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Enhanced Feeding and Diminished Postnatal Growth Failure in Very-Low-Birth-Weight Infants

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ABSTRACT

Objective: The aim of the present study was to determine whether an increased supply of energy, protein, essential fatty acids, and vitamin A reduces postnatal growth failure in very-low-birth-weight infants.

Methods: Fifty infants with birth weight <1500 g were randomized to an intervention (n = 24) or a control (n = 26) feeding protocol within 24 hours after birth. Forty-four infants were included in the final analysis. This study was discontinued because of an increased occurrence of septicemia in the intervention group.

Results: The intervention group had a lower mean birth weight ($P = 0.03$) and a higher proportion of infants small-for-gestational age ($P = 0.04$) than the control group. Other baseline characteristics were similar. The median (interquartile range) energy and protein supplies during the first 4 weeks of life were higher in the intervention group: 139 (128–145) versus 126 (121–128) kcal · kg^{-1} · day^{-1} ($P < 0.001$) and 4.0 (3.9–4.2) versus 3.2 (3.1–3.3) g · kg^{-1} · day^{-1} ($P < 0.001$). The infants in the intervention group regained birth weight faster ($P = 0.001$) and maintained their z scores for weight and head circumference from birth to 36 weeks' postmenstrual age (both $P < 0.001$). The median (interquartile range) growth velocity was 17.4 (16.3–18.6) g · kg^{-1} · day^{-1} in the intervention group and 13.8 (13.2–15.5) g · kg^{-1} · day^{-1} in the control group ($P < 0.001$). In line with the improved growth in the intervention group, the proportion of growth-restricted infants was 11 of 23 both at birth and at 36 weeks' postmenstrual age, whereas this proportion increased among the controls from 4 of 21 to 13 of 21 ($P = 0.04$).

Conclusions: Enhanced supply of energy, protein, essential fatty acids, and vitamin A caused postnatal growth along the birth percentiles for both weight and head circumference.

Key Words: growth, infants, nutrition therapy, very-low-birth-weight

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The target for premature nutrition is to achieve growth similar to normal fetal growth coupled with satisfactory functional development (1). Failure to supply adequate nutrients may promote nutritional deficits and growth failure (2–6). Unfortunately, many neonatal intensive care units fail to comply with the recommended nutritional guidelines (7,8), especially during the first week after birth (9). Preterm infants subjected to growth failure in early life are at risk for several long-term consequences, including impaired cognitive function, impaired growth compared with that of term peers, and cardiovascular disease in adult life (5,10,11). The mechanisms behind cognitive impairment are not fully understood, but may be related to inadequate nutrient supply during the period of critical postnatal brain growth (12–14). Cardiovascular risk has been related to hyperalimentation and catch-up growth (10,15,16), but in a recent review by Lapillonne and Griffin (17), growth during late infancy and childhood appears to be the major determinant of later metabolic and cardiovascular disease risk, whereas early postnatal growth does not seem to affect this risk profile. Thus, in very-low-birth-weight (VLBW) infants, current evidence favors proactive nutritional support to enable growth similar to the intrauterine rate and optimize brain development

In a Norwegian study in VLBW infants, the proportion of growth-restricted infants (weight <10th percentile for age) increased from 33% at birth to 58% by discharge (18). Hence, we investigated the effect of a feeding protocol with higher supply of energy, protein, vitamin A, and essential fatty acids (intervention), as opposed to a standard (control) diet, on postnatal growth and brain maturation. Essential fatty acids were supplied because preterm born infants are deprived of the placental transfer occurring during the last trimester of pregnancy (19). Vitamin A was added to the intervention to reduce morbidity and mortality during hospital stay (20). Furthermore, we used a standardized nutritional regimen to accommodate current nutritional recommendations.

The primary objective of our present study was to reduce postnatal growth restriction. We describe the nutritional interventions and report infant growth during the first 4 weeks of life as well as growth status at 36 weeks' postmenstrual age (PMA).

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METHODS

Study Design

The present open randomized controlled multi-intervention trial was conducted at the neonatal intensive care units at Akershus University Hospital and Oslo University Hospital (Ullevål and Rikshospitalet) in Norway, after approval by the Regional Committee for Medical and Health Research Ethics, REC South East B (2009/1946).

Eligible participants were infants with a birth weight (BW) <1500 g and age <24 hours of life. Fifty infants were recruited from August 17 to December 21, 2010. Exclusion criteria were congenital malformations, chromosomal abnormalities, critical illness with short life expectancy, and clinical syndromes known to affect growth and development.

The primary investigators or the attending physician was responsible for recruiting patients to the trial. The allocation of participants to the intervention and control group was performed by an investigator without clinical involvement in the trial. To ensure balance between the 2 groups, we used a computer-generated block randomization, with groups of 4 stratified according to hospital. Sealed opaque envelopes were used for the allocation and opened in a numerical order by a staff nurse after informed parental consent was obtained. The infants were randomized at birth to reduce potential bias. Twins or triplets who met the inclusion criteria were randomized to the same group as the first born.

Study Procedures

The nutritional intervention was standardized with equal volumes, trace elements, and electrolytes in both groups, except for the phosphate and vitamin supplies, which were higher in the intervention group as a result of a higher initial parenteral lipid supply. As enteral feeding was increased successfully, parenteral nutrition was gradually reduced (supplementary Tables 1A and B, *http://links.lww.com/MPG/A280* and *http://links.lww.com/MPG/A281*).

Parenteral Nutrition

Standard 2-in-1 parenteral solutions were delivered by Fresenius Kabi (Halden, Norway) (supplementary Table 1C, *http://links.lww.com/MPG/A282*). Additional amino acid solutions (Vaminolact; Fresenius Kabi) were given separately to achieve a higher amino acid supply. The amino acid solutions were also used in the arterial lines (if needed) to avoid saline or dextrose solutions, normally causing excessive sodium load or interference with blood glucose determinations (21,22). To ensure adequate supply of the long-chain polyunsaturated fatty acids docosahexaenoic acid (22:6, n-3; DHA) and arachidonic acid (20:4, n-6; AA), the intervention group received a fish oil–containing lipid emulsion (SMOF; Fresenius Kabi), whereas the control group received the lipid emulsion used in our units (Clinoleic; Baxter, Oslo, Norway). Vitamins and micronutrients were added either in the hospital pharmacy or the neonatal intensive care units according to local practices.

The intervention group started with 3.5 g · kg^{-1} · day^{-1} of amino acids and 2.0 g · kg^{-1} · day^{-1} of intravenous lipids, whereas the control group started with 2.0 g · kg^{-1} · day^{-1} of amino acids and 0.5 g · kg^{-1} · day^{-1} of lipids. The protein supply was then gradually increased in both groups, mostly by enhancing the enteral supply of unfortified and later fortified human milk (10–20 mL · kg^{-1} · day^{-1}) (supplementary Table 1A and B, *http://links.lww.com/MPG/A280* and *http://links.lww.com/MPG/A281*). If full parenteral nutrition was required, the parenteral amino acid supply was gradually increased to 4.0 g · kg^{-1} · day^{-1} in the intervention group and to 3.0 to 3.5 g · kg^{-1} · day^{-1} in the control group. There was also a gradual increase in the amount of parenteral lipids supplied up to a maximum level of 3.4 g · kg^{-1} · day^{-1} in both groups. The supply of carbohydrates was kept similar in both groups, with a minimum supply of 5.8 g · kg^{-1} · day^{-1} on day 1 (23).

Enteral Nutrition

All of the infants were fed human milk (supplementary Table 1D, *http://links.lww.com/MPG/A283*) (24,25). Banked human donor milk was provided until the mothers were able to supply their infants with breast milk. Storage and handling of human milk followed strict hygienic routines (26). The supply of human milk was increased equally in both groups, starting with 5 to 10 mL/kg on day 1, with a gradual increase of 10 to 20 mL · kg^{-1} · day^{-1} (supplementary Tables 1A and B, *http://links.lww.com/MPG/A280* and *http://links.lww.com/MPG/A281*) (27,28). If the infants tolerated less or more milk than that mentioned in the original protocol, strictly defined alternative protocols were followed. The parenteral solutions were more concentrated than human milk, thereby giving room for medication fluids in the sick infants. When the infants reached/tolerated an enteral volume of 110 mL · kg^{-1} · day^{-1} of human milk, standardized fortification was gradually introduced (4.2 g Nutriprem [Nutricia, Oslo, Norway]/100 mL human milk). In addition, the intervention group received enteral supplementation with amino acids (0.6 g Complete Amino Acid Mix [Nutricia]/100 mL of human milk), 60 mg · kg^{-1} · day^{-1} each of the long chain polyunsaturated fatty acids DHA and AA (Formulaid; Martek, Columbia, MD), as well as 1500 μg · kg^{-1} · day^{-1} of vitamin A (Aas Laboratory, Aas, Norway). Fortification was started before parenteral nutrition was tapered, to ensure adequate supply of nutrients (29). Full enteral feeding was defined as 170 mL · kg^{-1} · day^{-1} of fortified human milk and provided 166 kcal· kg^{-1} · day^{-1}, including 4.4 g · kg^{-1} · day^{-1} protein, to the intervention group, and 146 kcal · kg^{-1} · day^{-1}, including 3.6 g · kg^{-1} · day^{-1} protein, to the control group. The estimated difference was approximately 10% for energy and 20% for protein, and was in the intervention group estimated to cover the cumulative deficits generated during the early postnatal period (9).

Postdischarge Feeding

Toward discharge, the enteral volume was gradually reduced and fortification tapered. To increase the protein intake in the breast-fed infants, the intervention group was given 1 "protein shot" (1.6 g Complete Amino Acid Mix [Nutricia]/20 mL human milk) per kilogram of body weight up to a maximum of 3 daily shots, or if in need of formula, a special preterm formula (Enfalac Premature, 81 kcal/100 mL; Mead Johnson, Oslo, Norway). This intervention was maintained until 52 weeks' PMA or a body weight of 5.5 kg. The control group was fed according to current practice, either breast-fed or given a preterm discharge formula (PreNan Discharge; Nestlé, Oslo, Norway).

Primary and Secondary Outcomes

Our primary outcome was to reduce the proportion of VLBW infants discharged as growth restricted from 60% to 40%. Growth restriction was defined as weight below the 10th percentile for gestational age, according to Norwegian growth charts for fetal growth based on live births (30). Other outcomes were days to regain BW, growth velocity (GV; g · kg^{-1} · day^{-1}), and

changes in z scores for weight, head circumference (HC), and length from birth to 36 weeks' PMA.

Data Collection

The actual nutrient supply was recorded daily. The estimated human milk energy content was 71 kcal/100 mL, based on a protein content of 1.3 g/100 mL, a carbohydrate content of 7.2 g/100 mL, and a fat content of 4.1 g/100 mL (24). The macronutrient composition of the human milk fortifiers, the preterm infant formulas, and the parenteral solutions were based on the labeled information provided by the manufacturers. To estimate the energy content, we used the factors 4 kcal/g for protein and carbohydrate, 9 kcal/g for enteral fat, and 10 kcal/g for parenteral fat. Body weight (grams) was measured daily with an electronic scale. In case of missing data, the average of 2 consecutively measured weights was calculated. Length and HC were assessed weekly and measured in centimeters with a nonstretchable measuring tape. Sex-specific weight z scores were calculated by subtracting the median value of the Norwegian reference population from the observed value and then dividing it by the standard deviation of the reference population (30,31). This enabled statistical analysis, including sexes and comparison of growth relative to the reference population and across time intervals (32). Nonsex-specific z scores for HC and length were obtained similarly by Fenton growth chart calculations (*http://ucalgary.ca/fenton*) (33). Average GV between 2 different days was calculated by the exponential model described by Patel et al (34): weight gain in $g \cdot kg^{-1} \cdot day^{-1} = (1000 \times (\ln W_n - \ln W_1))/(D_n - D_1)$, where W_1 is the weight at the first day (D_1) and W_n the weight at the last day (D_n) of the interval. Furthermore, we assessed morbidity and mortality during hospitalization. Necrotizing enterocolitis was reported at Bell stage 2 or higher (35). Cerebral intraventricular hemorrhage was defined and graded by Papile et al (36) and periventricular leukomalacia was defined by the classification by de Vries et al (37). Retinopathy of prematurity was diagnosed by an ophthalmologist (38) and classified as severe if it required therapy. Bronchopulmonary dysplasia was defined as oxygen supplementation at 36 weeks' PMA. Persistent ductus arteriosus was diagnosed by echocardiography. Late-onset septicemia was defined as age $\geq$4 days with growth of bacteria in blood culture together with clinical signs of septicemia. In episodes with coagulase-negative staphylococci isolates, an increase in C-reactive protein (>11 mg/L) and antibiotic treatment for at least 5 days (or until death) were also required for the diagnosis.

Safety Monitoring

To evaluate potentially negative effects of the nutritional intervention, a planned safety analysis was performed by an independent safety monitoring committee after inclusion of 50 infants. Because of a significantly increased occurrence of septicemia in the intervention group, we decided to halt further recruitment of infants, which was supported by the Regional Committee for Medical and Health Research Ethics.

Statistical Analysis

On the basis of the observed proportion of postnatal growth restriction in the Norwegian study by Henriksen et al (18), we calculated that a sample size of 120 infants per group (including 10% deaths and dropouts) was required to achieve 80% power to detect a reduction of infants discharged as growth restricted from 60% to 40%, at a 2-sided significance level of 5%.

To evaluate differences between groups, we used the Student t test for continuous variables and the χ^2 test or the Fisher exact test for categorical variables depending on the expected cell numbers. For continuous variables not normally distributed, the Mann-Whitney U test was used. Baseline characteristics and clinical outcomes are presented as frequencies (%) for categorical variables, and as means (ranges or standard deviations) or medians (interquartile ranges) for continuous variables. Mean differences are presented with 95% confidence intervals (CIs). Linear regression analysis was used to adjust for growth status at birth. To evaluate the development of postnatal growth failure between the 2 groups, the change in growth status (growth status at discharge minus growth status at birth) was assessed by the Fisher exact test. Statistical analysis was performed using SPSS for Windows, version 20 (SPSS Inc, Chicago, IL). Significance was assumed for $P < 0.05$, and all of the statistical tests were 2-sided and performed on an intention-to-treat basis. Moreover, we performed per-protocol analysis for growth outcomes.

RESULTS

Demographic and Clinical Characteristics

Fifty VLBW infants were randomized to the study and 44 were included in the analysis (Fig. 1). Demographic and clinical characteristics are presented in Table 1. The significantly higher occurrence of septicemia and electrolyte deviations observed in the intervention group have recently been reported (39).

Nutritional Intervention

The nutritional intervention started within 24 hours after birth in all but 1 patient. Trophic feeding was initiated on the first day of life and there were no significant differences in the initiation of human milk fortifier, days on parenteral nutritional support, or days until full enteral feeds with fortification (Table 2). The majority of the infants received nutritional supply according to the protocol. This resulted in a significantly higher supply of energy, protein, fat, vitamin A, AA, and DHA during the first 4 weeks of hospitalization in the intervention group compared with the control group, without a significant difference in total fluid volume or amount of human milk provided (Table 3 and supplementary Table 2 [*http://links.lww.com/MPG/A284*]).

Growth

The average weight z score change was congruent in the 2 groups during the first days of life (Fig. 2). Thereafter, improved growth occurred in the intervention group with a median GV from birth to 36 weeks' PMA of approximately 17 compared with 14 $g \cdot kg^{-1} \cdot day^{-1}$ in the control group ($P < 0.001$) (Table 4). GV and weight z score change among the small-for-gestational age (SGA) and the appropriate-for-gestational age (AGA) infants of the intervention and the control groups are presented separately (Table 5). When adjusting for SGA status at birth in a linear regression model, the difference in GV from birth to 36 weeks' PMA remained significant ($P = 0.001$).

The infants in the intervention group maintained their weight z score from birth to 36 weeks' PMA, whereas the infants in the control group had a negative weight z score change and fell off their expected growth trajectories (Table 6). The mean difference in z score change between the groups was 0.65 (95% CI 0.34–0.95). The weight z score change was also significantly different between the groups when adjusted for SGA status at birth ($P = 0.01$). Furthermore, we observed a catch-up growth in HC with

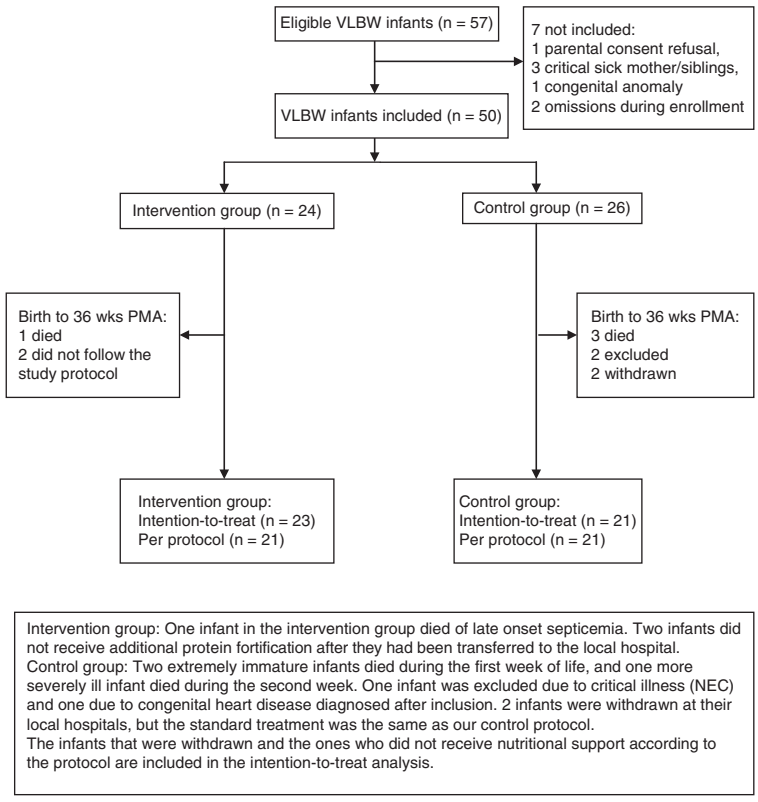

FIGURE 1. Flowchart of study participants. PMA = postmenstrual age; VLBW = very-low-birth-weight.

a mean HC z score change of 0.63 in the intervention group compared with a fall in HC z score of −0.25 in the control group (0.87, 95% CI 0.49–1.26). Unfortunately, data regarding length were missing in 1 infant at birth and in 3 infants at 36 weeks' PMA (2 infants in each group). Although the decline in z score length was less pronounced in the intervention group, the difference between the groups was nonsignificant (0.51, 95% CI −0.13 to 1.15). The per-protocol analysis showed similar results for GV and z score changes (data not presented).

Postnatal growth was further assessed in infants with a change in growth status from birth to 36 weeks' PMA. In the intervention group, 4 SGA infants exhibited improved growth and were not growth restricted at 36 weeks' PMA, whereas 4 AGA infants experienced postnatal growth restriction. All of the SGA

TABLE 1. Baseline characteristics and clinical outcomes

	Intervention, n = 23	Control, n = 21	*P*
Gestational age, wk, mean (range)	28.1 (25.0–33.6)	28.5 (24.0–32.6)	0.51
Birth weight, g, mean (range)	936 (460–1311)	1097 (571–1414)	0.03
Small-for-gestational age, n (%)	11 (48)	4 (19)	0.04
Sex, boys, n (%)	14 (61)	14 (67)	0.69
Cesarean section, n (%)	16 (70)	17 (81)	0.38
Apgar score, 5-min, median (IQR)	8 (6–9)	8 (6–9)	0.50
Prenatal steroid exposure, n (%)	21 (91)	21 (100)	0.49
Late-onset septicemia, n (%)	14 (61)	6 (29)	0.04
NEC, n (%)	1 (4)	1 (5)	0.95
IVH, grade ≥3, n (%)	2 (9)	2 (10)	0.92
PVL, grade ≥3, n (%)	0 (0)	0 (0)	N/A
ROP (grade III/+disease), n (%)	3 (13)	1 (5)	0.61
O_2 dependency at 36 wk PMA, n (%)	5 (22)	5 (24)	0.87
PDA treatment (medical/surgical), n (%)	6 (26)	3 (23)	0.46
Hypokalemia (<3.5 mmol/L), n (%)	20 (87)	9 (43)	0.002
Hypophosphatemia (<1.4 mmol/L), n (%)	17 (77)*	4 (19)	<0.001

Data are mean (range), median (interquartile range; IQR), or frequencies (%). IVH = intraventricular hemorrhage; N/A = not applicable; NEC = necrotizing enterocolitis; PDA = persistent ductus arteriosus; PMA = postmenstrual age; PVL = periventricular leukomalacia; ROP = retinopathy of prematurity.
* Missing information from 1 infant.

TABLE 2. Details about initiation of enteral nutrition and termination of parenteral support

	Intervention, n = 23	Control, n = 21	*P*
Human milk first day, mL· kg^{-1}· d^{-1}	5.2 (4.1–9.0)	5.5 (4.4–13.7)	0.61
Initiation of human milk fortifier, day of life	7 (7.0–12.0)	7 (6.5–8.5)	0.41
Duration of parenteral nutrition, d	9 (8.0–16.0)	8 (4.0–22.0)	0.08
Full enteral feeds (fortified), day of life	11 (10–17)	10 (9.5–12.5)	0.18

Values are medians (interquartile ranges).

infants in the control group remained growth restricted, and another 9 AGA infants developed growth restriction during hospitalization. This change in growth status was significantly different between the groups (intention-to-treat: $P = 0.04$; per-protocol: $P = 0.01$).

DISCUSSION

In the present randomized controlled trial of VLBW infants, the intervention group received significantly higher supplies of energy, protein, fat, AA, DHA, and vitamin A compared with the control group. This resulted in growth along the percentile band from birth to 36 weeks' PMA for weight and in catch-up growth for HC. Thus, postnatal growth restriction was also significantly reduced.

The extra supplementation with essential fatty acids, vitamin A, and amino acids in the intervention group resulted in a higher energy supply during periods of hospitalization than recent nutritional recommendations for adequate growth (1,40,41). Actual nutrient intakes were similar to the prescribed intakes during the study and demonstrate that a strict nutritional protocol and the use of ''standard'' bags make it possible to reach the nutritional goals. Our study also demonstrates that it is possible to meet the nutritional requirements of VLBW infants with fortified human milk within 9 to 10 days after birth.

The infants in the intervention group followed the same weight percentile band between birth and 36 weeks' PMA, demonstrating a median GV of approximately 17 g · kg^{-1} · day^{-1}, which is according to current recommendations (1,42). The

TABLE 3. Calculated daily nutrient supply during the first 4 postnatal weeks

Nutrients	Intervention group, n = 23	Control group, n = 21	*P*	ESPGHAN guidelines 2010
Total supply				
Fluid, mL/kg	160 (155–164)	160 (157–165)	0.84	135–200
Human milk, mL/kg	133 (110–139)	134 (124–141)	0.37	150–180
Formula, mL/kg*	0 (0–0)	0 (0–0)*	0.14	150–180
PN, mL/kg	21 (19–41)	21 (16–31)	0.42	
Macronutrients				
Energy, kcal/kg	139 (128–145)	126 (121–128)	<0.001	110–135
Protein, g/kg	4.0 (3.9–4.2)	3.2 (3.1–3.3)	<0.001	3.5–4.5
Fat, g/kg	7.3 (6.5–7.6)	5.9 (5.6–6.1)	<0.001	4.8–6.6
Carbohydrate, g/kg	14.4 (13.4–14.8)	14.7 (14.3–15.1)	0.12	11.6–13.2
Fatty acids				
AA, mg/kg	68 (57–73)	24 (23–25)	<0.001	18–42
DHA, mg/kg	87 (81–91)	36 (34–38)	<0.001	12–30
Vitamins				
Vitamin A, μg/kg	1300 (1105–1442)	252 (238–257)	<0.001	400–1000
Vitamin D, μg/kg	5.8 (4.9–6.2)	6.0 (5.5–6.3)	0.14	20–25
Vitamin E, mg/kg	6.1 (4.8–9.6)	5.0 (3.7–8.7)	0.12	2.2–11
Vitamin K, μg/kg	83 (52–153)	58 (30–88)	0.17	4.4–28
Vitamin C, mg/kg	14 (12–15)	15 (14–16)	0.03	15–25
Thiamin (B_1), mg/kg	0.21 (0.19–0.21)	0.21 (0.20–0.21)	0.63	0.14–0.30
Riboflavin (B_2), mg/kg	0.30 (0.28–0.30)	0.30 (0.29–0.30)	0.77	0.2–0.4
Pyridoxine (B_6), mg/kg	0.20 (0.18–0.22)	0.19 (0.18–0.21)	0.42	0.045–0.3
Cobalamin (B_{12}), μg/kg	0.34 (0.31–0.35)	0.33 (0.32–0.34)	0.57	0.1–0.77
Niacin, mg/kg	3.4 (3.2–3.5)	3.5 (3.3–3.5)	0.24	0.38–5.5
Folic acid, μ/kg	64.6 (54.3–69.7)	68.1 (62.7–72.1)	0.08	35–100
Minerals				
Sodium, mmol/kg	2.8 (2.5–4.1)	3.1 (2.6–4.4)	0.38	3.0–5.0
Potassium, mmol/kg	3.1 (2.7–3.3)	3.2 (3.0–3.3)	0.23	1.6–3.3
Chloride, mmol/kg	3.5 (3.1–4.9)	3.8 (3.2–5.1)	0.47	2.9–5.0
Calcium, mmol/kg	3.0 (2.5–3.2)	3.1 (2.9–3.2)	0.09	3–3.5
Phosphate, mmol/kg	2.3 (1.9–2.5)	2.4 (2.3–2.5)	0.09	1.9–2.9
Magnesium, mmol/kg	0.45 (0.38–0.49)	0.48 (0.45–0.50)	0.06	0.3–0.6
Nonprotein energy/g protein	31 (28–31)	35 (34–36)	<0.001	

Values are medians (interquartile ranges). DHA = docosahexaenoic acid; ESPGHAN = European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; PN = parenteral nutrition.

* One infant in the control group received some formula (Enfalac 68 kcal/100 mL) during the third and fourth weeks of life.

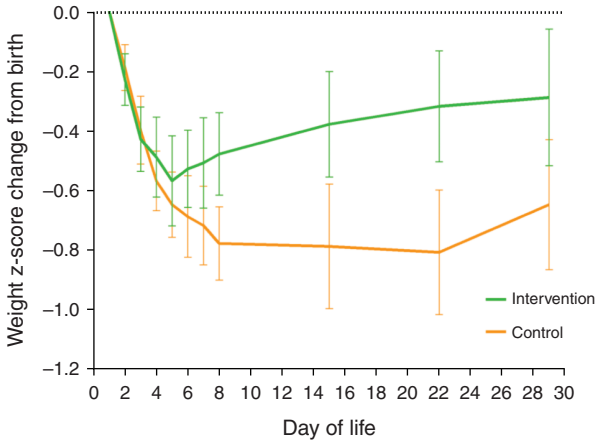

FIGURE 2. Average weight *z* score change in the control and intervention groups from birth to 4 weeks of age. Means and 95% confidence interval, n = 44.

improved growth was also reflected in the observed reduction in postnatal growth failure in the intervention group compared with the controls, indicating that postnatal growth restriction may be prevented by sufficient nutrient supply.

Our findings are in accordance with results from studies on ''early aggressive'' nutrition to VLBW infants (43–46); however, the infants studied mostly fell off their expected intrauterine growth curves by discharge (2–4,43,45,47,48). The total protein and energy supplies in these studies were more similar to the supply of nutrients in our control group, thereby not compensating for the accumulated nutritional deficits during the first days or weeks of life. In 2011, Senterre and Rigo (49,50) demonstrated that it is possible to accommodate recent nutritional recommendations. As in our study, the infants were supplied a standard ready-to-use parenteral solution with a complementary amino acid solution, but the protein and energy supplies were lower than those in our intervention group. After the initial decline in weight *z* score of 0.7, the infants in that study remained within their growth trajectory. The authors suggest that the weight *z* score at 3 days of age should be used as baseline to evaluate postnatal growth (49). The initial weight loss reflects physiological loss of extracellular fluid and presumably catabolism (42,51 [references 51–63 can be viewed online only at *http://links.lww.com/MPG/A286*]). If the weight *z* score at 3 days of age is used as baseline, with a target postnatal growth rate of 16 to 17 $g \cdot kg^{-1} \cdot day^{-1}$, the weight of an ex-premature infant will remain less than that of a full-term peer, because a *z* score drop of 0.67 corresponds to the width of each percentile band on standard growth charts (52). Several studies on VLBW infants concerning total brain volume and developmental outcomes have demonstrated correlations to postnatal energy/protein intake (5,6,53). An underestimation of postnatal growth potential in VLBW infants (51) may put them at risk of inadequate nutrient supply during periods of critical brain growth (5). The significantly enhanced HC *z* score change in our intervention groups supports this assumption.

Increased catch-up growth may be associated with increased risk of metabolic and cardiovascular diseases later in life (10,15,16). In a recent review, Lapillonne and Griffin (17) have, however, suggested that it is growth in later childhood and adolescence that has an effect on metabolic and cardiovascular disease risk—not the early postnatal growth. A mean weight *z* score change of 0.08, as seen in our intervention group from birth to 36 weeks' PMA, implicates that the infants followed their weight percentiles and did not exhibit clinically significant catch-up growth defined as a positive *z* score change of 0.67 (52). The SGA infants in the intervention group (the infants with the highest GV) demonstrated a weight *z* score change of 0.01 from birth to 4 weeks and a weight *z* score change of 0.29 from birth to 36 weeks' PMA. Length *z* score decreased during hospital stay. The mean *z* score drop in the intervention group was 0.5 less than in the control group, albeit not significant. These findings indicate that the intervention improved overall growth, although we cannot differentiate between lean body mass and fat deposition.

In our present study, we observed a significantly higher occurrence of late-onset septicemia and electrolyte disturbances in the intervention group compared with the control group. We have carefully reviewed several aspects of the study, and we find an association between the electrolyte disturbances and the enhanced susceptibility for septicemia (39,54,55).

Increased occurrence of both hypophosphatemia and hypokalemia has also been reported in other studies with early protein supply to VLBW infants (56–59) and may indicate accelerated protein synthesis (44). High intake of amino acids in premature infants is associated with increased endogenous insulin production and flux of phosphate and potassium to the intracellular compartment to support energy production along with synthesis of glycogen, fat, and protein (44). New studies document the need for balanced parenteral solutions, providing sufficient macro- and micronutrients postnatally to permit tissue growth (39,55,60). The marked electrolyte deviations found in our study as compared with those in other studies may, in addition to inadequate electrolyte supply, partly be because of the high proportion of SGA and extremely LBW infants in the intervention group, and partly be because of nutrient supply in the upper range of current recommendations during the first days after birth.

We hope that our setbacks described above do not distract attention from the fact that the infants in our intervention group

TABLE 4. Postnatal growth data in all 44 infants followed from birth to 36 weeks' PMA

	Intervention, n = 23	Control, n = 21	*P*
Postnatal weight loss, %	7.0 (4.9–10.5)	10.1 (5.3–12.8)	0.21
Weight nadir, day of life	3.0 (3.0–5.0)	4.0 (3.0–7.0)	0.03
Time to regain birth weight, days	7.0 (5.0–8.0)	10.0 (8.0–13.0)	0.001
GV first wk, $g \cdot kg^{-1} \cdot d^{-1}$	3.0 (−1.5 to 9.1)	−5.6 (−13.3 to −1.5)	0.001
GV second wk, $g \cdot kg^{-1} \cdot d^{-1}$	21.7 (17.1–26.2)	18.1 (11.6–25.3)	0.29
GV third wk, $g \cdot kg^{-1} \cdot d^{-1}$	21.7 (17.9–25.0)	17.9 (13.7–22.7)	0.12
GV fourth wk, $g \cdot kg^{-1} \cdot d^{-1}$	23.4 (12.8–25.2)	21.5 (18.2–26.1)	0.49
GV birth to 4 wk of age, $g \cdot kg^{-1} \cdot d^{-1}$	16.8 (14.7–19.2)	13.2 (9.6–16.0)	0.001
GV birth to 36 wk PMA, $g \cdot kg^{-1} \cdot d^{-1}$	17.4 (16.3–19.0)	13.8 (13.2–15.5)	<0.001

Values are medians (interquartile ranges). GV = growth velocity; PMA = postmenstrual age. GV was calculated by the exponential model described by Patel et al (34).

TABLE 5. Postnatal GV and weight *z* score change (Δ*z* score weight) stratified by growth status at birth in 44 infants

	n	Intervention	n	Control	*P*
GV birth to 4 wk					
AGA infants, g · kg^{-1}· d^{-1}	12	14.9 (13.6–17.4)	17	12.9 (9.5–15.6)	0.07
SGA infants, g · kg^{-1}· d^{-1}	11	17.6 (16.7–20.7)	4	14.8 (13.3–16.2)	0.02
GV birth to 36 wk PMA					
AGA infants, g · kg^{-1}· d^{-1}	12	16.5 (14.8–17.7)	17	13.8 (13.2–15.3)	0.001
SGA infants, g · kg^{-1}· d^{-1}	11	18.8 (16.9–19.4)	4	14.8 (12.8–17.3)	0.03
Δ *z* score weight birth to 4 wk					
AGA infants	12	−0.56 (0.49)	17	−0.79 (0.47)	0.22
SGA infants	11	0.01 (0.40)	4	−0.19 (0.06)	0.12
Δ*z* score weight birth to 36 wk PMA					
AGA infants	12	−0.11 (0.48)	17	−0.66 (0.51)	0.007
SGA infants	11	0.29 (0.51)	4	−0.15 (0.24)	0.07

Values are medians (interquartile ranges) or means (standard deviations). AGA = appropriate-for-gestational age; GV = growth velocity; PMA = postmenstrual age; SGA = small-for-gestational age.

showed postnatal growth along the birth percentiles. Based on accumulating evidence demonstrating the importance of early optimal nutrition and growth on long-term health, it should be possible to continue on this path of research with sharpened attention to electrolyte balance.

Our study has some limitations. The early termination resulted in a lower test power than planned. Despite the randomized controlled design, the infants in the intervention group had significantly lower BW and a higher proportion of infants being SGA as compared with those in the control group. Because SGA infants exhibit increased catch-up growth compared with AGA infants (49,61), we have adjusted for the difference at baseline in our statistical analysis (62). The subgroup analyses have low statistical strength. Other limitations were the estimates of the nutrient supply. There is a large variation in protein and fat composition of human milk (29,63). Our estimates of carbohydrates, fat, and energy were higher than those in previous studies (29,49,63). Thus, also taking into account the lower fat absorption in preterm infants (63), we may have overestimated the energy supply. Although most of the endpoints fulfilled objective and defined criteria, awareness of the treatment may have influenced outcome measures. Ideally, we would have used 1 growth chart for reference growth for weight, HC, and length, but Norwegian growth charts for HC and length are not available. Because we compared the different *z* score changes between 2 groups, we chose to use Fenton's growth chart to obtain *z* scores for HC and length. Although the multi-intervention design made it difficult to draw mechanistic conclusions, we reduced the risk of inadequate growth. Furthermore, our strict standardization of the nutritional protocols reduced other confounding factors, making it easier to interpret the data.

CONCLUSIONS

Enhanced supply of energy, protein, AA, DHA, and vitamin A to VLBW infants during neonatal hospitalization promoted postnatal growth along the birth percentiles for weight and catch-up growth for HC. These findings suggest that the true growth potential in these infants is underestimated. We also observed an increased risk of electrolyte disturbances and late-onset septicemia in the intervention group, highlighting the importance of sufficient supply of both macro- and micronutrients to compensate for the accumulated deficits in the early postnatal period. Further randomized trials are needed to identify more specifically the optimal nutrient composition for growth.

TABLE 6. Growth data at birth and 36 weeks postmenstrual age

	Birth			36 wk		
	Intervention	Control	*P*	Intervention	Control	*P*
	n = 23	n = 21		n = 23	n = 21	
Weight, g	936 (223)	1097 (245)	0.03	2375 (503)	2283 (254)	0.44
z score weight	−1.32 (1.15)	−0.90 (0.65)	0.14	−1.24 (1.07)	−1.46 (0.50)	0.37
				n = 23	n = 21	
Δ*z* score weight	—	—	—	0.08 (0.48)	−0.56 (0.51)	<0.001
	n = 23	n = 21		n = 22	n = 21	
HC, cm	25.7 (1.96)	26.7 (2.29)	0.09	33.4 (1.50)	32.5 (1.41)	0.06
z score HC	−0.22 (0.93)	0.27 (0.64)	0.05	0.40 (0.82)	0.02 (0.71)	0.12
				n = 22	n = 21	
Δ*z* score HC	—	—	—	0.63 (0.65)	−0.25 (0.58)	<0.001
	n = 23	n = 20		n = 21	n = 20	
Length, cm	35.0 (3.10)	35.9 (3.01)	0.39	43.9 (3.15)	43.3 (1.96)	0.47
z score length	−1.02 (1.46)	−0.71 (1.07)	0.43	−1.19 (1.10)	−1.48 (0.89)	0.36
				n = 21	n = 19	
Δ*z* score length	—	—	—	−0.31 (1.11)	−0.82 (0.87)	0.12

Values are means (standard deviations). Δ*z* score = *z* score change; HC = head circumference.

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