

## Original Research Article

# Pattern of growth and neurodevelopmental outcome of preterm babies born $\leq 34$ weeks of gestation in a South Indian tertiary care hospital

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## ABSTRACT

**Background:** Advances in neonatal care since the early days have led to an increase of survival in preterm infants. Developmental sequelae, however are still a major problem mostly because babies who would previously have been expected to die are now surviving due to neonatal intensive care. There is scarcity of data regarding the outcome of prematurity from low and middle-income countries like India in literature.

**Methods:** 140 preterm babies born at or before 34 weeks of gestation were enrolled and followed up for 1 year. All babies were screened for retinopathy of prematurity and hearing impairment. Anthropometric measurements were taken at 40 weeks, 3 months, 6 months, 9 months and 12 months of corrected age. Neurodevelopmental assessment was done using the Bayley scales of infant and toddler development III at 1 year of age.

**Results:** Among 140 preterm babies, 6 babies expired before 1 year. Majority had catch up growth by 1 year of age. Growth and neurodevelopment were inversely proportional to birth weight and gestational age. Incidence of severe ROP requiring intervention was 8.6% and hearing aid was needed in 4%. At 1 year 24% had cognitive delay, 27% had language delay and 29% had motor delay. Intraventricular hemorrhage, culture proven sepsis, shock and DIC in newborn period were strong predictors of neurodevelopmental impairment.

**Conclusions:** Majority of preterm babies showed catch up growth and had good neuro developmental outcome at 1 year of corrected age.

**Keywords:** Bayley scales of infant and toddler development III, Growth, Hearing impairment, Neurodevelopment, Preterm, Retinopathy of prematurity

## INTRODUCTION

Advances in neonatal care since the early days have led to an increase of survival in preterm infants. Developmental sequelae, however, are still a major problem mostly because babies who would previously have been expected to die are now surviving neonatal intensive care. Follow up studies have shown that developmental problems increase with age. This makes long term follow up mandatory for timely identification of children in need of extra help. Most preterm infants have good neurodevelopmental outcome and cannot be

distinguished from term infants. But a few preterm babies however do develop important and lasting neurodevelopmental problems.

The period between 20-32 weeks after conception is one of rapid brain growth and development.<sup>1</sup> Illness, undernutrition and infection during this time may compromise neurodevelopment. The clinical consequences can include serious neuromotor problems principally cerebral palsy, visual and hearing impairments, learning difficulties, psychological, behavioural and social problems.

**METHODS**

140 preterm babies born at or <34 weeks of gestation discharged from the NICU of IMCH during the period January 2014 to July 2014 were recruited for this single group cohort study. Institute research ethics committee approved the study and informed consent was obtained from the parents. Gestational age was calculated from the expected date of confinement. They were followed up at 40 weeks, 3 months, 6 months, 9 months and 12 months of corrected age.

At each visit the anthropometric measurements, weight, length and head circumference were taken. Evaluation of vision was done by ROP screening and hearing evaluation was done with DPOAE (Distortion Product Oto Acoustic Emission). Bayley scales of infant and toddler development III was used to assess the neurodevelopment in three domains; cognitive, language (expressive and receptive) and motor (fine and gross) at the end of 1 year. Based on the score in each domain, the children were categorized into 4 groups (normal, mild, moderate and severe disability).

**Table 1: Bayley scales of infant and toddler development III.**

Category	Bayley scores
Normal	90 and above
Mild disability	80-89
Moderate disability	70-79
Severe disability	69 or less

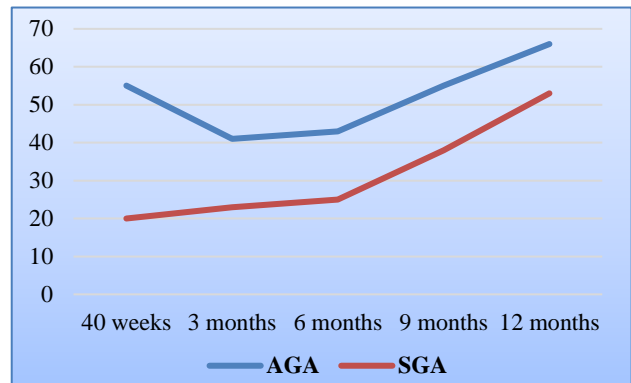
**RESULTS**

Of the 140 infants, 117 (84%) were followed up throughout the study. 17 were lost to follow up and 6 babies expired. Study characteristics included mean birth weight of 1550±350 g and mean gestation of 32±1.8 weeks. 58% were males and 42% were females. 70% of total babies were appropriate for gestational age and 30% were small for gestational age. 10 babies had birth weight less than 1000 g (ELBW). Smallest baby weighed 660 g and largest baby weighed 2270 g. 47% were between 33 and 34 weeks of gestation, 33% were between 31 and 32 weeks, 11% were between 29 and 30 weeks and 9% were below 28 weeks.

Common complications encountered in the new-born period were RDS (52%), NNHB (83%), hypoglycemia (21%), sepsis (12%), DIC (21%), AKI (6%), NEC (2%), PDA (7%), shock (6%), IVH (7%) and apnoea (5%).

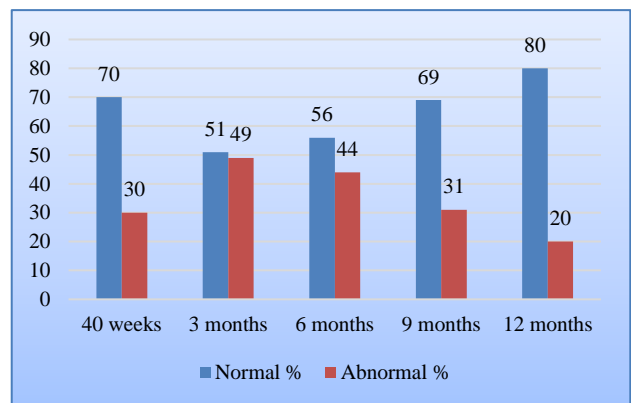
After discharging from the NICU, babies were followed up at 40 weeks, 3 months, 6 months, 9 months and 12 months of corrected age. During each visit anthropometric measurements (weight, height and head circumference) were taken. Catch-up growth was defined as reaching an SD score of more than 2 SDS of the

reference population (126). The proportion of preterm SGA babies who had achieved catch up growth at 40 weeks was only 20%, but as the age advanced more number of babies achieved catch up growth. It became 23% at 3 months, 25% at 6months, 38% at 9 months and 53% at 12 months. Among AGA babies 55% achieved catch up growth at 40 weeks. However, it was noticed that at 3 months, only 41% of babies met the criteria of catch up growth. Then there was a gradual increase to 43% at 6 months,55% at 9months and 66% at 12 months (Figure 1).



**Figure 1: Catch up growth in males and females.**

At each visit length was measured using infantometer with an accuracy of 0.1cm. Length below -2 SDS was taken as abnormal. Mean length at birth was 41.5±3.58 cm. At 12 months mean length was 72.58±3.4 cm. At 40 weeks 26% were below 2 SDS, then at 3 months it was 40%, at 6 months 36%, at 9 months 24 % and at 12 months 16% (Figure 2).



**Figure 2: Pattern of increase in length.**

Head circumference was measured using non-stretchable tape with an accuracy of 0.1cm at each visit and value less than -2 SDS from the reference median in WHO chart was taken as abnormal.

Mean head circumference at birth was 28.9±2.1 cm. At 12 months of corrected age it was 44±1.73 cm. At 40

weeks 6.4% had microcephaly at 3 months it was 11.4%, at 6 months 5.7% and 5% at 9 months and 12 months.

At the end of 1-year neurodevelopment was assessed using Bayley scales of Infant and Toddler development III. Seventy four percent of the cohort had a normal neurodevelopment.

The probability of being classified as abnormal neurologically increased steadily as birth weight decreased. Whereas 9% of infants with LBW had neurodevelopmental impairment, this increased to 35% in VLBW and 62 % in ELBW. Among extremely preterm babies 40% had neurodevelopmental impairment (Table 2).

**Table 2: Pattern and severity of neurodevelopmental impairment.**

Bayley III score	Cognition, n (%)	Motor, n (%)	Language, n (%)
90 and above	107(76.4%)	99(70.7%)	102(72.9%)
80-89	7(5%)	14(10%)	7(5%)
70-79	3(1.4%)	3(1.4%)	2(0.8%)
<70	1(0.7%)	1(0.7%)	6(4.3%)

Statistical evaluation was done to assess the association between immediate neonatal complications and neurodevelopmental impairment.

**Table 3: Risk factors for neurodevelopmental impairment.**

Variables	No. (%)	RR (95% CI)	P value
Male	17 (26%)	1.4 (0.7-2.9)	0.3
SGA	11 (31%)	1.7 (0.9-3.2)	0.2
Hypoglycemia	7 (29%)	1.4 (0.7-2.9)	0.4
IVH	5 (71%)	3.7 (2-6.7)	0.007
Apnoea	2 (50%)	2.3 (0.8-6.6)	0.2
Sepsis	6 (46%)	2.4 (1.2-4.8)	0.03
DIC	10 (44%)	2.5 (1.3-4.8)	0.007
Shock	4 (80%)	4 (2.5-7.1)	0.002
NEC	1 (33%)	1.5 (0.3-7.7)	0.7

Screening for retinopathy of prematurity was done in all babies and those who were having stage III ROP or more were subjected to laser photocoagulation or surgery. The number of babies who had severe ROP and required treatment were 12 (8.6%).

**ROP and gestational age**

Distortion Product Otoacoustic Emissions (DPOAE) was recorded in 119 children as part of hearing evaluation. Fifteen children had persistently failed test (13%). Among them 9 had undergone detailed evaluation with Brainstem Evoked Response Audiometry (BERA). Five

among them had abnormal BERA and were fitted with hearing aid (4.2%).

**DISCUSSION**

During follow up six babies expired before reaching 1<sup>st</sup> birthday. Stephens et al reported that survival remains directly proportional to gestational age and birth weight.<sup>1,2</sup> Same was observed in this study too. Mortality rate of LBW babies were 1.4% while in VLBW babies it was 5.5% and ELBW babies, it was 20%. Considering gestational age, mortality rate in extremely preterm babies was 25% which came down to 12.5% in very preterm babies and 1.5% in moderate preterm babies.

In this study maximum number of preterm births occurred following multiple pregnancy (44%). Other risk factors identified were PIH (22%), PPROM (16%) and APH (2%). 16% had unidentified cause for preterm birth. Studies conducted by Zeitlin et al and Blondel et al reported that multiple pregnancy is the major risk factor for preterm delivery.<sup>3,4</sup>

The proportion of preterm SGA babies who had achieved catch up growth at 40 weeks was only 20% where as it was 55% in AGA babies. Even then they showed a steady increase in growth as the age advanced, but they were behind AGA babies in catch up growth. According to Euser et al, similar to term infants born SGA, most preterm born infants (approximately 80%) show catch-up growth in weight, length and head circumference after initial postnatal growth failure, generally starting early in the first months of life and often achieved within the first 2 years of life.<sup>5</sup>

Considering gender and growth pattern, male babies were found to lag behind female babies in catch up growth. As the age advanced the percentage of females who attained catch up growth increased steadily, but there was an initial fall followed by an increase in rate of growth in males. Euser et al reported that male sex is negatively associated with early postnatal growth in preterm babies.<sup>5</sup>

**Table 4: Comparison of neurodevelopmental impairment in various studies.**

Study	Study population	Developmental test used	NDI (%)
Betty et al <sup>6</sup>	ELBW	BSID II	37%
Mukhopadhyay et al <sup>7</sup>	ELBW	DDST	25%
Setanen et al <sup>8</sup>	≤1500 g and ≤37 weeks	WPPSI I	22%
Present study	GA ≤34 weeks	BSID III	26%

Seventy four percent of the cohort had a normal neurodevelopment. According to Stephens et al rates of

disability generally increase with decreasing gestational age and birth weight.<sup>2</sup> In this study also the probability of being classified as abnormal neurologically increased steadily as birth weight decreased. Whereas 9% of infants with LBW had neurodevelopmental impairment, this increased to 35% in VLBW and 62% in ELBW. In a study conducted by Betty et al on ELBW babies, 37% had neurodevelopmental impairment.<sup>6</sup> They used the Bayley Scales of Infant Development II. The low incidence of disability in their study may be because they had reported only severe neurodevelopmental impairment. Among extremely preterm babies 40% had neurodevelopmental impairment (Table 4).

Statistical evaluation was done to assess the association between immediate neonatal complications and neurodevelopmental impairment.

It was found that 37% of babies who had respiratory distress syndrome, developed neurodevelopmental impairment and it was statistically significant (p value 0.03). In a study conducted by Athena et al 11% of babies with RDS had disability and 23% had developmental delay.<sup>9</sup>

In this study, 71% of babies with IVH had neurodevelopmental impairment where as it was only 19% in babies without IVH. Statistically significant difference occurred between the two groups (p value 0.001) and babies with IVH were found to have 3.7 times greater risk for developing disability compared to those without IVH [RR 3.673(95% CI 2.005-6.732)].

These findings add to the growing number of studies from different populations reporting similar concerns with IVH and neurodevelopment.

In a study conducted by Sreenivas et al on extremely preterm babies, those with grade III-IV intra ventricular hemorrhage had higher rates of developmental delay (17.5%), cerebral palsy (30%), deafness (8.6%), and blindness (2.2%). Grade I-II IVH infants also had increased rates of neurosensory impairment (22% vs 12.1%), developmental delay (7.8% versus 3.4%), cerebral palsy (10.4% versus 6.5%), and deafness (6.0% versus 2.3%) compared with the no IVH group.<sup>10</sup>

Patra and colleagues from United States, in an institutional study of extremely low birth weight infants born from 1992 to 2000, reported that the 104 infants with isolated IVH had a significantly lower mean mental developmental index (MDI) score than the 258 infants with a normal cranial ultrasound. They had significantly higher rates of low MDI <70 (45% versus 25%; OR 2.00), major neurologic abnormality (13% versus 5%; OR 2.60), and neurodevelopmental impairment (47% versus 28%; OR 1.83) at 20 months' corrected age, even when adjusting for confounding factors.<sup>11</sup> Similarly, another recent institutional study from Austria by Klebermass-Schrehof and colleagues showed abnormal

neurodevelopmental outcomes up to 5.5 years in preterm infants, 32 weeks' gestation with IVH.<sup>12</sup>

46% of babies with sepsis developed neuromotor impairment compared to 21% babies without sepsis. There was statistically significant difference between the two groups (0.03) and babies with sepsis had 2.4 times risk of developing disability compared to those without sepsis. RR: 2.354 [95% (CI) 1.161-4.771].

Luregn et al in a multicenter Swiss cohort study of 541 infants, 136 (25%) had proven sepsis, 169 (31%) had suspected sepsis, and 236 (44%) had no signs of infection. CP occurred in 14 of 136 (10%) infants with proven sepsis compared with 10 of 236 (4%) uninfected infants (odds ratio: 2.90 [95% (CI): 1.22-6.89]; P=.016). Neurodevelopmental impairment occurred in 46 of 134 (34%) infants with proven sepsis compared with 55 of 235 (23%) uninfected infants (OR:1.85 [95% CI: 1.12-3.05]; P = .016). Multivariable analysis confirmed that proven sepsis independently increased the risk of CP (OR: 3.23 [95% CI: 1.23-8.48]; P = 0.017) and neurodevelopmental impairment (OR: 1.69 [95% CI: 0.96-2.98]; P =.067). In contrast, suspected sepsis was not associated with neurodevelopmental outcome (P >0.05).<sup>13</sup>

Thirty-three percentage of babies having NEC in new-born period were disabled compared to 22% of those not having NEC. NEC in new-born period had 1.5 times risk for developing neurodevelopmental impairment in preterm babies (RR-1.493). But there was no statistically significant difference between the two groups (p value 0.7). In a study done by Amuchou et al 24% of infants with NEC had one major neurodevelopmental disability compared with 10% among control infants. Infants who developed NEC had significantly higher cognitive delay (i.e. cognitive index <70) and visual impairment.<sup>14</sup>

Shock (p value 0.002, RR: 4 [95% CI: 2.249-7.116]) and DIC (p value 0.007, RR : 2.5 [95%CI :1.312-4.763]) were also strong predictors of long term adverse neurodevelopmental outcome in the present study.

**Table 5: Incidence of severe ROP in various Indian studies.**

Study	Period	Birth weight and GA	Severe ROP incidence (%)
Varughese et al <sup>17</sup>	1999-2000	BW <1500 g and GA <34 weeks	6.3%
Jalali et al <sup>16</sup>	1999-2002	BW <2000 g and GA <36 weeks	11%
Hungi et al <sup>15</sup>	2008-2010	BW <2000 g and GA ≤34 weeks	10.2%
Present study	2014-2015	GA ≤34 weeks	8.6%



Screening for retinopathy of prematurity was done in all babies and those who were having stage III ROP or more were subjected to laser photocoagulation or surgery. The number of babies who had severe ROP and required treatment were 12 (8.6%).

In a study conducted by Hungi et al in southern India the incidence of severe ROP was 10.2% where as in two other studies, conducted by Jalali et al and Varughese et al the incidence of severe ROP were 11% and 6.3% respectively (Table 5).<sup>15-17</sup>

There was an inverse relationship between severe ROP and birth weight. No one in LBW group had severe ROP where as it became 13% in VLBW group and 40% in ELBW group.

As the gestational age came down, a steep increase in ROP was noted. In babies less than 28 weeks of gestation, incidence of severe ROP requiring intervention was as high as 43% whereas it came down to 5% in babies born at 31-32 weeks and no case of ROP was reported in 33-34 weeks of gestation. It was interesting to note that babies born at 29-30 weeks of gestation had the maximum incidence of ROP (54%).

This was probably because of increased survival rate in babies at 29-30 weeks of gestation compared to less than 28 weeks babies. But no one in the present study was blind at 1 year of age. This may be due to timely detection and treatment of severe ROP. There was statistically significant increase in severe ROP for babies who had RDS (p value 0.001).

**Table 6: Incidence of hearing impairment in various studies.**

Study	Study population	DPOAE	Hearing aid
Betty et al <sup>6</sup>	ELBW	11%	3%
DAE Roth et al <sup>18</sup>	VLBW	3%	0.3%
Present study	GA ≤34 weeks	13%	4.2%

Distortion Product Otoacoustic Emissions (DPOAE) was recorded in 119 children as part of hearing evaluation. Fifteen children had persistently failed test (13%). Among them 9 had undergone detailed evaluation with Brainstem Evoked Response Audiometry (BERA). Five among them had abnormal BERA and were fitted with hearing aid (4.2%). This was comparable with the study conducted by Betty et al where they reported 11% hearing impairment and requirement of hearing aid in 3%.<sup>6</sup> In another study conducted by DAE Roth et al hearing impairment was noted only in 3%.<sup>18</sup>

In the above mentioned study, DPOAE was found to be an effective first stage in-hospital screening tool for VLBW infants, with a pass rate of 87.2%.<sup>19</sup> Here the pass percentage was 82% (Table 6).

**CONCLUSION**

Majority of preterm babies showed catch up growth and had good neuro developmental outcome at 1 year of corrected age.

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