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Early Neonatal Deaths among Preterm and Term Neonates: A Comparative Study at the University Teaching Hospital, Lusaka

BY

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DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS OF THE DEGREE OF MASTER OF MEDICINE IN OBSTETRICS AND GYNAECOLOGY

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ABSTRACT

Background: Globally, 15 million babies are born preterm (<37 weeks gestation) each year, and more than 1 million of those do not survive their first month of life. (Lawn, 2006). Preterm birth accounts for 75% of all perinatal mortality in some series. Causes of deaths and antecedent pregnancy and delivery factors are different in deaths of preterm and term neonates. This study aimed to establish factors associated with preterm deaths at the University Teaching Hospital (UTH) compared to those of term neonatal deaths.

Objective: To compare how early neonatal deaths among preterm infants differ from term neonatal deaths.

Methods: A case-control study was conducted among 208 neonates that were early neonatal deaths (eNND) (within 7 days) in neonatal intensive care unit (NICU) at UTH in 2015. Antenatal and intrapartum details (parity, multiple pregnancy, birthweight, antenatal steroid exposure, antibiotic exposure, and the indication of admission to NICU) were obtained from 104 neonates that were preterm (between 24-36 completed weeks gestation) and had died and of a further 104 term neonates (>37 weeks gestation) that died around the same time. The data was collected by interviewer-administered structured questionnaire and analyzed by SPSS v21. Bivariate analysis was used to identify variables for multivariate logistic regression model to identify obstetric determinants amongst deaths in neonates that were preterm compared to those born at term.

Results: There was few difference between the two groups. More preterm neonates that died had received steroids compared to term neonates that had died (P<0.001) and had received antibiotics (p=0.004). By contrast, more term neonates that died were male (P=0.0031) and had a very poor Apgar score (1-3) (P=0.0048). Both the indications for admission to NICU and cause of death were different in the two groups (P<0.0001 and P=0.0309 respectively). On multivariate regression analysis, poor Apgar score was associated with a six-fold odds of RDS. None of the other factors reached statistical significance (adjOR 6.0, 95% CI 3.03-11.92, p<0.0001). Poor Apgar score was also the only factor associated with sepsis, though it was a neonate with a good Apgar score that had higher odds of dying due to sepsis. Primiparity was associated with a 2.6-fold odds (95% CI 1.03 to 6.68, p=0.04) of hypoxic ischaemic encephalopathy.

Conclusions: Hypoxic ischaemic encephalopathy as a cause of early neonatal death is commoner in term neonates but also common in preterm. Sepsis is commoner in preterm neonates as a cause of early neonatal death. Comparing different causes of death, poor Apgar score featured in all cases calling for improved resuscitation.

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ABBREVIATIONS

AOR	Adjusted odds ratio
GA	Gestation Age
HIE	Hypoxic ischemic encephalopathy
LBW	Low birth weight
MOH	Ministry of health
NICU	Neonatal intensive care unit
PMR	Perinatal mortality rate
PROM	Premature Rupture of membranes
RDS	Respiratory distress syndrome
SPSS	Statistical Package for Social Sciences
UTH	University Teaching Hospital
WHO	World Health Organization
ZDHS	Zambia demographic health survey

1. INTRODUCTION

Prematurity is a key issue in public health, especially for developing countries like Zambia. It remains a significant perinatal challenge, with pre-term babies accounting for 5-25% of all deliveries and up to 75% of all perinatal mortality in some series (Fuch, 1976). Preterm birth, defined as childbirth occurring at less than 37 completed weeks or 259 days of gestation, is a major determinant of neonatal mortality and morbidity and has long- term adverse consequences for health. The morbidity associated with preterm birth often extends to later life, resulting in enormous physical, psychological and economic costs (Petrou, 2005). Premature delivery even in developed countries is the most important determinant of infant morbidity and mortality. Among hospital deliveries in developing countries, prematurity is associated with poorer indicators of child morbidity and mortality (Enkin,2000). The survival of these pre-term infants is a function of both their biological maturity and technological advancement. The latter has continued to improve in most developed countries, with continuing progress in neonatal intensive care, shifting the limit of variability towards younger gestational ages, with greater than 80% survival at 28 weeks gestation. Such improvements are also being seen in some developing countries, especially in Asia with survival rates of 50-60% being recorded at 26-27 weeks gestation. The same cannot be said for most African countries with poor health infrastructure. The World Health Organization has established a goal of reducing its incidence by one third in the next decade with the objective of improving child mortality rates (WHO, 2005).

Globally, 15 million babies are born preterm each year, and more than 1 million of those do not survive their first month of life. Three –quarters of these could be saved with current, cost effective interventions. Across 184 counties around the world, the rate of preterm birth ranges from 5-18% of babies born. In lower income countries on the average 12% of the babies are born too early compared with 9%in higher income countries. The situation is especially dire in low and middle-income countries where 98% of all neonatal deaths occur. Approximately 60% of preterm births take place in Africa and Asia. The highest rates of preterm mortality are in West Africa. In Nigeria, preterm babies account for 40-60% of all perinatal deaths (Njokanma, 1994). In the last decade increases in medically indicated labour induction and caesarean delivery

have resulted in rising rates of preterm birth (PTB). In the United States alone this increase was estimated to be 45.1 per 1,000 between 1995-96 and 1999-2000 (Joseph, 2007). This temporal trend is also observed in developing countries. Data from Latin America show a rise in preterm birth due to elective induction and delivery by elective caesarean section from 10% in 1985-1990 to 18.5% in recent years (Barros, 2006).

Of all early neonatal deaths (deaths within the first 7 days of life) that are not related to congenital malformations, 28% are due to preterm birth. (Lawn, 2006) Preterm birth rates have been reported to range from 5% to 7% of live births in some developed countries, but are estimated to be substantially higher in developing countries. These figures appear to be on the rise. Events leading to preterm birth are still not completely understood, although the aetiology is thought to be multifactorial. It is, however, unclear whether preterm birth results from the interaction of several pathways or the independent effect of each pathway. Causal factors linked to preterm birth include medical conditions of the mother or fetus, genetic influences, environmental exposure, infertility treatments, behavioral and socioeconomic factors and iatrogenic prematurity. Approximately 45–50% of preterm births are idiopathic, 30% are related to preterm rupture of membranes (PROM) and another 15–20% are attributed to medically indicated or elective preterm deliveries (Pennell ,2007). Estimation of preterm birth rates and, ideally, their proper categorization (e.g. spontaneous versus induced) are essential for accurate determination of global incidence in order to inform policy and programmes on interventions to reduce the risk of premature labour and delivery.

Preterm infants are at risk of many complications due to immaturity of various organs. Among the complications include; asphyxia, hypothermia, pulmonary syndrome, cerebral haemorrhage, infection, jaundice, anemia, and retinopathy of prematurity. The chance of survival is directly related to the birth weight. The deaths are due to complications already mentioned and increased incidence of congenital malformations. Most of the deaths (two-thirds) occur within 48 hours.

Although Zambia has a perinatal mortality rate of 24/1000 live births (ZDH2013), there is not much documentation about the survival rate and determinants of preterm deaths for babies sent to Neonatal Intensive Care Unit (NICU) at University Teaching

Hospital (UTH). This study was aimed at establishing the magnitude and risks associated with preterm deaths at UTH. Additionally, ascertained information regarding the causes and timing of death in prematurity may guide research efforts.

2. LITERATURE REVIEW

World Health Organization (WHO) defines preterm birth as birth less than 37 completed gestational weeks but most studies have focused on very preterm infants less than 32 because of their high risk of mortality and morbidity. Additionally, World Health Organization (WHO) reports that up to half of perinatal deaths per year occur as a direct consequence of poorly managed deliveries. In developing countries, suboptimal care has been identified in up to 70% of perinatal deaths in hospital based studies.

Few studies in low-income and middle income countries have investigated differences in mortality by extent of prematurity, intrauterine growth restriction (IUGR), or the two in combination (Marchant, 2012) or mortality risk in infants who are small for gestation age (SGA) stratified by gestational age (Kristensen, 2007). Examination of the mortality risk by degree of prematurity and SGA as a proxy for IUGR might be crucial in understanding the attributable disease burden.

Many studies have accounted for the risk factors for preterm delivery and for low birth weight (LBW) as well as for neonatal outcomes. The short-term outcomes on ante partum, labour and postpartum care of LBW infants have not yet been properly focused. There is no consensus on whether LBW foetuses are more susceptible to foetal distress than normal weight, and that there is a difference in gender between LBW and normal weight newborns.

Prematurity and its complications cause about 25% of neonatal deaths. The later the baby is born, the more likely he is to survive. Almost 30% percent of the babies born at 23 weeks of pregnancy survive, while about 50-60% of babies born at 24 weeks, about 75% born at 25weeks, and more than 90% born at 27-28weeks survive. More than 12% of babies born in the United States each year are premature.

Fetal heart rate monitoring is a cornerstone of ante partum surveillance in high-risk pregnancies (Kolatat,2000). LBW is closely associated with preterm birth and heart

rate records of premature fetuses show decreased variability and little fluctuation before 28 weeks (Munz,2000). Despite that, there is no general agreement that fetuses who turn out to be LBW infants show more often non-reassuring or ominous heart rate patterns than those with normal weight. In the uterus passage of meconium is also a sign of fetal compromise and is associated with adverse perinatal outcomes even for preterm or very LBW newborns (birth weight ≤ 1,500 grams). Low Apgar scores at the first and the fifth minute are associated with increased risk of neurologic sequel in term infants. Low birth weight infants also present an increased risk of developing perinatal asphyxia. In fact, birth weight has been shown to be independently associated with birth asphyxia.

The mode of delivery of infants weighting less than 1,500 grams is associated with perinatal morbidity and mortality. Caesarean section is associated with increased rate of bronchopulmonary dysplasia and vaginal delivery with increased ventricular haemorrhage and higher mortality rates (Munz,2005). Vaginal breech delivery of premature infants is associated with increased neonatal mortality and morbidity (birth trauma, birth asphyxia) (Robilio, 2007). On the other hand, some authors suggest that caesarean is a safer route of delivery for extremely low birth weight infants. (Barber, 2007).

It is believed that infants with birth defects (either chromosomal or structural abnormalities) are more likely to have LBW. Gender also plays a role in determining perinatal outcomes. Male fetuses are more likely to be delivered prematurely than females and show worse morbidity and mortality rates. Male sex itself is considered an independent risk factor for poor pregnancy outcome (Renzo, 2007).

Undiagnosed subclinical viral and bacterial infection is also associated with low birth weight which can ultimately lead to preterm death. There is also some association between preterm fresh stillbirths and low birth weight and this is attributed to reluctance on the part of doctors to deliver preterm infants at risk of stillbirth earlier because of fear of poor survival of such neonates (Stringer, 2011).

In the last decade increases in medically indicated labour induction and caesarean delivery have resulted in rising rates of preterm births. In the USA alone this increase is estimated to be 45.1 per 1000. In 2004, births prior to 24 weeks in the United States were 0.8% of total live births and were responsible for 46.3% of infant deaths.

Frequency of prematurity is increasing worldwide, with the possible exception of France and Finland. In Brazil, in 2004, there were 3,026,548 births, of which 34,012 (1.1%) weighed < 1,500 g. During the same year, 54,183 children died before 1 year of age, 15,560 (29%) of whom had birth weights < 1,500 g and 11,426 (73%) of these died before completing 7 days of life. In India, the incidence of preterm labour is 10-15%. Data from Latin America show a rise in preterm birth from 10% in 1985-1990 to 18.5% in recent years. Progress in the frontiers of neonatology has continually pushed back the limit of viability and significantly improved the survival of extremely preterm infants coupled with the increased hospital stays.

Perinatal mortality is defined as deaths among foetuses weighing 1000g or more at birth (28week gestation) that die before or during delivery or within the first 7 days of delivery. The perinatal mortality rate is expressed in terms of such deaths per 1000 total births. The perinatal mortality rate reflects both the standards of medical care and effectiveness of social and public health measures. According to World Health organisation, the limit of viability has been brought down to a foetus weighing 500g. Most of the data on the recurrence of perinatal deaths have come from a few developed countries that have efficient systems for the registration of perinatal deaths. Little is known about the risks of such recurrence in developed countries, partly because the recording of perinatal deaths in such countries which often have no reliable maternal and neonatal databank linked to personal identification number is generally poor and difficult (Lawn, 2006).

The global estimation of perinatal mortality rate (PMR) is 10 per 1000 births in developed countries, 50 per 1000 births in developing countries and 60 per 1000 births in least developed countries. Perinatal mortality rates are highest in Africa where it is more than six times higher than in developed region. Perinatal deaths result from complications of preterm birth, asphyxia or trauma during birth, infections, severe malformations and other causes. From the foregoing, it can be shown that maternal health is important for neonatal health, and maternal infections contribute to adverse pregnancy outcomes (Baird, 1999)

Globally, 3 million babies die in the first seven days of life (early neonatal period). It is estimated that more than 3.3 million babies are stillborn every year; one in three of these deaths occurs during delivery and could largely be prevented. In the less

developed countries, which account for 98% of perinatal deaths, these deaths are not always registered. Majority of foetal deaths occur before the onset of labour. Major global causes of perinatal mortality are asphyxia at birth, low birth weight, and prematurity. Low cost interventions, including training in neonatal resuscitation and kangaroo care may effectively reduce deaths from these causes. It has been estimated that introducing these interventions as a package might decrease perinatal deaths by 50% or more (Zupan, 2005).

The survival rates of preterm and very low weight newborn infants reflect the quality of antenatal care, of the care provided during labour and delivery and the infrastructure for the neonatal care in the different regions and countries of the world. It is expected that richer countries have lower rates of early and late neonatal mortality than countries where healthcare is less robust. In contrast, the frequency of prematurity is higher in poorer countries exactly because of the less stable health conditions of the expectant mother. Low birth weight infants also present an increased risk of developing perinatal asphyxia (Barg, 2003). In fact, birth weight has been shown to be independently associated with birth asphyxia (Kolatat, 2000).

Preterm birth rate has increased in developing countries over the past decade. Most studies have focused on infants born after 33wks of gestation which account for approximately 75% of preterm births. Early preterm infants are more likely to have clinical problems than late preterm infants. The outcome of early preterm infants can not only be related to physiological immaturity but also to maternal complications leading to preterm births (Raju, 2008).

In developing countries, accurate and complete population data and medical records usually do not exist. Furthermore, estimates of the rate of preterm birth in developing countries are influenced by a range of factors including varying procedures used to determine gestational age, national differences in birth registration processes, heterogeneous definitions used for preterm birth, differences in perceptions of the viability of preterm infants and variations in religious practices such as local burial customs, which can discourage the registering of preterm births. These issues make measurement of preterm birth and comparisons across and between developing countries difficult (Graafmans, 2001).

Preterm birth rates available from some developed countries, such as the United Kingdom, the United States and the Scandinavian countries, show a dramatic rise over the past 20 years (Callaghan,2006). Factors possibly contributing to but not completely explaining this upward trend include increasing rates of multiple births, greater use of assisted reproduction techniques, increases in the proportion of births among women over 34 years of age and changes in clinical practices, such as greater use of elective Caesarean section. For example, the increasing use of ultrasonography rather than the date of the last menstrual period to estimate gestational age may have resulted in larger numbers of births being classified as preterm. Changes in the definitions of fetal loss, stillbirth and early neonatal death may also have contributed to the substantial increases in preterm birth rates recorded in developed countries in the past two decades (Stanton, 2006).

3. STATEMENT OF THE PROBLEM

Globally, prematurity is the leading cause of death among neonates. In almost all countries with reliable data, preterm birth rates are increasing. In low–income countries like Zambia, about 50 percent of the babies born at 32 weeks die due to a lack of basic care for infections and breathing difficulties. In high income countries, almost all of these babies survive. Although the mortality rate for preterm infants have dramatically improved over the last 3-4 decades in the western world, infants born preterm remain vulnerable to many complications including respiratory distress syndrome, injury to the intestines, a compromised immune system, cardiovascular disorders and neurological insults. Despite significant improvements in perinatal care, there has not been a concomitant reduction in the rate of deaths in preterm neonates in developing countries like Zambia. About 12.9% of babies born in low income countries like Zambia are preterm compared with 9% in higher income countries and yet the perinatal outcomes associated with preterm birth have not been properly determined.

4. STUDY JUSTIFICATION/RATIONALE

Causes of deaths in preterm and term neonates are believed to have different antecedent causes (i.e. in pregnancy and delivery). There are no detailed comparative studies on causes of neonatal deaths in preterm and term neonates. This information

can lead to effective pregnancy and delivery interventions targeted at the two groups of neonates

5. RESEARCH QUESTION

How do early neonatal deaths (within 7 days of birth) among preterm neonates differ from term neonatal deaths?

6. OBJECTIVE

To compare how early neonatal deaths among preterm infants differ from term neonatal deaths

6.1 Specific objectives

i. To determine causes of early neonatal deaths in preterm neonates compared to term neonates at the neonatal intensive care unit of UTH.
ii. To identify maternal and fetal factors associated with preterm and term early neonatal deaths.

7. RESEARCH METHODOLOGY

7.1 Study design

This was a case-control study. The exposure of interest was preterm birth (of less than 37-weeks gestation) and outcome was mortality within seven days among such babies. A comparative group was that of term babies (of greater than 37-weeks gestation) admitted to the same unit who had also died within seven days.

7.2 Study site

The study was conducted at the labour ward and neonatal intensive care unit (NICU) of UTH.

7.3 Target and Study populations

Target population was all preterm and term deliveries that occurred in UTH.

Study population- was preterm and term babies that met eligibility criteria as set by the inclusion and exclusion criteria.

7.4 Inclusion criteria

Preterm neonates

- Preterm (24-36wks completed weeks)
- born at UTH
- Died in UTH NICU within 7 days
- Mothers gave consent to participate

Term neonates

- Term (>37 weeks)
- born at UTH
- Died in UTH NICU within 7 days
- Mothers gave consent to participate

7.5 Exclusion criteria

Gestation weeks before 24wks and above 36wks

Any neonate with congenital malformations

Mothers did not give consent to participate

7.6 Study duration

The study took 7 months from July 2015 to January 2016.

7.7 Variables

- Independent- age of mother, parity, gestational age, education, residence, antibiotic and steroid exposure, weight of the neonate, mode of delivery/IOL, medical conditions in mother, multiple pregnancy, admission to NICU, PPROM
- Dependent – early neonatal mortality (within 7 days)

Table 1: Operational definition of variables in the analysis.

Variable	**Operational definition**
dependant variable	
Early neonatal death	Within seven days of birth
independent variable	
Age of mother	self reported number of years in current pregnancy
Parity	self reported number of children as primipara, multipara and Grandmultiparity
Residential area	Place of residence High. Low or Medium and Rural
Antibiotic exposure	receipt of antibiotics in the mother
Steroid exposure	Receipt of steroids in the mother in preventing RDS
PPROM	Ruptured membranes before labour
Multiple pregnancy	Mother with twins or triplets
Weight	the birth weight of the neonate
Respiratory morbidity	RDS, Asphyxia

7.8 Participant recruitment

Identification of premature babies (24-27 weeks gestation) was done after delivery and followed up to 7 days to note if they survived. Further details only obtained of those that had died. Details of a term neonate that died that day was also done.

7.9 Outcomes

The following delivery details were considered: onset of labour (spontaneous, elective caesarean, induction), mode of delivery (vaginal cephalic, vaginal breech, forceps, caesarean), and indication for caesarean (acute fetal distress, cephalopelvic disproportion, breech, preeclampsia, previous caesarean, placental abruption, other).

The perinatal outcomes included first and fifth minute Apgar score (7-10, <7), somatic gestational age (≥37 weeks, <37 weeks), gender (male, female). For each variable with missing information, the correspondent records were excluded when statistical analysis was performed. Although it would be worth to have a differentiation between low birth weight (LBW) due to preterm birth or fetal growth restriction, this was not done.

Early neonatal deaths were regarded as deaths within first seven days of life. Apgar score at 1 minute of 0-3 was taken as severe birth asphyxia, 4-7 as mild to moderate birth asphyxia and >8 as normal. Birth weight of <2.5 kg was taken as LBW, 1.0 - <1.5kg as very low birth weight (VLBW) and <1.0 kg as extremely low birth weight (ELBW).

7.10 Sample size

The sample size was calculated using Kelsey method on Open Epi software with 80% power. This sample was based on the hypothesis that 25% of cases would have poor outcome compared to 5% of controls. There were 210 with 105 preterm and 105 term neonates in each arm.

Two sided confidence level	95%
Power (chance of detection)	80%
Ratio of sample size, unexposed to exposed	1

Percentage of unexposed with outcome	5%
Odds ratio	2
Percentage of exposed with outcome	25% Risk/prevalence ratio 1.3

7.11 Data collection

An interviewer administered questionnaire was used to collect information. (See Appendix 1) after obtaining informed consent from the mother (Appendix 2). The medical records of consenting participants were also reviewed for relevant information.

7.12 Data analysis and management

Data was entered in the MS Excel spread sheet and exported to SPSS version 21 for analysis. Bivariate analysis was initially carried out where the outcomes were cross tabulated with preterm death. The odds ratio (OR) and 95% confidence interval (95% CI) were calculated for the occurrence of outcomes comparatively between preterm and normal birth weight infants. These results were controlled by confounding factors for the adjustment of the respective OR (e.g. maternal age, educational level and admission to NICU) using the logistic regression analysis with adjustment for OR.

The maternal and neonatal characteristics included in the model were maternal age. The minimum and maximum age was 15 and 45 years respectively with the mean of 27.6, marital status of mother (dichotomous: unmarried = 0, married = 1), education of mother (dichotomous: mother not of any schooling = 0, schooling = 1), inhabitants in the place of residence (dichotomous: 0 = low density, 1 => medium and high density), type of delivery (dichotomous: 0 = vaginal, 1 = caesarean), sex of newborn (dichotomous: 0 = female, 1 = male), birth order (dichotomous: 0 = 1–4, 1 => 4), gestational age (dichotomous: 0 = ≤ 36.6 weeks, 1 => 36 weeks). Adjusted odds ratio (OR) and 95% confidence intervals (CI) were calculated. Chi-square was used to study association between categorical variables and T test was used for continuous variables. P value <0. 05 was considered statistically significant throughout.

Results were presented as percentages, proportions, and means of various factors. The odds ratio and 95% confidence interval (95% CI) were calculated for the occurrence of outcomes comparatively between preterm and normal birth weights infants.

7.13. Ethical consideration

Ethical approval was obtained from ERES Converge IRB to conduct the study (Appendix 3), while informed consent was obtained from parents of eligible participants. It was made clear to the parents that their participation in the study was voluntary and that they were free to withdraw from the study at any time without any prejudice to further medical care. Furthermore, participant confidentiality was maintained throughout the study. Regarding patients consent form, information was given and explained in a language that the caregivers understood using the information sheet. Concerns and questions that the parents had were answered and clarified.

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8 RESULTS

Summary of variables stratified by preterm and term

The various factors related to the preterm and term neonates that died are presented in table 1 stratified by the gestation (preterm or term). The chi-square p-value result is summarized in table 2. More preterm neonates that died had received steroids compared to term neonates that had died (P<0.001) and had received antibiotics (p=0.004). By contrast, more term neonates that died were male (P=0.0031) and had a very poor Apgar score (1-3) (P=0.0048). Both the indications for admission to NICU and cause of death were different in the two groups (P<0.0001 and P=0.0309 respectively).

Table 1: Bivariate analysis of factors stratified by gestation (preterm or term)

Variable	Preterm N=104		Term N= 104		Chi square P value
	N	%	n	%	
Age (years)					
<20	12	11.5	12	11.5	0.2886
20-24	28	26.9	17	16.3	
25-34	51	49.0	62	59.6	
35+	13	12.5	13	12.5	
Marital status					
single	9	8.7	9	8.7	0.999
married	95	91.3	95	91.3	
Education					
none	3	2.9	1	1.0	0.1394
primary	24	23.1	29	27.9	
secondary	76	73.1	68	65.4	
tertiary	1	1.0	6	5.8	
Residence					
High	74	71.2	79	76.0	0.8788
medium	17	16.3	14	13.5	
low	10	9.6	8	7.7	
rural	3	2.9	3	2.9	
Parity					
1	36	34.6	34	32.7	0.0879
2	30	28.8	35	33.7	
3	13	12.5	22	21.2	
4+	25	24.0	13	12.5	

Variable	Preterm N=104		Term N= 104		Chi square P value
	N	%	n	%	
Gestation (weeks)					
Extremely preterm (<28)	28	26.9	0	0	< 0.0001
Very preterm (28 - <32	51	49.0	0	0	
Moderate preterm (32 - <34)	19	18.3	0	0	
Late preterm birth (34 - <37)	6	5.8	0	0	
>37 weeks	0	0.0	104	100	
HIV status					
reactive	28	26.9	21	20.2	0.4701
unreactive	66	63.5	74	71.2	
unknown	10	9.6	9	8.7	
Syphylis					
reactive	0	0.0	0	0.0	-
unreactive	43	41.3	29	27.9	
unknown	61	58.7	65	62.5	
Previous Preterm Birth					
Yes	10	9.6	3	2.9	0.0504
N0	94	90.4	101	97.1	
PPROM					
Yes	15	14.4	10	9.6	0.2971
No	89	85.6	94	90.4	
Steroids					
Yes	74	71.2	30	28.8	<0.001
No	30	28.8	74	71.2	
Antibiotics					
Yes	40	38.5	17	16.3	0.0004
No	64	61.5	87	83.7	
Caesarean					
Yes	4	3.8	4	3.8	0.9999
No	100	96.2	100	96.2	
Breech					
Yes	8	7.7	3	2.9	0.1362
No	96	92.3	101	97.1	
Apgar score					
1 to 3	17	16.3	36	34.6	0.0048
4 to 6	45	43.3	42	40.4	
7+	42	40.4	26	25.0	

Variable	Preterm N=104		Term N= 104		Chi square P value
	N	%	n	%	
Neonate Gender					
male	52	50.0	67	64.4	0.0031
female	52	50.0	37	35.6	
Birthweight					
<1000g	41	39.4	0	0.0	<0.0001
1000-1499g	58	55.8	16	15.4	
1500-2499g	4	3.8	45	43.3	
>2500g	1	1.0	43	41.3	
Indication for NICU admission					
Asphyxia	16	15.4	66	63.5	<0.0001
Hypothemia	8	7.7	5	4.8	
failure to breath	6	5.8	1	1.0	
prematurity	67	64.4	18	17.3	
other	7	6.7	14	13.5	
Cause of Death					
HIE	44	42.3	62	59.6	0.0309
SEPSIS	41	39.4	36	34.6	
RDS	17	16.3	6	5.8	
asphyxia	1	1.0	0	0.0	
other	1	1.0	0	0.0	
Day of death					
<1 day	41	39.4	27	26.0	0.0674
2 to 3	32	30.8	46	44.2	
4 to 7	31	29.8	31	29.8	

Table 2: Summary of associations of factors between preterm and term neonates resulting in Early Neonatal Deaths

Variable	P value (chi square)	
Age	0.2886	No difference in two groups
Parity	0.0879	
Education	0.1394	
Residence	0.8788	
HIV status	0.4701	
Previous preterm birth	0.0504	
PROM	0.2971	
Mode of delivery	> 0.9999	
Breech	0.1362	
Antenatal steroids	< 0.0001	A feature of preterm
Antibiotics	0.0004	
Apgar scores (term less)	0.0048	Less A.S in term neonates
birthweight	< 0.0001	By definition
sex	0.0031	More term males died
Cause of Death	0.0309	Different in two groups
Days surviving	0.0674	

Gestation and causes of early neonatal death

The causes of early neonatal death differed in whether the neonate was preterm or term. Figure 1 summarises the main causes by a breakdown of gestation. Hypoxic ischaemic encephalopathy (HIE) was commonest in all groups except the 28-32 week group in which sepsis was commonest. Respiratory distress syndrome (RDS) was the third commonest.

Similarly, figure 2 illustrates the causes of early neonatal death by term or preterm gestation. HIE was commoner in term neonates, though sepsis and RDS was commoner in preterm neonates.

Figure 1: Distribution* of gestation by cause of early neonatal death

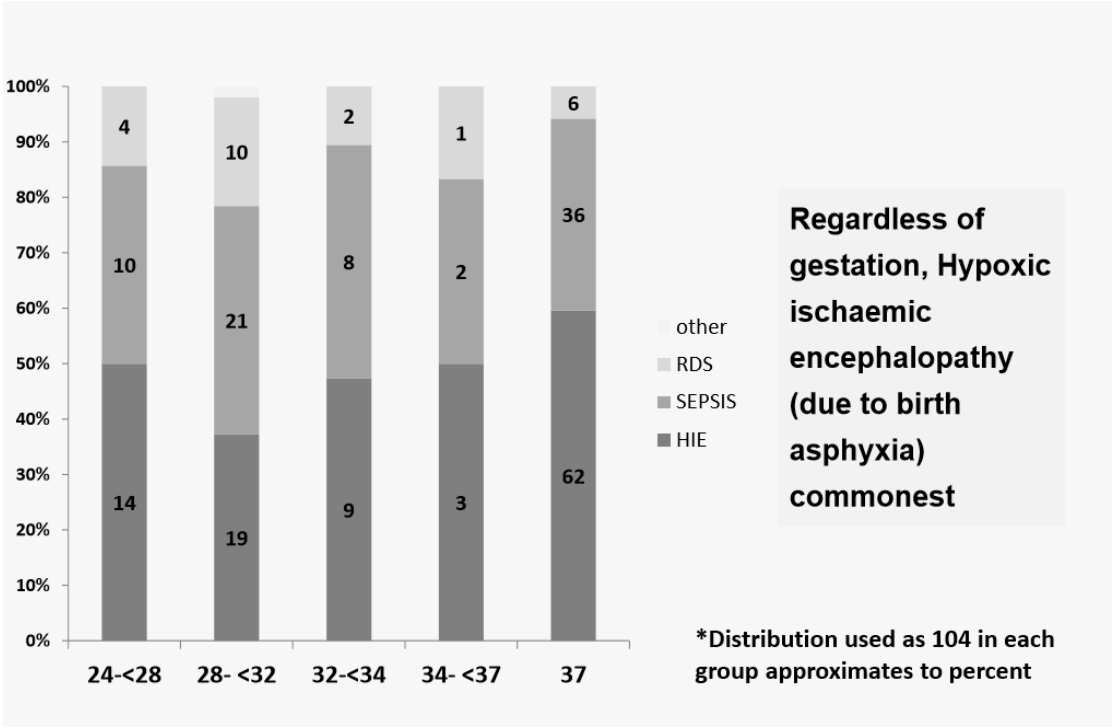
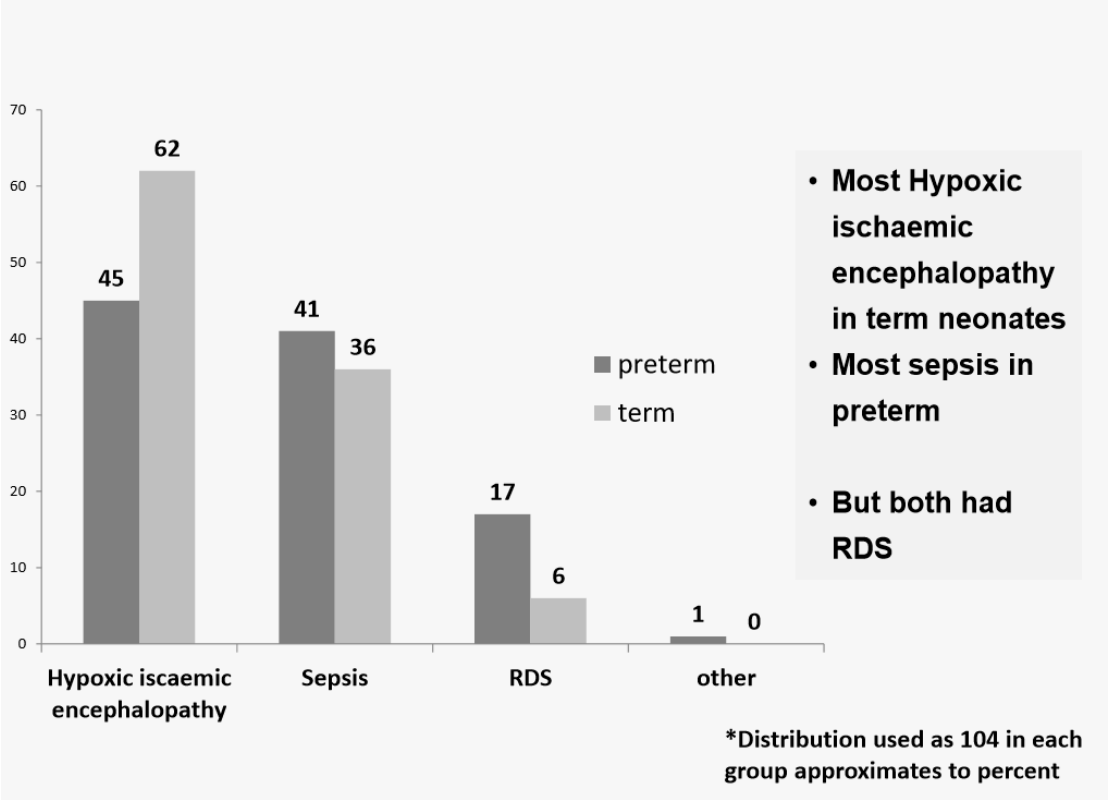


Fig 2: Distribution* of cause of early neonatal death gestation by preterm or term



Logistic regression analysis

To determine which cause of death was associated with particular pregnancy or neonatal conditions, multivariate logistic regression analysis results are presented in tables 3,4 and 5. These have the three main causes as the dependent variable (RDS, Sepsis and HIE).

Poor Apgar score was associated with a six-fold odds of RDS. None of the other factors reached statistical significance (adjOR 6.0, 95% CI 3.03-11.92, p<0.0001).

Poor Apgar score was also the only factor associated with sepsis, though it was a neonate with a good Apgar score that had a higher odds of dying due to sepsis.

Primiparity was associated with a 2.6-fold odds (95% CI 1.03 to 6.68, p=0.04) of hypoxic ischaemic encephalopathy. Interestingly, poor Apgar score was initially protective.

Table 3: Logistic regression: RDS

Parameter	Adjusted Odds Ratio	(95% Conf. Int.)	P value
Preterm	1.3	(0.46 to 3.646)	P = 0.623
Primip	0.9	(0.48 to 1.78)	P = 0.8151
Previous Preterm Birth	1.6	(0.47 to 5.41)	P = 0.4577
Breech	1.1	(0.27 to 4.17)	P = 0.9442
Poor Apgar score (<7)	6.0	(3.03 to 11.92)	P < 0.0001
day in NICU <1	1.0	(0.53 to 1.96)	P = 0.9489
LBW	0.4	(0.13 to 1.05)	P = 0.0613
female	1.5	(0.81 to 2.91)	P = 0.1901

Table 4: Logistic regression: Sepsis

Parameter	Adjusted Odds Ratio	(95% Conf. Int.)	P value
Preterm	0.6	(0.20 to 1.56)	P = 0.267
Primip	0.7	(0.35 to 1.31)	P = 0.251
Previous Preterm Birth	0.4	(0.09 to 1.47)	P = 0.1563
Breech	1.1	(0.230 to 4.31)	P = 0.854
Poor Apgar score (<7)	0.3	(0.15 to 0.54)	P = 0.0001
day in NICU <1	0.8	(0.39 to 1.45)	P = 0.3934
LBW	2.5	(0.88 to 7.01)	P = 0.0867
female	0.7	(0.37 to 1.317)	P = 0.2639

Table 5: Logistic regression: HIE

Parameter	Adjusted Odds Ratio	(95% Conf. Int.)	P value
Preterm	2.1	(0.394 to 11.668)	P = 0.3769
Primip	2.6	(1.03 to 6.68)	P = 0.0442
Previous Preterm Birth	2.4	(0.54 to 10.81)	P = 0.2488
Breech	0.8	(0.08 to 6.84)	P = 0.8022
Poor Apgar score (<7	0.3	(0.13 to 0.84)	P = 0.02
day in NICU <1	1.8	(0.70 to 4.41)	P = 0.2346
LBW	1.3	(0.22 to 7.14)	P = 0.795
female	0.9	(0.34 to 2.17)	P = 0.7393

9 DISCUSSION

The study conducted involved 208 neonates from July 2015 to January 2016. There were 104 preterm and 104 term neonates. Although on bivariate analysis a number of factors were noted to be different in comparing preterm and term neonates that died, on multivariate logistic regression analysis only a few were related to deaths in the two groups. Poor Apgar score (less than 7 at 5 minutes) was associated with a higher odds of respiratory distress syndrome (RDS) but paradoxically with a lower odds for HIE and sepsis. There may be other factors not included in the model (as not captured

The relationship between maternal age and LBW has been looked at in many studies, with teenagers and older mothers at highest risk and subsequently having a preterm death however, this particular trend was not revealed by this study which did not show a high risk of LBW in older mothers, neither was this association observed in the analysis even after regression. This finding may be typical of UTH in which maternal care of those referred from the clinics has improved, and complicated pregnancies, that are more frequent in older mothers, are provided more prenatal care. In this study, the majority of women were from lower socioeconomic class. It was observed that preterm death was directly related to birth weight. Majority of these deaths can be prevented by reducing the incidence of preterm labour through regular antenatal checkups, screening of high risk cases and use of short term glucocorticoids for improving lung maturity. We found that there was 51% mortality reduction in those with steroid exposure in comparison with other studies where they had found a 53% reduction (Kambafwile, 2010).

Strong associations have previously been reported between birth rank and the risks of neonatal death (Arokiasamy, 2008). Similarly, in the analysis higher birth rank provided higher odds of preterm deaths than lower rank. This could be related to lack of resources especially that most of the women in the study were from the high-density areas-compounds.

During the study, the leading causes of preterm and term early neonatal death were HIE, sepsis and RDS. This observation is similar to what was found in Pakistan at both local hospital and community based studies (Bhutta, 2005). Incidence of deaths due to sepsis was very high and should be reduced by improving the aseptic

conditions in the labour ward and in the neonatal care unit and by use of broad spectrum antibiotics in preterm labour especially for those mothers with ruptured membranes. Overall improvement in the neonatal care facilities will help in the improvement of neonatal outcome.

Smaller infant size emerged as one of the strongest predictors of neonatal mortality. When it was replaced by the birth weight variable in the final model, there was a consistency of effect demonstrating the significant influence of birth weight on neonatal death. This finding is supported by other literatures that have identified low birth weight as a strong predictor of preterm mortality. A study in Bangladesh reported that approximately 75 per cent of neonatal deaths associated with low birth weight were attributed to preterm birth rather than small for gestational age infants (Yasmin, 2001). However, in this study, we were unable to differentiate between preterm and small for gestational age infants.

The sex of the neonate significantly influenced the odds of dying, and consistent with other reports we found females had lower odds of mortality than males during the first week of life. This and other studies have shown higher neonatal mortality among males compared to female neonates (Renzo, 2007). On bivariate analysis, more term neonatal deaths were in males, this pattern was not seen in the multivariate regression. The bivariate finding is higher than in the study conducted in Ethiopia where it was lower (Mekonnen, 2013). The biological factors that have been implicated with this increased risk of neonatal deaths in male infants include immunodeficiency increasing the risks of infectious diseases in males, late maturity resulting in a high prevalence of respiratory diseases in males (Alonso and Fuster, 1975)

Studies have shown that HIV is associated with an increase in perinatal mortality (Aiken 1992). Contrary to the usual expectation in this study, HIV infection was not associated with an increased risk of preterm death as an independent variable although the analysis did not go further to compare newborns whose mothers took antiretroviral medication for prevention of mother to child transmission and those who did not. However, the study conducted by (Stringer et al., 2011) found that HIV-exposed infants whose mothers took no antiretroviral were at increased risk of stillbirth.

In this study, maternal education did not differ in the two groups or neonates that had died. The measures of socio-economic status were limited to marital status and educational level which were both not significant; thus the analyses may have been affected by residual confounding owing to unmeasured socio-economic factors.

10 CONCLUSION

Although there were a number of differences in the characteristics of preterm and term neonates that died in the first week in the neonatal intensive care unit, there were few concrete differences. The study suggests that initial cause of morbidity and certain factors (parity, gestation, birthweight, gender) may influence the different causes of death. However, no striking factors were observed in this study.

11 LIMITATIONS

Limitations of this study included relative lack of stratification of certain variables based on underlying diseases. For example, the variable “respiratory morbidity” included diseases such as RDS, transient tachypenia of the new baby, and other conditions causing respiratory distress in the newborn. It would perhaps have been informative if analysis of the deaths was on the basis of week of gestation rather than grouping infants at 24 to 36.6 weeks’ gestation. Unfortunately, because of the nature of the data collecting tool that was designed, it was not possible to analyze in this way. There is need to do additional prospective studies at UTH which would examine this categorizing early and late preterm deaths. The analysis had other limitations and the results might have been biased in selection, misclassification, or confounding. The target population in this study consisted of all preterm and term newborns admitted to NICU who subsequently died. However, selection bias could have pertained to the comparison of LBW newborns compared to "term babies". However, since the comparison group (term neonates that died) originated from newborns who were delivered at UTH and sent to NICU, they belong to the same overall population of ‘preterm cases’, thus reducing the risk of selection bias. A longer prospective cohort would be a useful addition to this study.

12 RECOMMENDATIONS

- Nurses should advocate for Kangaroo care method for preterm babies to prevent sepsis.

- Health workers should comprehensively manage neonates especially preterm babies in the first 24 hours of delivery as most mortality occurs early in this group.

- Labour ward and NICU should ensure that perinatal mortality meetings are held according to recommended schedule to discuss antenatal, intrapartum and resuscitation strategies to prevent morbidity and mortality in neonates admitted to NICU.

- Neonatal resuscitation equipment and drugs should be readily available in labour ward and NICU.

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APPENDICES

APPENDIX 1. QUESTIONNAIRE AND DATA ABSTRACTION FORM

DETERMINANTS OF PRETERM DEATHS AMONG NEONATAL DEATHS AT UTH, LUSAKA.

Initials: _____ File #:_____ Firm: ____ Age: _____ Marital Status: _____ LMP: _____ GA: _____ Gravidity

Please tick or enter in the appropriate space.

Socio-demographics of mother

1. Level of education

0. None ( )

1. Primary ( )

2. Secondary ( )

3. Tertiary ( )

2. Are you employed?

0. Formal ( )

1. Informal ( )

2. Not employed ( )

4. Residence (write name of place of stay) _____

0. High density ( )

1. Medium density ( )

2. Low density ( )

3. Rural ( )

ANTENATAL CLINIC

5. Do you have any chronic physical conditions when you are pregnant? Yes( ) NO ( )

6. Do you regularly take any medication when you are not pregnant? Yes( ) NO ( )

7. Did you have frequency and pain on passing urine? YES ( ) NO ( )

8. If YES, did they treat you? YES ( ) NO ( )

9. Was there any history of acute fever? YES ( ) NO ( )

11.Did you ever do an ultrasound to check for the normality of the baby?YES( )NO( )

12. Any previous history of preterm labor. YES ( ) NO ( )

13. Did you receive any steroids to help mature lungs of the baby? YES ( ) NO ( )

14. Did you receive any antibiotics? YES ( ) NO ( )

15. Have you suffered from any hypertensive disorder? YES ( ) NO ( )

16(a) Any history of cervical incompetence? YES ( ) NO ( )

(b) Any cerclage YES ( ) NO ( )

17. Any vaginal bleeding other than the first trimester spotting? YES ( ) NO ( )

18. Have you had any history of urinary tract infection? YES ( ) NO ( )

19. How was the baby delivered? Vaginally ----- by caesarean -----?

20. Was the caesarean section an emergency or elective YES ( ) NO ( )

21. Was labour induced YES ( ) NO ( ) if yes what methods were used
Drip of oxytocin ( ) breaking of the waters ( ) don't know ( )

22. How long were you in labour...<8hours ( ) >8hours ( ) don't know ( )

3. Was your baby breech? YES ( ) NO ( )

24. Was the baby delivered by instruments? YES ( ) NO ( )

25. Did the baby breathe or cry spontaneously after delivery? YES ( ) NO ( )

26. What was the Apgar score at 1 minute and 5 minutes? ……

27. How long did the baby stay in NICU? <1day ( ) 2-3days ( ) 4-7 days ( )

28. Was the child ever on the ventilator? YES ( ) NO ( )

29. Did you touch and hold the child in NICU? YES ( ) NO ( ) don't know ( )

30. Did you use kangaroo care i.e. skin to skin contact? YES ( ) NO ( )

HISTORY-SYMPTOMS

31. Did the waters break before going into established labour? YES ( ) NO ( )

32. Did the watery vaginal discharge smell bad? YES ( ) NO ( )

HISTORY-SIGNS

33. What was your body temperature on admission? <38^{o} ( ), >38^{o} ( ) don't know ( )

34. Any history of fever? YES ( ) NO ( )

35. Abdominal pain on admission? YES ( ) NO ( )

36. Any per vagina bleeding on admission? YES ( ) NO ( )

HISTORY-SOCIAL

31 Have you been smoking in this pregnancy? YES ( ) NO ( )

If YES How many cigarettes/day did you smoke <5 ( ) >5 ( ) don't know ( )

38 Do you take alcohol? YES ( ) NO ( )

If YES How many alcoholic drinks/day <5 ( ) >5( ) don't know ( )

39 Total household income <K1000 ( ) K 5000-10000( ) >K10000 ( )

FETAL OUTCOME

40

i. Weight (kg) ___

ii. Apgar scores: 1min____5min ____10 min____

iii. Sex F ( ) M ( )

iv. Admission to NICU, reason _____

v. Cord prolapsed YES ( ) NO ( )

vi. Sent to kangaroo ward YES ( ) NO ( )

DATA EXTRACTION SHEET FROM PATIENTS FILES

1 Number of weeks during the first antenatal visit <24 ( ) 24- 28( ) >28 ( )

2 Birth weight of the baby <1000g ( ) 1000-1500g ( ) 1500-2500g ( )

3 Reason for admission to NICU Asphyxia ( ) Hypothermia ( ) Apnea ( )

4 Cause of death……

5 HIV status of mother R ( ) NR ( ) unknown ( )

6 If reactive is she on HAART? YES ( ) NO ( )

7 For how long on HAART? <6months ( ) 6-12months ( ) >12months ( )

8 Syphilis status R ( ) NR ( ) Unknown ( )

9 If syphilis test was positive, was it treated? YES ( ) NO ( )

10 Septic screen for infection in NICU YES ( ) NO ( )

11 Final line of Antibiotic of the baby first ( ) second ( ) third ( )

12 Did the baby have any yellowing of the eyes? YES ( ) NO ( )

13 For how long was yellowing of the eyes? <24hrs ( ) 24-72hrs ( ) >72hrs ( )

14 Neonatal complications Anemia ( ) Apnea ( ) Sepsis ( )

15 Was the baby ever on continuous positive pressure ventilation? YES ( ) NO ( )

16 If yes for how many days? <2 ( ) 2-4 ( ) 4-7 ( )

APPENDIX 2. INFORMATION SHEET AND CONSENT FORM

DETERMINANTS OF PREMATURITY DEATHS AMONG NEONATAL DEATHS AT UTH, LUSAKA ZAMBIA

Dear Participant,

My name is Paul Kamfwa a Medical Doctor in the Department of Obstetrics and Gynecology at UTH conducting a study on the Determinants of Prematurity Deaths among Neonatal Deaths at UTH. This is part of the requirement for the award of a Master's degree in Medicine.

We shall be asking you questions to help us know you better, while some other information will be extracted from the Medical records.

The study will ensure strict confidentiality. There are no known risks. You may not immediately benefit from the study but the information will help to understand the poor outcomes and explain the factors associated with prematurity so as to improve perinatal survival.

Your participation is completely voluntary. You are free to withdraw at any time and this will not affect the level of care your baby will receive.

If you agree to take part, please sign the consent form which will allow us to interview you if you chose to be part of the study.

In case you need some clarification you can contact me on the address below.

Dr Paul Kamfwa 0969168372 kamfwap@yahoo.com Dept of OBGY, UTH

Or

ERES Converge IRB

33 Joseph Mwila Road

Rhodes park Lusaka, Zambia

eresconverge@yahoo.co.uk 260 955 155633 OR 260 955 155634

CONSENT FORM

DETERMINANTS OF PREMATURITY DEATHS AMONG NEONATAL DEATHS AT UTH, LUSAKA, ZAMBIA

I have read and understood all the information concerning Prematurity and what this Study is all about is clear to me. I therefore voluntarily consent to take part in this study.

Parent/Guardian Name: _____

Signature: _____ Date: _____

Right Thumb Print: _____ Date: _____

Witness

Name: _____

Signature: _____ Date: _____

Right Thumb Print: _____ Date: _____

Name of person taking consent: _____

Signature: _____ Date: _____

APPENDIX 3 ETHICS APPROVAL

33 Joseph Mwilwa Road
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I.R.B. No. 00005948
E.W.A. No. 00011697

12th July, 2015

Ref. No. 2015-May-002

The Principal Investigator
Dr. Paul Kamfwa
University of Zambia
School of Medicine
Dept. of Obstetrics and Gynaecology
P.O. Box 50110,
LUSAKA.

Dear Dr. Kamfwa,

RE: DETERMINANTS OF PREMATURITY DEATHS AMONG NEONATAL DEATHS AT UTH, LUSAKA, ZAMBIA.

Reference is made to your corrections dated 26th June, 2015. The IRB resolved to approve this study and your participation as principal investigator for a period of one year.

Review Type	**Ordinary**	Approval No. **2014-May-002**
Approval and Expiry Date	Approval Date: 12th July, 2015	Expiry Date: 11th July, 2016
Protocol Version and Date	Version-Nil	11th July, 2016
Information Sheet, Consent Forms and Dates	• English.	11th July, 2016
Consent form ID and Date	Version-Nil	11th July, 2016
Recruitment Materials	Nil	11th July, 2016
Other Study Documents	Questionnaire, Data Extraction Sheet.	11th July, 2016
Number of participants approved for study	280	11th July, 2016

Specific conditions will apply to this approval. As Principal Investigator it is your responsibility to ensure that the contents of this letter are adhered to. If these are not adhered to, the approval may be suspended. Should the study be suspended, study sponsors and other regulatory authorities will be informed.

Conditions of Approval

- No participant may be involved in any study procedure prior to the study approval or after the expiration date.
- All unanticipated or Serious Adverse Events (SAEs) must be reported to the IRB within 5 days.
- All protocol modifications must be IRB approved prior to implementation unless they are intended to reduce risk (but must still be reported for approval). Modifications will include any change of investigator/s or site address.
- All protocol deviations must be reported to the IRB within 5 working days.
- All recruitment materials must be approved by the IRB prior to being used.
- Principal investigators are responsible for initiating Continuing Review proceedings. Documents must be received by the IRB at least 30 days before the expiry date. This is for the purpose of facilitating the review process. Any documents received less than 30 days before expiry will be labelled "late submissions" and will incur a penalty.
- Every 6 (six) months a progress report form supplied by ERES IRB must be filled in and submitted to us.
- ERES Converge IRB does not "stamp" approval letters, consent forms or study documents unless requested for in writing. This is because the approval letter clearly indicates the documents approved by the IRB as well as other elements and conditions of approval.

Should you have any questions regarding anything indicated in this letter, please do not hesitate to get in touch with us at the above indicated address.

On behalf of ERES Converge IRB, we would like to wish you all the success as you carry out your study.

Yours faithfully,
ERES CONVERGE IRB

Dr. E. Munalula-Nkandu
BSc (Hons), MSc, MA Bioethics, PgD R/Ethics, PhD
CHAIRPERSON