewe gusinya ayamasezerano, ariko mugihe ntamubyeyi numwe uhari (nyina w'umwana arembye cyane kandina se w'umwana adahari, nyina w'umwana yitabye Imana kandi na se w'umwana adahari),umwe mumuryango cyangwa umurwaza abayemerewe kuba yasinya aya masezerano.

Mu gihe waba ufite ikibazo cyangwa se ukigize nyuma, niyo ubushakashatsi bwaba bwara tangiye wakibaza aba bakurikira:

+250783498822 Dr BAZAMBANZADjamar, +250 788438837; DrAGABA Faustine

+2507886595939; Dr RUTAGARAMAFlorent, +250788847366 Dr RUZIGANAGoerge.

Ububushakashatsi bwemejwe n' ishamirishinzwe kugenzura ubushakashatsi muri kaminuzay'u Rwanda, n'ishamirishinzwe kugenzura ubushakashatsi mubitaro by'a kaminuza by'i Kigali. Hari byinshi wifuza kumenya kubijyanye nibi, wabariza aha hakurikira: Uhagarariye ishami rishinzwe kugenzura ubushakashatsi muri kaminuza y'uRwanda"Dr.Stefan JANSEN,sjansen.ur@gmail.com,+250784575900". N'uhagarariye ishami rishinzwe kugenzura ubushakashatsi mubitaro by'akaminuza by' iKigali "Dr. Emmanuel RUSINGIZA,erkamanzi@gmail.com,+250785466254

Igicecya II: Igice cyemeza kwitabira ububushakashatsi

Nyuma yoguhabwa amakuru kuri ububushakashatsi, nkabaza ibibazo byose narimfite nkanahabwa ibisubizo muburyo bunyuze; nemeye kwitabira ubu bushakashatsi kubushake

Amazinay’uwitabiriye ubushakashatsi……

Amazinay’umubyeyi/y’umurwaza……..……

Isinyay’umubyeyi/y’umurwaza……..….

Itariki…….

Igihe umubyeyi cyangwa umurwaza atazi gusoma nokwandika

Ndi umuhamya wo kwemeza ko habaye ho gusomerwandetse no gusobanukirwa kubijyanye naya masezerano y'ubushakashatsi, ndetse usinya yahawe umwanya wokubaza ibibazo. Ndemeza ko uyu usinya aya masezerano yemeye kubushake ntagahato.

Izinary'umuhamya……

igikumwecy'umubyeyi/cy'umurwazaIsinyay'umuhamya……

Itariki……

Inyandiko yemeza y'umushakashatsi

Ndemeza ko uwitabiriye ubu bushakashatsi yahawe umwanya uhagije wokubaza no gusobanurirwa ibibazo muburyo bubanogeye. Ntamuntu numwe twasabywe kwitabira ubu bushakashatsi kugahato, uyu witabiriye yabikoze kubushake bwe kandi atishyuwe.

Uwitabiriye ububushakashatsi nawe yasigaranye iyi nyandikoy'amasezerano.

Amazinay'umushakashatsi……

Isinyay'umushakashatsi…….

Itariki…….

CONSENT FOR PARTICIPATION IN A STUDY ON "SHORT TERM OUTCOMES OF PREMATURE BABIES BORN TO MOTHERS WITH PREGNANCY INDUCED HYPERTENSION AT UNIVERSITY TEACHING HOSPITAL OF KIGALI AND RWANDA MILITARY HOSPITAL"

This Informed Consent Form has two parts:

- Information Sheet (to share information about the research with you)
- Certificate of Consent (for signatures if you agree to take part)

PART I: Information Sheet

I am BAZAMBANZA Djamar. We are researching outcomes of premature babies born to mothers with pregnancy-induced hypertension comparing to others born to nonhypertensive mothers. I am going to give you information and invite you to be part of this research.

Pregnancy-induced hypertension complicates many pregnancies with different adverse outcomes on neonates. In our settings, little is known regarding outcomes of a premature baby born to mothers with pregnancy-induced hypertension in comparison to those born to normotensive mothers.

With this research, we will increase knowledge for health care personnel and improving the quality of care of premature babies born to mothers with pregnancy hypertension.

It will be an observation study for admitted premature neonates at CHUK (Kigali Teaching Hospital) and RMH (Rwanda Military Hospital), no intervention will be done on the participant.

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the care you receive will continue and nothing will change.

If you choose to participate in this study, you will receive no money or other benefits. This study will cause no harm to you. The information collected will be kept confidential. No one but the researchers will be able to see it, and your identification will be coded.

You do not have to take part in this research if you do not wish to do so. You may also stop participating in this research at any time you choose. It is your choice and all your rights will still be respected.

One among the parents is the one allowed to provide this informed consent, but when parents are not available (critically mother in the context of a father who is not available, died mother in the

context of the father who is not available), one of the relative or care-taker can provide this informed consent form.

If you have questions, you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following:

+250 783498822 Dr BAZAMBANZA Djamar, + 250 788438837Dr AGABA Faustine + 250 7886595939 Dr RUTAGARAMA Florent, +250788847366 Dr RUZIGANA George.

This proposal has been reviewed and approved by the IRB of CMHS/UR and the Research Ethics Committee (REC) of CHUK and RMH, which are committees whose task is to make sure that research participants are protected from harm. If you wish to find more about the IRB of CMHS/UR, you may contact the director of research "Dr. Stefan JANSEN, sjansen.ur@gmail.com, +250784575900". For REC, you may contact the chairperson "Dr. Emmanuel RUSINGIZA, erkamanzi@gmail.com, +250785466254". At CHUK, and Lt Col Dr. SERUYANGE Eric, Eseruyange@rmh.rw, +250788531651 at RMH.

PART II: Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Name of Participant …….

Parent Name / Caretaker's name ……..……

Signature of parent/caretaker……..….

Date …….

If illiterate

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Name of witness …… The thumbprint of parent/carer taker

Signature of witness……

Date ……

Statement by the researcher

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands the aspects of our research.

I confirm that the participant was allowed to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this IC F has been provided to the participant.

Name of Researcher ……

Signature of Researcher …….

Date ……

APPENDIX. 3. APPROVAL DOCUMENTS

CENTRE HOSPITALIER UNIVERSITAIRE
UNIVERSITY TEACHING HOSPITAL

Ethics Committee / Comité d'éthique

14th Jun,2021 Ref.:EC/CHUK/072/2021

Review Approval Notice

Dear BAZAMBANZA DJAMAR,

Your research project: "short term of premature baby born to mothers with pregnancy induced hypertension at university teaching hospital of Kigali and Rwanda Military Hospital "

During the meeting of the Ethics Committee of University Teaching Hospital of Kigali (CHUK) that was held on 14th Jun,2021 to evaluate your request for ethical approval of the above mentioned research project, we are pleased to Inform you that the Ethics Committee/CHUK has approved your research project.

You are required to present the results of your study to CHUK Ethics Committee before publication by using this link:www.chuk.rw/research/fullreport/?appid=3866&&chuk.

PS: Please note that the present approval is valid for 12 months.

Yours sincerely,

Dr Emmanuel Rusingiza Kamanzi
The Chairperson, Ethics Committee,
University Teaching Hospital of Kigali

ETHICS COMMITTEE
CHUK

Scan code to verify.

" University teaching hospital of Kigali Ethics committee operates according to standard operating procedures (Sops) which are updated on an annual basis and in compliance with GCP and Ethics guidelines and regulations "

Web Site : www.chuk.rw ; B.P. 655 Kigali- RWANDA Tel.: 00 (250) 252575462, E-Mail: chuk.hospital@chuk.rw

REPUBLIC OF RWANDA
RWANDA MILITARY HOSPITAL
Website: www.rwandamilitaryhospital.rw
P.O. Box: 3377 Kigali, Tel: (+250)252586420, Hotline: 4060
Email: info@rmh.rw

REF/.03. /RMH/COMDT/2021 **June 23, 2021**

Dr. BAZAMBANZA Djamar
UNIVERSITY OF RWANDA
COLLEGE OF MEDICINE AND HEALTH SCIENCES
SCHOOL OF MEDICINE AND PHARMACY
PEDIATRIC DEPARTMENT/PGY IV
EMAIL: badjan06@gmail.com
TEL: +250 783498822

RE: APPROVAL NOTICE

1. In reference to your letter dated 04 June 2021, requesting for approval of the research project, I am pleased to confirm that your research project entitled **"Short Term Outcomes of Premature Baby Born to Mothers with Pregnancy Induced Hypertension at University Teaching Hospital of Kigali and Rwanda Military Hospital",** have been approved by the Rwanda Military Hospital Institutional Review Board (RMH/IRB).

2. Please note that approval of this protocol is valid for **12 months.**

3. Attached is the review notice from RMH/IRB for your reference.

Sincerely,

Dr E RURANGWA
Brig Gen
Commandant

CC:

- Chairperson Institutional Review Board, RMH
- Clinical Services Division Manager, RMH

UNIVERSITY of RWANDA

COLLEGE OF MEDICINE AND HEALTH SCIENCES

DIRECTORATE OF RESEARCH & INNOVATION

CMHS INSTITUTIONAL REVIEW BOARD (IRB)

Kigali, 24th /May /2021

Dr Bazambanza Djamar
School of Medicine and Pharmacy, CMHS, UR

Approval Notice: No 171/CMHS IRB/2021

Your Project Title ***"Short Term Outcomes Of Premature Babies Born To Mothers With Pregnancy Induced Hypertension At University Teaching Hospital Of Kigali And Rwanda Military Hospital"*** has been evaluated by CMHS Institutional Review Board.

Name of Members	Institute	Involved in the decision		
		Yes	No (Reason)	
			Absent	Withdrawn from the proceeding
Prof Kato J. Njunwa	UR-CMHS	X		
Dr Stefan Jansen	UR-CMHS	X		
Dr Brenda Asiimwe-Katoora	UR-CMHS	X		
Prof Ntaganira Joseph	UR-CMHS	X		
Dr Tumusiime K. David	UR-CMHS	X		
Dr Kayonga N. Egide	UR-CMHS	X		
Mr Kanyoni Maurice	UR-CMHS		X	
Prof Munyanshongore Cyprien	UR-CMHS	X		
Mrs Ruzindana Landrine	Kicukiro district		X	
Dr Gishoma Darius	UR-CMHS	X		
Dr Donatilla Mukamana	UR-CMHS	X		
Prof Kyamanywa Patrick	UR-CMHS		X	
Prof Condo Umutesi Jeannine	UR-CMHS		X	
Dr Nyirazinyoye Laetitia	UR-CMHS	X		
Dr Nkeramihigo Emmanuel	UR-CMHS		X	
Sr Maliboli Marie Josee	CHUK	X		
Dr Mudenge Charles	Centre Psycho-Social	X		

After reviewing your protocol during the IRB meeting of where quorum was met and revisions made on the advice of the CMHS IRB submitted on 21st May 2021, **Approval has been granted to your study.**
Please note that approval of the protocol and consent form is valid for **12 months**.

Email: researchcenter@ur.ac.rw P.O Box 3286 Kigali, Rwanda www.ur.ac.rw