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Two-Year Neurodevelopment and Growth Outcomes for Preterm Neonates Who Received Low-Dose Intravenous Soybean Oil

Margaret L. Ong, MD¹, Isabell B. Purdy, PhD², Orly L. Levit, MD³, Daniel T. Robinson, MD⁴, Tristan Grogan, MS⁵, Martiniano Flores, MS⁶, and Kara L. Calkins, MD, MS^{2,*}

¹David Geffen School of Medicine, University of California, Los Angeles, California, USA

²Neonatal Research Center of the UCLA Children's Discovery and Innovation Institute, Division of Neonatology and Developmental Biology, Department of Pediatrics, David Geffen School of Medicine, University of California, Los Angeles, California, USA

³Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut, USA

⁴Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

⁵Statistics Core, Department of Medicine, University of California, Los Angeles, California, USA

⁶Department of Biostatistics, Fielding School of Public Health, University of California, Los Angeles, California, USA

Abstract

Background—In some studies, the dose of intravenous soybean oil (SO) has been associated with a decreased incidence of intestinal failure–associated liver disease. The effect of lipid sparing on neurodevelopment (ND) and growth remains unknown. This study investigated the impact of SO dose on ND and growth over the first 2 years of age in preterm neonates.

Materials and Methods—This is a single-site prospective follow-up study. Neonates with a gestational age ≥ 29 weeks were randomized to low-dose (LOW) or standard-dose (CON) SO. Bayley Scales of Infant Development III and anthropometric measurements were collected at approximately 6, 12, and 24 months corrected gestational age.

Results—Subjects were premature, with a mean ($\pm$ SD) gestational age of 28 ± 1 and 27 ± 1 weeks ($P = .3$) for LOW and CON, respectively. Thirty subjects completed follow-up (LOW = 15, CON = 15). There were no differences for ND and growth outcomes when LOW was compared with CON, with the exception of a higher 12-month follow-up cognitive scaled score in the LOW group ($P = .02$).

*Corresponding author: Kara L. Calkins, MD, MS, Neonatal Research Center of the UCLA Children's Discovery and Innovation Institute, Division of Neonatology and Developmental Biology, Department of Pediatrics, David Geffen School of Medicine at UCLA, 10833 Le Conte Avenue, Room B2375 MDCC, Los Angeles, CA 90095, USA. kcalkins@mednet.ucla.edu.

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Conclusion—A reduced SO dose did not adversely affect ND or growth in this cohort of preterm neonates. However, larger studies are needed to determine the long-term safety of SO dose reduction before this strategy can be adopted.

Keywords

neonates; prematurity; lipids; fatty acids; soybean oil; parenteral nutrition; growth; neurodevelopment

Introduction

Neonates who are extremely premature (gestational age [GA] <29 weeks) and low birth weight (<1 kg) depend on parenteral nutrition (PN) for optimal nutrition. Prolonged courses of PN are associated with intestinal failure–associated liver disease (IFALD), defined as a direct bilirubin level >2 mg/dL when other causes of liver dysfunction have been excluded.^{1–4} On liver biopsy, IFALD is initially characterized by cholestasis.⁵ Reports indicate that after approximately 6 weeks of PN, cholestasis can be accompanied by fibrosis, which can progress to liver failure.⁵ Neonates, especially preterm neonates, are at high risk for IFALD for several reasons—a lack of enteral nutrition (EN) due to feeding intolerance and necrotizing enterocolitis, sepsis, and an immature liver.^{5,6}

Intravenous fat emulsions are prescribed with PN to provide essential fatty acids and nonprotein energy. In the United States, the only Food and Drug Administration–approved fat emulsion is soy based and typically dosed at 3 g/kg/d in this population. The dose of soybean oil (SO) is linked to IFALD. SO contains high concentrations of proinflammatory omega-6 (ω -6) fatty acids and hepatotoxic phytosterols (plant derived sterols). Inflammation and phytosterols suppress bile acid and bilirubin transporters, causing cholestasis.^{7,8} Given this biological mechanism, clinicians often empirically decrease the dose of SO in attempt to reduce the incidence and severity of IFALD.

While observational data suggest that low-dose (LOW) SO prevents IFALD, in a randomized controlled trial of neonates with a GA <29 weeks, we found no benefit over standard therapy.⁹ Low-dose SO may not be without risks in preterm neonates, since inadequate fat intake and energy could impair growth and neurodevelopment (ND).^{10,11} This is particularly important because 20%–50% of very low birth weight infants have ND delays and growth failure is prevalent in this population.^{10,12}

SO contains the essential fatty acids linoleic (ω -6) and α -linolenic acid (ω -3) but lacks arachidonic (ARA; ω -6) and docosahexaenoic (DHA; ω -3) acids (Table 1). The essential fatty acids serve as precursors to ARA and DHA. Despite SO's provision of linoleic and α -linolenic acid, extremely low birth weight neonates are at high risk for DHA and ARA deficiencies because of premature disruption of the in utero maternal supply of long-chain polyunsaturated fatty acids, decreased exogenous provisions, inadequate conversion of the essential fatty acids into downstream fatty acids, and decreased adipose stores. These deficiencies have been linked to poor growth and ND impairment.^{13–15} Because preterm neonates have suboptimal DHA and ARA stores and a concomitant increased ARA and

DHA need, reducing the dose of SO may exacerbate the risk for an ARA and DHA deficiency.

Therefore, in preterm neonates, it remains unclear if the potential benefit of SO sparing outweighs the potential risk. This study's objective was to determine the impact of LOW SO (approximately 1 g/kg/d, intravenous) compared with standard dose (CON) SO (approximately 3 g/kg/d, intravenous) on ND and growth in preterm neonates over the first 2 years of age.

Methods

Study Outcomes

The primary outcome was ND over time, which was assessed by scaled scores in 5 domains (cognitive, receptive, and expressive language; fine and gross motor) as part of the Bayley Scales of Infant Development III (BSID-III).¹⁶ Secondary outcomes included growth over time (z scores: weight, length, and head circumference for age).^{17,18}

Patient Population

This study was a prospective follow-up (FU) study for the original unmasked multicenter randomized controlled trial (NCT01050660).⁹ Only 1 of the 3 sites participated in this FU study. The other 2 sites were unable to participate due to the inability to assess long-term growth and ND prospectively for 2 years. In the original trial, preterm neonates were randomized after birth to either the LOW or CON group. Inclusion criteria included GA ≥ 29 weeks and age < 48 hours. Exclusion criteria included congenital intrauterine infection, hepatic structural abnormalities, genetic disorders, in-born errors of metabolism, and pH < 6.8 at birth.

Subjects from the original trial were included in this FU study if ND and growth data points were available for at least 1 outpatient visit after discharge from the neonatal intensive care unit (NICU). The healthcare professionals who performed the FU evaluation were unaware of group assignment. Written informed consent was obtained from parents or legal guardians. The University of California, Los Angeles, Institutional Review Board approved the study.

Study Procedures and Methods

Subjects received SO (Intralipid; Fresenius Kabi, Uppsala, Sweden; Table 1).

The primary medical team, using standard NICU guidelines, dictated medical care, EN, and PN prescription, with the exception of SO dose.⁹ PN was infused continuously over 24 hours. Per standard NICU guidelines, maternal breast milk is encouraged, and if not available, donor breast milk is used until approximately 34 weeks corrected GA (CGA) and/or a weight of 1500 g is achieved. Breast milk, donor milk, and premature formula are routinely fortified to ensure optimal nutrition. All neonates receive approximately 2–4 mg/kg/d of iron, along with 800 IU of vitamin D via EN and/or supplements. Upon discharge from the NICU, neonates routinely receive fortified premature formula and breast

milk or fortified premature formula exclusively (if breast milk is not available), along with iron and vitamin D supplements.

Subjects were evaluated as part of routine care at the High Risk Infant Follow-Up Clinic at approximately 6, 12, and 24 months CGA (FU1–FU3, respectively). The BSID-III test was used to measure ND and was conducted by 3 doctorally trained clinicians who work as a team in the High Risk Infant Follow-Up Clinic for clinical and research evaluations. These clinicians have established interrater reliability for the BSID-III examination, which is annually monitored for recertification for local, statewide, and national research projects and clinical assessments.¹⁶

Growth was assessed by z scores, absolute growth measurements, and growth percentiles at birth, status (defined as 60 days of age, transfer to another institution, or death, whichever is first), and FU.^{17–20} Growth measurements were adjusted for prematurity. Growth curves were used as formulated by Olsen et al (for CGA <39 weeks), the World Health Organization (for CGA 39 weeks to 24 months), and the Centers for Disease Control and Prevention (for CGA >24 months). Means and standard deviations to calculate z scores were obtained from data published by Olsen et al (for CGA <39 weeks) and the Centers for Disease Control and Prevention (for CGA >39 weeks).^{17–20} Due to limitations on available data for weight-for-length calculations prior to achieving term age, weight-for-length percentiles and z scores were assessed at FU but not at birth or status. Weight-for-length percentile was calculated by inputting weight, length, and sex into the Baby Infant Growth Chart Calculator with World Health Organization data (for CGA <24 months) and the Children Growth Chart Calculator with Centers for Disease Control and Prevention data (for CGA >24 months).^{21,22} Weight-for-length z scores were then collected with the online Percentile to Z Score Calculator.²³

Statistical Methods and Analysis

Analysis was performed as intention to treat. Continuous variables were analyzed with the Student's t test. Categorical variables were analyzed with the Fisher's exact test. An autoregressive regression model with an analysis of variance set up for time was used for a comparative analysis of growth over time based on the estimated difference in rates of increase from birth, status, and FU1 to FU3 between the 2 groups. This model was also used for comparative analysis for weight for length over time based on estimated difference in rate of change from FU1 to FU3 between the 2 groups. To maximize the statistical power of this procedure given the small sample size, no additional confounding information was included in these models. An autoregressive regression model was also used for a comparative analysis for total and parenteral energy, glucose infusion rates, and SO dose over the first 28 days of age. Univariate regression models were used to investigate the association of birth weight and GA with BSID-III scores. Results are presented as a mean ($\pm$ SD); results from the regression analysis are presented as a mean ($\pm$ SE). Statistical significance was determined as $P < .05$. All statistical analyses were analyzed with SAS 9.3 (SAS Institute Inc, Cary, NC) and R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

At the University of California, Los Angeles, 37 subjects (LOW = 18, CON = 19) consented for the original study. There were no significant differences for GA, birth weight, and common neonatal comorbidities and treatments when the 2 groups were compared (Table 2). Thirty subjects completed FU (LOW = 15, CON = 15; Figure 1). For subjects who completed FU and the 7 subjects who were lost to FU, these variables were similar when the LOW group was compared with the CON group (data not published). FU rates for the LOW and CON groups were comparable (data not published) and approximately 77%, 71%, and 71% for FU1, FU2, and FU3, respectively. When the LOW group was compared with the CON group, GA at status (35 ± 1 vs 35 ± 2 weeks, $P = .5$) and CGA at FU1 (6 ± 1 vs 6 ± 1 months, $P = .6$), FU2 (12 ± 2 , vs 12 ± 3 months, $P = .8$), and FU3 (21 ± 3 vs 21 ± 2 months, $P = .8$) were similar for the 2 groups.

EN was initiated at 11 ± 5 and 8 ± 6 days of age in the LOW and CON groups, respectively ($P = .2$). The majority of subjects received breast milk for the first feed (100% in LOW vs 94% in CON, $P = 1.0$). PN duration was also comparable (LOW: 27 ± 11 days vs CON: 26 ± 16 days, $P = .8$). At 28 days of age, 42% of the LOW group and 44% of the CON group were receiving PN ($P = 1$). As expected, the LOW group received less SO than the CON group at 28 days of age (1.0 ± 0.2 vs 2.6 ± 0.2 g/kg/d, $P < .0001$) and over time (mean difference over the first 28 days, -1.5 g/kg/d, $P < .0001$). However, total energy, PN energy, and glucose infusion rates were similar for the 2 groups (Table 3).

All subjects who completed the study achieved full feeds prior to discharge from the NICU. There was no difference in the type of EN at the time of discharge ($P = .8$). Fifty-three percent of the LOW group and 44% of the CON group were receiving both breast milk and formula, while the remaining subjects were receiving either breast milk or formula exclusively. Ninety-four percent of the LOW group and 89% of the CON group were receiving fortified EN ($P = 1$).

The BSID-III cognitive scaled score was higher in the LOW group versus the CON group at FU2 (12 vs 9, $P = .02$). All other scores were comparable (Figure 2). Composite scores revealed a similar pattern (108 for LOW vs 97 for CON, $P = .02$). There were no significant differences when the LOW group was compared with the CON group for the frequencies of developmental domain scaled and composite scores <1 SD below the normative mean (<7 and <85 , respectively) during FU (Table 4). The frequency of scaled and composite scores falling <2 SD (<4 and <70 , respectively) was rare; thus, no comparisons were made ($n = 2$ for LOW and CON for all scores at all FU time points).

Univariate regression analyses did not reveal a significant association across birth weight, GA, and subtest scaled scores during FU (data not published). The 2 groups were similar for caretaker education level. There were no significant differences between LOW and CON for educational status. Twenty-five percent of the LOW group and 33% of CON group had a high school level or less education. Seventy-five percent of the LOW group and 67% of the CON group had some college education or completed a degree ($P = 1$).

Weight, length, and head circumference z scores, as well as absolute measurements, at each time point were not statistically different between the LOW and CON groups ($P > .4$ for all; Figure 3). Likewise, the frequency for measurements <10th percentile was not significantly different when the 2 groups were compared ($P = .1$, data not published). Z-score changes from FU1 to FU3 were not significantly different when the LOW group was compared with the CON group for weight, length, and head circumference (-0.6 ± 0.9 vs 0.2 ± 1.1 , $P = .08$; 0.6 ± 1.9 vs 0.8 ± 1.6 , $P = .8$; and 0.5 ± 1.2 vs 0.06 ± 0.8 , $P = .4$, respectively). Moreover, an autoregressive regression model to estimate the increase in anthropometric measurements and z scores from birth, status, and FU1 to FU3 demonstrated similar growth over time (Table 5).

Last, weight-for-length percentiles at FU1–FU3 were also similar between the LOW and CON groups. Mean z scores for weight-for-length percentiles were comparable for LOW vs CON at FU1 (-0.4 ± 1.4 vs -0.1 ± 1.3 , $P = .6$), FU2 (-0.1 ± 1 vs -0.2 ± 1 , $P = .7$), and FU3 (-0.4 ± 1.4 vs -0.1 ± 1.3 , $P = .6$). There were no significant differences in means for absolute weight-for-length percentiles between the 2 groups for all 3 FU time points ($P > .4$ for all, data not published). An autoregressive regression model to estimate changes in z scores for weight for length (LOW = -0.3 ± 0.3 , CON = 0.03 ± 0.3 , difference of -0.3 ± 0.5 ; 95% confidence interval, $-0.6, 1.2$; $P = .5$) from FU1 to FU3 showed similar growth over time between the LOW and CON groups.

Discussion

SO serves as a rich source of nonprotein energy, fat, and fatty acids, which are important for premature neonates who are at high risk for nutrient deficiencies, failure to thrive, and ND impairment.^{11,15} However, in some studies, higher doses of SO have been linked to IFALD.^{1–4} Two small randomized controlled trials demonstrated that surgical neonates who received 1 g/kg/d of SO had a slower rise in levels of bilirubin and bile acids when compared with neonates who received 3 g/kg/d of SO.^{3,4} Uncontrolled studies in surgical neonates have also suggested that SO dose reduction prevents and biochemically reverses IFALD.^{1,2} Specifically, in a study by Cober et al, total bilirubin concentrations decreased by 0.73 mg/dL/wk in surgical neonates with IFALD who received 1 g/kg/d of SO twice a week. Yet, total bilirubin concentrations increased by 0.29 mg/dL/wk in historical controls.¹

Such studies prompted our initial investigation: the first multicenter randomized controlled trial that treated 136 very low birth weight infants with either low- or standard-dose SO shortly after birth. In contrast to the above studies, the original study demonstrated that a reduced SO dose did not decrease the incidence of cholestasis or adversely affect short-term growth in extremely premature neonates.⁹ These negative results could be due to this cohort's relatively short PN course and low rate of intestinal surgeries. In our original study, preterm neonates had a median PN duration of approximately 3 weeks.⁹ The mean PN duration for this FU cohort was slightly longer (26–27 days). In contrast, in the randomized controlled trials in surgical neonates described above, the mean PN duration was approximately 5 weeks.^{3,4}

Nevertheless, the effect of fat restriction during a period of critical development on ND and growth beyond the NICU remains unknown and controversial—particularly in preterm neonates without IFALD. In a study of neonatal piglets who were receiving PN, SO dose reduction (10 to 5 g/kg/d) led to a decrease in brain size, which may be concerning for future ND impairments.²⁴ For this reason, we believed that it was important to perform long-term FU on this population. In this study, the LOW and CON groups had similar ND and growth outcomes. The results of this research support a recent retrospective study evaluating growth and development in surgical infants with a mean GA of 35 weeks. Sixty-two neonates qualified for the study, and 25 subjects consented. This study demonstrated no association between SO dose reduction and negative ND outcomes, as measured by 3 parent-reported surveys performed at a subject mean age of 4.5 years (range, 1.5–5.4 years).²⁵ While our study was limited to a FU of approximately 2 years CGA, ND and growth assessments were performed longitudinally and consistently at specific intervals. Other advantages to our research, when compared with this retrospective study, include the study design (prospective), a more homogeneous population (preterm infants only), and a higher FU rate (approximately 70%). In addition, professionals conducted a masked evaluation of ND with the BSID-III, a standardized objective instrument for measurement of early child development. Last, our study population would be considered at higher risk for ND and growth impairments based on their GA and comorbidities.^{10–12}

Important confounders for ND were considered in this study.²⁶ There was no difference between the 2 groups for conditions that are well known to affect growth and ND (grade 3 or 4 intraventricular hemorrhage, necrotizing enterocolitis, sepsis, and bronchopulmonary dysplasia).²⁶ In addition, there were no significant differences between the LOW and CON groups for caretaker education. While we were unable to assess caretaker educational status at each FU, information was available for 70% of our cohort who completed the study. Because of the small sample size, these variables were not included in our regression models.

The scaled and composite BSID-III scores for subjects in our study fell within 1 SD of the standardized mean, suggesting that ND for these preterm infants is not only similar between groups but possibly comparable to the general population. Moreover, our subjects' ND scores are consistent with scores from other preterm populations with the BSID-III.²⁷ Some studies have suggested that the BSID-III may underestimate developmental delay when using a cutoff <2 SD below the normative mean, the standard cutoff for the Mental Developmental Index for the BSID-II.^{27–29} In a study of 185 extremely preterm neonates, BSID-III cognitive and language scores <1 SD were found to have the best agreement with Mental Developmental Index scores <2 SD, previously defined as ND impairment.²⁸ Because the BSID-III is used at our institution and we did not want miss ND impairment, we opted to use a cutoff of <1 SD. With this cutoff, there was no difference between the groups for the frequency of BSID-III scaled scores <7 or composite scores <85, which is equivalent to <1 SD below the normative mean.

Despite these reassuring results, limiting fat intake in preterm neonates may result in a fatty acid deficiency and/or growth failure.^{1,30} An essential fatty acid deficiency is often diagnosed by measuring a serum triene:tetraene ratio (mead acid:ARA). When ω -6 and ω -3

fatty acids are deficient, ω -9 fatty acids are metabolized, resulting in increased mead acid concentrations. Elevated triene:tetraene ratios of >0.2 and 0.05 are considered diagnostic for an essential fatty acid deficiency and subclinical essential fatty acid deficiency, respectively.³⁰ In a cohort of 9 children with intestinal failure who received a mean SO dose of 0.6 g/kg/d, none of the subjects developed IFALD, and the median triene:tetraene ratio was 0.03 .³¹ However, 2 subjects demonstrated a subclinical essential fatty acid deficiency, and mean linoleic acid and/or mead acid concentrations were abnormal in 3 subjects.³¹ In the study by Cober et al, approximately 80% of neonates who received a restricted dose of SO for >1 month exhibited a triene:tetraene ratio >0.05 .¹ In addition, linoleic acid, α -linolenic acid, and ARA concentrations were abnormally low in 3 subjects.¹ In our study, we did not measure fatty acid profiles. Also, we were unable to determine the subjects' fatty acid intake since the majority of our subjects received breast milk and the fatty acid composition of breast milk changes over time and varies among mothers.³² As a result, it remains unknown if any of the subjects in the LOW group developed a subclinical fatty acid or an ARA or DHA deficiency. Future research should include the measurement of fatty acid profiles, specifically for preterm neonates who receive PN for prolonged periods, exhibit poor growth, and/or receive <1 g/kg/d of SO.

Additionally, there is concern for the effect of SO dose reduction on growth. No change in overall growth occurred upon comparison of the 2 groups. Growth in this study was suboptimal as compared with national means, which is consistent with published studies.¹¹ In a study by Rollins et al comparing surgical neonates who received standard SO dose with those who received a lower dose, the latter demonstrated a significantly larger decrease in weight z scores.⁴ In our study, comparison of z-score changes from FU1 to FU3 showed a trend toward poorer weight gain in the LOW group versus the CON group ($P = .08$). Absolute weight difference within an autoregressive regression model demonstrated a similar trend toward decreased weight gain from FU1 to FU3 in the LOW group versus the CON group. It is unclear whether this trend is due to a lower dose of SO or chance, given the study's small sample size.

This FU study shows no significant adverse effect of SO dose reduction on ND and growth outcomes in this specific cohort of preterm neonates. However, caution should be used when interpreting this study's results due its sample size and single-site participation. Moreover, in our original randomized controlled trial, when compared with standard therapy, low-dose SO did not reduce the incidence of cholestasis.⁹ Considering that preterm neonates remain at high risk for growth failure, ND impairment, and fatty acid deficiencies, a low dose of SO is not without potential risks in this population. Hence, the risk-benefit ratio of SO dose reduction in preterm neonates without intestinal pathology, such as necrotizing enterocolitis or IFALD, remains unclear. Future studies with a larger sample size are needed to address this controversial question.

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Clinical Relevance Statement

While it remains to be determined if a low dose of intravenous soybean oil safely decreases the incidence of pediatric intestinal failure–associated liver disease, this strategy has become common clinical practice in many neonatal intensive care units. There is a concern that intravenous lipid sparing could negatively affect neurodevelopment and growth. In this prospective follow-up study, premature neonates who received low-dose intravenous soybean oil had similar neurodevelopment and growth when compared with premature neonates who received a higher dose of soybean oil.

Figure 1.
CONSORT flow diagram.

Figure 2. Neurodevelopmental scores

Mean $\pm$ SD Bayley scaled scores at follow-up time points (A) 6 months, (B) 12 months, and (C) 24 months corrected gestational age. * $P=.02$, 95% confidence interval (0.04, 4.11). Gray bars, low dose. Black bars, standard dose.

Figure 3. Growth

Mean $\pm$ SD for absolute measurements: (A) weight, (B) length, and (C) HC over time. Z-scores for (D) weight, (E) length, and (F) HC over time. $P > .05$ for all. B, birth; CON, standard dose; HC, head circumference; LOW, low dose; St, status; 1–3, follow-up at 6, 12, and 24 months corrected gestational age.

Table 1**Fatty Acid Composition of Intravenous Soybean Oil**

Fatty Acid	Intralipid 20%
Acid, g/100 mL	
Linoleic	5
α -Linolenic	0.9
Arachidonic	0
Eicosapentaenoic	0
Docosahexaenoic	0
Egg phospholipids, g/L	12
Glycerol, g/L	22

Table 2Baseline Characteristics and Common Neonatal Morbidities.^a

Variable	Dose	
	Low	Standard
Baseline characteristics		
Gestational age, wk	28 ± 1	27 ± 1
Birth		
Weight, g	1033 ± 279	1023 ± 306
Length, cm	36 ± 3	36 ± 5
Head circumference, cm	25 ± 2	25 ± 2
Sex: male	14 (78)	12 (63)
Race: white	15 (83)	16 (84)
Ethnicity: Hispanic	6 (33)	7 (37)
Apgar		
1 min	5 ± 3	6 ± 2
5 min	7 ± 2	8 ± 2
Small for gestational age ^b	2 (11)	3 (16)
Antenatal steroids	17 (94)	17 (89)
Common neonatal morbidities and treatments		
Intraventricular hemorrhage grade 3	2 (11)	1 (5)
Periventricular leukomalacia	2 (11)	1 (5)
Necrotizing enterocolitis	2 (11)	1 (5)
Sepsis		
Early onset ^c	0 (0)	0 (0)
Late onset ^d	1 (6)	2 (11)
Bronchopulmonary dysplasia ^e	4 (22)	5 (26)
Postnatal steroid use	1 (6)	2 (11)
Surgery, n	0.8 ± 1	0.5 ± 1
Home oxygen requirement	1 (6)	4 (21)

^aData are presented as mean ± SD or n (%). P > .05 for all.^bSmall for gestational age was defined as birth weight <10th percentile.^cEarly-onset sepsis was defined as positive blood culture before 72 hours of age.^dLate-onset sepsis was defined as positive blood culture after 72 hours of age.^eBronchopulmonary dysplasia refers to oxygen requirement at 36 weeks corrected gestational age.

Table 3Autoregressive Regression Model for Estimated Changes in Nutrition Variables From Days 1–28.^a

Variable	Day 1			Day 28			Rate of Change per 28 d		
	Low Dose	Standard Dose	P Value	Low Dose	Standard Dose	P Value	Low	Standard	P Value
Energy, kcal/kg/d									
Total	32.5 ± 4.0	33.6 ± 4.0	.9	95.8 ± 4.0	98.5 ± 4.0	.6	-1.6 ± 8.0		.8
PN	32.5 ± 6.1	33.6 ± 6.1	.9	28.0 ± 6.1	32.8 ± 6.1	.6	-3.7 ± 12.3		.8
EN	0 ± 6.5	0 ± 6.5	1	67.8 ± 8.6	65.7 ± 8.6	.8	2.1 ± 12.2		.9
GIR, mg/kg/min	5.3 ± 0.8	5.4 ± 0.8	.9	8.0 ± 0.8	9.2 ± 0.8	.3	-1.1 ± 1.4		.4
SO, g/kg/d	0.3 ± 0.1	0.4 ± 0.1	.6	1.0 ± 0.2	2.6 ± 0.2	<.0001	-1.5 ± 0.4		<.0001

EN, enteral nutrition; GIR, glucose infusion rate; PN, parenteral nutrition; SO, intravenous soybean oil.

^aData are presented as mean ± SE.

Table 4Frequency of Low Developmental Domain Scores <1 SD Below the Normative Mean.^a

Domain	Dose, n (%)	
	Low	Standard
Scaled (< 7)		
Cognitive		
FU1	0 (0)	1 (8)
FU2	0 (0)	1 (8)
FU3	3 (27)	2 (14)
Receptive language		
FU1	3 (23)	2 (15)
FU2	2 (17)	2 (15)
FU3	2 (18)	4 (29)
Expressive language		
FU1	2 (15)	2 (15)
FU2	2 (17)	5 (38)
FU3	2 (18)	3 (21)
Fine motor		
FU1	2 (15)	2 (15)
FU2	1 (8)	2 (15)
FU3	2 (18)	1 (7)
Gross motor		
FU1	3 (23)	3 (23)
FU2	3 (25)	3 (23)
FU3	1 (9)	2 (14)
Composite (< 85)		
Cognitive		
FU1	0 (0)	1 (8)
FU2	0 (0)	1 (8)
FU3	3 (27)	2 (14)
Language		
FU1	3 (23)	6 (46)
FU2	2 (17)	5 (38)
FU3	2 (18)	4 (29)
Motor		
FU1	3 (23)	5 (38)
FU2	4 (33)	5 (38)
FU3	2 (18)	1 (7)

FU1-3, follow-up at 6, 12, and 24 months corrected gestational age, respectively.

^aP > .05 for all.

Table 5

Autoregressive Regression Model for Estimated Changes in Absolute Growth Measurements and *Z* scores From Birth, Status, and Follow-Up 1 to Follow-Up 3.^a

Variable	Dose, Mean ± SE		
	Low	Standard	Low-Standard
Growth Change			
Weight, kg			
Birth	9.9 ± 0.5	10.4 ± 0.4	−0.5 ± 0.6
Status	8.9 ± 0.5	9.4 ± 0.4	−0.5 ± 0.6
FU1 ^b	3.7 ± 0.3	4.5 ± 0.3	−0.8 ± 0.4
Length, cm			
Birth	48 ± 1.6	49 ± 1.6	−1.2 ± 2.3
Status	40 ± 1.7	42 ± 1.6	−2.3 ± 2.4
FU1	18 ± 1.7	21 ± 1.5	−2.4 ± 2.3
HC, cm			
Birth	23 ± 0.4	23 ± 0.5	−0.01 ± 0.6
Status	18 ± 0.5	17 ± 0.4	0.2 ± 0.7
FU1	4.9 ± 0.5	5.0 ± 0.5	−0.03 ± 0.7
Z-score Change			
Weight			
Birth	−1 ± 0.3	−0.9 ± 0.4	−0.1 ± 0.5
Status	0.2 ± 0.3	0.6 ± 0.3	−0.4 ± 0.4
FU1	−0.3 ± 0.3	0.3 ± 0.3	−0.6 ± 0.4
Length			
Birth	−0.2 ± 0.3	−0.3 ± 0.5	0.1 ± 0.6
Status	1.0 ± 0.4	1.4 ± 0.5	−0.4 ± 0.6
FU1	0.4 ± 0.5	0.8 ± 0.4	−0.4 ± 0.6
HC			
Birth	0 ± 0.2	−0.2 ± 0.3	0.2 ± 0.3
Status	1.1 ± 0.3	0.7 ± 0.2	0.4 ± 0.3
FU1	0.3 ± 0.3	0.2 ± 0.2	0.2 ± 0.4

HC, head circumference; FU1, follow-up at 6 months corrected gestational age.

^aP = .1 for all.

^bP = .08. 95% confidence interval = −1.7 to 0.1.