

Neurodevelopmental Profile of Preterm Babies in the First Year of Life: A Prospective Cohort Study

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ABSTRACT

Introduction: Improved survival of preterm babies has also increased the incidence of neurodevelopmental problems. The first year of life is the most sensitive period for early intervention and hence targeting early detection principles to this age will be most useful.

Aim: To study the neurodevelopmental profile of preterm babies (<35 weeks), born in a tertiary care hospital, till the age of 12 months of Corrected Gestational Age (CGA).

Materials and Methods: The prospective cohort study was conducted between January 2014 and August 2015 at Christian Medical College and Hospital, Ludhiana, Punjab, India. All preterm newborns (<35 weeks) born in the tertiary care hospital during the study period were included. A total of 57 babies were enrolled. Neuromotor assessment at discharge and on follow-up at six and 12 months of CGA was done using Infant Neurological International Battery (INFANIB) and Developmental Assessment Scales for Indian Infants (DASII). One-way Analysis of Variance (ANOVA), Chi-square test, Fischer's-Exact test and inter-rater kappa agreement were used for statistical analysis.

Results: A total of 78 preterm (35 weeks) were born, 21 were excluded, 57 were enrolled and 42 babies were followed-up till 12 months of CGA. The mean INFANIB score at discharge, 6 months and 12 months of CGA were 58.93 ± 5.11 , 68.74 ± 7.71 and 82.95 ± 5.90 , respectively. At 12 months of CGA, 64% of the babies were normal, 33.33% were transient and 2.8% were abnormal as per INFANIB. The mean DASII score for Motor Development Quotient (MoDQ) at six and 12 months were 89.84 ± 8.41 and 93.49 ± 10.39 , respectively, whereas Mental Development Quotient (MeDQ) at six and 12 months, were 70.39 ± 10.54 and 65.58 ± 13.19 , respectively. The neuromotor assessment of infants with INFANIB compared well with the motor developmental score on DASII with an inter-rater kappa agreement of 1 (kappa=1).

Conclusion: The preterm babies showed improvement in motor development quotient, but not in mental development quotient. Results of INFANIB and DASII matched in their motor assessment. The INFANIB is a reliable and quick tool for neuromotor assessment.

Keywords: Infants, Motor mental delay, Neuromotor assessment, Prematurity

INTRODUCTION

Preterm birth is single largest cause of neonatal and under five deaths worldwide [1]. Advances in intensive care of neonates, have led to improved survival of these children [2,3]. However, there is increased risk of significant long term neurodevelopmental complications in these surviving children. A study on 171 children showed that 37.8% of them had Neuromotor Impairment (NMI) [4]. According to the World Health Organisation (WHO), the prevalence of Neurodevelopment Disorders (NDDs) is between 1-20 %. NMIs are the most common NDDs affecting children. The most common form of NMI is Cerebral Palsy (CP), with a prevalence of 1.2-2.5 per 1,000 live births. The NDDs other than NMI includes epilepsy, intellectual disability, autism specific disorder, attention deficit hyperactivity disorders, hearing impairment, vision impairment, and speech and language disorders [5]. There is scarcity of data about the NDD of preterm babies from middle income countries like India. Nair M et al., reported 24% cognitive delay, 27% language delay and 29% motor delay, intraventricular haemorrhage, shock DIC, sepsis are important risk factors for NDI [6]. Preterm SGA are also increased risk of developmental delays [7].

A preterm follow-up program is multidisciplinary and requires a careful assessment and follow-up of tone and posture along with screening for sensory problems like hearing and vision. Assessment of tone and posture are conventionally done using the Amiel-Tison angles, primitive reflexes, symmetry in tone and posture and monitoring of timely achievement of milestones. Several researchers have developed scores based on angles, posture, symmetry and various motor milestones. The scores are then interpreted for ranges of normality

and asymmetry. The Infant Neurological International Battery (INFANIB) and Hammersmith Infant Neurological Examination (HINE) scales are two such neurodevelopmental assessment tools [8,9].

Developmental Assessment Scales for Indian Infants (DASII) has been used since decades for assessment of motor and mental development of children between three months and 2.5 years of age [10]. However, it needs a DASII kit and training to administer. It is time consuming; it needs scoring and effective interpretation. INFANIB is a reliable, specific and sensitive tool which assesses the neurological integrity in the infants [11]. It is less time consuming, easy to administer, has 20 items (Amiel-Tison angles are included) and requires only goniometer for assessment. Neuromotor status is classified as normal, transient and abnormal based on the scores at different ages. Both these scales have their own pros and cons.

The present study was conducted with the objective to study the neurodevelopmental profile of preterm babies born before gestational age of 35 weeks using INFANIB and DASII and evaluate the usefulness of INFANIB in the outpatient setting, as there is scarcity of data in regards of developmental delay from our country.

MATERIALS AND METHODS

The prospective cohort study was conducted between January 2014 and August 2015 at Christian Medical College and Hospital, Ludhiana, Punjab, India. Institutional Ethics Committee approval (CMC/3422) was taken and all procedures followed were in accordance with the standards mentioned in Helsinki declaration of 1975 and revised in 2013.

Inclusion criteria: All preterm newborns (<35 weeks) born in the hospital during study period were included in study.

Exclusion criteria: Babies with major congenital malformations, those who left against medical advice and died were excluded from the study.

Study Procedure

Total 57 preterm babies (<35 weeks) born in a tertiary care hospital with a level II B accredited NICU, over a period of six months, were enrolled for the present study and followed up at discharge, six months and 12 months of CGA, at the Early Intervention Clinic. After getting parental consent, data was noted on a predesigned proforma a Antenatal and intrapartum details of mother, details of new born at birth (gestational age, birth weight, weight for gestational age), INFANIB score, results of Behaviour Response Audiometry (BOA), neuroimaging and eye evaluation were noted at discharge by the first author. Patients were called for follow-up via telephone by the author. The first author performed DASII [10] and INFANIB for the babies.

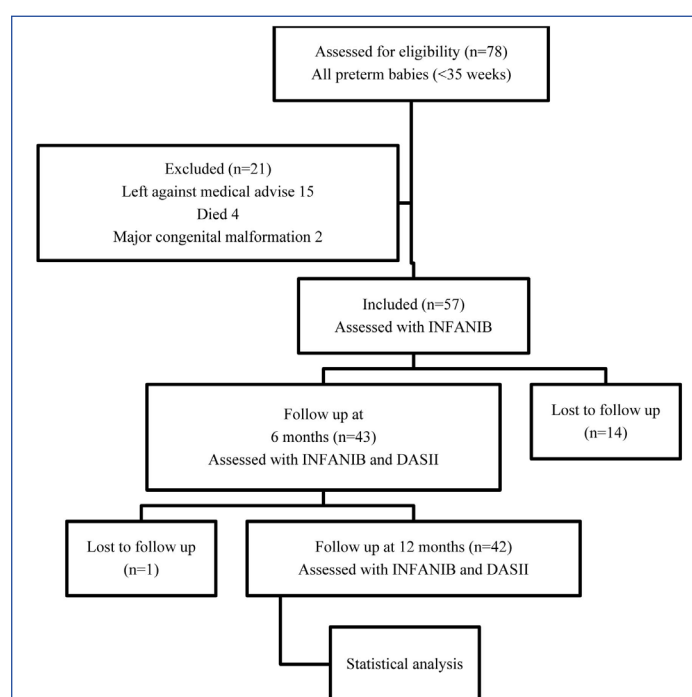
Follow-up of Neuromotor assessment was done using INFANIB at discharge, six months and 12 months of CGA. Babies were neurologically classified as normal, transient and abnormal as per INFANIB score [11]. Developmental assessment was also done using DASII at six and 12 months of CGA. Development Quotient (DQ) on DASII was recorded. The DQ was expressed as Motor Developmental Quotient (MoDQ) and Mental Developmental Quotient (MeDQ). Babies were categorised as normal for developmental quotient >70 or delayed if developmental quotient ≤70 [10].

STATISTICAL ANALYSIS

Data was entered in Microsoft Excel spreadsheet and the final analysis was done with the use of Statistical Package For Social Sciences (SPSS) software (version 22.0). One-way Analysis of Variance (ANOVA), Chi-square test, Fischer's-Exact test and inter-rater kappa agreement was used to do final analysis. For statistical significance, p-value <0.05 was considered as significant.

RESULTS

A total of 78 babies were eligible, 21 were excluded (15 left against medical advice, four died, two major congenital malformations). A total of 57 babies were included. At six and 12 months of CGA, 43 and 42, respectively, came for follow-up and were included in the statistical analysis [Table/Fig-1]. There were 39 (68.42%) males and 18 (31.57%) females. Baseline characteristics of babies included in final analysis are shown in [Table/Fig-2,3].



[Table/Fig-1]: Flow Diagram of Participants.

Variables	Number (n)	Percentage (%)
Gestational age (weeks)		
28-30	8	14.04
31-32	26	45.61
33-34	23	40.35
Weight (gm)		
750-999	1	1.75
1000-1499	17	29.82
1500-1999	25	43.86
>2000	14	24.57
Gestational categories		
Small for Gestational Age	6	10.53
Appropriate for gestational age	44	77.19
Large for Gestational Age	7	12.28
Mother's Educational status (n=54)		
Illiterate	7	12.96
Primary school	7	12.96
Secondary school	5	9.25
Intermediate (+2)	12	22.22
Graduate	14	25.92
Postgraduate	9	16.66

[Table/Fig-2]: Baseline characteristics of babies and the educational status of the mothers.

Variables	n (%)
Maternal Morbidity	
Anaemia	26 (45.61)
Diastolic cut off in ultrasound	8 (14.04)
Threatened preterm	6 (10.53)
Pre-eclampsia / Eclampsia	6 (10.53)
Twin delivery	6 (10.53)
Foetal distress	5 (8.77)
Placenta previa	3 (5.26)
Abruption placentae	2 (3.51)
Malposition	1 (1.75)
Preterm Premature Rupture of the Membranes (PPROM)	1 (1.75)
Breech	1 (1.75)
Neonatal Morbidity	
Hyaline Membrane Disease	22 (38.60)
Birth asphyxia*	17 (29.82)
Intrauterine pneumonia	8 (14.04)
Respiratory failure	8 (14.04)
Metabolic acidosis	8 (14.04)
Shock	6 (10.53)
Sepsis	5 (8.77)
Periventricular leukomalacia**	4 (7.02)
Anaemia of prematurity	3 (5.26)
Thrombocytopenia	2 (3.51)
Congenital heart disease	2 (3.51)
Necrotising enterocolitis	2 (3.51)
Metabolic problems	2 (3.51)
Ventricular associated pneumonia	1 (1.75)
Apnoea of prematurity	1 (1.75)

[Table/Fig-3]: Maternal (n=54) and neonatal morbidities (n=57).

Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) Score less than equal sign 6;

**Grade 1 and 2

At the time of discharge all 57 (100%) babies had normal behavioral observation audiometry. By three months of CGA, 27 (47.36%)

babies got Brainstem Evoked Response Audiometry (BERA) done, all of which were normal. Total 47 (82.45%) babies underwent eye examination before discharge out of which, 42 (89.36%) had normal visual assessment, 1 (2.13%) had Retinopathy of Prematurity (ROP) immature zone I and 4 (8.51%) had ROP immature zone II. None required laser photocoagulation. Ultrasound of cranium was done for 47 (82.45%) babies before discharge. Of these, 32 (68.09%) were normal, 12 (25.53%) had Periventricular Leukomalacia (PVL) grade I and 3 (6.38%) had PVL grade II.

The mean INFANIB score at discharge, six months and 12 months of CGA were 58.93 ± 5.11 , 68.74 ± 7.71 and 82.95 ± 5.90 , respectively. It showed that the INFANIB scores increased with age indicating an improvement in tone over first 12 months of age. Total 48 preterm babies (84%) were discharged with a neurological classification of transient. By the end of 12 months, 20 babies in transient category had moved to normal. One abnormal baby remained abnormal during the entire study period [Table/Fig-4].

Neurological Categories	Corrected Gestational Age (CGA)			p-value
	At discharge n (%)	At 6±1 months n (%)	At 12±1 months n (%)	
Normal	7 (12.28)	16 (37.21)	27 (64.29)	<0.0005
Transient	48 (84.21)	26 (60.47)	14 (33.33)	
Abnormal	2 (3.51)	1 (2.33)	1 (2.38)	
Total	57 (100.00)	43 (100.00)	42 (100.00)	

[Table/Fig-4]: Neurological categorisation based on INFANIB.

*df=4, * $\chi^2=28.929$

Further statistical analysis showed that babies with higher weight and higher gestation, Appropriate for gestational age (AGA) had a greater chance of moving from transient to normal category [Table/Fig-5]. It was further noted that the prolonged NICU stay (>7 days) [Table/Fig-5], diastolic cut-off on ultrasound (absent diastolic blood

Corrected Gestational Age (CGA)									
Variables	At Discharge (n=57)			At 6±1 Months CGA (n=43)			At 12±1 Months CGA (n=42)		
	N	T	AB	N	T	AB	N	T	AB
Weight at birth (gm)									
750-999	0	1	0	0	1	0	1	0	0
1000-1499	1	15	1	2	6	1	6	3	1
1500-1999	3	22	0	8	12	0	9	10	0
≥2000	3	10	1	6	7	0	11	1	0
Total	7	48	2	16	26	1	27	14	1
Gestational age (weeks)									
28-30	0	8	0	1	6	1	3	4	1
31-32	3	22	1	6	11	0	8	8	0
33-34	4	18	1	9	9	0	16	2	0
Total	7	48	2	16	26	1	27	14	1
Gestational categories									
SGA	0	6	0	0	3	0	3	0	0
AGA	5	37	2	15	17	1	20	11	1
LGA	2	5	0	1	6	0	4	3	0
Total	7	48	2	16	26	1	27	14	1
NICU stay (days)									
<3	0	1	0	1	0	0	1	0	0
3-7	2	12	1	5	8	0	8	4	0
>7	5	35	1	10	18	1	18	10	1
Total	7	48	2	16	26	1	27	14	1

[Table/Fig-5]: Association of weight categories, gestational age, growth status at birth and duration of NICU stay with neurological status (as per INFANIB score) at discharge, 6±1 months and 12±1 months of corrected gestational age.

N= normal, T=transient, AB= abnormal; SGA: Small for gestational age; AGA: Appropriate for gestational age; LGA: Large for gestational age

flow in prenatal ultrasound), anaemia in mother (Haemoglobin <10.9 g/dL), Hyaline Membrane Disease (HMD) (diagnosed clinically and radiologically) and birth asphyxia in neonates had significant impact on the motor development of the babies [Table/Fig-6].

Variables				Corrected Gestational Age (CGA)						p-value
				At 6±1 Months CGA			At 12±1 Months CGA			
	N	T	AB	N	T	AB	N	T	AB	
Maternal co-morbidities										
Anaemia	3	21	2	7	9	0	12	5	0	0.002
Diastolic cut-off	1	7	0	1	3	0	4	0	0	0.011
Neonatal co-morbidities										
HMD	2	19	1	7	10	0	10	7	0	0.017
Birth asphyxia	1	16	0	6	9	0	11	4	0	<0.001

[Table/Fig-6]: Statistically significant association of maternal and neonatal morbidities with neurological category (infanib score) at discharge, 6±1 months and 12±1 months of corrected gestational age.

N – Normal, T – Transient, AB – Abnormal, HMD – Hyaline membrane disease.

The mean DASII score for MoDQ at 6 and 12 months of CGA were 89.84 ± 8.41 and 93.49 ± 10.39 whereas for MeDQ at six and 12 months CGA were 70.39 ± 10.54 and 65.58 ± 13.19 , respectively. On DASII assessment, the MoDQ was delayed for only one baby at 6 and 12 months of CGA whereas the MeDQ was further hampered with age, as there were only 13 (30.95%) babies with MeDQ of ≥ 70 at 12 months of CGA [Table/Fig-7]. Prolonged ventilation was a single important association with poor MeDQ at six and 12 months CGA [Table/Fig-8].

Developmental quotient	Corrected Gestational Age (CGA)			p-value
	6±1 Month n (%)		12±1 Month n (%)	
MoDQ	≤70	1 (2.33)	1 (2.38)	1.000
	>70	42 (97.67)	41 (97.62)	
MeDQ	≤70	22 (51.16)	29 (69.05)	0.092
	>70	21 (48.84)	13 (30.95)	

[Table/Fig-7]: Development status according to developmental quotient (as per DASII) at 6±1 months and 12±1 months of Corrected Gestational Age (CGA).

*df=1, * $\chi^2= 2.832$: Motor Development Quotient (MoDQ), Mental Development Quotient (MeDQ)

Developmental quotient	Ventilation/ DQ	Corrected Gestational Age (CGA)				p- value
		6±1 months CGA (n=43)		12±1 months CGA (n=42)		
		≤70	>70	≤70	>70	
MoDQ	No	1 (5.88%)	16 (94.12%)	1 (6.25%)	15 (93.75%)	1
	Yes	0	26 (100.00%)	0	26 (100.00%)	-
	Total	1 (2.33%)	42 (97.67%)	1 (2.38%)	41 (97.62%)	-
MeDQ	No	10 (58.82%)	7 (41.18%)	10 (62.50%)	6 (37.50%)	0.829
	Yes	12 (46.15%)	14 (53.85%)	19 (73.08%)	7 (26.92%)	0.048*
	Total	22 (51.16%)	21 (48.84%)	29 (69.05%)	13 (30.95%)	-

[Table/Fig-8]: Association of ventilation with motor and mental developmental quotient at 6±1 and 12±1 months of Corrected Gestational Age (CGA).

MoDQ: Motor development quotient; MeDQ: Mental development quotient

At 12 months of CGA, only 10% of preterm babies with birth weights between 1000 and 1499 gm had deficits in motor development. However 70% of them had some form of mental deficits. Furthermore, an increase in prevalence of mental deficits at 12 months follow-up (69.05%) when compared to the 6 month follow-up (51%) was observed. The prevalence of mental deficit in groups with birth weight 750-999 gm, 1500-1999 gm and >2000 gm were 100%, 84.21% and 41.67%, respectively [Table/Fig-9].

Developmental quotient	Weight at birth (gm) gm/dq	Corrected Gestational Age (CGA)				p-value
		6 ± 1 months CGA (n=43)		12 ± 1 months CGA (n=42)		
		≤70	>70	≤70	>70	
MoDQ	750-999	0	1 (100.00%)	0	1 (100.00%)	-
	1000-1499	1 (11.11%)	8 (88.89%)	1 (10.00%)	9 (90.00%)	1
	1500-1999	0	20 (100.00%)	0	19 (100.00%)	-
	≥2000	0	13 (100.00%)	0	12 (100.00%)	-
	TOTAL	1 (2.33%)	42 (97.67%)	1 (2.38%)	41 (97.62%)	-
MeDQ	750-999	1 (100.00%)	0	1 (100.00%)	0	-
	1000-1499	5 (55.56%)	4 (44.44%)	7 (70.00%)	3 (30.00%)	0.65
	1500-1999	11 (55.00%)	9 (45.00%)	16 (84.21%)	3 (15.79%)	1
	≥2000	5 (38.46%)	8 (61.54%)	5 (41.67%)	7 (58.33%)	0.092
	TOTAL	22 (51.16%)	21 (48.84%)	29 (69.05%)	13 (30.95%)	-

[Table/Fig-9]: Association of weight category with developmental quotients at 6±1 months and 12±1 months of Corrected Gestational Age (CGA)

The scores of INFANIB and DASII were similar as far as motor domain is concerned. The inter-rater kappa agreement between INFANIB and DASII at 6 and 12 months of CGA, showed perfect agreement between the two scales in the motor domain (Kappa=1, p-value <0.0001) [Table/Fig-10].

INFANIB		DASII		Total n (%)
		Normal >70 n=42 (%)	Abnormal ≤70 n=1 (%)	
At 6 months	Normal/Transient	42 (97.67)	0	42 (97.67)
	Abnormal	0	1 (2.33)	1 (2.33)
	Total	42 (97.67)	1 (2.33)	43 (100)
At 12 months	Normal/Transient	42 (97.67)	0	42 (97.67)
	Abnormal	0	1 (2.33)	1 (2.33)
	Total	42 (97.67)	1 (2.33)	43 (100)

[Table/Fig-10]: Inter-rater kappa agreement between INFANIB and DASII at 6 and 12 months.

*Kappa=1, *p-value <0.0001

DISCUSSION

The findings of present study reveal that motor development improves with age as per assessments by both INFANIB and DASII whereas mental assessment by DASII showed increase in number of babies with mental delay. Furthermore, significant association of lower mental development was observed with lower birth weight and lower gestation age. This correlates with the findings of study by Mukhopadhyay K et al., in which neurodevelopmental profile of 101 very low birth weight babies was assessed up to two years of CGA, a score of <70 was found in 17% (MeDQ) and 25.7% (MoDQ) babies [12]. Krishna GS and Suvana SG, performed INFANIB on 100 preterm infants who were born between 24-31 weeks with the age group from 4-9 months and found delayed pattern of motor development which is different from term [13]. Another study by Pederson SJ et al., suggested motor evaluation before seven months to be unsatisfactory as dystonia till this age is often transient. However, a normal neuromotor assessment at seven months was highly predictive of subsequent normal motor function [14].

In the current study, a statistically significant impact of prolonged NICU stay and birth asphyxia on the motor development was observed. Similar results have been published in earlier studies as

well [15-17]. NICU related stress and pain can have long standing effects on the development of preterm babies that can pass over childhood through epigenetic alterations of imprinted and stress related genes [18].

Also, severe asphyxia of long duration is known to cause lack of energy in brain. This leads to failure of Adenosine Triphosphate (ATP) dependent pumps resulting in the loss of neuronal trans membrane potential, thereby causing tissue necrosis in the most sensitive areas of the brain [19]. Prior to the cooling era approximately 26.4% of infants with neonatal encephalopathy survived with moderate to severe neurodevelopmental impairment and a further 14% survived with mild impairment [20]. In another study by Halloran D et al., on 182 infants, 42 (23%) had birth asphyxia and 13(31%) had abnormal neurological examination at discharge [21].

As the age of the baby increases, motor development improves. Using trial and error, the infant enhances his/her ability to use gross motor, vocalisation and manual activities [22]. Improvement in fine and gross motor performance until adulthood and deterioration thereafter has been also been reported. Maturation has an essential role in the process of motor development. Motor milestones are delayed in preterm as compared to the term infants [23]. In a Greek study, Alberta Infant Motor Scale (AIMS) performance of preterm infants were compared with the full term infants found that AIMS trajectories of preterm infants were far below those of term infants [24].

Children with moderate encephalopathy at birth were reported to developed more disability in late adolescence. Furthermore, 30% children were found to have CP whereas 70% of those without CP had cognitive disability which compromised their daily routine activities [20]. Hintz SR et al., compared neurodevelopmental outcomes in babies born before 25 weeks between years 1999-2001 (epoch 1) and between 2002 and 2004 (epoch 2) and reported no difference in Mental Development Index (MDI) between two groups during both time periods [25].

In the present study, ventilation had significant impact on the mental development. In preterm babies, mechanical ventilation has increased likelihood of brain injury and inflammation. The channel involving ventilation activated brain injury includes both complicated inflammatory and haemodynamic pathways. [26] In a study by Bozynski ME et al., showed that extended mechanical ventilation shows evenly low performance at every age. It also serves as an important marker for poor development, in babies weighing ≤1200 gm at birth [27]. Similar observations about increased deficit in mental development, cognitive developments, ability to comprehend and solve mental problems with age has been published in previous studies [28-29].

Karimi M et al., studied children with birth weight (1500-2499 gm) and (2500-4000 gm) at five years using Ages and Stages Questionnaire (ASQ) and found that frequency of developmental delay in gross motor, fine motor and problem solving domains were significantly lower in lower birth weight group [28]. Modi M et al., compared 37 Very Low Birth Weight (VLBW) with 35 normal birth weight babies using DASII at one year of CGA and found that DQ is significantly lower in VLBW infants [29]. A similar trend of moving from transient to normal category was observed in current study for babies with higher weight (N=11, 91.67%) and gestation (N= 16, 88.89%).

Neuromotor assessment by using INFANIB and DASII was comparable in current study. The INFANIB was found to be quick and reliable and can be of great help in busy clinics where time is a constraint. In a similar study comparing INFANIB and DASII by Rao PNS et al., INFANIB was reported to have better sensitivity

and negative predictive value (>90%) and it detected transient neurologic abnormalities in 69% of infants included in the study [30]. Charpark N et al., reported 77.2% sensitivity and 91.1% specificity (receiver operating characteristic 0.84%) as INFANIB scoring was done by different paediatricians [31]. Dadkhah SF et al., found it valid for both normal and abnormal group with sensitivity, specificity, positive predictive value and negative predictive value of 90%, 83%, 79% and 93% respectively [32]. Liao W et al., showed that the interclass and intraclass correlation coefficient values for INFANIB at three, seven and 10 months were >0.8, indicating excellent reliability with regard to inter and intra-observer differences [33].

Low birth weight and gestational age are potent predictors of unsatisfactory neurological outcome in the long term. Other significant factors include sepsis, structural abnormalities of brain, male babies and neonatal intensive unit period [34].

Other studies show that, low arterial pH, low APGAR scores, lower maternal education, intraventricular haemorrhage, chorioamnionitis, moderate to severe bronchopulmonary dysplasia, prolonged mechanical ventilation and seizures increase the risk of developmental delay [18].

Longo S et al., reported long NICU stay, male gender, BPD, late onset sepsis significant risk factors for developmental delay. However in the present study association with male gender and sepsis were not significant, probably due to the smaller sample size [35]. Kohat D et al., reported that, preterm newborns with absent/ reversed end diastolic flow (A/REDF) are significantly increased risk of death/ major NDD at one year of corrected age [36]. In the current study, also significant association was found with NDD and diastolic cut-off on foetal ultrasound.

Limitation(s)

The current study had small sample size and the follow-up was up to one year only. Similar study with bigger sample size and longer follow-up are recommended to validate the results of this study.

CONCLUSION(S)

Motor development of preterm babies improves with age but deficit in mental development persists. The INFANIB and DASII are comparable so far as the assessment of motor development of preterm babies are concerned.

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