Earlier achievement of full enteral feeding in extremely low birth weight neonates is not associated with growth improvement in the first 2 years of life

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Abstract

Limiting the number of days until achievement of full enteral feeding in extremely low birth weight neonates (ELBW; < 1000 g) might affect growth in the first years of life. This study compared the Z scores in growth over time of two cohorts of ELBW neonates that were comparable on maternal and neonatal characteristics and characteristics of hospitalization, but differed in enteral feeding strategy during neonatal admission. In the 2010–2014 cohort, full enteral feeding was achieved on average 16 days earlier than in the 2000–2005 cohort. In both cohorts, weight, height, and head circumference were recorded at birth and at the corrected ages of 9 and 24 months. A linear mixed model with repeated measures controlling for neonates small for gestational age showed no significant effect of different strategies in achievement of full enteral feeding on any anthropometric Z scores over time. Although full enteral feeding was achieved earlier in the 2010–2014 cohort, this was not associated with growth patterns during the first two years of life.

Conclusion: The effect of a change in strategy to achieve full enteral feeding at an earlier stage in ELBW neonates was assessed. Early enteral feeding strategies do not necessarily improve growth during the first two years of life.

What is Known:

- Feeding strategies during neonatal stay may affect growth in the first years of life.
- Strategies to achieve full enteral feeding earlier were implemented, but data on the impact on subsequent growth after discharge are limited.

What is New:

- Full enteral feeding was achieved earlier, but this was not associated with improved growth during the first 2 years of life after discharge.
- Early enteral feeding strategies do not necessarily improve growth during the first 2 years of life.

Keywords ELBW · Growth · Z score · Full enteral feeding

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Abbreviations

BPD	Broncho-pulmonary dysplasia
ELBW	Extremely low birth weight
GA	Gestational age
ICH	Intra-cerebral hemorrhage
LMM	Linear mixed model
NEC	Necrotizing enterocolitis
PREMATCH	PREMATurity as predictor of Children's cardiovascular and renal Health
PPROM	Premature preterm rupture of membranes
ROP	Retinopathy of prematurity
SD(S)	Standard deviation (score)
SGA	Small for gestational age
SIFT	Speed of increasing milk feeds trial

Introduction

Guidelines, practices, and concepts related to enteral feeding of preterm neonates evolved substantially over the last decades. Feeding strategies influence several short- and long-term health outcomes including the incidence of late onset nosocomial infection or necrotizing enterocolitis (NEC), as well as the time until full achievement of enteral feeding and growth patterns [1, 22]. Moreover, poor post-natal growth is associated with adverse neurocognitive outcomes, whereas rapid post-natal growth and catch up are supposedly harmful for future development of metabolic and cardiovascular diseases [15]. These effects are known as the “thrifty phenotype hypothesis.” In fact, those born with a reduced weight often are early overweight/obese subjects and are prone to develop the metabolic syndrome. That is possibly due both to their anxious mothers, who overfeed them to rapidly gain weight, as well as probably to alterations in these children metabolic pathways, which favors fat deposition, thus increasing also cardiovascular risk [13]. Another recent study on conservative vs progressive early enteral feeding strategies (enteral fasting vs trophic feeding, delayed vs earlier introduction, slower vs faster advancement) showed neither significant differences in NEC incidence nor in all-cause mortality; the authors however suggested that more data are needed to document the effects of early enteral feeding on the relevant outcome variables in former preterm neonates [22]. The speed of increasing milk feeds trial (SIFT) study aimed to compare a slower to a faster rate of increase in milk feeds (18 to 30 ml/kg/day). The primary outcome (i.e., survival without moderate or severe neurodevelopmental disability at 24 months) of this protocol stresses the need of post-discharge data in addition to short-term outcomes [1].

We recently reported on growth characteristics in a cohort (2000–2005) of extremely low birth weight (ELBW, < 1000 g) neonates up to the age of 11 years [17]. These ELBW neonates displayed extra-uterine growth restriction in height, weight, and head circumference at birth, 9 and

24 months (non-outlier mean *Z* score for height: -0.77 , -1.74 , -1.38 ; weight: -0.93 , -1.98 , -1.99 ; head circumference: -0.46 , -0.85 , -0.97). Compared to the 2000–2005 cohort, the neonatology department changed its feeding strategy from delayed to earlier initiation of enteral feeding with the intention to attain earlier full enteral feeding. This provided us with the opportunity to explore and compare growth patterns post-discharge in a more recently (2010–2014) admitted cohort of ELBW neonates compared to the cohort described earlier.

This study tests two hypotheses. First, we confirmed that both cohorts differ in strategy in days until enteral feeding. Second, we hypothesized that the different feeding strategies might affect growth in the first two years of life.

Materials and methods

Cohort description

This study compares two cohorts of extremely low birth weight neonates (ELBW; < 1000 g) all admitted in the University Hospitals of Leuven, Belgium. Data of the 2000–2005 cohort were part of the PREMATurity as predictor of Children's cardiovascular and renal Health (PREMATCH) study [16]. Similar data of the 2010–2014 cohort were also retrieved retrospectively. Of the 151 ELBW neonates born in the 2000–2005 cohort, 140 survived. Of the 171 ELBW neonates born in the 2010–2014 cohort, 142 survived. Figure 1 shows a flow-chart of survivors and follow-up-rates of both cohorts.

Cohort characteristics

The collected data included maternal and neonatal characteristics as well as characteristics of hospitalization. Maternal characteristics included tocolytics, betamethasone admission for long maturation, pre-eclampsia, and premature preterm rupture of membranes (PPROM).

Neonatal characteristics included gender, gestational age (GA), birth anthropometrics (weight, height, and head circumference), intubation, Apgar scores, and small for gestational age (SGA; Y/N). SGA was defined as birth weight below the 10th percentile on the growth charts of Flemish cohort of preterm neonates as published by the Study Center of Perinatal Epidemiology [12]. Anthropometrics were also collected at the corrected ages of 9 and 24 months (chronological age minus degree of prematurity).

Characteristics of hospitalization included the number of ventilation and oxygenation days, and the administration of post-natal steroids or ibuprofen (NSAIDs). Any intra-cerebral hemorrhage (ICH) was noted based on the available cerebral ultrasounds and it was checked whether the ophthalmoscopy showed a retinopathy of prematurity of stage 3 or above (ROP

Fig. 1 Flowchart of survivors and follow-up rates of the 2000–2005 and 2010–2014 extremely low birth weight neonates (ELBW; < 1000 g) born in the University Hospitals of Leuven, Belgium

≥ stage 3). Finally, the first day of full enteral feeding (either oral or nasogastric) was recorded.

Our neonatology department changed its feeding strategy from delayed to earlier initiation of enteral feeding. The former ELBW neonates of both cohorts were fed by parental or enteral route with a relatively low protein diet (2.8 g/kg/day) [4]. Although we cannot exclude that the micronutrients or actual nutritional intake differed slightly between the two cohorts (i.v. intake vs enteral intake), the intention to “treat” (feed) was comparable except for timing. This provided us with the opportunity to explore and compare growth patterns post-discharge in a more recently (2010–2014) admitted cohort of ELBW neonates compared to the cohort described earlier.

For this study, we included all cases with valid anthropometric measures on all three time points (birth, 9 and 24 months) and valid records on the days until enteral feeding (cohort 2000–2005 $n = 57$, cohort 2010–2014 $n = 91$). We tested for selection bias in included and non-included cases. No significant differences between both groups were found for the listed characteristics (see Supplementary Table S1) or the anthropometric measures (see Supplementary Table S2).¹

Statistics

First, the comparability of both cohorts on all characteristics except for days until enteral feeding was assessed by

comparing the mean scores or frequency distributions of maternal and neonatal characteristics and characteristics of hospitalization of the included cases in both cohorts. Outlier limits of covariates were set by extending the 25th and 75th percentile with 2.2 times the interquartile range [9, 10]. Missing values were considered random, since no variables had 5% missing values or more. Additionally, no discernable patterns of missing values could be detected in cases with 5% missing values or more ($n = 10$). Differences in means were assessed using a Mann-Whitney U test. Differences in frequency distributions between cohorts were tested using a contingency chi-square test.

The anthropometric data were measured at birth and the corrected ages of 9 and 24 months. Data were converted to Z scores using regionally validated growth charts [19]. Outlier limits for Z scores were set at $Z = |3.29|$. Differences in means were assessed using Student’s t test. For each cohort and for each time point, the assumption of normality was assessed using the Shapiro-Wilk test. In 5 out of 18 measures (2 cohorts $\times$ 3 measures $\times$ 3 time points), the null hypothesis was rejected. However, visual inspection of QQ-plots still allowed proceeding with parametric analysis of anthropometric data.

Next, a linear mixed model (LMM) with repeated measures was run to determine the effect of different strategies in days until enteral feeding over time on growth in weight, height, and head circumference. The LMM allows to test whether both cohorts differ in their anthropometric measures over time. The models control for the being SGA and any other characteristics for which both cohorts differ significantly. Both main effects and interaction effects with time are tested.

¹ The Z score for head circumference on 24 months is lower for the included cases in cohort 2010–2014 (mean $\pm$ SD, -0.97 ± 1.24 vs. -2.33 ± 1.57 , $P = 0.034$). However, only four of the non-included cases had valid measurements.

Results

Cohort comparison

Table 1 reports the absence of differences in the maternal and neonatal characteristics in both cohorts. The time until full enteral feeding was successfully shortened in the 2010–2014 cohort compared to the 2000–2005 cohort (23.9 days vs. 40.2 days, $P < 0.001$) (see also Fig. 2). Hospitalization characteristics revealed two more differences in both cohorts. A significant lower percentage of neonates in the 2010–2014 cohort received post-natal steroids (30.8% vs. 54.4%, $P = 0.004$). Furthermore, prevalence of any ICH was higher in the 2010–2014 cohort (36.3% vs. 17.5%, $P = 0.015$).

Table 2 shows that Z scores of anthropometric measures do not differ significantly between cohorts at any of the time points.

Days until full enteral feeding and growth

The LMMs reveal no significant effect between the anthropometric measures and post-natal steroids or ICH (data not shown). Consequently, these characteristics are not included in the final models. The final LLMs control for the main effect of time, cohort, and SGA, as well as for the two-way interaction effect of SGA and cohort, and the three-way interaction effect of SGA, cohort, and time (see Supplementary Table S3 for full model statistics). Z scores of all anthropometric measures vary over time. The main effect of time shows that there is a statistically significant difference in weight between time points ($F = 16.59$, $P < 0.001$), in height between time points ($F = 44.66$, $P < 0.001$), and in head circumference between time points ($F = 6.76$, $P = 0.002$) *within* cohorts. However, the variation in Z scores for all anthropometric measures over time does not differ between both cohorts. This is evidenced

Table 1 Comparison of maternal and neonatal characteristics and characteristics of hospitalization of included extremely low birth weight neonates (ELBW; < 1000 g) born in the University Hospitals of Leuven, Belgium in the 2000–2005 and 2010–2014 cohorts

	Included ELBW neonates ^a				
	2000–2005 (<i>n</i> = 57)		2010–2014 (<i>n</i> = 91)		<i>P</i>
Maternal characteristics					
Factors	Valid %	<i>n</i>	Valid %	<i>n</i>	
Tocolytics	29.8	17	39.6	36	0.23
Prenatal steroids	85.7	48	90.1	82	0.42
Pre-eclampsia	26.3	15	28.6	26	0.77
Premature rupture of membranes	23.6	13	36.3	33	0.11
Neonatal characteristics					
Covariates	<i>m</i> ± SD (med)	<i>n</i>	<i>m</i> ± SD (med)	<i>n</i>	
Gestational age (weeks)	27.4 ± 1.8 (27.0)	57	27.0 ± 2.0 (27.0)	91	0.13
Birth weight (g)	797.8 ± 127.3 (810.0)	57	806.4 ± 142.0 (815.0)	91	0.67
Factors	Valid %	<i>n</i>	Valid %	<i>n</i>	
Sex (girls/boys)	30/27	57	48/43	91	0.99
Intubation at birth	70.2	40	69.2	63	0.90
Small for gestational age	33.3	19	28.6	26	0.54
Characteristics of hospitalization					
Covariates	<i>m</i> ± SD (med)	<i>n</i>	<i>m</i> ± SD (med)	<i>n</i>	
Any oxygen need (days)	40.1 ± 30.7 (37.0)	52	45.9 ± 38.3 (41.0)	91	0.69
Ventilation days	11.9 ± 12.5 (7.0)	56	14.5 ± 17.2 (8.0)	90	0.92
Days to full enteral feeding	40.2 ± 19.6 (37.0)	57	23.90 ± 12.1 (21.0)	91	< 0.001
Factors	Valid %	<i>n</i>	Valid %	<i>n</i>	
Post-natal steroids	54.4	31	30.8	28	0.004
Ibuprofen use	47.4	27	48.4	44	0.91
Any intra-cerebral hemorrhage	17.5	10	36.3	33	0.015
Retinopathy of prematurity, any stage	17.5	10	27.8	25	0.16
Retinopathy of prematurity > stage 3	17.5	10	19.3	17	0.79

Legend: m = mean, SD = standard deviation, med = median, P = asymptotic two-sided significance of Pearson chi-square test for factors and of Mann-Whitney U test for covariates

^a Selection: at least for one anthropometric indicator valid measure at all three points in time and valid measures for days to full enteral feeding

Fig. 2 Boxplot of time to full enteral feeding of the included 2000–2005 and 2010–2014 extremely low birth weight neonates (ELBW; < 1000 g) born in the University Hospitals of Leuven, Belgium

by the absence of statistically significant interactions between different strategies in days until enteral feeding *between* cohorts on weight over time ($F = 0.63$, $P = 0.53$), on height over time ($F = 1.07$, $P = 0.35$), or on head circumference over time ($F = 1.59$, $P = 0.21$) (see Fig. 3).

Discussion

We investigated two hypotheses in this study. First, we investigated if both cohorts differed mainly and significantly on the strategy in days until enteral feeding and not or only marginal

on other characteristics. Second, we tested if there was any effect of different strategy in days until enteral feeding on growth in the first two years of life. The main difference between the 2000–2005 and 2010–2014 cohorts of extremely low birth weight neonates (ELBW; < 1000 g) born in the University Hospitals of Leuven, Belgium was indeed the number of days until full enteral feeding was achieved. The 2000–2005 cohort averaged 40 days, whereas the 2010–2014 cohort averaged 24 days. This confirmed our intention to shorten the time until achievement of full enteral feeding.

There were hardly any other differences in maternal and neonatal characteristics and characteristics of hospitalization between the 2000–2005 and 2010–2014 cohort. The only significant differences were administration of post-natal steroids (higher in 2000–2005 cohort) and prevalence of any ICH (higher in 2010–2014 cohort). However, these differences did not affect growth up to the age of 2 years in our study. In our opinion, a strategy with focus on all the different time intervals of post-natal nutrition (parenteral, enteral, oral, post-discharge) is needed to influence medium term growth outcomes. Only change in short-term feeding practices (faster switch from parenteral to enteral) was studied in the present study.

Goisbault et al. have shown improved neonatal length growth with shorter parental nutrition duration, but this could not be extrapolated to a later age [8]. However, there was a positive correlation between height at 2 years and neonatal length growth. Other factors that could contribute to a slower neonatal length growth include lower GA, broncho-pulmonary dysplasia (BPD), ibuprofen use, and a higher length Z score at birth [8].

Table 2 Comparison of arithmetic mean non-outlier Z scores of weight, height, and head circumference over time of included extremely low birth weight neonates (ELBW; < 1000 g) born in the University Hospitals of Leuven, Belgium in the 2000–2005 and 2010–2014 cohorts

	Included ELBW neonates ^a		<i>P</i>
	2000–2005 (<i>n</i> = 57)	2010–2014 (<i>n</i> = 91)	
Z score weight	<i>m</i> ± SD (med)	<i>m</i> ± SD (med)	
Birth	−0.88 ± 0.84 (−1.00)	−0.68 ± 0.94 (−0.70)	0.19
9 months	−1.73 ± 0.88 (−1.77)	−1.46 ± 1.16 (−1.74)	0.16
24 months	1.68 ± 0.94 (−1.79)	−1.57 ± 1.10 (−1.67)	0.55
Z score height	<i>m</i> ± SD (med)	<i>m</i> ± SD (med)	
Birth	−0.67 ± 0.80 (−0.67)	−0.58 ± 1.06 (−0.67)	0.55
9 months	−1.72 ± 1.06 (−1.75)	−1.79 ± 1.23 (−1.74)	0.72
24 months	−1.25 ± 1.01 (−0.93)	−1.50 ± 1.07 (−1.47)	0.15
Z score head circumference	<i>m</i> ± SD (med)	<i>m</i> ± SD (med)	
Birth	−0.45 ± 0.72 (−0.43)	−0.34 ± 0.87 (−0.33)	0.43
9 months	−0.83 ± 1.19 (−0.69)	−0.86 ± 1.29 (−1.01)	0.87
24 months	−0.78 ± 1.17 (−0.88)	−0.97 ± 1.24 (−0.92)	0.36

Legend: *m* = mean, SD = standard deviation, med = median, *P* = two-tailed significance of Student's *t* test with correction of degrees of freedom in case equal variance were not assumed based on Levene's test

^a Selection: at least for one anthropometric indicator valid measure at all three points in time and valid measures for days to full enteral feeding

Fig. 3 Estimated marginal means of **a** weight, **b** height, and **c** head circumference over time of the included 2000–2005 and 2010–2014 extremely low birth weight neonates (ELBW; < 1000 g) born in the University Hospitals of Leuven, Belgium

The way early nutrition affects growth patterns in ELBW children is still rather unclear. Early aggressive nutrition has a

significant correlation with cognitive development at 18 months and 3 years, head circumference at 3 years [14], and post-natal

growth [5]. However, it does not seem to have an effect on weight or height at 3 years [14]. Different feeding strategies were suggested in literature; higher caloric intake has a significant positive correlation with post-natal growth [6]. Extra-uterine growth restriction and the time to regain birth weight are both positively affected by rapid advancement of enteral feeding [11]. Early catch-up growth can be promoted by initiating oropharyngeal colostrum in the first 2 post-natal days [20]. Catch-up growth from discharge to 6 months is correlated to a higher average protein intake, where the average energy, carbohydrate, and lipid intake do not correlate with the catch-up growth [21]. Weight at 12 and 24 months was not significantly improved by early and high amino acid supplementation, and surprisingly, it had a slightly negative effect [2]. The advantage of exclusive human milk above bovine milk-based feedings for growth or neurodevelopment has not been proven [3].

An abundance of other factors may have an effect on the growth patterns of ELBW-born children, given they undergo many procedures and may attract multiple complications during their stay at the neonatal intensive care unit. Table 1 shows some significant differences; less use of post-natal corticosteroids, and a higher number of intra-ventricular hemorrhage. Interestingly, neither antenatal or post-natal corticosteroids, GA, birth weight Z scores, BPD, nor periventricular leukomalacia seems to affect adult height [18], although many of these factors have shown to affect post-natal growth and catch-up growth. A height at 5 years below -2 SD will result in an SDS of -2.5 in growth restraint preterm children [7].

The present study should be interpreted within its limitations and relate to its retrospective design. Firstly, we cannot exclude that the micronutrients or actual nutritional intake in terms of macronutrients differed slightly between the two cohorts. Moreover, the cohorts are a decade apart from each other and other practices might have been changed over time. However, the intention to “treat or feed” was comparable except for timing. Secondly, the numbers of included infants are relatively limited and there was no randomization. Therefore, we cannot fully exclude inclusion bias. However, we used the same inclusion strategy for both cohorts. Thirdly, we did not include short-term growth data. More specifically, weight loss during the first weeks of life could seriously affect long-term growth. Nevertheless, the cohorts were comparable regarding biometric data, both at birth as well as at 2 years. Lastly, we cannot confirm other potential benefits from earlier enteral feeding. For example, it might be that infection rates are lower. In addition, the mortality rates in the second cohort were substantially higher (Fig. 1), which might indicate a difference in disease severity as well as the relative high number of post-natal steroid use. However, our study did neither have the intention nor the power to include these potential effects. Nevertheless, early enteral feeding might have additional benefits like lower costs and lower infection risks, but was not associated with differences in growth patterns in the first 2 years of life.

To conclude, comparing the Z scores of weight, height, and head circumference as being administered at birth and the corrected ages of 9 and 24 months in both cohorts allows assessing the effect of a change in strategy to achieve full enteral feeding at an earlier stage in ELBW neonates. No such effect has been found. We cannot exclude that the micronutrients or actual nutritional intake differed slightly between the two cohorts; the intention to “treat”/feed was comparable except for timing. Longitudinal studies are needed to examine whether there is a long-term effect on growth of early full enteral feeding and whether there are other additional benefits.

Authors' contributions K.A. and A.R. designed the study. C.B. and A.R. collected data. T.P.v.T. analysed the data, C.B., T.P.v.T., and A.R. interpreted the data and drafted the article. M.R. and K.A. provided critical revision or the paper. All authors approved the final version of the manuscript.

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Compliance with ethical statements

Conflicts of interest The authors declare that there are no conflicts of interest.

Ethical approval/informed consent The study was conducted in accordance with the Helsinki declaration for investigations in human subjects. The local Ethics Committee of the University Hospitals Leuven (Belgium) approved the study protocol. Parents gave informed consent prior to the PREMATCH studies.

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