1

Head circumference growth among extremely preterm infants in Denmark has improved during the past two decades

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ABSTRACT

INTRODUCTION: Treatment of extremely preterm and low birth weight infants is still evolving and improving. In this study, we evaluated if growth has improved from birth to two years of corrected age (CA) among extremely low birth weight (BW) and preterm born infants in Denmark. **METHODS:** This was an observational study with comparison of head circumference (HC), weight and length growth in two Danish cohorts of extremely preterm (gestational age (GA) < 28 weeks) and extremely low birth weight (ELBW with a BW < 1,000 g) infants (A: 1994-1995 and B: 2004-2008).

RESULTS: Infants in cohort A (n = 198) and B (n = 64) had a median GA and BW of 27 + 2 weeks and 948 g in A, and 27 + 3 weeks and 934 g in B. At discharge, infants in B compared with A had increased more in HC (p = 0.000), length (p = 0.008) and weight (p = 0.000). At two years CA, HC was still significantly larger in cohort B than A (p = 0.03), while no significant difference was recorded for length or weight. **CONCLUSION:** Growth during hospitalisation seems to have improved among extremely preterm and low birth weight infants from 1994-1995 to 2004-2008. This may be a result of improved nutrition in combination with improved intensive care during hospitalisation.

TRIAL REGISTRATION: For the 1994-1995 study, all eight regional Research Ethics Committees in Denmark at that time approved the study. The 2004-2008 study was approved by the Danish National Committee on Biomedical Research Ethics, and handling of data and registrations were approved by the Danish Data Protection Agency.
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The treatment of very preterm infants (gestational age (GA) < 32 weeks) during the neonatal period has improved significantly during past decades, and great improvements in survival rates have been achieved. However, during the last trimester of pregnancy, the brain of the foetus develops rapidly. A major concern in the very preterm infant is therefore impaired brain development during this period of life since this has implications for neurodevelopmental outcomes. Thus, a major challenge in the neonatal intensive care units (NICUs) is to improve brain development, and one area of intervention is optimisation of nutrition and growth. This was demonstrated in a large multicentre, prospective cohort study from 1994-1995, published in 1999 by Ehrenkranz et al. This study found postnatal growth failure or extra-uterine growth restriction among 1,660 infants with a birth weight (BW) between 501 and 1,500 g. At discharge, most infants born between 24 and 29 weeks of gestation had not achieved the median birth weight of the reference foetus at the same post-menstrual age (PMA) [1]. A subset of the cohort was followed and evaluated at the age of 18-22 months' corrected age (CA). The study found a strong correlation between an increase in head circumference (HC) growth and improved neurodevelopmental outcome, which suggests, that growth velocity during hospitalisation of extremely low birth weight (ELBW) infants possibly exerts an independent effect on neurodevelopmental and growth outcomes in early childhood [2].

The growth curves demonstrating postnatal growth restriction by Ehrenkranz et al in 1999 [1] have been referred to and reprinted several times during the past decade, including in very recent papers reviewing nutrition and growth for very low birth weight (VLBW) infants [3-5]. The papers all conclude that extrauterine growth restriction or growth failure is correlated with impaired neurocognitive outcome, and they all recommend early aggressive nutrition, particularly with protein.

In 2010, the European Society on Paediatric Gastroenterology, Hepatology and Nutrition committee recommended: "The major goal of enteral nutrition for preterm infants is to achieve growth similar to foetal growth coupled with a satisfactory functional development" and "the preferred nutrition for preterm infants is fortified human milk or alternatively special designed preterm formula" [6]. A Cochrane review from 2013 based on two small trials reported no statistically significant effect on neurodevelopment outcome from adding a multinutrient fortifier to human milk post discharge for preterm infants [7].

ORIGINAL ARTICLE

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TABLE 1

Cohort A (1994-1995) and cohort B (2004-2008) for comparison of growth from birth to two years of corrected age.

	Cohort A	Cohort B	A vs B		
Infants, n	198	64	-		
GA, days, median (minmax.); weeks + days	191 (170-224); 27 + 2	191.5 (169-213); 27 + 3	n.s.		
BW, g, median (minmax.)	948 (557-1,400)	934 (535-1,221)	n.s.		
SGA infants, n (%)	53 (26.8)	17 (26.6)	n.s.		
Received fortification during hospitalisation, n (%)	127 (64)	64 (100)	-		
Nutrition at discharge	Nutrition unknown	All infants breastfed	-		
BW = birth weight; GA = gestational age; n.s. = non-significant; SGA = small for gestational age.					

The aim of this study was to investigate if growth (gain in weight, length and HC) has improved among extremely preterm infants (GA < 28 weeks) or ELBW infants (BW < 1,000 g) from 1994-1995 to 2004-2008 by comparing growth in two Danish cohorts from birth to two years of age.

METHODS

Comparison of growth in two cohorts *Cohort A*

The infants born in 1994-1995 composed a national cohort of extremely preterm infants with GA < 28 + 0 weeks and/or ELBW infants with BW < 1,000 g treated at one of the 18 neonatal units in Denmark. The infants formed part of a national Danish observational study evaluating the approach of treatment with early nasal continuous positive airway pressure, and the infants were followed until two years of age at the local outpatient clinics [8]. Available for this study were data on nutrition with fortification of breast milk during hospitalisation and anthropometric data (weight, length and HC) at birth, discharge, five, 12 and 24 months of CA.

Post discharge nutrition was not registered in the 1994-1995 cohort, but data on growth from all the included extremely preterm and/or ELBW infants were used in this study.

Cohort B

The infants born in 2004-2008 formed part of a prospective, randomised and controlled birth cohort trial (RCT) on infants with a GA \leq 32 + 0 weeks, recruited consecutively from four neonatal units in Denmark (Odense, Aarhus, Holbaek and Kolding) from July 2004 to August 2008 [9]. The infants were seen at the outpatient clinics at term, two, four, six, 12 and 24 months of CA. To make the cohorts similar, only infants who were extremely preterm and/or ELBW participated from cohort B in the present study. Data on nutrition and anthropometric data (weight, length and HC) at birth, during hospitalisation, at discharge and during follow up were available for the present study.

During both study periods, HC (occipital-frontal) was obtained using a measuring tape during hospitalisation and post discharge. Length (crown-heel) was obtained using a measuring tape during hospitalisation and post discharge using a measuring rod or stapediometer (the infant lying until one year of age). During hospitalisation, weight was obtained using the same weighing machine for each child and post discharge using the same type of weighing machines at the outpatient clinics.

To optimise the comparison in the present study, we excluded infants from both cohorts with severe diseases that could possibly influence their eating- and feeding-ability at discharge; necrotising enterocolitis (NEC), bronchopulmonary dysplasia (BPD), intraventricular haemorrhage stage 3-4 (IVH) and periventricular leukomalacia (PVL).

The number of breastfed and formula-fed infants at discharge was unknown in cohort A, while 65% were breastfed and 35% were fed with a nutrient-enriched preterm formula at discharge in the original cohort from 2004-2008 [9]. Since it has been shown, that feeding preterm infants a nutrient-enriched formula after hospitalisation, improves growth among VLBW preterm infants compared with breastfeeding and feeding a term formula [10], infants fed a nutrient enriched formula (only in cohort B) have been excluded from this study. In the present study, only breastfed infants in cohort B participated for comparison with cohort A, because the infants in A were either breastfed or fed a term formula post discharge.

Ethics

For the 1994-1995 study, all eight regional Research Ethics Committees in Denmark at that time approved the study, and all families from whom outcome was reported gave written informed consent to the assessment [8]. The 2004-2008 study was approved on 1 July 2004 by the Danish National Committee on Biomedical Research Ethics (R. No. VF20030208) and handling of data and registrations were approved in February 2006 by the Danish Data Protection Agency (R. No. 2007-41-1349). Informed consent was obtained from the parents after oral and written information [9].

Statistical analyses

Data were analysed using STATA (version 11). For comparison of group A and B, the t-test was used for continuous variables and the chi-squared test for categorical variables. A multiple logistic regression model was used for comparison of growth between the cohorts. The explanatory variables in the model were sex, multiple birth, small for gestational age (SGA) and type of nutrition.

To compare the cohorts for outcomes on growth (weight, length and HC, respectively), Z-scores (standard deviation scores (SDS)) were calculated as the difference between the actual growth and the expected reference growth divided by one standard deviation (e.g. BW–ref. BW)/1 SD) for each gender separately. SGA was defined as a BW Z-score below –2 SDS. All Z-scores were calculated with Niklasson & Albertsson-Wikland [11] as the reference. By linear interpolation, weight, length and HC were estimated at PMA day 238 (34 weeks), day 252 (36 weeks) and at two, four, six, 12 and 24 months of CA as a basis for Z-score calculation. Change in Z-score (delta Z-score) was calculated from birth until day 252 (36 weeks), four, six, 12 and 24 months of CA, respectively.

Trial registration: For the 1994-1995 study, all eight regional Research Ethics Committees in Denmark at that time approved the study. The 2004-2008 study was approved by the Danish National Committee on Biomedical Research Ethics, and handling of data and registrations were approved by the Danish Data Protection Agency.

RESULTS

Cohort A

From the original cohort of 269 infants who survived until discharge, data on nutrition during hospitalisation and growth were available for 264 infants. Due to NEC, BPD, IVH 3-4 or PVL, 66 infants were excluded which left 198 infants for comparison in the present study.

Cohort B

From the original cohort of 320 very preterm infants with GA < 32 weeks, 98 infants were either extremely preterm and/or ELBW. Sixty-four of these infants were breastfed at discharge.

For comparison of growth from birth to two years CA, description and comparison of cohort A and B are shown in **Table 1**.

At discharge, infants in cohort B had improved more in HC (p = 0.000), length (p = 0.000) and weight (p = 0.000) than cohort A. At four months of CA, infants in B were still larger in HC (p = 0.000), length (p = 0.046) and weight (p = 0.01) than infants in A. At 12 months of CA, infants in B were heavier (p = 0.008) and had a larger HC (p = 0.02), but there was no difference with regard to length. At 24 months of CA, infants in cohort B still had a larger HC (p = 0.03), but no differences with regard to length or weight were detected. Comparison of growth from birth to two years of CA is illustrated in **Figure 1** and **Table 2**.

DISCUSSION

In this observational study, data indicate that growth in weight, length and HC during hospitalisation improved among extremely preterm and low birth weight infants in Denmark from 1994 to 2004. Head circumference growth, in particular, seems to have improved, and the improvement seems to be upheld until two years of corrected age, at least.

We are aware that our comparison has limitations. The observed differences, especially in HC growth, could be a result of bias. It is known that preterm birth often results in brain tissue alterations with white matter injuries that appear to be associated with neurodevelopmental deficits in early childhood. Risk factors described to induce changes in brain tissue volumes include use of postnatal corticosteroids, PVL, IVH, BPD, surgery and growth restriction [12]. We did not have data on infection (early or late), days treated on ventilator, use of postnatal corticosteroids or other variables indicating severe diseases during hospitalisation. We tried to optimise the comparison by excluding infants with some of the well-defined morbidities (NEC, BPD, PVL and severe IVH) and we included only infants with similar GA and BW in the study.

Data on nutrition from the 1994-1995 cohort were very limited and it is therefore difficult to conclude that the improved growth is a result of an improved nutritional strategy ten years later. Furthermore, and unfortunately we do not have data on the use of parenteral nutrition in the two cohorts. However, we still find it interesting that especially the HC growth was better in the 2004-2008 cohort and that the difference persisted at the age of two years, and we speculate that improved nutrition owing to a change in nutritional strategy may be a contributing factor.

Human milk is recommended for all infants, including preterm infants. The protein content in human milk decreases within the first months after birth [13], and feeding solely human milk may therefore lead to an insufficient intake of protein and energy. Protein and

ABBREVIATIONS

AGA = appropriate for gestational age, BW Z-score between -2 and +2 SDS according to a reference BW = birth weight, g CA = corrected age (weeks, months or years after term) Catch-up growth = a period of accelerated growth greater than expected for the age in question following a period of growth restriction ELBW = extremely low BW (< 1,000 g) GA = gestational age at birth, weeks + days HC = head circumference, cm PMA = post-menstrual age, GA + weeks and/or, days since birth SGA = small for gestational age, BW Z-score ≤ -2 SDS according to a reference

FIGURE 1

Comparison of growth between cohort A (1994-1995) and cohort B (2004-2008) illustrated with Z-scores and delta Z-scores.



HC = head circumference; SDS = standard deviation score.

energy supplementation has been demonstrated to be associated with improved rates of weight gain and nitrogen balance, and increments in length and HC [14-16]. To improve the protein and energy content of human milk for preterm infants, commercially available cow's milk based human milk fortifiers (HMF) have been used for almost 30 years. In Denmark, fortifiers were introduced in the NICUs in the 1990s, but their use was limited, which our data also indicate with only 64% of the 1994-1995 cohort receiving HMF.

TABLE 2

Delta Z-scores: differences in Z-scores between cohort A (1994-1995) and cohort B (2004-2008).

	Weight (p-value)	Length (p-value)	HC (p-value)	
Discharge				
(36th week PMA)	0.5 (0.000)	0.8 (0.000)	1.0 (0.000)	
4 months of CA	0.4 (0.01)	0.5 (0.046)	1.0 (0.000)	
6 months of CA	0.6 (0.001)	0.2 (n.s.)	0.5 (0.04)	
12 months of CA	0.5 (0.008)	0.2 (n.s.)	0.5 (0.02)	
24 months of CA	0.2 (n.s.)	–0.1 (n.s.)	0.6 (0.03)	
CA = corrected age; HC = head circumference; n.s. = non-significant;				

CA = corrected age; HC = head circumference; n.s. = non-significan PMA = post-menstrual age. The increased use of human milk fortifiers during hospitalisation may be part of the explanation why we observed improved HC growth, in particular among the extremely preterm and ELBW infants in the 2004-2008 cohort compared with the infants in the 1994-1995 cohort. The nutritional strategy with fortification of breast milk used in 2008 is still recommended in Danish Paediatric Society.

Follow-up studies have demonstrated a close positive correlation between HC catch-up growth and neurodevelopment outcome; and even more convincingly, this was demonstrated in a study among both term and preterm born infants with brain injuries [17].

Infants in the 2004-2008 cohort also seem to have achieved normal weight and HC for their age prior to hospital discharge. Since catch-up growth in both weight and HC seems to have been achieved before hospital discharge among extremely preterm and ELBW infants, the question is if further protein supplementation (fortification of human milk, preterm or post discharge formula) after hospital discharge is necessary. Feeding a nutrient- enriched formula compared with a term formula for preterm infants post discharge has demonstrated improvement in growth, but not on neurodevelopment outcome [10, 18]. Fortified human milk compared with unfortified human milk after hospital discharge was evaluated in two randomised controlled trials [9, 19, 20] and in a Cochrane review in 2013. The review concluded that the available data are limited and do not provide convincing evidence that feeding preterm infants with multi-nutrient fortified breast milk compared with unfortified breast milk post discharge affects important outcomes, including growth rates during infancy [7].

Results on this topic are divergent and few. Studies on nutrition in extremely preterm infants and outcome on growth (weight, length and HC) and development are still needed.

CONCLUSION

Growth seems to have improved among extremely preterm infants from 1994-1995 to 2004-2008 in Denmark. This improvement in HC, in particular, may be a result of improved treatment in general during hospitalisation, including optimised nutritional strategies and a reduction of risk factors known to induce brain injuries.

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