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Original article

Three-year growth trajectories and catch-up patterns in extremely low birth weight infants: a focus on early nutritional interventions

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Abstract. *Introduction:* Growth trajectories of preterm infants, particularly those with extremely low birth weight (ELBW) defined as less than 750 grams, are notably complex and highly variable. *Objective:* We tracked the growth patterns of 35 ELBW infants born in a tertiary care facility, fed with preterm formula for the first 3-6 months of life. *Results:* ELBW infants showed significant initial deficits in weight, length, and head circumference, yet demonstrated considerable catch-up growth over 3 years. The initial mean weight-for-age Z-score (WAZ) was - 8.70, a stark deviation from the median of the reference population. By 36 months, the WAZ improved to -1.24, although 25.7% of infants continued to be underweight. The length-for-age Z-score (LAZ) began at -9.95, indicative of a pronounced deficiency in length, but by the third year, it had markedly improved to -0.35, with 11.4% of infants still measuring below the norm. The weight-for-length Z-score (WLZ) was initially -19.41, suggesting acute malnutrition; however, it fluctuated and improved to -1.75 by 36 months, with 31.4% of the cohort still at risk for malnutrition. Head circumference-for-age Z-score (HCZ) showed an initial value of -9.52 and improved to -1.75 by 36 months, but recovery in head growth was slower, with 6 out of 35 infants remaining below the reference curve. *Conclusion:* Our findings reveal that ELBW infants exhibit significant improvements in WAZ, LAZ, WLZ, and HCZ over a period of three years, with most of the catch-up growth occurring within the first year, and LAZ continuing to improve into the third year. (www.actabiomedica.it)

Key words: extremely low birth weight, catch-up, length, weight, head circumference, infants

Introduction

Advancements in obstetrical and neonatal care have significantly improved survival rates for very low birth weight (VLBW) infants. Bertino et al. (1) evaluated and highlighted improvements in the postnatal growth of very low birth weight infants. Similarly, González-García et al. (2) observed growth improvements in VLBW preterm infants both during the neonatal period and at two years of age.

The postnatal growth of VLBW infants, especially those weighing less than 750 grams, presents a complex landscape influenced by multiple factors. While the majority of small-for-gestational-age (SGA) infants exhibit catch-up growth by 2 years of age, about 10% do not, as noted in studies by Saenger et al. (3), Lee et al. (4), and others (5-8). These infants who fail to catch up may remain short throughout childhood, with approximately 10% continuing to fall below the 3rd percentile of height into adulthood.

General postnatal growth patterns can be divided into three phases: infancy, childhood, and puberty. Failure to grow during any of these phases can reduce growth potential and eventually result in adult short stature. VLBW neonates may experience a compensatory growth spurt in infancy and childhood, but the timing of this growth spurt is not well described. Catch-up growth (CUG) in SGA infants mainly occurs from 6 months to 2 years, and about 85% of SGA children will have caught up by two years of age, according to Karlberg et al. (9) and Leger et al.(10). However, prematurely born babies who are SGA may take around four years to achieve CUG, as noted by Ong et al. (11).

On the other hand, a study in North India by Sinha et al. (12) compared SGA-LBW infants with AGA-LBW counterparts during the first six months and revealed higher stunting risks and lower growth metrics in SGA-LBW infants, with about 55% displaying CUG by six months. Prenatally, the Women First trial emphasized the importance of intrauterine growth for postnatal development, showing that preconception and early pregnancy nutritional supplementation significantly influences birth length and subsequent growth (13). Postnatally, insufficient protein and energy intake might account for a substantial portion of the postnatal growth restriction in these infants (14).

In addition to nutritional factors, different researchers present a diverse picture of postnatal growth in VLBW infants influenced by gestational age, environmental factors, and early stimulation (15,16). The implications of growth status at birth and postnatal growth for neurodevelopmental outcomes and the development of metabolic abnormalities later in life in VLBW infants are crucial areas of focus.

This diversity in postnatal growth patterns underscores the need for longitudinal studies to better understand the unique growth trajectories of VLBW infants.

The aim of this study is to evaluate the postnatal growth and weight gain in preterm babies with a birth weight of ≤ 750 grams born in a tertiary care center over three years.

Patients and methods

This study involved anthropometric measurements of 35 randomly selected infants born with a birth weight ≤ 750 grams. These infants were born between September 2016 and September 2018. The anthropometric data, expressed as z-scores, were collected at birth and at 2, 4, 6, 12, 18, 24, and 36 months of age. Among these infants, 32 were classified as appropriate for gestational age (AGA), based on Fenton growth curves, with an average gestational age of 22.5 ± 2.2 weeks (17). The mortality rate at birth for ELBW < 750 grams was 42.5 %.

The anthropometric data of these infants were compared to the standard growth benchmarks for normal age and sex, as outlined in the World Health Organization (WHO) growth standards. Importantly, this comparison was made without correction for gestational age. All preterm infants in the study received preterm formula for an average duration of 6 months.

"Our strategy for early nutritional intervention in infants born with a birth weight of ≤ 750 grams prioritizes the use of fortified human breast milk as the primary source of nutrition. This preference is due to the unique benefits of breast milk, which, when fortified, can better meet the specific needs of these infants. If fortified breast milk is unavailable, we provide a specialized preterm formula designed for the nutritional requirements of very low birth weight infants. For the initial week, a preterm formula with a lower nutrient concentration, known as 'preterm formula 22' which offers 22 calories per ounce, is recommended to accommodate the infant's maturing digestive system. Subsequently, we transition to a higher calorie formula, referred to as 'preterm formula 24,' providing 24 calories per ounce, and continue this for 3 to 6 months to promote proper weight gain and development. Regular monitoring and assessment of the infant's growth allow for timely adjustments to the feeding regimen as needed."

Statistical methods

Statistical analysis was performed using Excel statistical software. Descriptive statistics, such as mean and standard deviation, were used to summarize the anthropometric data. The growth trajectories of the infants were analyzed using a mixed-effects model to account for repeated measurements over time. This model allowed for the assessment of growth trends and the identification of significant deviations from the expected growth patterns.

Comparisons between the infants' growth data and WHO standards were conducted using independent t-tests or Mann-Whitney U tests, depending on the data distribution. The Shapiro-Wilk test was employed to assess the normality of data distribution.

To assess the impact of early nutrition (preterm formula) on growth outcomes, linear regression analysis was conducted, with adjustments made for potential confounders such as gestational age and sex. The association between gestational age and growth parameters was also evaluated using Pearson or Spearman correlation coefficients, as appropriate. A P-value of less than 0.05 was considered statistically significant.

Table 1. Postnatal growth data for infants born with ELBW (for 3 years).

	n = 35	WAZ	LAZ	WLZ	HCZ
Birth	Mean	-8.70	-9.95	-19.41	-9.52
	SD	0.35	2.22	1.92	3.98
2 mon	Mean	-8.84	-9.63	-5.09	-8.89
	SD	1.37	1.39	4.19	1.83
4 mon	Mean	-6.36	-7.43	0.13	-5.17
	SD	1.55	2.13	2.20	1.85
6 mon	Mean	-4.23	-5.69	-0.09	-3.56
	SD	1.58	2.13	1.65	1.66
12 mon	Mean	-2.08	-2.86	-0.44	-1.72
	SD	0.91	1.38	1.19	1.14
18 mon	Mean	-1.42	-1.73	-0.96	-1.34
	SD	1.08	1.12	0.96	0.98
24 mon	Mean	-1.38	-1.73	-0.82	-1.36
	SD	0.97	1.42	1.45	1.01
36 mon	Mean	-1.24	-0.35	-1.75	-1.25
	SD	1.28	1.61	1.06	0.9

Results

This study examined the postnatal growth trajectory of 35 infants with birth weights below the standard, measuring Weight-for-Age Z-score (WAZ), Length-for-Age Z-score (LAZ), Weight-for-Length Z-score (WLZ), and Head Circumference Z-score (HCZ) from birth to 36 months. (Table 1 and Figure 1)

WAZ

At birth, the mean WAZ was -8.70, indicating significant deviation from the median reference. Over the course of 36 months, there was a notable increment towards the reference median, with the mean WAZ improving to -1.24, although still indicative of underweight status in the population studied. At the end of the second and third year 8/35 (22.8%) and 9/35 (25.7 %) had WAZ < -2.

LAZ

The initial mean LAZ was -9.95, suggestive of substantial length deficit. A consistent improvement was observed, with the 36-month mean LAZ markedly higher at -0.35, nearing the reference median and indicating significant catch-up growth in stature. At the end of 3 years 4/53 (11.4%) had LAZ <-2.

WLZ

The mean WLZ began at -19.41, reflecting acute malnutrition. The score improved over time, crossing into positive territory at 4 months but regressed to -1.75 by 36 months, suggesting an ongoing risk of malnourishment. At the end of 2nd and third years 10/35 (28.6%) and 11/35 (31.4%) had WLZ < -2.

HCZ

The HCZ mean at birth was -9.52, denoting smaller head circumferences. There was a steady increase in HCZ, with a 36-month mean of -1.75, revealing a tendency to slower recovery in head growth compared to other measures. At the end of the 3rd year 6/35 (17.1%) had HCZ <-2.

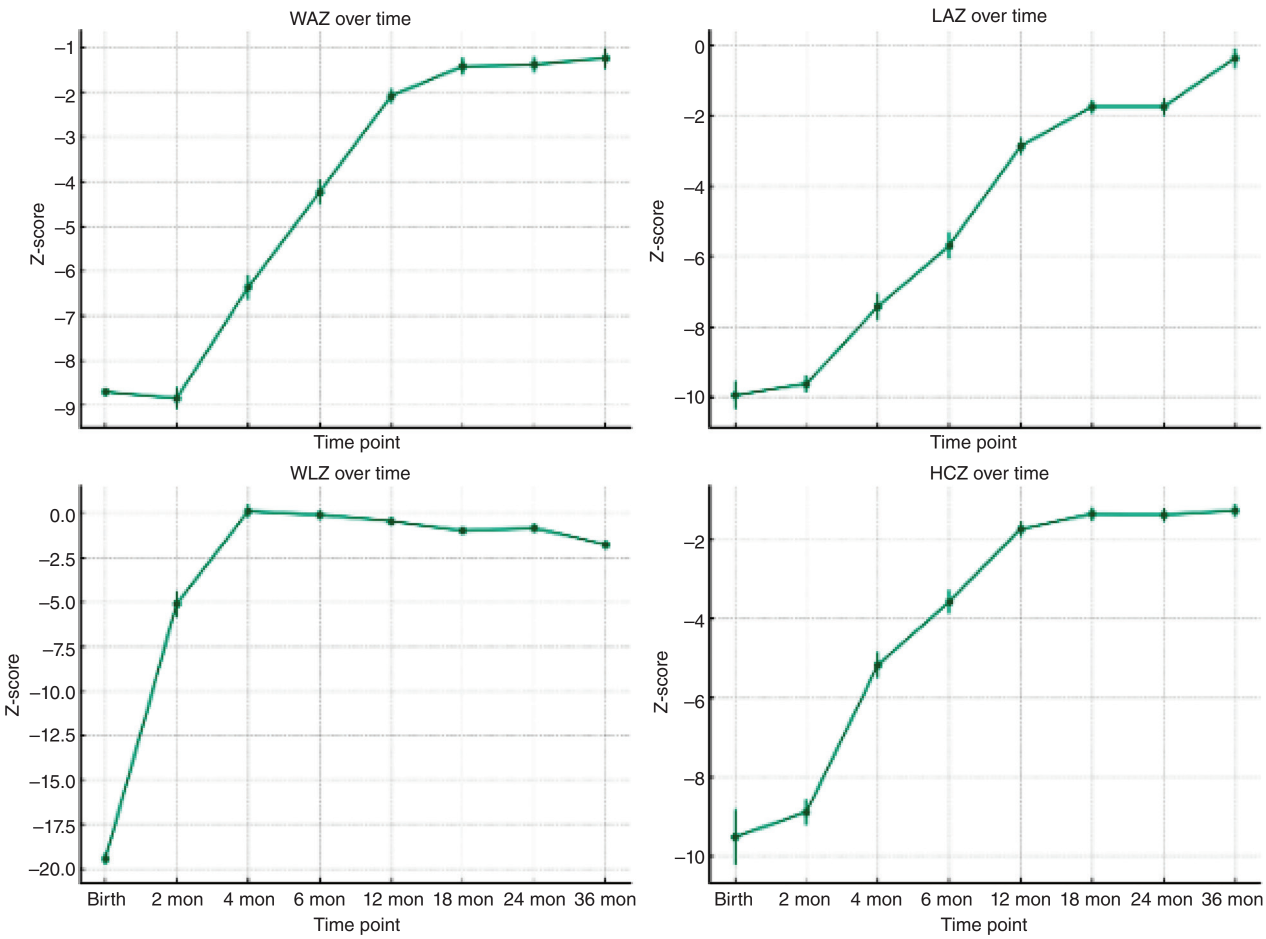

Figure 1. Postnatal growth from birth to 3 years, including WAZ (Weight-for-Age Z-score), LAZ (Length-for-Age Z-score), and HCZ (Head Circumference Z-score).

In summary: The infants in this cohort exhibited significant catch-up growth across all measured parameters. However, their growth parameters remained below the median of WHO child growth standards at 36 months. The standard deviations suggest variability in the rates of catch-up growth among the cohort, with notable dispersion in WLZ across the time points. These findings underscore the need for ongoing nutritional and developmental support for infants born below the standard weight.

(a) Birth WAZ was correlated significantly with LAZ and WAZ at 24 months (r = 0.66, P: <0.001 and r: 0.42, P: 0.04, respectively) (Figures 2 and 3); (b) WAZ at 6 months was correlated with WAZ and LAZ at 12 months (r = 0.65 and 0.49; P: <0.01) and with WAZ at 36 months (r = 0.54; P: <0.01); (c) Birth LAZ with LAZ at 24 months (r = 0.40; P: < 0.01 and (d) HCZ at birth was correlated significantly with LAZ and WAZ at 36 months (r = 0.67 and 0.35 respectively; P: < 0.01). These significant correlations pointed to the link between birth WAZ, LAZ and HCZ and the postnatal growth for 2 -3 years.

In summary, the correlations performed in our study disclosed the following:

a. Birth WAZ and growth metrics at 24 months: A significant positive correlation of 0.66 between birth WAZ and LAZ at 24 months suggests that infants with higher (or lower) weight for age at birth tend to have higher (or lower) length for age at 24 months. The correlation of 0.42 between birth WAZ and WAZ

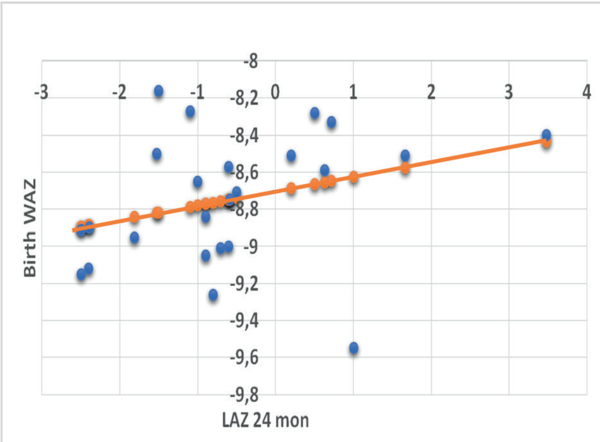

Figure 2. Correlation between birth WAZ and LAZ at 24 months (r:0.66, P: < 0.01).

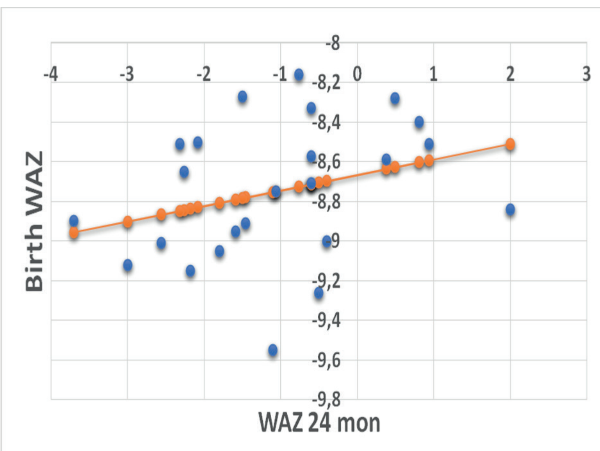

Figure 3. Correlation between WAZ at birth and at 24 months (r:0.42, P:0.04).

at 24 months, although lower than the correlation with LAZ, still indicates a moderate positive relationship, meaning infants with higher birth WAZ also tend to have higher WAZ at 24 months.

b. WAZ at 6 months and later growth: There was a strong positive correlation (r = 0.65) between WAZ at 6 months and WAZ at 12 months, suggesting that infants' relative weight for age at 6 months is a good predictor of their weight for age at 12 months. Similarly, the correlation of WAZ at 6 months with LAZ at 12 months (r = 0.49) indicates a moderate positive relationship. Moreover, WAZ at 6 months is moderately positively correlated with WAZ at 36 months (r = 0.54), indicating that weight for age at 6 months can predict weight for age three years later.

c. LAZ and LAZ at 24 months: A moderate positive correlation of 0.40 between birth LAZ and LAZ at 24 months suggests that longer or shorter babies at birth tend to maintain their length status relative to their peers at 24 months.

d. HCZ at birth and growth metrics at 36 months: A significant positive correlation of 0.67 between head circumference for age at birth (HCZ) and LAZ at 36 months indicates a strong relationship where infants with larger or smaller head circumferences relative to age at birth tend to have longer or shorter length for age at 36 months. Additionally, there's a positive correlation of 0.35 between HCZ at birth and WAZ at 36 months, although this is weaker than the correlation with LAZ. This suggests that head circumference at birth is a better predictor of length for age than weight for age at 36 months.

Discussion

Our data shows a trend of significant improvement in the Z-scores (WAZ, LAZ, and WLZ) for infants born with extremely low birth weight ≤ 750 g postnatally. Most of the catch-up in WAZ, LAZ and HCZ occurred during the first year of life, however gradual improvement in the three parameters occurred during the second year. LAZ continues to increase during the third year while WAZ and HCZ showed a plateau. In agreement with our data, Monset-Couchard and de Bethmann (17) observed catch-up growth in height, weight, and head circumference in SGA premature infants, with significant proportions achieving this before the age of three (18).

A study by Sinha et al. (12) North Indian SGA-LBW infants found a 55% catch-up growth in SGA-LBW infants by six months, with significant differences in growth trajectories of their LBW infants compared to AGA-LBW infants. They showed a general trend of catch-up in LAZ > 0.67 SD in 87% of their LBW infants at 6 months. A cohort study in Australia suggested that catch-up growth (defined by ≥ 0.67 SD change) is frequent in LBW infants and most of the catch-up growth is observed at approximately 4 months of age (19).

A systematic review that included 11 studies showed that 87% of the SGA children reported that 58% of the SGA infants achieved catch-up growth at 6 months age, while 69–82% infants showed catch-up by 1 year of age. However, they found that catch-up growth may occur later in life (ranging between 1 and 18 years). In our study LBW infants continue to catch up in LAZ during their 3rd year of life (20).

On the other hand, Durá-Travé et al. (20) found that 35% of their ELBW (<1,000 g) and only 7% of their VLBW infants (>1,000 g and < 1,500 g) remained short at 10 years of age. In support of our correlation between birth size and later growth, they reported that all VLBW children who had a normal height at ages 2, 4 and 10 years had exhibited adequate weight catch-up in first year of life. While Brandt et al. (21,22) found that only 46% of their VLBW SGA (21 of 46) had complete height catch-up by adult age. They reported that 59% of the SGA preterm infants showed complete HC catch-up growth by the age of 12 months, but mostly before 6 months In support of the relation between head size and height catch up, we found that HCZ at birth had significant correlation with LAZ and WAZ at 3 years, and Brandt et al. (21), found that infants who had early HC catch-up achieved height catch-up as well.

Darendeliler et al. (23), reported that 24.6% only of their preterm AGA infants had catch up when they assessed their growth at 4.7 years. In support of our correlation between birth LAZ and WAZ and 24 month LAZ and WAZ, they reported that catch up in height was best explained by birth length and catch up in weight by birth weight. In addition, Park et al. (24) reported that AGA-VLBW infant showed that in LBW -AGA infants, 53% were at the <10th percentile weight reference at 40-week post conception (PCA), and 21% PCA 24 months. 49% were at the <10th percentile height reference at PCA 40 weeks, and 13% at PCA 24 months (25).

It is worth mentioning that the accelerated linear growth in early infancy in the LBW infants appears to compensate for intrauterine growth restriction, and unfortunately, those infants not showing catch-up growth may be a high-risk group for short stature in adult life (26). Albertsson-Wikland et al. (26), reported that children born SGA who do not show postnatal catch-up growth in length at 2 years of age, have a higher risk of short stature (LAZ < -2 SD) in later life, with a relative risk at 18 years of age of 5.2 if born light. Moreover, Upadhyay et al. (27), found a significant association of LAZ and neurodevelopment score assessed by Bayley Scales of infant and toddler development (cognitive, motor and language scores) at 12 months of corrected age (N = 516).

Nutrition interventions appeared to be important for the degree of CUG. Krebs et al. (14) and Perumal et al. (28) highlight the importance of nutrition and appropriate growth standards. While the table does not specify nutritional interventions, the improvement in growth indices suggests that the infants may have received adequate nutrition postnatally, which is crucial for catch-up growth.

Our data reflect a positive trend in growth among AGA-ELBW infants, who were fed premature formula for the first 6 months of their postnatal life, which is consistent with outcomes reported in the literature where adequate postnatal care, nutrition, and stimulation contribute to substantial improvements in growth and development.

Conclusion

Infants born ELBW who were fed preterm formula for 4-6 months had significant fast postnatal growth pattern with normalization of their LAZ, WAZ and WLZ during the first 12 months of life. Slower and gradual catch-up in LAZ, WAZ and HCZ continues during the second year. Catch-up in LAZ continued during the third year of life. Correlation studies highlight the importance of early growth indicators in predicting future growth and can be crucial in developing early intervention programs for preterm infants to support optimal growth and development.

Ethics Approval: Not applicable

Conflict of Interest Statement: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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