ORIGINAL ARTICLE

Probiotics-supplemented feeding in extremely low-birth-weight infants

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Objective: The objective of this trial was to test whether probiotic-supplemented feeding to extremely low-birth-weight (ELBW) infants will improve growth as determined by decreasing the percentage of infants with weight below the 10th percentile at 34 weeks postmenstrual age (PMA). Other important outcome measures, such as improving feeding tolerance determined by tolerating larger volume of feeding per day and reducing antimicrobial treatment days during the first 28 days from the initiation of feeding supplementation were also evaluated.

Study Design: We conducted a multicenter randomized controlled double-blinded clinical study. The probiotics-supplementation (PS) group received *Lactobacillus rhamnosus* GG and *Bifidobacterium infantis* added to the first enteral feeding and continued once daily with feedings thereafter until discharge or until 34 weeks (PMA). The control (C) group received unsupplemented feedings. Infant weight and feeding volumes were recorded daily during the first 28 days of study period. Weights were also recorded at 34 weeks PMA.

Result: A total of 101 infants were enrolled (PS 50 versus C 51). There was no difference between the two groups in the percentage of infants with weight below the 10th percentile at 34 weeks PMA (PS group 58% versus C group 60%, (*P* value 0.83)) or in the average volume of feeding during 28 days after study entry (PS group 59 ml kg⁻¹ versus C group 71 ml kg⁻¹, (*P* value 0.11)). Calculated growth velocity was higher in the PS group compared with the C group (14.9 versus 12.6 g per day, (*P* value 0.05)). Incidences of necrotizing enterocolitis (NEC), as well as mortality were similar between the two groups.

Conclusion: Although probiotic-supplemented feedings improve growth velocity in ELBW infants, there was no improvement in the percentage of

infants with growth delay at 34 weeks PMA. There were no probiotic-related adverse events reported.

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Introduction

The decline in infant mortality rate of extremely low-birth-weight (ELBW) infants in the previous decade has been well documented.¹ The importance of establishing enteral nutrition and optimal early growth in those infant is one of the greatest priorities of their care.² Failure to establish this nutritional goal could contribute negatively to the morbidity and neurodevelopmental outcome of ELBW infants.³

Probiotics might promote feeding tolerance and help to prevent diseases in preterm infants such as necrotizing enterocolitis (NEC).^{4,5} The role of probiotic supplementation (PS) on feeding tolerance and growth in preterm infants is not well established, and the mechanism by which it conveys this effect remains unclear. The hypothetical benefit of commensal organisms on the gut is likely related to the microbial–epithelial interaction between the colonizing bacteria and the intestinal epithelium. Some of the key functions of this healthy interaction include maintaining mucosal barrier integrity, regulating appropriate bacterial colonization, activating general intestinal immune defenses and modulating intestinal inflammation.^{5–7} Multiple human and animal studies have demonstrated that probiotic organisms maintain intestinal mucosal integrity by reducing mucosal permeability, strengthening intestinal tight junctions and inhibiting bacterial translocation.^{8–14}

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Additionally, probiotic augments immune host defense by increasing the production of mucosal IgA and increasing blood leukocyte phagocytosis.^{15–19} Finally, probiotic organisms affect intestinal inflammation by decreasing the production of pro-inflammatory cytokines and increasing anti-inflammatory cytokines.^{20–23} Kitajima *et al.*²⁴ reported improved weight gain and feeding tolerance when *Bifidobacterium breve* was given to very low birth weight (VLBW) infants. A more recent randomized controlled trial concluded that PS may improve gastrointestinal tolerance to enteral feeding in infants weighing >1000 g.²⁵ In the most recent meta-analysis of 11 randomized controlled trials of PS,^{8,24–33} Deshpande *et al.*³⁴ found a significant benefit of probiotic supplements in reducing death and disease (NEC) in preterm neonates. However they showed no significant reduction in the time to reach full feeds in the probiotic versus control group. Despite these apparently strong results, the routine use of probiotics has not been encouraged, in part due to large variety of organisms that have been tested and the limited data on specific commercially available products.³⁵

We designed this multicenter, randomized controlled, blinded-pilot study to evaluate the safety and efficacy of PS in ELBW infants. We hypothesized that probiotic-supplemented feeding with *Bifidobacteria* and *Lactobacilli* to ELBW infants will improve growth and feeding tolerance and reduce days of antimicrobial treatment.

Patients and methods

From 1 January 2008 to 21 April 2009, a prospective double-blinded randomized control trial was conducted at the neonatal intensive care units of three medical centers in United States. The study protocol was approved by the institutional review board of each hospital. All premature infants with birth weight 501 to 1000 g, appropriate for gestational age (AGA), and less than or equal to 14 days of age at the time of feeding initiation were eligible for enrollment in the study after informed parental consent was obtained. Eligible infants were randomly assigned to either the PS or control (C) group at each center after an IRB-approved informed consent was obtained from parents/legal guardian. Subjects who had major congenital anomalies, and have known PS before study entry were excluded.

The PS group was given supplement consisting of *Lactobacillus rhamnosus* GG LGG (Culturelle, Amerifit Brand, Cromwell, CT, USA) 500 million colony forming units (CFU) and *Bifidobacterium infantis* (Align, Procter and Gamble, Cincinnati, OH, USA) 500 million CFU suspended in 0.5 ml of infant's milk. Probiotic supplementation was added to the first enteral feeding and continued once daily with feedings thereafter until discharge or until 34 weeks postmenstrual age (PMA). The control group received unsupplemented milk added to their daily feeding. Feeding supplement (probiotic and control) was prepared by either

pharmacy (two centers) or a nutritional nurse (one center) who was not involved in the care of infants. Bedside caretaker received the feeding supplement at the bedside as prepared by either pharmacy (two centers) or a nutritional nurse (one center) who was not involved in the care of infants. Instruction for preparing PS was distributed to the participating centers. A specimen from each batch of probiotic product was cultured before its use in the study to confirm the organism species and ensure absence of contamination with unwanted organisms.

Enteral feeding was initiated when deemed appropriate by the attending neonatologist. Feeding schedule guidelines were implemented with emphasis on minimal feeding of 10 ml kg⁻¹ per day in the first 2–3 days. If tolerated, the amount of feeding given was advanced slowly with an incremental increase of not more than 20 ml kg⁻¹ per day. Caloric density of the feeding milk was changed to 24 kcal/oz when feeding volume was at 80 ml kg⁻¹ per day. Target full feeding volume intake was set at 140–160 ml kg⁻¹ per day. Feeding was stopped, if there were signs of feeding intolerance (bilious emesis, abdominal distention or bloody stools) or concerning systemic signs (shock and hypotension). Total parental nutrition was given to all infants until oral nutrition was tolerated at a volume of 100–120 ml kg⁻¹ per day.

Standard forms for data collection, created by the Vermont Oxford Network, were used by all centers. These forms were designed to collect data/information about subject's demographics, status before study entry, status during first 28 days of the study, status at 34 weeks PMA or discharge, complication of prematurity, adverse event and any protocol deviation. Data collected in the first 28 days of the study included weight, intravenous fluids volume, enteral feeding volume, type of respiratory support received, central line days and medication. Infant weight at the time of birth, feeding initiation, 28 days after feeding initiation and at 34 weeks postmenstrual age or discharge was recorded. Definitions of antenatal steroids use, prolonged rupture of membrane, maternal chorioamnionitis, small for gestational age and complication of prematurity including patent ductus arteriosus, chronic lung disease, sepsis, periventricular-intraventricular hemorrhage, cystic periventricular leukomalacia, retinopathy of prematurity and NEC were as described by Vermont Oxford Network at time of discharge or 6 month of chronological age.

The event rate for sample size calculation was based on review of the Vermont Oxford Network database demonstrating that over one quarter of the participating hospitals have a significant problem with poor weight gain; with 60% or more of the infants at these hospitals discharged with a weight less than the 10th percentile for the corresponding postmenstrual age. To demonstrate a 50% reduction in the number of infants discharged with a weight of less than the 10th percentile (from 60 to 30%), the total number needed to verify our hypothesis was 84 (alpha error set at <0.05, and beta error set at <0.2). Analyses of the primary and secondary outcomes were based on intention-to-treat analysis of all

randomized, eligible subjects. Growth velocity calculation using the exponential model reported by Patel *et al.*³⁶ was carried out. The χ^2 test was used to analyze the categorical data. The student's *t* test was used to analyze the continuous data. Univariate logistic regression models were used to estimate relative risks and 95% confidence intervals.

Data collected from the three centers participating in this study were sent to Vermont Oxford Network for analysis. An independent Data and Safety Monitoring Committee (DSMC) was formed. Reports for the DSMC were prepared after 6 months of patient enrollment. All statistical tests were two sided, and a *P* value of <0.05 was considered to indicate statistical significance. Analyses were carried out with SAS v9.2 software (SAS institute, Cary, NC, USA).

Results

The flow of subjects through the study is shown in Figure 1. There were 217 infants with birth weight equal or less than 1000 g admitted to the three participating NICUs during the study period. A total of 137 subjects met the eligibility criteria for the study, out of which 36 did not consent to the study (22 subjects due to parental refusal, 14 subjects not approached). A total of 101 infants were enrolled in the study, with 51 infants in the C group and 50 in the PS group. The infant's demographic characteristics did not differ between the two groups as shown in Table 1. In all, 43 infants were enrolled with birth weight between 500–750 g (20 C group, 23 PS group) versus 58 infants with birth weight between 750–1000 g (31 C group, 28 PS group). Infant's clinical characteristics (respiratory support, use of continuous distending pressure versus assisted ventilation) and complication of

prematurity (including patent ductus arteriosus, and periventricular-intraventricular hemorrhage) before study entry did not differ between the two groups (data not shown).

The primary and secondary outcomes of the study are shown in Table 2. There was no difference in the percentage of infants with

Table 1 Demographics data for study infants

Characteristics	PS group	C group	P-value
<i>N</i>	50	51	
Birth weight (g) (mean $\pm$ s.d.)	778 $\pm$ 138	779 $\pm$ 126	0.96
Gestational age (weeks) (mean $\pm$ s.d.)	25.7 $\pm$ 1.4	25.7 $\pm$ 1.4	0.97
Age at study entry (days) (mean $\pm$ s.d.)	4.2 $\pm$ 2.1	4.1 $\pm$ 2.3	0.71
Male, <i>N</i> (%)	22 (44%)	28 (55%)	0.27
Race, <i>N</i> (%)			
African American	25 (50%)	28 (55%)	0.62
White	25 (50%)	23 (45%)	
Hispanic	0 (0%)	1 (2%)	
Birth-weight strata, <i>N</i>			
Stratum one (501–750 g)	23	20	
Stratum A (day 1–7)	20	19	
Stratum B (day 8–14)	3	1	
Stratum two (751–1000 g)	27	31	
Stratum A (day 1–7)	26	29	
Stratum B (day 8–14)	1	2	
Cesarean section, <i>N</i> (%)	22 (44%)	30 (59%)	0.14
Antenatal steroids, <i>N</i> (%)	42 (84%)	43 (84%)	0.97
Multiple births, <i>N</i> (%)	8 (16%)	10 (20%)	0.64
Apgar scores (median)			
1 min	5	5	0.55
5 min	7	8	0.46

Abbreviations: C, control; PS, probiotics supplementation.
The main stratum shown in bold.

Table 2 Primary and secondary outcomes

Outcome	PS group (n = 50)	C group (n = 51)	P-value
Weight <10th percentile at 34 weeks	27/47 (58%)	28/47 (60%)	0.83
PMA, <i>N</i> (%)			
Average volume of feeding (mean $\pm$ s.d.), ml kg ⁻¹ a	59 $\pm$ 33	71 $\pm$ 36	0.11
Growth velocity (mean $\pm$ s.d.), g per day ^a	14.9 $\pm$ 6.5	12.6 $\pm$ 4.5	0.05
Average daily weight gain (mean $\pm$ s.d.), g ^a	14.3 $\pm$ 7.4	11.8 $\pm$ 4.8	0.06
Antimicrobial days (mean $\pm$ s.d.)	15.3 $\pm$ 9.0	13.0 $\pm$ 8.5	0.20
Antibacterial days (mean $\pm$ s.d.)	12.6 $\pm$ 8.5	11.7 $\pm$ 7.3	0.57
Antifungal days (mean $\pm$ s.d.)	13.7 $\pm$ 8.9	11.0 $\pm$ 8.6	0.29

Abbreviations: C, control; PMA, postmenstrual age; PS, probiotics supplementation.

^aOnly for cases with 28 days of data.

Figure 1 Subject enrollment—flow chart.

weight below the 10th percentile for postmenstrual age at 34 weeks PMA, average volume of feeding or the number of antimicrobial days between the C group and the PS group. During the first 28 days from feeding initiation, although average daily volume of feeding (ml kg^{-1}) was higher in the C group compared with the PS group (Figure 2), the average daily weight (g) was higher in PS group (Figure 3). The total parental fluids intake was not different between the two groups ((mean $\pm$ s.d.) 2069 $\pm$ 837 PS group versus 1776 $\pm$ 945 C group (P value 0.11)); however, the average

Figure 2 Graph of average daily feeding volume (ml kg^{-1}) during the first 28 days of feeding initiation.

Figure 3 Graph of average daily weight in gram during first 28 days of feeding initiation.

daily weight gain showed a higher trend in the PS group compared with the C group ((mean $\pm$ s.d.) 14.3 $\pm$ 7.4 g PS group versus 11.8 $\pm$ 4.8 g C group (P value 0.06)) and the calculated growth velocity was significantly higher in the PS group compared with the C group ((mean $\pm$ s.d.) 14.9 $\pm$ 6.5 g per day versus 12.6 $\pm$ 4.5 g per day, P value of 0.05).

Study outcomes for different weight groups in the PS and C groups are seen in Table 2a. The number of subjects in each group is limited and therefore the ability to analyze subgroups is limited. Average daily weight gain and growth velocity were significantly higher in the PS infants weighing 501–750 g (P value 0.02, 0.01, respectively) compared with C infants. In infants weighing 751–1000 g, although the average volume of feeding during study period was significantly higher in the C group compared with PS group, the average daily weight gain and growth velocity were similar in the two groups.

Treatments given to subjects in both groups during the first 28 days of study period were similar. There were no significant differences in respiratory support required (conventional/high frequency ventilation, NCPAP or Nasal Cannula), medication use (methylxanthines, postnatal steroids and PPI/H2 blockers), or central venous line days between the two groups (data not shown).

Table 3 demonstrates subjects' status at 34 weeks PMA. Mortality was not different between the two groups in over all analysis between the two groups (PS group 6% versus C group 7.7% (RR 0.77, 95% CI 0.18, 3.25)) or in the subgroups analysis as shown in Table 3a. Complications of prematurity at time of discharge or at 6-month chronological age in the PS and C group are presented in Table 4. There were no significant differences in the incidence of NEC, sepsis, severe intra-ventricular hemorrhage and chronic lung disease between the PS and C group. Although there was a trend for higher incidence of focal GI perforation periventricular leukomalacia and severe retinopathy of prematurity in the PS group compared with the C group, the differences were not statistically significant. No sepsis was detected related to probiotic organisms used in our study. In addition, no report of any adverse

Table 2a Primary and secondary outcomes for different weight groups

Outcome	501–750 g			751–1000 g		
	PS group (n = 23)	C group (n = 20)	P-value	PS group (n = 27)	C group (n = 31)	P-value
Weight <10th percentile at 34 wks PMA, <i>N</i> (%)	16/21 (76%)	12/17 (71%)	0.7	11/26 (42%)	16/30 (53%)	0.41
Average volume of feeding (mean $\pm$ s.d.), $\text{ml kg}^{-1}\text{a}$	50 $\pm$ 38	48 $\pm$ 35	0.9	67 $\pm$ 27	84 $\pm$ 30	0.03
Growth velocity (mean $\pm$ s.d.), g per day ^a	16.8 $\pm$ 4.7	13.1 $\pm$ 4.1	0.01	13.3 $\pm$ 7.3	12.4 $\pm$ 4.7	0.60
Average daily weight gain (mean $\pm$ s.d.), g ^a	13.9 $\pm$ 4.7	10.4 $\pm$ 4.0	0.02	14.6 $\pm$ 9.2	12.6 $\pm$ 5.2	0.34
Antimicrobial days (mean $\pm$ s.d.)	18.1 $\pm$ 7.4	16.0 $\pm$ 7.9	0.37	13.0 $\pm$ 9.6	11.1 $\pm$ 8.5	0.43

Abbreviations: C, control; PMA, postmenstrual age; PS, probiotics supplementation.

^aOnly for cases with 28 days of data.

<i>Status at 34 weeks PMA</i>	<i>PS group (n = 50)</i>	<i>C group (n = 50)</i>	<i>Relative risk (95% CI)</i>
Alive, <i>N</i> (%)	47 (94%)	47 (92%)	0.77 (0.18, 3.25)
Dead, <i>N</i> (%)	3 (6%)	4 (8%)	
Discharge/transferred before 34 weeks PMA	3 (6.0%)	2 (4%)	
Weight at 34 weeks PMA (mean ± s.d.) g	1750 ± 340	1719 ± 310	<i>P</i> = 0.65

Table 3a Status at 34 weeks PMA for different weight groups

Status at 34 weeks PMA	501–750 g			751–1000 g		
	PS group	C group	Relative risk	PS group	C group	Relative risk
	(n = 23)	(n = 20)	(95% CI)	(n = 27)	(n = 31)	(95% CI)
Alive, N (%)	21 (91%)	17 (85%)	0.58 (0.11, 3.13)	26 (96%)	30 (97%)	1.15 (0.08, 17.49)
Dead, N (%)	2 (9%)	3 (15%)		1 (4%)	1 (3%)	
Discharge/transferred before 34 weeks PMA	1 (4%)	1 (5%)		2 (7%)	1 (3%)	
Weight at 34 weeks PMA (mean ± s.d.) g	1656 ± 282	1599 ± 296	P = 0.55	1826 ± 368	1787 ± 302	P = 0.67

or significant event related to PS was reported in the study population.

It has been proposed that PS promotes enteral feeding and growth in neonates although the mechanism by which it conveys this effect remains unclear. The majority of clinical trials available in the literature that evaluated PS in premature infants have mainly focused on VLBW infant population, and only few of them have used enteral feeding and weight gain parameters as the targeted primary outcome. Knowing that establishment of nutrition and early growth is a crucial issue in the management of ELBW neonates, we felt it is prudent to attempt to address this role of PS in our current clinical trial, especially as the safety of this supplementation in ELBW infants remains a major concern. In an earlier trial, Kitajima *et al.*²⁴ conducted a randomized controlled trial of *B. breve* supplementation in VLBW infants. The supplementation was provided within the first 24 h and continued for 28 days. They showed significantly higher colonization rate for *B. breve* at 2 weeks of age in the supplemented group compared with the control group. They also demonstrated better weight gain in the supplemented group as a result of earlier establishment of enteral feeding and tolerance of greater feeding volume. In a more recent report, Rouge *et al.*²⁵ carried out a double-blinded, randomized controlled clinical trial of *Bifidobacterium longum* and *L. rhamnosus* LGG supplementation in VLBW infants. Probiotic supplementation was started at the time of feeding initiation and continued till discharge. The primary endpoint was the percentage of infants receiving >50% of their nutritional needs

Other randomized clinical studies indicated the effect of PS on enteral feeding and weight gain without this being the targeted primary outcome. These trials have not shown favorable benefit for PS on enteral feeding. Bin-Nun *et al.*²⁸ randomized VLBW neonates to either receive daily feeding supplement with probiotic mixture (*Bifidobacterium infantis*, *Streptococcus thermophilus* and *Bifidobacterium bifidus*) or no feeding supplement. The primary outcome was reducing the incidence and severity of NEC; however, the feeding data showed that full feeds were reached at similar ages in the two groups. The same results were demonstrated by Manzoni *et al.*³⁰ in their randomized trial designed to evaluate the effect of *L. rhamnosus* supplementation in preventing enteric colonization with candida species in VLBW neonates. Finally Lin *et al.*³² illustrated no difference in weight gain or age at which full feeding was achieved between the PS group and the control group in their recent trial conducted to evaluate the role of oral probiotics in preventing NEC in VLBW infants.

Our study is the first clinical trial designed to evaluate the role of PS on enteral feeding and growth in ELBW infants. Choosing which probiotic organisms to use in our trial was a major challenge as clinical studies to date have used different organisms with different administration regimens (dosage, length of treatment). Knowing that *Bifidobacterium* and *Lactobacillus*

Table 4 Complications of prematurity*

Outcomes	PS group N (%)	C group N (%)	Relative risk (95% CI)
NEC	3/50 (6%)	4/51 (8%)	0.77 (0.18, 3.25)
<i>Bell's stage</i>			
I	1/50 (2%)	2/51 (4%)	
II	0/50 (0%)	0/51 (0%)	
III	2/50 (4%)	2/51 (4%)	
Focal GI perforation	4/49 (8%)	1/51 (2%)	4.16 (0.48, 35.95)
NEC surgery	2/50 (4%)	2/51 (4%)	1.02 (0.15, 6.96)
<i>Sepsis</i>			
Any bacterial and fungal	13/50 (26%)	16/51 (31%)	0.83 (0.45, 1.54)
Any bacterial	11/50 (22%)	16/51 (31%)	0.70 (0.36, 1.36)
Bacterial pathogen	4/50 (8%)	8/51 (16%)	0.51 (0.16, 1.59)
Coag-negative <i>Staphylococcus</i>	10/50 (20%)	12/51 (24%)	0.85 (0.40, 1.79)
Any fungal pathogen	2/50 (4%)	0/51 (0%)	
<i>Cranial ultrasound performed</i>			
Any IVH	48/50 (96%)	47/51 (92%)	
Severe IVH	19/47 (40%)	14/47 (30%)	1.36 (0.78, 2.37)
PVL	10/47 (21%)	7/47 (15%)	1.43 (0.59, 3.43)
	4/50 (8%)	1/51 (2%)	4.08 (0.47, 35.25)
Chronic lung disease	31/49 (63%)	34/51 (67%)	0.95 (0.71, 1.27)
<i>ROP exam performed</i>			
Any ROP	44/50 (88%)	48/51 (94%)	
Severe ROP	32/44 (73%)	28/48 (58%)	1.25 (0.92, 1.68)
	8/44 (18%)	4/48 (8%)	2.18 (0.71, 6.74)

Abbreviations: IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PS, probiotics supplementation; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

*Noted before discharge or at 6 months chronological age.

form the larger portion of the intestinal flora in breast-fed infants, we felt it is prudent to have these two organisms in our probiotic regimen. It is not clear whether subspecies selection has a major role on the effect demonstrated by any organism specie.

Our study shows that *LGG* and *B. infantis* supplementation did not improve growth in ELBW infants, as it did not significantly lower the percentage of infants with weight below the 10th percentile at 34 weeks PMA. However, PS-improved growth velocity during the first 28 days after feeding initiation in the PS group compared with C group. It is not clear whether this effect on growth velocity was not carried along till 34 weeks PMA because of differences in feeding and nutrition practice among the participating centers after the initial 28 days of the study. Moreover, PS did not have any effect on the number of days of antimicrobial agents and did not decrease the incidence of sepsis episodes.

The most recent meta-analysis of Deshpande *et al.*³⁴ demonstrated a significant reduction in NEC and mortality in

infants given PS. Our study did not demonstrate a difference in NEC or mortality. This is most likely related to the small number of subjects enrolled in our trial and the lack of power to detect such differences. However, the lack of these important clinical effects could be due to the fact that we enrolled ELBW infants exclusively, infants at the highest risk for both complications.

Importantly, no adverse events or sepsis related to the organisms supplemented has been reported in any of the infants studied in our trial. The safety of PS has been a major concern to this treatment modality, especially in ELBW infants. Kunz *et al.*³⁷ reported *Lactobacillus bacteremia* in two premature infants who had short-gut syndrome while receiving *L. rhamnosus* (LGG) supplement. Also, few cases of infection with probiotic organisms in immuno-compromised patients have been reported in the Scandinavian literature.^{38,39} More recently, Ohishi *et al.*⁴⁰ reported a *B. breve* septicemia associated with postoperative PS in a term neonate with omphalocele.⁴⁰ However, none of the clinical trials carried out in premature infants reported any possible sepsis attributable to probiotic organisms supplemented. The number of ELBW infants who received probiotic in our trial and the Lin trial (only trials reported number of ELBW subject enrolled) is 152 infants (50 our study, 102 Lin study), which is a relatively small number to determine the safety of PS in such vulnerable infants. However, it is definitely more encouraging of a number and support future larger multicenter clinical trial targeted to the high-risk ELBW population.

We conclude that PS feeding with LGG and *B. infantis* does not improve growth delay seen at 34 weeks PMA in ELBW infants in spite of improving growth velocity. Large multicenter trials are warranted to address the safety and efficacy for routine use of PS to decrease NEC and mortality incidence in ELBW infants.

Conflict of interest

The authors declare no conflict of interest.

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