Early and exclusive enteral nutrition in infants born very preterm

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Received 15 June 2023
Accepted 15 December 2023

ABSTRACT

Objective To characterise the effects of early and exclusive enteral nutrition with either maternal or donor milk in infants born very preterm (28 0/7 32 6/7 weeks of gestation).

Design Parallel-group, unmasked randomised controlled trial.

Setting Regional, tertiary neonatal intensive care unit.

Participants 102 infants born very preterm between 2021 and 2022 (51 in each group).

Intervention Infants randomised to the intervention group received 60 80 mL/kg/day within the first 36 hours after birth. Infants randomised to the control group received 20 30 mL/kg/day (standard trophic feeding volumes).

Main outcome measures The primary outcome was the number of full enteral feeding days (>150 mL/kg/day) in the first 28 days after birth. Secondary outcomes included growth and body composition at the end of the first two postnatal weeks, and length of hospitalisation.

Results The mean birth weight was 1477 g (SD: 334). Half of the infants were male, and 44% were black. Early and exclusive enteral nutrition increased the number of full enteral feeding days (+2; 0 2 days; p=0.004), the fat-free mass-for-age z-scores at postnatal day 14 (+0.5; 0.1 1.0; p=0.02) and the length-for-age z-scores at the time of hospital discharge (+0.6; 0.2 1.0; p=0.002). Hospitalisation costs differed between groups (mean difference favouring the intervention group: −$28 754; −$647 to −$56 861; p=0.04).

Conclusions In infants born very preterm, early and exclusive enteral nutrition increases the number of full enteral feeding days. This feeding practice may also improve fat-free mass accretion, increase length and reduce hospitalisation costs.

Trial registration number NCT04337710.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Current feeding protocols for very preterm infants typically involve slow advancement of enteral feeding volumes, which delays the establishment of full enteral feeding and prolongs the need for intravenous access and parenteral nutrition.

WHAT THIS STUDY ADDS

- This study suggests that early and exclusive enteral nutrition in very preterm infants leads to more full enteral feeding days, improved lean mass accretion, increased length at discharge and reduced hospitalisation costs.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Implementing feeding practices that promote early and exclusive enteral nutrition soon after birth could potentially reduce the need for parenteral nutrition, improve growth outcomes and lower hospitalisation costs.

INTRODUCTION

Feeding protocols for preterm infants born in high-income countries (HICs) often differ from those in low and middle-income countries (LMICs).[1–3] In HICs, most neonatal units start parenteral nutri-

risk of adverse neurodevelopment outcomes[9] and cardiometabolic disease later in life.[6 7 10 11]

In LMICs, early and exclusive enteral nutrition has shown potential superiority over slow feeding progression in infants born very preterm.[1 2 12 13] A 2020 Cochrane review of six clinical trials in India found that early and exclusive enteral nutrition could lead to shorter hospitalisations and more weight gain without increasing the risk of necrotising enterocolitis (NEC).[13] However, the generalisability of these findings to preterm infants in HICs has been limited likely due to differences in healthcare systems (availability of nutritional resources and health workers trained in intensive neonatal care) and several differences in clinical conditions at baseline, including the prevalence of fetal growth restriction and sepsis.

To bridge this gap in knowledge, we

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To cite: Razzaghy J, Shukla VV, Gunawan E, et al. Arch early Dis Child Fetal Neonatal Ed
Epub ahead of print: [please include Day Month Year]. 15 doi:10.1136/archdischild-2023-325969

tion soon after birth and introduce enteral nutrition gradually. This method that often leads to extended periods of parenteral nutrition and delayed achievement of full enteral nutrition[4–7] has come under increasing scrutiny in recent years.[8] Growth failure remains common in this population, catch-up growth in these infants is compositionally different from that of term infants and poor quality of postnatal preterm growth has been linked to a higher

conducted a trial to investigate the effects of early and exclusive enteral nutrition in infants born very preterm (28–32 weeks of gestation) within an HIC. By increasing the provision of human milk in the early postnatal days, and exclusive enteral nutrition holds the potential to shape gastrointestinal maturation,[14] improve growth[13] and ultimately reduce hospitalisation costs.[16]

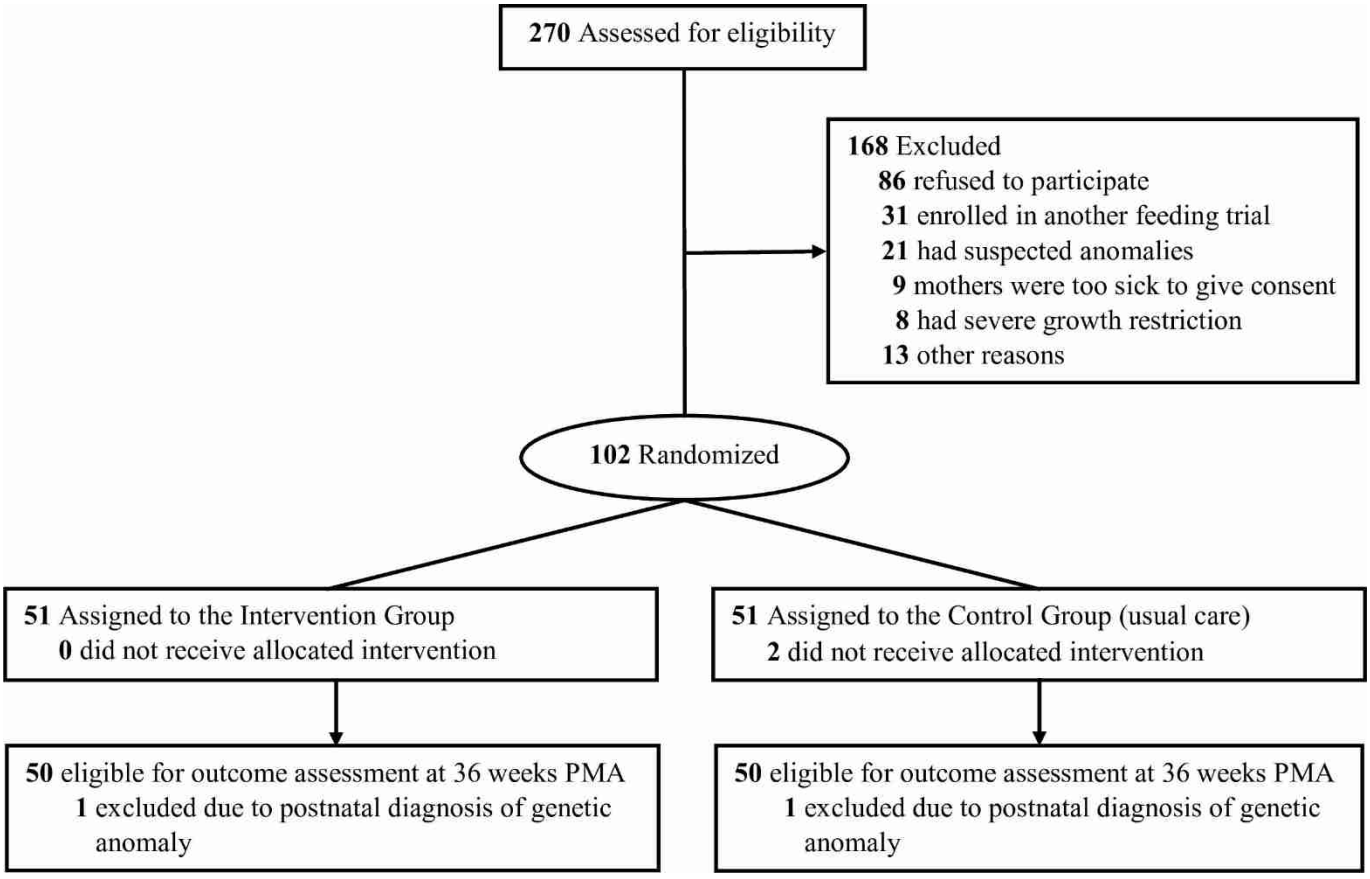

Figure 1 Flow diagram. From May 2021 to August 2022, a total of 270 infants were born very preterm at the University of Alabama at Birmingham Hospital. Eighty-six families declined participation. Twenty-nine of these infants did not meet eligibility criteria. Thirty-one additional infants were not eligible due to concurrent enrolment in another feeding study. One hundred and two infants were consented and randomised. Two infants, one randomised to the control group and one randomised to the intervention group, were excluded from the data analysis after randomisation due to postnatally diagnosed genetic anomalies. Two infants randomised to the intervention group (one of whom was also diagnosed with an excluding genetic anomaly) did not receive early and exclusive enteral nutrition due to clinical instability and ultimately died secondary to complications of their underlying diseases and were therefore excluded from analysis. PMA, postmenstrual age.

METHODS

Study design

This was an unmasked, parallel-group randomised controlled trial with a 1:1 allocation ratio conducted at a tertiary-level regional unit in Birmingham, Alabama.

Participants

Infants born between $28_{0/7}$ and $32_{6/7}$ weeks of gestation and admitted to the University of Alabama at Birmingham neonatal unit within the first 36 hours after birth were eligible. Infants with known major congenital or genetic anomalies, extreme growth restriction (defined as birth weight at the first percentile), clinical instability that would preclude feeding (severe metabolic acidosis and inotropic support within the first 24 hours after birth) or those with a terminal illness in which decisions to with- hold or limit support had been made were excluded.

Randomisation

Parents of eligible infants were approached for consent within the first 36 hours after birth. Immediately after birth, prior to obtaining study consent, infants received parenteral fluids based on their birth weight. Infants weighing >1500 g were provided with dextrose fluids, while those weighing <1500 g received parenteral fluids consisting of dextrose and amino acids. Once

written consent was obtained, infants were randomised using a computer-generated random block sequence. The sequence was used to create individual cards placed in sequentially numbered, opaque and sealed envelopes. After the study team obtained written informed consent, envelopes were sequentially opened. Following randomisation, the study team notified the primary medical team of the feeding group assigned. Multiples were randomised individually.

Interventions

Infants in the intervention group received enteral nutrition with maternal or donor milk (if maternal milk was unavail - able) starting at 60–80 mL/kg/day within the first 36 hours after birth. After the medical team chose the preferred volume within this range, they reduced or discontinued the intravenous fluids initiated shortly after birth in order to achieve the desired total fluid intake for each infant. Enteral feeding volumes were then increased over the following days by our unit standard of 20–30 mL/kg/day to a goal of 150 mL/kg/day or more. Infants in the control group received enteral nutrition with maternal or donor milk (if maternal milk was unavailable) starting at 20–30 mL/kg/day within the first 96 hours after birth (usual care). As with the intervention group, enteral feeding volumes were increased gradually by 20–30 mL/kg/day to a goal of 150

mL/kg/day or more. All study participants received exclusive human milk diets for at least 14 days after birth. If maternal milk was unavailable after postnatal day 14, infants were transitioned to preterm formula. The timing of human milk fortification was not defined by the study protocol.

The primary medical team assessed feeding intolerance and ordered imaging studies as needed. They made decisions on whether to continue, decrease or hold enteral nutrition. The assigned study intervention was discontinued if an infant developed spontaneous intestinal perforation (SIP) or NEC.

Outcomes

The primary efficacy outcome focused on the duration of full enteral feeding, defined as the number of days infants received enteral feeding volumes >150 mL/kg/day during the initial 28 days following birth. In cases where an infant was discharged home prior to reaching postnatal day 28 while still receiving full enteral feeding, we made the conservative assumption that this feeding regimen persisted until postnatal day 28. To minimise potential bias, we additionally reported the primary efficacy outcome for the first 15 days after birth. Secondary efficacy outcomes included weight, length and head circumference at 36 weeks of postmenstrual age (PMA) or at the time of hospital discharge if an infant met discharge criteria before 36 weeks PMA, body composition measurements around postnatal day 14, length of hospitalisation and healthcare costs. The primary safety outcomes of the trial were SIP, NEC stage 2 or 3 and death.

Growth assessments

Infants underwent routine weight, length and head circumference measurements from birth to discharge. These measurements were converted into z-scores using the Fenton charts.

As part of the trial, infants also had a body composition assessment with air-displacement plethysmography (ADP) using the PeaPod between postnatal days 14 and 21. Body composition measurements were then transformed into sex-specific z-scores, using an updated chart.[17] For invalid results due to extremely low body fat, a conservative value of 3% body fat was assigned.

This choice was informed by the inherent difficulty in estimating fat mass accurately in infants <1500 g.[18] In exceptional circumstances in which an infant could not undergo a body composition assessment between postnatal days 14 and 21 but had ADP assessments at 36 weeks PMA for reasons unrelated to this trial, we assumed that the body fat percentage at postnatal day 14 was 8% lower than the body fat percentage measured at 36 weeks PMA.[19]

Other assessments

Hospitalisation costs were estimated for each infant based on birth weight, singleton status and length of hospital stay. The cost was estimated in 2017 US dollar values.[20]

Sample size

To achieve 90% power with a two-sided 5% significance level and an expected 5-day difference in the number of full enteral feeding days with an SD of 7 days, a sample size of 84 patients was required. We included 102 patients, anticipating a 20% attrition rate.

Statistical methods

Continuous data were summarised with mean±SD or median and IQRs. Categorical data were summarised using frequencies and percentages. All efficacy and safety outcomes of the trial were analysed following the intention-to-treat principle. Group differences were evaluated using independent t-tests or the Wilcoxon test for continuous variables and χ^2 tests for categorical variables. All statistical analyses were performed using SAS V.9.4 (SAS Institute).

RESULTS

A total of 102 infants were randomised (figure 1). The baseline characteristics of the study participants are summarised in table 1. Seventy-four infants were randomised within the first 24 hours after birth. The mean birth weight was 1477 g (SD: 334).

Infants in the intervention group spent more days receiving full enteral feeding (≥150 mL/kg/day) (table 2). The cumulative intake of human milk during the first week after birth was significantly higher in the intervention group (625 mL/kg vs 501 mL/kg; p<0.0001). The difference in the use of total parenteral nutrition within the first week after birth was not significantly different between groups (4% vs 12%; relative risk: 0.3; 95% CI 0.1 to 1.6; p=0.17).

Table 1 Baseline characteristics

	Intervention group (n=51)	Control group (n=51)
Demographic characteristics		
Birth weight in grams, mean–SD	1571–317*	1385–336*
Gestational age in weeks, median (IQR)	31 (30 32)	30 (29 32)
Small for gestational age, n (%)	3 (6)	2 (4)
Weight-for-age z-score, mean–SD	−0.05–0.74*	−0.38–0.69*
Length at birth in centimetre, mean–	41–3	39–3
Male, n (%)	24 (48)	26 (52)
Black race, n (%)	23 (46)	20 (40)
Exposure to antenatal steroids, n (%)	44 (90)	46 (92)
Maternal diabetes, n (%)	5 (10)	7 (14)
Maternal hypertension, n (%)	31 (61)	37 (74)
Clinical characteristics		
Randomised within the first 24 hours, n	36 (71)	38 (75)
Supported with room air within the first 24 hours after birth, n	26 (52)	22 (44)

*Mean–SD (all such values).
Median; 25th 75th percentiles in parentheses (all such values).

Table 2 Primary and secondary outcomes

	Intervention group (n=48)	Control group (n=49)	Relative risk or median/mean difference (95% CI)
Days of full enteral feeding ≥150 mL/kg/day in the first 28 days, median (IQR)	23 (21 23)*	21 (20 22)*	MD: 2 (0 to 2); p=0.004
Days of full enteral feeding ≥150 mL/kg/day in the first 15 days, median (IQR)	9 (8 10)*	8 (7	MD: 1 (0 to 2); p=0.0003
Days to exclusive human milk feeding, median (IQR)	4 (3 5)	6 (5 6)	MD: 2 (0 to 2); p<0.0001
Days to achieve full enteral feeding, median (IQR)	6 (5 7)	7 (6 8)	MD: 1 (0 to 2); p=0.0004
Days to achieve full enteral feeding for 3 days, median (IQR)	8 (7 10)	9 (8 10)	MD: 1 (0 to 2); p=0.0009
Fat-free mass z-score at 14 postnatal days, mean–SD	−1.48–1.01	−2.01–1.04	MD: 0.52 (0.09 to 0.95); p=0.02
Fat mass z-score at 14 postnatal days, median (IQR)	−0.97 (−1.54 to −0.13)*	−1.25 (−1.59 to−0.46)*	MD: 0.14 (−0.15 to 0.50); p=0.35
Weight z-score at 36 weeks PMA/discharge, mean–SD	−0.9–0.8	−1.2–0.7	MD: 0.2 (−0.1 to 0.5); p=0.14
Length z-score at 36 weeks PMA/discharge, mean–SD	−0.9–0.9	−1.5–0.8	MD: 0.6 (0.2 to 1.0); p<0.01
Head circumference z-score at 36 weeks PMA/discharge, mean–SD	−0.8–1.1	−0.8–0.9	MD: 0 (−0.4 to 0.4); p=1.00
Weight <10th centile at 36 weeks PMA/discharge§, n (%)	15 (31)	21 (43)	RR: 0.73 (0.43 to 1.24); p=0.24
Regain birth weight by postnatal day 14, n (%)	23 (47)	20 (40)	RR: 1.17 (0.75 to 1.84); p=0.49
Hospitalisation costs in 2017 US dollars, mean–SD	99 970–63 820	128 722–74 470	MD: −28 754 (−647 to −56 861); p=0.04
Length of stay in days, mean–SD	40–18	47–21	MD: −7 (−15 to 1); p=0.08
NEC or SIP, n (%)	1 (2)	1 (2)	RR: 1.02 (0.07 to 15.86); p=0.99

*Median; 25th 75th percentiles in parentheses (all such values).
n=90; 46 in the intervention group and 44 in the control group.
Mean–SD (all such values).
§Discharge criteria included: maintaining normal temperatures in an open crib for 2 days, breathing room air, tolerating full oral eeding and not having apnoea or brady f episodes at rest for 5 days.
NEC, necrotising enterocolitis; PMA, postmenstrual age; SIP, spontaneous intestinal perforation.

cardia

Eighty-nine infants underwent body composition assessments around postnatal day 14. No adverse events associated with these assessments were identified. Valid results were obtained for 76 infants. Two of the 13 infants with invalid results had a valid body composition assessment at 36 weeks PMA. Eleven infants did not have any body composition assessments. Fat- free mass-for-age z-scores were higher around postnatal day 14 in infants randomised to the intervention group. At 36 weeks PMA or hospital discharge, infants receiving early and exclusive enteral nutrition had higher length-for-age z-scores. Weight gain in g/kg/day from birth to 36 weeks PMA did not differ between groups (11 vs 11; p=0.62).

After adjusting for birth weight z-scores through an ordinal logistic regression analysis, we found that the difference in full enteral feeding days remained significant (adjusted median: 22 vs 20 days; p=0.01). Other adjusted analyses with birth weight z-score as covariate are shown in table 3.

Three infants in the intervention group experienced bilious emesis in the first five postnatal days, and enteral nutrition was temporarily held for further investigation of a cause. The surgical team evaluated them, and two of the three infants underwent upper gastrointestinal imaging studies that were normal. All three infants resumed enteral nutrition within 48 hours of the initial evaluation.

The length of hospital stay ranged from 12 to 103 days. There was no significant difference in length of hospital stay between randomisation groups. Donor milk use did not differ between randomisation groups (mean difference: 360 mL; 95% CI −60 to 780; p=0.10). A significant difference in the percentage of maternal milk use at discharge was not found (59% vs 49%; p=0.31).

Table 3 Secondary outcomes adjusted by birth weight z-score

	Intervention group (n=48)	Control group (n=49)	P value
Fat-free mass z-score at 14 postnatal days, adjusted mean–SEM*	−1.68–0.07	−1.80–0.07	0.23
Weight gain in g/kg/day, adjusted mean–SEM	10–0.5	11–0.5	0.19
Weight z-score at 36 weeks PMA/discharge, adjusted mean–	−1.08–0.05	−1.03–0.05	0.56
Length z-score at 36 weeks PMA/discharge, adjusted mean–	−1.01–0.08	−1.29–0.08	0.02
Head circumference z-score at 36 weeks PMA/discharge, adjusted mean–	−0.98–0.12	−0.72–0.12	0.13
Declines in weight z-score from birth to 36 weeks PMA/discharge, adjusted mean–	−0.85–0.06	−0.81–0.06	0.56
Declines in head circumference z-score from birth to 36 weeks PMA/discharge, adjusted mean–SEM	−0.88–0.13	−0.54–0.13	0.07

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Declines in length z-score from birth to 36 weeks PMA/discharge, adjusted mean–	−0.97–0.10	−1.17–0.10	0.18
Hospitalisation costs in 2017 US dollars, adjusted mean–SEM	106 788–9117	122 042–9022	0.24
*n=90; 46 in the intervention group and 44 in the control group. PMA, postmenstrual age.			

DISCUSSION

We evaluated the effects of early and exclusive enteral nutrition in a pragmatic trial that included infants born preterm. Our results suggest that infants who received early and exclusive enteral nutrition had more favourable outcomes, including Delta more full enteral feeding days, greater fat-free mass accretion at which postnatal day 14 and higher length z-scores at 36 weeks PMA. Additionally, hospitalisation costs were lower for infants who received early and exclusive enteral nutrition. Rates of maternal milk feeding at discharge did not decrease despite the transient increase in donor milk use during the first few days after birth.

The findings of our study suggest that early and exclusive enteral nutrition in preterm infants can have positive effects factored on fat-free mass accretion and length, which are important Conse- markers for organ growth and neurodevelopment outcomes.[9] concerns This improvement could potentially be attributed to an interaction between early human milk feeding and gastrointestinal tract colonisation.[15 21] While previous clinical trials have not specifically assessed body composition outcomes after early and exclusive enteral nutrition, ongoing trials that include infants of 30–33 weeks of gestation are expected to provide more precise effect estimates of the potential benefits of this practice on growth outcomes.[22]

This trial included infants with an average gestational age of 30 weeks born in an HIC, which led to a significant proportion infants weighing over 1500 g at birth, who may not require parenteral fluids in some neonatal units. In contrast, trials conducted in LMICs involving infants of up to 36 weeks of gestation reported significantly lower birth weights.[1] This discrepancy highlights the need for birth weight inclusion criteria in future trials and emphasises that both small-for-gestational-age (SGA) appropriate-for-gestational-age (AGA) infants born preterm from early and exclusive enteral nutrition. Considering that AGA infants with a short hospital stay may experience minimal weight gain from birth to discharge, it is important to recognise that assessing the advantages of early and exclusive enteral nutrition in AGA infants, compared with SGA infants, may pose greater difficulty if body composition outcomes are not simultaneously evaluated.

This trial compared early and exclusive enteral nutrition with improve early progression of enteral nutrition. The control group in our hospitalisa- trial was fed according to a feeding protocol that promotes early progression of enteral feeding volumes. Early progression of enteral feeding volumes versus minimal enteral nutrition appears beneficial in itself. [23–25] Therefore, it is possible that if we had compared early and exclusive enteral nutrition to a much slower, more conventional feeding protocol, the beneficial effects reported would have been greater. The smaller- than- expected difference in the total number of full enteral feeding days between groups indicates that, except for the feeding volumes targeted within the first 36 hours after birth, there was minimal variability in other feeding practices during the trial period.

Several limitations should be taken into consideration when (IRB-This study involves human participants and was approved by the 300004922). interpreting the findings of this trial. The primary outcome Participants gave informed consent to participate in the study before taking part. is a process measure, not a traditional outcome like NEC. With an NEC rate of 2%, we would need a trial of more than

The adjusted analyses, rigorously carried out in adherence to recommended best practices,[27] upheld the original direction of all reported outcomes and provided valuable information for future trials. Moreover, the representativeness of the sample was impacted by external factors, particularly during the and Omicron waves of the SARS-CoV-2 pandemic, resulted in a notable proportion of eligible infants not being approached for enrolment.

Another limitation was the lack of specific criteria to define feeding intolerance, which is a common issue in preterm infants.[28] Some infants with feeding intolerance had enteral nutrition discontinued, advanced imaging ordered and surgery consultations requested. However, our cost analysis in only birth weight, singleton status and length of stay. quently, the cost implications associated with increased for feeding intolerance were not included.

Compliance was objectively measured during daily follow-up visits until full enteral feeding was established to avoid differential non-compliance that could result in selection bias. Traditional enteral feeding practices persist in part out of fear of increasing the risk of NEC. They often disregard evidence suggesting that extending the duration of trophic feeds might delay gastrointestinal maturation and favour dysbiosis,[13 25] and often become a barrier to implementing more aggressive enteral nutrition. During the first quarter of the trial, monitoring for of compliance and managing care team reservations and hesitations towards the study intervention were crucial. Notably, as clinical comfort with early and exclusive enteral nutrition improved, feeds were started earlier and advanced sooner in the control group. Non-compliance with either study intervention consistently reduces the effect size of an intervention, moving it closer and to null, which likely contributed to the smaller-than-expected could benefit differences observed in efficacy and safety endpoints between groups. Nonetheless, analysing the results in accordance with the intention-to-treat principle increases the generalisability of our findings and offers valuable context for interpreting their clinical significance.

In conclusion, this trial demonstrates that early and exclusive enteral nutrition in very preterm infants increases the number of full enteral feeding days. This feeding practice may also fat-free mass accretion, increase length and reduce tion costs.

Funding AAS is supported by a research grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (K23HD102554) and the UAB Pittman Scholars Program.

Competing interests AAS has a patent for an instrumented feeding bottle. Additionally, AAS has provided scientific advice to Resbiotic, received consulting fees for participating in advisory board meetings for Reckitt/Mead Johnson Nutrition and received speaking fees for participating in educational activities organised by p-value communications and WebMD.

Patient consent for publication Parental/guardian consent obtained.

Ethics appr University of **oval**Alabama at Birmingham Institutional Review Board

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

5000 infants to show any effect on NEC, if indeed there is The lack of masking in the study design introduces the of surveillance and ascertainment biases, potentially leading to an underestimation of the risk of NEC in the control group.[25 26] The presence of an imbalance in birth weights between the groups and the wide variation in length of stay pose additional potential sources of bias in this trial.

Deidentified individual participant data will be made available upon publication to one. researchers who provide a methodologically sound proposal for use in achieving possibility the goals of the approved proposal. Proposals should be submitted to asalas@uab.edu.

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REFERENCES

1 Sanghvi KP, Joshi P, Nabi F, et al. Feasibility of exclusive enteral feeds from birth in VLBW infants >1200 G--an RCT. Acta Paediatr 2013;102:e299 304.
2 Nangia S, Vadivel V, Thukral A, et al. Early total enteral feeding versus conventional enteral feeding in stable very-low-birth-weight infants: a randomised controlled trial. very-low- Neonatology 2019;115:256 62.
3 Bora R, Murthy NB. In resource limited areas complete enteral feed in stable very low birth weight infants (1000-1500 G) started within 24 H of life can improve nutritional
4 outcomeWiechers C. J Matern F,Avellina etal Neonatal MedV, Luger B, et al. Body composition of preterm infants following 2017;30:2572 7. 18
first 6 mo of lifeForsum E, Olhager E,. Am J T rnqvist CClin Nutr 2019;109:1353 60..An evaluation of the pea pod system for assessing
rapid transition to enteral feeding. Neonatology 2022;119:246 54.
5 Fenin A, Newman JC, Taylor SN. Very low birth weight infants receive full enteral nutrition within 2 postnatal weeks. J Perinatol 2020;40:1849 56.
6 LØvy E, Delvin E, MØnard D, et al. Functional development of human fetal
8 a2Johnson MJequivn0d04g;alent age:r1o8w:3th9, fWa4 c4ootton SA, a systematic review and meta-t. or-mediat Leaf ed re AA,gula et altory . Preterm birth and body
composition at term mechaanalysisnisms. C. aPnediatricsJ Gastr 2012;130:e640 9.oenterol
202122 Phibbs CSmothers and neonates in California,Yand metabolome
among extremely preterm infants with postnatal growth failureRepMitchell EJcontrolled trial of full milk feeds versus introunge NE, 2019;9:8167., Schmitt SK,, Meakin G Newgarc
CB, Cooper M,Anderson J, Cotten CM,, et alet al 2009-et al.. Birth hospitalization costs and days of care for The feed1 trial:2011..avenous fluids with gr DisruptedmaturJ Pediatr
protocol for a r 2019;204:118 25.ation of the microbiota adual feeding for andomised . Sci
gastrointestinal tract. Methods Mol Biol 2009;550:205 24.
7 MØnard D. Functional development of the human gastrointestinal tract: hormone-
9 Ramel SE, Haapala J, Super J, et al. Illness and body composition in very low birth weight preterm infants: implications for nutritional management and neurocognitive outcomes. Nutrients 2020;12:145.
10 Markopoulou P, Papanikolaou E, Analytis A, et al. Preterm birth as a risk factor for metabolic syndrome and cardiovascular disease in adult life: a systematic review and meta-analysis. J Pediatr 2019;210:69 80.
11 Casirati A, Somaschini A, Perrone M, et al. Preterm birth and metabolic implications
preterm infants (30-33 weeks gestational age). Trials 2022;23:64.
23 Modi M, Ramji S, Jain A, et al. Early aggressive enteral feeding in neonates weighing 750-1250 grams: a randomized controlled trial. Indian Pediatr 2019;56:294 8.
24 Salas AA, Li P, Parks K, et al. Early progressive feeding in extremely preterm infants: a randomized trial. Am J Clin Nutr 2018;107:365 70.
25 Oddie SJ, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database Syst Rev
15 Salas AA, Willis KA, Carlo WA, et al. The gut microbiome of extremely preterm infants randomized to the early progression of enteral feeding. Pediatr Res 2022;92:799 804.
16 Johnson TJ, Patel AL, Bigger HR, et al. Economic benefits and costs of human milk feedings: a strategy to reduce the risk of prematurity-related morbidities in birth-weight infants. Adv Nutr 2014;5:207 12.
17 Norris T, Ramel SE, Catalano P, et al. New charts for the assessment of body composition, according to air-displacement plethysmography, at birth and across the
2017;30:2572 7.
body composition of moderately premature infants. Nutrients 2016;8:238.
19 Salas AA, Jerome ML, Chandler-Laney P, et al. Serial assessment of fat and fat-free mass accretion in very preterm infants: a randomized trial. Pediatr Res 2020;88:733 8.

on later life: a narrative review focused on body composition. Front Nutr 2022;9.
12 Nangia S, Bishnoi A, Goel A, et al. Early total enteral feeding in stable very low birth weight infants: a before and after study. J Trop Pediatr 2018;64:24 30.
13 Walsh V, Brown JVE, Copperthwaite BR, et al. Early full enteral feeding for preterm or low birth weight infants. Cochrane Database Syst Rev 2020;12.
14 Beghetti I, Biagi E, Martini S, et al. Implications of the milk microbiome for preterm infants health. Nutrients 2019;11.
2021;8.
26 Morgan J, Young L, McGuire W. Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database Syst Rev 2014.
27 Holmberg MJ, Andersen LW. Adjustment for baseline characteristics in randomized clinical trials. JAMA 2022;328:2155 6.
28 Ortigoza EB. Feeding intolerance. Early Hum Dev 2022;171.