

# Growth and Neurodevelopmental Outcomes of Very Low Birth Weight Infants upto Six Months of Age at a Tertiary Level NICU in Central India: A Prospective Cohort Study

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## ABSTRACT

**Introduction:** The long-term outcomes of Very Low Birth Weight (VLBW) infants are influenced by prematurity, as well as the occurrence of various short-term morbidities, such as Respiratory Distress Syndrome (RDS), sepsis, Necrotising Enterocolitis (NEC), Patent Ductus Arteriosus (PDA), Intraventricular Haemorrhage (IVH), Periventricular Leukomalacia (PVL), Retinopathy Of Prematurity (ROP), and Chronic Lung Disease (CLD). It has been estimated that approximately half of all VLBW infants develop cognitive and behavioural deficits in the future. Therefore, studying VLBW infants and providing longitudinal follow-up after their hospital discharge is increasingly important. This helps in the early diagnosis of neurodevelopmental abnormalities and enables timely intervention for a better quality of life in the future.

**Aim:** To assess the growth and neurodevelopmental outcomes of VLBW infants discharged from the NICU until six months of age.

**Materials and Methods:** A prospective cohort study was conducted in the Neonatal Intensive Care Unit (NICU) at NSCB Medical College, Jabalpur, Madhya Pradesh, India. The duration of the study was one year and six months, from March 2018 to September 2019. A total of 40 VLBW infants were enrolled and followed-up for six months. The infants were divided into two groups: Group 1 (<32 weeks) and group 2 (>32 weeks). Physical parameters such as weight, length, and head circumference were recorded on admission and at one, three and six months of corrected gestational age. Developmental assessment was performed using the Denver Developmental Screening Test-II (DDST-II) method. The association of risk factors with

neurodevelopmental outcomes was also assessed. Data were analysed using Statistical Package for Social Sciences (SPSS) version 20.0, and the Chi-square test, Fisher's-exact test, and Student's t-test were used. A p-value less than 0.05 was considered significant.

**Results:** Among the 40 subjects, 12 (30%) were <32 weeks, and 28 (70%) were ≥32 weeks. Overall, parameters were higher in infants ≥32 weeks. Weight and head circumference gain velocity were greater in infants ≥32 weeks during the first three months of life (p<0.05). From three to six months, <32 weeks infants showed a significant increase (p<0.001) in weight and head circumference gain velocity. The length gain velocity in both groups was comparable since birth, and <32 weeks VLBW infants demonstrated good catch-up growth, which was statistically significant (p<0.05). At six months of corrected age, 16 (40%) infants out of the total 40 infants had abnormal neurodevelopmental outcomes. A total of 7 (58.33%) of the <32 weeks VLBW infants and 9 (32.14%) of the ≥32 weeks VLBW infants had Neurodevelopmental Delay (NDD). Hypoglycaemia, shock, hyaline membrane disease, and mechanical ventilation were significantly associated with an increased risk of NDD.

**Conclusion:** The incidence of NDD was significantly higher in infants with lower gestational age, lower birth weight and the presence of associated factors such as hyaline membrane disease, hypoglycaemia, shock, ventilation, and hyperbilirubinaemia. Improved perinatal care, early assessment of development using appropriate tools, and early intervention are necessary to improve the outcomes of these infants.

**Keywords:** Denver scale, Developmental delay, Growth velocity, Neonatal intensive care unit

## INTRODUCTION

Prematurity is defined as a gestational age of less than 37 completed weeks. VLBW is defined as a birth weight of less than 1500 grams. An estimated 0.78 to 3.9 million children are preterm neonates weighing less than 1500 gm out of the 130 million children born annually worldwide and are considered VLBW infants [1]. The prevalence of low birth weight infants in developed countries is estimated to be around 6.8-7.2 per 100 live births [1,2]. VLBW infants account for almost 2.8% of all live births according to the Indian Institute of Public Health (IIPH) [3]. In India, although VLBW infants constitute only 3.4% of total live births, they are responsible for around 1/3<sup>rd</sup> (29.7%) of the total neonatal deaths [4].

Many premature infants show significant catch-up growth. The catch-up growth is mostly first noted in the infant's head circumference, which is followed by the infant's weight and length. This usually occurs during the initial two to three years of life and is at its maximum at around 36 to 40 weeks after conception [5]. Premature infants with intrauterine growth retardation without any catch-up growth have a higher risk of NDD and other medical problems than premature infants with a normal growth rate and a significant catch-up growth [6]. The long-term outcome of VLBW infants is affected by prematurity, as well as the presence of many short-term morbidities such as RDS, sepsis, NEC, PDA, IVH, PVL, ROP, and CLD [5]. Early identification of these morbidities and efforts to modify the factors associated with these morbidities will help improve the survival of these VLBW infants [5].

Most of these high-risk infants are born preterm and hence are prone to maladjustment to the outside environment and experience various complications compared to term, normal birth weight infants. Many survivors of such infants face a lifetime of disability ranging from severe handicaps such as cerebral palsy, cognitive impairment, blindness, and hearing loss to impairments of short-term memory, language delays, strabismus, learning difficulties, and behavioural disorders [7]. Remarkable international advances in technology and pharmacology, particularly in recent decades, have transformed neonatal intensive care, leading to a drastic increase in VLBW infants' survival at levels that seem harder and harder to exceed. The survival rate for VLBW infants in developed countries ranges from 80% to 85% [7]. Among the long-term complications associated with prematurity, the growth pattern of VLBW infants has been of great concern to parents and medical professionals alike because growth after discharge is a good measure of the physical, neurologic, and environmental well-being of VLBW infants [8].

Although "catch-up" growth has been reported in many studies, large-sample studies have revealed the persistence of poor growth among VLBW infants from birth to adolescence [9,10]. There is mounting evidence that very low birth weight or prematurity and medical complications are negatively associated with postnatal growth [11]. Very little is known regarding the factors that determine the catch-up growth that occurs in very preterm or VLBW infants. Additionally, it has been estimated that approximately half of all VLBW infants develop cognitive and behavioural deficits in the future [11]. It is increasingly important to study VLBW infants and provide longitudinal follow-up after their hospital discharge to ensure early diagnosis of neurodevelopmental abnormalities and enable timely intervention for a better quality of life in the future. Therefore, the present study aimed to assess the growth and neurodevelopmental outcomes of VLBW infants discharged from the tertiary level NICU until six months of age and to find an association between risk factors and NDD.

## MATERIALS AND METHODS

This Prospective cohort study was conducted at tertiary level NICU, in the Department of Paediatrics at NSCB Medical College, Jabalpur, Madhya Pradesh, India. The duration of the study was one year and six months, from March 2018 to September 2019. The sample size was estimated using data from the last three years of the NICU, based on the number of VLBW infants discharged from the NICU of NSCB Medical College Jabalpur, which was approximately 35 infants per year. Ethical clearance was obtained from the Institutional Ethics Committee (No.IEC/2023/4127). Written informed consent was obtained from parents at the time of enrollment of infants.

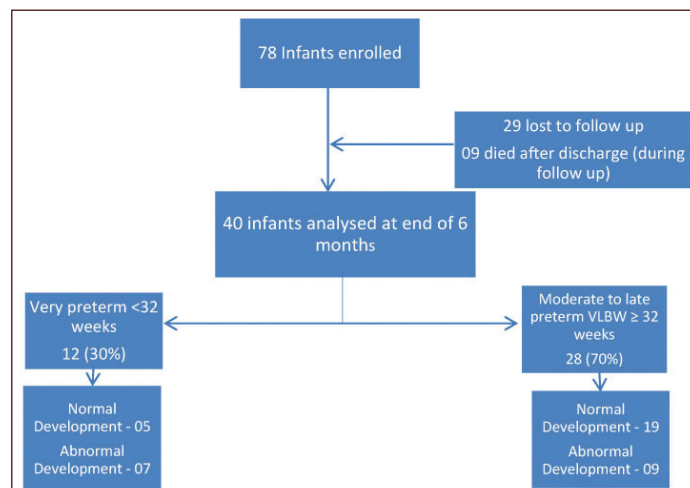
**Inclusion criteria:** All VLBW babies admitted and discharged from a tertiary level NICU from March 2018 to September 2019 were included in the study.

**Exclusion criteria:** Gross congenital malformation, a history of birth asphyxia, dropouts, and those not giving consent were excluded from the study.

### Study Procedure

The total number of infants enrolled in the study was 78, out of which 29 were lost to follow-up and nine infants died after discharge from the hospital. Hence, 40 infants comprised the total sample size of the study [Table/Fig-1]. Infants were divided into two groups: <32 weeks and ≥32 weeks and prospectively followed until six months of corrected gestational age. A detailed proforma

was filled including details of the neonate and mother. Baseline characteristics included were gestational age, mode of delivery, and gender.



[Table/Fig-1]: Summary of study participants.

Appropriate for Gestational Age/Small for Gestational Age (AGA/SGA) were noted. Gestational age was recorded based on first-trimester ultrasonography or, if not available, by the date of the last menstrual period. Simple anthropometric measurements such as weight (in kg), length (in cm), and head circumference (in cm) were taken at birth, one month, three months, and six months of corrected age.

Corrected gestational age was calculated from the expected date of delivery of the neonate. Weight was measured using an electronic weighing machine with a precision of 10 grams. Length was measured using an infantometer, and head circumference was measured using a non stretchable tape. Neurodevelopmental assessment was done at one, three, and six months using the DDST-II [12]. Infants were labelled as normal if their Development Quotient (DQ) was more than 70% in all domains, otherwise, they were labelled as abnormal and referred to the Regional Early Intervention Centre (REIC) located at the Institute. Risk factors were identified from the case records of infants, and infants at risk were managed according to the protocol [13]. To improve follow-up, periodic reminders were sent to parents through telephone calls. Standard treatment was provided to the infants, and appropriate interventions were made during follow-up when required.

The data was analysed using MS Excel and SPSS version 20.0 for Windows. Categorical variables were tabulated as frequency (n) with percentage (%) distribution, and continuous variables were summarised as mean and Standard Deviation (SD). Student's t-test was used to compare two independent means. The normality test was applied before using parametric tests. Chi-square test and Fisher's-exact test were used to find associations between risk factors and NDD, with a p-value of <0.05 considered significant.

## RESULTS

Out of 40 infants, 12 (30%) were very preterm VLBW (<32 weeks) and 28 (70%) were moderate to late preterm (≥32 weeks). A total of 24 (60%) infants were male, and 16 (40%) were female. Baseline characteristics and anthropometric measurements of the study group are shown in [Table/Fig-2,3], respectively. All anthropometric parameters of weight gain, length, and head circumference were higher in the ≥32 weeks VLBW group at six months of corrected gestational age [Table/Fig-3]. Out of the 40 infants studied at the end of six months

of corrected age, 16 (40%) infants were found to be abnormal, and 24 (60%) were found to be normal [Table/Fig-4]. Hypoglycaemia (p=0.021), shock (p=0.007), hyaline membrane disease (p=0.001), mechanical ventilation (p=0.0001), and hyperbilirubinaemia (p=0.004) had a significant association with an increased risk of NDD. A total of 64% of infants with hypoglycaemia, 50% of infants with shock, 73.3% of infants with Hyaline Membrane Disease (HMD), 100% of infants who required mechanical ventilation, and 55.6% of infants with hyperbilirubinaemia had abnormal NDD, and this was statistically significant [Table/Fig-5].

Characteristics	Group 1	Group 2	Total
	<32 weeks n (%)	≥32 weeks n (%)	
<b>Gender</b>			
Male	7 (29.2)	17 (70.8)	24
Female	5 (31.3)	11 (68.7)	16
Total			40
<b>Gestational age</b>	12 (30)	28 (70)	40
<b>Mode of delivery</b>			
Vaginal	20 (62.5)	12 (37.5)	32
LSCS	1 (12.5)	7 (87.5)	8
Total			40
<b>AGA/SGA</b>			
AGA	11 (52.4)	10 (47.6)	21
SGA	1 (5)	18 (95)	19
Total			40

**[Table/Fig-2]:** Baseline characteristics of study groups (N=40). LSCS: Lower segment caesarean section; AGA: Appropriate for gestational age; SGA: Small for gestational age

Parameters	Group 1 (<32 weeks)	Group 2 (≥32 weeks)	t-test	p-value
<b>Weight gain (in kg)</b>				
Age (in months)	Mean±SD	Mean±SD		
On admission	1.242±0.108	1.368±0.048	5.169	0.0001*
1 month	1.623±0.266	1.970±0.163	5.073	0.0001*
3 months	2.480±0.334	3.192±0.298	6.683	0.0001*
6 months	4.398±0.427	5.110±0.427	4.83	0.0001*
<b>Length gain (in cm)</b>				
On admission	39.51±1.85	42.25±1.14	5.792	0.0001*
1 month	43.56±2.39	46.33±1.16	4.965	0.0001*
3 months	49.44±3.01	51.66±1.43	3.178	0.003*
6 months	56.99±4.02	59.97±1.85	3.236	0.003*
<b>Head circumference gain (in cm)</b>				
On admission	29.33±1.69	31.73±0.90	5.842	0.0001*
1 month	30.61±1.95	33.16±0.95	5.578	0.0001*
3 months	34.50±2.19	37.47±0.95	6.038	0.0001*
6 months	38.27±2.78	41.11±0.83	4.263	0.0001*

**[Table/Fig-3]:** Anthropometric parameters of the two study groups. t-test, \*p-value <0.05: significant

Gestational age	Normal n (%)	Abnormal n (%)
Group 1 (<32 weeks)	5 (41.7)	7 (58.33)
Group 2 (≥32 weeks)	19 (67.9)	9 (32.14)
Total	24 (60)	16 (40)

**[Table/Fig-4]:** Comparison of neurodevelopmental outcome by DDST II at six months of corrected age. Chi-square=2.40, p-value=0.121

Risk factors	n	Developmental delay at six months		Chi-square	p-value
		Normal	Abnormal		
		n (%)	n (%)		
Hyaline membrane disease	15	4 (26.7)	11 (73.3)	11.11	0.001*
Sepsis	25	15 (60)	10 (40)	0	1
Necrotising enterocolitis	12	6 (50)	6 (50)	0.71	0.398
Hypoglycaemia	14	5 (35.7)	9 (64.3)	5.29	0.021*
Shock	30	15 (50)	15 (50)	7.31	0.007*
Ventilation	7	0	7 (100)	12.73	0.0001*
Hyperbilirubinaemia	27	12 (44.4)	15 (55.6)	8.38	0.004*
Oxygen requirement	29	15 (51.7)	14 (48.3)	3.01	0.083
Vasopressors	23	13 (56.5)	10 (43.5)	0.27	0.601

**[Table/Fig-5]:** Association of risk factors with Neurodevelopmental Delay (NDD) among study groups. Test applied: Chi-square, \*p-value <0.05

## DISCUSSION

The present study was conducted to assess the growth and neurodevelopmental outcomes of VLBW infants upto six months of age and also to find associations between risk factors and NDD. Out of 40 babies, 24 (60%) were male. Weight gain velocity was higher in infants born at ≥32 weeks from birth upto three months compared to infants born at <32 weeks, and this difference was statistically significant. Regarding length velocity, both <32 weeks and ≥32 weeks infants showed an increase in length velocity from birth to six months. Infants born at ≥32 weeks had more head circumference gain from one month to three months, whereas very preterm VLBW infants had more head circumference gain velocity from three to six months. The prevalence of NDD was 20 (50%) at the first month, 18 (45%) at three months, and 16 (40%) at six months of age. In the present study, VLBW infants (<32 weeks) had a significant lag in the growth of all physical parameters at six months of corrected gestational age. These findings are consistent with the observations made by Babson SG, Drillien CM, and Sridhar K et al., [14-16].

The anthropometric parameters in the present study correlated well with the study conducted by Bhargava SK et al., among infants weighing <1500 grams [17]. Although anthropometric characteristics were better at birth in the present study compared to Oliveira MG et al., the final weight, length, and head circumference gains were significantly lower in present study [18]. This difference may be attributed to variations in NICU care conditions. In the case of Oliveira MG et al., total parenteral nutrition with amino acids was initiated for all infants weighing <1250 grams within the first hour after birth, and mother's milk or preterm formula was supplemented with polyunsaturated fatty acids for other eligible infants. These differences in care, along with genetic, socioeconomic, sociocultural, and demographic factors, could have contributed to the disparities observed. These findings highlight the importance of nutrition in determining the growth and neurodevelopmental outcome of VLBW infants. Adequate emphasis should be placed on nutrition during both NICU stay and subsequent follow-ups [19,20]. The prevalence of NDD in the present study was 20 (50%) at the first month of life, 18 (45%) at three months of life, and 16 (40%) at six months of life. At six months of life, 7 (58.33%) out of 12 infants born at <32 weeks had NDD, compared to 9 (32.14%) out of 28 infants born at ≥32 weeks, similar to the findings of Mukhyopadhyay K et al., [21]. A slightly higher incidence in the above study may be due to the inclusion of a greater number of Extremely Low Birth

Weight (ELBW) infants and extremely premature infants (<28 weeks), compared to none in the present study. Complications such as IVH, the requirement for mechanical ventilation, and CLD were more common in their study compared to the current study. However, there was a lower incidence of NDD at 18 months in the study by Mukhyopadhyay K et al., using the Development Assessment Scale for Indian Infants (DAS-II) [21]. This could be because DDST-II is a screening test that can be used to screen many infants, whereas DAS-II is a confirmatory test that is applied to those who tested positive. The detection rate may be more accurate and lower in DAS-II, as it is a definitive test compared to DDSTII, which is just a screening test [21].

In a study by Sur S et al., using DDST at 12 months, the incidence of NDD was lower compared to the present study [22]. They observed only 24.4% NDD, as there were fewer co-morbidities in their study, and it was screened at one year compared to six months in current study. Early screening and intervention can reduce the incidence of NDD. In studies by Sudhir U et al., and Khan MR et al., on preterm infants, the number of VLBW infants was lower compared to the present study, which may have accounted for the higher incidence of NDD in their studies [23,24]. Although the number of VLBW subjects was comparable to the study in Ghanghoria PK et al., the NDD rate was higher [25]. This may be because their study focused on twin infants, and twinning itself is an independent risk factor for NDD, along with VLBW, as observed in the study by Ghanghoria PK et al., [25]. Modi R et al., found a higher incidence of NDD in their study compared to the present study, as they had fewer study subjects and more co-morbidities [26].

In the present study, NDD was found in 40% of sepsis cases, which corresponds well with a study by Stoll BJ et al., where NDD was observed in 43% of cases [27]. Furthermore, in current study, NDD was found in 64.3% of hypoglycaemia cases. This association is statistically significant and correlates well with a study by Melana N et al., where NDD at six months, assessed using DDSTII, was reported to be 66.6% [28].

There was 50% NDD in NEC cases in present study, which is comparable to Schulzke SM et al., in which NDD was seen in 42.9% of cases [29]. In the present study, there was NDD in 50% of cases with shock, and it is statistically significant and correlates well with a study by Chirla DK, in which NDD was found in 50% of cases [30]. In the present study, NDD was found in 55.6% of hyperbilirubinaemia cases. However, jaundice was more often a co-morbidity in the current study. According to Babu A and Bhat V, significant NDD was found in cases with pathological jaundice [31].

The above studies also indicate that as gestational age and birth weight decrease, the severity and chance of co-morbidity increase, such as RDS, NEC, shock, hypoglycaemia, which contribute significantly to NDD. The lower the gestational age and birth weight, the higher the chances of NDD.

### Limitation(s)

The sample size was small, and the follow-up duration was only six months. Additionally, the DDST is a screening tool, not a confirmatory test. Studies with larger sample sizes, longer follow-ups, and confirmatory tools might provide a better outlook for these infants.

### CONCLUSION(S)

The VLBW infants <32 weeks showed a considerable lag in growth and development at six months of corrected age compared to ≥32 weeks VLBW infants. The incidence of NDD was significantly

higher in lower gestational ages, lower birth weights, and if associated risk factors were present, such as hypoglycaemia, hyaline membrane disease, shock, hyperbilirubinaemia, and the use of mechanical ventilation. It is difficult to diagnose NDD in infants under six months of life because very few domains are available for screening. Hence, early screening through frequent follow-up can lead to early detection of at-risk infants for NDD and result in early stimulation therapy and better neurodevelopmental outcomes.

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**PLAGIARISM CHECKING METHODS:** [Jain H et al.]

- Plagiarism X-checker: Mar 13, 2023
- Manual Googling: Oct 02, 2023
- iThenticate Software: Oct 05, 2023 (15%)

**ETYMOLOGY:** Author Origin

**EMENDATIONS:** 8

**AUTHOR DECLARATION:**

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Mar 02, 2023**

Date of Peer Review: **Apr 24, 2023**

Date of Acceptance: **Oct 06, 2023**

Date of Publishing: **Dec 31, 2023**