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Early or Delayed Enteral Feeding for Preterm Growth-Restricted Infants: A Randomized Trial



WHAT'S KNOWN ON THIS SUBJECT: Preterm, growth-restricted infants are at high risk of necrotizing enterocolitis (NEC). NEC occurs most frequently in infants who have received enteral feeds. It is common practice to delay introduction of enteral feeds in these infants.



WHAT THIS STUDY ADDS: Early introduction of enteral feeds results in earlier achievement of full enteral feeding. Early feeding is not associated with a higher risk of NEC. Delayed feeding is associated with a higher risk of cholestasis.

abstract

BACKGROUND: Growth-restricted preterm infants are at increased risk of developing necrotizing enterocolitis (NEC) and initiation of enteral feeding is frequently delayed. There is no evidence that this delay is beneficial and it might further compromise nutrition and growth.

METHODS: Infants with gestation below 35 weeks, birth weight below the 10th centile, and abnormal antenatal umbilical artery Doppler waveforms were randomly allocated to commence enteral feeds “early,” on day 2 after birth, or “late,” on day 6. Gradual increase in feeds was guided by a “feeding prescription” with rate of increase the same for both groups. Primary outcomes were time to achieve full enteral feeding sustained for 72 hours and NEC.

RESULTS: Four hundred four infants were randomly assigned from 54 hospitals in the United Kingdom and Ireland (202 to each group). Median gestation was 31 weeks. Full, sustained, enteral feeding was achieved at an earlier age in the early group: median age was 18 days compared with 21 days (hazard ratio: 1.36 [95% confidence interval: 1.11–1.67]). There was no evidence of a difference in the incidence of NEC: 18% in the early group and 15% in the late group (relative risk: 1.2 [95% confidence interval: 0.77–1.87]). Early feeding resulted in shorter duration of parenteral nutrition and high-dependency care, lower incidence of cholestatic jaundice, and improved SD score for weight at discharge.

CONCLUSIONS: Early introduction of enteral feeds in growth-restricted preterm infants results in earlier achievement of full enteral feeding and does not appear to increase the risk of NEC. *Pediatrics* 2012;129:e1260–e1268

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KEY WORDS

infant premature, infant very low birth weight, enterocolitis, necrotizing, enteral nutrition, Doppler ultrasound imaging, blood flow velocity

ABBREVIATIONS

ADEPT—Abnormal Doppler Enteral Prescription Trial
AREDFV—absent or reversed end-diastolic flow velocity
CI—confidence interval
HR—hazard ratio
IQR—interquartile range
IUGR—intrauterine growth restriction
NEC—necrotizing enterocolitis
RR—relative risk
SDS—SD score
SGA—small for gestational age

This trial has been registered with the ISRCTN Register (<http://isrctn.org>) (identifier ISRCTN87351483).

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Pregnancies complicated by suspected intrauterine growth restriction (IUGR) are usually monitored by Doppler ultrasound to measure fetal blood flow. A pattern of absent or reversed end-diastolic flow velocity (AREDFV) in the umbilical artery is associated with fetal growth restriction and increased risk of intrauterine death.^{1,2} Management of such complicated pregnancies often results in the preterm delivery of a growth-restricted infant. The authors of studies suggest that blood flow to the head is preserved to support brain growth at the expense of blood flow to the abdomen and growth of visceral organs.^{1,3,4} Increasing use of Doppler ultrasound in clinical practice has revealed an association between AREDFV and necrotizing enterocolitis (NEC), thought to be a result of this relative gut ischemia.^{5,6} A meta-analysis of 14 observational studies confirmed an increased incidence of NEC in preterm infants who had exhibited fetal AREDFV compared with controls, with an odds ratio of 2.13 (95% confidence interval [CI]: 1.49–3.03).⁷

As NEC mostly occurs after infants have received enteral feeds, it has become common practice to delay the start of enteral feeding in those considered to be at highest risk.⁸ The evidence base to support this practice is weak, particularly as authors of published studies frequently do not give clarity on fetal growth restriction. In interpreting other studies, we have defined small for gestational age (SGA) as birth weight below 10th centile, which may include some small-normal infants. IUGR defines those infants who have a history of abnormal antenatal Doppler blood flow, indicating a pathologic reduction in growth below their genetic potential; these infants are frequently, but not necessarily, also SGA. A Cochrane review of early or late commencement of progressive enteral feeds for preterm infants published in 2008 identified 3

small trials with 115 participants. All infants were preterm and low birth weight but were not specifically SGA or IUGR. “Early” feeds were started within 4 days of birth, and “late” feeds between 5 and 10 days. No difference was seen in rates of NEC, but the authors concluded that the available data were insufficient to inform clinical practice.⁹ The authors of 1 published trial have specifically investigated early or late feeding of SGA IUGR infants born after abnormal Dopplers.¹⁰ Eighty-four infants were randomly assigned to start feeds either before or after 5 days after birth; no difference was found in incidence of NEC or feed intolerance. An updated Cochrane review published in 2011 incorporated data from this study, as well as incomplete data from our study,¹¹ thus combining data from IUGR, SGA, and appropriate for gestational age infants. With a total of 600 infants, their conclusion regarding NEC was unchanged.¹²

Postnatal growth restriction is common in preterm infants and is associated with adverse neuro-developmental outcomes.¹³ Limited published evidence suggests that severe IUGR is associated with an increased risk of neuro-developmental impairment.¹⁴ Early introduction of enteral feeds may improve nutrition and growth and subsequent outcomes but may increase the risk of NEC.^{15,16} Conversely, late introduction may result in villous atrophy and reduced hormone and enzyme production¹⁷ due to lack of intestinal stimulation. Late introduction may also result in prolonged use of parenteral nutrition with increased risks of sepsis,¹⁶ cholestatic jaundice,^{18,19} and vitamin and mineral deficiencies.

Advances in fetal medicine have resulted in increased numbers of infants being born preterm after AREDFV, but there is a paucity of robust data on which to base feeding practice. IUGR infants have often been specifically excluded from preterm infant feeding

studies because of their perceived high risk status.^{20,21} The Abnormal Doppler Enteral Prescription Trial (ADEPT) was designed to evaluate the effect of an early compared with a late enteral feeding regimen on the time to establish full enteral feeding and incidence of NEC and other gastrointestinal complications in a group of SGA, IUGR infants identified by antenatal Doppler studies.

METHODS

Trial Design and Participants

ADEPT was a multicenter randomized controlled trial, and the methods are reported in full in the published protocol.²² Infants were eligible if they were born preterm (up to 34⁺⁶ weeks of gestation), SGA (birth weight below 10th centile²³), <48 hours postnatal age, and had abnormal antenatal Doppler studies indicative of IUGR. This was defined as the following: (1) AREDFV in the umbilical artery seen on at least 50% of waveforms on at least 1 occasion during pregnancy, or (2) cerebral redistribution (umbilical artery pulsatility index >95th centile and middle cerebral artery pulsatility index <5th centile for gestation).²⁴ Exclusion criteria were as follows: major congenital anomaly, twin-twin transfusion, Rhesus iso-immunization, previous intrauterine or exchange transfusion, multiorgan dysfunction, inotropic drug support, or enteral feeding before trial entry. Informed written parental consent was obtained within the first 48 hours after birth.

Intervention

Infants were randomly allocated to early (between 24 and 48 hours after birth) or late (between 120 and 144 hours after birth) enteral feeding regimen, which was identical apart from the time it commenced. Feeds were gradually increased according to an “enteral prescription” tailored to birth weight,

aiming to reach 150 mL/kg per day over 13 days in the smallest infants (<600 g) and 9 days in the largest infants (>1250 g).²² It was expected that parenteral nutrition would be started within 24 to 48 hours of birth and continued until milk feeding established. Mother's breast milk was recommended as the first choice of initial milk, followed by donor breast milk and infant formula. Fortification of human milk was recommended once 150 mL/kg per day was reached, if additional nutrient support was required. Ventilation support or presence of umbilical catheters was not viewed as a contraindication to feeding.

Outcomes

Primary outcomes were (1) age in days to achieve full enteral feeding of at least 150 mL/kg per day sustained for 72 hours and (2) a diagnosis of NEC (modified Bell's stage 1, 2, or 3).²⁵ Intake was recorded daily on a feed log, and full feeds had to be sustained for 72 hours to ensure genuine milk tolerance.

Secondary outcomes were as follows: death before hospital discharge; duration of hospital stay, intensive care, high-dependency care (defined in protocol²²), and parenteral nutrition; gastrointestinal perforation; gastrointestinal surgery; culture-positive sepsis; patent ductus arteriosus requiring treatment; cholestasis (conjugated bilirubin >25 $\mu\text{mol/liter}^*$); cranial ultrasound abnormality (ventricular dilatation ≥ 4 mm above 97th centile, parenchymal hemorrhage or infarct, cystic periventricular leukomalacia); type of milk at discharge; and oxygen therapy, weight, and head circumference at 36 weeks' postmenstrual age and at discharge.

A designated form was completed for each episode of NEC or other abdominal pathology. Local investigators were asked to document clinical signs

and laboratory, radiologic, and histopathologic findings, and to make a "final diagnosis" for each episode. All forms were reviewed by a blinded committee.

Sample Size

Unpublished nutrition data from a UK regional database of very low birth weight infants²⁶ revealed an SD of 9 days in the time taken to reach full enteral feeding. We calculated that 380 infants would be required to show a difference of 3 days in this outcome with 90% power. The incidence of NEC from published literature is $\sim 15\%$ in this population, and a sample of 400 would be sufficient to show a 50% change in the incidence of NEC with 60% power.

Randomization

Infants were randomly assigned between 20 and 48 hours after birth by using a secure Web-based randomization service hosted by the National Perinatal Epidemiology Unit Clinical Trials Unit. A minimization algorithm was used to ensure a balanced allocation within hospital of recruitment, gestational age group (<29 weeks or ≥ 29 weeks), and type of Doppler abnormality (AREDFV or cerebral redistribution).

Blinding

Masking clinicians to allocation was not possible. However, a blinded committee reviewed all NEC and abdominal pathology forms, as well as any cases where there was uncertainty about the primary end point being met.²²

Statistical Methods

Infants were analyzed in their allocated group by using Stata (version 10; Stata Corp, College Station, TX), regardless of the feeding regimen they actually received or deviation from the protocol. A time to event analysis using Cox

regression was performed to compare the age in days at which full enteral feeding was reached between the early and late group. This enables the infants who died before reaching full feeds to be included in the denominator (until the time they died). Kaplan-Meier curves were plotted and the hazard ratios (HRs) presented. Two-sided hypothesis tests and 95% CIs are presented throughout.

SD scores (SDSs) were calculated for growth data, and the change in SDS from birth to 36 weeks and discharge were analyzed by using analysis of covariance, adjusting for birth weight SDS. A prespecified subgroup analysis was planned by using a statistical test of interaction, stratifying by gestation at delivery (<29 or ≥ 29 weeks) and type of Doppler abnormality.

RESULTS

Recruitment and Retention

Four hundred four infants were recruited from April 2006 to May 2009 from 54 hospitals in the United Kingdom and Ireland (Fig 1). Clinical characteristics at trial entry were well balanced between groups, though there was a slightly higher proportion of infants ≥ 1250 g in the early group (Table 1).

Compliance With Introduction of Enteral Feeds

There was clear separation between groups in the distribution of time of first feed. Feeding started within the specified time for 164/198 (83%) infants in the early group and 147/194 (76%) infants in the late group. This increased to 87% and 86%, respectively, when a 2-hour tolerance was allowed during either side of the specified times.

Although not specified as an outcome, 155/198 (78%) of infants in the early group and 179/191 (94%) in the late group received an initial feed containing at

*Conversion factor: 17.1 $\mu\text{mol/Liter (SI)} = 1 \text{ mg/dL}$.

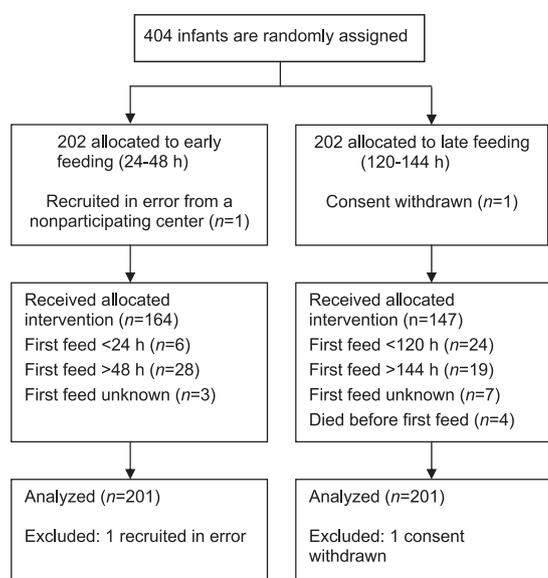


FIGURE 1
Flow of participants.

least some of their mother's own breast milk; for some, this was supplemented with either donor breast milk or formula.

Overall, 146/198 (74%) and 173/191 (91%) received exclusively human milk in the first feed.

TABLE 1 Antenatal and Infant Details at Randomization

	Early Feeding Group: <i>n</i> = 201, <i>n</i> (%) ^a	Late Feeding Group: <i>n</i> = 201, <i>n</i> (%) ^a
Pregnancy induced hypertension		
Any	83 (41)	76 (38)
Treated	51 (25)	51 (25)
Multiple pregnancy		
Twins	47 (23)	42 (21)
Triplets	2 (1)	4 (2)
Onset of labor		
Spontaneous	8 (4)	1 (1)
Induced	4 (2)	0 (0)
Caesarean before onset of labor	189 (94)	200 (100)
Type of Doppler abnormality		
Cerebral redistribution	10 (5)	6 (3)
Absent or reversed flow	191 (95)	195 (97)
Gestation at delivery		
Mean (SD)	31.0 (2.3)	31.0 (2.3)
<29 wk	44 (22)	42 (21)
≥29 wk	157 (78)	159 (79)
Boys	104 (52)	112 (56)
Birth weight, g		
Mean (SD)	1042 (303)	1021 (308)
<600	10 (5)	15 (7)
600–749	23 (11)	26 (13)
750–999	65 (32)	64 (32)
1000–1249	46 (23)	48 (24)
≥1250	57 (28)	48 (24)
Median (IQR) Apgar score at 5 min	9 (9–10)	9 (9–10)
Positive pressure ventilation	27 (13)	20 (10)
Nasal continuous airway pressure	68 (34)	77 (38)
Umbilical artery catheter in situ	27 (13)	28 (14)

IQR (25th–75th percentile).
^a Unless otherwise specified.

Primary Outcomes and Abdominal Pathology

Full enteral feeding was reported in 190 (95%) infants in each group (Table 2). Full feeds were achieved at an earlier age in the early group; median age was 18 days (interquartile range [IQR] 15–24) compared with 21 days (IQR 19–27; HR: 1.36 [95% CI: 1.11–1.67]; $P = .003$)[†] (Fig 2). This indicates that the relative likelihood of establishing full feeds at any given time was 36% higher in the early group compared with the late group. The analysis was repeated adjusting for birth weight category (defined in Table 1) because there was a slight imbalance between groups, which could have explained some of the difference seen in feeding advancement. The adjusted HR was 1.45 (95% CI: 1.19–1.78; $P < .001$), which does not alter the conclusions of the main analysis.

The number of episodes of all-stage NEC was 36 (18%) in the early group and 30 (15%) in the late group (relative risk [RR]: 1.20 [95% CI: 0.77–1.87; $P = .42$]). The incidence of stages 2 and 3 NEC, which is of greater clinical importance, was 8% in both groups. More infants in the early group had at least 1 episode of “abdominal pathology”: 59 (29%) vs 42 (21%; RR: 1.40 [95% CI: 1.00–1.98]), which was mainly due to a higher rate of dysmotility, meconium plug, and stage 1 NEC. There were no between-group differences in the number of infants with septic ileus, intestinal perforation, surgery, or death as a result of gastrointestinal complications.

Other Secondary Outcomes

Cholestatic jaundice was less common in the early group; 25/195 (13%) compared with 43/195 (22%; RR: 0.58 [95% CI: 0.37–0.91]; Table 3). The incidence of late onset sepsis was 55/198 (28%) in the early group and 69/199 (35%) in the

[†]The P value for the log-rank test was 0.002.

TABLE 2 Primary Outcomes and Abdominal Pathology

	Early Feeding: <i>n</i> = 201, <i>n</i> (%) ^a	Late Feeding: <i>n</i> = 201, <i>n</i> (%) ^a	RR (95% CI)	<i>P</i>
No. of infants for whom full enteral feeding was established	190 (95)	190 (95)	—	—
Died before reaching full enteral feeding	9 (4)	8 (4)	—	—
Daily feed log forms missing or incomplete	2 (1)	3 (1)	—	—
Age (d) at which full enteral feeding was established, median (25th–75th percentile) ^b	18 (15–24)	21 (19–27)	1.36 (1.11–1.67)	.003
NEC	36 (18)	30 (15)	1.20 (0.77–1.87)	.42
Highest stage				
Stage 1	18 (9)	12 (6)	—	—
Stage 2	10 (5)	7 (3)	—	—
Stage 3	7 (3)	11 (5)	—	—
Not known	1 (0)	0 (0)	—	—
Septic ileus	10 (5)	11 (5)	0.91 (0.39–2.09)	.82
NEC or septic ileus	43 (21)	37 (18)	1.16 (0.78–1.72)	.45
Dysmotility or meconium/milk plug	12 (6)	3 (2)	4.00 (1.15–14.0)	.02
Intestinal perforation	6 (3)	5 (2)	1.20 (0.37–3.87)	.76
Surgery				
Laparotomy	10 (5)	10 (5)	1.00 (0.43–2.35)	1.00
Bowel resection	5 (2)	7 (3)	0.71 (0.23–2.21)	.56
Stoma	5 (2)	7 (3)	0.71 (0.23–2.21)	.56
Bowel resection and stoma	3 (1)	6 (3)	0.50 (0.13–1.99)	.32
Died of gut pathology	4 (2)	6 (3)	0.67 (0.19–2.33)	.52

^a Unless otherwise specified.

^b Median time to event with percentiles. Effect measure is HR.

late group, which was not statistically significant (RR: 0.80 [95% CI: 0.60–1.08]). Early feeding resulted in shorter duration of parenteral nutrition (amino acids and lipid) and high-dependency care, but there was no difference in overall length of hospital stay or duration of intensive care (Table 3).

Infants were severely growth-restricted at birth with a mean weight SDS of -2.32 in the early group and -2.41 in the late group, and underwent a period of further postnatal growth restriction. By the time of discharge, weight SDS was still below birth levels in both groups, with a greater degree of postnatal growth restriction in the late group ($P = .04$). Head circumference revealed some “catch-up” growth, and there was no between-group difference.

Subgroup Analysis

Eighty-six (21%) infants were below 29 weeks’ gestation, and 316 (79%) were 29 weeks or above. In infants <29 weeks’

gestation, mortality was 5/44 (11%) in the early group versus 6/42 (14%) in the late group, and there were 17 (39%) and 16 (38%) cases of NEC, respectively (8 in each group were stage 2 or 3). Full enteral feeding was established by 38/43 (88%) in the early group and 35/41 (85%) in the late group. Median age to achieve full feeds was 25 days and 29 days, respectively (HR: 1.23 [95% CI: 0.78–1.96]). In infants ≥ 29 weeks’ gestation, mortality was 4/157 (3%) in the early group versus 2/159 (1%) in the late group. There were 19 (12%) and 14 (9%) cases of NEC, respectively; 9 (early group) and 10 (late group) were stage 2 or 3. Full enteral feeding was established in 152/156 (97%) of the early group and 155/157 (99%) in the late group, and the median age to achieve full feeds was 17 days and 21 days, respectively (HR: 1.54 [95% CI: 1.23–1.93]).

The statistical test of interaction between treatment group and gestational age was not significant for median age

to achieve full feeds ($P = .38$) or for incidence of all-stage NEC ($P = .47$), implying consistency of treatment effect in the 2 subgroups for the primary outcomes.

Type of Doppler abnormality was predefined for subgroup analysis; however, because fewer than 5% of infants had a pattern of cerebral redistribution, this was not carried out.

DISCUSSION

Awareness that growth-restricted preterm infants are at high risk for feeding intolerance and NEC has led to a common practice of delaying the introduction of enteral feeds. Our results suggest that this practice is not justified. Infants in ADEPT who started feeds earlier achieved sustained enteral feeding at a significantly earlier age, with an average difference of 3 days. No difference was found in the incidence of NEC, particularly for serious Bell’s stage 2 or 3. Rates of all-stage NEC at 18% in the early group and 15% in the late group were consistent with those found in our systematic review.⁷ Although slightly more infants in the early feeding group had stage 1 NEC and intestinal dysmotility, there was no difference in the number requiring bowel surgery and no difference in death related to gastrointestinal complications.

Other related benefits of starting feeds earlier were a shorter duration of parenteral nutrition and of high-dependency care and a lower incidence of cholestatic jaundice. Among preterm infants receiving parenteral nutrition, those with IUGR and with sepsis are at particular risk of cholestasis.²⁷ Because cholestasis impairs fat absorption and may further compromise nutrition and growth, policies aimed at reducing it should be preferred. We found no significant difference in the incidence of late onset sepsis.

Our study infants were severely growth restricted at birth, being below the second centile for weight. After birth,

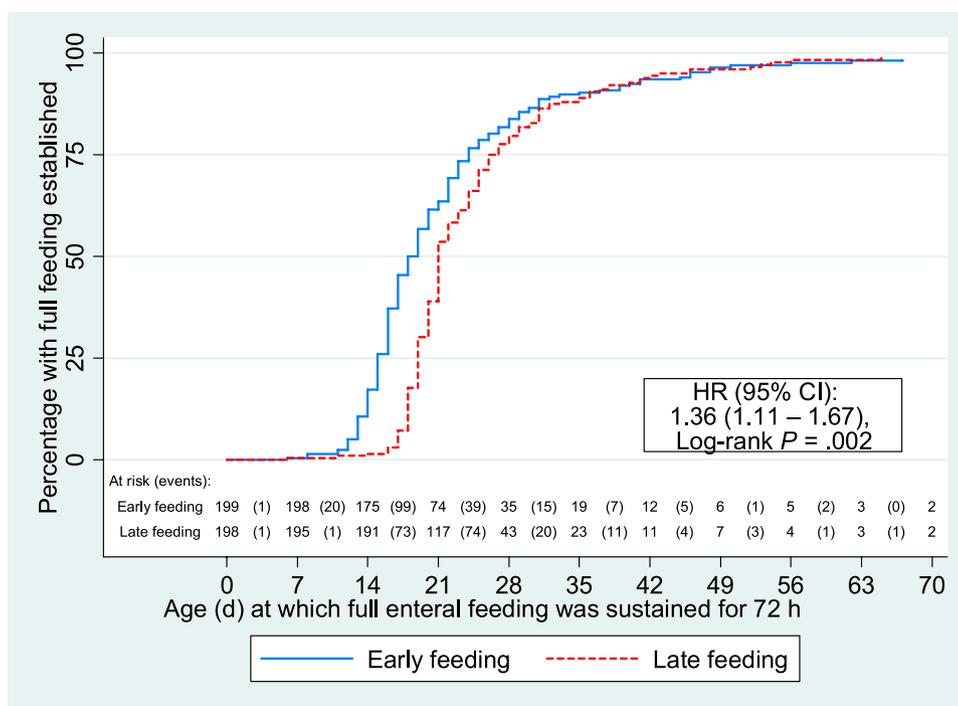


FIGURE 2

Proportion of infants with full enteral feeding established by feeding group.

they experienced further growth restriction such that at discharge their weight SDSs were lower than at birth. This reduction in SDS was significantly less marked in the early feeding group, allowing speculation that even a 3-day difference in establishment of enteral feeding may have a positive impact on growth.

This is the largest interventional study to date in this patient population, with IUGR related to antenatal AREFDV, but our findings are compatible with relevant published data. The study by Karagianni et al¹⁰ has been discussed earlier. Van Elberg et al²⁸ investigated early versus late introduction of “trophic feeding” in SGA preterm infants, most of whom had abnormal antenatal Doppler scans. Neither study revealed a difference in incidence of NEC or other clinical outcomes.

Trophic feeding has been suggested as a way of promoting intestinal adaptation and avoiding the adverse effects of total enteral fasting in infants at high risk for NEC. The authors of a systematic

review summarized 9 trials, involving 754 preterm infants.²⁹ Seven trials defined eligibility by gestational age, birth weight, or both, appearing to include both appropriate for gestational age and SGA infants; 1 trial excluded those who were SGA, and 1²⁸ included only infants who were SGA. Meta-analysis did not demonstrate a significant effect on feed tolerance, weight gain, or NEC.²⁹ The authors’ conclusion was that there were insufficient data to exclude either a harmful or beneficial effect of trophic feeding.

We recognize that ADEPT had only 60% power to detect a 50% difference in the incidence of NEC and did not show this. What it has demonstrated, in keeping with other published work, is that the intervention of delaying feeds is unlikely to produce large effects. A negative trial with 90% power would require 6400 infants to exclude a difference in all-stage NEC rates of 18% vs 15%. We excluded infants receiving inotropes and those with perinatal complications likely to further compromise gut per-

fusion, so our findings may not be applicable to all infants born after AREFDV. Introduction of a standardized feeding regimen has been shown to reduce the incidence of NEC compared with retrospective control groups.³⁰ The failure of our standardized “enteral prescription” to reduce NEC rates compared with previous published studies may be due to the large number of study centers and relatively small number of patients recruited from each. Breast milk has been shown to offer protection against NEC,^{31,32} and we were reassured to observe that even in our early group, more than 75% of infants received their mother’s breast milk at the initial feed.

CONCLUSIONS

Our trial revealed no evidence of benefit in delaying the introduction of small volumes of enteral feeds in preterm, IUGR infants beyond 24 to 48 hours. Early introduction allows establishment of full feeds earlier with a reduction in cholestatic jaundice and improved

TABLE 3 Secondary Outcomes

	Early Feeding		Late Feeding		RR ^b (95% CI)	P
	Number analyzed ^a	n (%) ^b	Number analyzed ^a	n (%) ^b		
Outcomes						
Discharged from the hospital	198	186 (94)	197	184 (93)	0.92 (0.43 to 1.96)	.83
Died before discharge	—	12 (6)	—	13 (7)	—	—
Late sepsis	198	55 (28)	199	69 (35)	0.80 (0.60 to 1.08)	.14
Cholestasis	195	25 (13)	195	43 (22)	0.58 (0.37 to 0.91)	.02
Patent ductus arteriosus requiring treatment	194	16 (8)	195	16 (8)	1.01 (0.52 to 1.95)	.99
Cranial ultrasound abnormality	200	3 (2)	200	5 (3)	0.60 (0.15 to 2.48)	.48
Receiving oxygen at 36 wk gestational age	185	47 (25)	187	46 (25)	1.03 (0.73 to 1.47)	.86
Feeding at discharge home						
Mother's breast milk only	186	31 (17)	183	38 (21)	0.80 (0.52 to 1.23)	.31
Mother's breast milk + formula or fortifier	—	51 (27)	—	57 (31)	—	—
Formula only	—	104 (56)	—	88 (48)	—	—
Receiving oxygen therapy at discharge	186	16 (9)	184	16 (9)	0.99 (0.51 to 1.92)	.97
Duration of hospital stay to discharge or death^c						
Median (IQR)	198	47 (31 to 73)	197	49 (33 to 75)	−1 (−7 to 4)	.59
(Minimum, maximum)	—	(8 to 379)	—	(5 to 385)	—	—
Days in intensive care^c						
Median (IQR)	198	4 (0 to 18)	197	4 (0 to 13)	0 (0 to 0)	.98
(Minimum, maximum)	—	(0 to 119)	—	(0 to 215)	—	—
Days in high dependency care^c						
Median (IQR)	198	11 (7 to 23)	197	15 (11 to 23)	−3 (−5 to −1)	.002
(Minimum, maximum)	—	(0 to 179)	—	(0 to 102)	—	—
Duration of parenteral nutrition—amino acids, d^c						
Median (IQR)	190	12 (9 to 16)	190	15 (13 to 19)	−3 (−4 to −2)	<.001
(Minimum, maximum)	—	(0 to 81)	—	(2 to 61)	—	—
Duration of parenteral nutrition—lipids, d^c						
Median (IQR)	190	10 (7 to 14)	190	13 (11 to 16)	−3 (−4 to −2)	<.001
(Minimum, maximum)	—	(0 to 77)	—	(3 to 46)	—	—
Weight SDS, mean and between group difference in change from birth^{d,e}						
Birth	201	−2.32 (0.68)	201	−2.41 (0.64)	—	—
36 wk postmenstrual age	187	−2.87 (0.77)	187	−3.00 (0.76)	0.05 (−0.06 to 0.16)	.38
Discharge	185	−2.80 (0.74)	183	−3.01 (0.92)	0.16 (0.01 to 0.30)	.04
Head circumference SDS, mean and between group difference in change from birth^{d,e}						
Birth	188	−1.86 (1.11)	190	−1.90 (1.20)	—	—
36 wk postmenstrual age	183	−1.83 (1.08)	185	−1.99 (1.14)	0.11 (−0.10 to 0.32)	.29
Discharge	178	−1.53 (1.18)	170	−1.72 (1.08)	0.10 (−0.11 to 0.31)	.37

IQR (25th to 75th percentile).

^a Denominators for secondary outcomes vary due to deaths and missing data.

^b Unless otherwise specified.

^c Effect measure is median difference and P value from 2 sample Wilcoxon Rank Sum tests.

^d SDSs calculated by using The British 1990 growth reference (revised September 1996). These indicate how far an infant is from the population mean weight and head circumference for infants of the same age and gender.

^e Effect measure is the between group difference in change from birth (early versus late group) adjusted for baseline value. P value from analysis of covariance.

weight gain. The challenge now is to understand how best to progress feeds to support healthy maturation and function of the immature gut while minimizing excessive and harmful inflammation.

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Early or Delayed Enteral Feeding for Preterm Growth-Restricted Infants: A Randomized Trial

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