Risk Factors for Mortality in Low Birth Weight Infants at Harare Hospital (Maternity Unit), Zimbabwe

Loyce T Zvenyika-Hlatywayo¹, Chimhuya S¹, Gumbo FZ¹, Nyandoro G²* and Kambarami R³

¹Department of Paediatrics, College of Health Sciences, University of Zimbabwe, Zimbabwe
²Department of Community Medicine, College of Health Sciences, University of Zimbabwe, Zimbabwe
³Maternal and Child Health Integrated Programme, Zimbabwe

Abstract

Background: Research evidence highlights that in low income countries half the infants born before 32 weeks gestation continue to die. More than 75% preterm infant deaths can be prevented without ICU care as these infants die from preventable causes such as hypothermia and hypoglycemia. According to WHO estimates, Zimbabwe is one of the 11 countries with a high preterm birth rate of over 15%.

Methods: In the current prospective cohort study, the researchers followed up infants less than 2000 g at birth through the first 28 days of life to determine the mortality rate and age-related risk factors for mortality in the follow up period.

Results: The overall mortality rate in the first 28 days was 51.2%. Mortality in the ELBW was 91.1%, VLBW - 54.4% and LBW - 28.8%. More than half the deaths (53%) happened in the first 48 hours of life predominantly in the first 12 hours. The independent risk factors for mortality in the first 12 hours of life were Respiratory Distress Syndrome (RDS), (RR 1.58 (95% CI 1.039-2.405)) and infants born to mothers with Diabetes Mellitus (RR 2.31 (95% CI 1.46-3.65)). The late preterm infant had a significant risk of dying between day 3 and end of first week of life compared to other time periods (RR 3.14; 95% CI 1.18-4.30).

Conclusion: Our study demonstrates that neonatal mortality rate in this cohort was very high. The majorities of the deaths occurred within 12 hours of birth and were largely due to extremely low birth weight. Use of life support mechanisms is very low at this unit due to resource constraints and shortage of nurses. Interventions to reduce mortality should address these issues in particular to improve treatment and monitoring during the initial critical 12 hours of life.

Introduction

More than 20 million infants worldwide representing 15.5% of all births are born with Low Birth Weight (LBW) [1] particularly in developing countries where, approximately 16.5% of all births are LBW. Globally 6.6 million children less than 5-years-old die every year and 44% of these deaths happen in the first 28 days of life [1]. Of the neonatal deaths, 60% are as a result of LBW which means that indirectly LBW is a big contributor to neonatal mortality. An estimated 2.8 million infants are born both preterm and Small for Gestation Age (SGA) in developing countries annually. These infants with both LBW and SGA are 10-40 times more likely to die in the first month of life [2]. Mortality in LBW infants is associated with multiple complications that can affect all the systems [2]. In the respiratory system, an LBW infant may develop respiratory distress syndrome, air leaks and apnea as short term complications [2]. In the gastrointestinal system, they may have feeding intolerance, necrotizing enterocolitis and growth failure [2]. Intraventricular hemorrhage and periventricular white matter disease may also complicate the central nervous system of a low birth weight premature infant [2]. Hypotension, and patent ductus arteriosus are some of the complications in the cardiovascular system [2]. An LBW infant is more prone to perinatal infection and nosocomial infection...

*Corresponding author: Nyandoro G, Department of Community Medicine, College of Health Sciences, University of Zimbabwe, Zimbabwe, E-mail: georgenyandoro@yahoo.com

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than a normal weight term baby [2].

A prospective study done by Fanaroff, et al. in the USA from January 1997-December 2002 [3], looked at the neonatal morbidity and mortality for VLBW in 16 participating centers. All infants born with a weight between 501 g and 1500 g, a total of 18,153 infants were followed up for 120 days or until death or discharge. They found that 87% of the infants, who died, did so by 28 days of life. The risk for mortality in the lowest birth weights was greatly influenced by sex with males being more vulnerable than females. Early onset sepsis was an important risk factor for mortality. Thirty seven percent of infants with early onset sepsis died compared to 13% of those without early onset sepsis [3-5]. The strengths of this study are that it was done over a long period of time and the results could be generalized in their setting. However, in a developing country the results may not be the same because of limited resources e.g. ventilator machines and surfactant replacement therapy. The majority (95.6%) of the low birth weight infants are born in developing countries.

Zimbabwe has a comparable prevalence of LBW (11%) to its neighboring countries (Angola 12%, Botswana 10%, Mozambique 14%, Namibia 14%, Zambia 12%) [6-9]. According to the Zimbabwe Demographic and Health Survey, the incidence of LBW in Zimbabwe marginally increased in the period 2001-2010 (incidence of LBW 2001 to 2005 - 10%, 2007 to 2009 - 11%, 2006 to 2010 - 12%). The neonatal mortality rate also increased from 24 per 1000 in the 2001 - 2005 period to 31 per 1000 in the 2006 - 2010 periods [10]. Studies that explored factors associated with mortality in LBW infants in Zimbabwe were carried out over 20 years ago. Mujuru HA [11] carried out a prospective study in 1993 (over a six-month period) at Harare Maternity Unit to identify factors affecting early outcome and morbidity trends in VLBW infants. In this study (unpublished data), the in-hospital mortality was 60.2%. The factors associated with in-hospital mortality were gestational age, duration of rupture of membranes, birth weight, APGAR scores, respiratory distress and sepsis. Age specific mortality and risk factors was not determined. In 2000, Kambarami RA, et al. [12] undertook a prospective study at Harare Hospital where factors for mortality in infants born with birth weight below 1800 g were identified. The study found that the in-hospital mortality rate was 39.4%. The risk factors for mortality were birth weight less than 1500 g, breech delivery and unbooked pregnancies. Although the researcher looked at ELBW, VLBW and some LBW infants only their overall mortality was reported.

Although it has been established that overall mortality of LBW infants is high, the age specific risk factors for death in the first 28 days of life in these high-risk infants have not been studied adequately in a low resource setting, Zimbabwe. Knowledge of these factors will help both the clinicians and health care managers to identify and prioritize interventions that might avert unnecessary mortality.

Materials and Methods

Information on maternal demographics, antenatal care, was obtained from the Maternity registers, mother’s booklet and through interviewing the mothers within 48 hours of delivery. Infants were examined within 48 hours of delivery by the researcher. Gestational age was calculated from the Last Normal Menstrual Period (LMP), first trimester USS. In the event that the mother was not sure of dates and did not have a first trimester Ultrasound scan a New Ballard’s score alone was used [7,13,14]. The principal investigator enrolled newborns that were admitted, examined them on day one, two and day three of life recording down any complications noted during the first three days of life and then once every week until discharge. A research assistant in the department of pediatrics helped with following up the infants that were discharged by reviewing them at the outpatient clinic.

Study procedures

The study participants were followed up on day one, two, three, seven then weekly until death or discharge. At each follow up, the weight, method of feeding, the type of milk, the method of care and medication were recorded. Complications that the patient was treated for were noted. The babies that were discharged before 28 days were followed up and examined once a week at the preterm baby clinic. Mothers were reimbursed transport fees every time they came for a study review. The mothers that failed to come back for the visits were phoned and a phone interview was carried out to find out if the baby was alive and if there were any complications that warranted admission. Mothers were encouraged to take the infants to a local clinic for weighing and ongoing care and to bring the infant at the next clinic. In the case of death at home, a verbal autopsy was carried out. To minimize bias, the weighing scales were calibrated before commencement of the study and every morning. The principal researcher examined all infants within 48 hours of admission to minimize inter observer differences. On the day of admission, objective measurements and definitions were used to describe the clinical state of the infants. The midwives and junior doctors continued to weigh infants, assign APGAR scores and measure skin temperatures. The management of the infants was led by a team comprising of a Pediatrician consultant, senior resident medical officer and a pediatric registrar working on the unit.
Study rationale

The study aimed to determine the mortality rates and relative risk ratios in infants born at the Maternity Unit weighing less than 2000 g and to identify time related risk factors for death in the first 28 days of life. The study design was a Hospital based prospective cohort study of infants born alive weighing less than 2000 g. The infants were followed up until day 28 of life or death whichever was earliest. This study targeted a population of all liveborn infants weighing less than 2000 g admitted to the Neonatal Unit at Harare Central Hospital. The Inclusion Criteria: All infants’ singletons and multiples born alive at the Maternity Unit weighing less than 2000 g. Exclusion Criteria: We excluded from study infants weighed less than 500 g, infants whose parents were unlikely to fulfill the follow up schedule by relocating far out of Harare City. We enrolled 399 participants after determining, a required minimum sample size of 367 which was calculated at 95% confidence interval and 5% level of significance to detect a mortality of 39.4% detected by Kambarami, et al. at Harare Maternity Unit in infants born weighing less than 2000 g [12-14]. Allowing 10% loss to follow up and a design effect of 1.1, (catering for age specific risk factors) we finally enrolled 399 participants. Infants weighing less than 2000 g (up to 1999 g) were identified from labour ward and Maternity Theatre delivery registers each morning during the study period. All eligible infants had equal opportunity to be enrolled into the study. Mothers who agreed to participate on the study were asked to sign a consent form.

Data entry and processing

All data was collected by the principal investigator and the research assistant. The questionnaire was checked for completeness and consistency of answers in the field. The data was then entered into Epi Info version 4 (2000) USA database and data cleaning was done. After data cleaning, data was transported to STATA, USA package for further cleaning. A statistician helped with the data cleaning and analysis.

Data analysis

The data was analyzed using STATA (USA) statistical package. Frequencies were calculated to describe mother and infant demographic details. The risk factors associated with mortality were identified using regression analysis, we began with univariate analysis and then forward regression procedure was used to calculate adjusted estimates/multivariate analysis; Poisson generalized linear model with a logarithmic link function regression model with robust variance were used to estimate the adjusted relative risk ratios. Kaplan-Meier survival graphs were determined to show mortality patterns. Cohort study univariate analysis in STATA was done and then generalized linear model using Poisson regression to estimate relative risks adjusted for confounders.

Ethical considerations

Permission to carry out the study was obtained from the Harare Central Hospital Ethics Review Committee, Joint Research Ethical Committee and the Medical research council of Zimbabwe. Informed verbal and written consent was obtained from mothers or fathers prior to enrollment. Data was kept confidential by limiting access to patient details. Medication was not withheld from any study participant and treatment was in accordance with the existing nursery protocols.

Results

Data was collected for 399 infants over a seven-month period from the 1st of August 2014 to the 28th of February 2015. There were five hundred and ninety-two (592) infants admitted into the unit with a weight below 2000 g during the study period. One hundred and ninety-three (193) infants were not enrolled into the study because sixty-seven (67) of them lived outside Harare and 126 did not consent. Three hundred and ninety-nine (399) infants were enrolled with 367 (92%) of the infants completing the study. One hundred and eighty-eight (188) infants died within the 28 days of follow up giving an overall mortality rate of 51% (95 CI 46.5%-56%). Thirty-two (8%) infants were lost to follow up. Figure 1 below shows the number of recruited infants and those infants that were lost to follow up.

Maternal and neonatal characteristics

The mean age of the mothers with complete follow up was 24.23 ± 0.30 years, 360 (98.09%) of the mothers had at least grade 7 level of education and 81 (22.07%) were HIV positive. The median age of mothers who completed the study was 25 years (IQR 20-29 years). Only 215 males (59%) and 152 females (41%) infants had complete follow up. The infants had an overall mean weight of 1400.88 g ± 19.93. Ninety-two infants (24.2%) were extremely premature (less than 28 weeks gestation), 176 (46.3%) very preterm infants (28-32 weeks), 102 (26.8%) late preterm (between 32 weeks and 37 weeks gestation) and 10 (2.6%) were born at term gestation (more than 37 completed weeks). The majority (70%) of the infants were Appropriate for Gestational Age (AGA). More than half the infants (70.1%) had a temperature less than 36.5°C on admission and 63.5% of the infants had respiratory distress on admission into the unit.

Mortality

The Overall mortality rate over 28 days was 51.2% (95% CI 46.0%-56.0%). Twenty four percent of the infants who deceased were between 28 and 32 weeks of gestation. Thirty four percent of those that died had hy-
The probability of survival increased from 2 weeks of age.

An assessment of the effect of low birth weight using a univariate approach (based on $2 \times 2$ cohort study tables) has shown that mortality differed according to birth weight (Table 2). The mortality rates for the weight band categories were as follows: Mortality rate 91% for weight less than 1000 g, 54% for weight between 1000 g and 1499 g, and 29% for weight between 1500 g and 1999 g (Table 2). Again Table 2 below shows the mortality, incidence rate and relative risks according to weight categories.

### Time specific factors associated with mortality

A univariate analysis was done to determine risk factors for mortality at different time points i.e. < 12 hours, 13-24 hrs, 25-48 hours, day three to seven, second week, third week and fourth week and the results are shown in Table 3. In the first 12 hours of life infants with RDS had a relative risk of dying of RR 1.44 $p = 0.040$ (95% CI 1.02-2.04). Infant born to a diabetic mother also a significant risk of dying within the first 12 hours of life RR 1.93 $p = 0.000$ (95% CI 1.65-2.26). After adjusting for confounders respiratory distress syndrome RR 1.58 (95% CI 1.039-2.405), and infant of a diabetic mother RR 2.31 (95% CI 1.46-3.65) were independent risk factors for mortality.
Figure 2: Kaplan-Meier survival curve comparing mortality probability between male and female infants at various post-natal age.

Table 2: Mortality according to birth weight category.

| Birth weight       | Number who died | Number who survived | Mortality (per weight band) | Incidence Rate Ratio (95% CI) | RR (95% CI) |
|--------------------|-----------------|---------------------|-----------------------------|-------------------------------|-------------|
| < 1000 g (n = 77)  | 72              | 5                   | 91.1%                       | 4.22 (3.10-5.72)              | 2.34 (2.01-2.73) |
| 1000-1500 g (n = 125) | 68            | 57                  | 54.4%                       | 1.08 (0.79-1.47)              | 1.10 (0.89-1.35) |
| 1501-1999 g (n = 163) | 47            | 116                 | 28.8%                       | 0.30 (0.21-0.43)              | 0.41 (0.32-0.54) |

Table 3: Results of univariate analysis for risk factors for mortality in the first 12 hours of life.

| Study factor       | Relative Risk | p-value | 95% CI |
|--------------------|---------------|---------|--------|
| HIV positive mother| 1.24          | 0.245   | 0.86   | 1.78  |
| Booked             | 1.05          | 0.777   | 0.77   | 1.42  |
| PIH                | 0.71          | 0.217   | 0.42   | 1.22  |
| Antenatal steroids | 1.07          | 0.768   | 0.68   | 1.67  |
| Natural birth      | 0.90          | 0.578   | 0.63   | 1.29  |
| Temperature < 36   | 1.03          | 0.867   | 0.72   | 1.47  |
| Temperature 36.4-37.4 | 1.06      | 0.768   | 0.71   | 1.59  |
| Temperature 37.5-38.5 | 0.92      | 0.810   | 0.49   | 1.76  |
| Temperature > 38.5 | 0.73          | 0.572   | 0.25   | 2.17  |
| < 1000 g           | 0.85          | 0.346   | 0.61   | 1.19  |
| 1000 g-1499 g      | 1.09          | 0.571   | 0.80   | 1.50  |
| 1500 g-1999 g      | 1.09          | 0.636   | 0.77   | 1.55  |
| APGAR at 1 min < 5 | 0.84          | 0.325   | 0.60   | 1.19  |
| APGAR at 1 min 5-7 | 1.12          | 0.500   | 0.81   | 1.54  |
| APGAR at 1 min > 7 | 1.12          | 0.620   | 0.72   | 1.73  |
| APGAR at 5 min < 5 | 0.98          | 0.913   | 0.62   | 1.52  |
| APGAR at 5 min 5-7 | 0.84          | 0.304   | 0.60   | 1.17  |
| APGAR at 5 min > 7 | 1.21          | 0.246   | 0.88   | 1.66  |
| *RDS               | 1.44          | 0.040   | 1.02   | 2.04  |
| Breech             | 0.93          | 0.841   | 0.43   | 1.98  |
| Vertex             | 1.08          | 0.841   | 0.504  | 2.32  |
| Hypothermia on admission | 1.17 | 0.409   | 0.81   | 1.70  |
### Table 4: Factors associated with mortality in the first 2 weeks of life.

| Risk Ratio (95% CI) | 13-24 hrs (1 day) | 25-48 hrs (2 days) | 49-72 hrs (3 days) | 73-168 hrs (1 week) | 169-336 hrs (2 weeks) |
|---------------------|------------------|-------------------|-------------------|--------------------|----------------------|
| **CAESARIAN BIRTH** | 1.11             | 0.578             | 0.77              | 1.58               |                      |
| **STEROIDS**        | 1.07             | 0.768             | 0.68              | 1.67               |                      |
| **FEMALE**          | 1.16             | 0.345             | 0.85              | 1.58               |                      |
| **MATERNAL APH**    | 1.22             | 0.347             | 0.81              | 1.85               |                      |
| **IDM**             | 1.93             | 0.001             | 1.65              | 2.26               |                      |
| **MARRIED**         | 1.23             | 0.638             | 0.52              | 2.95               |                      |

*Statistically significant at 95% CI-(Confidence Interval).
Notes: Only IDM and RDS were statistically significant.

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Table 4 show, time specific relative risks for all the study factors in the first 2 weeks of life. After controlling for confounders using multivariate analysis only the following factors were significant at respective specific times: at 13-24 hrs (1 day), only Apgar 1 min 5-7 score ; at 25-48 hrs (2 days), only EGA Term, Apgar 1 min score 5-7 score and RDS ; at 49-72 hrs (3 days), only EGA Late preterm, HIV, Temp 36.5-37.4, Temp 36.5-37.4, Temp 37.5-38.5 and Apgars 1 min 1-5; at 73-168 hrs (1 week), only EGA Late preterm, HIV, Apgars 5 min 1-5 score, PIH, Birth weight < 1000 g and Apgars 5 min 1-5 score.

**Discussion**

This study found that the overall mortality in the first 28 days of life among infants born weighing less than 2000 g was very high 51% (95% CI 46%-56%). Most of the deaths (52.6%) happened in the first 48 hours of life. This mortality was higher than the mortality rate of 39.4% reported by R Kambarami in 2000 [12]. However, Kambarami’s study was restricted to in hospital mortality whereas the current study also included post discharge mortality. In another unpublished report by Mujuru in 1993 [11] mortality was highest (94%) among infants weighing less than 1000 g. This figure was similar to the one (91%) observed in this study. Mortality rates in infants born with weights between 1000 g and 1499 g are also similar between the two studies. Whereas Mujuru reported a 49% in hospital mortality the current study found 54% including post discharge follow up. Survival of these high-risk infants has not changed over time despite current shortage of human resources, medicines and basic commodities. Comparing the in-hospital mortality in the VLBW observed in Harare maternity unit by Mujuru it is almost double the 26.6% observed at Charlotte Maxeke Johannesburg Academic Hospital in 2013 [7]. In another public hospital in Lilongwe Malawi, a low resource country, the calculated mortality rate was 93% in ELBW infants, 48% in VLBW infants and 10% for LBW infants [6], these figures are similar to this study.

In developed countries mortality in low birth weight infants especially in the extreme low birth weight infant has been decreasing [4] owing to the improvement of care that includes the routine use of surfactant and the respiratory support measures such as CPAP and mechanical ventilation. The average mortality in VLBW in the developed countries is as low as 15-28% depending on the hospitals level of care [15]. As indicated in Table 1, 60% of the deaths in the current cohort occurred in the first 72 hours of life. This rate is much lower than 82% mortality which was found at a public hospital in Lilongwe for the same period of time [6]. In a center in Brazil the mortality of VLBW infants within the first week of life was found to be 28% [16] and this is significantly lower than the mortality 70% calculated in this study. Further analysis on the risk factors for mortality in the first 12 hours of life showed that the significant independent risk factors for mortality were respiratory distress syndrome and infants born to diabetic mothers. Infants with RDS often need intensive care nursing with ventilatory support and surfactant replacement therapy. At the unit that the study was carried out these lifesaving interventions were not available leaving a lot of infants without the appropriate care and at risk of dying. Infants that were born to diabetic mothers succumbed to death more in the first 12 hours probably from hypoglycemia and they may also get respiratory distress syndrome as a complication. These infants are at a higher risk of hypoglycemia because of the higher insulin levels at birth therefore requiring an early feed and close glucometer readings. In the unit that the study was carried out there were inadequate resources and staff and close glucometer readings were not done. RDS was also an independent risk factor for mortality between 25 hours and 48 hours. A few studies have looked at the factors associated with mortality, in a study done in Malawi at a public hospital RDS was one of the factors that contributed to a high mortality in the first three days of life [6]. In the developed countries RDS is no longer a factor associated with mortality because of the wide use of surfactant replacement therapy either as prophylactic treatment or therapeutic [17]. The use of continuous positive airway pressure has also reduced mortality from RDS [17].

This study showed that the late preterm infants had a high risk of dying from day 3 of life to the end of the first week. Mortality in the late preterm is not surprising because of their low birth weight they are at risk of complications commonly hypothermia, hypoglycemia and infections [18].
The Kangaroo Mother Care (KMC) intervention was introduced in 1978 in Colombia in response to overcrowding and insufficient resources in neonatal intensive care units associated with high morbidity and mortality [14]. The KMC method supports low birth weight babies by encouraging continuous skin to skin contact between the mother and the infant, exclusive breastfeeding often resulting in early home discharge. Studies to understand the effectiveness of this intervention have found that body temperature and weight gain are increased significantly [14]. Implementation of KMC in African countries began in 1986. A meta-analysis by Lawn JE, et al. in 2009 showed a major reduction in mortality of 51% in babies with birth weight < 2000 g [2]. The results of the effect of KMC on neonatal mortality in a study done by Prof Kambarami [7] in 1998 at Harare Central Hospital were not significant. At the unit the study was carried out late preterm infants are often nursed in an open cot whilst waiting for an available bed for the mother to start KMC. This delay in starting KMC could predispose them to other complications such as hypothermia and nosocomial infections. In a univariate analysis infant exposed to HIV in utero had a higher risk of mortality from the third day of life to the 7th day of life. However, after multivariate logistic regression analysis it was not a significant predictor of mortality this contradicted a study that was done on VLBW in South Africa which reported that infants who were HIV exposed had a higher mortality rate compared to those not exposed to HIV [19].

APGAR scores were predictors of mortality in the first 24 hours in this study especially low APGARS at 1 minute. A low APGAR was also found to be a predictor of early neonatal death in a study that was done in Brazil [16]. APGAR scores in these low birth weight infants are indicators for the need of resuscitation and therefore emphasis should be put on resuscitating the low birth weight infant [6].

The risk factors for mortality in the second week of life were PIH, a birth weight less than 1000 g and a low APGAR at 5 min (see Table 3 above). However, it was not possible to calculate the adjusted relative risk because of the small number of deaths from two to four weeks of life. A larger sample size would be required for such calculations. Although autopsies were not done on the infants that died the causes of mortality were established clinically as complications of prematurity, anemia, necrotizing enterocolitis and sepsis. The risk of dying for infants born to mothers that had PIH was high in the second week of life RR 3.00 (1.43 to 6.27) and this could be explained by the fact that these infants often have intra-uterine growth restriction. Studies have shown that their risk of dying is more than in infants who are appropriate for gestational age. They are at increased risk of necrotizing enterocolitis, thrombocytopenia and temperature instability and could explain the deaths in the second week of life.

Conclusion

Neonatal mortality in infants less than 2000 g is very high at Harare Maternity Unit. The majority of the deaths happen within the first 48 hours of life with highest mortality being in the extremely low birth weight infants. The probability of dying declines with increasing postnatal age. The independent risk factors for mortality were RDS and hypoglycemia in the first 12 hours of life. Hypoglycemia can be prevented easily by initiating feeds early and close monitoring especially in the first 12 hours of life. RDS remains a significant cause of mortality in the first 48 hours of life at Harare Maternity Unit. This highlights the need to capacitate the neonatal intensive care unit with adequate life support mechanisms such as CPAP machines, ventilators and surfactant. This study also showed that the late preterm infants and the IUGR infants had an increased risk of dying in the second week of life. This may highlight the need to relook at the discharge weight criteria and avoid too early discharges in these infants should be avoided.

Conflict of Interest

The authors have none to declare. The study was funded by Maternal and Child Health Integrated Programme (MCHIP).

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