Maternal Risk Factors and Morbidity Pattern of Very Low Birth Weight Infants: A NICU Based Study at Eastern Nepal

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Abstract

Background: Preterm deliveries of babies weighing less than 1500 grams (VLBW, very low birth weight) are of major concern because of maximum perinatal morbidity and mortality found in this group. VLBW babies overload the neonatal intensive care unit (NICU) and their mortality contributes significantly to neonatal and infant mortality. **Objectives:** To study the common maternal risk factors associated with VLBW births. To study the morbidity and mortality patterns of VLBW babies. **Methods:** This was a hospital based retrospective study done in NICU of BP Koirala Institute of Health Sciences. Data were collected from medical records of VLBW babies admitted in NICU over a period of three years (13 April 2005 to 12 April 2008). Data were analyzed with SPSS 10.0 software. **Results:** Data of 140 VLBW babies were analyzed. Mean birth weight was 1188.9 (±212.78), 10.7% were home deliveries, 24.3% were twins, 31.4% required active resuscitation at birth and 46.4% were exposed to antenatal steroid. Common maternal risk factors associated with premature deliveries were inadequate antenatal check up (ANC) visits (95.7%), twin pregnancy (24.3%), antepartum hemorrhage (APH, 28.6%), premature rupture of membrane (23.6%), pregnancy induced hypertension (12.9%), bad obstetric history (12.9%) and maternal age less than 20 years (8.6%). Common morbidities among VLBW babies were clinical sepsis (77.1%), non physiological hyperbilirubinemia (73.6%), apnea (48.6%), shock (42.9%), hypoglycemia(39.3%), anemia (29.3%), hyaline membrane disease (HMD, 21.4%), patent ductus arteriosus (15.0%), severe hypothermia (12.1%), culture proven sepsis (15.7%), retinopathy of prematurity (5.7%), and bronchopulmonary dysplasia (3.6%). Overall survival was 54.3% and major causes of death were HMD (51.0%) and sepsis (34.7%). Median durations of hospital stay were 17.5 days for survivors and five days for expired cases. **Conclusion:** Increasing the coverage of ANC visits, early diagnosis and treatment of APH and pregnancy induced hypertension, discouraging the childbirth at too young age, early diagnosis and treatment of acute infections and chronic medical diseases in mothers are important measures to decrease the burden of VLBW births. Common morbidities in VLBW babies are sepsis, HMD, apnea, hyperbilirubinemia, patent ductus arteriosus, shock, anemia, hypoglycemia, hypothermia and hypocalcemia. Common causes death of VLBW babies are HMD and sepsis. Overall survival of VLBW babies in our settings is less. More numbers of well equipped NICUs and services like surfactant therapy are needed to improve survival of VLBW infants in our set up.

Key words: Maternal risk factors, Morbidity, Mortality, Very low birth weight.

Introduction

BP Koirala Institute of Health Sciences (BPKIHS) is a tertiary care centre and medical college located at eastern Nepal. It is running a seven bedded level II neonatal intensive care unit (NICU) with two neonatal ventilators. Advances in both perinatal and neonatal care over the past two decades mean that increasing numbers of preterm and very low birth weight (birth weight < 1500 grams; VLBW) infants are surviving[1]. It is estimated that in Nepal, approximately two third of all deaths in first year of life occur in the first months of life.[2] Of these deaths approximately two third occur in the first week of life.[2] A significant number of these

deaths may be contributed by deaths of VLBW infants. It is reported that 60.0% to 80.0% of neonatal mortality and morbidity is due to preterm birth[3]. In developing countries, neonatal mortality already accounts for more than 50.0% of the infant mortality coefficient[4]. So in order to improve infant mortality rate, it is essential to prevent preterm births and improve survival of neonates, especially preterm neonates. The consequence of preterm birth also leads to significant direct and indirect costs that have to be borne by parents and society. Hence a better understanding of antenatal factors contributing to preterm birth and morbidity pattern in very low birth weight infants are needed to improve the perinatal care. Local data on risks of preterm birth and morbidity pattern of VLBW infants will help to plan special care pattern for prevention and management of VLBW infants. Hence, we present this retrospective study of risks for VLBW birth and morbidity pattern in VLBW infants.

Methods

This was a retrospective and longitudinal study. The study was done in NICU of BPKIHS, Nepal. All VLBW infants were identified by reviewing the admission registry of NICU. Cases admitted between 13 April 2005 to 12 April 2008 were identified and their record files were obtained from medical record section. Inborn as well as outborn babies were included. Cases without documented birth weight (taken before 24 hours of life) and having grossly inadequate data were excluded. Medical records were reviewed and data extracted regarding perinatal characteristics, morbidity and mortality. Mothers with less than three antenatal check up (ANC) visits to health care facility were defined to have inadequate ANC visits. The gestational age (GA) was assessed using date of last menstrual period and confirmed by modified Ballard score method. In cases of gross discrepancy, Ballard score method was taken as valid. A birth weight less than 10th percentile for GA was classified as small for gestational age (SGA)[5]. Those babies who required resuscitation in the form of bag and mask ventilation or further steps were defined to have required active resuscitation at birth. Regarding Apgar score and use of maternal antenatal steroid, data were not available for few cases due to no documentation in home delivered and some out of hospital delivered babies. So those two parameters were analyzed separately including the cases with available data. Blood sugar level <40 mg per deciliter was defined as hypoglycemia. Ionized calcium <4 mg per deciliter was defined as hypocalcemia[5]. Axillary temperature below 35.5^{0}F was defined as severe hypothermia as per WHO Integrated Management of Childhood Illness guideline. Any level of serum bilirubin requiring intervention was defined as non physiological hyperbilirubinemia[5]. Hematocrit level less than 30 was taken as anemia. Data were analyzed using SPSS 10.0 statistical software.

Results

There were 1135 admissions in NICU during three years. Among them 150 were VLBW infants. It was 13.2% of total NICU admissions. In 10 cases, there were grossly inadequate data. So, those 10 cases were excluded from the study. Final analysis was done in 140 cases. Mean birth weight was 1189.9 grams with standard deviation (SD) of 212.78.mean gestational age (GA) was 30.8 (SD 2.37) weeks. Among VLBW infants, 7.1% were born before 28 weeks GA, 71.4% were born between 28 weeks to 32 weeks GA, and 21.4% were born after 32 weeks of GA. Extremely low birth weight (birth weight <1000grams; ELBW) babies accounted for 17.9% cases. Documented Apgar scores were available for only 91 cases. Among those, mean Apgar scores at one minute, five minutes and 10 minutes were 5.08 (SD 1.73), 6.45 (SD 1.41) and 7.56 (SD 1.19) respectively. Among those 91 cases, Apgar score at one minute was <5 in 31 (22.1%) cases and Apgar score at 10 minutes was <5 in 13 (14.3%) cases. Active resuscitation was required in 44 (31.4%) cases at birth. Among those 44 cases 75.0% required bag and mask ventilation and remaining 25.0% required further steps of resuscitation. Other baseline characters of VLBW infants are presented in Table 1.

Mean maternal age was 24.66 (SD 4.79) years. Mean gravidity of mothers was 1.77 (SD 1.18). Possible maternal risk factors for birth of VLBW infants were evaluated. They are presented in Table 2. Occurrence of various morbidities among VLBW infants are presented in Table 3. Major morbidity was sepsis. Sepsis was diagnosed in 130 (92.9%) cases. Only 22 cases (15.7%) had blood culture proven sepsis. Non physiological hyperbilirubinemia was seen in 103 (73.6%) cases. Among those 103 cases, 29 (28.2%) cases required double volume exchange transfusion and remaining were managed with phototherapy alone. None of them developed kernicterus.

ANC: Antenatal check up; PROM: Premature rupture of membrane, PIH: Pregnancy induced hypertension. *Chronic medical diseases: Rheumatic heart disease 2, Chronic hypertension 2, Bronchial asthma 1, Systemic lupus erythematosus 1, Hyperthyroidism 1, severe anemia 1. #Acute infections: Urinary tract infection 5, Pneumonia 1, Hepatitis E 1, mumps 1.

HMD: Hyaline membrane disease; UGI: Upper gastrointestinal; PDA: Patent ductus arteriosus; DIC: Disseminated intravascular coagulation; HIE: Hypoxic ischemic encephalopathy.

As far as the treatment is regarded; 139 (99.3%) cases were treated with intravenous fluid. All of them were also given supplemental calcium in fluid. Those who developed hypocalcemia were given therapeutic

doses of calcium. Oxygen supplementation was required in 131 (93.6%) cases. All 130 (92.9%) cases diagnosed to have clinical sepsis were treated with intravenous antibiotics and six (4.3%) cases were also treated with antifungal agent. Among 68 (48.6%) babies who had apnea spells, 60 (88.2%) cases were treated with aminophylline. Cases with shock were treated with volume replacement and vasopressor support (dopamine and, or dobutamine). None of the 30 (21.4%) cases who developed hyaline membrane disease (HMD) were treated with surfactant because of financial constraint. Assisted ventilation due to respiratory failure was required in 56 (40.0%) cases. Mechanical ventilation was offered for 40 (28.6%) cases. Remaining 16 (11.4%) cases had to be managed with manual ventilation using resuscitation bag and endotracheal tube because of inadequate numbers of mechanical ventilator to meet the demand. Improved cases were transferred to intermediate care nursery and pediatric ward and later discharged home as per hospital protocol. There were 76 (54.3%) cases that improved and discharged home. Death occurred in 49 (35.0%) cases and 15 (10.7%) cases left against medical advice. Among those 15 cases that left against medical advice, nine cases left despite improvement due to financial problems. Remaining six cases left due to poor chance of survival.

Primary causes of death were HMD in 25 cases, sepsis in 17 cases and hypoxic ischemic encephalopathy in four cases, accounting for 51.5%, 34.7% and 8.1% of total deaths respectively. Other less common primary causes of death were necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH) and tracheoesophageal fistula in one (0.7%) cases each. Mean duration of stay in NICU was 8.38 (SD 7.04) and median duration was seven days. Mean duration of total hospital stay was 14.37 (SD 12.20) days and median duration was 12 days. Median duration of hospital stay was 17.5 days for survivors and five days for expired cases.

Table 1: Showing Baseline Characters of Very Low Birth Weight Infants

Characteristics	Number of Patients	Percentage (%)
Born in BPKIHS	88	62.9
Born at home	15	10.7
Twins	34	24.3
Male sex	85	60.7
Extremely low birth weight	25	17.9
Appropriate for GA*	105	75.0
Small for GA	35	25.0
Cesarean delivery	21	15.0
Requirement of active resuscitation at birth	44	31.4
Cephalic presentation	120	85.7
Exposed to antenatal steroid	65	46.4

**GA: Gestational age.*

Table 2: Showing Risk Factors for Premature Delivery in Mothers of VLBW Infants.

Risk factors	Number of Patients	Percentage (%)
Inadequate ANC visit	134	95.7
Antepartum hemorrhage	40	28.6
Twin pregnancy	34	24.3
PROM	33	23.6
Bad obstetric history	18	12.9
PIH	18	12.9
Maternal age <20 years	12	8.6
Chronic medical diseases*	9	6.4
Acute infections#	8	5.7
Grand multiparity	6	4.3
Clinical chorioamnionitis	6	4.3
Oligohydramnios	4	2.9
Polyhydramnios	3	2.1
Maternal age >35 years	2	1.4
Infertility	2	1.4

Table 3: Showing Morbidities of VLBW Infants.

Morbidity	Number of Patients	Percentage (%)
Clinical sepsis	108	77.1
Non Physiological Jaundice	103	73.6
Apnoea	68	48.6
Shock	60	42.9
Hypoglycemia	55	39.3
Anemia	41	29.3
Hypocalcemia	35	25.0
HMD	30	21.4
UGI bleeding	28	20.0
Culture positive sepsis	22	15.7
PDA	21	15.0
DIC	21	15.0
Hypothermia	17	12.1
Feed intolerance	15	10.7
Necrotizing enterocolitis	12	8.6
Acute renal failure	12	8.6
HIE	11	7.9
Retinopathy of prematurity	8	5.7
Seizure	7	5.0
Meningitis	5	3.6
Bronchopulmonary dysplasia	5	3.6
Intraventricular hemorrhage	4	2.9
Pulmonary hemorrhage	4	2.9

Discussion

Preterm deliveries of VLBW babies are of major concern because of maximum perinatal morbidity and mortality found in this group[3]. The retrospective analysis of maternal antenatal profile in this study represents the various high risk factors responsible for preterm delivery of VLBW babies. Most common factor in this study was inadequate ANC visits. Lack of adequate antenatal care has been reported as a common factor leading to preterm birth by various studies[6,7,8]. So, encouraging pregnant women to have adequate ANC visits will reduce the burden of VLBW births. Antepartum hemorrhage (APH) was the second most common factor associated with preterm delivery in this study, accounting for 28.6% cases. There is a strong association between preterm labor and APH[3,8]. In a study by Kayastha et al. at another hospital of Nepal, APH was present in 5.8% mothers of low birth weight infants[9]. In another Indian study, APH was present in 9.7% mothers of VLBW infants.[3] In this study, APH was present in higher proportion of cases as compared to those studies. Twin pregnancy was the third most common factor associated with VLBW births in this study accounting for 24.3% cases. In a study by Roy et al. at India, 11.9% mothers of VLBW babies had multiple pregnancy[3]. In another study at Japan by Kusuda et al., 30.0% of total VLBW infants were because of multiple pregnancy[10]. Hence, twin pregnancy is an important determinant for VLBW. Other common associations with VLBW births in this study were premature rupture of membrane, bad obstetric history, pregnancy induced hypertension, maternal acute infections, maternal chronic diseases and maternal age less than 20 years. These factors has been seen to be associated with low and very low birth weight deliveries in different other studies[3,6,9,10,11]. Maternal urinary tract infection, which was present in 3.6% mothers, was also a common association with VLBW births in this study. Roy et al. found urinary tract infection in 13.0% mothers of VLBW infants at India[3]. Similarly; Kayastha et al. reported urinary tract infection to be present in 11.6% mothers of low birth weight infants at Nepal[9].

So, in order to prevent the births of premature babies and decrease the burden of VLBW infants in our set up, few important measures should be taken. These measures are, increasing the coverage of ANC visits among pregnant women, early diagnosis and treatment of APH and pregnancy induced hypertension and discouraging the marriage and childbirth at too young age. Early diagnosis and treatment of acute infections and chronic medical diseases in mothers are also important measures to decrease the burden of VLBW

births. When multiple pregnancies occur, preterm birth should be timely expected so as to manage appropriately. Mean birth weight of VLBW babies in this study was 1188.9 grams. In other similar studies at Japan, Saudi Arabia and Taiwan, the mean birth weights of VLBW babies were 1018 grams, 1133 grams and 1024 grams respectively[10,11,12]. Mean birth weight of VLBW babies is comparable to those from studies at different other parts of world[10,11,12]. The proportion of extremely low birth weight (ELBW, weighing less than 1000 grams) babies among VLBW babies in this study was 17.9%. In a study by Roy et al at India, this proportion was 33.9%.[3] In another Thai study, this proportion was 24.0%.[13] In another study at Brazil, this proportion was 38.0%.[14] Hence, we had lower proportion of ELBW babies among VLBW babies. One reason for this might be because of lower proportion of ELBW births in our part. But another more likely reason could be because less numbers of ELBW babies in our part are surviving enough to come to hospital. This needs to made clear by population based studies. The proportion of SGA babies in this study was 25.0%. Similar to this study, the proportion was 25.8% in a study at Taiwan.[12] The proportions of SGA babies among VLBW infants reported from studies done at Japan (36.0%) and Brazil (39.0%) are higher as compared to that from this study[10,14].

In this study, 31.4% babies required active resuscitation at birth. This was similar to data from a study at Thailand[3]. In another study by Tsou et al. at Taiwan, 68.1% VLBW babies' required active resuscitation at birth.[12] These figures implicate that a significant proportion of VLBW babies require active resuscitation at birth. So, preterm birth should always be conducted at centers where adequate facilities and equipments for neonatal resuscitation are available. Among 91 babies with available Apgar scores, mean Apgar scores at one, five and ten minutes were 5.08, 6.45 and 7.56 respectively in this study. This is similar to study by Mansouri et al.[11] This shows that VLBW babies tend to have low Apgar scores. That is why large numbers of them require active resuscitation at birth.

Corticosteroids given to promote fetal lung maturation have become a mainstay in the management of women at risk of preterm birth. It has been found that the use of antenatal steroid to be associated with lower mortality rates in VLBW infants[13]. In this study, only 46.4% women received at least one dose of antenatal steroid. A large multicentric study at Japan also showed that only 41.0% mothers of VLBW infants received antenatal steroid[10]. Using antenatal steroid to treat women at risk of preterm birth might be an inexpensive method to improve survival of VLBW infants in our set up.

Sepsis was the most common morbidity encountered among VLBW babies in this study. Sepsis was diagnosed clinically in 77.1% cases but only 15.7% cases had blood culture proven sepsis. The proportion of cases with culture proven sepsis among VLBW infants in this study resembles the data from the similar studies done at developing countries like India and Kenya[3,15]. However, incidence of culture proven sepsis in this study is higher than the data from study done at developed country like Japan[10]. So, incidence of culture proven sepsis seems to be higher in our set up as compared to that in developed countries. Since any illness in VLBW infant may resemble sepsis clinically, we are probably over diagnosing sepsis clinically. This scenario is not much different in other parts of world also. For example, in the same Japanese study, 80.0% VLBW infants received antibiotics though there were only 8.0% cases of culture proven sepsis.[10] The second most common morbidity in this study was non physiological hyperbilirubinemia which was diagnosed in 73.6% cases. This data resembles those from studies done at Saudi Arabia and India[11,16]. Since hyperbilirubinemia requiring intervention is such a common morbidity among VLBW infants, there is a need for evaluation of prophylactic therapies, which would prevent hyperbilirubinemia and would decrease the need as well as cost of intervention. The third most common problem was apnea, which occurred in almost half of the cases. In a study by Tsou et al. at Taiwan, 66.1% VLBW infants had apnoea[12]. Therefore apnea monitoring should be an integral component of care of VLBW infants.

HMD was diagnosed in 21.4% of VLBW infants in this study, which is similar to data from an Indian study.[3] HMD was diagnosed in 54.0% to 79.3% VLBW infants in different other studies done at Japan, Saudi Arabia, Taiwan, and Malaysia[10,11,12,17]. Hence, HMD is a common problem among VLBW infants. However, it seems to be less common in South Asia region as compared to other parts of Asia, especially developed countries[3,10,11,12,17]. In this study, 15.0% VLBW infants were diagnosed to have patent ductus arteriosus (PDA). This figure is much less than the figures given by different other studies, where PDA was diagnosed in 24.3% to 36.0% VLBW babies[10,18,19]. This difference may be because we detected only clinically significant PDA by clinical examination alone. We did not perform echocardiography routinely in all VLBW infants. So, clinically insignificant PDA might have been missed in this study. Anemia was another common problem diagnosed in 29.3% cases. Simiyu et al. detected anemia in 17.0% VLBW infants[15]. So, anemia is common problem among VLBW infants, mainly because of repeated blood sampling and anemia of prematurity.

Other common morbidities in this study were shock (42.9%), severe hypothermia (12.1%), and disseminated intravascular coagulation (15.0%). These three morbidities frequently co-exist together and one may lead to another. Hypothermia was diagnosed in as high as 45.0% VLBW infants in a study done at even a developed country like United States.[20] Metabolic problems like hypoglycemia and hypocalcemia were also common in this study which were diagnosed in 39.3% and 25.0% cases respectively. Venkataraman et al. detected hypocalcemia in 53.3% VLBW infants in a study[21]. So, VLBW infants should be routinely monitored for these metabolic problems. Feed intolerance was another problem in 10.7% VLBW infants in this study. Boo et al. detected feed intolerance in 64.4% of VLBW infants and they recommended that to promote tolerance of enteral feeds, intermittent orogastric feed should be started as soon as possible during first 72 hours of life in VLBW infants[22]. NEC was diagnosed in 8.6% VLBW infants in this study, which was similar to finding of other studies.[13,19] In one study done at Turkey, NEC was diagnosed in 26.3% VLBW infants.[23] It has been shown that oral probiotics reduce the incidence and severity of NEC in VLBW infants[24]. This needs to be confirmed by more studies and if found to be effective, it can be used in VLBW infants in our set up also. The incidence of IVH in this study was only 2.9%. This figure is much less than those reported by many other studies.[3,10,17,19] We don't have bedside ultrasound facility to routinely screen VLBW infants for IVH. So, we diagnosed IVH by cranial ultrasound only after strong clinical suspicion. Hence, we might have under diagnosed IVH in VLBW infants. Similarly, routine check up of all VLBW infants for retinopathy of prematurity (ROP) is not strictly done in our hospital because most patients do not come for follow up. That is why we probably under diagnosed ROP, which was diagnosed in only 10.5% of survivors. This is much less than those reported by other studies (19.0% to 31.0%)[3,10,19,25]. We diagnosed this condition in those babies who stayed long enough in hospital. All VLBW infants, especially those who are born before 32 weeks gestation, should be strictly followed up and routinely subjected for eye evaluation. We diagnosed bronchopulmonary dysplasia in only 3.6% of cases, which is also much less than those reported by other studies (12.6% to 33.0%)[10,12,13,19,23]. This might be simply because less numbers of VLBW infants who develop HMD and require mechanical ventilation are surviving enough to develop bronchopulmonary dysplasia in our set up.

Overall survival of VLBW babies in this study was 54.3%. This survival rate is less than the survival rates reported by other studies done at different parts of world, where survival rates were 78.3% to 90.3%.[1,3,10,12,19,23] In this study, lower survival rate in comparison to that of developed countries was because of reasons like poor affordability of parents, limited resources, lack of adequate equipments and ventilators, and limited availability of advanced services such as surfactant therapy and subspeciality services in the study hospital. For example, none of the HMD cases in this study could afford for the surfactant therapy. When needed, 16 cases did not get mechanical ventilator and they had to be managed by manual ventilation. Hence, more numbers of more equipped NICUs are needed in our country to improve survival of VLBW babies. In this study, common causes of death were HMD and sepsis accounting for 51.0% and 34.7% of the total deaths respectively. Due to lack of resources and financial constraints, none of the babies received either prophylactic or therapeutic surfactant therapy. That was the reason for large number of deaths due to hyaline membrane disease. In study by Sritipsukho et al. at Thailand, HMD was the most common cause of death (47.0%) followed by sepsis (20.0%).[13] This is similar to the finding of this study. In one of the studies at Taiwan, the most common cause of death was sepsis.[12] In another Malaysian study, three most common causes of death were HMD (33.2%), sepsis (29.6%) and IVH (17.9%)[17]. Hence, common causes of death match with those of this study. The median duration of hospital stay among survivors in this study was 17.5 days, with a range of one to 51 days. In a Thai study, it was 31.5 days[13]. In a Japanese study, mean duration of stay was 97 days[10]. In another study at Taiwan, the mean duration of hospitalization was 67.2 days[19]. This difference is because, in resource rich countries, they keep the babies in hospital till babies reach appropriate weight for discharge as per hospital guideline. Hospitals in developing countries can not follow weight guideline for discharge strictly because of limited resources to be shared by many babies and poor affordability of parents for prolonged hospital stay.

Conclusion

Preterm deliveries of VLBW babies are of major concern because of maximum perinatal morbidity and mortality found in this group. Inadequate ANC visits, APH, multiple pregnancy, pregnancy induced hypertension, young maternal age and medical diseases in mothers are the common associations with VLBW births in our set up. Increasing the coverage of ANC visits, early diagnosis and treatment of APH and pregnancy induced hypertension and discouraging the childbirth at too young age, early diagnosis and treatment of acute infections and chronic medical diseases in mothers are important measures to decrease the burden of VLBW births. Using antenatal steroid to treat women at risk of preterm birth might be an inexpensive method to improve survival of VLBW infants in our set up. Common morbidities in VLBW

babies are sepsis, HMD, apnea, hyperbilirubinemia, PDA, shock, anemia, hypoglycemia, hypothermia and hypocalcemia. Common culprits for death of VLBW babies are HMD and sepsis. Due to lack of adequate resources we are over diagnosing sepsis and under diagnosing conditions like IVH, PDA and ROP. Overall survival of VLBW babies in our settings is less. More numbers of well equipped NICUs and services like surfactant therapy are needed to improve survival of VLBW infants in our set up.

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