A Randomized Trial of Parenteral Nutrition Using a Mixed Lipid Emulsion Containing Fish Oil in Infants of Extremely Low Birth Weight: Neurodevelopmental Outcome at 12 and 24 Months Corrected Age, A Secondary Outcome Analysis

Margarita Thanhaeuser, MD[1], Renate Fuiko, PhD[1], Christiane Oberleitner-Leeb, MSc[1], Sophia Brandstaetter, MD[1], Christoph Binder, MD[1], Alexandra Thajer, MSc, PhD[1], Mercedes Huber-Dangl, MD[1], Nadja Haiden, MD, MSc[2], Eleonore Pablik, Boecc[3], Angelika Berger, MD, MBA[1], and Andreas Repa, MD[1]

Objective To examine whether parenteral nutrition using a mixed lipid emulsion containing fish oil improves the neurodevelopmental outcomes of extremely low birth weight infants.

Study design The study is a secondary outcome analysis of a double-blind randomized trial of 230 extremely low birth weight infants performed at a single level IV neonatal care unit (Medical University Vienna; June 2012 to June 2015). Participants received either a mixed lipid emulsion composed of soybean oil, medium chain triglycerides, olive oil, and fish oil, or a soybean oil-based lipid emulsion for parenteral nutrition. Neurodevelopment of study participants was assessed at 12 and 24 months corrected age (August 2013 to October 2017) using the Bayley Scales of Infant-Toddler Development, third edition.

Results At discharge, 206 of the 230 study participants were eligible. At 12 and 24 months corrected age, 174 of 206 (85%) and 164 of 206 (80%) infants were evaluated. At 12 months, there was no significant difference in cognitive (mixed lipid: median, 95 [IQR, 85-101]; soybean oil: median, 95 [IQR, 85-100]; $P = .71$), language (mixed lipid: median, 86 [IQR, 77-94], soybean oil: median, 89 [IQR, 79-94]; $P = .48$), or motor scores (mixed lipid: median, 88 [IQR, 76-94], soybean oil: median, 88 [IQR, 79-94]; $P = .69$). At 24 months, there was again no significant difference in cognitive (mixed lipid: median, 95 [IQR, 80-105], soybean oil: median, 95 [IQR, 90-105]; $P = .17$), language (mixed lipid: median, 89 [IQR, 75-97], soybean oil 89 [IQR, 77-100]; $P = .54$), and motor scores (mixed lipid: median, 94 [IQR, 82-103], soybean oil: median, 94 [IQR, 85-103]; $P = .53$).

Conclusions Parenteral nutrition using a mixed lipid emulsion containing fish oil did not improve neurodevelopment of extremely low birth weight infants at 12 and 24 months corrected age. *(J Pediatr 2020;226:142-8)*.

Trial registration ClinicalTrials.gov: NCT01585935.

Extremely low birth weight (ELBW) infants are at high risk for adverse neurodevelopment owing to injuries to the developing brain, such as intraventricular hemorrhage or cystic periventricular leukomalacia.[1] Preterm infants have distinct nutritional requirements, and optimal nutrient supply supports a favorable motor and cognitive development.[2,3]

Docosahexaenoic acid (DHA) is an ω-3 long-chain polyunsaturated fatty acid (LC-PUFA) that is considered crucial for normal brain development.[4] In the last trimester of pregnancy an estimated 40 to 67 mg/kg/d of DHA is transferred from the mother to the fetus.[4-7]

After preterm birth, placental transfer of DHA is interrupted. Soybean oil-based lipid emulsions that are used for parenteral nutrition are almost devoid of DHA. Thus, enteral nutrition is the main source of DHA for preterm infants, but supply falls short of fetal accretion, and infants of ELBW accumulate large DHA deficits.

A mixed lipid emulsion composed of soybean oil, medium-chain triglycerides, olive oil, and fish oil is licensed for pediatric use in Europe. Fish oil provides DHA

ARA	Arachidonic acid
Bayley-III	Bayley Scales of Infant and Toddler Development, third edition
DHA	Docosahexaenoic acid
ELBW	Extremely low birth weight
EPA	Eicosapentaenoic acid
GMFCS	Gross Motor Function Classification System
LC-PUFA	Long-chain polyunsaturated fatty acid

From the [1]Department of Pediatrics and Adolescent Medicine, Division of Neonatology, Pediatric Intensive Care Medicine and Neuropediatrics; [2]Department of Clinical Pharmacology; and [3]Section for Medical Statistics, CeMSIIS, Medical University of Vienna, Vienna, Austria

Funded by the Austrian Science Fund (FWF, KLI99-B00). Study emulsions were provided free of charge by Herba Chemosan (Graz, Austria). Fresenius Kabi (Graz, Austria) provided funding to employ a clinical research nurse. The companies had no role in the study, in particular concerning the design, analysis, interpretation or reporting of results and preparation of the manuscript. A.R. received a research grant by Fresenius Kabi (Graz, Austria). The authors declare no conflicts of interest.

Portions of this study were presented at the 5th International Conference on Nutrition and Growth, March 1-3, 2018, Paris, France; and the 7th Congress of the European Academy of Paediatric Societies, October 30-November 3, 2018, Paris, France.

https://doi.org/10.1016/j.jpeds.2020.06.056

and eicosapentaenoic acid (EPA), which is a precursor of DHA. Parenteral nutrition using the mixed lipid emulsion provides infants of ELBW with amounts of DHA comparable with in utero transfer rates.[8] By attenuating their DHA deficit, the neurodevelopment of preterm infants of ELBW might be improved.[5]

In a randomized trial, we assigned 230 infants of ELBW to receive either a mixed lipid emulsion or a soybean oil-based lipid emulsion for parenteral nutrition to evaluate its effect on liver injury.[8] Analysis of amplitude-integrated electroencephalography in study participants measured from birth to discharge revealed acceleration of electrophysiologic brain maturation using a mixed lipid emulsion.[9] The aim of the present study was to analyze the effect of a mixed lipid emulsion on the neurodevelopmental outcome of study participants at 12 and 24 months corrected age.

Methods

The study is a prespecified secondary outcome analysis of a double-blind, randomized trial (ClinicalTrials.gov: NCT01585935, EudraCT 2011-005456-33) on the preventive effect of a mixed lipid emulsion on parenteral nutrition associated cholestasis. The study was conducted from June 2012 to June 2015 at a level IV neonatal care unit (University Children's Hospital, Medical University of Vienna, Austria). The study design was previously described in detail, the protocol is accessible at ClinicalTrials.gov.[8] Inclusion criteria included birth weight of <1000 g and admission within the first 24 postnatal hours. Higher order multiples, infants with chromosomal aberrations, and infants with conditions associated with cholestasis were not eligible. Participants were randomized and stratified (sex and birth weight <750 g) within their first 120 hours of life to receive parenteral nutrition using either a mixed lipid emulsion (SMOFLipid 20%; Fresenius Kabi, Bad Homburg, Germany; composed of 30% soybean oil, 30% medium chain triglycerides, 25% olive oil, and 15% fish oil; ω-6:ω-3 ratio 2.5:1) or a soybean oil-based lipid emulsion (Intralipid 20%; Fresenius Kabi, Bad Homburg, Germany; ω-6:ω-3 ratio 8:1). The mixed lipid emulsion contains 2.2% DHA, 2.4% EPA, and 0.4% arachidonic acid (ARA). The soybean oil-based lipid emulsion contains 0.2% DHA, no EPA, and 0.3% ARA.[10,11] Parenteral and enteral nutrition of participants were previously described in more detail.[9,10] Lipids were dosed ≤3 g/kg/day. Serum triglycerides were measured at least weekly. Full parenteral nutrition was provided until 140-160 mL/kg/day of enteral nutrition. Parenteral vitamins (2 mL/kg Soluvit; 4 mL/kg Vitalipid N Infant; Fresenius Kabi, Bad Homburg, Germany) were provided unless enteral nutrition with own mother's milk or donor milk was fortified at 100 mL/kg using a fat-free fortifier (Aptamil FMS; Milupa Nutricia GmbH, Frankfurt, Germany). Donor milk was used if mothers' own milk was unavailable and switched to preterm formula at 32 weeks of postmenstrual age. This follow-up study, investigating neurodevelopment at 12 and 24 months corrected age, was performed at the hospital's outpatient clinic from August 2013 to October 2017. Infants with congenital cerebral malformations were excluded from this analysis. Patients and observers were blinded, as were the 2 psychologists performing neurodevelopmental testing.

Baseline Characteristics

Perinatal clinical and demographic characteristics were collected. A full course of prenatal steroids was defined as 2 doses of betamethasone. Surfactant (Curosurf; Chiesi, Parma, Italy) was administered prophylactically in infants born at $<28^{0/7}$ weeks of gestation or if surfactant deficiency was suspected clinically.[12] Anthropometric Z-scores were calculated using growth curves by Fenton et al.[13] Small for gestational age was defined as birth weight of <10th percentile.

Neonatal morbidity and lipid intakes of infants during hospitalization were collected. Necrotizing enterocolitis was diagnosed clinically (Bell stage ≥IIa) or after exploratory surgery. Intraventricular hemorrhage and cystic periventricular leukomalacia were diagnosed by cerebral ultrasound. Retinopathy of prematurity was diagnosed by direct ophthalmoscopy. Chronic lung disease was defined as supplementary oxygen after $36^{0/7}$ weeks postmenstrual age. Data on parental education were collected at the follow-up visits and coded based on highest educational level attained by either parent. Low parental education was defined as primary education only (compulsory schooling until the age of 15).

Follow-Up

Study participants were followed at 12 and 24 months corrected age as part of clinical routine care. Follow-up included anthropometric measurements (with Z-scores and body mass index) and assessment of neurodevelopment using the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III; Harcourt Assessment, San Antonio, United States, 2006.). The Bayley-III consists of 5 subtests: cognition, receptive, and expressive communication, as well as fine and gross motor function. Scaled scores are calculated for each subtest with a mean of 10 and a standard deviation of 3. Scaled scores are converted into cognitive, language, and motor composite scores with a mean of 100 ± 15.[14] Results were calculated using the US norms. The tests were performed and scored by 2 certified clinical psychologists.

Infants with a diagnosis of cerebral palsy were assessed using the Gross Motor Function Classification System (GMFCS) at 24 months corrected age. The GMFCS includes 5 levels based on functional abilities and quality of movement.[15]

Statistical Analyses

Differences between groups were analyzed by Mann-Whitney *U* test for composite scores of cognitive, language, and motor development as well as gross motor function. Subgroup analyses were carried out by sex and increased risk for unfavorable development (birth weight of <750 g and low parental education). Sensitivity analysis was performed using a mixed

model linear regression analysis with mother and child as random factor and included the confounders sex, gestational age, intraventricular hemorrhage grades III and IV, and parental education. SPSS statistical software system version 25.0 (SPSS Inc., Chicago, Illinois) and R version 3.5.1 (R foundation, Vienna, Austria) were used for calculations. Assessment of neurodevelopmental outcome was a predefined secondary outcome of the trial, confounders, and subgroup analyses were defined post hoc after analysis of the whole cohort.

Ethics and Registration

The study was conducted in accordance with the Declaration of Helsinki, ICH GCP guidelines, and the respective European Union directives embedded in the Austrian drug act. Written consent from 1 parent was sufficient owing to the low risk for participants. Patients were insured as legally required. The study was approved by the institution's ethics committee (EK 2011/1030).

Results

In total, 230 infants were randomized (June 2012 to June 2015; **Figure 1** [available at www.jpeds.com]) and 223 infants were eligible for analysis of the primary outcome. At discharge, 206 of 230 study participants were eligible for neurodevelopmental assessment at follow-up, with 174 infants (85%) analyzed at 12 months and 164 infants (80%) at 24 months corrected age. Follow-up lasted from August 2013 to October 2017. Loss to follow-up did not vary significantly by lipid group (at 12 months: 16% vs 15%, $P = .95$; at 24 months: 21 vs 20%, $P = .94$).

Demographic and perinatal characteristics of infants evaluated at 12 and 24 months corrected age are shown in **Table I**. Neonatal morbidities and lipid intakes did not differ significantly between groups, except for DHA and EPA, which were significantly higher in infants receiving the mixed lipid emulsion owing to the intervention (**Table II**). Important characteristics of patients lost to follow-up (**Table III**; available at www.jpeds.com) did not differ significantly between the lipid assignment groups. Neonatal morbidities and lipid intakes of the subgroup of infants with birth weights of <750 g (**Table IV**; available at www.jpeds.com) were also not significantly different. Anthropometric data at 12 and 24 months corrected age are shown in **Table V**. There were no significant differences between the 2 groups.

The results of neurodevelopmental testing (Bayley-III) are shown in **Table VI**. At 12 and 24 months, there were no significant differences in cognitive, language, or motor

Table I. Perinatal and demographic characteristics

Characteristics	12 months corrected age		24 months corrected age	
	Mixed lipid emulsion (n = 86)	Soybean oil (n = 88)	Mixed lipid emulsion (n = 81)	Soybean oil (n = 83)
Maternal				
Multiple pregnancy	19 (22)	27 (31)	19 (24)	26 (31)
Cesarean delivery	79 (92)	82 (93)	75 (93)	78 (94)
Prenatal steroids (full course)	57 (66)	52 (59)*	53 (65)	50 (60)*
Premature rupture of membranes	32 (37)	31 (35)	30 (37)	31 (37)
Preeclampsia	12 (14)	16 (18)	11 (14)	16 (19)
Highest parental education				
Primary school (thru age 15 years)	29 (34)†	28 (32)‡	28 (35)†	26 (31)‡
Secondary school (high school)	26 (30)†	23 (26)‡	26 (30)†	22 (27)‡
Postsecondary school	22 (26)†	20 (23)‡	21 (26)†	19 (23)‡
Age of mother at birth	31.5 [27-35]§	31 [27-37]¶	31.5 [27-35]§	31 [27-37]
Married/in partnership	71 (82.6)†	74 (84.1)†	67 (82.7)†	70 (84.3)†
Caucasian	83 (96.5)	84 (95.5)	79 (97.5)	79 (95.2)
Neonatal				
Umbilical artery pH	7.31 [7.26 to 7.36]**	7.3 [7.25 to 7.35]**	7.31 [7.26 to 7.36]**	7.31 [7.25 to 7.35]**
Apgar score at 5 min	8 [8 to 9]	8 [8 to 9]§	8 [8 to 9]	8 [8 to 9]§
Male sex	51 (59)	57 (65)	48 (59)	56 (68)
Surfactant	77 (90)	76 (86)	72 (89)	72 (87)
Gestational age	$25^{5/7}$ [$24^{6/7}$ to $27^{1/7}$]	$26^{2/7}$ [$25^{0/7}$ to $28^{0/7}$]	$25^{6/7}$ [$24^{6/7}$ to $27^{2/7}$]	$26^{2/7}$ [$25^{0/7}$ to $28^{0/7}$]
Birth weight (g)	772.5 [650 to 835]	760 [630 to 895]	775 [650 to 855]	780 [630 to 900]
Z score	−0.4 [−1.1 to 0.2]	−0.7 [−1.4 to 0.1]	−0.4 [−1.1 to 0.2]	−0.6 [−1.3 to 0.1]
Birth length (cm)	34 [31 to 35]	33 [31 to 35]¶	34 [31 to 35]	33 [31 to 35]
Z score	−0.2 [−0.9 to 0.7]	−0.2 [−1 to 0.4]¶	−0.1 [−1 to 0.9]	−0.2 [−1 to 0.4]
Birth head circumference (cm)	24 [23 to 25]	24 [23 to 25]	24 [23 to 25]	24 [23 to 25]
Z score	0 [−0.7 to 0.6]	−0.2 [−0.8 to 0.3]	−0.1 [−0.7 to 0.6]	−0.2 [−0.7 to 0.4]
Small for gestational age	17 (20)	27 (31)	17 (21)	24 (29)

Categorical data are presented as number (%) and were tested using the χ^2 test. Continuous data are presented as the median [IQR] and were tested using the Mann-Whitney *U* test.
*Data of 3 patients missing.
†Data of 9 patients missing.
‡Data of 17 patients missing.
§Data of 1 patient missing.
¶Data of 2 patients missing.
**Data of 12 patients missing.

Table II. Neonatal outcomes

Outcomes	12 months corrected age			24 months corrected age		
	Mixed lipid emulsion (n = 86)	Soybean oil (n = 88)	*P* value	Mixed lipid emulsion (n = 81)	Soybean oil (n = 83)	*P* value
Hospitalization (d)	87 [70 to 109]	83 [69 to 99]	.40	86 [70 to 109]	82 [69 to 99]	.47
Cholestasis	8 (9.3)	13 (15)	.27	8 (9.9)	12 (15)	.37
Retinopathy of prematurity (any)	55 (64)	50 (57)*	.38	50 (62)	46 (55)	.41
Highest grade (grade 1-5)	1.5 [0 to 2]*	1 [0 to 2]	.50	1 [0 to 2]	1 [0 to 2]	.54
Requiring treatment (severe)	9 (11)	9 (10)*	.98	8 (9.9)	8 (9.6)	.96
Sepsis, culture proven	21 (24)	22 (25)	.93	19 (24)	20 (24)	.92
Intraventricular hemorrhage III/IV	8 (9.3)	4 (4.5)	.22	8 (9.9)	4 (4.8)	.21
Cystic periventricular leukomalacia	3 (3.5)	2 (3.4)	.98	3 (3.7)	3 (3.6)	.98
Necrotizing enterocolitis (grade ≥IIa)	3 (3.5)	5 (5.7)	.49	3 (3.7)	4 (4.8)	.72
Focal intestinal perforation	2 (2.3)	3 (3.4)	.70	2 (2.5)	3 (3.6)	.67
Abdominal surgery	8 (9.3)	10 (11)	.66	8 (9.9)	10 (12)	.66
Days on mechanical ventilation	0 [0 to 11]	1 [0 to 9]	.64	0 [0 to 10]	1 [0 to 9]	.60
Chronic lung disease	17 (20)	17 (19)	.94	15 (19)	17 (21)	.75
Steroid treatment	9 (11)	14 (16)	.29	8 (9.9)	13 (16)	.27
Patent ductus arteriosus requiring treatment	47 (55)	58 (66)	.13	43 (53)	56 (68)	.06
No. of ibuprofen cycles	1 [0 to 2]	1 [0 to 2]	.26	1 [0 to 2]	1 [0 to 2]	.15
Surgical ligation	4 (4.7)	6 (6.8)	.54	3 (3.7)	6 (7.2)	.32
Pulmonary hypertension	17 (20)	20 (23)	.63	16 (20)	18 (22)	.76
Inhaled nitric oxide/sildenafil treatment	14 (16)	19 (22)	.37	13 (16)	17 (21)	.46
Time to full enteral feeds (d)	24 [18 to 38]	24 [18 to 35]	.52	24 [18 to 38]	24 [18 to 35]	.50
Parenteral lipids (d)	22 [16 to 36]	21 [17 to 31]	.73	23 [16 to 36]	21 [17 to 31]	.57
Cumulative amount of parenteral lipids (g/kg)	43 [28 to 70]	42 [30 to 57]	.44	43 [29 to 72]	42 [30 to 57]	.36
Study lipids (g/kg/d)	2 [1.6 to 2.2]	1.9 [1.6 to 2.1]	.28	2 [1.6 to 2.2]	1.9 [1.6 to 2.1]	.29
DHA (mg/kg/d)	43 [35 to 48]	3.8 [3.2 to 4.2]	<.0001	43 [35 to 48]	3.8 [3.2 to 4.3]	<.0001
EPA (mg/kg/d)	47 [39 to 53]	0 [0 to 0]	<.0001	47 [39 to 52]	0 [0 to 0]	<.0001

Categorical data are presented as numbers (%) and were tested using the χ^2 test. Continuous data are presented as the median [IQR] and were tested using the Mann-Whitney *U* test. *P* values of <.05 were considered statistically significant.
*Data of 1 patient missing.

scores. Analysis of subgroups with particular risk for unfavorable outcome (birth weight of <750 g, **Table VII** [available at www.jpeds.com]; low parental education, **Table VIII** [available at www.jpeds.com]) revealed no statistically significant difference between the 2 groups. No significant sex specific effect of the mixed lipid emulsion on neurodevelopment (**Table IX**; available at www.jpeds.com) was found.

At 24 months corrected age, infants with cerebral palsy were classified using the GMFCS. In both groups, 13 infants were diagnosed with cerebral palsy with no difference in severity between those randomized to soybean oil (GMFCS 1, n = 11; GMFCS, 2 n = 1; GMFCS 3, n = 0; GMFCS 4, n = 1) and the mixed lipid emulsion (GMFCS, 1 n = 9; GMFCS 2, n = 2; GMFCS 3, n = 2; GMFCS 4, n = 0).

Table V. Anthropometry at 12 and 24 months corrected age

Parameter	12 months corrected age			24 months corrected age		
	Mixed lipid emulsion (n = 86)	Soybean oil (n = 88)	*P* value	Mixed lipid emulsion (n = 81)	Soybean oil (n = 83)	*P* value
Body weight (kg)	8.9 [8 to 10]*	8.95 [8.1 to 9.9]†	.98	11.4 [10.2 to 12.9]‡	11.6 [10.2 to 12.9]§	.84
Z-score	−0.57 [−1.5 to 0.4]*	−0.44 [−1.39 to 0.41]†	.93	−0.22 [−1.09 to 0.68]‡	−0.2 [−1.21 to 0.57]§	.95
Height (cm)	74 [72 to 76]‡	74 [71.63 to 76]¶	.90	85 [82 to 88]‡	85 [83 to 88]§	.83
Z score	−0.59 [−1.25 to 0.38]‡	−0.5 [−1.25 to 0.28]¶	.94	−0.59 [−1.4 to 0.23]‡	−0.59 [−1.29 to 0.22]§	.95
Body mass index	16.3 [15.1 to 17.9]‡	16.3 [14.9 to 17.2]†	.51	15.7 [14.9 to 16.9]‡	15.8 [14.9 to 17.1]§	.99
Head circumference (cm)	45 [43.9 to 46]§	45 [43.7 to 46.3]**	.78	47 [46 to 48.5]*	47 [46 to 48]†	.54
Z score	−1.2 [−2.06 to 0.01]§	−1.1 [−2.3 to 0.5]**	.94	−0.95 [−1.82 to 0.07]*	−0.98 [−2.49 to −0.33]†	.30

Continuous data are presented as the median [IQR] and were tested using the Mann-Whitney *U* test. *P* values of <.05 were considered statistically significant.
*Data of 8 patients missing.
†Data of 10 patients missing.
‡Data of 7 patients missing.
§Data of 9 patients missing.
**Data of 11 patients missing.
¶Data of 12 patients missing.

Table VI. Bayley-III scores at 12 and 24 months corrected age

Scores	12 months corrected age			24 months corrected age		
	Mixed lipid emulsion (n = 86)	Soybean oil (n = 88)	*P* value	Mixed lipid emulsion (n = 81)	Soybean oil (n = 83)	*P* value
Cognitive composite score	95 [85-101]	95 [85-100]*	.71	95 [80-105]*	95 [90-105]*	.17
Language composite score	86 [77-94]*	89 [79-95]†	.48	89 [75-97]‡	89 [77-100]§	.54
Motor composite score	88 [76-94]*	88 [79-94]*	.69	94 [82-103]*	94 [85-103]†	.53

Continuous data are presented as the median [IQR] and were tested using the Mann-Whitney *U* test. *P* values <.05 were considered statistically significant.
*Data of 1 patient missing.
†Data of 2 patients missing.
§Data of 3 patients missing.
‡Data of 5 patients missing.

Mixed Model Linear Regression Analysis

After exclusion of patients with missing values in covariates, the sample size for the regression analysis was 153 for infants and 139 for mothers. Parenteral nutrition using the mixed lipid emulsion had no significant influence on cognitive, language, or motor scores at 12 months (**Table X**; available at www.jpeds.com) and 24 months (**Table XI**; available at www.jpeds.com). Parental education was significantly associated with cognitive and language, but not motor scores at 24 months of corrected age. Intraventricular hemorrhage and male sex had a significant negative impact on all 3 scores at 12 and 24 months of corrected age. There were no associations between gestational age and 12 or 24 month developmental outcomes.

Discussion

There were no significant differences in neurodevelopmental outcomes at 12 and 24 months corrected age in ELBW infants participating in this randomized trial comparing neonatal parenteral nutrition using a mixed lipid emulsion containing fish oil with a soybean oil-based lipid emulsion. Follow-up studies on neurodevelopment are crucial to demonstrate safety of novel interventions in neonatology but studies of new lipid emulsions that provide DHA have not reported on neurodevelopmental outcome.[16,17]

DHA promotes the development of neurons and comprises 30%-40% of the brain's grey matter.[18-22] The in utero supply is regulated by the placenta and peaks in the third trimester.[22,23] Extremely preterm infants miss out this period of maximum DHA supply and cannot sufficiently convert precursor fatty acids to LC-PUFAs.[4] The hypothesis that an additional supply of DHA to preterm infants is beneficial for their neurodevelopment is based on high cerebral DHA levels, the subtle effects of DHA deprivation in animal studies, and more pronounced effects in vitro.[19,20,22,24-28] Yet, clinical trials in preterm infants that aimed at improving neurodevelopmental outcome by enteral DHA supplementation did not provide clear evidence for a benefit.[29] Whether parenteral DHA supply using lipid emulsions would be more efficient than enteral supply is speculative, but it might be of additional value. Parenteral lipid emulsions can be provided right after birth in adequate concentrations to close the gap in DHA supply until full enteral feeds are established, typically after a few weeks post partum.[30] Studies in piglets demonstrated enrichment of DHA in the brain using a mixed lipid emulsion.[31] In this context, our previous finding of accelerated maturation of amplitude-integrated electroencephalogram assessed between birth and hospital discharge may point out to cerebral DHA incorporation using the mixed lipid emulsion in preterm infants.[9] This created considerable expectations for neurodevelopmental follow-up, but we found no measurable impact on the neurodevelopmental outcome at 12 and 24 months corrected age in this study. In vitro studies showed positive effects of DHA on synaptic protein expression, but no influence on absolute neurite numbers.[18,28] It seems possible that changes in synaptic activity caused a transient impact on electrophysiologic brain activity using the mixed lipid emulsion in infants of this cohort, without significantly affecting their neurodevelopment, perhaps owing to a missing effect on total neurite numbers.[9,29,32]

Besides DHA, ARA is also highly concentrated in the brain and relevant for growth and neurodevelopment.[33,34] In enteral nutrition, ARA should meet at least DHA levels.[35] ARA concentrations are 5 times lower than DHA concentrations in the mixed lipid emulsion, but still higher than those found in a soybean oil-based lipid emulsion.[11] Yet, ARA levels in the blood have been shown to decrease in infants receiving the mixed lipid emulsion compared with soybean oil-based lipid emulsions.[16] This phenomenon could be due to decreased conversion, replacement of ARA by DHA/EPA, or a shift to other tissues.[36-38] Although DHA supply improves, ARA blood levels decrease, which may potentially outweigh positive effects of DHA. This raised concerns about long-term clinical safety concerning growth and development.[16] Yet, we did not find a statistically significant effect on neurodevelopment or growth.

Clinical trials on LC-PUFA enriched infant formula for preterm infants has inconsistently demonstrated a benefit for neurodevelopmental outcome.[32,39-43] Studies that found a significant influence did so only after subgrouping: Fewtrell et al found higher mental developmental indices in boys and Makrides et al reported on a similar benefit for girls.[39,40] An analysis of infants of this trial showed higher Bayley-III scores in girls, but no sex-specific neurodevelopmental

advantage using the mixed lipid emulsion. Furthermore, it is well-established that parental education influences children's cognitive abilities.[44] Lien et al proposed a benefit of LC-PUFA supplementation for disadvantaged infants with poor education.[23] In our trial, language and cognitive scores of preterm infants were strongly influenced by parental education (**Table X** and **Table XI**), but there was no significant effect of the mixed lipid emulsion in infants whose parents had a low educational background (**Table VIII**). Another subgroup with a particular risk for unfavorable development that might benefit from DHA supplementation are the smallest infants with birth weights of <750 g, but again there was no significant neurodevelopmental advantage of the mixed lipid emulsion (**Table IV**).

Our study has limitations. Neurodevelopment was a secondary outcome and the study was not powered for assessment of neurodevelopment, with rather small numbers leading to wide CIs. On the other hand, the quality of our trial was high with minimal risk for bias, loss to follow-up was low with 20%, and without a statistically significant difference in numbers and important clinical characteristics of patients lost to follow-up.[45]

The calculated parenteral supply with DHA using the mixed lipid emulsion was 43 mg/kg/d. This is at the lower end of published fetal accretion rates (40-67 mg/kg/d). Although infants received higher amounts of DHA using the mixed lipid emulsion, even more DHA would be needed to reach in utero supply in all infants. Moreover, DHA in enteral nutrition is still far too low to meet in utero levels after weaning from parenteral nutrition, and deficiency at discharge is likely. As analysis of plasma fatty acids was not part of our study, we cannot report on blood fatty acid levels.

It is also possible that the nutritional DHA deficits were not pronounced enough in our study to exert an effect on neurodevelopment. In this context, infants of ELBW who received parenteral nutrition for >3 weeks were shown to have a poorer neurodevelopment.[30] In our trial, full feeds were reached after 23 days (IQR, 17-37 days).[8] We thus cannot rule out an effect in infants of ELBW who depend on parenteral nutrition for much longer.

In this study, the type of parenteral lipid emulsion did not significantly affect the neurodevelopmental outcome of preterm infants of ELBW at 12 and 24 months corrected age. Further information on neurodevelopmental outcome will be gathered in another follow-up analysis using the Kaufmann Assessment Battery for Children at 5.5 years of age. Future trials should aim at investigating the effects of a combined approach of parenteral and enteral DHA supply starting from the first day of life, and should also consider providing ARA in amounts equal to DHA. ■

Submitted for publication Mar 3, 2020; last revision received Jun 18, 2020; accepted Jun 18, 2020.

Reprint requests: Andreas Repa, MD, Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria. E-mail: andreas.repa@meduniwien.ac.at

Data Statement

Data sharing statement available at www.jpeds.com.

References

1. Mercier CE, Dunn MS, Ferrelli KR, Howard DB, Soll RF, Vermont Oxford Network EIF-USG. Neurodevelopmental outcome of extremely low birth weight infants from the Vermont Oxford network: 1998-2003. Neonatology 2010;97:329-38.
2. Joosten K, Embleton N, Yan W, Senterre T. ESPGHAN/ESPEN/ESPR/CSPEN Working Group on Pediatric Parenteral Nutrition. ESPGHAN/ESPEN/ESPR guidelines on pediatric parenteral nutrition: energy. Clin Nutr 2018;37:2309-14.
3. Chan SH, Johnson MJ, Leaf AA, Vollmer B. Nutrition and neurodevelopmental outcomes in preterm infants: a systematic review. Acta Paediatr 2016;105:587-99.
4. Harris WS, Baack ML. Beyond building better brains: bridging the docosahexaenoic acid (DHA) gap of prematurity. J Perinatol 2015;35:1-7.
5. Koletzko B, Agostoni C, Carlson SE, Clandinin T, Hornstra G, Neuringer M, et al. Long chain polyunsaturated fatty acids (LC-PUFA) and perinatal development. Acta Paediatr 2001;90:460-4.
6. Lapillonne A, Jensen CL. Reevaluation of the DHA requirement for the premature infant. Prostaglandins Leukot Essent Fatty Acids 2009;81:143-50.
7. Smith SL, Rouse CA. Docosahexaenoic acid and the preterm infant. Matern Health Neonatol Perinatol 2017;3:22.
8. Repa A, Binder C, Thanhaeuser M, Kreissl A, Pablik E, Huber-Dangl M, et al. A mixed lipid emulsion for prevention of parenteral nutrition associated cholestasis in extremely low birth weight infants: a randomized clinical trial. J Pediatr 2018;194:87-93.e1.
9. Binder C, Giordano V, Thanhaeuser M, Kreissl A, Huber-Dangl M, Longford N, et al. A mixed lipid emulsion containing fish oil and its effect on electrophysiological brain maturation in infants of extremely low birth weight: a secondary analysis of a randomized clinical trial. J Pediatr 2019;211:46-53.
10. Rayyan M, Devlieger H, Jochum F, Allegaert K. Short-term use of parenteral nutrition with a lipid emulsion containing a mixture of soybean oil, olive oil, medium-chain triglycerides, and fish oil: a randomized double-blind study in preterm infants. JPEN J Parenter Enteral Nutr 2012;36:81S-94S.
11. D'Ascenzo R, Savini S, Biagetti C, Bellagamba MP, Marchionni P, Pompilio A, et al. Higher docosahexaenoic acid, lower arachidonic acid and reduced lipid tolerance with high doses of a lipid emulsion containing 15% fish oil: a randomized clinical trial. Clin Nutr 2014;33:1002-9.
12. Klebermass-Schrehof K, Wald M, Schwindt J, Grill A, Prusa AR, Haiden N, et al. Less invasive surfactant administration in extremely preterm infants: impact on mortality and morbidity. Neonatology 2013;103:252-8.
13. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr 2013;13:59.
14. Bayley NB. Scales of Infant and Toddler Development - Third Edition. J Psychoeduc Assess 2006;25:180-98.
15. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39:214-23.
16. Zhao Y, Wu Y, Pei J, Chen Z, Wang Q, Xiang B. Safety and efficacy of parenteral fish oil-containing lipid emulsions in premature neonates. J Pediatr Gastroenterol Nutr 2015;60:708-16.
17. Anez-Bustillos L, Dao DT, Baker MA, Fell GL, Puder M, Gura KM. Intravenous fat emulsion formulations for the adult and pediatric patient: understanding the differences. Nutr Clin Pract 2016;31:596-609.
18. Tanaka K, Farooqui AA, Siddiqi NJ, Alhomida AS, Ong WY. Effects of docosahexaenoic Acid on neurotransmission. Biomol Ther (Seoul) 2012;20:152-7.

19. Georgieff MK. Nutrition and the developing brain: nutrient priorities and measurement. Am J Clin Nutr 2007;85:614S-20S.
20. Calderon F, Kim HY. Docosahexaenoic acid promotes neurite growth in hippocampal neurons. J Neurochem 2004;90:979-88.
21. Dai YJ, Sun LL, Li MY, Ding CL, Su YC, Sun LJ, et al. Comparison of formulas based on lipid emulsions of olive oil, soybean oil, or several oils for parenteral nutrition: a systematic review and meta-analysis. Adv Nutr 2016;7:279-86.
22. Kuipers RS, Luxwolda MF, Offringa PJ, Boersma ER, Dijck-Brouwer DA, Muskiet FA. Fetal intrauterine whole body linoleic, arachidonic and docosahexaenoic acid contents and accretion rates. Prostaglandins Leukot Essent Fatty Acids 2012;86:13-20.
23. Lien EL, Richard C, Hoffman DR. DHA and ARA addition to infant formula: current status and future research directions. Prostaglandins Leukot Essent Fatty Acids 2018;128:26-40.
24. Mun JG, Legette LL, Ikonte CJ, Mitmesser SH. Choline and DHA in maternal and infant nutrition: synergistic implications in brain and eye health. Nutrients 2019;11:1125.
25. Janssen CI, Zerbi V, Mutsaers MP, de Jong BS, Wiesmann M, Arnoldussen IA, et al. Impact of dietary n-3 polyunsaturated fatty acids on cognition, motor skills and hippocampal neurogenesis in developing C57BL/6J mice. J Nutr Biochem 2015;26:24-35.
26. Kodas E, Galineau L, Bodard S, Vancassel S, Guilloteau D, Besnard JC, et al. Serotoninergic neurotransmission is affected by n-3 polyunsaturated fatty acids in the rat. J Neurochem 2004;89:695-702.
27. Tam EW, Chau V, Barkovich AJ, Ferriero DM, Miller SP, Rogers EE, et al. Early postnatal docosahexaenoic acid levels and improved preterm brain development. Pediatr Res 2016;79:723-30.
28. Cao D, Kevala K, Kim J, Moon HS, Jun SB, Lovinger D, et al. Docosahexaenoic acid promotes hippocampal neuronal development and synaptic function. J Neurochem 2009;111:510-21.
29. Moon K, Rao SC, Schulzke SM, Patole SK, Simmer K. Longchain polyunsaturated fatty acid supplementation in preterm infants. Cochrane Database Syst Rev 2016;12:CD000375.
30. Vohr BR, Wright LL, Dusick AM, Perritt R, Poole WK, Tyson JE, et al. Center differences and outcomes of extremely low birth weight infants. Pediatrics 2004;113:781-9.
31. Molina TL, Stoll B, Mohammad M, Mohila CA, Call L, Cui L, et al. New generation lipid emulsions increase brain DHA and improve body composition, but not short-term neurodevelopment in parenterally-fed preterm piglets. Brain Behav Immun 2019;85:46-56.
32. Wang Q, Cui Q, Yan C. The effect of supplementation of long-chain polyunsaturated fatty acids during lactation on neurodevelopmental outcomes of preterm infant from infancy to school age: a systematic review and meta-analysis. Pediatr Neurol 2016;59:54-61.e1.
33. Clandinin MT, Chappell JE, Leong S, Heim T, Swyer PR, Chance GW. Intrauterine fatty acid accretion rates in human brain: implications for fatty acid requirements. Early Hum Dev 1980;4:121-9.
34. Hadley KB, Ryan AS, Forsyth S, Gautier S, Salem N Jr. The essentiality of arachidonic acid in infant development. Nutrients 2016;8:216.
35. Koletzko B, Bergmann K, Brenna JT, Calder PC, Campoy C, Clandinin MT, et al. Should formula for infants provide arachidonic acid along with DHA? A position paper of the European Academy of Paediatrics and the Child Health Foundation. Am J Clin Nutr 2020;111:10-6.
36. Wainwright PE, Xing HC, Mutsaers L, McCutcheon D, Kyle D. Arachidonic acid offsets the effects on mouse brain and behavior of a diet with a low (n-6):(n-3) ratio and very high levels of docosahexaenoic acid. J Nutr 1997;127:184-93.
37. Calder PC. Mechanisms of action of (n-3) fatty acids. J Nutr 2012;142:592S-9S.
38. Garg ML, Wierzbicki AA, Thomson AB, Clandinin MT. Omega-3 fatty acids increase the arachidonic acid content of liver cholesterol ester and plasma triacylglycerol fractions in the rat. Biochem J 1989;261:11-5.
39. Makrides M, Gibson RA, McPhee AJ, Collins CT, Davis PG, Doyle LW, et al. Neurodevelopmental outcomes of preterm infants fed high-dose docosahexaenoic acid: a randomized controlled trial. JAMA 2009;301:175-82.
40. Fewtrell MS, Abbott RA, Kennedy K, Singhal A, Morley R, Caine E, et al. Randomized, double-blind trial of long-chain polyunsaturated fatty acid supplementation with fish oil and borage oil in preterm infants. J Pediatr 2004;144:471-9.
41. Meldrum SJ, D'Vaz N, Simmer K, Dunstan JA, Hird K, Prescott SL. Effects of high-dose fish oil supplementation during early infancy on neurodevelopment and language: a randomised controlled trial. Br J Nutr 2012;108:1443-54.
42. O'Connor DL, Hall R, Adamkin D, Auestad N, Castillo M, Connor WE, et al. Growth and development in preterm infants fed long-chain polyunsaturated fatty acids: a prospective, randomized controlled trial. Pediatrics 2001;108:359-71.
43. Westerberg AC, Schei R, Henriksen C, Smith L, Veierod MB, Drevon CA, et al. Attention among very low birth weight infants following early supplementation with docosahexaenoic and arachidonic acid. Acta Paediatr 2011;100:47-52.
44. Linsell L, Malouf R, Morris J, Kurinczuk JJ, Marlow N. Prognostic factors for poor cognitive development in children born very preterm or with very low birth weight: a systematic review. JAMA Pediatr 2015;169:1162-72.
45. Kapoor V, Malviya MN, Soll R. Lipid emulsions for parenterally fed preterm infants. Cochrane Database Syst Rev 2019;6:CD013163.

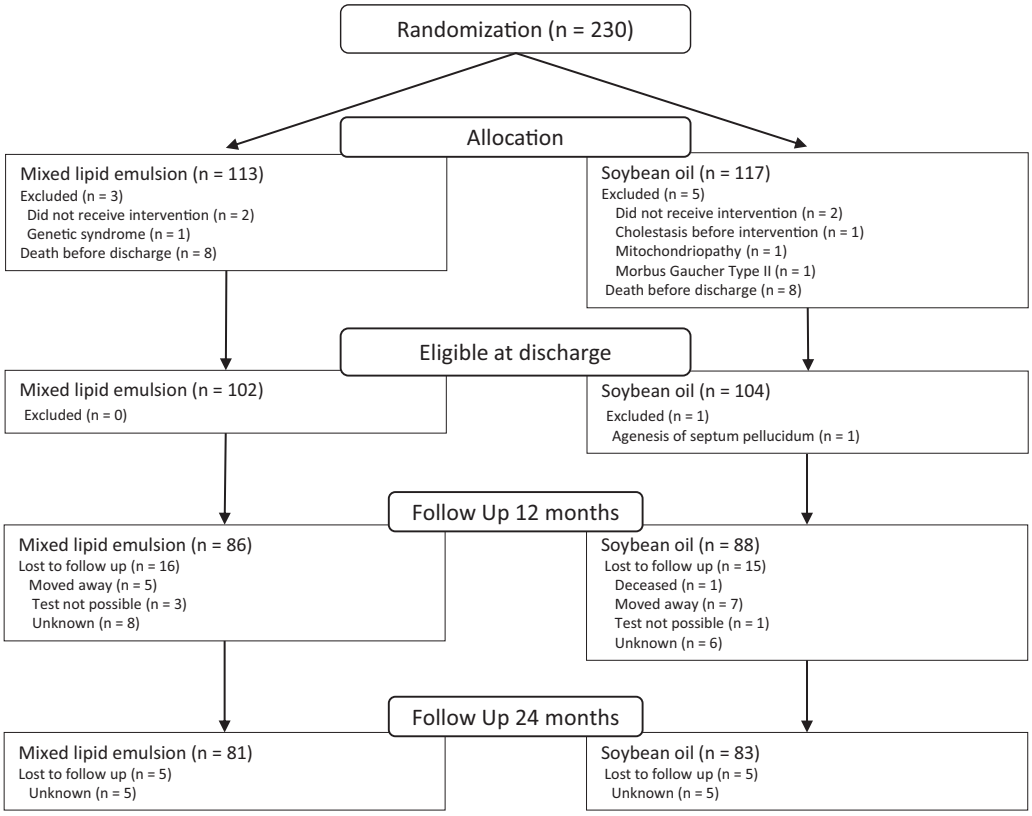

Figure. Patient flow chart with the reasons for study exclusion.

Table III. Characteristics of those lost to follow-up at 12 and 24 months corrected age

	12 months corrected age			24 months corrected age		
	Mixed lipid emulsion (n = 27)	Soybean oil (n = 28)	*P* value	Mixed lipid emulsion (n = 32)	Soybean oil (n = 33)	*P* value
Male sex	14 (51.9)	19 (65.5)	.23	17 (53.1)	20 (58.8)	.54
Gestational age	$26^{6/7}$ [$24^{3/7}$ to $28^{4/7}$]	$26^{0/7}$ [$24^{3/7}$ to $28^{0/7}$]	.44	$26^{4/7}$ [$24^{3/7}$ to $28^{2/7}$]	$26^{0/7}$ [$24^{3/7}$ to $28^{0/7}$]	.72
Birth weight (g)	890 [605 to 960]	737.5 [590 to 843]	.05	818.5 [612 to 956.3]	700 [582.5 to 840.5]	.07
Z score	−0.6 [−1.2 to 0]	−0.45 [−1.98 to −0.1]	.72	−0.5 [−1.1 to 0]	−0.7 [−1.9 to −0.1]	.33
Intraventricular hemorrhage III/IV	4 (14.8)	6 (20.7)	.53	4 (12.5)	6 (17.6)	.53

Categorical data are presented as number (%) and were tested using the χ^2 test. Continuous data are presented as the median [IQR] and were tested using the Mann-Whitney *U* test. *P* values of <.05 were considered statistically significant.

Table IV. Neonatal outcome in infants born <750 g

	12 months corrected age			24 months corrected age		
Variables	Mixed lipid emulsion (n = 35)	Soybean oil (n = 40)	*P* value	Mixed lipid emulsion (n = 32)	Soybean oil (n = 36)	*P* value
Hospitalization (d)	104 [85-115]	91.5 [82.3-113]	.313	104 [85.3-115.8]	91.5 [79.8-116]	.357
Cholestasis	3 (8.6)	10 (25)	.061	3 (9.4)	9 (25)	.092
Retinopathy of prematurity (any)	30 (85.7)	28 (70)	.105	27 (84.4)	24 (66.7)	.092
Requiring treatment (severe)	6 (17.1)	8 (20)	.751	5 (15.6)	7 (19.4)	.68
Sepsis, culture proven	10 (28.6)	15 (37.5)	.413	9 (28.1)	13 (36.1)	.482
Intraventricular hemorrhage III/IV	5 (14.3)	3 (7.5)	.342	5 (15.6)	3 (8.3)	.352
Cystic periventricular leukomalacia	1 (2.9)	0 (0)	.282	1 (3.1)	0 (0)	.285
Necrotizing enterocolitis (grade ≥IIa)	1 (2.9)	4 (10)	.216	1 (3.1)	3 (8.3)	.362
Focal intestinal perforation	2 (5.7)	2 (5)	.891	2 (6.3)	2 (5.6)	.903
Abdominal surgery	6 (17.1)	7 (17.5)	.967	6 (18.8)	7 (19.4)	.942
Days on mechanical ventilation	6 [0-14]	4.5 [0-16.8]	.934	6.5 [0-13.5]	4.5 [0-16.8]	.904
Chronic lung disease	7 (20)	8 (20)	1	6 (18.8)	8 (22.2)	.724
Steroid treatment	6 (17.1)	10 (25)	.407	5 (15.6)	9 (25)	.34
Patent ductus arteriosus requiring treatment	23 (65.7)	29 (72.5)	.525	21 (65.6)	27 (75)	.397
Surgical ligation	3 (8.6)	4 (10)	.832	3 (9.4)	4 (11.1)	.814
Pulmonary hypertension	10 (28.6)	13 (32.5)	.713	10 (31.3)	11 (30.6)	.951
Inhaled nitric oxide/sildenafil treatment	8 (22.9)	12 (30)	.485	8 (25)	10 (27.8)	.796
Time to full enteral feeds (d)	29 [22-48]	28 [20.3-39]	.69	30 [22-46.3]	28 [20.3-39]	.627
Parenteral lipids (d)	26 [19-39]	25.5 [20-38]	.89	26 [20.5-41.3]	25.5 [20-38]	.676
Cumulative amount of parenteral lipids (g/kg)	46.5 [30.5-73.8]	46.92 [35.3-63.2]	.987	48.4 [30.7-76.6]	49 [35.3-63.2]	.868
Study lipids (g/kg/d)	1.8 [1.6-2.1]	1.8 [1.6-2.0]	.932	1.8 [1.4-2.1]	1.8 [1.6-2.0]	.966
DHA (mg/kg/d)	40 [34.2-46.3]	3.9 [3.2-4.0]	<.0001	40 [31.8-46.1]	3.9 [3.2-4.0]	<.0001
EPA (mg/kg/d)	44.2 [37.3-50.5]	0 [0-0]	<.0001	44.1 [34.7-50.2]	0 [0-0]	<.0001

Categorical data are presented as number (%) and were tested using the χ^2 test. Continuous data are presented as the median [IQR] and were tested using the Mann-Whitney *U* test. *P* values of <.05 were considered statistically significant.

Table VII. Bayley-III scores at 12 and 24 months corrected age in patients born <750 g

	12 months corrected age			24 months corrected age		
Scores	Mixed lipid emulsion (n = 35)	Soybean oil (n = 39)	*P* value	Mixed lipid emulsion (n = 32)	Soybean oil (n = 36)	*P* value
Cognitive composite score	90 [80-95]	90 [80-100]*	.43	90 [80-105]*	93 [86-105]	.20
Language composite score	86 [77-97]*	89 [77-94]*	.90	89 [77-97]*	88 [74-100]†	.78
Motor composite score	82 [76-94]*	88 [73-94]*	.36	91 [82-100]	94 [85-104]†	.36

Continuous data are presented as the median [IQR] and were tested using the Mann-Whitney *U* test. *P* values <.05 were considered statistically significant.
*Data of 1 patient missing.
†Data of 2 patients missing.

Table VIII. Bayley-III scores at 12 and 24 months corrected age in patients with low parental education

	12 months corrected age			24 months corrected age		
	Mixed lipid emulsion (n = 29)	Soybean oil (n = 29)	*P* value	Mixed lipid emulsion (n = 28)	Soybean oil (n = 26)	*P* value
Cognitive composite score	95 [85-100]	95 [83-104]	.75	90 [71-105]	90 [80-105]	.79
Language composite score	86 [76-95]	85 [78-91]	.84	88 [63-95]*	81 [69-96]*	.73
Motor composite score	88 [77-97]	88 [77-94]	.89	91 [82-100]	91 [85-102]	.74

Continuous data are presented as the median [IQR] and were tested using the Mann-Whitney *U* test. *P* values of <.05 were considered statistically significant.
*Data of 2 patients missing.

Table IX. Bayley-III scores at 12 and 24 months corrected age in boys and girls

	12 months corrected age			24 months corrected age		
Scores	**Mixed lipid emulsion**	**Soybean oil**	***P* value**	**Mixed lipid emulsion**	**Soybean oil**	***P* value**
Boys	n = 51	n = 57		n = 48	n = 56	
Cognitive composite score	90 [80-100]	90 [85-100]*	.25	90 [79-100]	95 [85-105]*	.16
Language composite score	81 [74-91]*	86 [75-94]†	.67	83 [68-97]‡	83 [73-98]†	.53
Motor composite score	86 [73-94]*	88 [79-97]*	.42	91 [82-100]*	91 [85-103]*	.41
Girls	n = 35	n = 31		n = 33	n = 27	
Cognitive composite score	95 [95-105]	100 [95-105]	.77	100 [85-110]*	100 [90-115]	.42
Language composite score	89 [79-100]	94 [86-97]	.35	94 [81-108]*	97 [89-103]*	.62
Motor composite score	91 [82-97]	91 [88-94]	.68	100 [90-106]	97 [94-108]*	.52

Continuous data are presented as the median [IQR] and were tested using the Mann-Whitney *U* test. *P* values of <.05 were considered statistically significant.
*Data of 1 patient missing.
†Data of 2 patients missing.
‡Data of 4 patients missing.

Table X. Mixed model linear regression analysis at 12 months corrected

Scores	**Estimate**	**Std. error**	**95% CI**	***P* value**
Cognitive score				
Mixed lipid emulsion	0.672	1.736	−2.73 to 4.07	.70
Male sex	−5.576	2.022	−9.54 to −1.61	<.01
Gestational age (days)	0.041	0.085	−0.13 to 0.21	.63
Parental education	1.128	1.359	−1.54 to 3.79	.41
Intraventricular hemorrhage III-IV	−15.133	3.406	−21.81 to −8.46	<.0001
Language score				
Mixed lipid emulsion	0.259	2.304	−4.26 to 4.77	.91
Male sex	−7.775	2.397	−12.47 to −3.08	<.01
Gestational age (days)	−0.068	0.092	−0.25 to 0.11	.46
Parental education	−0.214	1.450	−3.06 to 2.63	.88
Intraventricular hemorrhage III-IV	−9.694	4.284	−18.09 to −1.3	<.05
Motor score				
Mixed lipid emulsion	0.383	2.075	−3.68 to 4.45	.85
Male sex	−1.064	2.257	−5.49 to 3.36	.64
Gestational age (days)	−0.042	0.089	−0.22 to 0.13	.64
Parental education	0.524	1.409	−2.24 to 3.28	.71
Intraventricular hemorrhage III-IV	−23.278	3.956	−31.03 to −15.52	<.0001

Bayley-III scores at 12 months were analyzed in a mixed model with mother and child as random factor, included confounders were male sex, gestational age, parental education, and intraventricular hemorrhage grade III and IV.

Table XI. Mixed model linear regression analysis at 24 months corrected

Scores	Estimate	Std. error	95% CI	*P* value
Cognitive score				
Mixed lipid emulsion	−2.350	2.003	−6.28 to 1.58	.25
Male sex	−8.830	2.485	−13.7 to 3.96	<.001
Gestational age (days)	−0.034	0.101	−0.23 to 0.16	.74
Parental education	5.812	1.648	2.58 to 9.04	<.001
Intraventricular hemorrhage III-IV	−21.527	4.322	−30.00 to −13.06	<.0001
Language score				
Mixed lipid emulsion	−2.640	1.982	−6.52 to 1.24	.19
Male sex	−5.990	2.338	−10.57 to −1.41	<.05
Gestational age (days)	−0.057	0.103	−0.26 to 0.15	.58
Parental education	5.696	1.675	2.41 to 8.98	<.001
Intraventricular hemorrhage III-IV	−11.639	3.813	−19.11 to −4.17	<.01
Motor score				
Mixed lipid emulsion	−2.791	2.008	−6.73 to 1.15	.17
Male sex	−7.780	2.317	−12.32 to −3.24	<.01
Gestational age (days)	−0.058	0.093	−0.24 to 0.12	.53
Parental education	2.700	1.498	−0.24 to 5.64	.07
Intraventricular hemorrhage III-IV	−25.067	3.985	−32.88 to −17.26	<.0001

Bayley-III scores at 24 months were analyzed in a mixed model with mother and child as random factor, included confounders were male sex, gestational age, parental education, and intraventricular hemorrhage grade III and IV.